RESEARCH ARTICLE

Global Differences in Risk Factors, Etiology, and Outcome of Ischemic Stroke in Young Adults—A Worldwide Meta-analysis

The GOAL Initiative

Mina A. Jacob, MD, Merel S. Ekker, MD, Youssra Allach, BsC, Mengfei Cai, MD, Karoliina Aarnio, MD, Antonio Arauz, MD, Marcel Arnold, MD, Hee-Joon Bae, MD, Lucrecia Bandeo, MD, Miguel A. Barboza, MD, Manuel Bolognese, MD, Pablo Bonardo, MD, Raf Brouns, MD, Batnairamdal Chuluun, MD, Enkhzaya Chuluunbatar, MD, Charlotte Cordonnier, MD, Byambasuren Dagvajantsan, MD, Stephanie Debette, MD, Adi Don, MD, Chris Enzinger, MD, Esme Ekizoglu, MD, Simon Fandler-Höfler, MD, Franz Fazekas, MD, Annette Fromm, MD, Thomas Gattringer, MD, Thiago F. Hora, MD, Christina Jern, MD, Katarina Jood, MD, Young Seo Kim, MD, Steven Kittner, MD, Timothy Kleinig, MD, Catharina J.M. Klijn, MD, Janika Kõrv, MD, Vinod Kumar, MD, Keon-Joo Lee, MD, Tsong-Hai Lee, MD, Noortje A.M. Maaijwee, MD, Nicolas Martinez-Majander, MD, João Pedro Marto, MD, Man M. Mehndiratta, MD, Victoria Mifsud, MD, Vinícius Montanaro, MD, Gisele Pacio, MD, Vinod B. Patel, MD, Matthew C. Phillips, MD, Bartlomiej Piechowski-Jozwiak, MD, Aleksandra Pikula, MD, Jose Ruiz-Sandoval, MD, Bettina von Sarnowski, MD, Richard H. Swartz, MD, Kay-Sin Tan, MD, David Tanne, MD, Turgut Tatlisumak, MD, Vincent Thijs, MD, Miguel Viana-Baptista, MD, Riina Vibo, MD, Teddy Y. Wu, MD, Nilüfer Yesilot, MD, Ulrike Waje-Andreassen, MD, Alessandro Pezzini, MD, Jukka Putaala, MD, Anil M. Tuladhar, MD, and Frank-Erik de Leeuw, MD

Correspondence
Prof. de Leeuw
frankerik.deleeuw@radboudumc.nl

Neurology® 2022;98:e573-e588. doi:10.1212/WNL.0000000000013195

Abstract

Background and Objectives

There is a worldwide increase in the incidence of stroke in young adults, with major regional and ethnic differences. Advancing knowledge of ethnic and regional variation in causes and outcomes will be beneficial in implementation of regional health care services. We studied the global distribution of risk factors, causes, and 3-month mortality of young patients with ischemic stroke, by performing a patient data meta-analysis from different cohorts worldwide.

Methods

We performed a pooled analysis of individual patient data from cohort studies that included consecutive patients with ischemic stroke aged 18–50 years. We studied differences in prevalence of

From Donders Institute for Brain, Cognition and Behaviour (M.A.J., M.S.E., Y.A., M.C., C.J.M.K., A.M.T., F.-E.d.L.), Department of Neurology, Radboud University Medical Center, Nijmegen, the Netherlands; Neurology (K.A., N.M.-M., T.T., J.P.), Helsinki University Hospital and University of Helsinki, Finland; National Institute of Neurology and Neurosurgery of Mexico (A.A.), Manuel Velasco Suárez, Mexico City; Department of Neurology (M.A.), Inselspital, University Hospital, University of Bern, Switzerland; Cerebrovascular Disease Center (H.-J.B., K.-J.L.), Seoul National University College of Medicine, Seoul National University Bundang Hospital, South Korea; Neurology Department (L.B., P.B., G.P.), Hospital Británico de Buenos Aires, Argentina; Neurosciences Department (M.A.B.), Hospital Dr. Rafael A. Calderon Guardia, CCSS, San Jose, Costa Rica; Neurocenter (M.B., N.A.M.M.), Department of Neurology and Neurorehabilitation, Lucerne Cantonal Hospital, Luzern, Switzerland; The Faculty of Medicine and Pharmacy (R.B.), Vrije Universiteit Brussel, Jette, Belgium; Department of Neurology (R.B.), ZorgSaam Hospital, Terneuzen, the Netherlands; International School of Traditional Medicine (B.C.) and Department of Neurology, School of Medicine (B.D.), Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; Department of Global Health (E.C.), School of Public Health, Taipei Medical University, Taiwan; U1172–LilNCog–Lille Neuroscience & Cognition (C.C.), Univ Lille, Inserm, CHU Lille; Team VINTAGE (S.D.), Bordeaux Population Health Research Center, Inserm, University of Bordeaux, France; School of Medicine (A.D.) and Department of Epidemiology and Preventive Medicine, School of Public Health (D.T.), Sackler Faculty of Medicine, Tel Aviv University, Israel; Department of Neurology (C.E., S.F.-H., F.F., T.G.) and Division of Neuroradiology, Department of Radiology (C.E., T.G.), Medical University of Graz, Austria; Department of Neurology (E.E., N.Y.), Istanbul University, Istanbul Faculty of Medicine, Turkey; Center for Neurovascular Diseases, Department of Neurology (A.F., U.W.-A.), Haukeland University Hospital, Bergen, Norway; SARAH Hospital of Rehabilitation (T.F.H., V. Montanaro), Brasilia, Brazil; Department of Laboratory Medicine, Institute of Biomedicine (C.J.), and Institute of Neuroscience and Physiology (K.J.), the Sahlgrenska Academy, University of Gothenburg; Departments of Clinical Genetics and Genomics (C.J.) and Neurology (K.J.), Sahlgrenska University Hospital, Gothenburg, Sweden; Department of Neurology (K.Y.S.), College of Medicine, Hanyang University, Seoul, South Korea; Department of Neurology (S.K.), Veterans Affairs Maryland Health Care System, University of Maryland School of Medicine, Baltimore; Department of Neurology (T.K.), Royal Adelaide Hospital, Australia; Department of Neurology and Neurosurgery (J.K., R.V.), University of Tartu, Estonia; Neurological Institute (V.K., V. Mifsud, B.P.-J.), Cleveland Clinic Abu Dhabi, United Arab Emirates; Department of Neurology (T.-H.L.), Chang Gung Memorial Hospital, Linkou Medical Center; College of Medicine (T.-H.L.), Chang Gung University, Guishan, Taoyuan, Taiwan; Department of Neurology (J.P.M., M.V.-B.), Hospital de Egas Moniz, Centro Hospitalar Lisboa Ocidental and CEDOC, NOVA Medical School, Universidade NOVA de Lisboa, Lisbon, Portugal; Department of Neurology (M.M.M.), G.B. Pant Institute of Medical Education and Research (GIPMER), New Delhi, India; Department of Neurology (V.B.P.), Nelson R. Mandela School of Medicine, Inkosi Albert Luthuli Central Hospital, Mayville, South Africa; Department of Neurology (M.C.P.), Waikato Hospital, Hamilton, New Zealand; Department of Medicine (Neurology), University Health Network (A. Pikula), and Department of Medicine (Neurology) (R.H.S.), Sunnybrook Health Sciences Center, University of Toronto, Canada; Department of Neurology (J.R.-S.), Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Mexico; Department of Neurology (B.v.S.), University Medicine, Greifswald, Germany; Department of Medicine (K.-S.T.), University of Malaya, Kuala Lumpur; Rambam Healthcare Campus (D.T.), Haifa, Israel; Stroke Theme (V.T.), Florey Institute of Neuroscience and Mental Health, University of Melbourne; Department of Neurology (V.T.), Austin Health, Melbourne, Victoria, Australia; Department of Neurology (T.Y.W.), Christchurch Hospital, New Zealand; and Department of Clinical and Experimental Sciences (A. Pezzini), Neurology Clinic, University of Brescia, Italy.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AF = atrial fibrillation; **CI** = confidence interval; **GOAL** = Global Outcome Assessment Lifelong After Stroke in Young Adults; **HICs** = high-income countries; **LMICs** = low and middle-income countries; **OR** = odds ratio; **PFO** = patent foramen ovale; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

risk factors and causes of ischemic stroke between different ethnic and racial groups, geographic regions, and countries with different income levels. We investigated differences in 3-month mortality by mixed-effects multivariable logistic regression.

Results

We included 17,663 patients from 32 cohorts in 29 countries. Hypertension and diabetes were most prevalent in Black (hypertension, 52.1%; diabetes, 20.7%) and Asian patients (hypertension 46.1%, diabetes, 20.9%). Large vessel atherosclerosis and small vessel disease were more often the cause of stroke in high-income countries (HICs; both $p < 0.001$), whereas "other determined stroke" and "undetermined stroke" were higher in low and middle-income countries (LMICs; both $p < 0.001$). Patients in LMICs were younger, had less vascular risk factors, and despite this, more often died within 3 months than those from HICs (odds ratio 2.49; 95% confidence interval 1.42–4.36).

Discussion

Ethnoracial and regional differences in risk factors and causes of stroke at young age provide an understanding of ethnic and racial and regional differences in incidence of ischemic stroke. Our results also highlight the dissimilarities in outcome after stroke in young adults that exist between LMICs and HICs, which should serve as call to action to improve health care facilities in LMICs.

