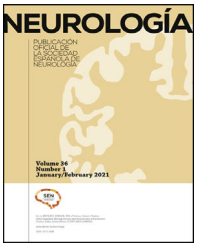
Neurología 39 (2024) 604—613

NEUROLOGÍA

www.elsevier.es/neurologia



ORIGINAL ARTICLE

Strength of association of classical vascular risk factors in young patients with ischaemic stroke: a case-control study

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Received 4 April 2022; accepted 24 July 2022
Available online 26 October 2022

KEYWORDS
Brain infarction;
Risk factors;
Stroke;
Middle-aged;
Young adult

Abstract
Introduction: Recent studies have reported an increasing incidence of ischaemic stroke among young adults. However, the strength of the association between traditional vascular risk factors has not been fully established.
Methods: We compared 120 patients with a first ischaemic stroke before the age of 55 years admitted to the stroke unit of our centre with 600 healthy non-stroke controls from a population-based cohort study (HERMEX), matched for sex. Risk factors assessed included: hypertension, obesity, auricular fibrillation, current smoking, estimated glomerular filtration rate (eGFR), total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C) and diabetes mellitus. We used logistic regression analysis and calculated population attributable risk. We performed an overall analysis, by sex and aetiological subgroup.
Results: Using logistic regression analysis, we found that overall, the significant risk factors were: hypertension (OR: 1.58; 95%CI: 1.01-2.50), atrial fibrillation (OR: 4.77; 95%CI: 1.20-19.00), low eGFR (OR: 4.74; 95%CI: 1.3-21.94) and low HDL-C (OR: 5.20; 95%CI: 3.29-8.21), as well as smoking for males (OR: 1.86; 95%CI: 1.14-3.03). LDL-C showed an inverse association with stroke. The population attributable risk for HDL-C was 37.8% and for hypertension 21.1%. In terms of aetiological subgroups, only low HDL-C was associated with stroke of undetermined aetiology.

DOI of refers to article: https://doi.org/10.1016/j.nrl.2022.07.006.
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https://doi.org/10.1016/j.nrleng.2022.07.006

Conclusions: Hypertension, auricular fibrillation, low eGFR, and low HDL-C, plus tobacco use in men, are the main risk factors among patients under 55 years of age with a first ischaemic stroke. We believe that it would be of particular interest to further explore the management of low HDL-C levels as part of preventive strategies in young stroke patients.

PALABRAS CLAVE
Ictus;
Infarto cerebral;
Factores de riesgo;
Edad media;
Adulto joven

Fuerza de asociación de factores de riesgo vascular clásicos en pacientes jóvenes con ictus isquémico: un estudio de casos y controles

Resumen
Introducción: Estudios recientes han informado una incidencia creciente del ictus isquémico entre adultos jóvenes. Sin embargo, la fuerza de la asociación entre los factores de riesgo vascular tradicionales no se ha establecido por completo.
Métodos: Comparamos a 120 pacientes con un primer ictus isquémico antes de los 55 años ingresados en la unidad de ictus de nuestro centro con 600 controles sanos sin ictus de un estudio de cohorte basado en la población (HERMEX), con emparejamiento según el sexo. Los factores de riesgo evaluados incluyeron: hipertensión, obesidad, fibrilación auricular, tabaquismo actual, tasa de filtración glomerular estimada (eGFR), colesterol total, colesterol de lipoproteínas de baja densidad (LDL-C), triglicéridos, colesterol de lipoproteínas de alta densidad (HDL-C) y diabetes mellitus. Utilizamos un análisis de regresión logística y calculamos el riesgo atribuible a la población. Realizamos un análisis global, por sexo y subgrupo etiológico.
Resultados: Mediante análisis de regresión logística comprobamos que globalmente los factores de riesgo significativos fueron: hipertensión (OR: 1,58; IC 95%: 1,01-2,50), la fibrilación auricular (OR: 4,77; IC 95%: 1,20-19,00), una eGFR baja (OR: 4,74; IC 95%: 1,3-21,94) y un HDL-C bajo (OR: 5,20; IC 95%: 3,29-8,21), así como el consumo de tabaco para los varones (OR: 1,86; IC 95%: 1,14-3,03). El LDL-C mostró una asociación inversa con el ictus. El riesgo atribuible a la población para el HDL-C fue del 37,8% y para la hipertensión del 21,1%. En cuanto a los subgrupos etiológicos, destaca que tan solo el HDL-C bajo se relaciona con el ictus de etiología indeterminada.
Conclusiones: La hipertensión, la fibrilación auricular, una eGFR baja y un HDL-C bajo, añadiendo el consumo de tabaco en varones, son los principales factores de riesgo entre los pacientes menores de 55 años con un primer ictus isquémico. Especial interés creemos que puede tener profundizar en el manejo de los niveles bajos de HDL-C dentro de las estrategias preventivas en pacientes jóvenes con ictus.

Introduction

Ischaemic stroke is much rarer in young adults than in older patients, although the underlying pathologies and risk factors are more diverse.[1] For this reason, the challenge in the diagnosis of cerebrovascular disease in young adults may be in differentiating it from stroke mimics and identifying the underlying cause or pathogenesis.[2]

Recent epidemiological studies suggest a significant upward trend in the incidence of ischaemic stroke in young adults.[3,4] In current series, approximately 10%-20% of all strokes occur in patients aged between 18 and 50 years.[5]

Traditional stroke risk factors, which are frequent among older adults (hypertension, dyslipidaemia, diabetes mellitus, smoking, and obesity), have been shown also to be common among younger patients with a first stroke.[6,7]

In these young patients with stroke, who seem to present a growing prevalence of traditional vascular risk factors,[8] it is debated whether these factors contribute to the cause of stroke and to what extent, especially in patients younger than 55 years.[8] However, there are also young patients presenting no classical risk factors, who may present other conditions with a weak or uncertain association with stroke. These diseases frequently represent a risk factor that may be strictly specific to young age.[9]

Their aetiological heterogeneity and the increased complexity of their classification suggest that the high prevalence of risk factors in young adults with ischaemic stroke does not translate into a high frequency of patients classified with typical causes of early-onset stroke.[10]

Differences are reported in the population attributable risk (PAR) of classical risk factors between young men and women with stroke; hypertension, diabetes, smoking, and alcohol consumption seem to be more prevalent in men, and sedentary lifestyle and obesity are more prevalent in women.[11]

The aim of this study was to determine the strength of association between 10 vascular risk factors and ischaemic stroke in young adults, stratifying the analysis by sex and the main stroke aetiologies.

