

## **Clonal hematopoiesis is associated with higher risk of stroke**

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## Supplemental Methods

### **Atherosclerosis Risk in Communities (ARIC) study**

The ARIC study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up examinations, a fifth exam in 2011-2013, a sixth exam in 2016-2017, and a seventh exam in 2018-2019. The ARIC study has been described in detail previously (The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: Design and objectives. *American Journal of Epidemiology* 1989;129:687-702). Hospitalized strokes that occurred by December 31, 2011 are included. During annual telephone contacts, trained interviewers asked each ARIC participant to list all hospitalizations during the past year. Hospital records for any hospitalizations identified were then obtained. In addition, all local hospitals annually provided lists of stroke discharges (International Classification of Diseases, Ninth Revision, Clinical Modification codes 430 to 438), which were scrutinized for ARIC participant discharges. Details on quality assurance for ascertainment and classification of stroke are described elsewhere<sup>25</sup>. Briefly, the stroke diagnosis was assigned according to criteria adapted from the National Survey of Stroke<sup>26</sup>. Strokes secondary to trauma, neoplasm, hematologic abnormality, infection, or vasculitis were excluded, and a focal deficit lasting <24 hours was not considered to be a stroke. Out-of-hospital stroke was not ascertained and validated; thus, these potential stroke events were not included. Strokes were classified into hemorrhagic stroke (subarachnoid and intracerebral hemorrhage) and ischemic stroke. A stroke was classified as ischemic when a brain CT or MRI revealed acute infarction and showed no evidence of hemorrhage. Only individuals free of stroke or TIA at baseline were included in the analysis.

### **BioMe™ Biobank (BioMe)**

The Charles Bronfman Institute for Personalized Medicine at Mount Sinai Medical Center (MSMC), BioMe Biobank, founded in September 2007, is an ongoing, broadly-consented electronic health record-linked clinical care biobank that enrolls participants non-selectively from the Mount Sinai Medical Center patient population. The MSMC serves diverse local communities of upper Manhattan, including Central Harlem (86% African American), East Harlem (88% Hispanic/Latino), and Upper East Side (88% Caucasian/White) with broad health disparities. For the current analysis, adult (>18 years of age) coronary artery disease (CAD) cases and controls were included. A Case-Definition-Algorithm (CDA), incorporating International Classification of Diseases (ICD) codes and Current Procedural Terminology (CPT) codes, was used to identify individuals with CAD along with suitable controls.

### **Cardiovascular Health Study (CHS)**

The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults 65 years and older conducted across four field centers<sup>27</sup>. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of people on Medicare eligibility lists from four US communities. Subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888. Institutional review committees at each field center approved the CHS, and participants gave informed consent. Blood samples were drawn from all participants at their baseline examination, and DNA was subsequently extracted from available samples. These analyses were limited to participants with available DNA who also consented to genetic studies. Participants were examined annually from enrollment to 1999 and continued to be under surveillance for stroke following 1999. Since baseline, participants have also been contacted twice a year to identify potential cardiovascular events, including stroke. In addition, all hospitalizations were screened for potential stroke events. For suspected fatal and non-fatal events occurring with or without hospitalization, information was collected from the participant or next of kin, from medical records, and if needed, from the participant's physician. When available, scans or reports of CT, MRI or both were reviewed centrally. Finally, at a consensus conference using all available information, vascular neurologists adjudicated the occurrence of fatal and non-fatal stroke, stroke types, and subtypes<sup>28</sup>.

### **Framingham Heart Study (FHS)**

FHS is a three-generation, single-site, community-based, ongoing cohort study that was initiated in 1948 to investigate prospectively the risk factors for CVD including stroke. It now comprises 3 generations of participants (N=10,333): the Original cohort followed since 1948<sup>29</sup>; their Offspring and spouses of the Offspring, followed since 1971<sup>30</sup>; and children from the largest Offspring families enrolled in 2000 (Gen 3)<sup>31</sup>. The Original cohort enrolled 5,209 men and women who comprised two-thirds of the adult population then residing in Framingham, MA. Survivors continue to receive biennial examinations. The Offspring cohort comprises 5,124 persons (including 3,514 biological offspring) who have been examined approximately once every 4 years. The population of Framingham was virtually entirely white (Europeans of English, Scots, Irish and Italian descent) in 1948 when the Original cohort was recruited. At the initial examination participants were asked for the country of birth and whether or not they had any Italian ancestry. At a later examination (the 8th) the Offspring cohort participants were asked to identify their race from the following choices: Caucasian or white, African-American or black, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska native or 'prefer not to answer'. They were either asked to identify their ethnicity as either 'Hispanic or Latino' or not. Almost all the FHS Original and Offspring participants are white/Caucasian and none were excluded from the discovery cohort. At each clinic exam, participants receive questionnaires, physical examinations, and laboratory testing; between examinations, they remain under surveillance (regardless of whether or not they live in the vicinity) via physician referrals, record linkage, and annual telephone health history updates. Incident strokes have been identified since 1948 through this ongoing system of FHS clinic and local hospital surveillance and methods used have been detailed previously<sup>32-34</sup>; they include a review of medical records and collaboration with local general practitioners, emergency rooms, and imaging facilities. If a participant saw a physician or was admitted to the hospital, visited an emergency room or obtained any brain imaging between biennial examinations for symptoms suggestive of TIA or stroke, a stroke neurologist from the Heart Study attempted to visit the person within 48 hours and recorded a complete history and neurological examination; this was repeated at 1, 3 and 6 months. All medical records from practitioners, hospitals, imaging centers, rehabilitation centers, and nursing homes were procured for review. A panel of 3 investigators (at least 2 neurologists) adjudicated the diagnosis of stroke and determined stroke subtype in each case based on the Framingham evaluations and external records. The recruitment of Original and Offspring cohort participants at FHS had occurred long before the DNA collection with the result that the majority of stroke events in the FHS (although ascertained prospectively) were prevalent at the time of DNA collection and were excluded from these analyses.