A prominent United Nations Sustainable Development Goal is to reduce the burden of noncommunicable diseases, including stroke, by one-third by 2030.[1] However, there has been a worldwide increase of up to 50% in the incidence of stroke in young adults over the past decade.[2,3] A stroke at young age, usually defined as age 18–50 years, has a large personal effect during a demanding period of life. Its increasing incidence also has detrimental socioeconomic consequences worldwide, as these patients have high rates of poststroke unemployment and a persistent increased long-term risk of death, resulting in decades of life lost.[3-6]

There are major, incompletely understood regional differences in the incidence of stroke in young adults, varying between 7 per 100,000 person-years in Europe to more than 100 per 100,000 person-years in Africa.[7-9] Also, ethnic and racial disparity in incidence has been reported, with a 50% higher incidence in Hispanic Americans and Black Americans than in Europeans.[7,10] These differences in stroke incidence at young age might reflect unidentified regional variation in burden of risk factors and causes of stroke. Apart from regional, ethnic and racial or genetic differences, economic inequality may also play a role, which may influence not only incidence, risk factor profile, and causes of stroke, but also outcome. Large cohort studies among elderly patients with stroke have shown a poorer prognosis in those residing in low and middle-income countries (LMICs) than those in high-income countries (HICs).[11,12] However, it is largely unknown whether this discrepancy also applies to young patients with stroke, often with a different etiology.

To address these knowledge gaps, a global approach is needed, with detailed data from individual patients with different regional and ethnic backgrounds. We therefore set up the Global Outcome Assessment Lifelong After Stroke in Young Adults (GOAL) initiative, combining data from individual young patients with stroke from different cohorts worldwide. In this study, we investigated the global distribution of risk factors and causes as well as 3-month mortality in an individual patient data meta-analysis among 17,663 young patients with ischemic stroke from all continents.

Methods

Study Design and Population

The GOAL initiative is an ongoing international multicenter initiative that collects individual patient data from hospital-based young stroke cohorts all over the world, with the aim to investigate the risk factors, etiology, and outcome in young individuals with stroke. A detailed description of the GOAL study protocol has been published previously.[13]

Relevant cohort studies conducted from 1970 onward were identified through a systematic search of PubMed using the MeSH major topics "young adult," "stroke," "risk factors," "stroke/etiology cause/etiology AND NOT stroke/etiology," "prognosis," and "secondary prevention." Detailed description of the search terms strategy is listed in eAppendix 1 (doi.org/10.5061/dryad.1rn8pk0t4).

The principal investigators were contacted and informed about the GOAL initiative with the request to participate. Furthermore, when participants indicated they knew of other cohorts or collaborators who might be interested in

participating, we contacted these researchers. A website for potential participants was developed to provide more information about the aims of the project.[14] An overview of the selection procedure of cohorts is illustrated in eFigure 1 (doi.org/10.5061/dryad.1rn8pk0t4).

Prospective and retrospective as well as hospital-based cohorts were considered eligible for enrollment if the patients would meet our selection criteria. Briefly, cohorts were eligible for inclusion if they recruited consecutive patients aged 18–50 years with a first-ever ischemic stroke. Exclusion criteria included stroke due to traumatic cerebral injury, intracerebral malignancy, cerebral venous thrombosis, iatrogenic stroke as a result of any medical intervention, or retinal infarct. A detailed overview of the inclusion and exclusion criteria are described in detail in the study protocol.[13] Ischemic stroke was defined according to the WHO definition.[15] We performed an individual patient data meta-analysis by analyzing data from cohorts who contributed data to the GOAL initiative until June 1, 2020.

Standard Protocol Approvals, Registrations, and Patient Consents

Before participating, each individual center had to obtain written ethical approval form a local ethical committee for international data sharing. Participating centers were requested to pseudonymize their data before sending it by using a standardized and encrypted electronic sheet containing prespecified variables of interest, according to the current laws and legislation concerning research conduct at each participating center, to the GOAL research team of the neurology department of the Radboudumc, Nijmegen. The key linking anonymized data to individual patients remained at the participating centers. This study was conducted according to the principles of the Declaration of Helsinki (version 60, 19 October 2013) and the Dutch law for human research (WMO). Written informed consent was obtained from all participants in the prospectively collected data; no informed consent was needed for retrospective cohorts of registered patients. Ethical approval was obtained from the Medical Review Ethics Committee region Arnhem-Nijmegen. All data are processed, stored, and will be destroyed after end of the study according to European Union General Data Protection Regulation.

Study Data

Study data included demographic characteristics, medical history including medication used on admission, and information on causes and risk factors of ischemic stroke based on diagnostic workup within 1 month after stroke.

Demographics

Date of admission, date of index stroke, age, sex, and ethnic and racial subgroups including White (i.e., non-Hispanic White individuals), Black (i.e., non-Hispanic Black individuals), Hispanic (i.e., individuals who self-identified as White Hispanic or Black Hispanic), Asian (i.e., individuals who self-identified as from Asian descendants), multiracial (i.e., individuals with 2 or more racial identities), other, or unknown, and geographic residence were registered. Ethnic and racial identity was assigned to participants via self-identification.

We included patients with ischemic stroke from 29 countries covering all continents except Antarctica. Europe was stratified into 3 regions because of previously reported regional differences in stroke incidence.[2] Countries were classified based on their income level at the start of their particular study according to the World Bank Classification as LMICs or HICs.[16] We grouped LMICs into one group for statistical reasons, as India was the only low-income country at the start of its study. An overview of participating cohorts is available from Dryad (eTable 1, doi.org/10.5061/dryad.1rn8pk0t4).

Risk Factors, Causes, and Outcome

Detailed definitions of collected risk factors are described in the study protocol[13] and summarized in eTable 2 (doi.org/10.5061/dryad.1rn8pk0t4). Risk factors included vascular risk factors, as stated by the 2014 guidelines of the American Stroke Association,[17] including hypertension, diabetes, dyslipidemia, ever smoking, atrial fibrillation (AF), patent foramen ovale (PFO), and obesity. Other risk factors collected (but not required for participation in the GOAL initiative) included migraine, excessive use of alcohol, and illicit drug use. Cohorts that applied a different definition for a given risk factor that could not be reclassified according to GOAL definitions were excluded from that particular subanalysis.

Cause of stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[18] Outcome was the vital status assessed 3 months after index stroke.

Data Quality Assessment

A database was created from data of all individual patients. Cohorts were requested to send data regarding risk factors with their definition of the risk factors to ensure that only variables matching our prespecified definitions (eTable 2, doi.org/10.5061/dryad.1rn8pk0t4) were included. All datasets underwent a standardized quality assessment for completeness and inconsistencies. In case of inconsistencies (for example, when small vessel disease was considered as the cause of stroke in the presence of AF), local principal investigators were contacted for reevaluation of their data. Patients with AF were assigned to either the subgroup "cardioembolism," or to "stroke due to 2 or more identified causes" in presence of other causes of stroke according to the TOAST criteria.

Data Analyses

To detect differences between increasing age and prevalence of risk factors and causes of ischemic stroke, age was categorized in 6 age groups (18–25, 26–30, 31–35, 36–40, 41–45, 46–50 years). Patients were also grouped based on the number of concurrent traditional vascular risk factors (0–4) by adding the following vascular risk factors in each patient: hypertension, diabetes, dyslipidemia, and ever smoking.[19]

First, we explored differences in mean age, sex, risk factors, causes of stroke (TOAST subtype), and death rates between subgroups stratified by demographic characteristics (age group, sex, ethnic and racial groups, geographic region, and socioeconomic level) with Mann-Whitney test or $\chi 2$ test when appropriate. Linear trends in frequencies of risk factors and causes according to ordinal scaled age groups were tested with χ^2 test. All univariate group tests were corrected with Bonferroni method to adjust for multiple comparisons to ensure 5% overall type I error rate.

Second, we studied variables associated with death within 3 months from index stroke with mixed-effects multivariable logistic regression, with study cohort set as random intercept effect to correct for intrinsic cohort heterogeneity. The independent variables of interest analyzed included demographic characteristics (sex, age, ethnic and racial groups, and socioeconomic level of country), stroke cause, and the number of vascular risk factors. Depending on each variable under study, we constructed different models with appropriate adjustments for different covariates that are known to affect mortality; that is, age, sex, ethnic and racial groups, cause of stroke, or vascular risk factor score. The selection of these confounding variables was based on availability of confounders, biological plausibility, and their known association with mortality, and they were often used in other studies.[11]

Patients with unreported ethnic and racial identity were classified as an independent group "unknown" during analyses. Because data of each other variable analyzed were present in >98% of all cases, we did not impute for missing values.

All analyses were performed using R version 4.1.1 or IBM SPSS Statistics, version 25.0 (IBM Corp.).

Data Availability

Data from the GOAL study including data supporting the findings of this study will be available from the corresponding author on request, after consent of all GOAL participating centers and approval of local institutional review boards.