Methods

We compared patients with a first ischaemic stroke before the age of 55 against a randomly selected sample of stroke-free controls or subjects with a symptomatic vascular disease from a population cohort study (Harmonizing Equations of Risk in Mediterranean Countries — Extremadura [HERMEX]).[12] This study was performed at the neurology department of Hospital Universitario de Badajoz and was approved by the hospital's ethics committee.

Population of cases

The stroke registry includes all patients younger than 55 years who were consecutively admitted in the last 2 years to our hospital's stroke unit with a diagnosis at discharge of first ischaemic stroke. Data on stroke risk factors were obtained from medical records and laboratory tests. Stroke subtypes were classified according to the modified criteria of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) study[13]: *1)* large-artery atherosclerosis, *2)* cardioembolism, *3)* small-vessel occlusion, and *4)* stroke of undetermined aetiology. Strokes meeting criteria for stroke of undetermined aetiology due to mixed causes, with one of these being a high-risk cardioembolic source, were classified as cardioembolic; and cases with other determined aetiology were classified as stroke of undetermined aetiology. All patients had undergone an exhaustive aetiological study, and a brain MRI study was performed during hospitalisation in all cases.

Informed consent was not necessary in this study, as it was based on hospital records.

Control population

The HERMEX project emerged from the need to generate information on the prevalence of risk factors and the frequency of cardiovascular disease onset in the population of Extremadura.[12] From a cohort of 2833 individuals aged between 25 and 79 years, we selected a random sample of 600 individuals aged between 25 and 55 years. Information on each individual was collected in an interview on their history of cardiovascular risk factors, pharmacological treatments received, and symptoms and history of cardiovascular disease, similarly to the methods of the MONICA project coordinated by the World Health Organization (WHO).[14]

We examined 10 well-established vascular risk factors, from which we extracted comparable variables: arterial hypertension, obesity, dyslipidaemia, diabetes, atrial fibrillation (AF), current smoking habit, estimated glomerular filtration rate (eGFR), high low-density lipoprotein cholesterol (LDL-C) level, low high-density lipoprotein cholesterol (HDL-C) level, and high triglyceride (TG) level.

Definition of risk factors

Hypertension was defined as treatment with antihypertensive drugs, previous diagnosis of hypertension, or diagnosis according to the 2003 WHO criteria (systolic arterial pressure $\geq$ 140 mm Hg or diastolic arterial pressure $\geq$ 90 mm Hg). Atrial fibrillation (AF) was defined as a diagnosis of AF or atrial flutter. Obesity was defined as a body mass index (BMI) $\geq$ 30, both in cases and in controls. In cases, current smoking was defined as smoking $\geq$ 1 cigarettes per day during the year prior to the stroke. Controls who currently smoked or had stopped smoking less than one year before inclusion in the HERMEX study were considered smokers. Diabetes mellitus in cases was defined as treated diabetes or history of diabetes before the stroke, with fasting plasma glucose levels $\geq$ 7 mmol/L (126 mg/dL) or a 2-hour oral glucose tolerance test results of $\geq$ 11.1 mmol/L (200 mg/dL), according to the data available in the medical records. In controls, diabetes was established in case of self-reported diagnosis in the questionnaire, diagnosis of diabetes in participants' medical records, or prescribed medication for diabetes due to a fasting plasma glucose level $\geq$ 7 mmol/L (126 mg/dL) or glycated haemoglobin values > 6.5%. The eGFR was calculated using the Modification of Diet in Renal Disease formula, and was considered low for values < 60 mL/min/1.73m^2. We defined the dichotomous variables of dyslipidaemia as high LDL-C ($\geq$ 116 mg/dL), low HDL-C (< 39 mg/dL), and high triglyceride levels ($\geq$ 177 mg/dL). An alternative dyslipidaemia variable was defined as treated dyslipidaemia, history of dyslipidaemia, or high total cholesterol level ($\geq$ 193 mg/dL). To measure lipid levels in cases, fasting blood samples were collected on the first working day after the stroke and were analysed at the hospital laboratory. Among controls, fasting blood samples were collected in medical check-up visits. The LDL-C level was calculated using the Friedenwald equation in all cases. If this equation could not be used due to very high triglyceride levels, the binary variable LDL-C was recorded as high.

Statistical analysis

Statistical analysis was conducted using SPSS version 22.0 for Mac. *P*-values < .05 were considered statistically significant.

First, we used the chi-square test and the Fisher exact test to compare groups. Prior to dichotomisation of the continuous variables (systolic and diastolic arterial pressure, LDL-C, HDL-C, TG, and eGFR), we confirmed that all these variables were normally distributed. To remove multicollinearity, we calculated variance inflation factors using a linear regression analysis and Cramer's V statistic for measuring association.

We calculated the univariate odds ratio (OR) for the 10 dichotomous risk factors. Subsequently, we introduced place, age, and each risk factor in a multivariate binary logistic regression model, for which we calculated adjusted OR and 95% confidence intervals. We used a backward stepwise logistic regression analysis with a statistical significance level of $P <$ .10.

We calculated PAR percentages from significant OR and 95% confidence interval values using the formula: prevalence of cases $\times$ [(OR $-$ 1)/OR] $\times$ 100.