### **Jackson Heart Study (JHS)**

JHS is a single-site, prospective, population-based study designed to explore the environmental, behavioral, and genetic factors that influence the development of CVD among African Americans. A total of 5,306 women and men between the ages of 21 and 94 were recruited between 2000 and 2004 from a tri-county area of Mississippi: Hinds, Madison, and Rankin Counties. Participants were recruited from four sources, including (1) randomly sampled households from a commercial listing; (2) ARIC participants; (3) a structured volunteer sample that was designed to mirror the eligible population; and (4) a nested family cohort. Overviews of the JHS including the sampling and recruitment, sociocultural, and laboratory methods have been described and published previously<sup>35-39</sup>. The institutional review boards of the following participating institutions approved the study: the University of Mississippi Medical Center, Jackson State University, and Tougaloo College. All participants provided written informed consent. Unrelated participants were between 35 and 84 years old, and members of the family cohort were  $\geq 21$  years old when consent for genetic testing was obtained and blood was drawn for DNA extraction. The baseline examination consisted of a home interview, self-administered questionnaires, and a clinic visit. Medications taken in the prior 2 weeks were brought to clinic and transcribed verbatim with subsequent coding by a pharmacist. After an overnight fast, anthropometric and seated blood pressure measurements were obtained and venipuncture/urine collection was performed in accordance with the National Committee for Clinical Laboratory Standards. Blood pressure at baseline was measured by trained technicians using a Hawksley random zero manometer and determined by the arithmetic average of two readings taken 1 minute apart after a five-minute rest<sup>39</sup>. In addition to the standard JHS examinations, participants were contacted by telephone annually beginning in 2005 to obtain interim information about cardiovascular events (ICD-9 code 428 for hospitalizations). During

the annual follow up phone call, participants or designated representatives provide self-reported information of hospitalization or death. Identification and abstraction of CVD illness and death data are performed by a certified medical record abstractor. Incident stroke is defined as stroke that occurred while the participants was enrolled the study, i.e. stroke event occurred after the baseline visit. Strokes are classified as either definite or probable stroke. The definition of stroke was based on the World Health Organization (WHO) criteria for definition of stroke or clinical criteria in which case the WHO criteria might not have been satisfied, but there is clinical evidence sufficient for a diagnosis of stroke to be made. More details on identification and classification of stroke events in the JHS have already been published<sup>40</sup>.

### **Multi-Ethnic Study of Atherosclerosis (MESA)**

The MESA study is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease<sup>41</sup>. MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Thirty-eight percent of the recruited participants are white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and the University of California - Los Angeles. The first examination took place over two years, from July 2000 - July 2002. It was followed by four examination periods that were 17-20 months in length. Participants have been contacted every 9 to 12 months throughout the study to assess clinical morbidity and mortality<sup>18</sup>. Prevalent stroke was an exclusion criterion for MESA at baseline. New occurrences of stroke were recorded over 9-years of follow-up. In brief, a telephone interviewer contacted each participant every 9–12 months. Information about all new cardiovascular conditions, hospital admissions, cardiovascular outpatient diagnoses, treatments, and deaths were obtained. To verify self-reported diagnoses, information was collected from death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses, using ICD-9 and ICD-10 codes. In the case of out-of-hospital deaths, next-of-kin interviews or questionnaires were administered to physicians, relatives or friends. Two physicians from the MESA study events committee independently reviewed all medical records for endpoint classification and assignment of incidence dates. The reviewers were blinded to the study data. If the reviewing physicians disagreed on the event classification, they adjudicated differences. Neurologists reviewed and classified stroke as present if there was a focal neurologic deficit lasting 24 hours or until death, or if <24h, there was a clinically relevant lesion on brain imaging and no nonvascular cause. Patients with focal neurological deficits secondary to brain trauma, tumor, infections, or other non-vascular cause were excluded<sup>42</sup>. Ischemic strokes were distinguished from hemorrhagic strokes using findings on imaging, surgery, autopsy, or some combination of these. Ischemic stroke subtypes were assigned based on an extension of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) scheme to try to reduce the number classified as undetermined.

### **Women's Health Initiative (WHI)**

WHI is a long-term, prospective, multi-center cohort study that investigates post-menopausal women's health<sup>43</sup>. WHI was funded by the National Institutes of Health and the National Heart, Lung, and Blood Institute to study strategies to prevent heart disease, breast cancer, colon cancer, and osteoporotic fractures in women 50-79 years of age. WHI involves 161,808 women recruited between 1993 and 1998 at 40 centers across the US. The study consists of two parts: the WHI Clinical Trial which was a randomized clinical trial of hormone therapy, dietary modification, and calcium/Vitamin D supplementation, and the WHI Observational Study, which focused on many of the inequities in women's health research and provided practical information about the incidence, risk factors, and interventions related to heart disease, cancer, and osteoporotic fractures. Stroke diagnosis requiring and/or occurring during hospitalization was based on the rapid onset of a neurological deficit attributable to an obstruction or rupture of an arterial vessel system. Hospitalized incident stroke events were identified by semiannual questionnaires and adjudicated following medical record review, which occurred both locally and centrally. Ischemic strokes were further classified by the central neurologist adjudicators according to the Trial of Org 10172 Acute Stroke Trial (TOAST) criteria to examine stroke subtypes. The TOAST classification focuses on the presumed underlying stroke mechanism and requires detailed investigations (such as brain computed

tomography, magnetic resonance imaging, angiography, carotid ultrasound, and echocardiography). Venous thromboembolism (VTE) cases were excluded from the control group.

