REVIEW ARTICLE

Adv Psychiatry Neurol 2023; 32 (1): 31-39
DOI: https://doi.org/10.5114/ppn.2023.126482

ADVANCES IN PSYCHIATRY & NEUROLOGY
POSTĘPY Psychiatrii i Neurologii

Correspondence to:

Dr. Michał Błaż
Department of Neurology
The John Paul II Hospital
Krakow, Poland
e-mail: m.blaz@szpitaljp2.krakow.pl

Submitted: 19.01.2023
Accepted: 28.02.2023

Family history of stroke – a useful clue for the primary care physician and stroke neurologist: a narrative review

Michał Błaż[1], Iwona Sarzyńska-Długosz[2]

[1] Department of Neurology, The John Paul II Hospital, Krakow, Poland
[2] 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

Abstract

Purpose: The heritability of ischemic stroke is a complex mechanism, involving the contribution of genetic traits and environmental factors, which is why in everyday practice clinicians often rely on the broad term "family history of stroke", defined as the case of any first-degree relative who has had a stroke. The aim of this review is to update the available data regarding family history of stroke in primary and secondary stroke prevention by searching the electronic Scopus database for the phrase TITLE-ABS-KEY ("family history" AND "stroke").

Views: A total of 140 articles met the pre-specified criteria and were included in the review. The prevalence of family history of stroke ranged from 37% in stroke-free individuals to 52% in patients with ischemic stroke. In primary prevention, family history of stroke was associated with increased risk of stroke, transient ischemic attack, stroke risk factors and stroke-like symptoms. In patients with ischemic stroke, it was more often associated with small- and large-vessel disease, though not with a cardioembolic etiology. Family history of stroke did not influence long-term functional outcomes after rehabilitation. In young stroke victims, it was related to symptom severity and the risk of a second stroke.

Conclusions: Consideration of family history of stroke in everyday practice may carry useful information both for primary care physicians and stroke neurologists.

Key words: family history, stroke, risk factors, primary prevention, secondary prevention.

INTRODUCTION

The heritability of stroke assessed by genome-wide association studies is estimated to be 38% [1]. Contributing factors include: monogenic diseases predisposing a person to stroke (such as Fabry disease), single-nucleotide gene polymorphisms (SNPs) (such as the blood type gene *ABO* or forkhead transcription factor [*FOXF2*]) [2], and polygenic risk factors (such as hypertension), as well as environmental and lifestyle factors, which are often shared by family members. Due to the complex interactions between genetic traits and shared familial environments, it might be difficult to rely on specific gene identification to predict an individual's risk of stroke. Instead, the guidelines of the American Heart Academy/American Stroke Association suggest obtaining "family history of stroke (FHS)" as a way of identifying individuals at increased risk (Class IIa; Level of evidence A) [3]. The association of FHS with stroke risk is well established and has been studied systematically [4-6]; however, to our knowledge its link to risk factors and stroke outcomes has not been updated systematically since 2004.

The purpose of this paper is to review the available data regarding family history of stroke. We will focus separately on information that is useful in primary and secondary stroke prevention. This review will not encompass monogenic disorders and SNPs predisposing to stroke, which have been broadly covered elsewhere [1, 2].

METHODS

We conducted this systematic review according to the PRISMA guidelines [7]. We searched the Scopus database up to 31st October 2022 for the phrase TITLE-ABS-KEY ("family history" AND "stroke"). Titles and abstracts were screened by one of the authors using the following criteria: observational studies or systematic reviews/meta-analyses, manuscript in English, definition of FHS as any first-degree relative who suffered from ischemic or hemorrhagic stroke at any age, clear report of association of FHS with the risk of stroke, stroke risk factors, and outcomes after stroke treatment. We excluded case reports, narrative reviews and studies relating to carotid artery

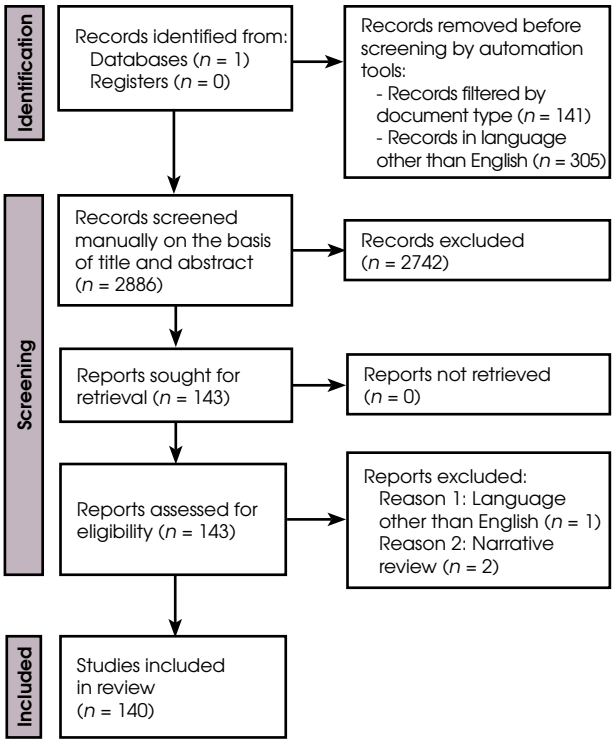

Figure I. Study identification protocol

dissection, subarachnoid hemorrhage or specific genetic stroke etiologies such as moyamoya disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), or mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS). Details on article selection are presented in Figure I.

RESULTS

A total of 140 articles met the pre-specified criteria and were included in the review. The most important associations are shown in Tables 1 and 2.

Family history of stroke in primary stroke prevention

The prevalence of family history of stroke in the stroke-free population reported in the literature ranged from 16% to 37% [8-13]. In 15-30% of the cases the relative who suffered from stroke was a sibling, otherwise one of the parents [8, 9, 14]. Information about the geographical distribution of FHS was available for Europe and it was found to be more prevalent in southern than central and northern parts of the continent [13].

