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Stroke incidence in young adults according to age, subtype, sex, and time trends

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Abstract

Objective

To investigate incidence of stroke and its subtypes in young adults, according to sex and age, and to study trends over time.

Methods

We established a nationwide cohort through linkage of national registries (hospital discharge, cause of death, and population register) with patients aged 18–50 years and those ≥50 years with first-ever ischemic stroke, intracerebral hemorrhage, or unspecified stroke, using ICD-9/ICD-10 codes between 1998 and 2010 in the Netherlands. Outcomes were yearly incidence of stroke stratified by age, sex, and stroke subtype, its changes over time, and comparison of incidence in patients 18–50 years to patients ≥50 years.

Results

We identified 15,257 patients (53% women; mean age 41.8 years). Incidence increased exponentially with age ($R^2 = 0.99$) and was higher for women than men, most prominently in the youngest patients (18–44 years). The relative proportion of ischemic stroke increased with age (18–24 years: 38.3%; 44–49 years: 56.5%), whereas the relative proportion of intracerebral hemorrhage decreased (18–24 years: 34.0%; 44–49 years: 18.3%). Incidence of any stroke in young adults increased (1998: 14.0/100,000 person-years: 2010: 17.2; +23%; $p < 0.001$), driven by an increase in those aged over 35 years and ischemic stroke incidence (46%), whereas incidence decreased in those ≥50 years (329.1%–292.2%; −11%; $p = 0.009$).

Conclusions

Incidence of any stroke in the young increases with age in patients over 35, is higher in women than men aged 18–44 years, and has increased by 23% in one decade, through an increase in ischemic stroke. Incidence of intracerebral hemorrhage is comparable for women and men and remained stable over time.

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Glossary

CI = confidence interval; **DWI** = diffusion-weighted MRI; **HDR** = Hospital Discharge Register; **ICD** = International Classification of Diseases; **IRR** = incidence rate ratio; **SAH** = subarachnoid hemorrhage.

An estimated 10%–15% of all first-ever strokes occur in people aged 18–50 years.[1,2] With a yearly stroke incidence of 15 million people worldwide, at least 1.5 million young adults are affected every year.[3] The consequences of stroke in the young are substantial and, due to their long survival after stroke, long-lasting. Sequelae of stroke in the young have specific implications in relation to their age, as young patients are often at crossroads in their lives with young families, demanding careers, and social interactions that may remain impaired for decades to come. In addition, the social–economic burden of stroke in the young is high, considering the number of productive life years lost.[4,5]

Despite improvement in the prevention and treatment of cardiovascular disease, recent studies have suggested an increase in the incidence of stroke in young adults, which is in contrast with the decrease in incidence observed in the elderly.[1,6–12] However, there are several uncertainties. Due to low patient numbers, it is unknown whether the suggested increase in incidence is present across all age strata for both men and women. In addition, most previous studies were (single) hospital-based (with the possibility of selection bias) or occurred in countries where not all patients with stroke were likely to be seen by a neurologist, were limited to either ischemic stroke or intracerebral hemorrhage or did not specify a stroke subtype, and included subarachnoid hemorrhage (SAH). The studies also had varying lower and upper age limits to define young adults, did not always adjust for the total number of individuals within the general population when reporting the (change of) incidence, and did not compare results with time trend in incidence of stroke in patients over 50 years of age to determine whether observed time trends were age-specific.

We therefore investigated age- and sex-specific incidence and incidence trends over time of first-ever ischemic stroke and intracerebral hemorrhage among young adults in the Netherlands.

Methods

Patients

Through linkage of the Dutch Hospital Discharge Register (HDR) and Population Register, all Dutch patients with a hospitalization for first-ever stroke (ischemic stroke, intracerebral hemorrhage, or stroke not otherwise specified) were identified between 1998 and 2010, using ICD-9 codes for stroke. We also utilized the Cause of Death Register with the Population Register to identify all Dutch persons who died from a first-ever stroke outside of the hospital between 1998 and 2010, using ICD-10 codes for stroke (table 1). The index event was operationalized through selecting the first admission for stroke from January 1, 1998, onwards, since we were unable to identify possible previous strokes before this date. We excluded patients with SAH or cerebral venous sinus thrombosis.

Table 1 Overview of used ICD-9 and ICD-10 codes

ICD-9 code	Definitions
Any stroke	
431	Intracerebral hemorrhage
433	Occlusion and stenosis of precerebral arteries with/without cerebral infarction
434	Occlusion of cerebral arteries with/without cerebral infarction
436	Stroke, unspecified as hemorrhagic or infarction
Intracerebral hemorrhage	
431	Intracerebral hemorrhage
Ischemic stroke	
433	Occlusion and stenosis of precerebral arteries with/without cerebral infarction
434	Occlusion of cerebral arteries with/without cerebral infarction
Unspecified stroke	
436	Stroke, unspecified as hemorrhagic or infarction
ICD-10	
Any stroke	
I61	Intracerebral hemorrhage
I63	Cerebral infarction
I64	Stroke, unspecified as hemorrhagic or infarction
Intracerebral hemorrhage	
I61	Intracerebral hemorrhage
Ischemic stroke	
I63	Cerebral infarction
Unspecified stroke	
I64	Stroke, unspecified as hemorrhagic or infarction

Abbreviation: ICD = International Classification of Diseases.