### **UK Biobank (UKBB)**

UK Biobank is a large long-term biobank study in the United Kingdom aimed to investigate the respective contributions of genetic predisposition and environmental exposure to the development of diseases. Only European ancestry and unrelated participants were included in the current analysis. Cases were defined through algorithmic combinations of coded information from UKBB's baseline assessment data collection (which included data from participants on their self-reported medical conditions, operations and medications), along with linked data from hospital admissions (diagnoses and procedures) and death registries. The classification is based on algorithms developed by the UKBB outcome adjudication group, aiming to classify disease outcomes with high positive predictive value (i.e. a high probability that people classified as being positive for a health-related event have indeed experienced that event).

Genotyping of UKBB participants was performed using either the Affymetrix UK BiLEVE Axiom array or the Affymetrix UK Biobank Axiom® array, with QC procedures performed at both the variants and the sample level ([http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank\\_genotyping\\_QC\\_documentation-web-1.pdf](http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web-1.pdf)). Imputation was performed based on reference panels from the Haplotype Reference Consortium, UK10K, and the 1000 Genome Phase 3 using MACH (<http://csg.sph.umich.edu/abecasis/MACH/index.html>). Genetic variants with MAF>0.1% and imputation quality score R<sup>2</sup>>0.3 were included in the association analysis.

### **Mass General Brigham Biobank (MGBB)**

The Mass General Brigham Biobank (MGBB) is a hospital-based biobank with linkage to the electronic health record (EHR) at the Mass General Brigham hospital system, including Brigham and Women's Hospital, Massachusetts General Hospital, Mass Eye and Ear Infirmary, Faulkner Hospital, Newton-Wellesley Hospital, McLean Hospital, North Shore Medical Center and Spaulding Rehabilitation Network. MGBB provides banked samples (plasma, serum, DNA, buffy coats) collected from patients who consented to broad-based research. These samples are linked to clinical data from the EHR, quantitative data derived from medical images, and survey data on lifestyle, environment, and family history. The Biobank also provides genotype data and exome sequencing data. Qualified users within the MGB system may query the biobank using a web-based portal where de-identified data is provided. Individual-level identifiable patient data may then be requested for IRB-approved protocols.

MGBB currently contains approximately 120,000 consented individuals, with around 40,000 with genotyping, 36,000 with imputed data available and around 7,400 subjects with exome sequencing data available. MGBB samples have been genotyped on MEGA, MEGA Ex, and MEG arrays. Exome variant calling was performed using the GATK (Genome Analysis Toolkit) GVCF workflow for variant discovery in high-throughput exome sequencing data using HaplotypeCaller in gVCF mode.

## SUPPLEMENTAL TABLES

**Supplemental Table I: ICD Codes For Definitions of Stroke in the MGBB cohort.** The following ICD 9 and 10 codes were used to define the outcomes listed – All Stroke, Ischemic Stroke, and Hemorrhagic Stroke. Phenotypes for SAH, TIA and cerebral aneurysm were used separately for exploratory analyses. (ICD, International Classification of Disease; MGBB, Mass General Brigham Biobank; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack)

Outcome	Code	Code Type	Description
Ischemic Stroke	362.3	ICD-9	Retinal vascular occlusion
Ischemic Stroke	433.01	ICD-9	Occlusion and stenosis of basilar artery with cerebral infarction
Ischemic Stroke	433.11	ICD-9	Occlusion and stenosis of carotid artery with cerebral infarction
Ischemic Stroke	433.21	ICD-9	Occlusion and stenosis of vertebral artery with cerebral infarction
Ischemic Stroke	433.31	ICD-9	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
Ischemic Stroke	433.81	ICD-9	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
Ischemic Stroke	433.91	ICD-9	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
Ischemic Stroke	434.01	ICD-9	Cerebral thrombosis with cerebral infarction
Ischemic Stroke	434.11	ICD-9	Cerebral embolism with cerebral infarction
Ischemic Stroke	434.91	ICD-9	Cerebral artery occlusion, unspecified with cerebral infarction
Ischemic Stroke	436	ICD-9	Acute, but ill-defined cerebrovascular disease
Ischemic Stroke	H34.1	ICD-10	Central retinal artery occlusion
Ischemic Stroke	I63.00	ICD-10	Cerebral infarction due to thrombosis of unspecified precerebral artery
Ischemic Stroke	I63.011	ICD-10	Cerebral infarction due to thrombosis of right vertebral artery
Ischemic Stroke	I63.012	ICD-10	Cerebral infarction due to thrombosis of left vertebral artery
Ischemic Stroke	I63.013	ICD-10	Cerebral infarction due to thrombosis of bilateral vertebral arteries
Ischemic Stroke	I63.019	ICD-10	Cerebral infarction due to thrombosis of unspecified vertebral artery
Ischemic Stroke	I63.02	ICD-10	Cerebral infarction due to thrombosis of basilar artery
Ischemic Stroke	I63.031	ICD-10	Cerebral infarction due to thrombosis of right carotid artery
Ischemic Stroke	I63.032	ICD-10	Cerebral infarction due to thrombosis of left carotid artery
Ischemic Stroke	I63.033	ICD-10	Cerebral infarction due to thrombosis of bilateral carotid arteries
Ischemic Stroke	I63.039	ICD-10	Cerebral infarction due to thrombosis of unspecified carotid artery
Ischemic Stroke	I63.09	ICD-10	Cerebral infarction due to thrombosis of other precerebral artery
Ischemic Stroke	I63.10	ICD-10	Cerebral infarction due to embolism of unspecified precerebral artery
Ischemic Stroke	I63.111	ICD-10	Cerebral infarction due to embolism of right vertebral artery
Ischemic Stroke	I63.112	ICD-10	Cerebral infarction due to embolism of left vertebral artery
Ischemic Stroke	I63.113	ICD-10	Cerebral infarction due to embolism of bilateral vertebral arteries
Ischemic Stroke	I63.119	ICD-10	Cerebral infarction due to embolism of unspecified vertebral artery
Ischemic Stroke	I63.12	ICD-10	Cerebral infarction due to embolism of basilar artery
Ischemic Stroke	I63.131	ICD-10	Cerebral infarction due to embolism of right carotid artery
Ischemic Stroke	I63.132	ICD-10	Cerebral infarction due to embolism of left carotid artery
Ischemic Stroke	I63.133	ICD-10	Cerebral infarction due to embolism of bilateral carotid arteries
Ischemic Stroke	I63.139	ICD-10	Cerebral infarction due to embolism of unspecified carotid artery
Ischemic Stroke	I63.19	ICD-10	Cerebral infarction due to embolism of other precerebral artery