Table 1. Associations of family history of stroke (FHS) in primary prevention

Parameter	Publications	Correlation
Stroke	(15-43)	FHS increases the risk of stroke by 30%.
TIA	(8, 69, 70)	FHS increases the risk of TIA, however, it does not predict the risk of stroke after TIA.
Hypertension	(8, 9, 15, 45, 55-58)	FHS is associated with increased prevalence of hypertension.
Atrial fibrillation	(8)	FHS was more prevalent in women with atrial fibrillation.
Diabetes mellitus	(8, 61, 65)	One study indicated a positive association of diabetes and FHS (8), other did not (61, 65).
Obesity	(8, 9, 59-61, 66)	There are studies showing positive (59, 60, 66), neutral (9, 61) and inverse (8) relationship of FHS and obesity.
Hypercholesterolemia	(9, 59-63)	FHS is associated with hypercholesterolemia.
Smoking	(9, 18, 61, 65, 67)	In several studies FHS was associated with smoking (18, 65, 67), however other authors did not confirm this (9, 61, 68).

Table 2. Associations of family history of stroke (FHS) in secondary prevention

Parameter	Publications	Correlation
Treatment outcomes	(78)	No difference in treatment outcomes in patients with and without FHS.
Second stroke	(41, 77, 78, 87-92)	FHS increased the overall risk of second stroke according to some (41, 87-90), but not other authors (77, 91-92), whereas one study confirmed this association only in subgroups (78).
Death	(11, 77, 91, 94-97)	One study showed increased mortality among patients with FHS (94), three studies confirmed it in subgroups (77, 95), others did not show this association (91, 96-97).
Physical disability	(80, 81, 139-141)	FHS was associated with improved short-term (80, 139), but not long-term physical rehabilitation outcomes (140, 141).
Cognitive and mental health	(142, 143)	FHS was a risk factor for post-stroke depression (142) and vascular dementia (143).
Etiology and risk factors	(45, 80, 82, 98, 104-117)	FHS was consistently associated with small vessel disease (80, 82, 104-108) and large vessel disease (80, 98, 105-108), but not with cardioembolic etiology (45, 116, 117).

The risk of stroke

According to the seminal systematic review from 2004 [4], the family history of stroke at any age increased a proband's stroke risk by 30% in prospective studies and 70% in case-control studies. However, when only high-quality case-control studies were included, the risk of stroke was similar to prospective cohorts (28%). Authors of studies not included or published after the completion of this systematic review also consistently reported increased risk of stroke in probands with FHS [15-43], except one [44]. Another large systematic review conducted in 2019 found that all types of FHS increase the risk of stroke – paternal by 40%, maternal by 36%, and sibling by 44% [5]. The risk increased with the number of relatives who had suffered strokes [10]. Other inferences regarding the association of FHS and the risk of stroke can be drawn from single studies. Some authors argued that FHS predisposes an individual to stroke at a younger age [31, 45-49], even in children [50], whereas others found the opposite [51]. Among patients with AF, having a sibling who has had an ischemic stroke increased the risk of stroke and all-cause mortality [52]. Family history of stroke was also associated with a higher calculated risk of stroke as determined by the ASA Risk Score [53], but not with the LS7 score [9].

Interaction with stroke risk factors

Generally, subjects with FHS were shown to accumulate risk factors over time [54]. The most frequently reported of these in subjects with FHS was hypertension [8, 9, 15, 45, 55-58]. This association was supported by evidence of aggregation of stroke and hypertension in families [12]. The second most consistently reported risk factor associated with FHS was hypercholesterolemia [9, 59-63]. In conjunction with a lack of physical exercise, it was shown to display additive interactions with FHS on stroke [64]. One study found a greater prevalence of FHS among women with atrial fibrillation [8]. Data on diabetes mellitus [8, 61, 65] and obesity [8, 59-61, 66] were conflicting. Similarly, in several studies FHS was associated with smoking [26, 65, 67], though other authors did not confirm this [9, 61, 68]. Apparently, subjects with positive FHS more often experienced transient ischemic attack (TIA) [8, 69]; however, in a prospective study the presence of FHS did not predict stroke after TIA [70]. In stroke- and TIA-free individuals FHS was linked to a greater prevalence of self-reported stroke symptoms in anamnesis [8] and increased anxiety [71]. Subjects with FHS were found to have higher blood levels of factor VII:C [72], homocysteine [73], C-reactive protein, insulin and diagnosed insulin resistance [63], as well as higher brachial-ankle pulse wave velocity, indicating arterial stiffness [74]. According to one study, stroke-free subjects with FHS more often had significant carotid artery stenosis [75], which however was not confirmed by other authors [76].

Family history of stroke in secondary stroke prevention

The prevalence of family history of stroke among patients with ischemic stroke ranged from 12 to 52% [4, 77-86]. It was more common in younger stroke probands [82] and in females, probably due to a more common maternal history of stroke [6]. Compared to the stroke-free group, a greater contribution of family history of stroke in siblings was noted (up to 45%) [79].

The risk of second stroke or death

Several papers postulated that FHS increases the overall risk of second stroke [41, 87-90], three authors did not confirm this [77, 91, 92], and others suggested it might hold true for younger patients and those with siblings who had suffered strokes [78]. The latter subgroup was also found to experience more severe stroke symptoms [93]. One meta-analysis found a greater risk of stroke mortality in all patients with FHS [94]; three studies confirmed this in subgroups: younger age [77, 95] and with parental FHS [11, 77]; three studies did not show any association of FHS with mortality [91, 96, 97].

Type of stroke, etiology, and interaction with risk factors

Most studies investigated the family history of stroke in survivors of ischemic stroke (or both ischemic and hemorrhagic stroke). Four papers specifically showed a higher prevalence of FHS in patients with hemorrhagic stroke [98-101] and one study did not find this association [102]. Notably, in a head-to-head comparison, FHS was more common among survivors of ischemic stroke than hemorrhagic [103].

With regards to stroke etiology, authors consistently reported an association of FHS with small vessel disease [80, 82, 104-108], subclinical lacunes [109, 110], intracranial artery stenosis [111-115] and large vessel disease [80, 98, 105-108], but not with cardioembolic stroke [45, 116, 117]. One paper found that FHS was related to lacunar stroke in older subjects and cryptogenic etiology in the younger [118]. Only one did not find any association of FHS with stroke subtype [119]. Similarly to primary prevention cohorts, it has been found that family history of stroke is associated with an increased prevalence of risk factors such as hypertension, diabetes mellitus and smoking [120-124].

