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Obesity and the Risk of Cryptogenic Ischemic Stroke in Young Adults

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Obesity and the Risk of Cryptogenic Ischemic Stroke in Young Adults

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Abbreviation: WHR, Waist-to-hip ratio; BMI, Body mass index; WC, Waist circumference; WSR, Waist-to-stature ratio; ABSI, A body shape index; CIS, Cryptogenic ischemic stroke; PFO, Patent foramen ovale; MA, Migraine with aura

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Objectives: We examined the association between obesity and early-onset cryptogenic ischemic stroke (CIS) and whether fat distribution or sex altered this association. *Materials and Methods:* This prospective, multi-center, case-control study included 345 patients, aged 18-49 years, with first-ever, acute CIS. The control group included 345 age- and sex-matched stroke-free individuals. We measured height, weight, waist circumference, and hip circumference. Obesity metrics analyzed included body mass index (BMI), waist-to-hip ratio (WHR), waist-to-stature ratio (WSR), and a body shape index (ABSI). Models were adjusted for age, level of education, vascular risk factors, and migraine with aura. *Results:* After adjusting for demographics, vascular risk factors, and migraine with aura, the highest tertile of WHR was associated with CIS (OR for highest versus lowest WHR tertile 2.81, 95%CI 1.43-5.51; *P*=0.003). In sex-specific analyses, WHR tertiles were not associated with CIS. However, using WHO WHR cutoff values (>0.85 for women, >0.90 for men), abdominally obese women were at increased risk of CIS (OR 2.09, 95%CI 1.02-4.27; *P*=0.045). After adjusting for confounders, WC, BMI, WSR, or ABSI were not associated with CIS. *Conclusions:* Abdominal obesity measured with WHR was an independent risk factor for CIS in young adults after rigorous adjustment for concomitant risk factors.

KeyWords: Cryptogenic stroke—Ischemic stroke—Obesity—Waist-to-hip ratio—Young adults

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Introduction

In young, under 55-year-old adults, ischemic stroke occurs relatively rarely, but the incidence has markedly increased over the past few decades,[1,2] making it an even major global health problem. Importantly, despite standardized, modern-day diagnostic procedures, in 33-50% of early-onset ischemic strokes, the etiology remains cryptogenic.[3,4]

Recent epidemiologic studies have suggested a concomitant increase in the prevalence of another major health issue, obesity, among young adults.[5,6] A 2017 study showed that the prevalence of obesity in young patients with ischemic stroke in the US was markedly higher in 2011-2012 (13.3-15.2% in men; 15.7-21.0% in women) compared to the previous decade (6.8-7.7% in men; 9.1-10.9% in women).[7] Numerous studies have linked obesity with several cardiovascular outcomes,[8,9] but few studies have focused on the association between obesity and ischemic stroke in young adults. The age-inclusive INTERSTROKE study demonstrated that an elevated waist-to-hip ratio (WHR) increased the risk of all strokes, examining both ischemic and hemorrhagic stroke as one group in young adults.[10] A study from 2015 that specifically focused on young adults showed that an elevated body mass index (BMI) was associated with an increased risk of ischemic stroke, but this association was not significant after adjusting for confounders; moreover, that study lacked indicators of abdominal obesity.[11] A recent Israeli study found an association with a high adolescent BMI with an increased stroke risk in young adulthood, but also lacked indicators of abdominal obesity.[12]

For decades, BMI has been extensively used to screen for obesity, but the use of BMI is limited, due to its inability to discriminate among different body fat distributions. Indicators of abdominal obesity, such as waist circumference (WC), WHR, and waist-to-stature ratio (WSR), were demonstrated to be more useful in evaluating visceral adipose tissue, and consequently, the risk of stroke.[13,14] In 2012, a body shape index (ABSI) was introduced as an additional predictor of premature obesity-related mortality,[15] and it was shown to be a potential indicator of mortality from cardiovascular diseases.[16]

It remains unknown to what extent obesity contributes to early-onset cryptogenic ischemic stroke (CIS). Therefore, we aimed to evaluate the association between obesity and CIS in young adults and determine whether this association was altered by body fat distribution or sex.

