Cannabis, Tobacco, Alcohol Use, and the Risk of Early Stroke

A Population-Based Cohort Study of 45 000 Swedish Men

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Background and Purpose—Current knowledge on cannabis use in relation to stroke is based almost exclusively on clinical reports. By using a population-based cohort, we aimed to find out whether there was an association between cannabis use and early-onset stroke, when accounting for the use of tobacco and alcohol.

Methods—The cohort comprises 49 321 Swedish men, born between 1949 and 1951, who were conscripted into compulsory military service between the ages of 18 and 20. All men answered 2 detailed questionnaires at conscription and were subject to examinations of physical aptitude, psychological functioning, and medical status. Information on stroke events up to ≈60 years of age was obtained from national databases; this includes strokes experienced before 45 years of age.

Results—No associations between cannabis use in young adulthood and strokes experienced ≤45 years of age or beyond were found in multivariable models: cannabis use >50 times, hazard ratios=0.93 (95% confidence interval [CI], 0.34–2.57) and 0.95 (95% CI, 0.59–1.53). Although an almost doubled risk of ischemic stroke was observed in those with cannabis use >50 times, this risk was attenuated when adjusted for tobacco usage: hazards ratio=1.47 (95% CI, 0.83–2.56). Smoking ≥20 cigarettes per day was clearly associated both with strokes before 45 years of age, hazards ratio=5.04 (95% CI, 2.80–9.06), and with strokes throughout the follow-up, hazards ratio=2.15 (95% CI, 1.61–2.88).

Conclusions—We found no evident association between cannabis use in young adulthood and stroke, including strokes before 45 years of age. Tobacco smoking, however, showed a clear, dose–response shaped association with stroke.

(*Stroke*. 2017;48:265-270. DOI: 10.1161/STROKEAHA.116.015565.)

Key Words: adolescent ■ cannabis ■ diet ■ stroke

Stroke is currently the third leading cause of death and disability in developed countries,[1] emphasizing its importance as a leading global health problem. Although the overall incidence of strokes has been declining in developed countries during the past 2 decades, the absolute number of people who have a stroke every year and live with its consequences is increasing.[1,2] Moreover, there is troubling evidence of an increasing incidence of strokes among young adults.[3]

Studies have shown that >90% of the stroke burden is attributable to modifiable risk factors, such as tobacco smoking, alcohol consumption, poor diet, low physical activity, and hypertension.[1,4] It has been demonstrated that several of these risk factors may be already present in late adolescence,[5] highlighting the potential for early identification and intervention. Recently, a growing body of research has linked cannabis use to stroke, particularly to those occurring before 45 years of age.[6,7] It seems cannabis-associated strokes usually occur in chronic or current cannabis users who also smoke tobacco,[8] either in combination with or immediately after cannabis use. The cerebrovascular effects of cannabis highlighted as possible mechanisms for subsequent strokes include hypotension, altered cerebral vasomotor function, vasospasm, cerebral vasoconstriction, and swings in blood pressure. However, currently there is a dearth of epidemiological data supporting an association between cannabis use and stroke.[8,9]

Thus, our current knowledge about cannabis-associated strokes is based almost exclusively on clinical reports.[10] Although there have been a few general population studies, these have been mostly based on hospital records and are, therefore, retrospective in nature. In general, many of these studies lack the ability to address questions of temporality, possible dose–response associations, and the importance of other concomitant factors (eg, alcohol and tobacco use). Consequently, whether cannabis is to be regarded as a risk factor for stroke is still unclear.

A recent study of the largest inpatient database in the United States found that cannabis use was associated with a 17%

Received September 27, 2016; final revision received November 23, 2016; accepted November 28, 2016.

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increase in the risk of hospitalization because of acute ischemic stroke,[6] even if both tobacco and amphetamine use constituted bigger risks. A previous case–control study in Australia found that patients experiencing an ischemic stroke or transient ischemic attack were more likely to use cannabis than nonstroke patients.[11] However, after adjusting for tobacco use, an association between cannabis and stroke could not be confirmed. Another cross-sectional study from the United States found that cannabis abuse or dependence was associated with ischemic but not hemorrhagic stroke.[12] Furthermore, in this study, use of tobacco and cocaine were more strongly associated with stroke, and amphetamine was the only drug that increased the risk of death from stroke. In a recent Australian study examining 7455 adults in the general community,[13] weekly cannabis users had a higher rate of nonfatal stroke or transient ischemic attack than noncannabis users. However, because this was a cross-sectional study, a causal relationship between stroke and cannabis use could not be inferred. Thus, longitudinal studies in the general population are lacking.