The validity of ICD codes for identifying patients with ischemic stroke and intracerebral hemorrhage has been demonstrated for stroke patients of all ages,[13,14] but not for young adults specifically. At young age, some stroke mimics like migraine and seizures may occur more frequently than in the elderly.[15] Therefore we assessed the validity of the ICD codes for 569 patients with a stroke at young age (301 with an ischemic stroke, 183 with intracerebral hemorrhage, and 85 with an unspecified stroke), hospitalized between January 1998 and May 2017 in 2 academic and 1 large nonacademic teaching hospital. We chose to analyze all data available of patients who had complete files including neuroimaging (n = 569), therefore not restricting the validation period to our study period, to sample as many young stroke patients as possible to provide a more reliable validation analysis. We compared all ICD-9 or ICD-10 codes logged as discharge codes in the local hospital administration with the main diagnosis (including findings on neuroimaging) in the medical files. Ischemic stroke was correctly diagnosed through registered ICD codes in 90.4% of cases, intracerebral hemorrhage in 86.3%, and unspecified stroke in 87.1%, comparable to the validity in the general stroke population. Of the 74 unspecified strokes, 67 (90.5%) were ischemic strokes and 7 (9.5%) were intracerebral hemorrhages (table 2).[13,14]

The HDR contains records of all individual hospital admissions of the participating Dutch hospitals, including information about primary diagnosis (4-digit ICD-9 codes) as well as date of birth, sex, and numeric part of the postal code. Using these personal identifiers, we linked the HDR admission records containing the selected ICD-9 codes for stroke with the Population Register to link multiple hospital admissions of one person. Approximately 85% of the Dutch population can be identified through a unique combination of their date of birth, sex, and postal code.[16] These registers and linkage procedures have been described in detail.[16–18]

In addition, we identified patients who were not admitted to the hospital because they died outside the hospital either primarily or secondarily from first-ever stroke through the cause of death register using ICD-10 codes (table 1).

From 2005 onwards, fewer hospitals participated in the HDR, leading to an increasing number of missing records. In 2005, 1.1% of records were missing, whereas between 2006 and 2010 the percentage of missing records varied between 10.5% and 14.0%. The estimated number of actual strokes by Statistics Netherlands is listed in the supplementary material, as

Table 2 Results of validation procedure

	Ischemic stroke, n (%)	Intracerebral hemorrhage, n (%)	Unspecified stroke, n (%)
Total	301	183	85
Correct diagnosis	272 (90.4)	158 (86.3)	74 (87.1)
Incorrect diagnoses	29 (9.4)	25 (13.7)	11 (12.9)
	5 (1.7): Conversion	4 (2.2): Traumatic ICH	4 (4.7): Conversion
	4 (1.3): Vestibulopathy	10 (5.5): PMH	3 (3.5): Neoplasm
	3 (1.0): TIA	3 (1.6): SAH	2 (2.4): TIA
	3 (1.0): ICH	8 (4.4): Ischemic stroke	1 (1.2): Traumatic ICH
	3 (1.0): SAH		1 (1.2): CADASIL
	2 (0.7): Neoplasm		
	2 (0.7): Encephalitis/meningitis		
	1 (0.3): Migraine with aura		
	1 (0.3): HaNDL syndrome		
	1 (0.3): SUSAC syndrome		
	1 (0.3): Subdural hematoma		
	1 (0.3): MS		
	1 (0.3): PMH		
	1 (0.3): traumatic ICH		

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; HaNDL syndrome = headache and neurologic deficit with CSF lymphocytosis; ICH = intracerebral hemorrhage; MS = multiple sclerosis; PMH = perimesencephalic hemorrhage; SAH = subarachnoid hemorrhage.

well as an overview of contributing centers, and a table concerning the regional coverage of the HDR from 2006 to 2010.

Case definition

Any stroke was defined as a first-ever hospitalization for ischemic stroke, intracerebral hemorrhage, or unspecified stroke (either ischemic or hemorrhagic, but not specified as such) or out-of-hospital death due to first-ever stroke. We defined young adults as those aged between 18 and 50 years at the time of stroke and the reference group as those aged ≥50 years.

Data analysis

We calculated the crude age-, sex-, and stroke subtype–specific incidence per 100,000 person-years for each consecutive year from 1998 to 2010. For this, we used the age-, sex-, and year-specific population estimates from Statistics Netherlands.[19]

We assessed age-specific differences in stroke incidence between men and women by calculating incidence rate ratios (IRR) including 95% confidence intervals (CIs) based on Poisson distribution.

We also calculated the relative proportions of stroke subtypes in young adults according to age and sex strata and under age 50 in the stroke population and compared differences by χ^2 test of proportions.