Methods

We retrieved data from the Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome (SECRETO; NCT01934725) study, which is a prospective case-control study including patients aged 18-49 years with a first ever CIS at 19 European university centers. As per STROBE guidelines,[17] we enrolled one sex- and age-matched (±5 years) stroke-free control for each patient. Controls were from the same region, based on the community or identified by random search through population registers. Standardized approaches for identifying sources of community-based controls were not prespecified due to e.g. differing country-specific legislation. The study design was described in detail previously.[18,19] Participants for the present analysis were enrolled between October 2013 and April 2020. Written informed consent was obtained from all participants, and the study was approved by the ethics committees of

the participating hospitals. The data that support the findings of this study are available from the corresponding author upon reasonable request.

According to the protocol, all patients were thoroughly examined with brain magnetic resonance imaging; intracranial and extracranial vascular imaging, with either computed tomography angiography or magnetic resonance angiography; routine laboratory tests; 12-lead electrocardiography; prolonged continuous electrocardiography, for a minimum of 24 h; and both transthoracic and transesophageal echocardiography. Transcranial Doppler ultrasound with a bubble screen was performed at selected study centers. All patients with patent foramen ovale (PFO)-related strokes were included, due to its uncertain causality. After a thorough diagnostic workup, CIS was defined according to the Atherosclerosis, Small vessel disease, Cardiac source, Other cause (ASCO) classification system, as either the absence of disease (grade 0), or as grade 2 (causality uncertain) or grade 3 (unlikely a direct cause) pathology.[20]

Anthropometric measurements

Anthropometric measurements were obtained in a standardized manner. Obesity metrics were analyzed in tertiles and based on generally accepted cutoff values. Due to differences in fat distribution between the sexes,[21] different cutoff points for WC and WHR were applied for men and women, according to WHO guidelines.[22]

WC was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. We used a stretch-resistant tape that provided a constant 100 g tension. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. Abdominal obesity was defined as WC >80 cm for women and >94 cm for men, according to WHO guidelines for Europeans.[22]

BMI was calculated as body weight divided by height squared (kg/m^2). BMI was categorized according to standard classifications: underweight: <18.5 kg/m^2; normal weight: 18.5-24.9 kg/m^2; overweight: 25-29.9 kg/m^2; obese: ≥30 kg/m^2.[23]

WHR was the WC/hip circumference, and the waist-to-stature ratio (WSR) was the WC/height. Abdominal obesity was defined as WHR >0.85 for women and >0.90 for men, or WSR >0.5 for both sexes.[22,24] ABSI was determined as WC/(BMI$^{2/3}$ × height$^{1/2}$), where WC and height were expressed in meters, and BMI was expressed in kg/m^2.[15]

Comorbidities

Based on medical records and structured interviews, we identified relevant comorbidities, such as diabetes mellitus (i.e., prior diabetes diagnosis and/or prior antidiabetic medication), hypertension (i.e., prior hypertension diagnosis, prior antihypertensive medication, or the mean of two office blood pressure measures >140/90 mmHg at study visit), history of cardiovascular disease (coronary heart disease, congestive heart failure, peripheral arterial disease, or atrial fibrillation), and migraine with aura (MA), assessed with a validated migraine screening protocol.[19]

Information on lifestyle factors was based on structured interviews conducted during study visits. Cigarette smoking was classified as smoking at least one cigarette during the year prior to the index stroke. Physical inactivity was assessed with the short version of the International Physical Activity Questionnaire,[25] and it was defined as not meeting the criteria for moderate or high levels of physical activity. Excessive alcohol consumption was defined as at least 5 doses of alcohol/day or 16 doses/week for women, and at least 7 doses of alcohol/day or 24 doses/-week for men.[26] Dietary habits were evaluated with a modified version of the Mediterranean diet score,[27] which excluded alcohol intake. The maximum score was 50 points, where a higher score indicated a healthier diet. Women were asked about their use of estrogen-containing contraception.

For the present study, PFO was identified in both patients and controls by the presence of a right−to−left shunt in a transcranial Doppler ultrasound with a bubble screen.

