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ORIGINAL ARTICLE

Association of Traditional and Nontraditional Risk Factors in the Development of Strokes Among Young Adults by Sex and Age Group: A Retrospective Case-Control Study

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BACKGROUND: Despite women having fewer traditional risk factors (eg, hypertension, diabetes), strokes are more common in women than men aged ≤45 years. This study examined the contributions of traditional and nontraditional risk factors (eg, migraine, thrombophilia) in the development of strokes among young adults.

METHODS: This retrospective case-control study used Colorado's All Payer Claims Database (2012–2019). We identified index stroke events in young adults (aged 18–55 years), matched 1:3 to stroke-free controls, by (1) sex, (2) age±2 years, (3) insurance type, and (4) prestroke period. All traditional and nontraditional risk factors were identified from enrollment until a stroke or proxy-stroke date (defined as the prestroke period). Conditional logistic regression models stratified by sex and age group first assessed the association of stroke with counts of risk factors by type and then computed their individual and aggregated population attributable risks.

RESULTS: We included 2618 cases (52% women; 73.3% ischemic strokes) and 7827 controls. Each additional traditional and nontraditional risk factors were associated with an increased risk of stroke in all sex and age groups. In adults aged 18 to 34 years, more strokes were associated with nontraditional (population attributable risk: 31.4% men and 42.7% women) than traditional risk factors (25.3% men and 33.3% women). The contribution of nontraditional risk factors declined with age (19.4% men and 27.9% women aged 45–55 years). The contribution of traditional risk factors peaked among patients aged 35 to 44 years (32.8% men and 39.7% women). Hypertension was the most important traditional risk factor and increased in contribution with age (population attributable risk: 27.8% men and 26.7% women aged 45 to 55 years). Migraine was the most important nontraditional risk factor and decreased in contribution with age (population attributable risk: 20.1% men and 34.5% women aged 18–35 years).

CONCLUSIONS: Nontraditional risk factors were as important as traditional risk factors in the development of strokes for both young men and women and have a stronger association with the development of strokes in adults younger than 35 years of age.

Key Words: coronary disease ■ epidemiology ■ sex characteristics ■ stroke ■ young adult

Stroke incidence in adults younger than 55 years of age has been steadily increasing in high-income countries compared with the precipitous decline in older adults.[1–3] This increased incidence had been attributed to the prevalence of traditional vascular risk factors (ie, hypertension, diabetes, hyperlipidemia, smoking,

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WHAT IS KNOWN

- Recent studies have shown that women younger than 45 years of age have a higher incidence of strokes than men.
- Most strokes are caused by traditional vascular risk factors such as hypertension, hyperlipidemia, and diabetes, and women generally have a lower prevalence of these risk factors than men.

WHAT THE STUDY ADDS

- Nontraditional risk factors such as migraines, autoimmune disease, and thrombophilia are significantly associated with the development of strokes in both young men and women.
- The burden of strokes attributable to nontraditional risk factors may be higher than traditional risk factors among adults younger than 35 years of age.
- More work needs to be done to understand the etiological mechanisms of nontraditional risk factors to identify potential targets for intervention.

Nonstandard Abbreviations and Acronyms

ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
OR	odds ratio
PAR	population attributable risk

obesity, low physical activity, alcohol abuse, and coronary heart disease).[4] However, recent data show an increased incidence of strokes even among young adults without hypertension, diabetes, hyperlipidemia, smoking, or obesity, corresponding to an increasing contribution of cryptogenic strokes.[5] Furthermore, this study noted declining rates of myocardial infarction and sudden cardiac death, which share these same traditional risk factors. Further confounding the role of traditional risk factors in the development of strokes among young adults is the recent finding that women younger than 45 years of age have more strokes compared with men of the same age. In large Dutch and American cohorts of young adults, there were more strokes in women than men among adults younger than 45 years of age.[6,7] For comparison, there were twice as many men with myocardial infarctions between the age of 35 and 45 years as women of the same age.[8]

Numerous studies have demonstrated the importance of traditional risk factors on the development of strokes among young adults.[4,9,10] One large case-control study accounted for 78.9% of the population attributable risk (PAR) of stroke in young adults aged 18 to 55 years from traditional risk factors.[11] Such studies led experts to highlight the growing contribution of traditional risk factors and the diminishing role of rare or nontraditional risk factors such as migraines, oral contraceptive use, and pregnancy or puerperium.[12] However, the prevalence of traditional risk factors is lower among women.[1,4] Thus, the higher incidence of stroke among women younger than 45 years of age is counterintuitive. A better understanding of how nontraditional risk factors inform the risk of strokes among young adults is needed and may also shed light on why the incidence of stroke continues to rise.

This study examined the relative associations of traditional versus nontraditional risk factors in the development of strokes among young adults by sex using a large population-based sample. We hypothesized that despite having fewer traditional vascular risk factors, nontraditional risk factors may contribute more to the development of strokes in women than in men younger than 45 years of age.

METHODS

This is a retrospective case-control study using a population-based sample from the Colorado All Payer Claims Database. The Colorado All Payer Claims Database was created by the Colorado State Legislation in 2010 and mandated all commercial insurance, Medicaid, and Medicare claims be submitted to a centralized database. Employee Retirement Income Security Act–based self-insured employer health plans, Veteran's Administration, Tricare, and Indian Health Services were exempt from the legislation although some Employee Retirement Income Security Act covered plans submit claims voluntarily. The Colorado All Payer Claims Database covers more than 5 million subscribers, which represents ≈70% of all Coloradans. Medical and pharmaceutical claims based on services performed during the study period of January 1, 2012, and April 30, 2019, were included in this analysis. This study protocol relied on a limited, secondary data set and was deemed exempt by the University of Colorado Institutional Review Board. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Case and Control Identification

Cases were defined as having an index stroke event with an inpatient admission associated with a primary diagnosis of ischemic stroke, hemorrhagic stroke, or subarachnoid hemorrhage using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes, a previously validated methodology in young adults (Supplemental Material).[7,13] Cases were excluded if they (1) had <6 months of continuous enrollment in both medical and pharmaceutical claims; (2) missing age, sex, insurance type, or 5-digit ZIP code; (3) had <2 months of enrollment before the index stroke; and (4) had *ICD-9* or *ICD-10* codes for stroke before their index stroke event. Controls were defined as not having any *ICD-9* or *ICD-10* codes for stroke and satisfied the same exclusion criteria as cases. Each control was given a proxy-stroke date based on their matched case.

Only risk factors identified in outpatient or inpatient encounters from enrollment until 1 day before the stroke or stroke proxy date were included in the analysis, defined as the prestroke period. Cases were matched to controls (1:3) based on (1) sex, (2) insurance type (commercial or public, defined as Medicare or Medicaid), (3) age (±2 years) at the beginning of enrollment, and (4) prestroke period (±2 months) using the greedy matching method.[14] During the admission for stroke, cases would have undergone a thorough workup that controls did not receive. We only considered risk factors before the stroke admission and matched on the prestroke period to give cases and control the same opportunity to exhibit risk factors.