Results

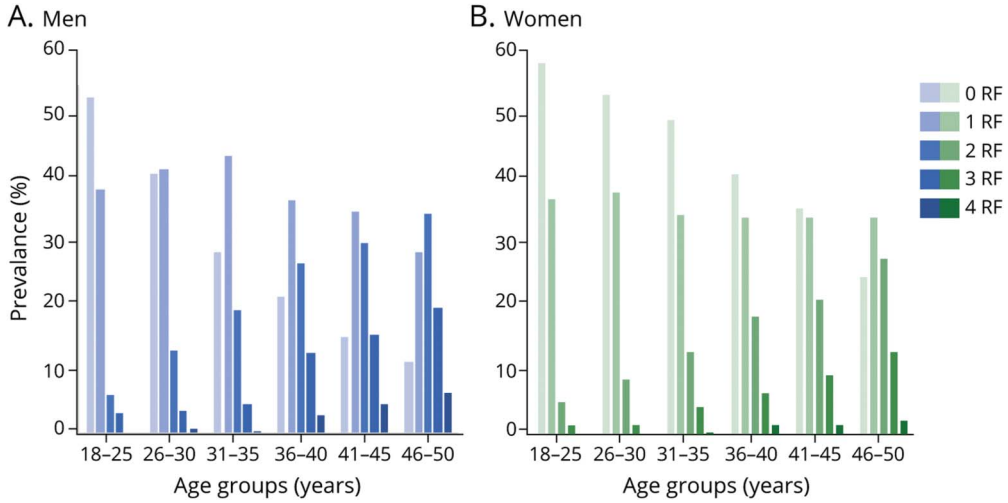
A total of 17,663 patients (n = 10,564 men; 61.2%) from 32 cohorts in 29 countries were included in this study (Figure 1; doi.org/10.5061/dryad.1rn8pk0t4). The overall mean age was 40.8 (SD 7.5) years, with men being older than women (41.5 [SD 7.2] vs 39.7 [SD 7.9] years; $p < 0.001$). There was a male predominance across all age strata, which increased with age (Table 1). Of patients included, 6,837 (38.7%) were Asian, 5,696 (32.2%) White, 1,730 (9.8%) Hispanic, and 507 (2.9%) Black. Most patients came from Europe (n = 7,265% [41.1%]) or Asia (n = 6,775% [38.7%]). A total of 14,392 (81.5%) patients were residents from HICs (Australia, Austria, Belgium, Canada, Finland, France, Germany, Israel, Italy, Korea, the Netherlands, New Zealand, Norway, Portugal, Sweden, Switzerland, Taiwan, United Arab Emirates, and the United States); 3,271 (18.5%) patients were from LMICs (Argentina, Brazil, Costa Rica, Estonia, India, Malaysia, Mexico, Mongolia, South Africa, and Turkey).

Patients residing in HICs were older than those in LMICs (41.2 [SD 7.3] vs 38.8 [SD 8.4] years; $p < 0.001$).

Global Distribution of Risk Factors

Smoking was the most common risk factor (49.2%), followed by hypertension (36.6%) and dyslipidemia (31.7%; Table 2). For 16,845 (95.4%) patients, the number of concurrent

Figure 1 Proportions of Patients With Concurrent Vascular Risk Factors Stratified by Age Groups and Sex



(A and B) Prevalence shown for presence of 0, 1, 2, 3, or 4 vascular risk factors (RFs) by age groups. Vascular risk factors included hypertension, dyslipidemia, diabetes, and smoking.

Table 1 Demographic Characteristics of Total Study Population

	Patients	Age, y, mean (SD)	Men	Women
Total population	17,663	40.8 (7.5)	10,683 (60.5)	6,980 (39.5)
Age group, y				
18–25	940 (5.3)	21.9 (2.2)	474 (50.4)	466 (49.6)
26–30	1,140 (6.5)	28.3 (1.4)	576 (50.5)	564 (49.5)
31–35	1,829 (10.4)	33.2 (1.4)	957 (52.3)	872 (47.7)
36–40	2,997 (17.0)	38.2 (1.4)	1,754 (58.5)	1,243 (41.5)
41–45	4,949 (28.0)	43.2 (1.4)	3,075 (62.1)	1,874 (37.9)
46–50	5,808 (32.9)	48.0 (1.4)	3,847 (66.2)	1,961 (33.8)
Ethnic and racial subgroups				
White	5,696 (32.2)	39.4 (7.5)	3,144 (55.2)	2,552 (44.8)
Black	507 (2.9)	41.3 (6.7)	275 (54.2)	232 (45.8)
Hispanic	1,730 (9.8)	38.1 (8.8)	864 (49.9)	866 (50.1)
Asian	6,837 (38.7)	42.7 (6.5)	4,779 (69.9)	2,058 (30.1)
Multiracial	23 (0.1)	39.4 (7.2)	10 (43.5)	13 (56.5)
Other	137 (0.8)	38.0 (7.1)	68 (45.0)	83 (55.0)
Unknown	2,733 (15.5)	40.7 (7.9)	1,553 (56.6)	1,189 (43.4)
Geographic region				
Oceania	658 (3.7)	40.1 (7.5)	376 (57.1)	282 (42.9)
Asia	6,775 (38.4)	42.7 (6.6)	4,740 (70.0)	2,035 (30.0)
Africa	91 (0.5)	36.1 (8.8)	49 (53.8)	42 (46.2)
Southern Europe	2,988 (16.9)	37.9 (7.4)	1,558 (52.1)	1,430 (47.9)
Central Europe	2,152 (12.2)	40.7 (7.6)	1,178 (54.7)	974 (45.3)
Northern Europe	2,125 (12.0)	41.4 (7.6)	1,275 (60.0)	850 (40.8)
North America	1,007 (5.7)	41.8 (6.0)	578 (57.4)	429 (42.6)
Central and South America	1,867 (10.6)	37.7 (8.8)	929 (49.8)	938 (50.2)
Country income classification				
High-income countries	14,392 (81.5)	41.2 (7.3)	8,914 (61.9)	5,478 (38.1)
Low and middle-income countries	3,271 (18.5)	38.8 (8.4)	1,769 (54.1)	1,502 (45.9)

Data are n (%) or mean (SD).

vascular risk factors could be calculated: 12,426 (73.8%) patients had at least 1 vascular risk factor and 6,896 (40.9%) patients had ≥2 risk factors (eTable 3; doi.org/10.5061/dryad.1rn8pk0t4). Of patients ≤30 years, 49.6% had at least 1 vascular risk factor. Traditional vascular risk factors (hypertension, diabetes, dyslipidemia, and smoking) were more common in men than in women and showed a higher prevalence with increasing age (all: $p_{trend} \leq 0.001$; Figure 1). Women, compared to men, more often had migraine (28.1% vs 14.0%; $p \leq 0.001$) and PFO (18.1% vs 12.7%; $p < 0.001$). Migraine and PFO were also significantly more prevalent in younger patients (both: $p_{trend} \leq 0.001$). Black and Asian people had the highest prevalence of ≥2 risk factors (eTable 3). They also had the highest prevalence of hypertension (Black, 52.1%; Asian, 47.1%) and diabetes (Black, 20.7%; Asian, 20.9%); White people had the highest prevalence of dyslipidemia (40.4%) and PFO (24.9%). Patients from Asia, North America, and Oceania showed higher frequencies of most vascular risk factors (especially obesity) compared to patients from Europe (Figure 2). The majority of vascular risk factors were significantly more prevalent in HICs compared to LMICs, particularly dyslipidemia (33.9% vs 21.7%; $p \leq 0.001$; Table 2).