Considering the fact that cannabis is the most used illicit drug worldwide, with an estimated 180 million annual users,[14] the interest in its possible health risks seems warranted. The current wave of decriminalization and liberalization of medical marijuana in the United States and in other countries may lead to its more widespread use. This potential makes it important to address the possible adverse health effects associated with cannabis, as they may begin to occur in the population at a greater frequency.[15]

By using a population-based cohort comprising 49 321 Swedish men, with data on cannabis use in late adolescence and on tobacco smoking, alcohol consumption, and several other risk factors and information on strokes from national health registers, we aimed to clarify the association between cannabis use and early onset of stroke including stroke before 45 years of age, when contrasted with tobacco and alcohol use.

Methods

Study Population

Data came from a national survey of Swedish men conscripted into military service in 1969/70, between 18 and 20 years of age. The survey has been described in detail elsewhere.[16] All men underwent a 2-day screening procedure, including an extensive health examination and the completion of 2 questionnaires—one focusing on social and behavioral factors and the other on substance use. Only 2% to 3% of the Swedish male population was exempted from conscription at this time, attributable to either severe disablements or congenital disorders.

Ethical approval was granted by the Research Ethics Committee of the Karolinska Institutet, Stockholm.

Assessment of Exposures (Cannabis, Tobacco, and Alcohol)

The conscripts were asked whether they had ever used drugs, which drugs they had used (from a list of alternatives), drug most commonly used, and frequency of use (fixed alternatives). Based on the most commonly used drugs and the frequency of use, we divided cannabis use into never, 1 to 10 times, 11 to 50 times, and >50 times. Regarding tobacco smoking, a single question was asked, "How many cigarettes do you smoke per day?" We divided tobacco smoking into no smoking, 1 to 10 cigarettes per day, 11 to 20 cigarettes per day, or >20 cigarettes per day. As for alcohol consumption, the conscripts were asked to report the average quantity and frequency of medium or strong beer, wine, and strong spirits that they drank. Through subsequent standard estimates of drink size (10–12 g 100% ethanol), consumption in grams of 100% alcohol per week was calculated.[17] As in previous studies of this cohort,[18] we divided alcohol consumption into abstention/never drinking (0 g 100% alcohol/week), light (1–100 g), moderate (101–250 g), and high (>250 g).

Assessment of Other Risk Factors (Covariates)

The conscription examination also provided information on body weight and height,[19] resting systolic and diastolic blood pressures,[20] cardiorespiratory fitness,[21] and any disorders as diagnosed by a physician. Body weight and height were used to determine body mass index, that is, kilograms per meter squared. Blood pressure measurements were made after 5 to 10 minutes of rest on the first day of the conscript examination. Cardiorespiratory fitness was rated on a scale from 1 to 9 based on a bicycle ergonometric test. Diagnoses of diabetes mellitus and migraine were recorded according to their *International Classification of Diseases-Eighth Revision* codes: 250 and 346, respectively. In addition, studying versus not studying at time of conscription was used to indicate the men's educational level. Furthermore, by linking conscripts' national identity numbers with parental records (held by Statistics Sweden), we obtained data on their parental history of cardiovascular disease (CVD) (from the National Cause of Death Register and National Board of Health and Welfare in Sweden) and participants' socioeconomic position during childhood.[22] A parental history of CVD was defined as any CVD-related death (mother or father) at ≤65 years of age. Information on childhood socioeconomic position came from the National Population and Housing Census of 1960 (99% response rate) and was classified on the basis of the head of household's (usually father's) occupation.