Finally, we calculated the 13-year relative change in incidence for each age and sex subgroup by using the following formula: (incidence 2010 − incidence 1998)/incidence 1998, and tested for significant trends in incidence rates over time by linear regression, by age and sex subgroup for individuals 18–50 years and those ≥50 years.

We used SPSS software version 22 (SPSS, Chicago, IL), R version 3.2.2 (Package rateratio.test), MedCalc statistical software 2018, and Microsoft Office Excel 2007 (Microsoft, Redmond, WA).

Data availability

All data used for analysis are presented in the tables. Data will be shared after ethics approval if requested by other investigators for purposes of replicating the results.

Standard protocol approvals, registrations, and patient consents

This study was performed according to the guidelines of the local research ethics committees.

Results

We identified 15,257 cases of first-ever stroke in adults aged 18–50 years between 1998 and 2010. Of these, 8,444 (55.3%) were ischemic stroke, 3,077 (20.2%) were intracerebral hemorrhage, and 3,736 (24.5%) were unspecified stroke. Fifty-three percent of all strokes occurred in women. Mean age at first-ever any stroke was 41.4 (SD 7.0) years for women and 42.3 (SD 6.5) years for men. Fewer than 1% of cases were out-of-hospital deaths.

Sex-specific variation in age at first-ever stroke

The incidence of first-ever any stroke in young adults increased exponentially with age in both sexes ($R^2 = 0.98$ in men and $R^2 = 0.99$ in women; R^2 is a measure of how close data points fit a regression line, which in this case indicates an exponential increase). In all age strata, the incidence in women was higher than in men, except in those aged 44–49 years (table 3). The IRR of women compared to men declined with age from 1.93 (95% CI 1.62–2.31) in 18- to 24-year-olds to 1.06 (95% CI 1.01–1.11) in 45- to 49-year-olds for any stroke. No age-related decline was found for intracerebral hemorrhage (table 4).

Sex-specific distribution of stroke subtypes in the different age strata

The proportion of ischemic stroke in the different age groups was significantly different for those aged 18–24 years, 38.3% in men and 55.9% in women ($p < 0.001$), and those aged 35–39 years old, 51.3% in men and 56.4% in women ($p = 0.018$), but not for the other age strata. In men, the relative percentage of intracerebral hemorrhage was significantly higher than that in women in the same age category in younger age strata, namely 44.0% in men and 26.6% in women aged 18–24 years old ($p < 0.001$) and 34.9% vs 21.1% in those aged 25–29 years old ($p < 0.001$). Similar results were seen for the age strata 30–34 years old ($p < 0.001$), 35–39 years old ($p = 0.002$), and 40–44 years old ($p < 0.001$). There was no significant difference in the relative percentage of intracerebral hemorrhage for men and women aged 45–49 years, 18.5% in men and 18.0% in women ($p = 0.591$). The percentage of unspecified stroke was significantly different in those aged 30–34 years, 17.6% in men and 25.9% in women ($p < 0.001$) (figure 1).

Sex- and age-specific time trends in the incidence of any stroke

Any stroke incidence among young adults increased from 14.0 per 100,000 person-years in 1998 to 17.2 per 100,000 person-years in 2010, resulting in a relative change of 23% ($p < 0.001$). This increase was present across all age strata over 35 years old, but not in patients aged 18–34 years (table 3 and figure 2A). The increase of any stroke incidence was observed both in men (23% increase; $p < 0.001$) and in women (17% increase; $p < 0.001$), and most prominently in those aged 44–49 years. In contrast, in patients aged 50 years or older, the incidence of first-ever stroke declined from 329.1 per 100,000 person-years in 1998 to 292.2 per 100,000 person-years in 2010, a relative decrease of 11% ($p = 0.009$; table 3). The proportion of stroke in young adults of the total number of strokes across all ages increased significantly over time from 13.3% in 1998 to 15.5% in 2010 ($p < 0.001$).