Covariates and Exposures

Individual race and ethnicity, based on insurance reporting, were missing for almost half of all subscribers in the Colorado All Payer Claims Database. This was not missing or undefined in an arbitrary manner as some insurers provided race and ethnicity, while others did not. To control for race and ethnicity, as well as socioeconomic status, we used the Centers for Disease Control and Prevention's social vulnerability index subindices for racial or ethnic minority status and socioeconomic status based on the geography of the subscriber's residence.[15] The race and ethnic minority index considered the proportion of the population, who were Hispanic (of any race), Black, American Indian, Alaska Native, Native Hawaiian, Pacific Islander, ≥2 races, or other races. The socioeconomic index considered 5 domains, including the proportion of the population below 150% of poverty, unemployment, housing cost burden, no high school diploma, and no health insurance. Each index is a percentile rank (range from 0 to 1) with values closer to 1 indicating greater social disadvantage. We used previously validated methods to link social vulnerability index indices at the census tract level to individual 5-digit ZIP codes.[16]

All potential traditional and nontraditional risk factors for stroke among young adults were identified based on a thorough review of the literature using original data examining risk factors of stroke in young adults (Supplemental Material). Healthcare Cost and Utilization Project Clinical Classification Software *ICD-9* and *ICD-10* codes were used to identify individual risk factors when available.[17] Where risk factors were not in the Healthcare Cost and Utilization Project (eg, sleep apnea, atrial fibrillation, tobacco use, vasculitis), we used validated *ICD-9* and *ICD-10* codes identified by literature (Table S1). Those risk factors without a unique corresponding *ICD-9* or *ICD-10* code (eg, antiphospholipid antibody syndrome, patent foramen ovale) were eliminated. Traditional risk factors were defined as being a well-established risk factor for stroke that is routinely considered during the stroke workup for older adults (aged ≥65 years).[12,13] Traditional risk factors captured include hypertension (including gestational hypertension), diabetes (including gestational diabetes), hyperlipidemia, sleep apnea, peripheral artery disease, atrial fibrillation, coronary artery disease, alcohol abuse, substance abuse, tobacco use, obesity, and congestive heart failure. Nontraditional risk factors were defined as risk factors that are rarely the cause of strokes in older adults (eg, autoimmune disease, cancer) or those unique to young adults (eg, pregnancy). Nontraditional risk factors captured include migraines, malignancy, HIV, hepatitis, thrombophilia (including history of deep vein thrombosis and pulmonary embolism), autoimmune disease, vasculitis, sickle cell disease, heart valve disease, and renal failure. Hormonal risk factors including oral contraceptives, pregnancy, or puerperium (up to 6 weeks from childbirth)[18] were considered separately in women.[19] Pharmacy claims were used to identify the use of oral contraceptives in women and to supplement the diagnosis of diabetes, dyslipidemia, migraines, malignancy, and HIV based on anatomic therapeutic chemical classification and algorithms validated in a previous study.[20] All risk factors where the number of cases was <10 were suppressed in reporting to protect confidentiality.

To account for controls and cases who were pregnant or up to 6 weeks postpartum during their stroke or proxy-stroke date, we used a previously validated methodology for administrative claims.[19] First, we identified all women with any *ICD-9* or *ICD-10* coding indicating a pregnancy end point (ie, delivery, spontaneous abortion, elected abortion) and then determined the beginning and end of the pregnancy to establish if the stroke or proxy-stroke date fell within the pregnancy or postpartum period (Table S2). To verify that no stroke-associated pregnancies were missed because the subscriber moved out of state before delivery, we looked for any antenatal care codes occurring within ≤9 months before the stroke or proxy-stroke date.[21] Cases of stroke-associated pregnancies not already identified by a pregnancy end point were reviewed by M.H.L. and S.S. Adjudication was reached by consensus. Reviewers were blinded to whether the instance was a case or control.

Statistical Analysis

Conditional logistic regression was performed to account for matching. Multivariable regression models were used to investigate the association between the development of stroke and traditional, nontraditional, or hormonal risk factors. Separate regression analyses were considered where risk factors entered into the models as counts of a particular type of risk factor or binary indicators of the presence of the particular risk factor. Social vulnerability index controlling for ethnic and racial minority status and socioeconomic status was included to adjust for confounding. To look for differences in the contribution of traditional and nontraditional risk factors in men and women, models were stratified by sex and prespecified age groups (18–35, 35–44, and 45–55 years).

First, conditional logistic regression models were used to assess the association between stroke and the count of traditional risk factors and the count of nontraditional risk factors. The stratified models by sex include counts of traditional and nontraditional risk factors and a binary indicator for the presence of hormonal risk factors in women. Both counts (and hormonal risk factors in applicable models) were tested for an interaction with categorical age to assess for effect modification. Secondary analysis examining stroke type was performed using an interaction term between each additional traditional, nontraditional, or hormonal risk factor and stroke type including ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage.

Second, conditional logistic models were adjusted for all individual risk factors. Due to the low prevalence of some risk factors within some sex and age categories, those risk factors were not included in the corresponding stratified model (Table 1). From these models, the PAR was calculated for individual risk factors and aggregated risk factors based on methods previously described and applied to young adult stroke cohorts.[11,22,23] The PAR assumes that the prevalence of

Table 1. Patient Characteristic by Sex in Cases and Controls

	Men			Women		
	Cases	Controls	*P* value	Cases	Controls	*P* value
All	1246	3725		1372	4102	
18–35, y	163 (13.1%)	477 (12.8%)	0.968	235 (17.1%)	700 (17.1%)	0.994
35–44, y	296(23.8%)	887 (23.8%)		337 (24.6%)	1003 (24.5%)	
45–55, y	787 (63.2%)	2361 (63.4%)		800 (58.3%)	2399 (58.5%)	
Commercial insurance	579 (46.5%)	1730 (46.4%)	0.987	585 (42.6%)	1752 (42.7%)	0.963
Hispanic	60 (4.8%)	180 (4.8%)	<0.001	62 (4.5%)	227 (5.5%)	0.074
Black	47 (3.8%)	60 (1.6%)		35 (2.6%)	70 (1.7%)	
White	205 (16.5%)	651 (17.5%)		281 (20.5%)	779 (19.0%)	
Other	281 (22.6%)	745 (20%)		274 (20%)	891 (21.7%)	
Missing	653 (52.4%)	2089 (56.1%)		720 (52.5%)	2135 (52%)	
Ischemic	928 (74.5%)	N/A		990 (72.2%)	N/A	<0.0001*
ICH	177 (14.2%)	N/A		154 (11.2%)	N/A	
SAH	141 (11.3%)	N/A		228 (16.6%)	N/A	
Traditional risk factors						
Hypertension	552 (44.3%)	815 (21.9%)	<0.0001	571 (41.6%)	803 (19.6%)	<0.0001
Diabetes	315 (25.3%)	503 (13.5%)	<0.0001	336 (24.5%)	594 (14.5%)	<0.0001
Hyperlipidemia	411 (33.0%)	894 (24.0%)	<0.0001	396 (28.9%)	751 (18.3%)	<0.0001
Sleep apnea	162 (13.0%)	367 (9.9%)	0.002	241 (17.6%)	472 (11.5%)	<0.0001
Peripheral artery disease	67 (5.4%)	61 (1.6%)	<0.0001	72 (5.2%)	65 (1.6%)	<0.0001
Atrial fibrillation	59 (4.7%)	33 (0.9%)	<0.0001	31 (2.3%)	20 (0.5%)	<0.0001
Coronary artery disease	164 (13.2%)	123 (3.3%)	<0.0001	107 (7.8%)	68 (1.7%)	<0.0001
Alcohol abuse	93 (7.5%)	176 (4.7%)	<0.001	71 (5.2%)	102 (2.5%)	<0.0001
Substance use	195 (15.7%)	326 (8.8%)	<0.0001	228 (16.6%)	332 (8.1%)	<0.0001
Tobacco use	359 (28.8%)	668 (17.9%)	<0.0001	450 (32.8%)	787 (19.2%)	<0.0001
Obesity	191 (15.3%)	434 (11.7%)	<0.001	362 (26.4%)	863 (21%)	<0.0001
Congestive heart failure	126 (10.1%)	70 (1.9%)	<0.0001	94 (6.9%)	53 (1.3%)	<0.0001
No. of traditional vascular risk factors						
0	414 (33.2%)	1940 (52.1%)	<0.0001	385 (28.1%)	1971 (48%)	<0.0001
1	198 (15.9%)	603 (16.2%)		265 (19.3%)	868 (21.2%)	
2	167 (13.4%)	475 (12.8%)		217 (15.8%)	540 (13.2%)	
≥3	467 (37.5%)	707 (19.0%)		505 (36.8%)	723 (17.6%)	
Hormonal risk factors						
Pregnant/postpartum	N/A	N/A		22 (1.6%)	98 (2.4%)	0.085
Oral contraceptive	N/A	N/A		200 (14.6%)	389 (9.5%)	<0.0001
Nontraditional risk factors						
Migraines	301 (24.2%)	398 (10.7%)	<0.0001	598 (43.6%)	994 (24.2%)	<0.0001
Malignancy	90 (7.2%)	180 (4.8%)	0.001	157 (11.4%)	346 (8.4%)	<0.001
HIV	14 (1.1%)	48 (1.3%)	0.65	Suppressed†	Suppressed†	
Hepatitis	49 (3.9%)	113 (3.0%)	0.122	47 (3.4%)	73 (1.8%)	<0.001
Thrombophilia	154 (12.4%)	154 (4.1%)	<0.0001	183 (13.3%)	164 (4.0%)	<0.0001
Autoimmune	36 (2.9%)	48 (1.3%)	<0.001	90 (6.6%)	131 (3.2%)	<0.0001
Vasculitis	Suppressed†	Suppressed†		14 (1.0%)	15 (0.4%)	0.004
Sickle cell disease	Suppressed†	Suppressed†		Suppressed†	Suppressed†	
Heart valve disease	134 (10.8%)	94 (2.5%)	<0.0001	153 (11.2%)	138 (3.4%)	<0.0001
Renal failure	193 (15.5%)	142 (3.8%)	<0.0001	151 (11.0%)	81 (2.0%)	<0.0001