Assessment of Stroke

Participants were followed to assess the initial occurrence of strokes (fatal or nonfatal) from 1971 until 2009, that is, between ages ≈20 and ≈59 years. Information on the onset of any stroke was obtained by record linkage with the National Hospital Discharge Register, administered by the Swedish National Board of Health and Welfare. The HDR covers all public inpatient care in Sweden and is complete as of 1987. As the incidence of strokes before age ≈36 to 37 years in general is low, only a few cases of stroke could be missed because of incomplete registers. Personal records were also linked with the National Cause of Death Register for information on death because of stroke. Codes according to the *International Classification of Diseases* code were as follows: 8th Revision, all strokes: 430, 431, 433, and 434; ischemic stroke: 433 to 434; 9th Revision, all strokes: 430 to 432, 434, and 436; ischemic stroke: 434; 10th Revision, all strokes, including transient ischemic attack: I60–I64, I66, and G45; ischemic stroke: I63.

Statistical Analysis

We used Cox proportional-hazards regression to examine cannabis use in young adulthood as a possible risk factor for all strokes and ischemic strokes until 59 years of age. Because of a limited number of cases, the association between cannabis use and hemorrhagic stroke was not examined separately. The association with strokes occurring before 45 years of age was also examined, but because of low numbers, these cases were not examined separately by stroke type. Censoring was made at the time of an initial fatal or nonfatal stroke, time of death, date of emigration, or December 31, 2009 (whichever occurred first).

After computation of crude models, the following were estimated: (1) a model adjusting for body mass index, systolic and diastolic blood pressure, cardiorespiratory fitness, migraine, diabetes mellitus, and early parental CVD; (2) additionally adjusting for indicators of socioeconomic status until young adulthood; and (3) additionally adjusting for tobacco smoking and alcohol consumption. Statistical analyses were performed using SAS version 9.4 for Windows.

We had complete data for all examined variables from the 45 081 men included in our analysis. The results from our sample were similar to those of the whole cohort when we included participants with missing data (8.8%).

Results

In total, 1037 first-time strokes occurred during the follow-up period until 59 years of age. Among these, ≈48% were ischemic strokes (n=498) and 23% were hemorrhagic strokes (n=233). Before 45 years of age, 192 first-time strokes had occurred; ≈40% were ischemic strokes, and 27% were hemorrhagic strokes.

The following factors were significantly more common among men who had a stroke before 60 years of age: a parental history of CVD, being overweight, low cardiorespiratory fitness, low socioeconomic position in childhood, short schooling, heavy smoking, and high alcohol consumption (Table 1). Although not statistically significant, higher proportions of men with a diagnosis of diabetes mellitus or migraine at the conscription examination were represented among those experiencing a stroke before 60 years of age. High blood pressure and heavy cannabis use seemed to be more prevalent among the men having a stroke before 45 years of age but did not differ to the same extent between men with and without stroke when followed until 60 years of age.

Cannabis use showed no association with stroke before 45 years of age (Table 2). Both cigarette smoking and alcohol use, on the contrary, showed clear dose–response shaped associations with stroke before 45 years of age in the crude models. Specifically, the incidence of stroke before 45 years of age was >6 times higher among men who reported smoking >20 cigarettes per day than in nonsmoking men and was 4 times higher among men reporting high alcohol consumption than in men reporting no alcohol use. However, in multivariable models, only cigarette smoking—not alcohol consumption—seemed robustly associated with stroke before 45 years of age.

There was no significant association between cannabis use in young adulthood and overall incidence of stroke until 59 years of age (Table 3). At the same time, there was a clear, dose–response shaped association between cigarettes (tobacco) smoked and stroke, and furthermore, an association between alcohol consumption and stroke was suggested. When adjusting for cigarette smoking and alcohol consumption, we found that none of the cannabis groups (1–10, 11–50, and >50) showed an elevated hazard of stroke.

Crude models demonstrated that the hazard of ischemic stroke until 59 years of age was almost 2 times higher among men who were heavy cannabis users in young adulthood than among nonusers. At the same time, a dose–response shaped association with ischemic stroke was seen only for cigarette smoking, that is, not for cannabis use or alcohol consumption. In multivariable-adjusted models, the elevated hazards of ischemic stroke were attenuated both in relation to heavy cannabis use and in relation to high alcohol consumption.