In addition to the analysis of the whole study population, we conducted an analysis by sex and aetiology. In the analysis by specific aetiology, the whole control group was used as controls.

Results

We selected 159 patients from the stroke registry, and excluded 32 cases of haemorrhagic strokes, 6 cases of stroke mimics, and one patient who was younger than 25 years, as no control was available. Therefore, the study population in the univariate analysis included 120 cases aged between 26 and 54 years (34 women and 86 men) and 600 controls (170 women and 430 men); the case:control ratio for both sexes was 1:5. The mean age of cases was 46.8 (SD: 7.0) years, and controls were younger (42.4 [7.9]). Cases presented a mean of 1.8 (1.5) risk factors, whereas controls presented a mean of 1.4 (1.2); this was a significant difference ($P =$ .017).

In the study population, the risk factors analysed were more prevalent among cases than in controls, with the exception of dyslipidaemia, obesity, and high LDL-C level. In the multivariate logistic regression analysis, the risk factors with significant strength of association were low eGFR, AF, low HDL-C level, and hypertension. High

Table 1 Univariate and multivariate logistic regression analysis of risk factors for ischaemic stroke in young patients.

	Patients N = 120; n/N (%)	Controls N = 600; n/N (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	PAR (95% CI)
Hypertension	44/120 (36.7)	118/600 (19.7)	2.36 (1.55-3.61)	1.58 (1.01-2.50)	21.1 (10.3-32.0)
Obesity	25/120 (20.8)	182/600 (30.3)	0.60 (0.38-0.97)	0.53 (0.33-0.86)	−12.0 (−20.4 to 1.5)
Dyslipidaemia	26/120 (21.7)	162/600 (27.0)	0.75 (0.47-1.20)	0.56 (0.37-0.96)	−6.8 (−15.7 to 4.2)
Diabetes mellitus	16/120 (13.3)	34/600 (5.7)	2.56 (1.36-4.81)	1.76 (0.92-3.39)	8.1 (1.4-14.8)
Tobacco use	60/120 (50.0)	265/600 (44.2)	1.26 (0.85-1.87)	1.38 (0.91-2.07)	10.4 (−6.7 to 27.7)
Atrial fibrillation	5/120 (4.2)	4/596 (0.7)	6.48 (1.71-24.50)	4.77 (1.20-19.00)	4 (0.6-14.8)
eGFR (< 60)	4/120 (3.3)	3/600 (0.5)	6.86 (1.51-31.07)	4.74 (1.3-21.94)	2.8 (−1.8 to 7.4)
High LDL-C level	43/120 (35.8)	382/599 (63.8)	0.31 (0.21-0.48)	0.23 (0.15-0.36)	−43.5 (−51.8 to −31.9)
Low HDL-C level	49/120 (40.8)	69/599 (11.5)	5.30 (3.41-8.25)	5.20 (3.29-8.21)	37.8 (23.5-52.2)
High TG level	30/120 (25.0)	94/600 (15.7)	1.79 (1.12-2.86)	1.55 (0.96-2.51)	3.1 (−8.9 to 15.2)

* Adjustment for age and each risk factor was necessary for inclusion in the multivariate model. 95% CI: 95% confidence interval; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; n/N: number of subjects divided by the total number of subjects; OR: odds ratio; PAR: percentage of population-attributable risk; TG: triglycerides.

LDL-C level and obesity were inversely associated with ischaemic stroke (Table 1).

Regarding the risks attributable to the whole young population with stroke, we found higher percentages of attributable risk for low HDL-C level, followed by hypertension, smoking, diabetes, and AF, which together would explain more than 70% of all strokes (Table 1; Fig. 1).

In the sex-specific analysis (Table 2), hypertension, diabetes, and low HDL-C level were significantly associated with ischaemic stroke in both sexes. However, smoking, high TG levels, and AF were only identified as significant risk factors in men. Obesity and high LDL-C levels were inversely associated with stroke in men, with no such association in women.

In the analysis by aetiological subtype (Table 3), large artery atherosclerosis showed significant associations with hypertension, smoking, diabetes, low eGFR, and low HDL-C level. Cardioembolic aetiology was significantly associated with AF, hypertension, diabetes, low eGFR, low HDL-C level, and high TG level. For small-vessel disease, hypertension, smoking, diabetes, low HDL-C level, and high TG level were identified as risk factors. Only low HDL-C level showed a significant association as a risk factor in stroke of undetermined aetiology. In these 4 aetiological groups, high LDL-C level was inversely associated with stroke, although this association was not significant in the case of cardioembolic stroke. Due to the absence of cases with a positive risk factor, AF could not be analysed in subgroups other than the cardioembolic stroke group, and eGFR could not be analysed in the subgroup of lacunar infarcts (Fig. 2).

Discussion

Our study shows a strong association between stroke in young patients and hypertension, AF, low eGFR, and low HDL-C level, as well as smoking among men. Furthermore, we found differences in the risk profiles between aetiological subgroups. Interestingly, stroke of undetermined aetiology, the most prevalent subtype, was not significantly associated with any of these classical risk factors except for low HDL-C level; therefore, we should insist on the search for new risk factors that might help us to explain this type of stroke and design new prevention strategies.