(*Continued*)

Table 1. Continued

	Men			Women		
	Cases	Controls	*P* value	Cases	Controls	*P* value
No. of nontraditional risk factors						
0	695 (55.8%)	2924 (78.5%)	<0.0001	556 (40.5%)	2698 (65.8%)	<0.0001
1	300 (24.1%)	552 (14.8%)		467 (34%)	1011 (24.6%)	
2	139 (11.2%)	162 (4.3%)		185 (13.5%)	275 (6.7%)	
3	112 (9.0%)	87 (2.3%)		164 (12.0%)	118 (2.9%)	

ICH indicates intracranial hemorrhage; N/A, not applicable; and SAH, subarachnoid hemorrhage.
**P* value comparing men vs women by stroke type.
†Suppressed with n<10.

risk factors in the control group is reflective of what would be observed in the overall young adult population. PAR indicates the proportion of incidence of stroke in the population due to risk factor(s) exposure. Statistical significance was determined as $P<0.05$. All analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

There was a total of 2618 cases (52% women; 73.3% ischemic strokes) and 7827 controls (Figure 1). Duration of prestroke period by sex and age group is provided in Tables S3 and S4, respectively. All traditional risk factors were more prevalent among cases than controls. The most prevalent traditional risk factors among cases were hypertension (44.3%), hyperlipidemia (33%), and tobacco use (28.8%) in men and hypertension (41.6%), tobacco use (32.8%), and hyperlipidemia (28.9%) in women. The most prevalent nontraditional risk factors among cases were migraines (24.2%), renal failure (15.5%), and thrombophilia (12.4%) in men and migraines (43.6%), thrombophilia (13.5%), and malignancy (11.4%) in women. Women with stroke were less likely to be pregnant but more likely to be taking oral contraceptives than controls. There were more controls without any risk factors than cases.

Counts of Risk Factors

In men, each additional traditional vascular risk factor was significantly associated with increased odds of stroke, and there was no difference in the magnitude

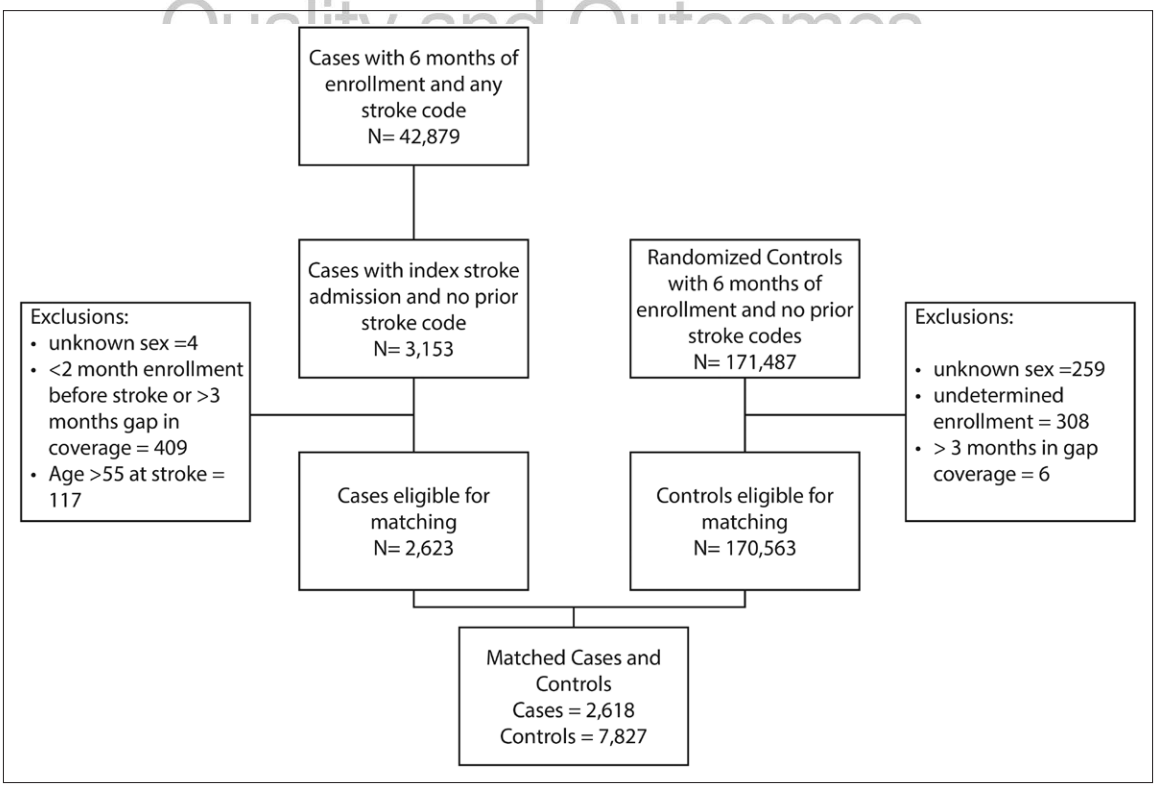

Figure 1. Eligibility and inclusion flowchart from the Colorado All Payer Claims Database for young adults aged between 18 and 55 y from January 1, 2012, to April 30, 2019.

of association between the age groups (Figure 2). Each additional nontraditional risk factor in men was also associated with an increased risk of stroke, but this effect was significantly higher in the youngest age group (odds ratio [OR], 2.4 [95% CI, 18–34] years) than in the oldest age group (OR, 1.4 [95% CI, 45–55] years; *P* for interaction, 0.004). Similarly, each additional traditional vascular risk factor in women significantly increased the odds of stroke by the same magnitude in each age group. In contrast, each additional nontraditional risk factor increased the odds of stroke but was significantly higher in the 2 younger age groups (OR, 2.1 [95% CI, 18–34] and [95% CI, 35–44] years) compared with women in the oldest age group (OR, 1.5 [95% CI, 45–55] years; $P \leq 0.001$). Pregnancy and oral contraceptives increased the odds of stroke in women 35 or older but not in women younger than 35 years of age.

