LUND UNIVERSITY

Lifestyle Risk Factors for Ischemic Stroke and Transient Ischemic Attack in Young Adults in the Stroke in Young Fabry Patients Study

von Sarnowski, Bettina; Putaala, Jukka; Grittner, Ulrike; Gaertner, Beate; Schminke, Ulf; Curtze, Sami; Huber, Roman; Tanislav, Christian; Lichy, Christoph; Demarin, Vida; Basic-Kes, Vanja; Ringelstein, E. Bernd; Neumann-Haefelin, Tobias; Enzinger, Christian; Fazekas, Franz; Rothwell, Peter M.; Dichgans, Martin; Jungehulsing, Gerhard J.; Heuschmann, Peter U.; Kaps, Manfred; Norrving, Bo; Rolfs, Arndt; Kessler, Christof; Tatlisumak, Turgut

Link to publication

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Lifestyle Risk Factors for Ischemic Stroke and Transient Ischemic Attack in Young Adults in the Stroke in Young Fabry Patients Study

Bettina von Sarnowski, Jukka Putaala, Ulrike Grittner, Beate Gaertner, Ulf Schminke, Sami Curtze, Roman Huber, Christian Tanislav, Christoph Lichy, Vida Demarin, Vanja Basic-Kes, E. Bernd Ringelstein, Tobias Neumann-Haefelin, Christian Enzinger, Franz Fazekas, Peter M. Rothwell, Martin Dichgans, Gerhard J. Jungehulsing, Peter U. Heuschmann, Manfred Kaps, Bo Norrving, Arndt Rolfs, Christof Kessler, Turgut Tatlisumak and on behalf of the sifap1 Investigators

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/44/1/119

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/11/13/STROKEAHA.112.665190.DC1.html

---

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/

Lifestyle Risk Factors for Ischemic Stroke and Transient Ischemic Attack in Young Adults in the Stroke in Young Fabry Patients Study

Bettina von Sarnowski, MD*; Jukka Putaala, MD*; Ulrike Grittner, PhD; Beate Gaertner, PhD;
Ulf Schminke, MD; Sami Curtze, MD; Roman Huber, MD; Christian Tanislav, MD;
Christoph Lichy, MD; Vida Demarin, MD, PhD; Vanja Basic-Kes, MD; E. Bernd Ringelstein, MD;
Tobias Neumann-Haefelin, MD; Christian Enzinger, MD; Franz Fazekas, MD;
Peter M. Rothwell, MD, PhD; Martin Dichgans, MD; Gerhard J. Jungehulsing, MD;
Peter U. Heuschmann, MD, MPH; Manfred Kaps, MD; Bo Norrving, MD; Arndt Rolfs, MD;
Christof Kessler, MD†; Turgut Tatlisumak, MD†; on behalf of the sifap1 Investigators

Background and Purpose—Although many stroke patients are young or middle-aged, risk factor profiles in these age groups are poorly understood.

Methods—The Stroke in Young Fabry Patients (sifap1) study prospectively recruited a large multinational European cohort of patients with cerebrovascular events aged 18 to 55 years to establish their prevalence of Fabry disease. In a secondary analysis of patients with ischemic stroke or transient ischemic attack, we studied age- and sex-specific prevalences of various risk factors.

Results—Among 4467 patients (median age, 47 years; interquartile range, 40–51), the most frequent well-documented and modifiable risk factors were smoking (55.5%), physical inactivity (48.2%), arterial hypertension (46.6%), dyslipidemia (34.9%), and obesity (22.3%). Modifiable less well-documented or potentially modifiable risk factors like high-risk alcohol consumption (33.0%) and short sleep duration (20.6%) were more frequent in men, and migraine (26.5%) was more frequent in women. Women were more often physically inactive, most pronouncedly at ages <35 years (18–24: 38.2%; 25–34: 51.7%), and had high proportions of abdominal obesity at age 25 years or older (74%). Physical inactivity, arterial hypertension, dyslipidemia, obesity, and diabetes mellitus increased with age.

Conclusions—In this large European cohort of young patients with acute ischemic cerebrovascular events, modifiable risk factors were highly prevalent, particularly in men and older patients. These data emphasize the need for vigorous primary and secondary prevention measures already in young populations targeting modifiable lifestyle vascular risk factors.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique Identifier: NCT00414583.   (***Stroke***. 2013;44:119-125.)

Key Words: cerebral infarct ■ ischemic stroke ■ risk factors ■ stroke in young adults ■ transient ischemic attack

Ischemic stroke remains a leading cause of death and disability worldwide.[1] Planning cost-effective preventive strategies requires precise knowledge of stroke risk factors.[2]

Approximately 10% of ischemic strokes occur at ages <45 years,[3] with major long-term socioeconomic consequences.[4] Stroke prevention results in greater quality-weighted life-year

---

gain in younger patients than in elderly patients, but has received less attention.

In the general population and in patient cohorts, risk factor profiles changed with increasing age.[5,6] Most studies of stroke patients aged <50 years were small and methodologically heterogeneous.[7–10] In the largest single-center study including 1008 ischemic stroke patients aged 15 to 49 years,[7] the most common risk factors were dyslipidemia (60%), smoking (44%), and arterial hypertension (39%), with accumulation in men and increasing age. However, only scarce data exist on the prevalence and risk potential of lifestyle risk factors such as physical inactivity, obesity,[7,8,11] body mass index, waist circumference,[12] and sleep pattern[13,14] in the young.

The Stroke in Young Fabry Patients (sifap1) study[15] prospectively recruited a large multinational European cohort of patients aged 18 to 55 years with cerebrovascular event (CVE) to establish their prevalence of Fabry disease. In a secondary analysis of patients with ischemic stroke and transient ischemic attack (TIA), we investigated frequencies of various stroke risk factors and specifically focused on those related to modifiable unfavorable lifestyle habits that may precede traditional risk factors and are associated with higher risk of subsequent stroke independently from traditional risk factors.[16,17] We sought to define sex- and age-specific risk factor profiles to optimize targeted prevention strategies.