Table 2 Risk Factors Stratified by Demographic Characteristics

	Patients with available data on risk factor										
	Hypertension (n = 17,409)	Diabetes (n = 17,631)	Dyslipidemia (n = 17,364)	Ever smoking (n = 17,328)	Coronary artery disease (n = 16,159)	Atrial fibrillation (n = 17,258)	Patent foramen ovale (n = 12,024)	Obesity (n = 13,217)	Migraine (n = 5,138)	Excessive alcohol use (n = 9,630)	Illicit drug use (n = 5,891)
Patients with risk factor	6,368 (36.6)	2,432 (13.8)	5,498 (31.7)	8,525 (49.2)	759 (4.7)	691 (4.0)	1,789 (14.9)	1,796 (13.6)	1,056 (20.6)	1,030 (10.5)	254 (4.3)
Mean age (SD) of patients with risk factor, y	43.6 (5.5)	44.3 (5.3)	42.8 (6.1)	41.7 (7.0)	43.0 (6.3)	43.5 (6.3)	38.0 (8.1)	41.9 (6.4)	37.8 (7.7)	40.6 (7.3)	38.5 (8.0)
Sex											
Men	4,294 (40.8)	1,657 (15.5)	3,668 (34.9)	6,198 (59.0)	506 (5.1)	432 (4.1)	922 (12.7)	1,114 (13.4)	383 (14.0)	896 (16.7)	174 (5.2)
Women	2,074 (30.1)	75 (11.1)	1,830 (26.7)	2,327 (34.1)	253 (4.0)	259 (3.8)	867 (18.1)	682 (14.0)	673 (28.1)	187 (4.4)	80 (3.1)
p	<0.001	<0.001	<0.001	<0.001	0.002	0.33	<0.001	0.35	<0.001	<0.001	<0.001
Age group, y											
18–25	64 (6.9)	24 (2.6)	97 (10.5)	325 (35.3)	18 (2.1)	13 (1.4)	181 (27.2)	38 (6.1)	94 (27.2)	52 (7.8)	26 (6.9)
26–30	137 (12.3)	35 (3.1)	183 (16.3)	435 (39.0)	23 (2.2)	26 (2.3)	164 (20.1)	81 (10.5)	107 (25.2)	68 (8.3)	21 (4.3)
31–35	367 (20.6)	112 (6.1)	415 (23.1)	743 (41.4)	51 (3.1)	38 (2.1)	258 (19.8)	180 (14.6)	162 (24.6)	131 (10.9)	26 (3.8)
36–40	914 (31.3)	307 (10.3)	904 (30.9)	1,396 (47.5)	101 (3.7)	95 (3.3)	372 (17.8)	299 (14.4)	245 (24.0)	185 (10.1)	52 (5.0)
41–45	1,955 (40.1)	693 (14.0)	1,671 (34.2)	2,534 (51.9)	226 (4.9)	177 (3.7)	496 (14.2)	545 (15.7)	306 (18.5)	313 (11.3)	78 (5.2)
46–50	2,931 (50.5)	1,261 (21.8)	2,228 (39.0)	3,092 (54.4)	340 (6.4)	342 (6.0)	318 (8.7)	653 (13.0)	142 (13.7)	334 (14.3)	51 (2.9)
p_{trend}	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.006
Ethnic and racial subgroups											
White	1,709 (30.2)	497 (8.7)	2,254 (40.4)	2,559 (45.8)	174 (3.5)	184 (3.2)	1,045 (24.9)	566 (19.2)	841 (20.9)	505 (9.4)	138 (6.3)
Black	264 (52.1)	105 (20.7)	128 (25.6)	262 (52.0)	55 (11.1)	14 (2.8)	6 (1.4)	221 (44.6)	0/42	15 (4.1)	48 (10.6)
Hispanic	397 (23.1)	190 (11.1)	247 (14.4)	840 (49.2)	52 (3.0)	74 (4.3)	171 (13.9)	157 (9.1)	17 (19.3)	248 (16.0)	38 (2.2)
Asian	3,061 (46.1)	1,426 (20.9)	1,948 (28.8)	3,611 (52.9)	335 (4.9)	324 (4.8)	239 (4.8)	634 (9.5)	48 (18.3)	215 (17.8)	15 (1.3)
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Geographic location											
Oceania	235 (36.3)	106 (16.2)	277 (46.6)	293 (46.1)	48 (7.3)	43 (6.5)	110 (19.4)	153 (27.5)	0/207	79 (14.0)	59 (11.9)
Asia	3,038 (46.2)	1,423 (21.0)	1,937 (28.8)	3,588 (53.1)	330 (4.9)	323 (4.8)	231 (4.7)	637 (9.6)	45 (19.0)	206 (17.9)	17 (1.4)

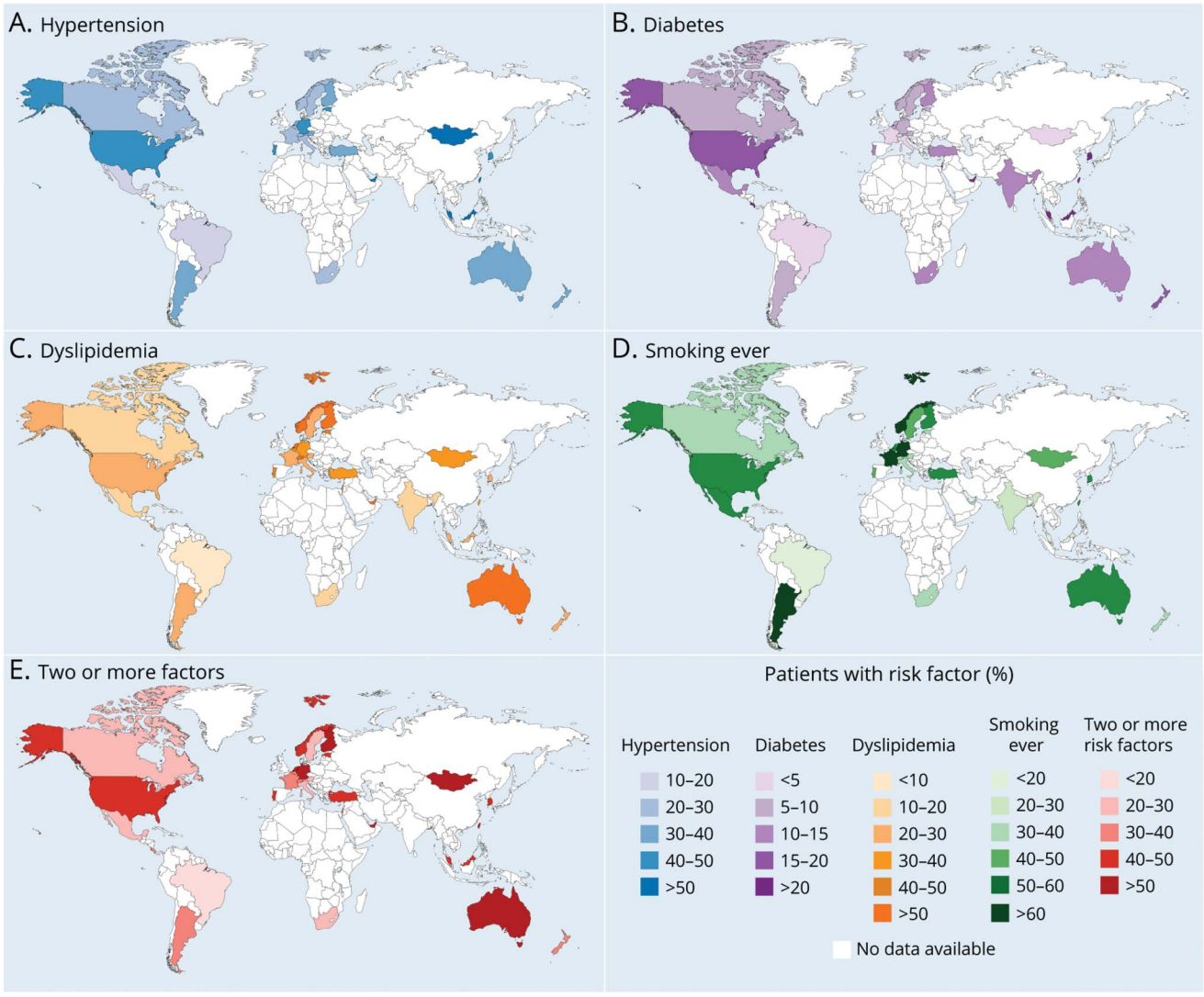
Continued

Table 2 Risk Factors Stratified by Demographic Characteristics *(continued)*

	Patients with available data on risk factor										
	Hypertension (n = 17,409)	**Diabetes (n = 17,631)**	**Dyslipidemia (n = 17,364)**	**Ever smoking (n = 17,328)**	**Coronary artery disease (n = 16,159)**	**Atrial fibrillation (n = 17,258)**	**Patent foramen ovale (n = 12,024)**	**Obesity (n = 13,217)**	**Migraine (n = 5,138)**	**Excessive alcohol use (n = 9,630)**	**Illicit drug use (n = 5,891)**
Africa	20 (22.0)	11 (12.1)	16 (18.0)	29 (32.6)	1 (1.1)	0/89	0/70	8 (10.8)	0/0	13 (14.4)	2 (2.2)
Southern Europe	777 (26.2)	213 (7.1)	880 (29.5)	1,166 (39.1)	35 (1.3)	92 (3.1)	742 (27.2)	59 (10.9)	558 (23.1)	255 (8.6)	13 (4.9)
Central Europe	669 (31.1)	138 (6.4)	849 (41.9)	1,071 (50.7)	92 (6.1)	45 (2.4)	324 (36.2)	99 (23.2)	159 (22.7)	97 (8.4)	6 (3.9)
Northern Europe	775 (36.5)	181 (8.5)	1,012 (48.1)	933 (49.3)	72 (4.6)	85 (4.1)	179 (32.0)	292 (13.9)	252 (18.2)	148 (12.0)	28 (2.8)
North America	427 (42.5)	163 (16.2)	266 (26.6)	578 (57.4)	128 (12.8)	26 (2.6)	25 (2.8)	387 (38.5)	25 (21.2)	20 (2.6)	82 (10.5)
Central and South America	427 (23.0)	197 (10.6)	261 (14.1)	867 (47.0)	53 (2.9)	77 (4.2)	178 (13.0)	161 (8.7)	17 (20.2)	265 (15.7)	47 (2.5)
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Country level of income											
High-income countries	5,345 (37.2)	2,054 (14.3)	4,806 (33.9)	7,137 (50.6)	588 (4.5)	539 (3.8)	1,594 (15.4)	1,494 (14.5)	987 (20.3)	739 (10.4)	190 (5.7)
Low and middle-income countries	1,023 (33.5)	378 (11.6)	692 (21.7)	1,388 (42.9)	171 (5.8)	152 (4.7)	195 (11.8)	302 (10.3)	69 (24.9)	344 (13.7)	64 (2.5)
p	<0.001	<0.001	<0.001	<0.001	<0.001	0.02	<0.001	<0.001	0.08	<0.001	<0.001

Data are n (%), mean (SD), or *p* value. Percentages are proportion of patients with the certain risk factor calculated based on the total patients with available data of the risk factor.

Figure 2 World Maps Illustrating Geographic Distribution of Vascular Risk Factors in Young Patients With Stroke



(A–E) Colors are based on proportion of particular risk factor (%).