Secondary prevention

FHS was related to increased intima-media thickening in young stroke victims [125], left ventricular hyper-

trophy [126], serum triglyceride [127] and lipoprotein (a) levels [128, 129], vitamin D deficiency [130], but not with inflammatory markers [131], homocysteinemia [132] or uricemia [133]. Subjects with FHS had negative screening results for thrombophilia [134, 135]. Importantly, the presence of FHS was associated with increased risk of a cardiovascular event after carotid artery stenting in patients > 70 years of age [136] and restenosis [137] or ischemic events [138] after carotid endarterectomy.

Rehabilitation outcomes

Data regarding the association of FHS with rehabilitation outcomes are conflicting. Some authors demonstrated improved short-term outcomes based on crude indices, such as modified Rankin scale and "discharge to home" [80, 139], whereas others found the opposite [81]. Using more complex functional measures in stroke patients at discharge from a rehabilitation unit, no difference was found between patients with positive and negative FHS [140, 141]. However, FHS was a risk factor for post-stroke depression [142] and vascular dementia [143].

Future perspectives

Recently, Hammerle *et al.* [144] introduced a "family risk score", which is based on information about family history of stroke weighted for disease onset and number of relatives. They demonstrated that it outperformed simple measures and was associated with increased risk of stroke independently from other risk factors or risk scores based on single-nucleotide polymorphisms (so-called "polygenic risk scores" [145, 146]). It seems that developing easy-to-administer scores combining information about family history of stroke and genetic investigations might increase predictive power in identifying individuals at increased risk of stroke.

Limitations of the studies analyzed

Among the studies analyzed there were only four systematic reviews with meta-analyses; otherwise they were single observational studies, among which there was substantial heterogeneity [4]. Most of the studies defined FHS as family history of total stroke, without separating the ischemic from the hemorrhagic type. Additionally, FHS was most often self-reported; however, this has been shown to be a reliable measure of the incidence of stroke [147].

CONCLUSIONS

A positive family history of stroke is associated with a greater prevalence of risk factors for stroke and increased risk of first-time TIA and stroke. In ischemic stroke patients this might indicate a non-cardioembolic etiology and increased risk of revascularization procedures. An association of FHS with the risk of second stroke, mortality or rehabilitation outcomes are debated. As such, information about family history of stroke may prove useful both for primary care physicians and stroke neurologists in everyday clinical practice.

Conflict of interest

Absent.

Financial support

Absent.

References

1. Bevan S, Traylor M, Adib-Samii P, Malik R, Paul NLM, Jackson C, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genomewide associations. Stroke 2012; 43: 3161-3167.
2. Boehme AK, Esenwa C, Elkind MSV. Stroke risk factors, genetics, and prevention. Circ Res 2017; 120: 472-495.
3. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45: 3754-3832.
4. Flossmann E, Schulz UGR, Rothwell PM. Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke. Stroke 2004; 35: 212-227.
5. Yu S, Su Z, Miao J, Yu Y, Zhang S, Wu J, et al. Different types of family history of stroke and stroke risk: results based on 655,552 individuals. J Stroke Cerebrovasc Dis 2019; 28: 587-594.
6. Touzé E, Rothwell PM. Sex differences in heritability of ischemic stroke: a systematic review and meta-analysis. Stroke 2008; 39: 16-23.