Methods

The sifap1 is a prospective multicenter European study that aimed to establish the prevalence of Fabry disease in 5023 young patients with CVE. The study was performed according to the Helsinki Declaration

Table 1.   Risk Factors Stratified by Sex and Age Group

Risk Factors (Valid n)	All (n=4467)	Males (n=2653)	Females (n=1814)	Age 18–44 Years (n=1787)	Age 45–55 Years (n=2680)	Sex, P Value*	Age, P Value†
Nonmodifiable risk factors							
Age (n=4467)	47 (40–51)	47 (42–51)	45 (39–50)			<0.001	
Male (n=4467)	59.4			53.2	63.6		<0.001
History of any cerebrovascular event (n=4466)	17.0	17.1	16.8	14.5	18.6	0.997	<0.001
History of transient ischemic attack (n=4409)	9.3	9.5	9.0	8.1	10.1	0.874	0.027
Family history of cardiovascular disease (n=4220)	41.3	37.9	46.3	38.2	43.4	<0.001	<0.001
Family history of cerebrovascular disease (n=4232)	37.3	35.8	39.5	33.8	39.6	0.004	<0.001
Well-documented and modifiable risk factors							
Tobacco smoking‡ (n=4421)	55.5	59.3	50.1	54.7	56.1	<0.001	0.968
Physical inactivity (n=4322)	48.2	46.6	50.4	44.5	50.6	0.011	<0.001
Hypertension (n=4439)	46.6	51.6	39.3	29.3	58.2	<0.001	<0.001
Dyslipidemia (n=4289)	34.9	39.3	28.5	23.7	42.3	<0.001	<0.001
High LDL cholesterol (≥3.37 mmol/L; n=3065)	41.5	44.2	37.4	34.0	46.1	0.002	<0.001
Low HDL cholesterol (≤1 mmol/L; n=3139)	28.0	37.8	13.5	26.7	28.8	<0.001	0.475
Obesity (BMI ≥30 kg/m²; n=4463)	22.3	22.6	21.8	19.5	24.1	0.865	<0.001
Diabetes mellitus (n=4443)	10.3	12.6	7.0	5.9	13.3	<0.001	<0.001
Cardiovascular disease (n=4348)	9.2	11.2	6.4	5.9	11.5	<0.001	<0.001
Coronary heart disease (n=4407)	4.2	5.6	2.1	2.0	5.6	<0.001	<0.001
Congestive heart failure (n=4429)	1.2	1.4	0.8	1.0	1.3	0.071	0.465
Myocardial infarction (n=4446)	3.1	4.3	1.4	1.4	4.3	<0.001	<0.001
Peripheral arterial disease (n=4422)	2.2	2.7	1.5	1.0	3.1	0.027	<0.001
Valvular disease (n=4408)	2.3	2.3	2.4	2.4	2.2	0.650	0.795
Atrial fibrillation (n=4428)	2.4	2.8	1.8	1.5	3.0	0.100	0.003
Less well-documented or potentially modifiable risk factors							
High-risk alcohol consumption (n=4276)	33.0	41.9	20.1	31.1	34.2	<0.001	0.821
Migraine, lifetime history (n=4352)	26.5	18.8	37.8	29.7	24.4	<0.001	0.010
Sleep ≤6 h (n=4458)	17.9	20.6	13.9	15.9	19.2	<0.001	0.031
Obstructive sleep apnea (n=4340)	3.3	4.5	1.6	2.4	3.9	<0.001	0.034

BMI, body mass index; HDL, high-density lipoprotein; and LDL indicates low-density lipoprotein.

Data are median (interquartile range) or percentage.

*Multiple regressions adjusted for sex and center heterogeneity.

†Multiple regressions adjusted for age and center heterogeneity.

‡Currently smoking or quit within past 5 years before qualifying event.

and approved by the Ethics Committees at the leading study center (Rostock) and at each study site. All patients or their legal representatives gave written informed consent. Patients were recruited between April 2007 and January 2010, at 47 centers in 15 European countries.[15] Inclusion criteria were CVE <3 months previously, age 18 to 55 years, and cerebral MRI ≤1 month of inclusion. Diagnostic procedures accorded with the European Stroke Organisation Guidelines.[18]

The present secondary analysis aimed to assess the frequency of various risk factors exclusively in patients with TIA (ie, symptoms <24 hours without infarction or hemorrhage on MRI) or ischemic stroke (ie, symptoms >24 hours without hemorrhage). According to current guidelines of the American Stroke Association,[2] risk factors were classified with respect to their strength of evidence and potential for modification: (1) nonmodifiable (ie, age, sex, history of CVE, and family history of cardiovascular or cerebrovascular disease); (2) well-documented and modifiable (so-called traditional risk factors, ie, coronary artery disease, peripheral arterial disease, congestive heart failure, myocardial infarction, valvular disease, atrial fibrillation, diabetes mellitus, arterial hypertension, dyslipidemia, tobacco smoking, obesity, and physical inactivity); and (3) less well-documented or potentially modifiable (ie, history of migraine, obstructive sleep apnea, short sleep duration, and high-risk alcohol consumption). Detailed Methods are provided in the Online Data Supplement.

Statistical Analyses

Patients were categorized into groups of none to ≥4 (of 8) well-documented modifiable risk factors. Using Wilson method, we calculated 95% confidence intervals for the sex- and age-specific risk factor proportions. Frequencies were compared between sexes and patients aged 18 to 44 years and 45 to 55 years. Logistic regression models with random intercepts accounted for center heterogeneity. Statistical analyses used SPSS 19.0 and SAS 9.2. *P*<0.05 was considered statistically significant.