In the stratified analysis by stroke type (ischemic, hemorrhagic stroke, and subarachnoid hemorrhage), most of the effect of increased odds of stroke with each additional risk factor type was driven by ischemic strokes (Table S5). Each additional traditional risk factor increased the odds of hemorrhagic stroke in men aged 45 to 55 years and the odds of subarachnoid hemorrhage in women of all age groups but not men. Meanwhile, each additional nontraditional risk factor increased the odds of intracranial and subarachnoid hemorrhage in men and women aged 35 to 44 and 45 to 55 years.

Individual Risk Factors by Type

The PAR of traditional risk factors increased with age and peaked in the 35- to 44-year age group in both men and women (Figure 3). Meanwhile, the PAR for nontraditional risk factors was highest in the 18- to 34-year age group and declined with age in both men and women. Notably, traditional and non-traditional risk factors were associated with similar degrees of stroke burden among men and women less than 45 years of age. The most important traditional risk factor in both men and women was hypertension, whose PAR increased with age. Conversely, the most important nontraditional risk factor in men and women was migraines, whose PAR declined with age.

Young Adults Aged 18 to 35 Years

Among young adults aged 18 to 34 years, 42.4% (95% CI, 24.6%–60.1%) of all strokes in men were associated with any risk factor, while 25.3% of strokes were associated with traditional risk factors and 31.4% were associated with nontraditional risk factors (Table 2). In men, hypertension (OR 3.1, [95% CI, 1.2–7.8]) was the only significant traditional risk factor, and migraines (OR, 3.9 [95% CI, 2.1–7.3]), heart valve disease (OR, 3.1 [95% CI, 1.0–9.7]), and renal failure (OR, 8.9 [95% CI, 1.9–4.3]) were significant nontraditional risk factors. Among women in this age group, 61.1% (95% CI, 49.1%–73%) of strokes were associated with any risk factor, 33.3%% of strokes were associated with traditional risk factors, and 42.7% of strokes were associated with nontraditional risk factors. In women, hypertension (OR, 3.2 [95% CI, 1.8–5.6]) was the only significant traditional risk factor, migraines (OR, 3.3 [95% CI, 2.2–4.3]), autoimmune disease (OR, 8.8 [95% CI, 2.4–32.9]), and heart valve disease (OR, 4.2 [95% CI, 1.7–10.5]) were significant nontraditional risk factors. Migraines were associated with 20.1% and 34.5% of strokes in men and women

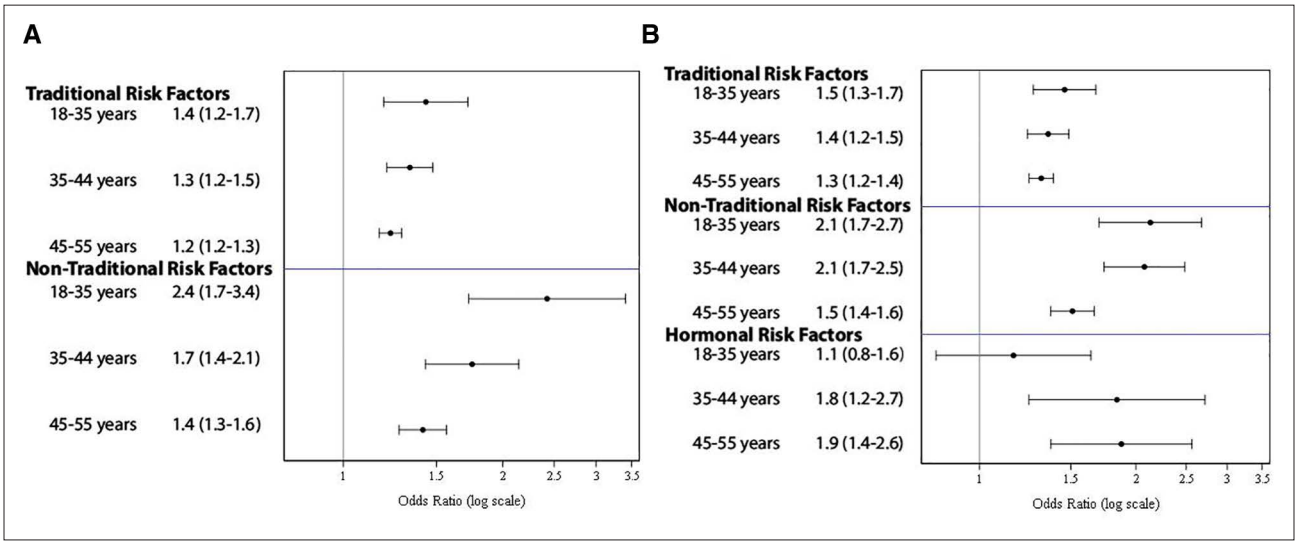

Figure 2. Odds ratio of traditional, non-traditional, and hormonal risk factors by sex and age group.
The odds ratio of the association of each additional risk factor compared with none (reference) with the development of strokes in (**A**) men and (**B**) women by age group.

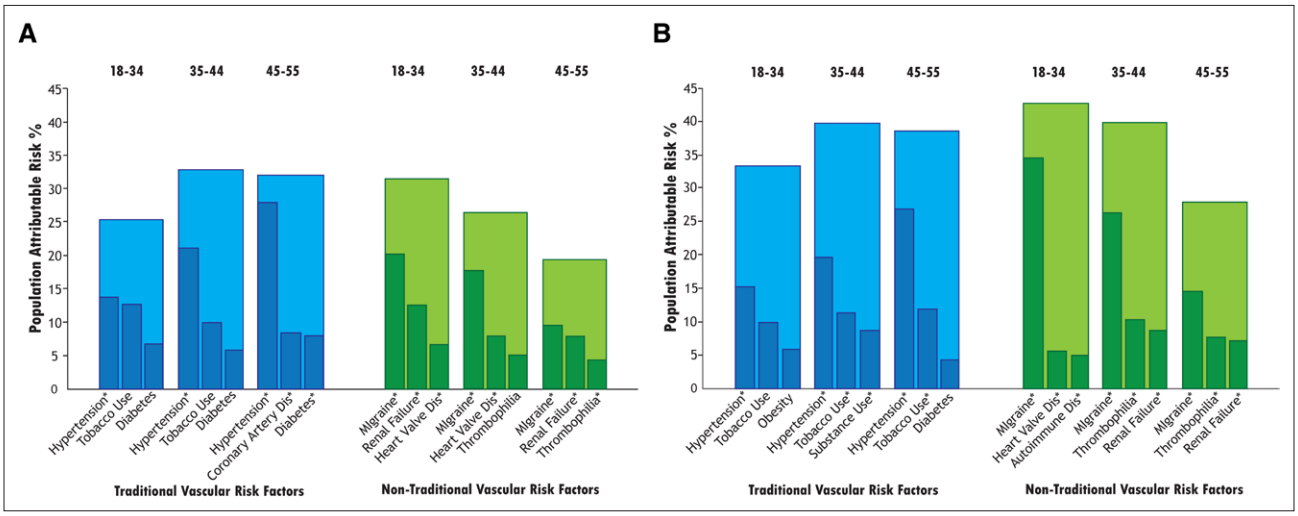

Figure 3. Population attributable risk of traditional and non-traditional risk factors by sex and age group.
Population attributable risk of traditional vascular and nontraditional risk factors with top 3 contributing individual risk factors in (**A**) men and (**B**) women by age group. Dis indicates disease. **P*<0.05 by age group.

compared with 13.8% and 15.2% associated with hypertension, respectively.