Whereas the prevalence of certain risk factors has been decreasing in the general population, the prevalence of modifiable vascular risk factors (hypertension, smoking, or diabetes) is increasing among younger patients with stroke.[6,9,15]

Some studies show that young patients with stroke present approximately twice as many risk factors as their peers in the general population.[8] If the risk of cerebrovascular events increases in association with the number of risk factors, this may explain the observed increase in stroke prevalence[4]; however, this is still to be clarified.[16]

The data collected in large cohort studies that have reported on risk factors from a global perspective show that a small subset of risk factors explain a large proportion of strokes internationally.[17] We do not know whether these findings are applicable to young patients with stroke, as the analysis was not stratified by age. The INTERSTROKE study, in which only 11.8% of patients were younger than 45 years, only showed differences between patients younger and older than 55 years in some risk factors.[18] To date, few studies have analysed the strength of association between stroke in young patients and vascular risk factors.[8,11,19]

Hypertension

In our study, 36.7% of cases presented hypertension, a rate similar to the prevalence rates published by other studies.[11,15,20] The Stroke in Young Fabry Patients (SIFAP) study showed that hypertension was the most important individual risk factor for ischaemic stroke, with a PAR of 25.5%, showing a significant association with stroke in young adults (OR: 2.3; 95% CI: 2.0-2.6)[21]; these data are similar to ours. A recent Finnish study detected somewhat smaller differences (PAR of 12.2% and OR of 1.43 [95% CI: 1.71-1.75]).[19]

Obesity

Obesity is an independent vascular risk factor for stroke.[22,23] Obesity, defined as a body mass index higher than 30, has been observed in more than 10% of young adults who present stroke.[24] We detected a higher percentage in our study (20.8%), but did not observe a positive association with stroke. The SIFAP study found that abdominal obesity was one of the main risk factors in women with stroke.[21] The study by Aigner et al.[11] showed that obesity in young adults was associated with greater risk of stroke, with a PAR of 6.9% (OR: 1.2% 95% CI: 1.5-2.3).[11]

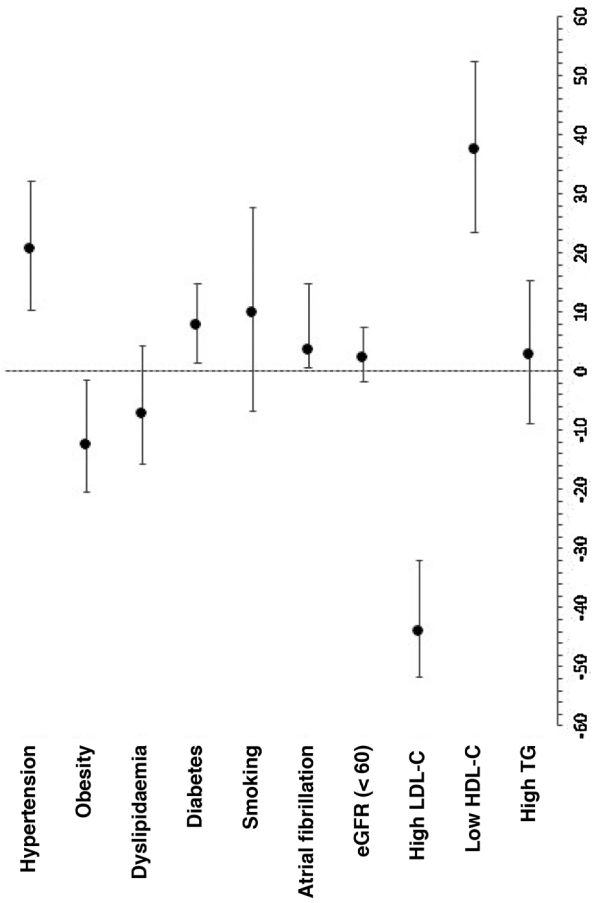

Figure 1 Percentage of population-attributable risk and 95% confidence interval for the total population with stroke.
eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides.

Table 2 Univariate and multivariate logistic regression analysis of risk factors of ischaemic stroke in young patients, stratified by sex.

Men	Patients N = 86; n/N (%)	Controls N = 430; n/N (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Hypertension	31/86 (36.0)	95/430 (22.1)	1.98 (1.21-3.26)	1.15 (0.67-1.96)
Obesity	17/86 (19.8)	140/430 (32.6)	0.51 (0.29-0.90)	0.43 (0.24-0.78)
Dyslipidaemia	23/86 (26.7)	131/430 (30.5)	0.83 (0.49-1.40)	0.65 (0.38-1.12)
Diabetes mellitus	12/86 (14.0)	28/430 (6.5)	2.32 (1.13-4.78)	1.35 (0.64-2.88)
Tobacco use	51/86 (59.3)	196/430 (47.9)	1.74 (1.09-2.78)	1.86 (1.14-3.03)
Atrial fibrillation	4/86 (4.7)	3/430 (0.7)	6.94 (1.52-31.60)	5.63 (1.20-28.37)
eGFR (< 60)	2/86 (2.3)	2/430 (0.5)	5.09 (0.71-36.68)	3.43 (0.45-25.71)
High LDL-C level	28/86 (32.6)	284/429 (66.2)	0.24 (0.15-0.40)	0.18 (0.11-0.31)
Low HDL-C level	45/86 (52.3)	64/429 (14.9)	6.26 (3.80-10.32)	6.32 (3.73-10.70)
High TG level	26/86 (30.2)	85/430 (19.8)	1.76 (1.05-2.95)	1.45 (0.85-2.49)
Women	N = 34; n/N (%)	N = 170; n/N (%)		
Hypertension	13/34 (38.2)	23/170 (13.5)	3.96 (1.74-8.98)	3.79 (1.58-9.10)
Obesity	8/34 (23.5)	42/170 (24.7)	0.94 (0.40-2.23)	0.87 (0.37-2.10)
Dyslipidaemia	3/34 (8.8)	31/170 (18.2)	0.43 (0.12-1.51)	0.37 (0.10-1.32)
Diabetes mellitus	4/34 (11.8)	6/170 (3.5)	3.64 (1.00-13.70)	3.46 (0.91-13.16)
Tobacco use	9/34 (26.5)	69/170 (40.6)	0.53 (0.23-1.20)	0.56 (0.24-1.29)
Atrial fibrillation	1/34 (2.9)	1/170 (0.6)	5.12 (0.31-83.95)	3.88 (0.23-66.03)
eGFR (< 60)	2/34 (5.9)	1/170 (0.6)	10.56 (0.93-110.9)	8.93 (0.77-103.52)
High LDL-C level	15/34 (44.1)	98/170 (57.6)	0.58 (0.28-1.22)	0.46 (0.21-1.01)
Low HDL-C level	4/34 (11.8)	5/170 (2.9)	4.40 (1.12-17.34)	4.04 (1.01-16.10)
High TG level	4/34 (11.8)	9/170 (5.3)	2.40 (0.70-8.25)	2.24 (0.64-7.79)

* Adjustment for age and each risk factor was necessary for inclusion in the multivariate model. 95% CI: 95% confidence interval; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; n/N: number of subjects divided by the total number of subjects; OR: odds ratio; TG: triglycerides.