Table 3 Sex-specific incidence of any stroke from 1998 to 2010

	Incidence per 100,000 person-years[a]														
Age, y	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**Change[b]**	**Time trend[c]**
18–49	13.99	14.00	14.51	14.76	15.26	15.80	16.64	17.60	16.73	16.81	16.61	17.07	17.24	0.23	***p* < 0.001**
Men	12.13	12.70	13.49	13.01	13.67	15.48	16.06	16.10	15.71	15.99	14.52	16.72	15.64	0.29	***p* = 0.001**
Women	15.93	15.34	15.56	16.56	16.89	16.12	17.24	19.14	17.77	17.64	18.74	17.43	18.86	0.18	***p* < 0.001**
Any ages	105.39	105.11	103.12	104.15	110.75	111.84	115.81	117.37	108.50	103.22	102.33	109.64	111.27	0.06	*p* = 0.450
Men	104.96	104.21	101.24	102.80	109.80	110.35	116.33	117.62	109.40	102.97	101.12	109.30	111.37	0.06	*p* = 0.359
Women	105.81	105.99	104.96	105.48	111.68	113.30	115.31	117.12	107.61	103.46	103.50	109.97	111.17	0.05	*p* = 0.581
18–24	2.36	2.31	2.92	2.69	2.31	2.52	2.51	2.43	2.36	2.72	2.77	2.28	3.29	0.40	*p* = 0.232
Men	2.18	1.76	1.92	2.80	2.20	2.48	2.19	1.60	2.47	2.18	1.87	2.11	2.21	0.01	*p* = 0.919
Women	2.54	2.87	3.94	2.58	2.42	2.56	2.85	3.28	2.24	3.29	3.70	2.46	4.41	0.73	*p* = 0.251
25–29	4.40	3.97	3.66	5.09	4.57	3.88	4.76	5.14	5.04	4.75	4.34	3.53	4.20	−0.05	*p* = 0.949
Men	2.32	2.72	2.19	3.37	3.52	2.31	3.15	3.82	4.22	3.43	2.42	2.41	3.98	0.71	*p* = 0.207
Women	6.56	5.26	5.16	6.85	5.64	5.47	6.38	6.47	5.86	6.07	6.28	4.66	4.43	−0.32	*p* = 0.245
30–34	7.29	5.87	7.61	7.44	8.37	7.10	7.90	8.73	9.33	7.77	6.83	6.35	7.20	−0.01	*p* = 0.808
Men	6.08	4.92	6.70	4.91	6.73	6.55	6.48	8.69	6.04	6.74	5.85	3.96	5.99	−0.01	*p* = 0.880
Women	8.56	6.87	8.56	10.06	10.07	7.67	9.34	8.77	12.64	8.80	7.80	8.73	8.42	−0.02	*p* = 0.699
35–39	10.90	12.73	12.55	10.92	11.96	11.93	14.20	14.31	12.69	14.20	12.71	13.50	13.21	0.21	***p* = 0.029**
Men	7.56	12.13	10.15	8.86	10.17	11.69	13.88	13.63	11.93	11.77	9.98	14.02	11.84	0.57	*p* = 0.060
Women	14.35	13.35	15.03	13.06	13.82	12.17	14.54	15.00	13.47	16.68	15.47	12.99	14.59	0.02	*p* = 0.403
40–44	23.79	22.87	23.47	21.61	22.91	23.99	25.44	25.69	24.87	25.12	25.33	25.63	23.75	0.00	***p* = 0.023**
Men	22.81	19.85	22.46	18.38	19.95	24.62	23.35	23.39	23.11	26.22	21.66	26.54	21.35	−0.06	*p* = 0.126
Women	24.79	25.96	24.50	24.94	25.95	23.34	27.58	28.06	26.68	23.99	29.10	24.69	26.21	0.06	*p* = 0.314
45–49	39.57	40.34	40.11	43.84	43.45	46.74	45.30	48.68	44.66	43.70	44.37	47.19	47.73	0.21	***p* = 0.003**
Men	35.95	38.75	41.02	42.89	41.51	46.44	47.58	44.75	44.78	42.74	42.15	46.65	44.76	0.24	***p* = 0.014**
Women	43.33	41.98	39.17	44.83	45.43	47.04	42.97	52.67	44.54	44.67	46.63	47.74	50.75	0.17	***p* = 0.019**
≥50	329.08	322.92	311.66	311.36	328.18	327.11	334.03	333.01	302.36	281.91	275.17	291.66	292.20	−0.11	***p* = 0.009**

Continued

Table 3 Sex-specific incidence of any stroke from 1998 to 2010 *(continued)*

Age, y	Incidence per 100,000 person-years[a] 1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Change[b]	Time trend[c]
Men	355.07	344.92	327.83	329.52	347.61	341.94	355.33	353.71	322.11	295.46	286.80	303.84	306.66	−0.14	**$p = 0.006$**
Women	307.02	304.13	297.75	295.67	311.29	314.14	315.31	314.75	284.87	269.85	264.79	280.73	279.18	−0.09	**$p = 0.014$**

[a] Incidence per 100,000 person-years calculated with Dutch population estimates.[22]
[b] Change = (incidence 2010 − incidence 1998)/incidence 1998.
[c] Time trends tested by linear regression.

Sex-specific time trends of incidence by stroke subtype

In young adults, the incidence of ischemic stroke increased by 46% from 7.4 in 1998 to 10.8 per 100,000 person-years in 2010 ($p < 0.001$). In women, the incidence of ischemic stroke increased from 8.9 in 1998 to 12.1 per 100,000 person-years in 2010, a relative change of 37% ($p < 0.001$) and in men from 6.0 to 9.5 per 100,000 person-years, a relative change of 60% ($p < 0.001$) (table 5 and figure 2B). The incidence of intracerebral hemorrhage and of unspecified stroke remained stable over the course of 13 years (table 5 and figure 2, C and D), without any sex differences.