7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. DOI: 10.1136/bmj.n71.
8. Błaż M, Banaszkiewicz K, Michalski M, Sarzyńska-Długosz I, Plens K, Undas A. Family history of stroke is associated with greater prevalence of certain risk factors and self-reported stroke symptoms. J Stroke Cerebrovasc Dis 2021; 30: 106074. DOI: 10.1016/j.jstrokecerebrovasdis.2021.106074.
9. Kulshreshtha A, Vaccarino V, Goyal A, McClellan W, Nahab F, Howard VJ, et al. Family history of stroke and cardiovascular health in a national cohort. J Stroke Cerebrovasc Dis 2015; 24: 447-454.
10. Tian T, Jin G, Yu C, Lv J, Guo Y, Bian Z, et al. Family history and stroke risk in China: evidence from a large cohort study. J Stroke 2017; 19: 188-195.
11. Eguchi E, Iso H, Wada Y, Kikuchi S, Watanabe Y, Tamakoshi A. Parental history and lifestyle behaviors in relation to mortality from stroke among Japanese men and women: the Japan Collaborative Cohort Study. J Epidemiol 2012; 22: 331-339.
12. Kondo T, Toyoshima H, Tsuzuki Y, Hori Y, Yatsuya H, Tamakoshi K, et al. Familial aggregation and coaggregation of history of hypertension and stroke. J Hum Hypertens 2005; 19: 119-125.
13. Putaala J, Yesilot N, Waje-Andreassen U, Pitkäniemi J, Vassilopoulou S, Nardi K, et al. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke. Stroke 2012; 43: 2624-2630.
14. Yanez ND, Burke GL, Manolio T, Gardin JM, Polak J. Sibling history of myocardial infarction or stroke and risk of cardiovascular disease in the elderly: the Cardiovascular Health Study. Ann Epidemiol 2009; 19: 858-866.
15. Mvundura M, McGruder H, Khoury MJ, Valdez R, Yoon PW. Family history as a risk factor for early-onset stroke/transient ischemic attack among adults in the United States. Public Health Genomics 2010; 13: 13-20.
16. Kodali NK, Bhat LD. Prevalence and associated factors of stroke among older adults in India: analysis of the longitudinal aging study in India – wave 1, 2017-2018. Indian J Public Health 2022; 66: 128-135.
17. Wang J, Wen X, Li W, Li X, Wang Y, Lu W. Risk factors for stroke in the Chinese population: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2017; 26: 509-517.
18. Alvarez J, Matias-Guiu J, Sumalla J, Molins M, Insa R, Moltó JM, et al. Ischemic stroke in young adults. I. Analysis of the etiological subgroups. Acta Neurol Scand 1989; 80: 28-34.
19. Gan Y, Wu J, Zhang S, Li L, Yin X, Gong Y, et al. Prevalence and risk factors associated with stroke in middle-aged and older Chinese: a community-based cross-sectional study. Sci Rep 2017; 7: 9501. DOI: 10.1038/s41598-017-09849-z.
20. Yi X, Luo H, Zhou J, Yu M, Chen X, Tan L, et al. Prevalence of stroke and stroke related risk factors: a population based cross sectional survey in southwestern China. BMC Neurol 2020; 20: 5. DOI: 10.1186/s12883-019-1592-z.
21. Ganguly SS, Gujjar AR, Al Harthi H, Al Hashmi A, Jaju S, Al-Mahrezi A, et al. Risk factors for ischaemic stroke in an Omani community: a case-control study. Sultan Qaboos Univ Med J 2021; 21: 585-590.
22. Chen J, Zhu Q, Yu L, Li Y, Jia S, Zhang J. Stroke risk factors of stroke patients in China: a nationwide community-based cross-sectional study. Int J Environ Res Public Health 2022; 19: 4807. DOI: 10.3390/ijerph19084807.
23. Yi X, Chen H, Wang Y, Yu M, Luo H, Wang C, et al. Prevalence and risk factors of high-risk population for stroke: a population-based cross-sectional survey in southwestern China. Front Neurol 2022; 13: 693894. DOI: 10.3389/fneur.2022.693894.
24. He C, Wang W, Chen Q, Shen Z, Pan E, Sun Z, et al. Factors associated with stroke among patients with type 2 diabetes mellitus in China: a propensity score matched study. Acta Diabetol 2021; 58: 1513-1523.
25. Alhazzani AA, Mahfouz AA, Abolyazid AY, Awadalla NJ. Risk factors of the first-time stroke in the southwest of Saudi Arabia: a case-control study. Brain Sci 2021; 11: 222. DOI: 10.3390/brainsci11020222.
26. Syarfaini, Nildawati, Aeni S, Surahmawati, Adha AS, Amansyah M. Risk factors preparation of stroke incidence in health institution employees who check up at the Health Service EXPO Event Indonesia. Gac Sanit 2021; 35 Suppl 1: S49-S52.
27. Adoukonou T, Yahouédéou B, Agbétou M, Hountada H, Choki B, Kossi O, et al. Prevalence of stroke survivors in Parakou in northern Benin: a door-to-door community survey. Rev Neurol (Paris) 2020; 176: 839-845.
28. Ma Z, Yue Y, Luo Y, Wang W, Cao Y, Fang Q. Clinical utility of the inflammatory factors combined with lipid markers in the diagnostic and prognostic assessment of ischemic stroke: based on logistic regression models. J Stroke Cerebrovasc Dis 2020; 29: 104653. DOI: 10.1016/j.jstrokecerebrovasdis.2020.104653.
29. Li Y, Zhang X, Sang H, Niu X, Liu T, Liu W, et al. Urban-rural differences in risk factors for ischemic stroke in northern China. Medicine (Baltimore) 2019; 98: e15782. DOI: 10.1097/MD.0000000000015782.
30. Ali I, Abuissa M, Alawneh A, Subeh O, Abu Sneineh A, Mousa S, et al. The prevalence of dyslipidemia and hyperglycemia among stroke patients: preliminary findings. Stroke Res Treat 2019; 2019: 8194960. DOI: 10.1155/2019/8194960.
31. Zhang S, Liu Z, Liu YL, Wang YL, Liu T, Cui XB. Prevalence of stroke and associated risk factors among middle-aged and older farmers in western China. Environ Health Prev Med 2017; 22: 6. DOI: 10.1186/s12199-017-0621-z.
32. Wu Y, Zhang L, Yuan X, Wu Y, Yi D. Quantifying links between stroke and risk factors: a study on individual health risk appraisal of stroke in a community of Chongqing. Neurol Sci 2011; 32: 211-219.
33. Seshadri S, Beiser A, Pikula A, Himali JJ, Kelly-Hayes M, Debette S, et al. Parental occurrence of stroke and risk of stroke in their children: the Framingham study. Circulation 2010; 121: 1304-1312.
34. Al-Rajeh S, Larbi EB, Bademosi O, Awada A, Yousef A, Al-Freihi H, et al. Stroke register: experience from the eastern province of Saudi Arabia. Cerebrovasc Dis 1998; 8: 86-89.
35. Lee TH, Hsu WC, Chen CJ, Chen ST. Etiologic study of young ischemic stroke in Taiwan. Stroke 2002; 33: 1950-1955.
36. Sadeq A, Baraka MA, Hamrouni A, Elnour AA. Retrospective cohort study on risk factors for developing ischemic stroke. Pharm Pract (Granada) 2022; 20: 2682. DOI: 10.18549/PharmPract.2022.3.2682.