Young Adults Aged 35 to 44 Years

Among young adults 35 to 44 years, 43.7% (95% CI, 37.3%–50.2%) of strokes in men were associated with any risk factor, while 32.8% of strokes were associated with traditional risk factors and 26.4% were associated with nontraditional risk factors (Table 3). In men, hypertension (OR, 2.2 [95% CI, 1.5–3.3]) was the only significant traditional risk factor, while migraines (OR, 3.1 [95% CI, 1.9–4.6]) and heart valve disease (OR, 3.8 [95% CI, 1.5–9.6]) were significant nontraditional risk factors. Among women in this age group, 62.5% (95% CI, 54.4%–70.6%) of strokes were associated with any risk factor, with 39.7% associated with traditional risk factors and 39.8% associated with nontraditional risk factors. In women, hypertension (OR, 2.0 [95% CI, 1.4–3.0]) and coronary artery disease (OR, 6.0 [95% CI, 2.0–17.9]) were significant traditional risk factors, while migraines (OR, 2.0 [95% CI, 1.5–2.8]), thrombophilia (OR, 3.0 [95% CI, 1.6–5.4]), autoimmune diseases (OR, 3.6 [95% CI, 1.4–9.5]), and renal failure (OR, 3.4 [95% CI, 1.6–7.5]) were significant nontraditional risk factors, and hormonal risk factors were also significant (OR, 8.7 [95% CI, 2.7–14.8]). The most important risk factor in women was again migraines (PAR, 26.2%) compared with hypertension (PAR, 19.6%). The most important risk factor in men was hypertension (PAR, 21%) compared with migraines (PAR, 17.7%).

Young Adults Aged 45 to 55 Years

Among young adults aged 45 to 55 years, 41.1% (95% CI, 35.5%–46.6%) of strokes in men were associated with any risk factor, with 32% associated with traditional risk factors and 19.4% associated with nontraditional risk factors (Table 4). In men, hypertension (OR, 2.2 [95% CI, 1.7–2.7]), diabetes (OR, 1.4 [95% CI, 1.1–1.7]), atrial fibrillation (OR, 1.8 [95% CI, 1.0–3.3]), coronary artery disease (OR, 2.0 [95% CI, 1.4–2.8]), substance use (OR, 1.5 [95% CI, 1.1–2.0]), and congestive heart failure (OR, 1.6 [95% CI, 1.0–2.6]) were significant traditional risk factors, while migraines (OR, 1.7 [95% CI, 1.3–2.2]), thrombophilia (OR, 1.5 [95% CI, 1.0–2.2]), and renal failure (OR, 1.9 [95% CI, 1.3–2.8]) were significant nontraditional risk factors. Notably in men, the diagnosis of sleep apnea (OR, 0.6 [95% CI, 0.5–0.8]) and obesity (OR, 0.7 [95% CI, 0.5–0.9]) was associated negatively with the development of stroke. In women aged 45 to 55 years, 53.9% (95% CI, 49.3%–58.5%) of strokes were associated with any risk factor, with 38.9% of strokes associated with traditional risk factors and 27.9% associated with nontraditional risk factors. In women, hypertension (OR, 2.2 [95% CI, 1.8–2.8]), tobacco use (OR, 1.6 [95% CI, 1.2–2.0]), and congestive heart failure (OR, 1.7 [95% CI, 1.0–3.0]) were significant traditional risk factors, while migraines (OR, 1.6 [95% CI, 1.3–2.0]), thrombophilia (OR, 2.3 [95% CI, 1.6–3.2]), heart valve disease (OR, 1.5 [95% CI, 1.0–2.1]), and renal failure (OR, 2.3 [95% CI, 4.6–3.5]) were significant nontraditional risk factors, and hormonal risk factors (OR, 1.8 [95% CI, 1.3–2.5]) were also significant. Hypertension was associated with 27.8% and 26.7% of strokes in men and women, respectively, and was the most important risk factor. OR and PAR for ischemic strokes by age group and sex are reported in Tables S6 through S8.

DISCUSSION

We found that nontraditional risk factors were just as important as traditional risk factors in the development of strokes for both men and women, associated with

Table 2. OR and PAR of Any Stroke in Young Adults Aged 18 to 34 Years by Sex

	Men		Women	
	OR (95% CI)	PAR (95% CI)	OR (95% CI)	PAR (95% CI)
Traditional vascular risk factors				
Hypertension	3.1 (1.2 to 7.8)*	13.8 (7.5 to 20.0)	3.2 (1.8 to 5.6)†	15.2 (8.8 to 21.7)
Diabetes	2.0 (0.7 to 5.6)	6.8 (−2.6 to 16.3)	1.1 (0.6 to 1.9)	0.7 (−7.0 to 8.5)
Hyperlipidemia	0.5 (0.2 to 1.6)	−9.0 (−36.1 to 18.1)	1.3 (0.6 to 2.7)	2.4 (−4.4 to 9.3)
Sleep apnea	0.4 (0.1 to 1.4)	−9.9 (−42.4 to 22.7)	1.1 (0.5 to 2.1)	0.5 (−6.8 to 7.9)
Peripheral artery disease	0.8 (0.1 to 8.8)	−0.4 (−14.5 to 13.7)	1.5 (0.2 to 14.3)	0.6 (−3.5 to 4.6)
Atrial fibrillation	Nim‡	Nim‡	Nim‡	Nim‡
Coronary artery disease	3.2 (0.3 to 31.2)	3.0 (−3.7 to 9.6)	9.0 (0.6 to 127.6)	1.9 (−0.4 to 4.1)
Alcohol abuse	1.3 (0.5 to 3.2)	1.8 (−4.9 to 8.4)	1.5 (0.5 to 4.4)	1.3 (−4.1 to 6.7)
Substance use	1.2 (0.5 to 2.6)	2.0 (−6.4 to 10.4)	1.5 (0.8 to 2.8)	5.4 (−0.9 to 11.7)
Tobacco use	1.8 (0.9 to 3.5)	12.7 (0.7 to 24.7)	1.5 (0.9 to 2.4)	9.8 (−0.5 to 20.2)
Obesity	1.6 (0.6 to 4.4)	3.8 (−6.3 to 13.8)	1.3 (0.8 to 2.1)	5.8 (−1.2 to 12.9)
Congestive heart failure	Nim‡	Nim‡	Nim‡	Nim‡
All traditional vascular risk factors		25.3 (13.0 to 37.7)§		33.3 (26.0 to 40.6)§
Nontraditional risk factors				
Migraines	3.9 (2.1 to 7.3)†	20.1 (12.6 to 27.6)	3.3 (2.2 to 4.8)†	34.5 (27.8 to 41.2)
Malignancy	1.0 (0.3 to 4.1)	0.1 (−6.5 to 6.6)	0.8 (0.4 to 1.8)	−1.3 (−7.4 to 4.7)
HIV	Nim‡	Nim‡	Nim‡	Nim‡
Hepatitis	0.4 (0.1 to 2.7)	−2.6 (−20.4 to 15.3)	0.8 (0.1 to 5.5)	−0.2 (−3.6 to 3.1)
Thrombophilia	2.9 (0.8 to 10.7)	5.6 (0.3 to 11.0)	1.2 (0.5 to 2.5)	1.4 (−6.7 to 9.5)
Autoimmune	0.8 (0.0 to 12.7)	−0.8 (−10.9 to 9.3)	8.8 (2.4 to 32.9)‖	4.9 (1.0 to 8.8)
Vasculitis	Nim‡	Nim‡	Nim‡	Nim‡
Sickle cell disease	Nim‡	Nim‡	Nim‡	Nim‡
Heart valve disease	3.1 (1.0 to 9.7)	6.6 (0.7 to 12.6)	4.2 (1.7 to 10.5)‖	5.5 (2.3 to 8.7)
Renal failure	8.9 (1.9 to 43.1)‖	12.5 (7.4 to 17.6)	3.7 (0.8 to 16.4)	3.7 (0.2 to 7.2)
All nontraditional risk factors		31.4 (16.0 to 47.0)§		42.7 (30.6 to 54.7)§
Pregnancy/postpartum/oral contraceptives			1.2 (0.8 to 1.7)	5.4 (−8.2 to 19.1)
All risk factors		42.4 (24.6 to 60.1)§		61.1 (49.1 to 73.0)§

Nim indicates not in model; OR, odds ratio; and PAR, population attributable risk.