Role of the Funding Source

The sponsors of the study had no role in the study design, data collection, analysis, interpretation, writing of the manuscript, or the decision to submit the manuscript for publication. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

Results

Among 5023 subjects enrolled in sifap1, 1071 (21.3%) had TIA, 3396 (67.6%) had ischemic stroke, and 271 (5.4%) had intracerebral hemorrhage (285 [5.7%] other and missing). In the present analyses, 4467 patients with TIA or ischemic stroke were considered; 59.4% were men; and women were younger than men (Table 1). Overall, only 238 (5.3%) patients were free from any of those 12 risk factors categorized as well documented and modifiable or as less well-documented or potentially modifiable. Furthermore, only 513 (11.5%) patients had none of the 8 risk factors classified as well-documented and modifiable. The proportion of patients without any well-documented and modifiable risk factor was smaller in older age groups. At ages 45 years and older, the proportion of men with ≥4 well-documented and modifiable risk factors was 29.2% compared with 20.3% in women (Figure 1).

Previous myocardial infarctions were rare, but nearly one-fifth reported a history of CVE. Smoking (55.5%), physical inactivity (48.2%), hypertension (46.6%), and dyslipidemia (34.9%) were the most common well-documented and modifiable risk factors (Table 1). Physical inactivity, arterial hypertension, dyslipidemia, obesity, and diabetes mellitus were more prevalent in older age groups. Cardiovascular diseases were relatively frequent in
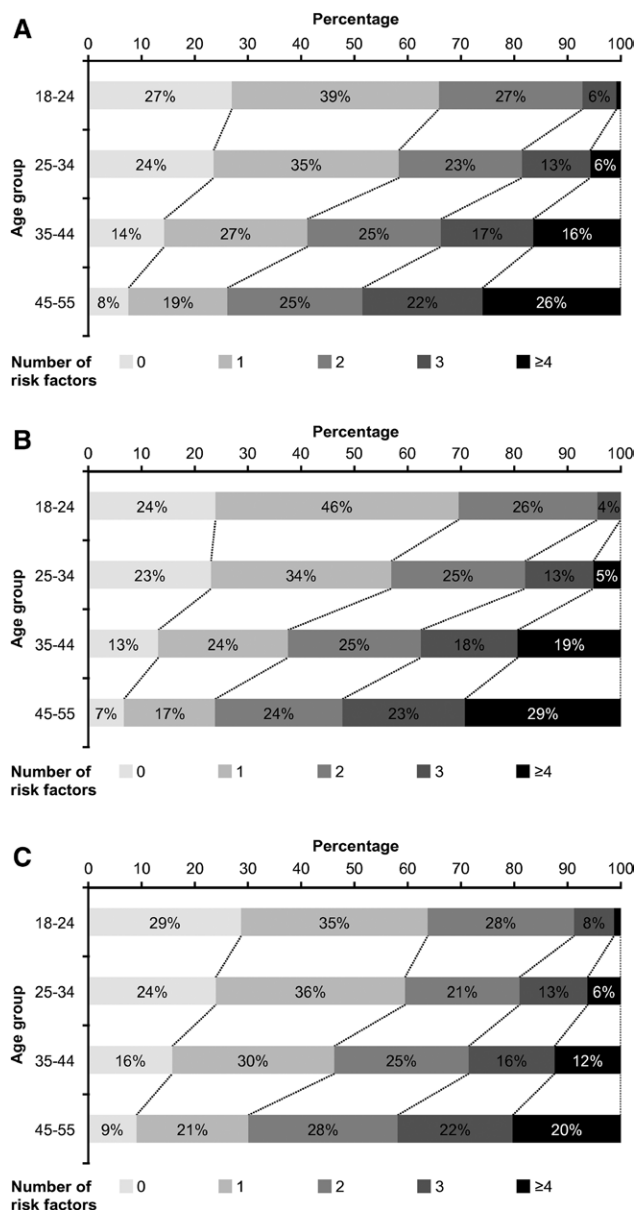
Figure 1. Proportions of patients with none to ≥4 well-documented and modifiable risk factors according to age group in (**A**) the entire cohort, (**B**) men, and (**C**) women.

the youngest age group and showed a J-shaped form as a function of age. Atrial fibrillation was rare (Figure 2).

Regarding sex-specific differences, dyslipidemia, smoking, hypertension, cardiovascular disease, and diabetes mellitus were more prevalent among men. For dyslipidemia and cardiovascular disease, these differences were most apparent in age groups 35 years or older. In contrast, women were more often physically inactive, especially at younger ages.

Regarding less well-documented or potentially modifiable risk factors, high-risk alcohol consumption (33.0%), and migraine (26.5%) were most frequent. High-risk alcohol consumption, shorter nocturnal sleep, and obstructive sleep apnea were more common among men. In contrast, migraine was the only risk factor in this category that was significantly more prevalent in women at ages 25 years or older. Prevalence was high at all ages and slightly peaked at ages 35 to 44 years (42.0%) (Figure 3).

Figure 2. Age- and sex-specific proportions of nonmodifiable and well-documented and modifiable risk factors. White bars represent all patients, dark gray bars represent men, and light gray bars represent women. Error bars indicate 95% confidence interval. TIA indicates transient ischemic attack.

Details of behavioral risk factors and anthropometric measures are shown in Table 2. Overall, most risk factors were more frequent in men and in subjects aged 45 years or older. However, we observed some exceptions. Although general obesity was similarly prevalent in both sexes, men were more frequently overweight than women. In contrast, abdominal obesity was more often noted in women than in men, and it was highly more frequent in both sexes than was general obesity. The proportion of normal weight, normal waist circumference, and physical activity decreased with increasing age.