37. Doborjeh M, Doborjeh Z, Merkin A, Krishnamurthi R, Enayatollahi R, Feigin V, et al. Personalized spiking neural network models of clinical and environmental factors to predict stroke. Cognit Comput 2022; 14: 2187-2202.
38. de Almeida Rocha LJ, da Silva KA, de Lima Chagas A, de Oliveira Veras A, Souto VGL, Valente MCMB, et al. Stroke in the state of Alagoas, Brazil: a descriptive analysis of a northeastern scenario. Arq Neuropsiquiatr 2022; 80: 550-556.
39. Yang Y, Yang Y, Jin G, Yang Y, Chen L, Jiang Z, et al. The prevalence of stroke and related risk factors among residents aged ≥ 40 years in Chongqing, Southwest China. J Public Health (Bangkok) 2021; 29: 1423-1432.
40. Deoke A, Deoke S, Saoji A, Hajare S. Profile of modifiable and non-modifiable risk factors in stroke in a rural based tertiary care hospital – a case control study. Glob J Health Sci 2012; 4: 158-163.
41. Zhang W, Chen Y, Liu P, Chen J, Song L, Tang Y, et al. Variants on chromosome 9p21.3 correlated with ANRIL expression contribute to stroke risk and recurrence in a large prospective stroke population. Stroke 2012; 43: 14-21.
42. Yokoyama H, Kawai K, Ohishi M, Sone H. Familial predisposition to cardiovascular risk and disease contributes to cardiovascular risk and disease interacting with other cardiovascular risk factors in diabetes – implication for common soil (JDDM 14). Atherosclerosis 2008; 201: 332-338.
43. Jungehülsing GJ, Müller-Nordhorn J, Nolte CH, Roll S, Rossnagel K, Reich A, et al. Prevalence of stroke and stroke symptoms: a population-based survey of 28,090 participants. Neuroepidemiology 2008; 30: 51-57.
44. Harmsen P, Lappas G, Rosengren A, Wilhelmsen L. Long-term risk factors for stroke. Stroke 2006; 37: 1663-1667.
45. Schulz UGR, Flossmann E, Rothwell PM. Heritability of ischemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies. Stroke 2004; 35: 819-824.
46. Lutski M, Zucker I, Shohat T, Tanne D. Characteristics and outcomes of young patients with first-ever ischemic stroke compared to older patients: the National Acute Stroke ISraeli Registry. Front Neurol 2017; 8: 421. DOI: 10.3389/fneur.2017.00421.
47. MacClellan LR, Mitchell BD, Cole JW, Wozniak MA, Stern BJ, Giles WH, et al. Familial aggregation of ischemic stroke in young women: the Stroke Prevention in Young Women Study. Genet Epidemiol 2006; 30: 602-608.
48. Kivioja R, Pietilä A, Martinez-Majander N, Gordin D, Havulinna AS, Salomaa V, et al. Risk factors for early-onset ischemic stroke: a case-control study. J Am Heart Assoc 2018; 7: e009774. DOI: 10.1161/JAHA.118.009774.
49. Bandasak R, Narksawat K, Tangkanakul C, Chinvarun Y, Siri S. Association between hypertension and stroke among young Thai adults in Bangkok, Thailand. Southeast Asian J Trop Med Public Health 2011; 42: 1241-1248.
50. Bigi S, Fischer U, Wehrli E, Mattle HP, Boltshauser E, Bürki S, et al. Acute ischemic stroke in children versus young adults. Ann Neurol 2011; 70: 245-254.
51. Meschia JF, Atkinson EJ, O'Brien PC, Brott TG, Brown RDJ, Hardy J. Familial clustering of stroke according to proband age at onset of presenting ischemic stroke. Stroke 2003; 34: e89-e91. DOI: 10.1161/01.STR.0000078312.07274.A4.
52. Berntsson J, Li X, Zöller B, Martinsson A, Andell P, Lubitz SA, et al. Risk of stroke in patients with atrial fibrillation is associated with stroke in siblings: a nationwide study. J Am Heart Assoc 2020; 9: e014132. DOI: 10.1161/JAHA.119.014132.
53. Claeys J, Gurvich O, Hadidi NN. Association between family history of stroke and stroke risk: a community survey. West J Nurs Res 2020; 42: 1174-1181.
54. Zhang P, Jin H, Guo ZN, Sun HJ, Zhang FL, Sun X, et al. The accumulation of key stroke risk factors and its association with the characteristics of subjects: a population based cross sectional study. Front Neurol 2018; 9: 949. DOI: 10.3389/fneur.2018.00949.
55. Aycock DM, Kirkendoll KD, Coleman KC, Clark PC, Albright KC, Alexandrov AW. Family history of stroke among African Americans and its association with risk factors, knowledge, perceptions, and exercise. J Cardiovasc Nurs 2015; 30: E1-E6. DOI: 10.1097/JCN.0000000000000125.
56. Flossmann E, Rothwell PM. Family history of stroke in patients with transient ischemic attack in relation to hypertension and other intermediate phenotypes. Stroke 2005; 36: 830-835.
57. Zhang Y, Yang H, Ren M, Wang R, Zhao F, Liu T, et al. Distribution of risk factors of hypertension patients in different age groups in Tianjin. BMC Public Health 2021; 21: 247. DOI: 10.1186/s12889-021-10250-9.
58. Li A, Ji Y, Zhu S, Hu Z, Xu X, Wang Y, et al. Risk probability and influencing factors of stroke in followed-up hypertension patients. BMC Cardiovasc Disord 2022; 22: 328. DOI: 10.1186/s12872-022-02780-w.
59. Mierzecki A, Bukowska H, Kłoda K, Chełstowski K, Gorący I, Naruszewicz M. Homocysteine and metabolic risk factors in individuals with family history of premature ischemic stroke. Pol Arch Med Wewn 2013; 123: 282-288.
60. van der Sande MA, Walraven GE, Milligan PJ, Banya WA, Ceesay SM, Nyan OA, et al. Family history: an opportunity for early interventions and improved control of hypertension, obesity and diabetes. Bull World Health Organ 2001; 79: 321-328.
61. Wannamethee SG, Shaper AG, Ebrahim S. History of parental death from stroke or heart trouble and the risk of stroke in middle-aged men. Stroke 1996; 27: 1492-1498.
62. Morrison AC, Fornage M, Liao D, Boerwinkle E. Parental history of stroke predicts subclinical but not clinical stroke. Stroke 2000; 31: 2098-2102.
63. Srilatha K, Bobby Z, Subrahmanyam DK, NithinKumar U. Insulin resistance and elevated C-reactive protein among first-degree relatives of ischemic stroke patients. Diabetes Metab Syndr 2017; 11 Suppl 2: S873-S878.
64. Liu J, Chen Y, Jin C, Chen D, Gao G, Li F. Analysis of prevalence and influencing factors of stroke in elderly hypertensive patients: based on the screening plan for the high-risk population of stroke in Jiading District, Shanghai. PLoS One 2021; 16: e0255279. DOI: 10.1371/journal.pone.0255279.
65. Liao D, Myers R, Hunt S, Shahar E, Paton C, Burke G, et al. Familial history of stroke and stroke risk. The Family Heart Study. Stroke 1997; 28: 1908-1912.