Statistical analyses

Univariate comparisons between patient and control groups were performed with McNemar's test, for dichotomized variables; the paired t-test, for normally distributed continuous variables; or the Wilcoxon signed rank test, for non-normally distributed continuous variables (expressed as the median and interquartile range [IQR]). When patients or controls were analyzed separately, we compared categorical variables with the Chi square or Fisher's exact test.

We assessed associations between abdominal obesity and CIS with conditional logistic regression to produce adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for the entire cohort and for groups defined by sex. Covariates were selected based on differences between cases and controls, biological plausibility, and existing evidence. Covariates included age, level of education, hypertension, diabetes mellitus, physical inactivity, current tobacco smoking, excessive alcohol use, and MA. In women, the models were further adjusted for the use of estrogen-containing contraception.

In an exploratory analysis, we tested whether there were interactions in the main analysis between obesity metrics and the presence or absence of comorbidities. Comorbidities included hypertension, current smoking, excessive alcohol use, physical inactivity, and MA. For this analysis, we used an interaction term in unmatched logistic regression models. Similarly, we assessed an

Table 1. *Anthropometric measurements of young patients with cryptogenic ischemic stroke and healthy controls.*

Measurement	All		
	Patients (n=345)	Controls (n=345)	*P* value
Weight (kg)	79.0 (69.0−93.0)	79.0 (68.0−89.0)	0.065
Height (cm)	173.0 (166.0−181.0)	173.0 (167.0−181.8)	0.836
WC (cm)	92.0 (82.0−102.0)	88.0 (81.0−98.0)	0.001
HC (cm)	102.0 (97.0−109.0)	102.5 (96.3−108)	0.868
BMI (kg/m^2)	26.4 (23.4−29.2)	25.4 (23.3−28.3)	0.044
WHR	0.90 (0.83−0.96)	0.87 (0.80−0.94)	<0.001
WSR	0.52 (0.47−0.58)	0.51 (0.46−0.56)	0.002
ABSI	0.079 (0.075−0.082)	0.077 (0.074−0.080)	0.001

Data are the median (interquartile range); WC: waist circumference; HC: hip circumference; BMI: body mass index; WHR: waist-to-hip ratio; WSR: waist-to-stature ratio; ABSI: a body shape index

interaction between PFO and obesity metrics, by analyzing the subcohort screened for the presence of PFO.

Details on diet scores were missing for 39 study participants. Of these, 81.6% were lacking information in a single random score component. For those components, values were imputed, based on mean values, to allow calculations of total scores. When values for other variables were missing, or when an entire questionnaire on diet, physical activity, or migraine was blank, we reported the frequency of missing values and excluded those individuals from the multivariable analyses.

Samples size estimations assumed an alpha of 0.05, a power of 80%, and European young-age-specific prevalence of overweight and obesity of 53%, 61%, and 46% for all controls, male controls, and female controls, respectively.[28] Thus, with total sample sizes of 690, 370, and 320, respectively, the predicted minimum detectable ORs in a 1:1 matched case-control analysis were 1.55, 1.88, and 1.89, respectively. We performed statistical analyses with IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, N.Y., USA) and R (http://www.r-project.org) version 3.6.3. *P*-values <0.05 were considered significant.

Results

We identified 347 patients and 347 sex- and age-matched healthy controls. Of these, two patient-control pairs were excluded, due to lack of all anthropometric data. Thus, 345 pairs were analyzed (median ages of male and female patients: 42.0, IQR: 36.4-46.6 and 39.4, IQR: 30.7-44.4, respectively). The proportion of men (53.6%) slightly exceeded that of women. Compared to controls, patients with CIS had less healthy diets and lower education levels. In addition, male patients with CIS reported excessive alcohol consumption and cigarette smoking more often than women with CIS. Moreover, patients with CIS reported MA more frequently than controls. A larger proportion of female patients used estrogen-containing contraception than female controls, but the difference was not significant (Supplemental Table 1).