Ischemic Stroke	I63.20	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries
Ischemic Stroke	I63.211	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral artery
Ischemic Stroke	I63.212	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral artery
Ischemic Stroke	I63.213	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries
Ischemic Stroke	I63.219	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral artery
Ischemic Stroke	I63.22	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of basilar artery
Ischemic Stroke	I63.231	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
Ischemic Stroke	I63.232	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries
Ischemic Stroke	I63.233	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries
Ischemic Stroke	I63.239	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid artery
Ischemic Stroke	I63.29	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries
Ischemic Stroke	I63.30	ICD-10	Cerebral infarction due to thrombosis of unspecified cerebral artery
Ischemic Stroke	I63.311	ICD-10	Cerebral infarction due to thrombosis of right middle cerebral artery
Ischemic Stroke	I63.312	ICD-10	Cerebral infarction due to thrombosis of left middle cerebral artery
Ischemic Stroke	I63.313	ICD-10	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
Ischemic Stroke	I63.319	ICD-10	Cerebral infarction due to thrombosis of unspecified middle cerebral artery
Ischemic Stroke	I63.321	ICD-10	Cerebral infarction due to thrombosis of right anterior cerebral artery
Ischemic Stroke	I63.322	ICD-10	Cerebral infarction due to thrombosis of left anterior cerebral artery
Ischemic Stroke	I63.323	ICD-10	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
Ischemic Stroke	I63.329	ICD-10	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
Ischemic Stroke	I63.331	ICD-10	Cerebral infarction due to thrombosis of right posterior cerebral artery
Ischemic Stroke	I63.332	ICD-10	Cerebral infarction due to thrombosis of left posterior cerebral artery
Ischemic Stroke	I63.333	ICD-10	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
Ischemic Stroke	I63.339	ICD-10	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
Ischemic Stroke	I63.341	ICD-10	Cerebral infarction due to thrombosis of right cerebellar artery
Ischemic Stroke	I63.342	ICD-10	Cerebral infarction due to thrombosis of left cerebellar artery
Ischemic Stroke	I63.343	ICD-10	Cerebral infarction due to thrombosis of bilateral cerebellar arteries
Ischemic Stroke	I63.349	ICD-10	Cerebral infarction due to thrombosis of unspecified cerebellar artery
Ischemic Stroke	I63.39	ICD-10	Cerebral infarction due to thrombosis of other cerebral artery
Ischemic Stroke	I63.40	ICD-10	Cerebral infarction due to embolism of unspecified cerebral artery
Ischemic Stroke	I63.411	ICD-10	Cerebral infarction due to embolism of right middle cerebral artery
Ischemic Stroke	I63.412	ICD-10	Cerebral infarction due to embolism of left middle cerebral artery
Ischemic Stroke	I63.413	ICD-10	Cerebral infarction due to embolism of bilateral middle cerebral arteries
Ischemic Stroke	I63.419	ICD-10	Cerebral infarction due to embolism of unspecified middle cerebral artery
Ischemic Stroke	I63.421	ICD-10	Cerebral infarction due to embolism of right anterior cerebral artery
Ischemic Stroke	I63.422	ICD-10	Cerebral infarction due to embolism of left anterior cerebral artery
Ischemic Stroke	I63.423	ICD-10	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
Ischemic Stroke	I63.429	ICD-10	Cerebral infarction due to embolism of unspecified anterior cerebral artery
Ischemic Stroke	I63.431	ICD-10	Cerebral infarction due to embolism of right posterior cerebral artery
Ischemic Stroke	I63.432	ICD-10	Cerebral infarction due to embolism of left posterior cerebral artery
Ischemic Stroke	I63.433	ICD-10	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
Ischemic Stroke	I63.439	ICD-10	Cerebral infarction due to embolism of unspecified posterior cerebral artery