Global Distribution of Causes of Stroke

Data regarding causes of stroke were available for 16,864 (95.4%) patients. Large vessel atherosclerosis was the cause of stroke in 16.6% of cases, small vessel disease in 14.8%, cardioembolism in 19.0%, other determined etiology in 22.7%, and undetermined etiology in 26.9% (Table 3). Large vessel atherosclerosis and small vessel disease were significantly more often the cause of stroke in men than in women (19.2% vs 12.7%; $p \leq 0.001$ for large vessel atherosclerosis: 17.0% vs 11.4%; $p \leq 0.001$ for small vessel disease); cardioembolism and other determined etiology prevailed in women (21.5% vs 17.4%; $p \leq 0.001$; respectively, 27.0% vs 20.0%; $p \leq 0.001$). The proportions of large vessel atherosclerosis and small vessel disease as cause of stroke significantly increased with age (both: $p_{trend} \leq 0.001$), whereas the proportion of cardioembolism and other determined etiology significantly decreased with age (both: $p_{trend} \leq 0.001$). Asian participants had at least a 3-fold higher prevalence of large vessel atherosclerosis (28.6%) compared to other ethnic and racial groups. Also, small vessel disease was most often the cause of stroke in Asian participants (22.0%), cardioembolism in White participants (24.5%), and undetermined etiology among Black participants (44.0%) (Table 3). Africa, Central and South America, and Southern Europe showed the highest prevalence of stroke of other determined etiology (all: >40%). Large vessel atherosclerosis and small vessel disease were more than twice as prevalent in HICs compared to LMICs (both: $p < 0.001$); other determined and stroke due to an undetermined etiology were more prevalent in LMICs (both: $p \leq 0.001$; Table 3).

Global Differences in Death at 3 months After Stroke

Information on vital status at 3 months after index stroke was available for 13,012 (75.4%) patients, of whom 481 (3.7%) had died; 331 (68.6%) of those died within the first month

Table 3 Causes of Stroke Stratified by Demographic Characteristics

	Total patients	Large vessel atherosclerosis	Small vessel disease	Cardioembolism	Other determined etiology	Undetermined etiology
Cases, n	16,864	2,802 (16.6)	2,496 (14.8)	3,199 (19.0)	3,829 (22.7)	4,538 (26.9)
Age, y, mean (SD)	40.8 (7.6)	43.8 (5.8)	43.2 (6.1)	39.8 (7.9)	37.8 (7.9)	40.8 (7.6)
Sex						
Men	10,240 (60.7)	1,963 (19.2)	1,744 (17.0)	1,777 (17.4)	2,043 (20.0)	2,713 (26.5)
Women	6,624 (39.3)	839 (12.7)	752 (11.4)	1,422 (21.5)	1,786 (27.0)	1,825 (27.6)
p		<0.001	<0.001	<0.001	<0.001	0.14
Age group, y						
18–25	896 (5.3)	55 (6.1)	41 (4.6)	225 (25.1)	344 (38.4)	231 (25.8)
26–30	1,104 (6.5)	86 (7.8)	51 (4.6)	241 (21.8)	411 (37.2)	315 (28.5)
31–35	1,755 (10.4)	174 (9.9)	126 (7.2)	368 (21.0)	608 (34.6)	479 (27.3)
36–40	2,850 (16.9)	412 (14.5)	339 (11.9)	604 (21.2)	761 (26.7)	734 (25.8)
41–45	4,723 (28.0)	815 (17.3)	744 (15.8)	882 (18.7)	1,058 (22.4)	1,224 (25.9)
46–50	5,536 (32.8)	1,260 (22.8)	1,195 (21.6)	879 (15.9)	647 (11.7)	1,555 (28.1)
p_{trend}		<0.001	<0.001	<0.001	<0.001	0.40
Ethnic and racial subgroups						
White	5,526 (32.8)	481 (8.7)	614 (11.1)	1,355 (24.5)	1,835 (33.2)	1,241 (22.5)
Black	502 (3.0)	33 (6.6)	93 (18.5)	89 (17.7)	66 (13.1)	221 (44.0)
Hispanic	1,720 (10.2)	157 (9.1)	128 (7.4)	343 (19.9)	605 (35.2)	487 (28.3)
Asian	6,622 (39.3)	1,895 (28.6)	1,455 (22.0)	789 (11.9)	868 (13.1)	1,615 (24.4)
p		<0.001	<0.001	<0.001	<0.001	<0.001
Geographic location						
Oceania	658 (3.9)	30 (4.6)	76 (11.6)	163 (24.8)	153 (23.3)	236 (35.9)
Asia	6,559 (38.9)	1,889 (28.8)	1,451 (22.1)	776 (11.8)	846 (12.9)	1,597 (24.3)
Africa	91 (0.6)	16 (17.6)	8 (8.8)	9 (9.9)	41 (45.1)	17 (18.7)
Southern Europe	2,897 (17.2)	228 (7.9)	265 (9.1)	834 (28.8)	1,291 (44.6)	279 (9.6)
Central Europe	1,959 (11.6)	250 (12.8)	189 (9.6)	519 (26.5)	355 (18.1)	646 (33.0)
Northern Europe	1,844 (10.9)	154 (8.4)	222 (12.0)	347 (18.8)	417 (22.6)	704 (38.2)
North America	999 (5.9)	70 (7.0)	153 (15.3)	187 (18.7)	83 (8.3)	506 (50.7)
Central and South America	1,857 (11.0)	165 (8.9)	132 (7.1)	364 (19.6)	643 (34.6)	553 (29.8)
p		<0.001	<0.001	<0.001	<0.001	<0.001
Country income classes						
High-income countries	13,817 (81.9)	2,505 (18.1)	2,260 (16.4)	2,591 (18.8)	3,004 (21.7)	3,457 (25.0)
Low and middle-income countries	3,047 (18.1)	297 (9.7)	236 (7.7)	608 (20.0)	825 (27.1)	1,081 (35.5)
p		<0.001	<0.001	0.13	<0.001	<0.001

Data are n (%), mean (SD), or *p* value. Percentages are proportion of patients with that specific cause of stroke calculated based on the total patients with available data on the Trial of Org 10172 In Acute Stroke Treatment (TOAST) classification.

(HICs: 1.7%; LMICs: 7.7%; $p < 0.001$). Differences in clinical characteristics between survivors and patients who died within 3 months are presented in Table 4.

In multivariable logistic regression analysis, there was no statistically significant difference in risk of death between men and women (odds ratio [OR] 1.09 [95% confidence interval (CI) 0.71–1.69]; Figure 3). Age (years) was a significant risk factor for mortality (OR 1.02 [95% CI 1.01–1.03]). Hispanic patients had a higher mortality risk than White patients (OR 1.91 [95% CI 1.40–2.52]) and Asian patients (OR 1.81 [95% CI 1.42–2.34]). Black patients were not included because of limited cases. Patients in LMICs had almost a 2.5-fold higher risk for mortality than patients residing in HICs, after adjusting for cohort heterogeneity, sex, age, and cause of stroke (OR 2.46 [95% CI 1.40–4.28]). Of the deceased patients, 39.7% had a stroke of undetermined etiology (Table 4), which was strongly associated with death (OR 3.19 [95% CI 2.10–4.86]), followed by cardioembolism (OR 2.74 [95% CI 1.76–4.27]) and large vessel atherosclerosis (OR 1.64 [95% CI 1.03–2.61]). The number of concurrent vascular risk factors was not significantly associated with mortality (Figure 3).

Discussion

We found large ethnic and racial, regional, and socioeconomic differences in the prevalence of risk factors, causes of stroke, and 3-month mortality among young patients with ischemic stroke worldwide. Traditional vascular risk factors were already present in 3 out of 4 young patients, and in 50% of patients ≤30 years of age. Furthermore, young patients with ischemic stroke living in LMICs had a 2.5 times higher 3-month mortality risk compared to those residing in HICs, despite the fact that they were significantly younger and had fewer vascular risk factors.

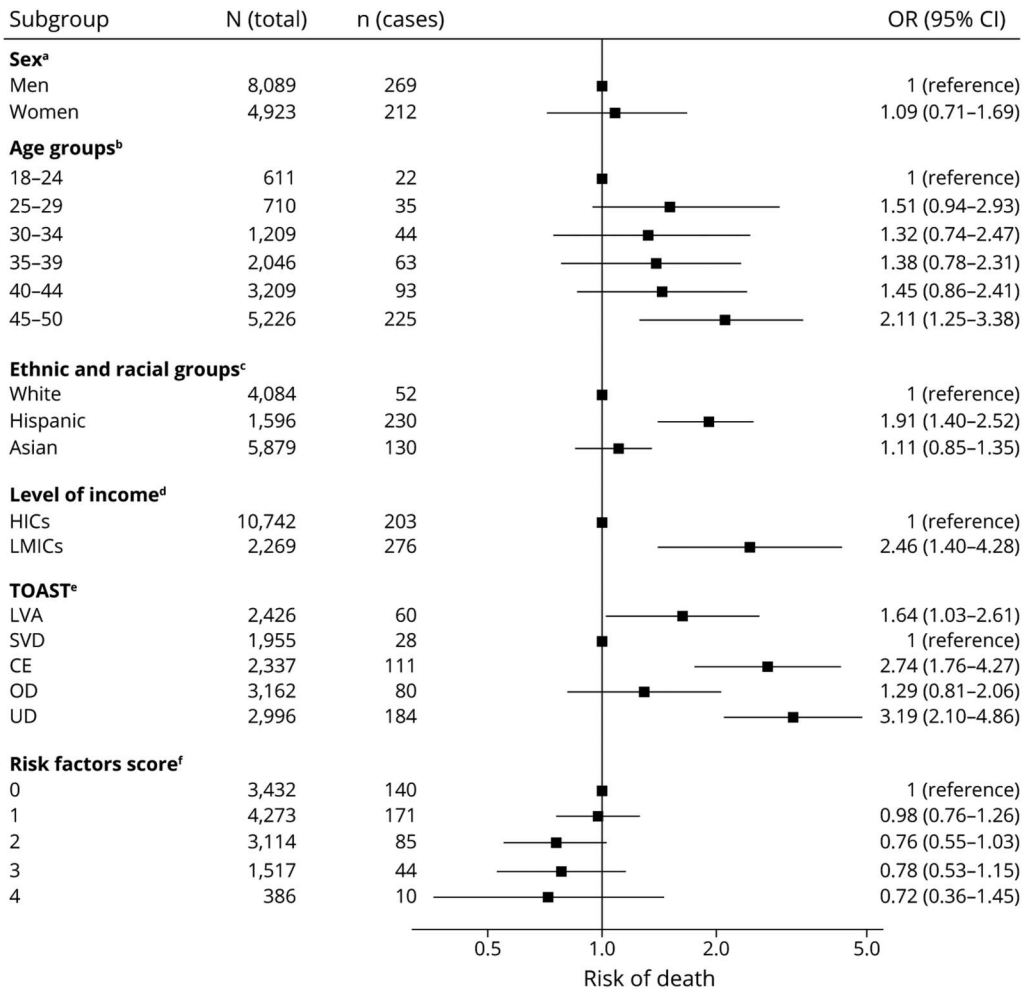
The regional and ethnic and racial variation in prevalence of vascular risk factors coincides with the reported regional and