Table 1. Baseline Distribution of Risk Factors in a Cohort of Swedish Men With or Without Stroke During Follow-Up

	No Stroke Before 60 y of Age		Stroke Before 60 y of Age			Stroke Before 45 y of Age	
No. of subjects	44 044		1037			192	
Baseline variables (age ≤20 y)	No	%	No	%	*P* Value	No	%
Parental history of CVD*	4374	9.93	128	12.34	0.0119	21	10.94
Overweight†	2884	6.55	102	9.84	<0.0001	19	9.90
High blood pressure‡	4257	9.67	103	9.93	0.7499	22	11.46
Low cardiorespiratory fitness§	8669	19.68	255	24.59	<0.0001	49	25.52
Diabetes‖	26	0.06	3	0.29	0.0284	1	0.52
Migraine¶	227	0.52	7	0.68	0.5056	0	…
Low SEP in childhood#	14 532	32.99	413	39.83	<0.0001	80	41.67
Short schooling**	21 541	48.91	591	56.99	<0.0001	122	63.54
Heavy cannabis use††	669	1.52	18	1.74	0.5216	4	2.08
Heavy smoking‡‡	1444	3.28	62	5.98	<0.0001	20	10.42
High alcohol consumption§§	1444	3.28	50	4.82	0.0083	15	7.81

CVD indicates cardiovascular disease; and SEP, socioeconomic position.
*Death because of CVD before 65 y of age in a parent.
†Body mass index of ≥25 kg/m^2.
‡Systolic and diastolic blood pressure >140/90 mm Hg.
§Fitness score below 5.
‖ICD codes (8th revision)=250.
¶ICD codes (8th revision)=346.
#Head of household's SEP=unskilled worker.
**No longer in school at 18 y of age.
††Use of cannabis >50 times.
‡‡Smoking of >20 cigarettes per day.
§§Consumption of >250 g 100% alcohol/wk.

Table 2. Strokes Before 45 y of Age in Relation to Cannabis Use, Cigarette Smoking, and Alcohol Consumption Before 20 y of Age

Stroke <45 y of Age	Cases, n	Crude*		Adjusted I†		Adjusted II‡		Adjusted III§	
	192	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Cannabis‖		Reference¶		Reference¶		Reference¶		Reference¶	
1–10	17	1.59	0.96–2.62	1.60	0.97–2.65	1.69	1.02–2.79	1.21	0.73–2.04
11–50	4	1.54	0.57–4.16	1.51	0.56–4.09	1.55	0.57–4.20	1.03	0.38–2.83
>50	4	1.59	0.59–4.28	1.55	0.57–4.19	1.53	0.56–4.14	0.93	0.34–2.57
Smoking#		Reference¶		Reference¶		Reference¶		Reference¶	
1–10	60	1.97	1.32–2.93	1.98	1.33–2.96	1.91	1.28–2.85	1.87	1.24–2.82
11–20	71	3.36	2.28–4.93	3.27	2.21–4.83	3.04	2.05–4.52	2.89	1.90–4.38
>20	20	6.63	3.88–11.32	6.33	3.68–10.89	5.70	3.28–9.87	5.04	2.80–9.06
Alcohol**		Reference¶		Reference¶		Reference¶		Reference¶	
1–100	123	1.51	0.70–3.23	1.53	0.71–3.27	1.52	0.71–3.26	1.04	0.48–2.29
101–250	47	2.12	0.96–4.70	2.10	0.95–4.65	2.02	0.91–4.49	1.08	0.47–4.03
>250	15	4.22	1.72–10.36	4.01	1.63–9.85	3.62	1.47–8.92	1.56	0.60–4.03

CI indicates confidence interval; and HR, hazard ratio.

*Adjusted for year of birth.

†Adjustment*+body mass index, migraine, diabetes mellitus, family history of cardiovascular disease, systolic and diastolic blood pressures, and cardiorespiratory fitness.

‡Adjustment†+childhood socioeconomic position and short schooling.

§Adjustment‡+cannabis use, tobacco smoking, and alcohol consumption.

‖Cannabis, times used: 1–10, 11–50, and >50.

¶Nonusers is reference category.

#Smoking, cigarettes/d: 1–10, 11–20, and >20.

**Alcohol, grams 100% alcohol/wk: 1–100, 101–250, and >250.

Discussion

Our study suggests no clear association between cannabis use in young adulthood and early stroke. The elevated hazard of ischemic stroke among heavy users of cannabis diminished after adjustments for cigarette smoking and alcohol consumption were made. Furthermore, the association between alcohol consumption and stroke was weak in the fully adjusted model. Cigarette smoking, on the contrary, showed a clear, dose–response shaped association with stroke in all models.