66. Mi D, Zhang L, Wang C, Liu L, Pu Y, Zhao X, et al. Impact of metabolic syndrome on the prognosis of ischemic stroke secondary to symptomatic intracranial atherosclerosis in Chinese patients. PLoS One 2012; 7: e51421. DOI: 10.1371/journal.pone.0051421.
67. Fan M, Lv J, Yu C, Guo Y, Bian Z, Yang S, et al. Family history, tobacco smoking, and risk of ischemic stroke. J Stroke 2019; 21: 175-183.
68. Gan Y, Wu J, Li L, Zhang S, Yang T, Tan S, et al. Association of smoking with risk of stroke in middle-aged and older Chinese: evidence from the China National Stroke Prevention Project. Medicine (Baltimore) 2018; 97: e13260. DOI: 10.1097/MD.0000000000013260.
69. Wang W, Sun P, Han F, Qu C. Sex differences in risk factors for transient ischemic attack in a Chinese population. Front Neurol 2021; 12: 615399. DOI: 10.3389/fneur.2021.615399.
70. Flossmann E, Rothwell PM. Family history of stroke does not predict risk of stroke after transient ischemic attack. Stroke 2006; 37: 544-546.
71. Reiner IC, Tibubos AN, Werner AM, Ernst M, Brähler E, Wiltink J, et al. The association of chronic anxiousness with cardiovascular disease and mortality in the community: results from the Gutenberg Health Study. Sci Rep 2020; 10: 12436. DOI: 10.1038/s41598-020-69427-8.
72. Lansbury AJ, Grant PJ, Catto AJ. Atherothrombotic risk factors in subjects with a family history of stroke. Cerebrovasc Dis 2002; 14: 153-160.
73. Kim HJ, Kim MK, Kim JU, Ha HY, Choi BY. Major determinants of serum homocysteine concentrations in a Korean population. J Korean Med Sci 2010; 25: 509-516.
74. Uemura H, Katsuura-Kamano S, Yamaguchi M, Nakamoto M, Hiyoshi M, Arisawa K. Family history of stroke is potentially associated with arterial stiffness in the Japanese population. Arch Cardiovasc Dis 2014; 107: 654-663.
75. Khaleghi M, Isseh IN, Jouni H, Sohn S, Bailey KR, Kullo IJ. Family history as a risk factor for carotid artery stenosis. Stroke 2014; 45: 2252-2256.
76. Park JH, Razuk A, Saad PF, Telles GJP, Karakhanian WK, Fioranelli A, et al. Carotid stenosis: what is the high-risk population? Clinics 2012; 67: 865-870.
77. Zheng X, Zeng N, Wang A, Zhu Z, Peng H, Zhong C, et al. Family history of stroke and death or vascular events within one year after ischemic stroke. Neurol Res 2019; 41: 466-472.
78. Chung JW, Kim BJ, Han MK, Kang K, Park JM, Park SS, et al. Family history and risk of recurrent stroke. Stroke 2016; 47: 1990-1996.
79. Choi JC, Lee JS, Kang SY, Kang JH, Bae JM. Family history and risk for ischemic stroke: sibling history is more strongly correlated with the disease than parental history. J Neurol Sci 2009; 284: 29-32.
80. Jood K, Ladenvall C, Rosengren A, Blomstrand C, Jern C. Family history in ischemic stroke before 70 years of age: the Sahlgrenska Academy Study on Ischemic Stroke. Stroke 2005; 36: 1383-1387.
81. Lisabeth LD, Smith MA, Brown DL, Uchino K, Morgenstern LB. Family history and stroke outcome in a bi-ethnic, population-based stroke surveillance study. BMC Neurol 2005; 5: 20. DOI: 10.1186/1471-2377-5-20.
82. Knottnerus ILH, Gielen M, Lodder J, Rouhl RPW, Staals J, Vlietinck R, et al. Family history of stroke is an independent risk factor for lacunar stroke subtype with asymptomatic lacunar infarcts at younger ages. Stroke 2011; 42: 1196-1200.
83. Touzé E, Rothwell PM. Heritability of ischaemic stroke in women compared with men: a genetic epidemiological study. Lancet Neurol 2007; 6: 125-133.
84. Lindgren A, Lovkvist H, Hallstrom B, Hoglund P, Jonsson AC, Kristoffersson U, et al. Prevalence of stroke and vascular risk factors among first-degree relatives of stroke patients and control subjects. A prospective consecutive study. Cerebrovasc Dis 2005; 20: 381-387.
85. Ilinca A, Kristoffersson U, Soller M, Lindgren AG. Familial aggregation of stroke amongst young patients in Lund Stroke Register. Eur J Neurol 2016; 23: 401-407.
86. Shah SMA, Shah SMS, Khan S, Rehman SU, Khan ZA, Ahmed W, et al. "Addressing the impact of stroke risk factors in a case control study in tertiary care hospitals": a case control study in Tertiary Care Hospitals of Peshawar, Khyber Phukhtoonkhwa (KPK) Pakistan. BMC Res Notes 2013; 6: 268. DOI: 10.1186/1756-0500-6-268.
87. Zhang X, Cheng S, Gu H, Jiang Y, Li H, Li Z, et al. Family history is related to high risk of recurrent events after ischemic stroke or transient ischemic attack. J Stroke Cerebrovasc Dis 2022; 31: 106151. DOI: 10.1016/j.jstrokecerebrovasdis.2021.106151.
88. Zhuo Y, Wu J, Qu Y, Yu H, Huang X, Zee B, et al. Clinical risk factors associated with recurrence of ischemic stroke within two years: a cohort study. Medicine (Baltimore) 2020; 99: e20830. DOI: 10.1097/MD.0000000000020830.
89. Omori T, Kawagoe M, Moriyama M, Yasuda T, Ito Y, Hyakuta T, et al. Multifactorial analysis of factors affecting recurrence of stroke in Japan. Asia Pac J Public Health 2015; 27: NP333-NP340.
90. Wang Y, Zhao X, Jiang Y, Li H, Wang L, Johnston SC, et al. Prevalence, knowledge, and treatment of transient ischemic attacks in China. Neurology 2015; 84: 2354-2361.
91. Wang XG, Wang CX, Yang HJ, Wang AX, Li D, Zheng HG, et al. Lack of association between family history of stroke and 1-year outcomes after acute ischemic stroke in Chinese. CNS Neurosci Ther 2013; 19: 845-846.
92. Gao Y, Xie YM, Cai YF, Shen XM, Zhao DX, Xie YZ, et al. Risk factors associated with recurrence within 90 days of ischemic stroke onset in Chinese medicine hospital: a national cross-sectional study in China. World J Tradit Chinese Med 2020; 6: 441-447.
93. Meschia JF, Case LD, Worrall BB, Brown RDJ, Brott TG, Frankel M, et al. Family history of stroke and severity of neurologic deficit after stroke. Neurology 2006; 67: 1396-1402.
94. Zhang Y, Yu H, Ke C, Sun Q. Systematic review and meta-analysis of various risk factors of death from emergency cerebrovascular diseases in the department of neurology. Ann Palliat Med 2021; 10: 10661-10673.