Table 3 Prevalence of risk factors per aetiological group.

	Atherothrombotic N = 17; n/N (%)	Cardioembolic N = 32; n/N (%)	Lacunar N = 22; n/N (%)	Undetermined N = 49; n/N (%)	Controls N = 600; n/N (%)
Age in years, mean (SD)	48.5 (6.3)	49.7 (4.8)	46.6 (7.5)	44.5 (7.7)	42.4 (7.9)
Sex (women)	1 (0.6)	8/32 (25.0)	3/22 (13.6)	22/49 (44.9)	170/600 (28.3)
Hypertension	7/17 (41.2)	14/32 (43.8)	9/22 (40.9)	14/49 (28.6)	118/600 (19.7)
Obesity	6/17 (35.3)	6/32 (18.8)	4/22 (18.2)	9/49 (18.4)	182/600 (30.3)
Dyslipidaemia	7/17 (41.2)	6/32 (18.8)	5/22 (22.7)	8/49 (16.3)	162/600 (27.0)
Diabetes mellitus	6/17 (35.3)	5/32 (15.6)	4/22 (18.2)	1/49 (2.0)	34/600 (5.7)
Tobacco use	12/17 (70.6)	16/32 (50.0)	16/22 (72.7)	16/49 (32.7)	265/600 (44.2)
Atrial fibrillation	0/17 (0.0)	5/32 (15.6)	0/22 (0.0)	0/49 (0.0)	4/596 (0.7)
eGFR (< 60)	1/17 (5.9)	2/32 (6.3)	0/22 (0.0)	1/49 (2.0)	3/600 (0.5)
High LDL-C level	4/17 (23.5)	15/32 (46.9)	8/22 (36.4)	16/49 (32.7)	382/599 (63.8)
Low HDL-C level	12/17 (70.6)	13/32 (40.6)	10/22 (45.5)	14/49 (28.6)	69/599 (11.5)
High TG level	5/17 (29.4)	11/32 (34.4)	8/22 (36.4)	6/49 (12.2)	94/600 (15.7)

eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; n/N: number of subjects divided by the total number of subjects; SD: standard deviation; TG: triglycerides.

Dyslipidaemia

Some studies report a prevalence of approximately 50% of dyslipidaemia in young patients with stroke, with higher rates in men than in women.[1,20] In our study, we did not find a significant association between dyslipidaemia and stroke, even in the analysis by sex. We even found a clear inverse association between stroke and LDL-C level, which has also been observed in other studies.[19]

This may be explained by the aetiological heterogeneity of stroke: in some aetiologies, dyslipidaemia may not be a risk factor, with the exception of stroke due to atherosclerosis or small-vessel disease. The subgroup analysis shows a higher prevalence of dyslipidaemia in the atherothrombotic stroke group than among controls (41.2% vs 27%). This has also been observed by other researchers.[8,11]