Ischemic Stroke	I63.441	ICD-10	Cerebral infarction due to embolism of right cerebellar artery
Ischemic Stroke	I63.442	ICD-10	Cerebral infarction due to embolism of left cerebellar artery
Ischemic Stroke	I63.443	ICD-10	Cerebral infarction due to embolism of bilateral cerebellar arteries
Ischemic Stroke	I63.449	ICD-10	Cerebral infarction due to embolism of unspecified cerebellar artery
Ischemic Stroke	I63.49	ICD-10	Cerebral infarction due to embolism of other cerebral artery
Ischemic Stroke	I63.50	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
Ischemic Stroke	I63.511	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
Ischemic Stroke	I63.512	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
Ischemic Stroke	I63.513	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
Ischemic Stroke	I63.519	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
Ischemic Stroke	I63.521	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
Ischemic Stroke	I63.522	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
Ischemic Stroke	I63.523	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries
Ischemic Stroke	I63.529	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
Ischemic Stroke	I63.531	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
Ischemic Stroke	I63.532	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
Ischemic Stroke	I63.533	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries
Ischemic Stroke	I63.539	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
Ischemic Stroke	I63.541	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
Ischemic Stroke	I63.542	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
Ischemic Stroke	I63.543	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
Ischemic Stroke	I63.549	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
Ischemic Stroke	I63.59	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
Ischemic Stroke	I63.6	ICD-10	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
Ischemic Stroke	I63.8	ICD-10	Other cerebral infarction
Ischemic Stroke	I63.81	ICD-10	Other cerebral infarction due to occlusion or stenosis of small artery
Ischemic Stroke	I63.89	ICD-10	Other cerebral infarction
Ischemic Stroke	I63.9	ICD-10	Cerebral infarction, unspecified
Ischemic Stroke	I64	ICD-10	Stroke, not specified as hemorrhage or infarction
Hemorrhagic Stroke	431	ICD-9	Intracerebral hemorrhage
Hemorrhagic Stroke	I61.0	ICD-10	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical
Hemorrhagic Stroke	I61.1	ICD-10	Nontraumatic intracerebral hemorrhage in hemisphere, cortical
Hemorrhagic Stroke	I61.2	ICD-10	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified
Hemorrhagic Stroke	I61.3	ICD-10	Nontraumatic intracerebral hemorrhage in brain stem
Hemorrhagic Stroke	I61.4	ICD-10	Nontraumatic intracerebral hemorrhage in cerebellum
Hemorrhagic Stroke	I61.5	ICD-10	Nontraumatic intracerebral hemorrhage, intraventricular
Hemorrhagic Stroke	I61.6	ICD-10	Nontraumatic intracerebral hemorrhage, multiple localized
Hemorrhagic Stroke	I61.8	ICD-10	Other nontraumatic intracerebral hemorrhage
Hemorrhagic Stroke	I61.9	ICD-10	Nontraumatic intracerebral hemorrhage, unspecified
SAH nontraumatic	430	ICD-9	Subarachnoid hemorrhage
SAH nontraumatic	I60.00	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified carotid siphon and bifurcation



SAH nontraumatic	I60.01	ICD-10	Nontraumatic subarachnoid hemorrhage from right carotid siphon and bifurcation
SAH nontraumatic	I60.02	ICD-10	Nontraumatic subarachnoid hemorrhage from left carotid siphon and bifurcation
SAH nontraumatic	I60.10	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery
SAH nontraumatic	I60.11	ICD-10	Nontraumatic subarachnoid hemorrhage from right middle cerebral artery
SAH nontraumatic	I60.12	ICD-10	Nontraumatic subarachnoid hemorrhage from left middle cerebral artery
SAH nontraumatic	I60.2	ICD-10	Nontraumatic subarachnoid hemorrhage from anterior communicating artery
SAH nontraumatic	I60.20	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified anterior communicating artery
SAH nontraumatic	I60.21	ICD-10	Nontraumatic subarachnoid hemorrhage from right anterior communicating artery
SAH nontraumatic	I60.22	ICD-10	Nontraumatic subarachnoid hemorrhage from left anterior communicating artery
SAH nontraumatic	I60.30	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified posterior communicating artery
SAH nontraumatic	I60.31	ICD-10	Nontraumatic subarachnoid hemorrhage from right posterior communicating artery
SAH nontraumatic	I60.32	ICD-10	Nontraumatic subarachnoid hemorrhage from left posterior communicating artery
SAH nontraumatic	I60.4	ICD-10	Nontraumatic subarachnoid hemorrhage from basilar artery
SAH nontraumatic	I60.50	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified vertebral artery
SAH nontraumatic	I60.51	ICD-10	Nontraumatic subarachnoid hemorrhage from right vertebral artery
SAH nontraumatic	I60.52	ICD-10	Nontraumatic subarachnoid hemorrhage from left vertebral artery
SAH nontraumatic	I60.6	ICD-10	Nontraumatic subarachnoid hemorrhage from other intracranial arteries
SAH nontraumatic	I60.7	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified intracranial artery
SAH nontraumatic	I60.8	ICD-10	Other nontraumatic subarachnoid hemorrhage
SAH nontraumatic	I60.9	ICD-10	Nontraumatic subarachnoid hemorrhage, unspecified
TIA	435.0	ICD-9	Basilar artery syndrome
TIA	435.1	ICD-9	Vertebral artery syndrome
TIA	435.2	ICD-9	Subclavian steal syndrome
TIA	435.3	ICD-9	Vertebrobasilar artery syndrome
TIA	435.8	ICD-9	Other specified transient cerebral ischemias
TIA	435.9	ICD-9	Unspecified transient cerebral ischemia
TIA	436	ICD-9	Acute, but ill-defined, cerebrovascular disease
TIA	G45.0	ICD-10	Vertebro-basilar artery syndrome
TIA	G45.1	ICD-10	Carotid artery syndrome (hemispheric)
TIA	G45.2	ICD-10	Multiple and bilateral precerebral artery syndromes
TIA	G45.3	ICD-10	Amaurosis fugax
TIA	G45.4	ICD-10	Transient global amnesia
TIA	G45.8	ICD-10	Other transient cerebral ischemic attacks and related syndromes
TIA	G45.9	ICD-10	Transient cerebral ischemic attack, unspecified
Cerebral Aneurysm	I67.1	ICD-10	Cerebral aneurysm, unruptured
Cerebral Aneurysm	437.3	ICD-9	Cerebral aneurysm, nonruptured
Stroke (All)	362.3	ICD-9	Retinal vascular occlusion
Stroke (All)	433.01	ICD-9	Occlusion and stenosis of basilar artery with cerebral infarction
Stroke (All)	433.11	ICD-9	Occlusion and stenosis of carotid artery with cerebral infarction
Stroke (All)	433.21	ICD-9	Occlusion and stenosis of vertebral artery with cerebral infarction
Stroke (All)	433.31	ICD-9	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
Stroke (All)	433.81	ICD-9	Occlusion and stenosis of other specified precerebral artery with cerebral infarction