Table 1 shows the anthropometric measures of the study population. Compared to controls, patients with CIS had significantly higher BMI, WC, WHR, WSR, and ABSI values. Both male and female patients had significantly higher WC, WHR, and WSR values, compared to corresponding controls, but the differences were greater among women (Supplemental Table 2, Fig. 1). In addition, female patients had significantly higher ABSI values than controls. When obesity categories were defined by cutoff values (Supplemental Table 3), patients had higher WHR values than controls, in both sexes. Furthermore, male patients had a higher WC than male controls.

Table 2 shows results of multivariable analyses of obesity metrics, defined by tertiles of the distributions. In the entire cohort, CIS was associated with the middle and highest tertiles of WHR and the highest tertiles of WSR and ABSI, after adjusting for age and level of education. The association between CIS and the highest WHR tertile persisted after adjusting for demographic features, vascular risk factors, and MA. Among men, CIS was associated with the middle and highest WHR tertiles, after adjusting for demographics, but the association lost significance with further adjustments. We found no other significant associations between CIS and obesity markers, after adjusting for confounders in the sex-specific tertile analyses.

Multivariable analyses of obesity metrics defined by WHO cutoff values demonstrated that CIS was associated with WHR, in the entire cohort and for both men and women separately, after adjusting for age and level of education. In the entire cohort, this association remained significant after further adjusting for vascular risk factors, but significance was lost after including an adjustment for MA. However, among women, elevated WHR was associated with CIS, even after adjusting for all the confounders. In contrast, among men, the association was lost after further adjusting for vascular risk factors and MA. CIS was not associated with BMI or WSR, defined by cutoff values, even when the models were only adjusted for demographics (Table 3).

Exploratory interaction analyses (Table 4) suggested that cigarette smoking significantly interacted with WHR

Table 2. *Adjusted cox regression model results show the risk of cryptogenic ischemic stroke in young adults with different obesity metrics, grouped by distribution tertiles; stratified by sex.*

Obesity Metric	Model adjusted for age and level of education	Model adjusted for age, level of education, and vascular risk factors*	Model adjusted for age, level of education, vascular risk factors*, and migraine with aura
All			
BMI			
T2 vs T1	0.75 (0.48-1.17)	0.67 (0.41-1.09)	0.63 (0.38-1.06)
T3 vs T1	1.21 (0.79-1.87)	0.87 (0.53-1.42)	0.84 (0.49-1.43)
WHR			
T2 vs T1	1.77 (1.06-2.96)	1.57 (0.92-2.70)	1.60 (0.88-2.90)
T3 vs T1	3.07 (1.74-5.44)	2.69 (1.45-5.01)	2.81 (1.43-5.51)
WSR			
T2 vs T1	1.07 (0.66-1.73	0.92 (0.55-1.54)	0.79 (0.45-1.37)
T3 vs T1	1.78 (1.10-2.88)	1.40 (0.81-2.42)	1.27 (0.71-2.27)
ABSI			
T2 vs T1	1.45 (0.93-2.26)	1.29 (0.81-2.05)	1.17 (0.70-1.94)
T3 vs T1	1.64 (1.03-2.60)	1.32 (0.80-2.16)	1.22 (0.72-2.09)
Men			
BMI			
T2 vs T1	0.92 (.051-1.65)	0.94 (0.49-1.81)	0.87 (0.44-1.74)
T3 vs T1	1.33 (0.73-2.43)	1.03 (0.49-2.16)	0.93 (0.42-2.06)
WHR			
T2 vs T1	2.92 (1.34-6.39)	2.24(0.93-5.39)	2.27 (0.89-5.81)
T3 vs T1	2.53 (1.20-5.33)	1.70 (0.73-3.97)	1.57 (0.64-3.88)
WSR			
T2 vs T1	1.45 (0.77-2.71)	1.25 (0.64-2.47)	1.18 (0.57-2.41)
T3 vs T1	1.33 (0.72-2.47)	1.08 (0.53-2.22)	0.98 (0.45-2.12)
ABSI			
T2 vs T1	1.90 (0.89-4.09)	2.22 (0.97-5.07)	1.67 (0.70-3.98)
T3 vs T1	1.95 (0.90-4.24)	1.94 (0.83-4.54)	1.58 (0.65-3.85)
Women			
BMI			
T2 vs T1	0.55 (0.29-1.03)	0.55 (0.28-1.06)	0.34 (0.15-0.76)
T3 vs T1	1.16 (0.63-2.12)	1.05 (0.54-2.06)	0.82 (0.38-1.75)
WHR			
T2 vs T1	0.69 (0.32-1.52)	0.66 (0.29-1.48)	0.71 (0.29-1.78)
T3 vs T1	1.33 (0.69-2.55)	1.11 (0.52-2.39)	1.23 (0.49-3.09)
WSR			
T2 vs T1	0.85 (0.43-1.68)	0.92 (0.44-1.91)	0.69 (0.30-1.63)
T3 vs T1	1.66 (0.80-3.46)	1.45 (0.61-3.43)	1.21 (0.44-3.32)
ABSI			
T2 vs T1	1.19 (0.67-2.12)	0.98 (0.53-1.79)	0.98 (0.49-1.96)
T3 vs T1	1.65 (0.88-3.11)	1.35 (0.69-2.27)	1.20 (0.56-2.60)