Our results on cannabis use and stroke did not confirm previous research,[13] and there are several possible explanations for this. First, the population-based study by Hemachandra et al was cross-sectional, with significantly less time occurring between cannabis use (past year) and stroke than ours. Additionally, that study did not include any detailed information on the amount of tobacco smoked, even though—as seen in our study—the number of cigarettes smoked is of clear importance in relation to stroke. Furthermore, it was based on self-reported data only and included transient ischemic attack, which could not be examined separately in the present study. In the study by Westover et al,[12] cannabis abuse and dependence were found to be associated with ischemic stroke, although tobacco use constituted a bigger risk.

In contrast, Barber et al[11] were not able to find an association between cannabis and stroke, independent of tobacco. This finding is in line with our results. Consistent with previous studies,[23] we found heavy tobacco smokers in late adolescence to have a 2-fold risk of stroke anytime during the follow-up and 5 times the risk of stroke before 45 years of age, compared with nonsmokers, after adjustment for several risk factors. However, unlike previous studies,[24] we did not find a clear association between high alcohol consumption and the risk of stroke once tobacco smoking was included as a covariate.

Important to note is the close link between tobacco smoking and cannabis use in our sample. In fact, few cases of stroke occurred among those men who reported having used cannabis frequently but used tobacco or alcohol infrequently, and almost no cases of stroke before 45 years of age occurred among them. Therefore, there is little evidence of cannabis independently affecting stroke. Furthermore, this highlights the difficulty in controlling for confounds; the association between cannabis use and stroke is not quantifiable in both users and nonusers of tobacco or users and nonusers of alcohol.

Recently, the World Health Organization[25] highlighted the urgent need for more studies on the potential health risks of cannabis (eg, stroke and CVD) and the need to better control the potential confounds of tobacco smoking. It is well known that cannabis and tobacco are often mixed together, and studies have reported that ≤90% of cannabis users are also tobacco smokers.[26] Moreover, tobacco is commonly added to cannabis cigarettes, so-called joints, so that the 2 substances are used simultaneously.[27] There is some evidence that tobacco may increase the rewarding effects of cannabis,[27] which may help explain the high prevalence of comorbid use.

Some limitations with our study need to be acknowledged. First, there is no follow-up data on the baseline measurements. Accordingly, we have no information on body mass index, blood pressures, and cardiorespiratory fitness later in the life

Table 3. Overall and Ischemic Stroke Before 60 Y of Age in Relation to Cannabis Use, Cigarette Smoking, and Alcohol Consumption Before 20 y of Age

Strokes <60 y	Cases, n	Crude*		Adjusted I†		Adjusted II‡		Adjusted III§	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Overall	1037								
Cannabis‖		Reference¶		Reference¶		Reference¶		Reference¶	
1–10	62	1.02	0.79–1.31	1.02	0.79–1.32	1.03	0.80–1.34	0.90	0.69–1.18
11–50	12	0.80	0.45–1.42	0.77	0.44–1.37	0.78	0.44–1.38	0.65	0.37–1.16
>50	18	1.23	0.77–1.97	1.19	0.75–1.91	1.17	0.74–1.88	0.95	0.59–1.53
Smoking#		Reference¶		Reference¶		Reference¶		Reference¶	
1–10	324	1.30	1.11–1.51	1.29	1.11–1.51	1.26	1.08–1.47	1.25	1.07–1.47
11–20	314	1.81	1.55–2.11	1.73	1.48–2.02	1.64	1.40–1.93	1.66	1.41–1.97
>20	62	2.50	1.91–3.28	2.31	1.76–3.04	2.14	1.63–2.83	2.15	1.61–2.88
Alcohol**		Reference††		Reference††		Reference††		Reference††	
1–100	735	1.43	1.05–1.94	1.44	1.06–1.96	1.43	1.05–1.94	1.24	0.91–1.69
101–250	208	1.49	1.08–2.07	1.47	1.06–2.03	1.42	1.02–1.96	1.11	0.79–1.56
>250	50	2.22	1.48–3.33	2.10	1.34–2.97	1.94	1.29–2.91	1.39	0.91–2.13
Ischemic	498								
Cannabis‖		Reference¶		Reference¶		Reference¶		Reference¶	
1–10	32	1.10	0.77–1.58	1.11	0.78–1.59	1.13	0.79–1.63	1.02	0.71–1.48
11–50	6	0.85	0.38–1.89	0.82	0.37–1.84	0.83	0.37–1.85	0.71	0.32–1.61
>50	13	1.89	1.09–3.27	1.85	1.07–3.22	1.82	1.05–3.17	1.47	0.83–2.56
Smoking#		Reference¶		Reference¶		Reference¶		Reference¶	
1–10	157	1.36	1.09–1.69	1.35	1.08–1.68	1.30	1.04–1.63	1.32	1.05–1.66
11–20	150	1.86	1.49–2.33	1.75	1.39–2.19	1.64	1.30–2.07	1.70	1.33–2.16
>20	34	2.95	2.04–4.28	2.65	1.82–3.86	2.42	1.66–3.53	2.43	1.63–3.63
Alcohol**		Reference¶		Reference¶		Reference¶		Reference¶	
1–100	357	1.27	0.84–1.92	1.27	0.84–1.93	1.26	0.83–1.90	1.07	0.70–1.63
101–250	89	1.17	0.74–1.83	1.14	0.72–1.78	1.09	0.69–1.71	0.81	0.50–1.30
>250	28	2.27	1.32–3.92	2.09	1.21–3.61	1.90	1.10–3.28	1.22	0.68–2.17