*P value<0.05.

†P value<0.0001.

‡Due to low numbers of risk factors within the sex and age category (n<2), some risk factor estimates were inestimable and, thus, not included in the model.

§Aggregated risk factors, traditional, non-traditional, or all.

‖P value < 0.01

as much stroke risk as traditional risk factors in adults younger than 45 years of age. The contribution of nontraditional risk factors declines with age, while the contribution of traditional risk factors peaks among patients aged 35 to 44 years. Hypertension was the most important traditional risk factor with increasing contribution with age in both men and women and accounted for 27.8% and 26.7% of strokes in men and women aged 45 to 55 years, respectively. Meanwhile, migraine was the most important nontraditional risk factor, with declining contribution with age, and accounted for 20.1% and 34.5% of strokes in men and women younger than 35 years of age, respectively. Contrary to our hypothesis, nontraditional risk factors were equally important to the development of strokes in young men and women. These findings underscore the importance of also considering nontraditional risk factors in the etiologies of strokes, among young adults.

Notably, significantly more risk factors were reported in women than men. Among controls, 52% and 34% of women had at least one traditional risk factor and nontraditional risk factor, respectively, compared with 48% and 22% of men with at least one traditional risk factor and nontraditional risk factor, respectively. This difference is likely because young women have more routine interactions with health care, for example, childbirth, birth control, annual gynecological exams, and mammograms, than men of the same age.[24] During these routine health care encounters, there is an opportunity to be diagnosed

Table 3. OR and PAR of Any Stroke in Young Adults Aged 35 to 44 Years by Sex

	Men		Women	
	OR (95% CI)	PAR (95% CI)	OR (95% CI)	PAR (95% CI)
Traditional vascular risk factors				
Hypertension	2.2 (1.5 to 3.3)*	21.0 (12.5 to 29.4)	2.0 (1.4 to 3.0)*	19.6 (9.6 to 29.6)
Diabetes	1.4 (0.8 to 2.4)	5.7 (−4.2 to 15.6)	1.1 (0.7 to 1.8)	3.2 (−9.2 to 15.5)
Hyperlipidemia	0.9 (0.6 to 1.4)	−3.0 (−18.0 to 12.0)	1.3 (0.8 to 2.0)	5.0 (−6.0 to 16.0)
Sleep apnea	0.8 (0.5 to 1.4)	−3.5 (−17.2 to 10.2)	1.6 (1.1 to 2.5)†	7.8 (−0.7 to 16.3)
Peripheral artery disease	1.2 (0.4 to 3.8)	0.7 (−5.2 to 6.5)	1.0 (0.3 to 3.0)	−0.1 (−3.7 to 3.5)
Atrial fibrillation	3.1 (0.7 to 13.0)	2.7 (−0.8 to 6.3)	0.4 (0.1 to 2.5)	−3.1 (−19.9 to 13.6)
Coronary artery disease	2.2 (0.8 to 5.9)	4.6 (−0.1 to 9.3)	6.0 (2.0 to 17.9)‡	7.2 (3.3 to 11.1)
Alcohol abuse	0.9 (0.4 to 1.9)	−0.7 (−8.8 to 7.5)	2.6 (1.0 to 6.5)†	2.7 (0.8 to 4.6)
Substance use	1.3 (0.7 to 2.5)	3.4 (−3.5 to 10.3)	1.9 (1.1 to 3.2)†	8.6 (1.8 to 15.3)
Tobacco use	1.5 (0.9 to 2.4)	9.8 (−3.1 to 22.6)	1.5 (1.0 to 2.2)†	11.3 (2.6 to 20.0)
Obesity	1.1 (0.7 to 1.8)	1.3 (−6.2 to 8.9)	0.7 (0.5 to 1.1)	−11.8 (−29.4 to 5.9)
Congestive heart failure	2.2 (0.8 to 6.1)	4.8 (0.6 to 8.9)	1.5 (0.6 to 4.0)	2.4 (−2.4 to 7.2)
All traditional vascular risk factors		32.8 (25.6 to 39.9)§		39.7 (32.7 to 46.7)§
Nontraditional risk factors				
Migraines	3.0 (1.9 to 4.6)*	17.7 (10.0 to 25.3)	2.0 (1.5 to 2.8)*	26.2 (16.2 to 36.2)
Malignancy	0.9 (0.4 to 2.0)	−0.4 (−5.5 to 4.7)	1.1 (0.7 to 1.9)	1.1 (−4.8 to 6.9)
HIV	Nim‖	Nim‖	Nim‖	Nim‖
Hepatitis	1.1 (0.3 to 3.8)	0.1 (−2.8 to 3.1)	1.5 (0.4 to 5.4)	1.1 (−1.8 to 4.1)
Thrombophilia	1.7 (0.8 to 3.4)	5.1 (−2.2 to 12.4)	3.0 (1.6 to 5.4)*	10.2 (5.6 to 14.9)
Autoimmune	1.1 (0.3 to 3.7)	0.1 (−2.9 to 3.2)	3.6 (1.4 to 9.5)‡	5.1 (−0.3 to 10.6)
Vasculitis	Nim‖	Nim‖	Nim‖	Nim‖
Sickle cell disease	Nim‖	Nim‖	Nim‖	Nim‖
Heart valve disease	3.8 (1.5 to 9.6)‡	8.0 (3.0 to 13.0)	1.1 (0.5 to 2.6)	1.1 (−6.2 to 8.4)
Renal failure	1.1 (0.5 to 2.4)	1.7 (−9.1 to 12.6)	3.4 (1.6 to 7.5)‡	8.6 (3.6 to 13.6)
All nontraditional risk factors		26.4 (15.5 to 37.3)§		39.8 (29.0 to 50.7)§
Pregnancy/postpartum/oral contraceptives			1.9 (1.3 to 2.9)‡	8.7 (2.7 to 14.8)
All risk factors		43.7 (37.3 to 50.2)§		62.5 (54.4 to 70.6)§

Nim indicates not in model; OR, odds ratio; and PAR, population attributable risk.
*P value<0.001.
†P value<0.05.
‡P value<0.01.
§Aggregated risk factors, traditional, non-traditional, or all.
‖Due to low numbers of risk factors within the sex and age category (n<2), some risk factor estimates were inestimable and thus not included in the model.

with risk factors. Consequently, we accounted for more of the total PAR of stroke among women than men in every age group breakdown. After controlling for other traditional risk factors, men aged 45 to 44 years diagnosed with sleep apnea or obesity were less likely to develop strokes. Because not all men routinely seek medical care, risk factor diagnosis was inadvertently conditioned on the index event of an outpatient visit. Such paradoxical associations have been previously reported, including the obesity paradox, where it appears to protect against recurrent coronary artery events.[25,26] Thus, after controlling for other traditional risk factors, the diagnosis of sleep apnea or obesity was predictive of care-seeking behavior, which was protective of stroke development.