Stroke (All)	433.91	ICD-9	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
Stroke (All)	434.01	ICD-9	Cerebral thrombosis with cerebral infarction
Stroke (All)	434.11	ICD-9	Cerebral embolism with cerebral infarction
Stroke (All)	434.91	ICD-9	Cerebral artery occlusion, unspecified with cerebral infarction
Stroke (All)	436	ICD-9	Acute, but ill-defined cerebrovascular disease
Stroke (All)	H34.1	ICD-10	Central retinal artery occlusion
Stroke (All)	I63.00	ICD-10	Cerebral infarction due to thrombosis of unspecified precerebral artery
Stroke (All)	I63.011	ICD-10	Cerebral infarction due to thrombosis of right vertebral artery
Stroke (All)	I63.012	ICD-10	Cerebral infarction due to thrombosis of left vertebral artery
Stroke (All)	I63.013	ICD-10	Cerebral infarction due to thrombosis of bilateral vertebral arteries
Stroke (All)	I63.019	ICD-10	Cerebral infarction due to thrombosis of unspecified vertebral artery
Stroke (All)	I63.02	ICD-10	Cerebral infarction due to thrombosis of basilar artery
Stroke (All)	I63.031	ICD-10	Cerebral infarction due to thrombosis of right carotid artery
Stroke (All)	I63.032	ICD-10	Cerebral infarction due to thrombosis of left carotid artery
Stroke (All)	I63.033	ICD-10	Cerebral infarction due to thrombosis of bilateral carotid arteries
Stroke (All)	I63.039	ICD-10	Cerebral infarction due to thrombosis of unspecified carotid artery
Stroke (All)	I63.09	ICD-10	Cerebral infarction due to thrombosis of other precerebral artery
Stroke (All)	I63.10	ICD-10	Cerebral infarction due to embolism of unspecified precerebral artery
Stroke (All)	I63.111	ICD-10	Cerebral infarction due to embolism of right vertebral artery
Stroke (All)	I63.112	ICD-10	Cerebral infarction due to embolism of left vertebral artery
Stroke (All)	I63.113	ICD-10	Cerebral infarction due to embolism of bilateral vertebral arteries
Stroke (All)	I63.119	ICD-10	Cerebral infarction due to embolism of unspecified vertebral artery
Stroke (All)	I63.12	ICD-10	Cerebral infarction due to embolism of basilar artery
Stroke (All)	I63.131	ICD-10	Cerebral infarction due to embolism of right carotid artery
Stroke (All)	I63.132	ICD-10	Cerebral infarction due to embolism of left carotid artery
Stroke (All)	I63.133	ICD-10	Cerebral infarction due to embolism of bilateral carotid arteries
Stroke (All)	I63.139	ICD-10	Cerebral infarction due to embolism of unspecified carotid artery
Stroke (All)	I63.19	ICD-10	Cerebral infarction due to embolism of other precerebral artery
Stroke (All)	I63.20	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries
Stroke (All)	I63.211	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral artery
Stroke (All)	I63.212	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral artery
Stroke (All)	I63.213	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries
Stroke (All)	I63.219	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral artery
Stroke (All)	I63.22	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of basilar artery
Stroke (All)	I63.231	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
Stroke (All)	I63.232	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries
Stroke (All)	I63.233	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries
Stroke (All)	I63.239	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid artery
Stroke (All)	I63.29	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries
Stroke (All)	I63.30	ICD-10	Cerebral infarction due to thrombosis of unspecified cerebral artery
Stroke (All)	I63.311	ICD-10	Cerebral infarction due to thrombosis of right middle cerebral artery
Stroke (All)	I63.312	ICD-10	Cerebral infarction due to thrombosis of left middle cerebral artery