95. Pezzini A, Grassi M, Lodigiani C, Patella R, Gandolfo C, Zini A, et al. Determinants of premature familial arterial thrombosis in patients with juvenile ischaemic stroke. Thromb Haemost 2015; 113: 641-648.
96. Kadota A, Okamura T, Hozawa A, Kadowaki T, Murakami Y, Hayakawa T, et al. Relationships between family histories of stroke and of hypertension and stroke mortality: NIPPON DATA80, 1980-1999. Hypertens Res 2008; 31: 1525-1531.
97. Gharios C, Leblebjian M, Mora S, Blumenthal RS, Jaffa MA, Refaat MM. The association of cardiovascular mortality with a first-degree family member history of different cardiovascular diseases. J Geriatr Cardiol 2021; 18: 816-824.
98. Zhang W, Chen Y, Wang Y, Liu P, Zhang M, Zhang C, et al. Short telomere length in blood leucocytes contributes to the presence of atherothrombotic stroke and haemorrhagic stroke and risk of post-stroke death. Clin Sci (Lond) 2013; 125: 27-36.
99. Okada H, Horibe H, Yoshiyuki O, Hayakawa N, Aoki N. A prospective study of cerebrovascular disease in Japanese rural communities, Akabane and Asahi. Part 1: evaluation of risk factors in the occurrence of cerebral hemorrhage and thrombosis. Stroke 1976; 7: 599-607.
100. Kubota M, Yamaura A, Ono J, Itani T, Tachi N, Ueda K, et al. Is family history an independent risk factor for stroke? J Neurol Neurosurg Psychiatry 1997; 62: 66-70.
101. Kim H, Friedlander Y, Longstreth WTJ, Edwards KL, Schwartz SM, Siscovick DS. Family history as a risk factor for stroke in young women. Am J Prev Med 2004; 27: 391-396.
102. Zodpey SP, Tiwari RR, Kulkarni HR. Risk factors for haemorrhagic stroke: a case-control study. Public Health 2000; 114: 177-182.
103. Shams Vahdati S, Ala A, Mousavi Aghdas SA, Adib A, Mirza-Aghazadeh-Attari MAF. Association between the subtypes of stroke and the various risk factors of cerebrovascular accidents: a cross-sectional study. Eurasian J Med 2018; 50: 86-90.
104. Polychronopoulos P, Gioldasis G, Ellul J, Metallinos IC, Lekka NP, Paschalis C, et al. Family history of stroke in stroke types and subtypes. J Neurol Sci 2002; 195: 117-122.
105. Jerrard-Dunne P, Cloud G, Hassan A, Markus HS. Evaluating the genetic component of ischemic stroke subtypes: a family history study. Stroke 2003; 34: 1364-1369.
106. Bogousslavsky J, Castillo V, Kumral E, Henriques I, Melle GV. Stroke subtypes and hypertension. Primary hemorrhage vs infarction, large- vs small-artery disease. Arch Neurol 1996; 53: 265-269.
107. Dardick JM, Flomenbaum D, Labovitz DL, Cheng N, Liberman AL, Esenwa C. Associating cryptogenic ischemic stroke in the young with cardiovascular risk factor phenotypes. Sci Rep 2021; 11: 275.
108. Matias-Guiu J, Alvarez J, Insa R, Moltó JM, Martin R, Codina A, et al. Ischemic stroke in young adults. II. Analysis of risk factors in the etiological subgroups. Acta Neurol Scand 1990; 81: 314-317.
109. Giuli V De, Grassi M, Besana M, Zedde M, Zini A, Lodigiani C, et al. Subclinical vascular brain lesions in young adults with acute ischemic stroke. Stroke 2022; 53: 1190-1198.
110. Morrison JA, Horvitz R, Khoury P, Laskarzewski P, Gartside PS, Kelly K, et al. Parental history of coronary heart disease, hypertension, diabetes, and stroke: relationship to coronary heart disease risk factor variables in their adult children. Prev Med 1980; 9: 773-786.
111. Kamal AK, Rasheed A, Mehmood K, Murtaza M, Zaidi M, Khan M, et al. Frequency and determinants of intracranial atherosclerotic stroke in urban Pakistan. J Stroke Cerebrovasc Dis 2014; 23: 2174-2182.
112. Hua Y, Jia L, Xing Y, Hui P, Meng X, Yu D, et al. Distribution pattern of atherosclerotic stenosis in Chinese patients with stroke: a multicenter registry study. Aging Dis 2019; 10: 62-70.
113. Niu JW, Gao S, Cui LY, Peng B, Zhu YC, Ni J, et al. Intracranial atherosclerosis in Chinese young adult stroke patients. J Stroke Cerebrovasc Dis 2014; 23: 1519-1523.
114. Zhang J, Sang H, Zhang X, Fang Y, Niu X, Liu T, et al. Comparison of the characteristics and risk factors of carotid atherosclerosis in high stroke risk populations between urban and rural areas in North China. Front Neurol 2020; 11: 554778. DOI: 10.3389/fneur.2020.554778.
115. Kaul S, Alladi S, Mridula KR, Bandaru VCSS, Umamashesh M, Anjanikumar D, et al. Prevalence and risk factors of asymptomatic carotid artery stenosis in Indian population: an 8-year follow-up study. Neurol India 2017; 65: 279-285.
116. Johansson A, Drake I, Engström G, Acosta S. Modifiable and non-modifiable risk factors for atherothrombotic ischemic stroke among subjects in the Malmö diet and cancer study. Nutrients 2021; 13: 1952. DOI: 10.3390/nu 13061952.
117. Hsu WC, Chen ST, Wu YR, Chang HS, Lyu RK, Lo LS. The association of stroke and family history of stroke depends on its subtypes and gender: a family history study in Taiwan. Acta Neurol Taiwan 2009; 18: 161-169.
118. Turanjanin N, Jovicevic M, Bozic K, Zarkov M. Frequency of ischemic stroke subtypes in relation to risk factors for ischemic stroke. HealthMED 2012; 6: 3463-3468.
119. Thijs V, Grittner U, Dichgans M, Enzinger C, Fazekas F, Giese AK, et al. Family history in young patients with stroke. Stroke 2015; 46: 1975-1978.
120. Hassan A, Sham PC, Markus HS. Planning genetic studies in human stroke: sample size estimates based on family history data. Neurology 2002; 58: 1483-1488.
121. Caicoya M, Corrales C, Rodriguez T. Family history and stroke: a community case-control study in Asturias, Spain. J Epidemiol Biostat 1999; 4: 313-320.
122. Diaz JF, Hachinski VC, Pederson LL, Donald A. Aggregation of multiple risk factors for stroke in siblings of patients with brain infarction and transient ischemic attacks. Stroke 1986; 17: 1239-1242.