Literature examining the attribution of risk factors toward the development of strokes among young adults has focused on traditional risk factors with some variability in estimates regarding their contribution. Aigner et al[11] estimated the PAR from hypertension to be 27%, compared with 12% estimated by Kivioja et al,[23] and 50% estimated by INTERSTROKE, an international study on stroke risk factors.[27] Notably, all 3 studies used the same definition of hypertension (blood pressure >140/90 mm Hg), in young adults aged <55 years (<50 years in reference [23]), though INTERSTROKE comprised a much more racially diverse population. Some of this discrepancy may be also due to the methodology used to identify risk factors; while all stroke cases had undergone a clinical exam, some studies relied on a survey to identify risk factors in controls. In

Table 4. OR and PAR of Any Stroke in Young Adults Aged 45 to 55 Years by Sex

	Men		Women	
	OR (95% CI)	PAR (95% CI)	OR (95% CI)	PAR (95% CI)
Traditional vascular risk factors				
Hypertension	2.2 (1.7 to 2.7)*	27.8 (20.1 to 35.4)	2.2 (1.8 to 2.8)*	26.7 (21.0 to 32.5)
Diabetes	1.4 (1.1 to 1.7)†	7.8 (0.1 to 15.6)	1.2 (0.9 to 1.5)	4.1 (−2.6 to 10.9)
Hyperlipidemia	0.8 (0.6 to 1.0)	−9.3 (−20.6 to 2.0)	1.1 (0.9 to 1.4)	3.1 (−4.0 to 10.2)
Sleep apnea	0.6 (0.5 to 0.8)‡	−8.3 (−15.2 to −1.3)	0.9 (0.7 to 1.2)	−2.2 (−8.5 to 4.1)
Peripheral artery disease	1.1 (0.7 to 1.8)	0.5 (−1.9 to 3.0)	1.5 (0.9 to 2.3)	2.2 (0.0 to 4.4)
Atrial fibrillation	1.8 (1.0 to 3.3)†	2.6 (0.1 to 5.0)	1.8 (0.8 to 3.9)	1.3 (−0.3 to 2.8)
Coronary artery disease	2.0 (1.4 to 2.8)*	8.3 (4.6 to 11.9)	1.4 (0.9 to 2.2)	2.8 (−0.4 to 6.0)
Alcohol abuse	1.0 (0.7 to 1.5)	0.2 (−3.7 to 4.1)	1.0 (0.6 to 1.6)	0.1 (−2.8 to 3.0)
Substance use	1.5 (1.1 to 2.0)†	5.4 (0.7 to 10.0)	1.2 (0.9 to 1.7)	3.0 (−2.9 to 8.8)
Tobacco use	1.1 (0.8 to 1.4)	2.2 (−5.3 to 9.7)	1.6 (1.2 to 2.0)*	11.7 (5.6 to 17.9)
Obesity	0.7 (0.5 to 0.9)‡	−7.1 (−12.8 to −1.4)	0.8 (0.6 to 1.0)	−6.0 (−15.7 to 3.6)
Congestive heart failure	1.6 (1.0 to 2.6)†	4.7 (1.0 to 8.3)	1.7 (1.0 to 3.0)†	3.4 (0.1 to 6.7)
All traditional vascular risk factors		32.0 (23.2 to 40.9)§		38.6 (32.7 to 44.5)§
Nontraditional risk factors				
Migraines	1.7 (1.3 to 2.2)*	9.5 (4.0 to 14.9)	1.6 (1.3 to 2.0)*	14.4 (9.1 to 19.6)
Malignancy	1.3 (0.9 to 1.8)	2.0 (−0.5 to 4.4)	1.1 (0.9 to 1.5)	1.6 (−1.6 to 4.8)
HIV	0.4 (0.2 to 1.0)†	−1.7 (−3.7 to 0.3)	0.8 (0.2 to 3.0)	−0.2 (−1.6 to 1.2)
Hepatitis	0.7 (0.4 to 1.1)	−2.6 (−6.0 to 0.9)	0.9 (0.5 to 1.5)	−0.5 (−3.5 to 2.4)
Thrombophilia	1.5 (1.0 to 2.2)†	4.3 (0.9 to 7.8)	2.3 (1.6 to 3.2)*	7.5 (3.4 to 11.7)
Autoimmune	1.3 (0.7 to 2.4)	0.7 (−0.9 to 2.2)	1.1 (0.7 to 1.6)	0.3 (−3.1 to 3.7)
Vasculitis	1.1 (0.3 to 4.8)	0.0 (−0.8 to 0.9)	0.9 (0.3 to 2.9)	−0.1 (−0.9 to 0.7)
Sickle cell disease	Nim‖	Nim‖	Nim‖	Nim‖
Heart valve disease	1.3 (0.8 to 2.0)	2.4 (−1.4 to 6.1)	1.5 (1.0 to 2.1)†	4.2 (−0.6 to 9.0)
Renal failure	1.9 (1.3 to 2.8)*	7.8 (4.6 to 11.1)	2.3 (1.6 to 3.5)*	7.0 (4.1 to 9.9)
All nontraditional risk factors		19.4 (12.8 to 25.9)§		27.9 (22.3 to 33.5)§
Pregnancy/postpartum/oral contraceptives			1.8 (1.3 to 2.5)*	4.4 (1.6 to 7.2)
All risk factors		41.1 (35.5 to 46.6)§		53.9 (49.3 to 58.5)§

Nim indicates not in model; OR, odds ratio; and PAR, population attributable risk.
*P value<0.001.
†P value<0.05.
‡P value < 0.01.
§Aggregated risk factors, traditional, non-traditional, or all.
‖Due to low numbers of risk factors within the sex and age category (n<2), some risk factor estimates were inestimable and thus not included in the model.

this study, cases and controls had the same opportunity to be diagnosed with risk factors because we considered only risk factors identified before the stroke admission. Our estimates of PAR from hypertension fall in line with Aigner et al and Kivioja et al, accounting for 14% in men and 15% in women aged 18 to 34 years and up to 28% in men and 27% in women aged 45 to 55 years.

Much less attention has been paid to nontraditional risk factors, including migraines, oral contraceptives, autoimmune diseases, thrombophilia, cancer, or pregnancy, which are shown to have an association with the development of strokes.[28–31] There have been several case-control studies examining the association of risk factors in young adults with the development of strokes (Table S9).[10,11,23,27,32–39] However, while all have examined an exhaustive list of traditional risk factors, few have considered nontraditional risk factors. Despite nontraditional risk factors accounting for more than half the overall risk of stroke in young adults aged 18 to 34 and 35 to 44 years, in our study, this contribution was likely an underestimate. We were unable to account for important nontraditional risk factors such as antiphospholipid antibody syndrome or patent foramen ovale because they lacked reliable administrative algorithms. Hence, the overall contribution of nontraditional risk factors to the development of strokes in young adults is likely greater and warrants further investigation.

Migraine was the most important nontraditional risk factor among young adults in this study. The association between migraine and ischemic strokes has been previously demonstrated.[39–42] Martinez-Majander et al[39] conducted a case-control study looking at any migraine,

migraine with aura, and migraine without aura with the development of cryptogenic ischemic stroke in young adults (18–49 years). They found any migraine and migraine with aura were associated with strokes, with ORs of 2.48 and 3.50, respectively, whereas migraine without aura was not. We did not have the ability to differentiate between migraine with aura and migraine without aura in this study, but our findings suggest that the association with stroke is stronger among the younger age group (OR, 3.9 and 3.3 in men and women aged 18–34 years, respectively) compared with the older age group (OR, 1.7 and 1.6 in men and women aged 45–55 years, respectively). Our study demonstrates, for the first time, the contribution of migraines to the overall attributable risk of strokes in young adults, which was half of the PAR in adults younger than 35 years of age. Given the higher prevalence of migraines in young women and its stronger association among the younger age groups (ie, 18–34 and 35–45 years), migraines could account for some of the sex differences that we are seeing in the development of strokes among young adults aged <35 years.