Discussion

This study shows that in young adults, the risk of stroke increased exponentially with age, with women more often affected than men in all age strata. The relative distribution of stroke subtypes was similar in women in all age strata with ischemic stroke occurring 2 to 3 times more frequently than intracerebral hemorrhage. In men, the proportion of intracerebral hemorrhages was relatively high in younger age strata, and declining with increasing age. In young adults, the incidence of ischemic stroke but not of intracerebral hemorrhage and unspecified stroke increased by almost 50% between 1998 and 2010, while the incidence of stroke in older patients decreased by 11%.

We found a relatively high increase of 46% in the incidence of ischemic stroke over a 13-year period among young adults, where previous studies reported percentages varying from 4.7% to 74%.[1,10,20–23] Differences may be explained by variation in the definition of patient groups (due to inclusion of different ICD codes) and the chosen lower and upper age limits that ranged from as low as 15 to as high as 60 years.[1,6–12] In our study, the increase in stroke incidence was limited to ischemic stroke; incidence was stable for those with an intracerebral hemorrhage and for those younger than 35 years at their first event. In contrast, others found a clear increase in incidence in those younger than 30 years. This might be partially explained by smaller patient numbers, hospital-based settings, or a broader definition of stroke also including SAH, TIA, other cerebrovascular disorders, and sequelae of stroke (ICD-9 codes 430–438).[6] Incidences and rates of increase may also vary in different parts of the world because of differences in genetic profile and occurrence and control of (cardiovascular) risk factors.[1,10,21]

There are several possible factors that may contribute to the increased incidence of stroke in young adults over the last 2 decades. First, we may diagnose stroke more often because of the improvement and accessibility of neuroimaging and the development of stroke-sensitive techniques, such as diffusion-weighted MRI (DWI), that allow for rapid and reliable detection of acute infarcts. This explanation is supported by studies that showed an increased incidence of stroke in young

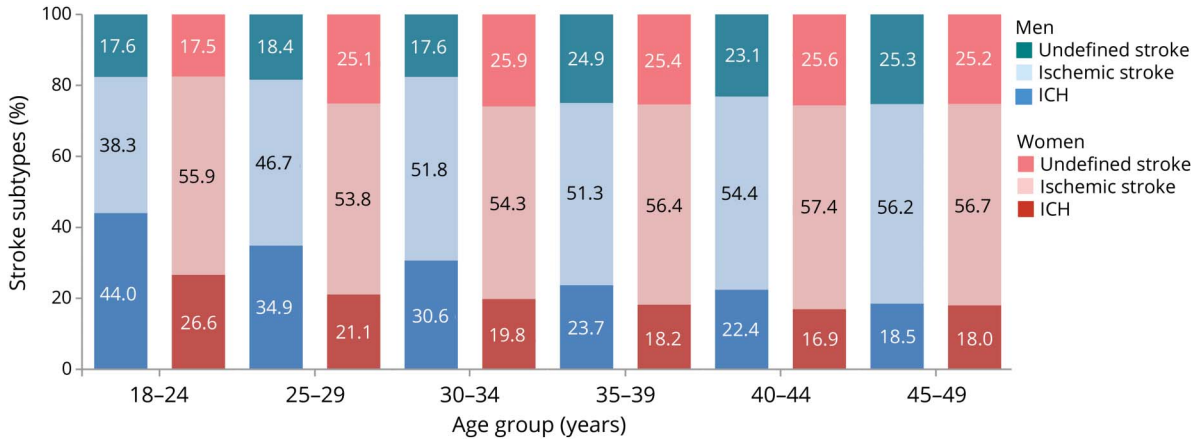
Table 4 Sex- and age-specific incidence of stroke subtypes