Stroke (All)	I63.313	ICD-10	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
Stroke (All)	I63.319	ICD-10	Cerebral infarction due to thrombosis of unspecified middle cerebral artery
Stroke (All)	I63.321	ICD-10	Cerebral infarction due to thrombosis of right anterior cerebral artery
Stroke (All)	I63.322	ICD-10	Cerebral infarction due to thrombosis of left anterior cerebral artery
Stroke (All)	I63.323	ICD-10	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
Stroke (All)	I63.329	ICD-10	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
Stroke (All)	I63.331	ICD-10	Cerebral infarction due to thrombosis of right posterior cerebral artery
Stroke (All)	I63.332	ICD-10	Cerebral infarction due to thrombosis of left posterior cerebral artery
Stroke (All)	I63.333	ICD-10	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
Stroke (All)	I63.339	ICD-10	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
Stroke (All)	I63.341	ICD-10	Cerebral infarction due to thrombosis of right cerebellar artery
Stroke (All)	I63.342	ICD-10	Cerebral infarction due to thrombosis of left cerebellar artery
Stroke (All)	I63.343	ICD-10	Cerebral infarction due to thrombosis of bilateral cerebellar arteries
Stroke (All)	I63.349	ICD-10	Cerebral infarction due to thrombosis of unspecified cerebellar artery
Stroke (All)	I63.39	ICD-10	Cerebral infarction due to thrombosis of other cerebral artery
Stroke (All)	I63.40	ICD-10	Cerebral infarction due to embolism of unspecified cerebral artery
Stroke (All)	I63.411	ICD-10	Cerebral infarction due to embolism of right middle cerebral artery
Stroke (All)	I63.412	ICD-10	Cerebral infarction due to embolism of left middle cerebral artery
Stroke (All)	I63.413	ICD-10	Cerebral infarction due to embolism of bilateral middle cerebral arteries
Stroke (All)	I63.419	ICD-10	Cerebral infarction due to embolism of unspecified middle cerebral artery
Stroke (All)	I63.421	ICD-10	Cerebral infarction due to embolism of right anterior cerebral artery
Stroke (All)	I63.422	ICD-10	Cerebral infarction due to embolism of left anterior cerebral artery
Stroke (All)	I63.423	ICD-10	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
Stroke (All)	I63.429	ICD-10	Cerebral infarction due to embolism of unspecified anterior cerebral artery
Stroke (All)	I63.431	ICD-10	Cerebral infarction due to embolism of right posterior cerebral artery
Stroke (All)	I63.432	ICD-10	Cerebral infarction due to embolism of left posterior cerebral artery
Stroke (All)	I63.433	ICD-10	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
Stroke (All)	I63.439	ICD-10	Cerebral infarction due to embolism of unspecified posterior cerebral artery
Stroke (All)	I63.441	ICD-10	Cerebral infarction due to embolism of right cerebellar artery
Stroke (All)	I63.442	ICD-10	Cerebral infarction due to embolism of left cerebellar artery
Stroke (All)	I63.443	ICD-10	Cerebral infarction due to embolism of bilateral cerebellar arteries
Stroke (All)	I63.449	ICD-10	Cerebral infarction due to embolism of unspecified cerebellar artery
Stroke (All)	I63.49	ICD-10	Cerebral infarction due to embolism of other cerebral artery
Stroke (All)	I63.50	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
Stroke (All)	I63.511	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
Stroke (All)	I63.512	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
Stroke (All)	I63.513	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
Stroke (All)	I63.519	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
Stroke (All)	I63.521	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
Stroke (All)	I63.522	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
Stroke (All)	I63.523	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries

Stroke (All)	I63.529	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
Stroke (All)	I63.531	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
Stroke (All)	I63.532	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
Stroke (All)	I63.533	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries
Stroke (All)	I63.539	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
Stroke (All)	I63.541	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
Stroke (All)	I63.542	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
Stroke (All)	I63.543	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
Stroke (All)	I63.549	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
Stroke (All)	I63.59	ICD-10	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
Stroke (All)	I63.6	ICD-10	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
Stroke (All)	I63.8	ICD-10	Other cerebral infarction
Stroke (All)	I63.81	ICD-10	Other cerebral infarction due to occlusion or stenosis of small artery
Stroke (All)	I63.89	ICD-10	Other cerebral infarction
Stroke (All)	I63.9	ICD-10	Cerebral infarction, unspecified
Stroke (All)	I64	ICD-10	Stroke, not specified as hemorrhage or infarction
Stroke (All)	431	ICD-9	Intracerebral hemorrhage
Stroke (All)	I61.0	ICD-10	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical
Stroke (All)	I61.1	ICD-10	Nontraumatic intracerebral hemorrhage in hemisphere, cortical
Stroke (All)	I61.2	ICD-10	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified
Stroke (All)	I61.3	ICD-10	Nontraumatic intracerebral hemorrhage in brain stem
Stroke (All)	I61.4	ICD-10	Nontraumatic intracerebral hemorrhage in cerebellum
Stroke (All)	I61.5	ICD-10	Nontraumatic intracerebral hemorrhage, intraventricular
Stroke (All)	I61.6	ICD-10	Nontraumatic intracerebral hemorrhage, multiple localized
Stroke (All)	I61.8	ICD-10	Other nontraumatic intracerebral hemorrhage
Stroke (All)	I61.9	ICD-10	Nontraumatic intracerebral hemorrhage, unspecified
Stroke (All)	430	ICD-9	Subarachnoid hemorrhage
Stroke (All)	I60.00	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified carotid siphon and bifurcation
Stroke (All)	I60.01	ICD-10	Nontraumatic subarachnoid hemorrhage from right carotid siphon and bifurcation
Stroke (All)	I60.02	ICD-10	Nontraumatic subarachnoid hemorrhage from left carotid siphon and bifurcation
Stroke (All)	I60.10	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery
Stroke (All)	I60.11	ICD-10	Nontraumatic subarachnoid hemorrhage from right middle cerebral artery
Stroke (All)	I60.12	ICD-10	Nontraumatic subarachnoid hemorrhage from left middle cerebral artery
Stroke (All)	I60.2	ICD-10	Nontraumatic subarachnoid hemorrhage from anterior communicating artery
Stroke (All)	I60.20	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified anterior communicating artery
Stroke (All)	I60.21	ICD-10	Nontraumatic subarachnoid hemorrhage from right anterior communicating artery
Stroke (All)	I60.22	ICD-10	Nontraumatic subarachnoid hemorrhage from left anterior communicating artery
Stroke (All)	I60.30	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified posterior communicating artery
Stroke (All)	I60.31	ICD-10	Nontraumatic subarachnoid hemorrhage from right posterior communicating artery
Stroke (All)	I60.32	ICD-10	Nontraumatic subarachnoid hemorrhage from left posterior communicating artery
Stroke (All)	I60.4	ICD-10	Nontraumatic subarachnoid hemorrhage from basilar artery