Discussion

Our prospectively recruited young European patients with acute CVE demonstrated high frequencies of both
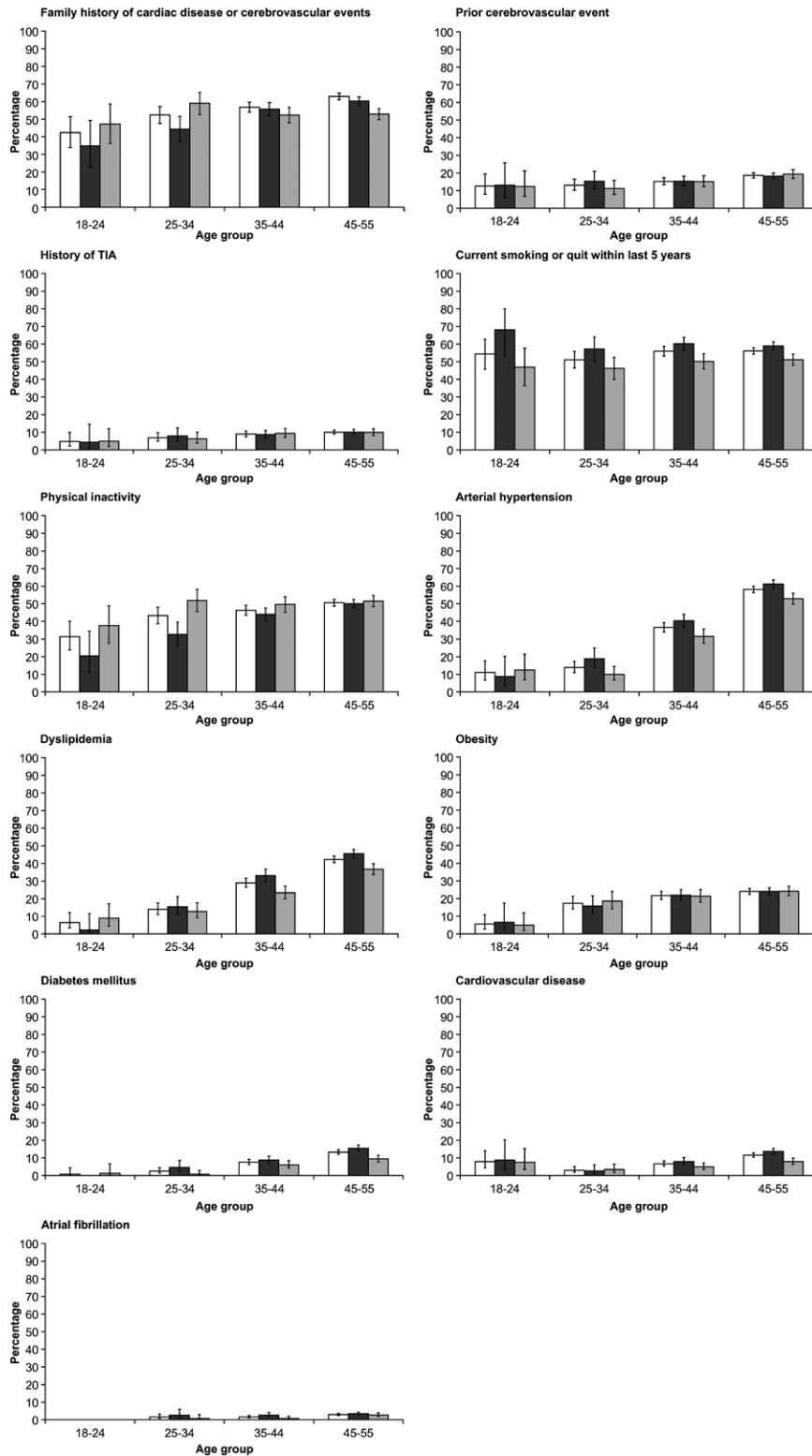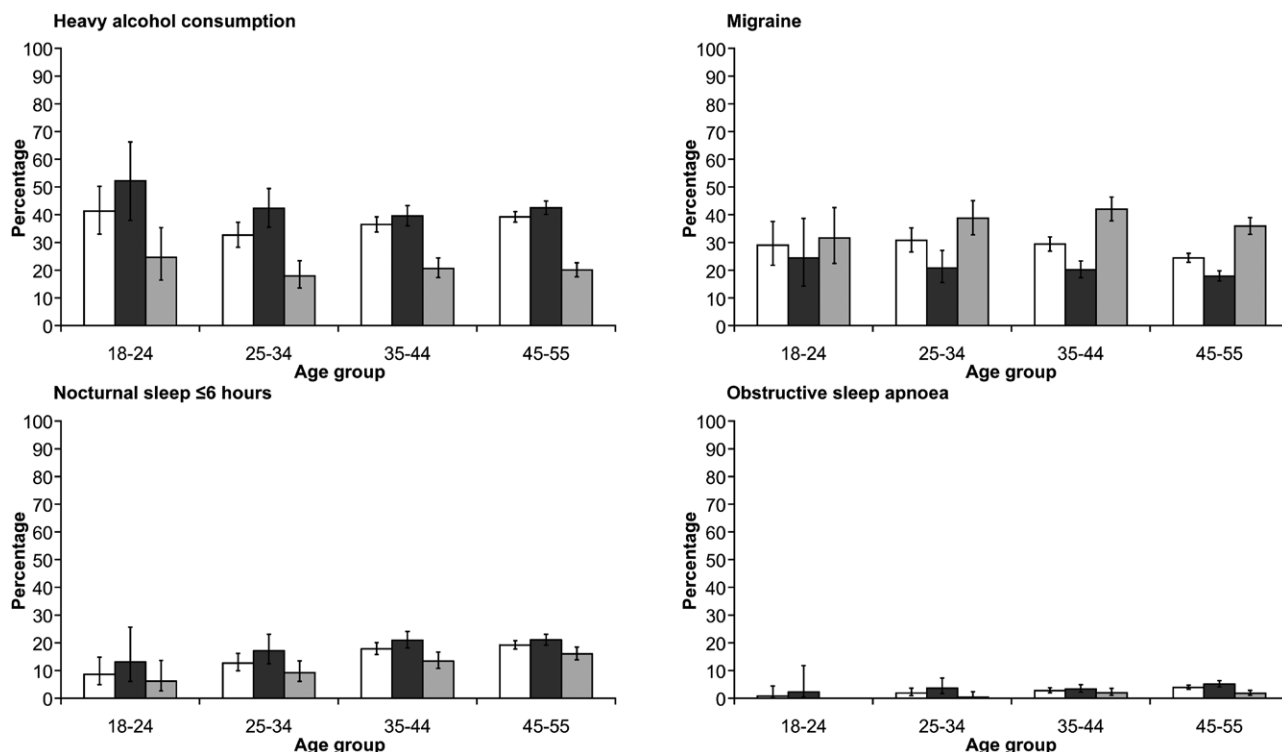
Figure 3. Age- and sex-specific proportions of less well-documented or potentially modifiable risk factors. White bars represent all patients, dark gray bars represent men, and light gray bars represent women. Error bars indicate 95% confidence interval.