Table 4 Differences in Baseline Characteristics Between Deceased Patients and Survivors at 3 Months of Index Stroke

	Total patients[a]	Dead	Survivors	*p* Value
Total reported cases	13.012	481 (3.7)	12.531 (96.3)	
Women	4,923 (37.6)	212 (44.1)	4,711 (37.6)	0.004
Age, y, mean (SD)	40.8 (7.6)	41.1 (8.2)	40.8 (7.6)	0.028
Risk factors				
Hypertension	4,654 (35.8)	149 (31.0)	4,505 (36.0)	0.025
Diabetes	1813 (13.9)	77 (16.0)	1736 (13.9)	0.172
Dyslipidaemia	4,037 (31.0)	100 (20.8)	3,937 (31.4)	<0.001
Ever/current smoking	6,344 (48.8)	214 (44.5)	6,130 (48.9)	0.202
Coronary artery disease	410 (3.2)	38 (7.9)	372 (3.0)	<0.001
Atrial fibrillation	525 (4.0)	45 (9.4)	480 (3.8)	<0.001
Patent foramen ovale	1,454 (11.2)	18 (3.7)	1,436 (11.5)	<0.001
Obesity	887 (6.8)	29 (6.0)	858 (6.8)	0.062
Migraine	935 (7.2)	3 (0.6)	932 (7.4)	0.001
Excessive alcohol use	801 (6.2)	41 (8.5)	760 (6.1)	0.890
Illicit drug use	81 (0.6)	5 (1.0)	76 (0.6)	0.474
TOAST classification				
Large vessel atherosclerosis	2,426 (18.8)	60 (13.0)	2,366 (19.1)	0.001
Small vessel disease	1955 (15.2)	28 (6.0)	1927 (15.5)	<0.001
Cardioembolism	2,337 (18.2)	111 (24.0)	2,226 (17.9)	0.001
Other determined	3,162 (24.6)	80 (17.3)	3,082 (24.8)	<0.001
Undetermined	2,996 (23.3)	184 (39.7)	2,812 (22.7)	<0.001

Abbreviation: TOAST = Trial of Org 10172 In Acute Stroke Treatment.
Data are n (%), mean (SD), or *p* value.
[a] Total number of patients with available data on mortality status after 3 months. Percentages are proportion of patients among total patients, total survivors, or total deaths.

Figure 3 Risk of Death Within 3 Months After Index Stroke



Data are presented as n (total patients with available mortality status), n (mortality cases), and odds ratio (OR) (95% confidence interval [CI]). All models were adjusted for cohort heterogeneity by taking study cohort as random effect in the multivariable logistic regression analysis. In addition, for each variable of interest, we constructed different models with appropriate adjustments for confounders. [a]Adjusted for age, ethnicity, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) category. [b]Adjusted for sex, ethnicity, and TOAST category. [c]Adjusted for age, sex, and TOAST category. [d]Adjusted for age, sex, and TOAST category. [e]Adjusted for age, sex, and ethnicity. [f]Adjusted for age, sex, and ethnicity. CE = cardioembolism; HICs = high-income countries; LMICs = low and middle-income countries; LVA = large vessel atherosclerosis; OD = other determined etiology; SVD = small vessel disease; UD = undetermined etiology.

ethnic and racial disparities in stroke incidence among young adults.[7-9] For example, North America, Asia, and Oceania showed higher prevalence of most vascular risk factors than Europe and South America, which might explain their higher incidence of stroke at young age, compared to Europe.[7,20] In addition, we observed a higher frequency of hypertension, diabetes mellitus, and smoking among Black and Asian participants than in White participants, risk factors typically related with atherosclerosis of larger and smaller vessels. This is in accordance with the higher cardiovascular burden in the general population of these ethnic groups, compared with, for example, White people.[21-23] Indeed, Black participants and Asian participants had the highest prevalence of large vessel atherosclerosis or small vessel disease as cause of stroke. Given the strong association between these traditional vascular risk factors and stroke occurrence, this could also partially explain the higher incidence of stroke in young patients reported in these ethnic and racial groups.[7,24] These differences in prevalence of risk factors have a multifactorial basis and involve many factors including racial and ethnic disparities in health care access and equity, socioeconomic determinants of health,[24] and their accompanying lifestyle.[23] However, genetic predispositions may also play a role (for example, Moyamoya disease is more often found in Asian people).[26,27] Further studies are warranted to better elucidate the link between different susceptibilities to certain vascular risk factors among individuals with different ethnic and racial subgroups.

Nontraditional risk factors may also explain additional variation in incidence and causes of stroke at young age across different ethnic and racial groups and regions. For example, we found the highest prevalence of PFO in White participants. We consider it unlikely that ascertainment bias plays a role

here, as cardiac ultrasound as part of routine examination was applied to a similar extent in the various regions (Table 2), but data regarding mode of cardiac ultrasound (transthoracic/transesophageal, with or without contrast) were not available. PFO was also more prevalent in women than men. The ethnic and racial and sex differences in PFO prevalence may contribute to the observed differences in causes of stroke, with cardioembolism as cause of stroke being mostly prevalent in White participants and women. These demographic differences in risk factors and causes of stroke suggest that targeted interventions to screen and manage (vascular) risk factors may have different effects on reduction of stroke incidence in different sex and ethnic groups. We noted a male preponderance in all age strata. Previous Western studies on young patients with ischemic stroke reported conflicting results in incidence between men and women, with higher preponderance of women in the younger age strata (<35 years).[26,27] Possible explanations for overrepresentation of men in our sample include the accumulation of traditional vascular risk factors in men and the inclusion of different cohorts worldwide as several Asian studies reported either no sex difference or male overrepresentation in stroke incidence at young age.[28,29]

Patients in LMICs were younger at stroke onset than those from HICs. This may be due to exposure to different risk factors between LMICs and HICs.[6] In HICs, the prevalence of vascular risk factors is higher, whereas in LMICs, environmental risks (e.g., air pollution) may play a larger role. There is growing attention to stroke occurrence attributable to environmental risk factors, which may contribute to a younger age at stroke onset in LMICs.[6,25] Traditional vascular risk factors are likely to become more prominent with aging. Relatively younger age at onset has also been reported in elderly patients with other cardiovascular events, such as myocardial infarction, in LMICs.[2,12]

There is inequality with respect to survival after stroke at young age, with patients from LMICs having 2.5 times the risk of dying within the first 3 months after stroke compared to patients from HICs, even though they were younger and had lower burden of vascular risk factors. Possible explanations include access to and affordability of health services (early diagnosis and treatment), secondary prevention, and population educational level.[12] This interpretation is supported by observations in the INTERSTROKE study showing less access to and availability of evidence-based acute treatments (i.e., IV thrombolysis) and health care services (i.e., stroke units and postdischarge rehabilitation centers) in LMICs.[11] However, limited access to health care resources in LMICs may also result in referral bias: patients who are admitted to the hospital are likely to have a more severe stroke than those who are not referred, with the accompanying higher risk of death. The increased mortality risk among Hispanic patients may be explained in this way, as 98.6% of them were from LMICs. Furthermore, the higher proportion of young patients with classic vascular risk factors in HICs could be explained by better health education, earlier detection, and better management strategies from acute treatment to rehabilitation compared to LMICs.[30]

In contrast to studies analyzing the long-term mortality of young patients with stroke, we did not find an association between number of risk factors and 3-month mortality. A possible explanation is that these risk factors do not lead to death within 3 months, but rather increase mortality risk in the long term.

Strengths of our study include the large number of patients, making it the largest study on young patients with ischemic stroke worldwide. It offers a unique opportunity to address existing knowledge gaps with respect to ethnic and racial and regional differences in stroke incidence at young age by comparing for the first time risk factor profiles, causes, and short-term outcome among young patients with stroke from different ethnicities and geographic regions, including a considerable proportion of young patients from LMICs, who have been underrepresented in prior studies. Other strong elements include the standardized operationalization of data across the diverse international cohorts, reducing misclassification and increasing the power of this study, inclusion of consecutive patients, and the more accurate estimations at subgroup level that arise from individual patient data meta-analyses.