	Male incidence, n[a]	Person-years[b] at risk	Female incidence, n[a]	Person-years[b] at risk	IRR (95% CI) of women compared to men	*p* Value
Any stroke						
18–24 y	2.15 (193)	8,974,907	3.02 (263)	8,722,640	1.93 (1.62–2.31)	<0.001
25–29 y	3.03 (212)	6,985,800	5.78 (398)	6,882,795	1.91 (1.61–2.26)	<0.001
30–34 y	6.15 (483)	7,859,303	8.94 (687)	7,680,769	1.46 (1.29–1.63)	<0.001
35–39 y	11.34 (966)	8,515,778	14.19 (1,175)	8,280,089	1.25 (1.15–1.36)	<0.001
40–44 y	22.63 (1888)	8,342,998	25.85 (2,102)	8,131,226	1.14 (1.07–1.22)	<0.001
45–49 y	43.14 (3,385)	7,846,997	45.62 (3,505)	7,683,179	1.06 (1.01–1.11)	0.021
Ischemic stroke						
18–24 y	0.82 (74)	8,974,907	1.69 (147)	8,722,640	2.04 (1.54–2.74)	<0.001
25–29 y	1.42 (99)	6,985,800	3.11 (214)	6,882,795	2.19 (1.72–2.81)	<0.001
30–34 y	3.18 (250)	7,859,303	4.87 (374)	7,680,769	1.53 (1.30–1.80)	<0.001
35–39 y	5.82 (496)	8,515,778	8.00 (662)	8,280,089	1.37 (1.22–1.31)	<0.001
40–44 y	12.32 (1,028)	8,342,998	14.84 (1,207)	8,131,226	1.20 (1.11–1.31)	<0.001
45–49 y	24.26 (1904)	7,846,997	25.89 (1989)	7,683,179	1.07 (1.00–1.14)	0.045
Intracerebral hemorrhage						
18–24 y	0.95 (85)	8,974,907	0.80 (70)	8,722,640	0.85 (0.61–1.18)	0.343
25–29 y	1.06 (74)	6,985,800	1.22 (84)	6,882,795	1.15 (0.83–1.60)	0.418
30–34 y	1.88 (148)	7,859,303	1.76 (135)	7,680,769	0.93 (0.73–1.19)	0.603
35–39 y	2.69 (229)	8,515,778	2.60 (215)	8,280,089	0.97 (0.80–1.17)	0.748
40–44 y	5.07 (423)	8,342,998	4.38 (356)	8,131,226	0.86 (0.75–1.00)	0.045
45–49 y	7.98 (626)	7,846,997	8.23 (632)	7,683,179	1.03 (0.92–1.15)	0.061
Unspecified stroke						
18–24 y	0.38 (34)	8,974,907	0.53 (46)	8,722,640	1.39 (0.87–2.224)	0.174
25–29 y	0.56 (39)	6,985,800	1.45 (100)	6,882,795	2.60 (1.78–3.87)	<0.001
30–34 y	1.08 (85)	7,859,303	2.32 (178)	7,680,769	2.14 (1.65–2.81)	<0.001
35–39 y	2.83 (241)	8,515,778	3.60 (298)	8,280,089	1.27 (1.07–1.51)	0.006
40–44 y	5.24 (437)	8,342,998	6.63 (539)	8,131,226	1.27 (1.11–1.44)	<0.001
45–49 y	10.90 (855)	7,846,997	11.51 (884)	7,683,179	1.06 (0.96–1.16)	0.266

Abbreviations: CI = confidence interval; IRR = incidence rate ratio.
[a] Incidence per 100,000 person-years calculated with Dutch population estimates.[18]
[b] Person-years at risk over 13 years (1998–2010).

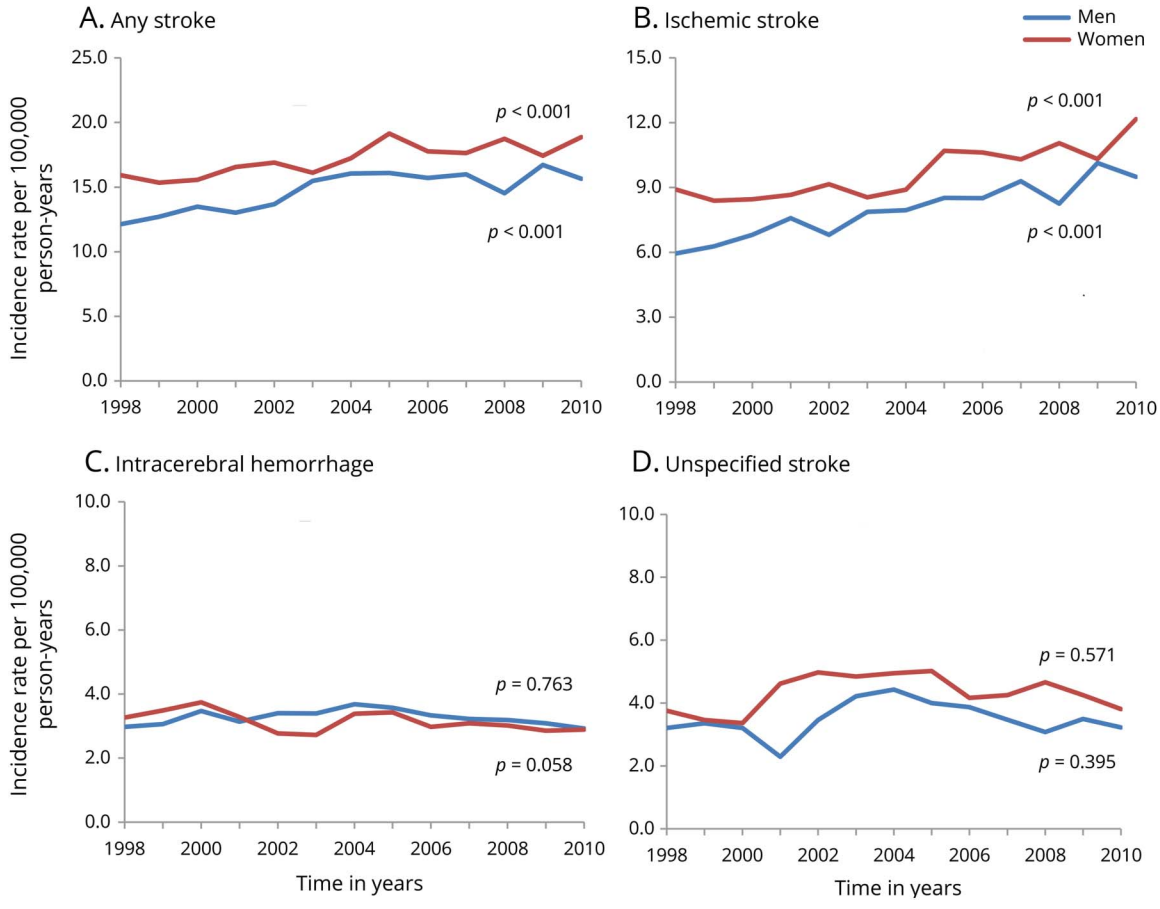
adults that coincided with the increased use of MRI during their study period, in particular in young adults, who more often had MRI in later years of these studies.[1,5] However, if the application of MRI would have had a large influence in our study, we would have expected an increase in incidence across all young stroke age strata, and perhaps even more in the youngest age strata. In contrast, we found a significant increase of stroke incidence only in those over 35 years. Therefore, the implementation of MRI seems to only partially explain the increase in incidence of ischemic stroke. A second explanation is an increased prevalence of traditional vascular risk factors already among children and young adults that could lead to atherosclerosis early in life and subsequently to stroke.[6,24] The effects of these risk factors are likely to become more prominent with aging, which is supported by findings of a higher prevalence of vascular risk factors in patients aged 45–49 years compared to younger participants in The Helsinki Young Stroke Registry and compatible with the increase