Data are the odds ratio (95% confidence interval); T1, T2, T3: lowest, middle, and highest tertiles, respectively; BMI: body mass index; WHR: waist-to-hip ratio; WSR: waist-to-stature ratio; ABSI: a body shape index

*Hypertension, diabetes mellitus, current tobacco smoking, physical inactivity, excessive alcohol use, unhealthy diet, and in women, estrogen-containing contraception use. In women, diabetes mellitus was excluded, due to its low frequency.

(*P*-value for interaction = 0.010). We did not find any other significant interactions between obesity markers and clinical comorbidities (Supplemental Tables 4, 5).

Transcranial Doppler ultrasound with a bubble screen was performed in 187 patients and 122 controls. PFOs were present in 122 (65.2%) patients and 55 (35.5%) controls. In the subgroup analysis of participants screened with transcranial Doppler ultrasound with a bubble screen (Supplemental Tables 6−8), the prevalence of abdominal obesity, measured by WSR, was higher among patients with PFO than among patients without PFO (75.0% vs. 59.4%, *P*=0.029). A similar, but non-significant trend was observed for WHR (59.0% vs. 47.7%, *P*=0.138), but not for BMI (61.5% vs. 59.4%, *P*=0.780). Among controls, no differences in prevalence were noted between those with/without PFO (WHR: 40.0% vs. 43.0%, *P*=0.717; WSR: 64.2% vs. 57.7%, *P*=0.443; BMI: 61.1% vs. 57.1%, *P*=0.635). Among patients with an elevated WHR,

Table 3. *Adjusted cox regression model results show the risk of cryptogenic ischemic stroke in young adults with obesity, defined by accepted cutoff values; stratified by Sex.*

Group: Obesity definition	Model Adjusted for Age and Level of Education	Model adjusted for Age, Level of education and Vascular Risk Factors*	Model Adjusted for Age, Level of Education, Vascular Risk Factors* and Migraine with Aura
All			
BMI†	1.20 (0.82-1.74)	0.99 (0.65-1.51)	0.95 (0.61-1.51)
WHR	1.93 (1.31-2.85)	1.56 (1.02-2.37)	1.52 (0.96-2.41)
WSR	1.28 (0.86-1.90)	1.00 (0.65-1.55)	0.94 (0.58-1.51)
Men			
BMI†	1.11 (0.65-1.98)	0.97 (0.52-1.81)	0.86 (0.44-1.69)
WHR	1.91 (1.09-3.36)	1.54 (0.82-2.90)	1.39 (0.72-2.69)
WSR	1.60 (0.88-2.93)	1.32 (0.67-2.60)	1.24 (0.60-2.56)
Women			
BMI†	1.30 (0.76-2.21)	1.22 (0.67-2.23)	1.19 (0.61-2.31)
WHR	2.09 (1.19-3.64)	1.82 (0.99-3.35)	2.09 (1.02-4.27)
WSR	1.07 (0.63-1.82)	0.93 (0.51-1.71)	0.75 (0.37-1.52)