This study also has limitations. First, data were collected at different time periods, during which primary and secondary preventive strategies, acute stroke treatment, and etiologic workup practices may have changed. Second, there were relatively few data from low-income countries and Africa as a continent to allow for a general conclusion. Third, appointing individuals into such broad ethnic and racial categories is accompanied by some limitations. Specifically, the same ethnic and racial categories are not applied in the same way across the different geographic regions, because of differences in historical and social contexts that define ethnic and racial categories. Nevertheless, these broad groups, which are widely used in literature, can be of great clinical importance for demonstrating differences that can be important for clinical practice, and for health care interventions aiming preventive strategies at subgroups at risk. Fourth, as we used data collected according to local protocols with initially different purposes, information on certain risk factors was missing for some patients. Fifth, although we harmonized and standardized the definitions for all risk factors, differential misclassification may have occurred. For example, dyslipidemia in Western countries was often based on lipid levels or the use of statins, while in many LMICs, it was primarily defined based on blood lipid level, which may result in an underestimation of the true prevalence of dyslipidemia in LMICs. Sixth, adjudicating the exact cause of stroke requires availability and access to additional investigations such as a cardiac ultrasound or neuroimaging (MRI). It is possible that these were not equally available for patients from LMICs and those from HICs,

which could also partly explain the higher prevalence of cryptogenic stroke in LICs compared to HICs. However, we found no significant difference in prevalence of cardioembolic stroke between HICs and LMICs (18.6% vs 20.0%), suggesting only minor misclassification of the cause of stroke. Furthermore, due to limited information on potential cardioembolic sources (e.g., intracardiac thrombus, left ventricular ejection fraction <30%, cardiac tumors), the extent of luminal stenosis in the brain-supplying arteries, and detailed topography of ischemic lesions, we were not able to distinguish strokes with an embolic source of undetermined etiology from other strokes with an undetermined etiology. As collection of these variables was not needed to answer our initial research question, information on these variables was not systematically requested from the participating centers. Seventh, we were not able to investigate regional differences with respect to lifestyle or ambient air pollution that are increasingly recognized to play a role in stroke etiology.[6] Finally, all cohorts included in our study were hospital-based studies, potentially introducing selection bias because patients with very mild or rapidly fatal strokes might not have gone to or reached the hospital and might therefore not have been included.

We found regional differences in (vascular) risk factors for ischemic stroke in young adults. This raises the question whether this also translates to regional differences in outcome (e.g., recurrent stroke) after stroke and secondary prevention strategies. The current secondary prevention strategy is a more or less "one size fits all approach" without taking into account regional or ethnic background, although it is known that ethnic differences in efficacy of secondary prevention exist.[31-33] Also, future research should investigate whether improvement of access and affordability of health care facilities in LMICs will improve outcomes after stroke in younger patients, and whether this helps in tackling the current existing inequality. For example, an established evidence-based approach to improve short-term stroke outcome is the implementation of stroke units,[11] which seems readily cost-effective with feasible implementation in LMICs. This could save lives, prevent permanent disability and loss of working capacity, decrease societal and health care costs, and improve the quality of life for millions of young individuals worldwide.

Our study has shown significant differences in risk factors and causes of ischemic stroke at young age between different ethnic and racial groups and geographic regions that help in understanding ethnic and regional differences in the incidence and clustering of risk factors of ischemic stroke among young adults. These insights may be used to develop region-specific policies on stroke prevention,[1] which could help in achieving the United Nations Sustainable Development Goals. The increasing awareness of the presence of vascular risk factors already at midlife for late life vascular disease, including the increased recognition of a role of these midlife vascular risk factors for late life cognitive decline,[34] underscores the importance of improving the health status of younger adults by managing vascular risk factors from as early as the third decade of life. Our results also visualize the inequalities in young stroke short-term mortality between LMICs and HICs and could help raise awareness of the magnitude of the problem to policy makers.

Acknowledgment

The authors thank the patients who originally signed informed consent and the physicians of participating centers who helped with the original data collection.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* February 5, 2021. Accepted in final form November 16, 2021.

Appendix Authors

Name	Location	Contribution
Mina A. Jacob, MD	Radboud University Medical Center, Nijmegen, the Netherlands	Contributed to study concept and design, data acquisition and analysis, drafted the manuscript and created the figures, revised the manuscript for intellectual content
Merel S. Ekker, MD	Radboud University Medical Center, Nijmegen, the Netherlands	Contributed to study concept and design, data acquisition and analysis, revised the manuscript for intellectual content
Youssra Allach, BsC	Radboud University Medical Center, Nijmegen, the Netherlands	Contributed to data acquisition and analysis, drafted the manuscript and created the figures, revised the manuscript for intellectual content
Mengfei Cai, MD	Radboud University Medical Center, Nijmegen, the Netherlands	Contributed to data analysis, created the figures, revised the manuscript for intellectual content
Karoliina Aarnio, MD	Helsinki University Hospital, Finland	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Antonio Arauz, MD	National Institute of Neurology and Neurosurgery of Mexico, Mexico City	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Marcel Arnold, MD	Inselspital University Hospital, Bern, Switzerland	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Hee-Joon Bae, MD	Seoul National University Bundang Hospital, Republic of Korea	Contributed to data acquisition and analysis, revised the manuscript for intellectual content

Continued

Appendix *(continued)*

Name	Location	Contribution
Lucre Bandeo, MD	Hospital Británico de Buenos Aires, Argentina	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Miguel Barboza, MD	Hospital Dr. Rafael A. Calderon Guardia, San Jose, Costa Rica	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Manuel A. Bolognese, MD	Lucerne Cantonal Hospital, Luzern, Switzerland	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Pablo Bonardo, MD	Hospital Británico de Buenos Aires, Argentina	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Raf Brouns, MD	ZorgSaam Hospital, Terneuzen, the Netherlands	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Batnairamdal Chuluun, MD	Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Enkhzaya Chuluunbatar, MD	Taipei Medical University, Taiwan	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Charlotte Cordonnier, MD	University Lille, France	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Byambasuren Dagvajantsan, MD	Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Stephanie Debette, MD	University of Bordeaux, France	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Adi Don, MD	Tel Aviv University, Israel	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Chris Ezinger, MD	Medical University of Graz, Austria	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Esme Ezikoglu, MD	Istanbul University, Istanbul Faculty of Medicine, Turkey	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Simon Fandler-Höfler, MD	Medical University of Graz, Austria	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Franz Fazekas, MD	Medical University of Graz, Austria	Contributed to data acquisition and analysis, revised the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Anette Fromm, MD	Haukeland University Hospital, Bergen, Norway	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Thomas Gattringer, MD	Medical University of Graz, Austria	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Thiago F. Hora, MD	SARAH Hospital of Rehabilitation, Brasilia, Brazil	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Christina Jern, MD	Sahlgrenska University Hospital, Gothenburg, Sweden	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Katarina Jood, MD	Sahlgrenska University Hospital, Gothenburg, Sweden	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Young Seo Kim, MD	Hanyang University, Seoul, Republic of Korea	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Steven Kittner, MD	University of Maryland School of Medicine, Baltimore	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Timothy Kleinig, MD	Royal Adelaide Hospital, Australia	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Catharina J.M. Klijn, MD	Radboud University Medical Center, Nijmegen, the Netherlands	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Janika Kõrv, MD	University of Tartu, Estonia	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Vinod Kumar, MD	Cleveland Clinic Abu Dhabi, United Arab Emirates	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Keon-Joo Lee, MD	Seoul National University Bundang Hospital, Republic of Korea	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Tsong-Hai Lee, MD	Chang Gung University, Guishan, Taoyuan, Taiwan	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Noortje A.M. Maaijwee, MD	Lucerne Cantonal Hospital, Luzern, Switzerland	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Nicolas Martinez-Majander, MD	Helsinki University Hospital, Finland	Contributed to data acquisition and analysis, revised the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
João Pedro Marto, MD	Universidade NOVA de Lisboa, Lisbon, Portugal	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Man M. Mehndiratta, MD	G.B.Pant Institute of Medical Education and Research (GIPMER), New Delhi, India	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Victoria Mifsud, MD	Cleveland Clinic Abu Dhabi, United Arab Emirates	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Vinícius Montanaro, MD	SARAH Hospital of Rehabilitation, Brasilia, Brazil	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Gisele Pacio, MD	Hospital Británico de Buenos Aires, Argentina	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Vinod B. Patel, MD	Inkosi Albert Luthuli Central Hospital, Mayville, South Africa	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Matthew C. Phillips, MD	Waikato Hospital, Hamilton, New Zealand	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Bartlomiej Piechowski-Jozwiak, MD	Cleveland Clinic Abu Dhabi, United Arab Emirates	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Aleksandra Pikula, MD	University of Toronto, Canada	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Jose L. Ruiz-Sandoval, MD	Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Mexico	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Bertina von Sarnowski, MD	University Medicine, Greifswald, Germany	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Richard H. Swartz, MD	University of Toronto, Canada	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Kay Tan, MD	University of Malaya, Kuala Lumpur, Malaysia	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
David Tanne, MD	Tel Aviv University, Israel	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Turgut Tatlisumak, MD	Helsinki University Hospital, Finland	Contributed to data acquisition and analysis, revised the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Vincent Thijs, MD	Austin Health, Melbourne, Australia	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Miguel Viana-Baptista, MD	Universidade NOVA de Lisboa, Lisbon, Portugal	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Riina Vibo, MD	University of Tartu, Estonia	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Teddy Y. Wu, MD	Christchurch Hospital, Christchurch, New Zealand	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Nilüfer Yesilot, MD	Istanbul University, Istanbul Faculty of Medicine, Turkey	Contributed to data acquisition and analysis, revised the manuscript for intellectual content
Ulrike Waje-Andreassen	Haukeland University Hospital, Bergen, Norway	Contributed to study concept and design, data acquisition and analysis, revised the manuscript for intellectual content
Alessandro Pezzini, MD	University of Brescia, Italy	Contributed to study concept and design, data acquisition and analysis, revised the manuscript for intellectual content
Jukka Putaala, MD	Helsinki University Hospital, Finland	Contributed to study concept and design, data acquisition and analysis, revised the manuscript for intellectual content
Anil M. Tuladhar, MD	Radboud University Medical Center, Nijmegen, the Netherlands	Contributed to study concept and design, data acquisition and analysis, revised the manuscript for intellectual content
Frank-Erik de Leeuw, MD	Radboud University Medical Center, Nijmegen, the Netherlands	Contributed to study concept and design, data acquisition and analysis, revised the manuscript for intellectual content