Figure 1 Sex- and age-specific distribution of stroke subtypes



in incidence in patients over 35 years.[25,26] Third, other risk factors may have gained importance over the last decade, including illicit drug use. In the Netherlands, the number of young adults who used illicit drugs before their ischemic stroke has been reported to increase from 3.8% in 1993 to 19.8% in 2005.[27–29] The increase in incidence is unlikely attributable to a shift from outpatient to clinical workup, because according to protocols during our study period, nearly all young patients with neurologic deficits would have been referred to a neurologist by general practitioners in the

Figure 2 Time trends in incidence of stroke and stroke subtypes in young adults from 1998 to 2010



Incidence per 100,000 person-years calculated with Dutch population estimates.[18] *p* Values calculated by linear regression. (A) Any stroke. (B) Ischemic stroke. (C) Intracerebral hemorrhage. (D) Unspecified stroke.

Table 5 Sex-specific incidence of stroke subtypes in young adults (<50 years) (1998–2010)

Stroke subtype	Incidence per 100,000 person-years[a]														
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Change, %[b]	Time trend[c]
Ischemic	7.40	7.32	7.62	8.11	7.96	8.21	8.42	9.60	9.55	9.80	9.64	10.23	10.82	46.22	***p* < 0.001**
Men	5.95	6.29	6.81	7.59	6.81	7.87	7.95	8.52	8.51	9.29	8.25	10.13	9.49	59.50	***p* < 0.001**
Women	8.91	8.39	8.46	8.66	9.15	8.55	8.91	10.70	10.62	10.31	11.06	10.32	12.16	36.48	***p* < 0.001**
Intracerebral hemorrhage	3.12	3.27	3.60	3.21	3.09	3.06	3.54	3.50	3.16	3.16	3.10	2.97	2.91	−6.73	*p* = 0.143
Men	2.97	3.06	3.47	3.14	3.40	3.39	3.68	3.57	3.33	3.23	3.19	3.08	2.92	−1.68	*p* = 0.763
Women	3.27	3.49	3.74	3.28	2.77	2.72	3.39	3.43	2.98	3.08	3.02	2.85	2.89	−11.62	*p* = 0.058
Unspecified	3.48	3.41	3.28	3.44	4.20	4.53	4.68	4.51	4.02	3.86	3.87	3.87	3.52	1.15	*p* = 0.384
Men	3.21	3.35	3.21	2.29	3.46	4.22	4.43	4.00	3.87	3.47	3.08	3.50	3.23	0.62	*p* = 0.571
Women	3.75	3.46	3.36	4.61	4.97	4.85	4.94	5.02	4.17	4.25	4.66	4.25	3.81	1.60	*p* = 0.395

[a] Incidence per 100,000 person-years calculated with Dutch population estimates.[18]
[b] Change = (incidence 2010 − incidence 1998)/incidence 1998.
[c] Time trend tested by linear regression.

Netherlands. Furthermore, the ICD codes used include both outpatient and inpatient diagnosis of a stroke. If the increase would be due to increased hospitalization, we would have expected the increase to occur across all age strata. We do not see an increase in incidence for intracerebral hemorrhage, which was already detectable with CT, in contrast with ischemic stroke, which is now more easily diagnosed with MRI-DWI. Also, intracerebral hemorrhage has a different etiology and is particularly frequent in young patients, often due to structural vessel abnormalities, who are less likely to be influenced by the increasing prevalence of modifiable, traditional risk factors like obesity and hypercholesterolemia, which play an important role in the pathogenesis of ischemic strokes.