There are many data-driven hypotheses explaining the relationship between migraines and strokes from (1) hypercoagulability due to elevated procoagulants exacerbated by smoking or exogenous estrogen to (2) hypoperfusion induced by cortical spreading depression, (3) endothelial dysfunction caused by accelerated atherosclerosis, (4) emboli induced through right to left shunts, (5) genetic associations causing both migraines and strokes, and (6) treatments rendered for migraines, including nonsteroidal anti-inflammatory drugs, triptans, and ergotamine (Figure 4).[43–45] However, how much each mechanism may contribute to the overall risk of stroke in migraineurs or whether migraine is a modifiable risk factor for stroke remains unknown. Thus far, the only intervention for stroke reduction in migraineurs is the Centers for Disease Control and Prevention's recommendation to avoid combined hormonal contraceptives in women with migraine with aura.[46] However, migraine and stroke can share similar clinical features in young adults, thus the potential for misdiagnosis and making this field more challenging to study.

This study has notable strengths and limitations. The strengths of our study include the inclusive population-based data set which captured a large, representative sample of strokes among young Coloradans. We had a large sample of well-matched controls, which allowed for PAR estimations of stroke. Finally, the same protocol for defining risk factors was applied to both cases and controls, which gave them the same opportunity to be identified with risk factors. There were also notable limitations; first, the risk factors were identified retrospectively based on an administrative data set; hence, we cannot account for risk factors that may have been present in controls or cases who did not seek care or whose diagnoses were not coded. As a result, risk factors were likely undercoded, especially in men, which speaks to the limitations of PAR as an outcome measure due to unmeasured bias and residual confounding. Second, given our study design, we are not able to establish causality of any individual risk factor. Risk factors that are along the same causal pathway were concurrently assessed potentially diminishing the contribution of each. This and insufficient power may have contributed to known associations (ie, diabetes) as insignificant. In a claims data set, the precursor risk factor (eg, hypertension, diabetes) may not have been captured, but the diagnosis of other sequelae (ie, myocardial infarction) may have. The goal of this study was to see how much of the overall association with strokes can be assessed from traditional or nontraditional risk factors and not to establish causality in any individual pathway. We sought to reproduce the analytical design of prior studies in this field to allow for comparability between studies. Third, this study was conducted in Colorado, where major metropolitan areas sit along the front range at a mile or more above sea level. Thus, altitude may create unique conditions that are not generalizable to other populations. An example is the low prevalence of sickle cell disease

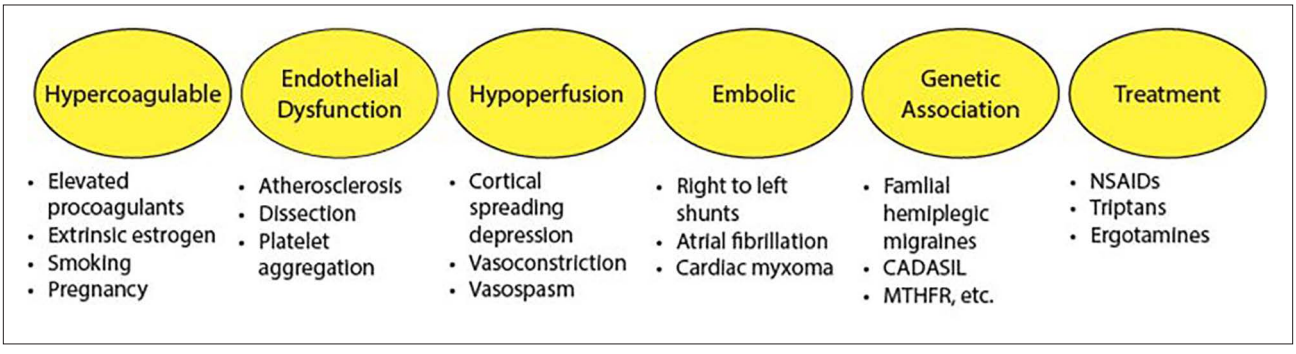

Figure 4. Why do migraines lead to strokes? Categories of etiological contributions (ovals) and specific mechanisms leading to stroke in migraineurs.

CADASIL indicates cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MTHFR, methylenetetrahydrofolate reductase; and NSAID, nonsteroidal anti-inflammatory drug.

among this study sample because altitude provokes a sickle crisis. This study should be replicated on other population-based cohorts. Finally, there are other potential confounders that we could not control in an administrative database such as physical activity, diet, or family history. Race and ethnicity were also notably missing in a high proportion of participants, and the social vulnerability index was used instead to control for minority status. Hence, causal relationships between traditional or nontraditional risk factors and the development of stroke cannot be definitively established.

CONCLUSIONS

Nontraditional risk factors were just as important as traditional risk factors in the development of strokes for both young men and women. In adults aged 18 to 34 years, more strokes were associated with nontraditional than traditional risk factors. Overall, nontraditional risk factors have as strong an association as traditional risk factors in the development of strokes among young adults aged 18 to 44 years. Further research is warranted to better understand how migraines contribute to the risk of strokes among young adults and to inform primary and secondary prevention measures in migraineurs.

ARTICLE INFORMATION

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Dr Leppert was supported by the American Heart Association Career Development Award. Dr Putaala has taken part in stroke studies: TASTE (Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation Trial), TEMPO-2 (A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion), and TWIST (Tenecteplase in Wake-Up Ischaemic Stroke Trial). Dr Schwamm reported serving on the American Heart Association/Get With The Guidelines stroke systems of care advisory group and the American Stroke Association Advisory Committee; stroke systems consultant to the Massachusetts Department of Public Health; scientific consultant regarding trial design and conduct to Genentech (late window thrombolysis, a member of steering committee TIMELESS [Tenecteplase in Stroke Patients Between 4.5 and 24 Hours; NCT03785678]); a member of a Data Safety Monitoring Board for Penumbra (MIND: Artemis in the Removal of Intracerebral Hemorrhage; NCT03342664); Diffusion Pharma (PHAST-TSC [Efficacy and Safety of Trans Sodium Crocetinate for Treatment of Suspected Stroke; NCT03763929]); a national principal investigator (PI) or a member of the National Steering Committee for Medtronic (Stroke AF [Rate of Atrial Fibrillation Through 12 Months in Patients With Recent Ischemic Stroke of Presumed Known Origin; NCT02700945]); a PI of the StrokeNet Network National Institute of Neurological Disorders and Stroke (NINDS; New England Regional Coordinating Center; U24NS107243); and a co-investigator of The Impact of Telestroke on Patterns of Care and Long-Term Outcomes, NINDS (R01NS111952). Dr Burke reports compensation from the American Heart Association for other services; he also serves as an associate editor for *Circulation: Cardiovascular Quality and Outcomes*. Dr Ho was supported by the National Heart, Lung, and Blood Institute, Veteran's Affairs Health Services and Development, and the University of Colorado School of Medicine. Dr Ho has a research agreement with Bristol-Myers Squibb through the University of Colorado. Dr Ho serves as the Deputy Editor of *Circulation: Cardiovascular Quality and Outcomes*. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Tables S1–S9
References 47–62

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