Data are the odds ratio (95% confidence interval); BMI: body mass index; WHR: waist-to-hip ratio; WSR; waist-to-stature ratio
*Hypertension, diabetes mellitus, current tobacco smoking, physical inactivity, excessive alcohol use, unhealthy diet; and in women, estrogen-containing contraception use. In women, diabetes mellitus was excluded, due to its low frequency.
†Definition includes individuals classified as overweight or obese

those with PFO tended to have a higher risk of CIS than those without PFO, but we found no significant interaction between the WHR and PFO (P=0.526) (Supplemental Table 7).

Discussion

This study demonstrated that a range of obesity measures, including BMI, WC, WHR, WSR, and ABSI, were higher in young patients with CIS than in age- and sex-matched controls. However, only abdominal obesity, measured with WHR, emerged as an independent, statistically strong risk factor for early-onset CIS, after adjusting for demographics, vascular risk factors, and even MA. Notably, women with an elevated WHR, defined by the WHO cutoff value, demonstrated an increased risk for CIS, but the association remained non-significant among men.

In this study, BMI—the most widely used obesity metric—was higher in patients with CIS than controls, but

Table 4. *Exploratory subgroup analyses of factors that might interact with the association between waist-to-hip ratio (Obesity Defined by Cutoff Values) and early-onset cryptogenic ischemic stroke.*

Interaction factor	Waist-to-hip ratio		Unadjusted OR (95% CI)	P for interaction*
	Normal	Obese		
Hypertension				0.107
No	118/154	112/97	1.51 (1.05-2.17)	
Yes	21/34	93/58	2.60 (1.38-4.90)	
Current smoking				0.010
No	108/154	122/124	1.40 (0.99-1.99)	
Yes	30/34	83/30	3.14 (1.65-5.97)	
Excessive alcohol use				0.734
No	108/164	163/135	0.55 (0.39-0.76)	
Yes	31/24	42/20	1.63 (0.77-3.45)	
Physical inactivity				0.761
No	126/170	165/129	0.58 (0.42-0.80)	
Yes	12/15	37/25	0.54 (0.22-1.35)	
Migraine with aura				0.354
No	77/158	127/129	2.02 (1.40-2.91)	
Yes	62/29	77/26	1.39 (0.74-2.59)	

Data are the number of patients with CIS /number of controls; OR: odds ratio; CI: confidence interval
*Probability value from logistic regression model, adjusted for age, hypertension, diabetes, current tobacco smoking, physical inactivity, excessive alcohol use, unhealthy diet, and migraine with aura

BMI did not remain associated with CIS after adjusting for relevant confounders. This finding was consistent with previous studies, which demonstrated a trend of higher BMI in young patients with ischemic stroke of any etiology, but it was not a strong, independent association. For example, a 2015 study demonstrated that an elevated BMI was associated with an increased risk of ischemic stroke in young adults, but the association was not significant after adjusting for smoking, hypertension, and diabetes mellitus.[11] Another German, nationwide case-control study of adults under 55 years old with first-ever strokes found that BMIs $\geq$30 kg/m^2 were associated with a slightly increased risk of ischemic stroke (OR: 1.2, 95% CI: 1.0-1.5). However, that study included predominantly women, which might have accounted for the association.[29] Moreover, that study gathered the heights and weights of healthy controls in telephone interviews, which predisposed to bias, and other obesity markers were not available for analysis.[29] A 2021 cohort study demonstrated an elevated risk for early-onset ischemic stroke in patients with a history of adolescent overweight (hazard ratio: 1.6, 95% CI: 1.3-2.0) and obesity (hazard ratio: 2.4, 95% CI: 1.9-3.1) defined by BMI. However, the results were not adjusted for lifestyle factors or MA.[12]