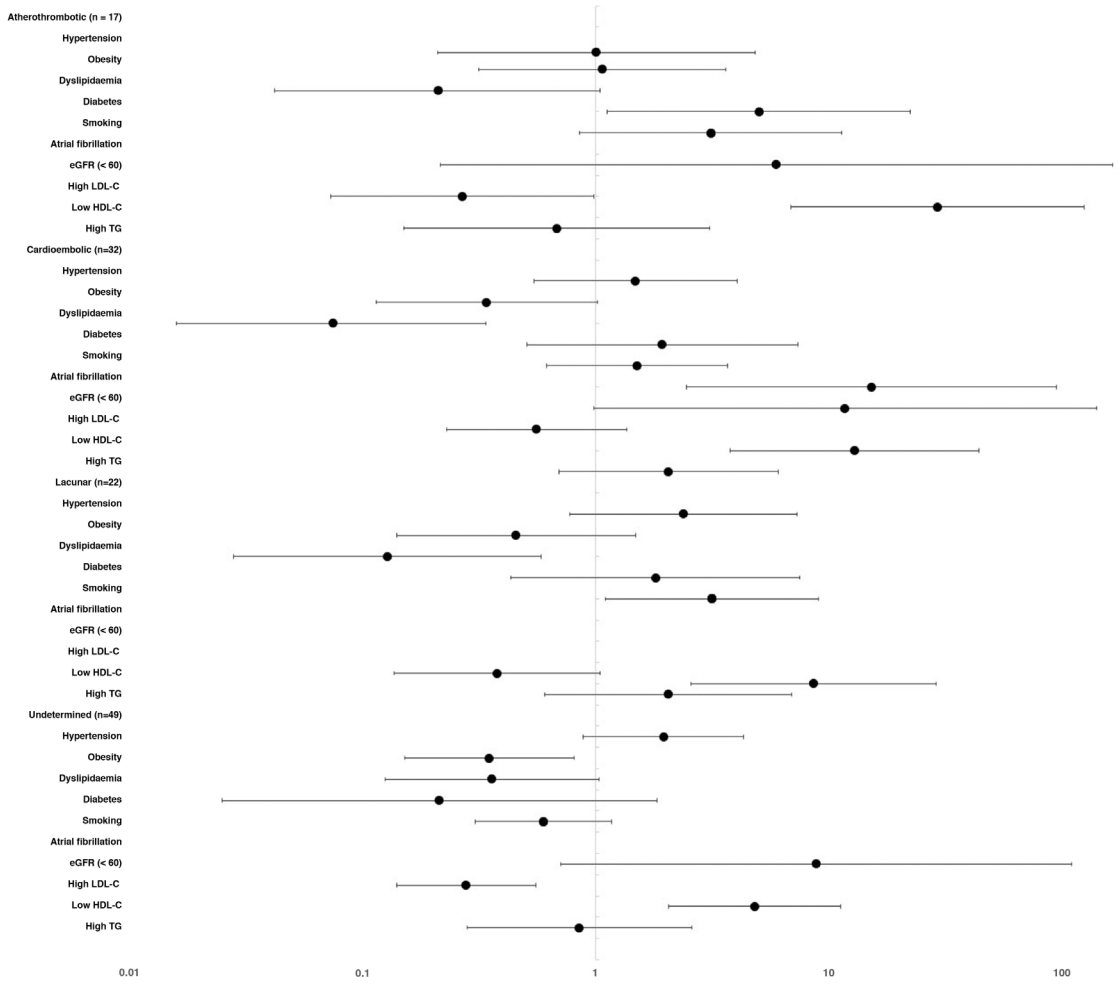

Figure 2 Multivariate logistic regression analysis of risk factors of early-onset ischaemic stroke, stratified by aetiology (odds ratio and 95% CI).
Adjusted for age and each risk factor included in the study. eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides.

Another explanation for why dyslipidaemia may not significantly contribute to the risk of ischaemic stroke in young adults may be that the majority of studies defined dyslipidaemia as a high LDL-C or low HDL-C level, but did not analyse the association between different lipid variables and stroke, which may be of clinical interest. For example, a Brazilian study revealed that the apolipoprotein B/apolipoprotein A-I ratio was strongly associated with ischaemic stroke (OR: 4.03; 95% CI: 1.62-10.03).[25]

We assessed additional lipid variables in our study. We found a clear and consistent association between low HDL-C level and stroke, both in the overall analysis and in the analysis by sex and stroke subtype. This has also been observed by other authors.[19,26,27] Experimental, epidemiological, genetic, and clinical studies suggest an independent inverse correlation between HDL-C levels and vascular disease.[28] Low HDL-C levels are the most prevalent lipid abnormality in patients with early atherosclerotic disease.[29] Furthermore, studies performed in cell cultures and in animal models have shown that HDL-C particles exert a vasoprotective effect.[30] In fact, the antiatherogenic effect of HDL-C seems to involve several mechanisms, including reverse cholesterol transport and cardiovascular, antioxidant, antiplatelet, anti-apoptotic, and anti-inflammatory protective action, which are not necessarily associated with cholesterol homeostasis.[31] The discovery of new genes and pathways participating in HDL-C metabolism may lead us to place greater emphasis on the diagnosis and management of low HDL-C levels in prevention strategies for young patients with stroke.[32]

Furthermore, low HDL-C level is not only a good marker of vascular risk, but may also indicate poorer health status due to concomitant factors that have not been analysed in our study, such as sedentary lifestyle or lower socioeconomic status.[33,34]

High TG level is a risk factor frequently overlooked by neurologists, although the number of studies showing an association between high TG levels and stroke is increasing.[35] Hypertriglyceridaemia may increase the risk of ischaemic stroke, as it predisposes patients to atherosclerosis, thrombosis, and hyperviscosity.[36] In our study, this

risk factor was more prevalent among cases and is non-independently associated with stroke and some aetiological subtypes.

Diabetes

In our study, diabetes acted as a global risk factor, for both sexes and for the atherosclerosis and small-vessel disease aetiological subgroups.

The studies performed to date have shown great variation in the strength of association between diabetes and stroke in young patients.[37] According to some authors, diabetes is present in up to 10% of young patients with stroke[15,16]; our study found a prevalence of 13%. Recent studies report PAR values ranging between 4.8% and 6.5%,[11,19] with our study showing 8.1%. Considering these data, we should be concerned by the increase in the incidence of diabetes type 2 in young adults, which contributes to the increase in the rate of stroke at earlier ages.[16]

Although there are no considerable differences between sexes in the prevalence of diabetes type 2,[21] the risk of stroke, according to some studies, would be higher in women than in men (hazard ratio: 2.8 vs 2.2).[38] In our study, we also observed that the strength of association of diabetes with stroke was stronger in women.

It is noteworthy that 2 of the most potent atherogenic components of diabetic dyslipidaemia are the increase in residual particles of TG and low HDL-C levels,[39] which we also observed in our series (data not shown).

Smoking

The proportion of smokers among young patients with stroke is high, with recent studies reporting that up to 50% of these patients are smokers.[8,10] Furthermore, during the last decade, the prevalence of smoking has increased among young adults.[40] According to our study, smoking contributes to stroke in men, and was more frequently reported among patients with stroke of atherothrombotic or lacunar aetiology. Similar findings have been reported in other studies.[18,40] Compared to adults older than 55 years, the dose-response relationship with stroke seems to be stronger at younger ages, both in men and in women.[41]

Glomerular filtration rate

Our study shows that eGFR acts as a potent risk factor and is specifically associated with all aetiological subtypes, with the exception of stroke of undetermined cause. In individuals with a moderate decrease in eGFR (30-59), the risk of cardiovascular death is up to 3 times higher than in subjects with normal eGFR values.[42] The applicable guidelines consider that all subjects with moderately decreased eGFR present a high risk of vascular disease, including stroke.[43] Kidney function, as determined by the eGFR, shows an inverse association, with a clearly increasing risk of stroke as the kidney function worsens.[44] Some authors have shown that proteinuria itself is a little-known risk factor for stroke, regardless of arterial pressure and diabetes; this, together with reduced kidney function, substantially increases the risk of stroke.[45]

Limitations

The limitations of our study include the potential biases inherent to case-control studies. Although we made thorough efforts to homogenise risk factors, some residual bias may remain. The prevalence of AF and low eGFR in controls was low; consequently, the estimated OR for these infrequent risk factors should be interpreted with caution. Furthermore, these variables could not be analysed in all aetiological subgroups.