well-documented and less well-documented cerebrovascular risk factors. Importantly, modifiable risk factors linked to lifestyle, such as smoking, physical inactivity, obesity, and high-risk alcohol consumption, were among the most prevalent.

Unfavorable behavioral patterns may provide the first link in a cause-and-effect chain that promotes the development of well-documented vascular risk factors such as arterial hypertension, diabetes mellitus, or hyperlipidemia, and ultimately lead to atherosclerosis and ischemic stroke. Other medical conditions or habits like migraine with aura[19] or excessive alcohol intake[18] may bear an increased risk of stroke not mediated by atherosclerosis. Unhealthy lifestyle is associated not only with higher risk of subsequent stroke[16,17] but also with higher all-cause mortality after stroke.[20] The high prevalence of unhealthy lifestyle in our cohort underlines the importance of improving adherence to healthy lifestyle behavior among stroke patients.

Both general and abdominal obesity are associated with subsequent ischemic stroke.[12,21,22] Obesity may be a culprit explaining women's increasing stroke rates over the past decade.[23] In sifap1, the proportion of obese patients increased with age. Women of all ages had a marked excess of abdominal obesity, amounting to nearly three-fourths at ages 25 years or older. Clearly, fewer patients were judged generally (men 23%, women 22%) than abdominally (men 64%, women 73%) obese. Corresponding to the preponderance of obesity, women at all ages, but especially those 35 years or younger, were more frequently physically inactive than men.

High-risk alcohol consumption is associated with ischemic stroke irrespective of the total amount of daily alcohol intake.[24] In sifap1, heavy alcohol consumption increased with age, particularly in men, and was low in women of childbearing age. Our

observations are in line with a Danish first-ever stroke registry, in which men consumed 3-times more often over the limit than women, and prevalence peaked at 55 years.[5] There are several potential explanations for the association between variable and regular excessive alcohol intake and ischemic stroke. It reverses the beneficial effect of regular light consumption on lipid metabolism.[25] It elevates the risk of acute ventricular and supra-ventricular cardiac arrhythmias, including short lasting atrial fibrillation, which may result in cardioembolic stroke in patients without detectable heart disease.[25] Finally, both withdrawal and excessive alcohol intake cause marked blood pressure elevation, platelet activation, and humoral hypercoagulability, which ultimately may promote ischemic stroke.[25]

Among the other less well-documented risk factors, migraine prevalence decreased with age and was clearly more frequent in women. This tallies with previous young stroke studies in which women had higher prevalence of migraine (12%–34%) than men (3%–20%).[7–10] However, the prevalence of migraine in women was similar over age groups, which is opposite to previous findings,[8] and may indicate a greater role of migraine in the pathogenesis of ischemic CVEs in young women.[26]

Both short and long nocturnal sleep duration are independently associated with cardiovascular diseases including stroke.[13,14] This association may be especially prominent at younger ages and may even dissolve after the age of 75 years.[13] In our study, short sleeping duration was more common among men and older age groups. This also may contribute to higher prevalence of CVE in young men. Another potential but less investigated risk factor related to sleep is daytime napping,[27] which was more common in older patients. Daytime napping may be an epiphenomenon of nocturnal sleep disturbance, which itself may predict stroke[14] but was

Table 2.   Anthropometric Measures and Behavioral Risk Factors According to Age Groups in Men and Women