Our results pointed to a nearly 3-fold increase in the risk of CIS among patients with a markedly elevated WHR. This risk estimate was higher than those reported in previous age-inclusive studies. The INTERSTROKE study demonstrated a weaker, but significant association between all strokes and an elevated WHR; interestingly, that association was slightly stronger among patients under 55 years old (OR for T3 vs. T1: 1.56, 95%CI: 1.23-1.98; OR for T2 vs. T1: 1.42, 95%CI: 1.15-1.75) compared to patients over 55 years (OR for T3 vs. T1: 1.39, 1.20-1.62; OR for T2 vs. T1: 1.16, 95%CI: 1.01-1.33).[10] Our results emphasize the importance of WHR and abdominal obesity as a risk factor for early-onset ischemic stroke, particularly among those with undetermined or PFO-related stroke etiology. As an abdominal obesity indicator, WHR reflects the amount of visceral fat tissue, which explained the strong association between an increased WHR and CIS. On the other hand, BMI cannot discriminate between lean and fat body masses, nor does it take into account the body fat distribution.[8]

In cardiovascular diseases the dysfunction of adipose tissue appears a crucial factor in the increased risk of thrombosis and, in particular, visceral obesity affects the risk of ischemic stroke.[7,8,30,31] Furthermore, sex hormones affect this fat distribution favoring visceral fat deposition in men and subcutaneous deposition in women.[20] Recent studies propose that visceral adipose tissue maintains a low-grade inflammation, oxidative stress, and endothelial dysfunction which lead to an increase susceptibility of thrombosis, and subsequently plays a key role in several cardiovascular outcomes. [7,8,30,32] The dysfunctional adipose tissue can modulate metabolism in the liver and skeletal muscle, as well as affecting insulin resistance.[30]

In our study, interaction analyses suggested a markedly increased risk for CIS amongst patients with abdominal obesity who smoked cigarettes compared to those, who did not. Obesity and cigarette smoking are both known risk factors of deep vein thrombosis and atrial fibrillation, as well as disrupters of the coagulation cascade, thus increasing the risk of thrombosis through several mechanisms.[33–35] Our results highlight the additive effect of concurrent abdominal obesity and smoking predisposing to CIS.

Our interaction analyses also suggested that, among individuals with elevated WHRs, the presence of a PFO might increase the risk of CIS, compared to the absence of a PFO. This finding suggests that, among individuals with PFOs, abdominal obesity could be a particularly important contributor to thrombus formation. However, we could not demonstrate a significant interaction between obesity markers and the presence of a PFO. Thus, our findings merely suggested that a more general thrombotic mechanism might underlie CIS.

The strengths of our study included the extensive diagnostic workup and structured data collection for all participants. We included several different obesity metrics, and we gathered anthropometric measurements in a standardized manner. Furthermore, we rigorously adjusted for a range of potential confounders, including MA which has been shown to act as an important risk factor for early-onset ischemic stroke in both sexes.[19]

Our study also had some limitations. First, case-control studies run the risk of a selection bias. Some patients with most severe strokes or marked difficulties in communication, such as patients with global aphasia, might have been left out. However, our sample can be considered well representative of young patients with ischemic stroke,[19] since in consecutive series free of any selection bias only one out of ten young patient presented with severe symptoms.[36] Regarding controls, any significant selection seems unlikely, as, for example, the prevalence of obesity and overweight among the controls (Supplemental Table 3) is well in line with that observed in the European population.[28] Second, the confounding risk factors, such as alcohol consumption, were based on interviews, which might be prone to recall bias, particularly for the most sensitive questions. Third, due to the cross-sectional case-control study design, we could not demonstrate causality. Fourth, the sample size may have been limited for multivariate analyses due to our rigorous adjustments for confounders, particularly in the subgroup analyses. A significantly larger sample size would most likely be necessary to distinguish more subtle differences between the sexes. Lastly, our results can be generalized for the European population, but not necessarily for eg the Asian.

Conclusions

This study underlined the importance of abdominal obesity as a risk factor for CIS in young adults. Our findings have important implications for the primary and secondary prevention of ischemic stroke in young adults due to the increasing global obesity epidemic and increasing incidence of early-onset ischemic strokes. Our results indicate that WC and hip circumference should be routinely measured for calculating WHRs in health checkups for young individuals, to provide more precise estimations of stroke risk.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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Supplementary materials

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