With regard to smoking, we could not analyse the dose-response relationship between smoking and stroke. We did not include any factor specifically related with risk among women, such as the use of contraception or migraine, or the risk inherent to childbearing age in women. With respect to the measurement of kidney function, subjects were classified according to a single eGFR determination, and although this is the typical practice in epidemiological studies, it is also known that calculations based on creatinine may present some limitations.

All models were adjusted for vascular risk factors, but not for use of statins, renin-angiotensin system inhibitors, or antiplatelet drugs. Neither did we include the progression time of risk factors, or other concomitant diseases, neoplasms, physical activity, socio-economic factors, or pollution, which have been also associated with cerebrovascular disease.

Conclusions

Hypertension, AF, low eGFR, low HDL-C level, and smoking are the main risk factors for stroke among individuals younger than 55 years. We consider it particularly important to conduct further studies into the management of low HDL-C levels with a view to developing prevention strategies for young patients with stroke. We should also seek to improve kidney health through the development of awareness campaigns, health education, and renal insufficiency prevention campaigns, at least in specific risk groups. The considerable differences in the risk profile between aetiological subgroups corroborate the significant pathogenic complexity of early-onset stroke. We should continue in the search of new risk factors may that might explain this type of stroke and focus on new prevention strategies.

References

1. Boot E, Ekker MS, Putaala J, Kittner S, De Leeuw F-E, Tuladhar AM. Ischaemic stroke in young adults: a global perspective. J Neurol Neurosurg Psychiatry. 2020;91:411—7, http://dx.doi.org/10.1136/jnnp-2019-322424.
2. Singhal AB, Biller J, Elkind MS, et al. Recognition and management of stroke in young adults and adolescents. Neurology. 2013;81:1089—97, http://dx.doi.org/10.1212/WNL.0b013e3182a4a451.
3. Ekker MS, Verhoeven JI, Vaartjes I, van Nieuwenhuizen KM, Klijn CJM, de Leeuw F-E. Stroke incidence in young