	Men					Women					Age	Sex
	Total (n=2653)	18–24 Years (n=46)	25–34 Years (n=195)	35–44 Years (n=709)	45–55 Years (n=1703)	Total (n=1814)	18–24 Years (n=80)	25–34 Years (n=242)	35–44 Years (n=515)	45–55 Years (n=977)	P Value*	P Value†
Body mass index												
Underweight, ≤18.5 kg/m²	20 (0.8)	1 (2.2)	3 (1.5)	5 (0.7)	11 (0.6)	45 (2.5)	8 (10.0)	6 (2.5)	10 (1.9)	21 (2.2)	<0.001	<0.001
Normal, >18.5–24.9 kg/m²	846 (31.9)	28 (60.9)	89 (45.6)	245 (34.6)	484 (28.4)	867 (47.9)	52 (65.0)	147 (60.7)	267 (51.9)	401 (41.1)		
Overweight, ≥25.0–29.9 kg/m²	1187 (44.8)	14 (30.4)	72 (36.9)	304 (42.9)	797 (46.8)	504 (27.8)	16 (20.0)	44 (18.2)	127 (24.7)	317 (32.5)		
Obesity ≥30.0 kg/m²	599 (22.6)	3 (6.5)	31 (15.9)	155 (21.9)	410 (24.1)	395 (21.8)	4 (5.0)	45 (18.6)	110 (21.4)	236 (24.2)		
Waist circumference												
Abdominally obese	1651 (64.1)	11 (23.9)	82 (42.3)	412 (59.8)	1146 (69.7)	1287 (72.8)	37 (47.4)	134 (56.5)	361 (72.2)	755 (79.1)	<0.001	<0.001
Physical activity												
Walking <1 mile/d	1199 (46.6)	9 (20.5)	60 (32.3)	305 (43.9)	825 (50.1)	883 (50.4)	29 (38.2)	122 (51.7)	245 (49.6)	487 (51.5)	<0.001	<0.001
20–30 min, 3 times/wk	764 (29.7)	18 (40.9)	60 (32.3)	213 (30.7)	473 (28.7)	542 (31.0)	32 (42.1)	66 (28.0)	159 (32.2)	285 (30.2)		
>30 min, >3 times/wk	608 (23.6)	17 (38.6)	66 (35.5)	176 (25.4)	349 (21.2)	326 (18.6)	15 (19.7)	48 (20.3)	90 (18.2)	173 (18.3)		
Tobacco smoking												
Former	732 (27.6)	9 (19.6)	35 (17.9)	174 (24.5)	514 (30.2)	402 (22.2)	10 (12.5)	54 (22.3)	105 (20.4)	233 (23.8)	<0.001‡	<0.001‡
Current	1193 (45.0)	23 (50.0)	86 (44.1)	317 (44.7)	767 (45.0)	706 (38.9)	28 (35.0)	74 (30.6)	198 (38.4)	406 (41.6)		
Regular alcohol consumption												
No	962 (36.9)	15 (33.3)	73 (37.8)	270 (38.7)	604 (36.1)	1133 (63.1)	45 (57.0)	167 (70.2)	316 (61.8)	605 (62.5)	0.142	<0.001
Yes	1644 (63.1)	30 (66.7)	120 (62.2)	428 (61.3)	1066 (63.8)	663 (36.9)	34 (43.0)	71 (29.8)	195 (38.2)	363 (37.5)		
Frequency of drinking >5 drinks/d												
Every day	208 (8.2)	1 (2.3)	7 (3.7)	41 (6.0)	159 (9.9)	30 (1.7)	0 (0.0)	0 (0.0)	6 (1.2)	24 (2.6)	<0.001‡	<0.001‡
At least once/wk	489 (19.3)	11 (25.0)	33 (17.6)	131 (19.2)	314 (19.5)	138 (7.9)	2 (2.6)	17 (7.2)	40 (8.0)	79 (8.4)		
At least once/mo	361 (14.3)	11 (25.0)	40 (21.3)	98 (14.3)	212 (13.1)	184 (10.5)	17 (22.4)	25 (10.6)	57 (11.4)	85 (9.1)		
At least once/y	255 (10.1)	2 (4.5)	22 (11.7)	79 (11.6)	152 (9.4)	105 (6.0)	5 (6.6)	13 (5.5)	33 (6.6)	54 (5.8)		
Not in the last y	1214 (48.0)	19 (43.2)	86 (45.7)	334 (48.9)	775 (48.1)	1292 (73.9)	52 (68.4)	180 (76.6)	363 (72.7)	697 (74.2)		
Daytime nap												
No or only occasionally	2356 (90.6)	42 (93.3)	181 (94.8)	629 (89.9)	1504 (90.4)	1656 (92.81)	72 (92.3)	229 (95.4)	480 (94.7)	875 (91.1)	0.033	0.030
Once or several times/d	244 (9.4)	3 (6.7)	10 (5.2)	71 (10.1)	160 (9.6)	129 (7.2)	6 (7.7)	11 (4.6)	27 (5.3)	85 (8.9)		
Night sleep												
≤6 h/night	546 (20.6)	6 (13.0)	33 (17.2)	148 (20.9)	359 (21.1)	252 (13.9)	5 (6.3)	22 (9.1)	69 (13.4)	156 (16.0)	0.063‡	<0.001‡
7 h/night	806 (30.4)	10 (21.7)	70 (36.5)	217 (30.6)	509 (29.9)	471 (26.0)	13 (16.3)	58 (24.1)	138 (26.8)	262 (26.9)		
8 h/night	806 (30.4)	18 (39.1)	49 (25.5)	218 (30.7)	521 (30.6)	594 (32.8)	22 (27.5)	92 (38.2)	183 (35.6)	297 (30.5)		
≥9 h/night	490 (18.5)	12 (26.1)	40 (20.8)	126 (17.8)	312 (18.3)	493 (27.2)	40 (50.0)	69 (28.6)	124 (24.1)	260 (26.7)		

Data are presented as number (percentage).
*Multiple regressions adjusted for sex and center heterogeneity.
†Multiple regressions adjusted for age and center heterogeneity.
‡Not adjusted for center heterogeneity because of low frequencies in some categories.

not recorded in the sifap1 study. Obstructive sleep apnea, which was not systematically screened for, was more frequent in men but the overall prevalence was low, akin to 2 previous reports.[7,10]

Regarding the accumulation of risk factors, which increased with age, surprisingly few patients (≈5%) had none of the 12 (potentially) modifiable risk factors. Clinical implications of this high risk factor burden go beyond primary prevention because recent reports suggest an association between accumulation of risk factors and risk of atherothrombotic events in young adults after first-ever ischemic stroke.[28]

Only few studies specifically of young stroke patients provided age-specific comparisons of vascular risk factors. Dyslipidemia, hypertension, smoking, coronary heart disease, history of myocardial infarction, peripheral arterial disease, diabetes mellitus, and atrial fibrillation have been more commonly observed among older age groups of young stroke patients.[7,8,10] This is in accordance with our observations.

Notably, women of childbearing age (25–34 years) smoked less frequently than did those in other age groups.

Our study has certain limitations. It represents a patient series and, therefore, cannot explore the strength of association of individual risk factors on stroke risk in the population. Patients were predominantly central European white, whereas prevalence may vary across ethnic groups and geographic regions. Including consenting patients at selected hospitals might have caused selection bias. Taking more less well-established stroke risk factors like infections, antiphospholipid antibodies, and illicit drug use into account might have decreased the proportion of patients with none or few risk factors. The sifap1 protocol required confirmation of self-reported variables by reviewing medical records and performing laboratory tests and clinical examinations. However, sex disparities regarding self-reported risk factors and comorbidities may exist because patients' awareness of

risk factors and physicians' adherence to treatment guidelines may differ between men and women.[29,30]

Conclusions

Young ischemic stroke and TIA patients showed a prominent accumulation of multiple well-documented and less well-documented risk factors that clearly were more pronounced among men. Our findings have implications for increasing awareness toward modifiable risk factors in principal prevention and in younger stroke patients.