CI indicates confidence interval; and HR, hazard ratio.

*Adjusted for year of birth.

†Adjustment*+body mass index, migraine, diabetes mellitus, family history of cardiovascular disease, systolic and diastolic blood pressures, and cardiorespiratory fitness.

‡Adjustment†+childhood socioeconomic position and short schooling.

§Adjustment‡+cannabis use, tobacco smoking, and alcohol consumption.

‖Cannabis, times used: 1–10, 11–50, and >50.

¶Nonusers is reference category.

#Smoking, cigarettes/d: 1–10, 11–20, and >20.

**Alcohol, grams 100% alcohol/wk: 1–100, 101–250, and >250.

course of these men. These are all factors that may contribute to, and explain, later strokes. Also, we do not know to what extent our sample have continued or discontinued using cannabis, alcohol, and tobacco into adulthood. The rate of overall drug use, including cannabis, in our cohort was low (11%, of which 9% was cannabis), and in contexts where rates are higher, an impact of cannabis on stroke may still be worth investigating. Moreover, the overall drug rate in our cohort was lower in comparison to the anonymous conscript surveys that took place both the year before and the year after (18% in 1968 and 16% in 1970).[28] Consequently, self-reported cannabis use is likely subject to under-reporting. On the contrary, studies of the same group of Swedish conscripts have shown that the young men generally gave correct information on their drug use,[29] suggesting that the material is valid for epidemiological analysis. Because this study only included men in Sweden born around 1950, the generalizability is limited. There are studies suggesting that some ethnic groups may face higher risks of stroke,[30] but whether this in turn would affect an association between cannabis and stroke is uncertain. Also,

a meta-analysis by Peters et al,[31] reported no sex differences in the relationship between tobacco smoking and stroke, indicating that our results may hold for women as well.

The strengths of our study include a large population-based cohort of 45 081 men and the long-term follow-up, enabling the analyses of stroke from early adulthood to middle age. The Swedish conscript survey is the longest follow-up to date of participants with baseline data about cannabis use. Additionally, we had information on several potential confounders known to be of importance. The follow-up data were obtained by record linkage covering all public inpatient care in Sweden from 1987 onwards. As the incidence of strokes before age ≈ 36 to 37 years is low, few cases of stroke could be missed because of a lack of coverage.

Conclusions

Previous studies on cannabis and stroke are mainly clinical, retrospective, and cross-sectional. We have expanded current knowledge by examining cannabis use in young adulthood in relation to the subsequent risk of stroke in a large population-based cohort. We found no evident association between cannabis use and stroke, including stroke before 45 years of age. Tobacco smoking, however, showed a clear, dose–response shaped association with stroke across multivariable models.

Sources of Funding

This study was supported by grants provided by the Research Council for Health, Working Life and Welfare (Forte 2014-0691). The funding source had no role in designing and executing the study.

Disclosures

None.

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Stroke. 2017;48:265-270; originally published online December 27, 2016;
doi: 10.1161/STROKEAHA.116.015565
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628