adults according to age, subtype, sex, and time trends. Neurology. 2019;92:e2444—54, http://dx.doi.org/10.1212/WNL.0000000000007533.
4. Ramírez-Moreno JM, Felix-Redondo FJ, Fernández-Bergés D, Lozano-Mera L. Tendencias en las tasas de hospitalización por ictus en Extremadura en el periodo 2002-2014. Cambiando la idea del ictus como una enfermedad propia de la senectud. Neurología. 2018;33:561—9, http://dx.doi.org/10.1016/j.nrl.2016.09.002.
5. Rosengren A, Giang KW, Lappas G, Jern C, Torén K, Björck L. Twenty-four-year trends in the incidence of ischemic stroke in Sweden from 1987 to 2010. Stroke. 2013;44:2388—93, http://dx.doi.org/10.1161/STROKEAHA.113.001170.
6. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79:1781—7, http://dx.doi.org/10.1212/WNL.0b013e318270401d.
7. Tibæk M, Dehlendorff C, Jørgensen HS, Forchhammer HB, Johnsen SP, Kammersgaard LP. Increasing incidence of hospitalization for stroke and transient ischemic attack in young adults: a registry-based study. J Am Heart Assoc. 2016;5, http://dx.doi.org/10.1161/JAHA.115.003158.
8. George MG, Tong X, Bowman BA. Prevalence of cardiovascular risk factors and strokes in younger adults. JAMA Neurol. 2017;74:695, http://dx.doi.org/10.1001/jamaneurol.2017.0020.
9. Putaala J. Ischemic stroke in the young: current perspectives on incidence, risk factors, and cardiovascular prognosis. Eur Stroke J. 2016;1:28—40, http://dx.doi.org/10.1177/2396987316629860.
10. Yesilot Barlas N, Putaala J, Waje-Andreassen U, Vassilopoulou S, Nardi K, Odier C, et al. Etiology of first-ever ischaemic stroke in European young adults: the 15 cities young stroke study. Eur J Neurol. 2013;20(11):1431—9, http://dx.doi.org/10.1111/ene.12228.
11. Aigner A, Grittner U, Rolfs A, Norrving B, Siegerink B, Busch MA. Contribution of established stroke risk factors to the burden of stroke in young adults. Stroke. 2017;48:1744—51, http://dx.doi.org/10.1161/STROKEAHA.117.016599.
12. Félix-Redondo FJ, Fernández-Bergés D, Fernando Pérez J, et al. Prevalencia, detección, tratamiento y grado de control de los factores de riesgo cardiovascular en la población de Extremadura (España). Estudio HERMEX. Atención Primaria. 2011;43:426—34, http://dx.doi.org/10.1016/j.aprim.2010.07.008.
13. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35—41, http://dx.doi.org/10.1161/01.STR.24.1.35.
14. Böthig S. WHO MONICA Project: objectives and design. Int J Epidemiol. 1989;18:S29—37.
15. Béjot Y, Delpont B, Giroud M. Rising stroke incidence in young adults: more epidemiological evidence, more questions to be answered. J Am Heart Assoc. 2016;5, http://dx.doi.org/10.1161/JAHA.116.003661.
16. Putaala J, Metso AJ, Metso TM, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke. Stroke. 2009;40:1195—203, http://dx.doi.org/10.1161/STROKEAHA.108.529883.
17. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388:761—75, http://dx.doi.org/10.1016/S0140-6736(16)30506-2.
18. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet. 2020;395:795—808, http://dx.doi.org/10.1016/S0140-6736(19)32008-2.
19. Kivioja R, Pietilä A, Martinez-Majander N, et al. Risk factors for early-onset ischemic stroke: a case-control study. J Am Heart Assoc. 2018;7, http://dx.doi.org/10.1161/JAHA.118.009774.
20. Putaala J, Yesilot N, Waje-Andreassen U, et al. Demographic and geographic vascular risk factor differences in european young adults with ischemic stroke. Stroke. 2012;43:2624—30, http://dx.doi.org/10.1161/STROKEAHA.112.662866.
21. von Sarnowski B, Putaala J, Grittner U, et al. Lifestyle risk factors for ischemic stroke and transient ischemic attack in young adults in the stroke in young fabry patients study. Stroke. 2013;44:119—25, http://dx.doi.org/10.1161/STROKEAHA.112.665190.
22. Oesch L, Tatlisumak T, Arnold M, Sarikaya H. Obesity paradox in stroke — myth or reality? A systematic review. PLoS One. 2017;12, http://dx.doi.org/10.1371/journal.pone.0171334, e0171334.
23. Mitchell AB, Cole JW, McArdle PF, et al. Obesity increases risk of ischemic stroke in young adults. Stroke. 2015;46:1690—2, http://dx.doi.org/10.1161/STROKEAHA.115.008940.
24. Winter Y, Rohrmann S, Linseisen J, et al. Contribution of obesity and abdominal fat mass to risk of stroke and transient ischemic attacks. Stroke. 2008;39:3145—51, http://dx.doi.org/10.1161/STROKEAHA.108.523001.
25. Sabino AP, De Oliveira Sousa M, Lima LM, et al. ApoB/ApoA-I ratio in young patients with ischemic cerebral stroke or peripheral arterial disease. Transl Res. 2008;152:113—8, http://dx.doi.org/10.1016/j.trsl.2008.06.005.
26. Marini C, Carolei A, Roberts RS, et al. Focal cerebral ischemia in young adults: a collaborative case-control study. Neuroepidemiology. 1993;12:70—81, http://dx.doi.org/10.1159/000110303.
27. Albucher JF. Serum lipids in young patients with ischaemic stroke: a case-control study. J Neurol Neurosurg Psychiatry. 2000;69:29—33, http://dx.doi.org/10.1136/jnnp.69.1.29.
28. Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020;41:2313—30, http://dx.doi.org/10.1093/eurheartj/ehz962.
29. März W, Kleber ME, Scharnagl H, et al. HDL cholesterol: reappraisal of its clinical relevance. Clin Res Cardiol. 2017;106:663—75, http://dx.doi.org/10.1007/s00392-017-1106-1.
30. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. J Clin Invest. 1990;85:1234—41, http://dx.doi.org/10.1172/JCI114558.
31. Camont L, Chapman MJ, Kontush A. Biological activities of HDL subpopulations and their relevance to cardiovascular disease. Trends Mol Med. 2011;17:594—603, http://dx.doi.org/10.1016/j.molmed.2011.05.013.
32. Zhang N, Zhang L, Wang Q, Zhao J, Liu J, Wang G. Cerebrovascular risk factors associated with ischemic stroke in a young non-diabetic and non-hypertensive population: a retrospective case-control study. BMC Neurol. 2020;20:424, http://dx.doi.org/10.1186/s12883-020-02005-7.
33. Barter PJ, Rye K-A. HDL cholesterol concentration or HDL function: which matters? Eur Heart J. 2017;38:2487—9, http://dx.doi.org/10.1093/eurheartj/ehx274.
34. Ko DT, Alter DA, Guo H, et al. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions. J Am Coll Cardiol. 2016;68:2073—83, http://dx.doi.org/10.1016/j.jacc.2016.08.038.

35. Freiberg JJ. Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA. 2008;300:2142, http://dx.doi.org/10.1001/jama.2008.621.
36. Liang H, Zhang Q, Hu Y, Liu G, Qi R. Hypertriglyceridemia: a neglected risk factor for ischemic stroke? J Stroke. 2022;24:21—40, http://dx.doi.org/10.5853/jos.2021.02831.
37. Rohr J, Kittner S, Feeser B, et al. Traditional risk factors and ischemic stroke in young adults: the baltimore-washington cooperative young stroke study. Arch Neurol. 1996;53:603—7, http://dx.doi.org/10.1001/archneur.1996.00550070041010.
38. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol. 2012;11:261—71, http://dx.doi.org/10.1016/S1474-4422(12)70005-4.
39. Carmena R. Riesgo elevado de disfunción lipoproteica en la diabetes mellitus tipo 2. Rev Española Cardiol Supl. 2008;8:19C—26C, http://dx.doi.org/10.1016/S1131-3587(08)73551-9.
40. de los Ríos F, Kleindorfer DO, Khoury J, et al. Trends in substance abuse preceding stroke among young adults. Stroke. 2012;43:3179—83, http://dx.doi.org/10.1161/STROKEAHA.112.667808.
41. Markidan J, Cole JW, Cronin CA, et al. Smoking and risk of ischemic stroke in young men. Stroke. 2018;49:1276—8, http://dx.doi.org/10.1161/STROKEAHA.117.018859.
42. Carmena R. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073—81, http://dx.doi.org/10.1016/S0140-6736(10)60674-5.
43. Cheung AK, Chang TI, Cushman WC, et al. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99:S1—87, http://dx.doi.org/10.1016/j.kint.2020.11.003.
44. Kelly DM, Ademi Z, Doehner W, et al. Chronic kidney disease and cerebrovascular disease. Stroke. 2021;52, http://dx.doi.org/10.1161/STROKEAHA.120.029680.
45. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. Nephrol Dial Transplant. 2015;30:1162—9, http://dx.doi.org/10.1093/ndt/gfv009.