References

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*. 2009;8:355–369.
2. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al; American Heart Association; American Stroke Association Stroke Council. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2006;113:e873–e923.
3. Nedeltchev K, der Maur TA, Georgiadis D, Arnold M, Caso V, Mattle HP, et al. Ischaemic stroke in young adults: predictors of outcome and recurrence. *J Neurol Neurosurg Psychiatr*. 2005;76:191–195.
4. Evers SM, Struijs JN, Ament AJ, van Genugten ML, Jager JH, van den Bos GA. International comparison of stroke cost studies. *Stroke*. 2004;35:1209–1215.
5. Andersen KK, Andersen ZJ, Olsen TS. Age- and gender-specific prevalence of cardiovascular risk factors in 40,102 patients with first-ever ischemic stroke: a Nationwide Danish Study. *Stroke*. 2010;41:2768–2774.
6. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321–329.
7. Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. *Stroke*. 2009;40:1195–1203.
8. Rasura M, Spalloni A, Ferrari M, De Castro S, Patella R, Lisi F, et al. A case series of young stroke in Rome. *Eur J Neurol*. 2006;13:146–152.
9. Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM. Etiology of and risk factors for cerebral infarction in young adults in western Norway: a population-based case-control study. *Eur J Neurol*. 2004;11:25–30.
10. Spengos K, Vemmos K. Risk factors, etiology, and outcome of first-ever ischemic stroke in young adults aged 15 to 45 - the Athens young stroke registry. *Eur J Neurol*. 2010;17:1358–1364.
11. Nightingale AL, Farmer RD. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. *Stroke*. 2004;35:1574–1578.
12. Hu G, Tuomilehto J, Silventoinen K, Sarti C, Männistö S, Jousilahti P. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Arch Intern Med*. 2007;167:1420–1427.
13. Magee CA, Kritharides L, Attia J, McElduff P, Banks E. Short and long sleep duration are associated with prevalent cardiovascular disease in Australian adults. *J Sleep Res*. 2012;21:441–447.
14. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. *J Sleep Res*. 2012;21:427–433.
15. Rolfs A, Martus P, Heuschmann PU, Grittner U, Holzhausen M, Tatlisumak T, et al. Protocol and methodology of the Stroke in Young Fabry Patients (sifap1) study: a prospective multicenter European study of 5,024 young stroke patients aged 18-55 years. *Cerebrovasc Dis*. 2011;31:253–262.
16. Kurth T, Moore SC, Gaziano JM, Kase CS, Stampfer MJ, Berger K, et al. Healthy lifestyle and the risk of stroke in women. *Arch Intern Med*. 2006;166:1403–1409.
17. Myint PK, Luben RN, Wareham NJ, Bingham SA, Khaw KT. Combined effect of health behaviours and risk of first ever stroke in 20,040 men and women over 11 years' follow-up in Norfolk cohort of European Prospective Investigation of Cancer (EPIC Norfolk): prospective population study. *BMJ*. 2009;338:b349.
18. European Stroke Organisation (ESO) Executive Committee. ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507.
19. Sacco S, Ricci S, Carolei A. Migraine and vascular diseases: a review of the evidence and potential implications for management. *Cephalalgia*. 2012;32:785–795.
20. Towfighi A, Markovic D, Ovbiagele B. Impact of a healthy lifestyle on all-cause and cardiovascular mortality after stroke in the USA. *J Neurol Neurosurg Psychiatr*. 2012;83:146–151.
21. Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, et al. Prospective study of body mass index and risk of stroke in apparently healthy women. *Circulation*. 2005;111:1992–1998.
22. Suk SH, Sacco RL, Boden-Albala B, Cheun JF, Pittman JG, Elkind MS, et al. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke*. 2003;34:1586–1592.
23. Towfighi A, Zheng L, Ovbiagele B. Weight of the obesity epidemic: rising stroke rates among middle-aged women in the United States. *Stroke*. 2010;41:1371–1375.
24. Sundell L, Salomaa V, Vartiainen E, Poikolainen K, Laatikainen T. Increased stroke risk is related to a binge-drinking habit. *Stroke*. 2008;39:3179–3184.
25. Puddey IB, Rakic V, Dimmitt SB, Beilin LJ. Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors–a review. *Addiction*. 1999;94:649–663.
26. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2009;339:b3914.
27. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J*. 2011;32:1484–1492.
28. Putaala J, Haapaniemi E, Kaste M, Tatlisumak T. How does number of risk factors affect prognosis in young patients with ischemic stroke? *Stroke*. 2012;43:356–361.
29. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation*. 2005;111:499–510.
30. Towfighi A, Zheng L, Ovbiagele B. Sex-specific trends in midlife coronary heart disease risk and prevalence. *Arch Intern Med*. 2009;169:1762–1766.

SUPPLEMENTAL MATERIAL

ONLINE SUPPLEMENT

Lifestyle Risk-Factors for Ischemic Stroke and TIA in Young Adults in the Stroke in Young Fabry Patients (sifap1) Study

Bettina von Sarnowski, MD[1]*; Jukka Putaala, MD[2]*; Ulrike Grittner, PhD[3, 12]; Beate Gaertner, PhD[3, 16]; Ulf Schminke, MD[1]; Sami Curtze, MD[2]; Roman Huber, MD[4]; Christian Tanislav, MD[5]; Christoph Lichy, MD[6]; Vida Demarin, MD, PhD[7]; Vanja Basic-Kes, MD[7]; E. Bernd Ringelstein, MD[8]; Tobias Neumann-Haefelin, MD[9]; Christian Enzinger, MD[10, 15]; Franz Fazekas, MD[10]; Peter M. Rothwell, MD, PhD[11]; Martin Dichgans, MD[17]; Gerhard J. Jungehulsing, MD[12]; Peter U. Heuschmann, MD, MPH[12, 18]; Manfred Kaps, MD[5]; Bo Norrving, MD[13]; Arndt Rolfs, MD[14]; Christof Kessler, MD[1]†; and Turgut Tatlisumak, MD[2]†; on behalf of the sifap1 Investigators