We found clear sex differences in both the overall occurrence and age-related increase in the incidence of stroke in young adults, with women being more often affected than men in all age strata. Previous studies have yielded conflicting results, some showing no difference or only in a specific age group, others showing a higher incidence in men, yet again possibly explained by differences in study design, age limits, and stroke definition.[6,7,9–12,26,30,31] Differences in prevalence of (women-specific) risk factors between men and women may also contribute to the varying incidences for men and women in the different study populations.[6,7,9–12,26,30,31] A possible explanation for the excess risk of stroke in young women may be found in risk factors that are more prevalent in women, such as migraine with aura, autoimmune disorders like antiphospholipid syndrome or systemic lupus erythematosus, or women-specific factors such as pregnancy or the use of oral anticonception, especially in combination with smoking.[5,32] Because the prevalence of these women-specific risk factors is very low and the exact effect size of their role in incidence unclear, other, yet unknown hormonal factors or genetic differences may also contribute.

Strengths of our study include the large sample size of the cohort and the fact that it was nationwide and included patients over a period of more than a decade. The large sample enabled us to perform age-, sex-, and stroke subtype–specific subgroup analyses. In addition, we were able to investigate the changes in incidence of stroke in young adults over a 13-year period. Finally, we created a cohort of well-defined stroke subtypes, whereas many previous studies were more heterogeneous, with the inclusion of TIA, SAH, unspecified intracranial hemorrhage, several other cerebrovascular diseases, and even sequelae of cerebrovascular disorders. We excluded SAH and unspecified intracranial hemorrhage based on their distinct underlying etiologies. Finally, we validated the ICD codes for young stroke patients specifically.

Our study has some limitations. First, we could not further specify stroke etiology, e.g., with Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, or look at underlying causes of intracerebral hemorrhage. In addition, there was a substantial number of strokes in our cohort classified as unspecified, meaning that the stroke could either be ischemic

or hemorrhagic.[33] Through our validation of the ICD codes in young stroke patients in several Dutch medical centers, we found 90.5% of unspecified strokes were in fact ischemic strokes and 9.5% were intracerebral hemorrhages (table 2). Therefore, it is likely that the majority of these unspecified strokes were in fact ischemic strokes and could be added to this group for trend analysis. However we chose to analyze the groups separately, thereby safeguarding the purity of the data. Furthermore, the incidence of unspecified stroke did not increase, whereas the incidence of ischemic stroke increased, which may be explained by a more reliable differentiation between ischemic stroke and intracerebral hemorrhage through the implementation of improved imaging techniques, such as DWI, leaving fewer strokes being classified as unspecified.

Second, we may have overestimated the total number of first-ever strokes because we had no information on strokes prior to 1998 and therefore may have misclassified some recurrent strokes as first-ever strokes. As the risk of recurrent stroke decreases by the number of years of event-free survival after the first-ever stroke, the chance of misclassification of a recurrent stroke as first-ever stroke becomes increasingly less likely over time, particularly for the later years of our study.[34,35] Third, because fewer hospitals contributed to the HDR register from 2006 onwards, the data are less reliable for estimating nationwide incidence after 2005. As a consequence, the rate of the increase of the incidence of stroke between 1998 and 2010 may have been underestimated. However, since there is no reason to assume these "missing records" are not missing at random, this will most likely have led to underestimation of the observed temporal trends of stroke incidence between 2006 and 2010 and does not affect subgroup analyses for specific age strata or sex comparisons performed within each year. Stroke care is provided throughout the Netherlands, so it is unlikely that when some centers no longer provide their discharge data this would lead to a specific loss of intracerebral hemorrhage diagnoses or ischemic stroke diagnoses. Finally, we may have missed nonfatal strokes for which patients were not admitted to a hospital. This may have led to underestimation of the incidence estimates but is unlikely to affect subgroup analyses and time trends. If the observed rise in incidence of ischemic stroke in young adults continues, the estimated number of strokes in young adults will have nearly doubled by 2020 in comparison to 2000. This will have large socioeconomic consequences. We urgently need to identify the main factors that have led to the increased incidence with a view to counter this worrisome trend. Further investigations of trigger factors, women-specific risk factors, and genetic causes may shed further light on the cause of stroke in the young.[36] The continuing increase of stroke in young adults asks for immediate public health strategies, including programs for better awareness of risk factors for vascular disease, already among young adults. This study shows a steep increase in the incidence of ischemic stroke in young adults over time, especially in those aged 35–50 years and with a higher incidence in women than in men. The pronounced female predominance in stroke incidence among young adults warrants specific attention to this group.

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Continued

Appendix *(continued)*

Name	Location	Role	Contribution
Koen M. Nieuwenhuizen	Brain Center Rudolf Magnus, University Medical Center Utrecht, the Netherlands	Author	Analyzed the data, revised the manuscript for intellectual content
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Stroke incidence in young adults according to age, subtype, sex, and time trends

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