References

1. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards sustainable development goal target 3.4. *Lancet.* 2018; 392(10152):1072-1088.
2. Ekker MS, Boot EM, Singhal AB, et al. Epidemiology, aetiology, and management of ischaemic stroke in young adults. *Lancet Neurol.* 2018;17(9):790-801.
3. Maaijwee NA, Rutten-Jacobs LC, Schaapsmeerders P, van Dijk EJ, de Leeuw FE. Ischaemic stroke in young adults: risk factors and long-term consequences. *Nat Rev Neurol.* 2014;10(6):315-325.
4. Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: the GBD 2013 study. *Neuroepidemiology.* 2015;45(3):161-176.
5. Ekker MS, Verhoeven JI, Vaartjes I, Jolink WMT, Klijn CJM, de Leeuw FE. Association of stroke among adults aged 18 to 49 years with long-term mortality. *JAMA.* 2019;321(21):2113-2123.
6. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol.* 2016;15(9):913-924.

7. Boot E, Ekker MS, Putaala J, Kittner S, De Leeuw FE, Tuladhar AM. Ischaemic stroke in young adults: a global perspective. *J Neurol Neurosurg Psychiatry.* 2020;91(4):411-417.
8. Sarfo FS, Ovbiagele B, Gebregziabher M, et al. Stroke among young West Africans: evidence from the SIREN (Stroke Investigative Research and Educational Network) large multisite case-control study. *Stroke.* 2018;49(5):1116-1122.
9. Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. *Presse Med.* 2016;45(12 pt 2):e391-e398.
10. Morgenstern LB, Smith MA, Lisabeth LD, et al. Excess stroke in Mexican Americans compared with non-Hispanic whites: the Brain Attack Surveillance in Corpus Christi project. *Am J Epidemiol.* 2004;160(4):376-383.
11. Langhorne P, O'Donnell MJ, Chin SL, et al. Practice patterns and outcomes after stroke across countries at different economic levels (INTERSTROKE): an international observational study. *Lancet.* 2018;391(10134):2019-2027.
12. Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med.* 2014;371(9):818-827.
13. Ekker MS, Jacob MA, van Dongen MME, et al. Global Outcome Assessment Lifelong After Stroke in Young Adults initiative: the GOAL initiative: study protocol and rationale of a multicentre retrospective individual patient data meta-analysis. *BMJ Open.* 2019;9(11):e031144.
14. GOAL Initiative. Available at: goalinitiative.org.
15. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ.* 1980;58(1):113-130.
16. World Bank. *The World by Income and Region*. Available at: datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html.
17. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for health care professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(7):2160-2236.
18. Adams HP Jr, 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.
19. Putaala J, Haapaniemi E, Kaste M, et al. How does number of risk factors affect prognosis in young patients with ischemic stroke? *Stroke.* 2012;43:356-361.
20. Marini C, Russo T, Felzani G. Incidence of stroke in young adults: a review. *Stroke Res Treat.* 2010;2011:535672.
21. Kurian AK, Cardarelli KM. Racial and ethnic differences in cardiovascular disease risk factors: a systematic review. *Ethn Dis.* 2007;17(1):143-152.
22. Howard G, Lackland DT, Kleindorfer DO, et al. Racial differences in the impact of elevated systolic blood pressure on stroke risk. *JAMA Intern Med.* 2013;173(1):46-51.
23. 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(10046):761-775.
24. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology.* 2012;79(17):1781-1787.
25. 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(10226):795-808.
26. Ekker MS, Verhoeven JI, Vaartjes I, van Nieuwenhuizen KM, Klijn CJM, de Leeuw FE. Stroke incidence in young adults according to age, subtype, sex, and time trends. *Neurology.* 2019;92(21):e2444-e2454.
27. Putaala J, Metso AJ, Metso TM, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. *Stroke.* 2009;40(4):1195-1203.
28. Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. *Circulation.* 2017;135(8):759-771.
29. Lee TH, Hsu WC, Chen CJ, Chen ST. Etiologic study of young ischemic stroke in Taiwan. *Stroke.* 2002;33(8):1950-1955.
30. Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA.* 2013;310(9):959-968.
31. Muntner P, Hardy ST, Fine LJ, et al. Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. *JAMA.* 2020;324(12):1190-1200.
32. Kaufman JS, Dolman L, Rushani D, Cooper RS. The contribution of genomic research to explaining racial disparities in cardiovascular disease: a systematic review. *Am J Epidemiol.* 2015;181(7):464-472.
33. Mensah GA, Jaquish C, Srinivas P, et al. Emerging concepts in precision medicine and cardiovascular diseases in racial and ethnic minority populations. *Circ Res.* 2019;125(1):7-13.
34. Gottesman RF, Schneider AL, Albert M, et al. Midlife hypertension and 20-year cognitive change: the Atherosclerosis Risk in Communities neurocognitive study. *JAMA Neurol.* 2014;71(10):1218-1227.
35. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with Type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care.* 2015;38(9):1777-1803.
36. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;24(suppl 1):9-160.

Global Differences in Risk Factors, Etiology, and Outcome of Ischemic Stroke in Young Adults —A Worldwide Meta-analysis: The GOAL Initiative

Mina A. Jacob, Merel S. Ekker, Youssra Allach, et al.

Neurology 2022;98;e573-e588 Published Online before print December 14, 2021
DOI 10.1212/WNL.0000000000013195

CORRECTION

Association of CSF, Plasma, and Imaging Markers of Neurodegeneration With Clinical Progression in People With Subjective Cognitive Decline

Neurology® 2022;99:86. doi:10.1212/WNL.0000000000200734

In the Research Article "Association of CSF, Plasma, and Imaging Markers of Neurodegeneration With Clinical Progression in People With Subjective Cognitive Decline" by Ebenau et al.,[1] the title should be "Associations of CSF, Blood, and Imaging Markers of Neurodegeneration With Clinical Progression in People With Subjective Cognitive Decline."

In addition, the first sentence of the fifth paragraph under Biomarkers should read as follows: "Nonfasted serum samples (n = 296 [72%]) were obtained through venipuncture and centrifuged on average within 2 hours from collection, at 1800*g*, 10 minutes at room temperature, before immediate storage at −80°C until analysis."

The authors regret the errors.

Reference

1. Ebenau JL, Pelkmans W, Verberk IMW, et al. Association of CSF, plasma, and imaging markers of neurodegeneration with clinical progression in people with subjective cognitive decline. *Neurology*. 2022;98(13):e1315-e1326.

CORRECTION & REPLACEMENTS

Mixed Method Examination of the Brain Health of Former NCAA Division I Football Players and Former NFL Players

Neurology® 2022;99:86. doi:10.1212/WNL.0000000000200762

In the 2021 Sports Concussion Virtual Conference abstract "Mixed Method Examination of the Brain Health of Former NCAA Division I Football Players and Former NFL Players" by Fuller et al.,[1] another abstract was inadvertently published twice and replaced the content of the abstract. The abstract has been updated with the correct text. The AAN scientific programming staff regrets the error.

Reference

1. Fuller S, Jain E, Nagirimadugu NV, Turner RW. Mixed method examination of the brain health of former NCAA Division I football players and former NFL players. *Neurology*. 2022;98(1 suppl 1):S1.

Global Differences in Risk Factors, Etiology, and Outcome of Ischemic Stroke in Young Adults—A Worldwide Meta-analysis

The GOAL Initiative

Neurology® 2022;99:86. doi:10.1212/WNL.0000000000200743

In the Research Article "Global Differences in Risk Factors, Etiology, and Outcome of Ischemic Stroke in Young Adults—A Worldwide Meta-analysis: The GOAL Initiative" by Jacob et al.,[1] the 39th author's name should be listed as "João Pedro Marto." The article has been replaced by a corrected version. The authors regret the error.

Reference

1. Jacob MA, Ekker MS, Allach Y, et al. Global differences in risk factors, etiology, and outcome of ischemic stroke in young adults—a worldwide meta-analysis: the GOAL initiative. *Neurology*. 2022;98(6):e573-e588.