*shared first authorship, †shared last authorship

Affiliations:
[1]Department of Neurology, University Medicine, Ernst Moritz Arndt University, Greifswald, Germany;
[2]Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland;
[3]Department of Biometrics and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, Germany;
[4]Department of Neurology, University of Ulm, Germany;
[5]Department of Neurology, University of Giessen, Germany;
[6]Department of Neurology, University of Heidelberg, Germany;
[7]Department of Neurology, University Hospital Sestre Milosrdnice, Zagreb, Croatia;
[8]Department of Neurology, University of Münster, Germany;
[9]Department of Neurology, University Hospitals, Frankfurt, Germany;
[10]Department of Neurology, Medical University of Graz, Austria;
[11]Stroke Prevention Research Unit, Department of Clinical Neurology, University of Oxford, UK;
[12]Centre for Stroke Research, Charité – Universitätsmedizin Berlin, Germany;
[13]Department of Neurology, Lund University Hospital, Sweden;
[14]Albrecht Kossel Institute for Neuroregeneration, Medical Faculty, University of Rostock, Germany;
[15]Section of Neuroradiology, Department of Radiology, Medical University of Graz, Austria;
[16]Robert Koch Institute, Department of Epidemiology and Health Monitoring, Berlin, Germany;
[17]Institute for Stroke and Dementia Research, Ludwig-Maximilians-University, Munich, Germany;
[18]Institute of Clinical Epidemiology and Biometry, Comprehensive Heart-Failure Center, University of Würzburg, Center for Clinical Studies, University Hospital of Würzburg, Germany.

Running title: Risk-Factors in Young Stroke Patients

Corresponding author:
Bettina von Sarnowski
Department of Neurology
University Medicine
Ferdinand-Sauerbruch-Straße
D-17475 Greifswald, Germany
phone:+493834866815
fax:+493834866806
e-mail: Bettina.vonSarnowski@uni-greifswald.de

Supplemental Methods

Medical history, co-morbidities and family history were obtained by interviewing the patients or their caregivers, by reviewing medical records or by contacting their primary care physicians. Coronary artery disease, peripheral arterial disease, congestive heart failure, myocardial infarction, valvular disease, atrial fibrillation, obstructive sleep apnea, diabetes mellitus, arterial hypertension, and dyslipidemia were recorded if either this disease had been formerly diagnosed by a physician, the patient was on specific medication or if the disease was diagnosed during hospital treatment for the index stroke. Electrocardiograms, blood tests for glucose, LDL-cholesterol and HDL-cholesterol, systolic and diastolic arterial blood pressure measurement were performed in all patients and results were registered in the sifap1 database. A history of migraine was taken from all patients and was defined as either suffering from at least one migraine attack within the previous year or suffering from >10 attacks in lifetime, which all comply with the criteria of the International Headache Society.[1] Tobacco smoking was classified as never, current or former smoking. The latter applied if the patient quit smoking at least five years prior to enrolment.

Sex-specific frequencies of risk-factors were stratified into four age groups: 18-24, 25-34, 35-44, and 45-55 years. Height (cm), body weight (kg), and waist circumference were measured at study inclusion. BMI as a marker for general obesity was categorized into: underweight (≤18.5), normal (18.6-24.9), overweight (25.0-29.9), and obese (≥30.0). According to reference values from the general population of north Glasgow, the cut-off for waist circumference as a marker for abdominal obesity was ≥94 cm for men and ≥80 cm for women.[2,3] Physical activity was categorized into minimal (walking <1 mile/day), moderate (20-30 min three times per week) and intense physical activity (>30 min >3 times per week) according to Centers of Disease Control and Prevention (CDC) guidelines.[4] Since even moderate physical activity is considered being effective for stroke prevention,[5] we compared individuals with moderate or intense physical activity with those who reported only minimal activity. Regular alcohol consumption was defined as consumption of ≥1 drink per week. A drink was equal to 10-14 g of pure alcohol or a 8-12-oz. glass of beer, a 5-oz. glass of wine, or a 1.5-oz. "shot" of 80%-proof distilled spirits or liquor.[6] High-risk alcohol consumption was defined as consuming >5 alcoholic drinks/day (i.e., >50-70 g pure alcohol/day) at least once/month within the previous year.[7] We categorized nighttime sleep duration into ≤6, 7, 8, or ≥9 hours/night and compared individuals who slept at least 6 hours with those who slept more than 6 hours/night. Daytime nap was classified as napping once or several times a day as opposed to no or occasional napping.

Assessment of risk-factors was mandatory in sifap1. The response rate was >95% for all risk-factor variables.

References

1. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd edition. *Cephalalgia*. 2004;24:9-160.

2. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *BMJ*. 1995;311:158-161.

3. Cornier MA, Després JP, Davis N, Grossniklaus DA, Klein S, Lamarche B, et al. American Heart Association Obesity Committee of the Council on Nutrition; Physical Activity and Metabolism; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing, Council on Epidemiology and Prevention; Council on the Kidney in Cardiovascular Disease, and Stroke Council. Assessing Adiposity: A Scientific Statement From the American Heart Association. *Circulation*. 2011;124:1996-2019.

4. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273:402-407.

5. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2006;113:e873-923.

6. CDC Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion website. Alcohol and Public Health. Frequently Asked Questions: What is a standard drink in the United States? http://www.cdc.gov/alcohol/faqs.htm#standDrink. Page last reviewed and updated: May 10, 2012. Accessed September 04, 2012.

7. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKEstudy): a case-control study. *Lancet*. 2010;376:112-123.