123. Graffagnino C, Gasecki AP, Doig GS, Hachinski VC. The importance of family history in cerebrovascular disease. Stroke 1994; 25: 1599-1604.
124. Vitullo F, Marchioli R, Di Mascio R, Cavasinni L, Pasquale AD, Tognoni G. Family history and socioeconomic factors as predictors of myocardial infarction, unstable angina and stroke in an Italian population. PROGETTO 3A Investigators. Eur J Epidemiol 1996; 12: 177-185.
125. Øygarden H, Fromm A, Sand KM, Kvistad CE, Eide GE, Thomassen L, et al. A family history of stroke is associated with increased intima-media thickness in young ischemic stroke – the Norwegian Stroke in the Young Study (NOR-SYS). PLoS One 2016; 11: e0159811. DOI: 10.1371/journal.pone.0159811.
126. Tentschert S, Greisenegger S, Wimmer R, Lang W, Lalouschek W. Association of parental history of stroke with clinical parameters in patients with ischemic stroke or transient ischemic attack. Stroke 2003; 34: 2114-2119.
127. Kim JY, Lee KJ, Kang J, Kim BJ, Han MK, Kang K, et al. Fasting and non-fasting triglycerides in patients with acute ischemic stroke. J Korean Med Sci 2022; 37: e100. DOI: 10.3346/jkms.2022.37.e100.
128. Torbus-Lisiecka B, Bukowska H, Jastrzebska M, Chelstowski K, Honczarenko K, Naruszewicz M. Lp(a), homocysteine and a family history of early ischemic cerebral stroke. Nutr Metab Cardiovasc Dis 2001; 11 Suppl 5: 52-59.
129. Woo J, Lam CWK. Association of serum lipoprotein(a) concentration with other cardiovascular risk factors in a Chinese population. J Clin Lab Anal 1991; 5: 335-339.
130. Faisal MS, Hayat W, Inayat A, Khalil KUR, Ishtiaq M. Association of vitamin D deficiency with stroke and its risk factors: in a teaching hospital, Peshawar. J Med Sci 2017; 25: 227-230.
131. Somani R, Grant PJ, Kain K, Catto AJ, Carter AM. Complement C3 and C-reactive protein are elevated in South Asians independent of a family history of stroke. Stroke 2006; 37: 2001-2006.
132. Kalita J, Kumar G, Bansal V, Misra UK. Relationship of homocysteine with other risk factors and outcome of ischemic stroke. Clin Neurol Neurosurg 2009; 111: 364-367.
133. Bhattacharyya S, Datta S, Bhattacherjee S. Evaluation of serum uric acid level among stroke patients in a tertiary care hospital of North Bengal, India. J Indian Acad Clin Med 2017; 18: 184-189.
134. Omran SS, Lerario MP, Gialdini G, Merkler AE, Moya A, Chen ML, et al. Clinical impact of thrombophilia screening in young adults with ischemic stroke. J Stroke Cerebrovasc Dis 2019; 28: 882-889.
135. Johal SC, Garg BP, Heiny ME, Williams LS, Saha C, Walsh LE, et al. Family history is a poor screen for prothrombotic genes in children with stroke. J Pediatr 2006; 148: 68-71.
136. Feng Y, Bai X, Li S, Zhu F, Wang Y, Chen Y, et al. Thirty-day outcome of carotid artery stenting in elderly patients: a single-center experience. World Neurosurg 2020; 138: e311-e316. DOI: 10.1016/j.wneu.2020.02.093.
137. Garzon-Muvdi T, Yang W, Rong X, Caplan JM, Ye X, Colby GP, et al. Restenosis after carotid endarterectomy: insight into risk factors and modification of postoperative management. World Neurosurg 2016; 89: 159-167.
138. Rong X, Yang W, Garzon-Muvdi T, Ye X, Caplan JM, Colby GP, et al. Risk factors associated with ipsilateral ischemic events following carotid endarterectomy for carotid artery stenosis. World Neurosurg 2016; 89: 611-619.
139. Stover Hertzberg V, Weiss P, Stern BJ, Frankel MR. Family history associated with improved functional outcome following ischemic stroke. Neuroepidemiology 2006; 27: 74-80.
140. Park HJ, Kim TU, Hyun JK, Kim JY. Family history and functional outcome in Korean stroke patients: a preliminary study. Ann Rehabil Med 2015; 39: 980-985.
141. Wang B, Guan TJ, You LL. Disability situation of patients with ischemic stroke and its influencing factors. Chinese Gen Pract 2016; 19: 216-219.
142. Hayee MA, Akhtar N, Haque A, Rabbani MG. Depression after stroke-analysis of 297 stroke patients. Bangladesh Med Res Counc Bull 2001; 27: 96-102.
143. Tu Q, Ding B, Yang X, Bai S, Tu J, Liu X, et al. The current situation on vascular cognitive impairment after ischemic stroke in Changsha. Arch Gerontol Geriatr 2014; 58: 236-247.
144. Hämmerle M, Forer L, Schönherr S, Peters A, Grallert H, Kronenberg F, et al. A family and a genome-wide polygenic risk score are independently associated with stroke in a population-based study. Stroke 2022; 53: 2331-2339.
145. Hachiya T, Kamatani Y, Takahashi A, Hata J, Furukawa R, Shiwa Y, et al. Genetic predisposition to ischemic stroke: a polygenic risk score. Stroke 2017; 48: 253-258.
146. Lu X, Niu X, Shen C, Liu F, Liu Z, Huang K, et al. Development and validation of a polygenic risk score for stroke in the Chinese population. Neurology 2021; 97: e619-e628. DOI: 10.1212/WNL.0000000000012263.
147. Øygarden H, Fromm A, Sand KM, Eide GE, Thomassen L, Naess H, et al. Can the cardiovascular family history reported by our patients be trusted? The Norwegian Stroke in the Young Study. Eur J Neurol 2016; 23: 154-159.