Stroke (All)	I60.50	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified vertebral artery
Stroke (All)	I60.51	ICD-10	Nontraumatic subarachnoid hemorrhage from right vertebral artery
Stroke (All)	I60.52	ICD-10	Nontraumatic subarachnoid hemorrhage from left vertebral artery
Stroke (All)	I60.6	ICD-10	Nontraumatic subarachnoid hemorrhage from other intracranial arteries
Stroke (All)	I60.7	ICD-10	Nontraumatic subarachnoid hemorrhage from unspecified intracranial artery
Stroke (All)	I60.8	ICD-10	Other nontraumatic subarachnoid hemorrhage
Stroke (All)	I60.9	ICD-10	Nontraumatic subarachnoid hemorrhage, unspecified

**Supplementary Table II: Gene-specific associations between CHIP and Stroke.** Stratifying CHIP status by the gene mutated, *TET2* is associated with all stroke, as well as ischemic stroke and hemorrhagic stroke. *DNMT3A* and *TET2* were the most commonly mutated CHIP genes, and there were many fewer samples with *ASXL1*, *JAK2*, or *TP53* mutations. (CHIP, Clonal Hematopoiesis of Indeterminate Potential; HR, Hazard Ratio; SE, standard error; PC, principal components of genetic ancestry).

Outcome	Gene	Covariates	HR	Beta	SE	P-value	Events	Total N	Gene Cases	Gene Controls
All Stroke	<i>DNMT3A</i>	Age, PC 1-10	1.08	0.08	0.10	0.424	4444	9344	233	302
All Stroke	<i>TET2</i>	Age, PC 1-10	1.85	0.61	0.22	0.004	4313	9052	102	110
All Stroke	<i>ASXL1</i>	Age, PC 1-10	0.96	-0.05	0.27	0.868	4238	8921	27	37
All Stroke	<i>JAK2</i>	Age, PC 1-10	1.32	0.28	0.35	0.420	4230	8898	19	20
All Stroke	<i>TP53</i>	Age, PC 1-10	0.62	-0.48	0.58	0.408	4216	8876	5	11
Ischemic Stroke	<i>DNMT3A</i>	Age, PC 1-10	1.03	0.03	0.11	0.752	3634	8548	182	303
Ischemic Stroke	<i>TET2</i>	Age, PC 1-10	1.93	0.66	0.24	0.006	3535	8289	83	112
Ischemic Stroke	<i>ASXL1</i>	Age, PC 1-10	0.95	-0.05	0.29	0.855	3474	8171	22	37
Ischemic Stroke	<i>JAK2</i>	Age, PC 1-10	1.42	0.35	0.36	0.328	3469	8152	17	21
Ischemic Stroke	<i>TP53</i>	Age, PC 1-10	0.30	-1.21	0.79	0.128	3454	8128	2	11
Hemorrhagic Stroke	<i>DNMT3A</i>	Age, PC 1-10	1.44	0.36	0.17	0.031	780	5694	50	303
Hemorrhagic Stroke	<i>TET2</i>	Age, PC 1-10	1.50	0.41	0.28	0.149	747	5501	17	112
Hemorrhagic Stroke	<i>ASXL1</i>	Age, PC 1-10	1.09	0.08	0.50	0.867	735	5432	5	37
Hemorrhagic Stroke	<i>JAK2</i>	Age, PC 1-10	0.43	-0.84	1.04	0.422	731	5414	1	21
Hemorrhagic Stroke	<i>TP53</i>	Age, PC 1-10	2.04	0.71	0.70	0.305	733	5407	3	11
All Stroke	<i>DNMT3A</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.07	0.07	0.10	0.506	4444	9344	233	302
All Stroke	<i>TET2</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.82	0.60	0.22	0.006	4313	9052	102	110
All Stroke	<i>ASXL1</i>	Age, PC 1-10, Diabetes, Ever Smoking	0.99	-0.01	0.27	0.958	4238	8921	27	37
All Stroke	<i>JAK2</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.29	0.26	0.35	0.469	4230	8898	19	20
All Stroke	<i>TP53</i>	Age, PC 1-10, Diabetes, Ever Smoking	0.64	-0.45	0.58	0.438	4216	8876	5	11
Ischemic Stroke	<i>DNMT3A</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.02	0.02	0.11	0.851	3634	8548	182	303
Ischemic Stroke	<i>TET2</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.90	0.64	0.24	0.009	3535	8289	83	112
Ischemic Stroke	<i>ASXL1</i>	Age, PC 1-10, Diabetes, Ever Smoking	0.99	-0.01	0.29	0.964	3474	8171	22	37
Ischemic Stroke	<i>JAK2</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.38	0.32	0.37	0.376	3469	8152	17	21
Ischemic Stroke	<i>TP53</i>	Age, PC 1-10, Diabetes, Ever Smoking	0.31	-1.17	0.80	0.142	3454	8128	2	11
Hemorrhagic Stroke	<i>DNMT3A</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.43	0.36	0.17	0.033	780	5694	50	303
Hemorrhagic Stroke	<i>TET2</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.50	0.41	0.28	0.148	747	5501	17	112

Hemorrhagic Stroke	<i>ASXL1</i>	Age, PC 1-10, Diabetes, Ever Smoking	1.09	0.08	0.50	0.866	735	5432	5	37
Hemorrhagic Stroke	<i>JAK2</i>	Age, PC 1-10, Diabetes, Ever Smoking	0.43	-0.85	1.04	0.417	731	5414	1	21
Hemorrhagic Stroke	<i>TP53</i>	Age, PC 1-10, Diabetes, Ever Smoking	2.03	0.71	0.70	0.309	733	5407	3	11

**Supplemental Table III: Age-stratified analysis of intracranial hemorrhage (ICH) in the Women’s Health Initiatives (WHI) cohort.** Cox proportional hazards model is adjusted for age at blood draw, race, hypertension, smoking status, type 2 diabetes mellitus, systolic blood pressure, and BMI.

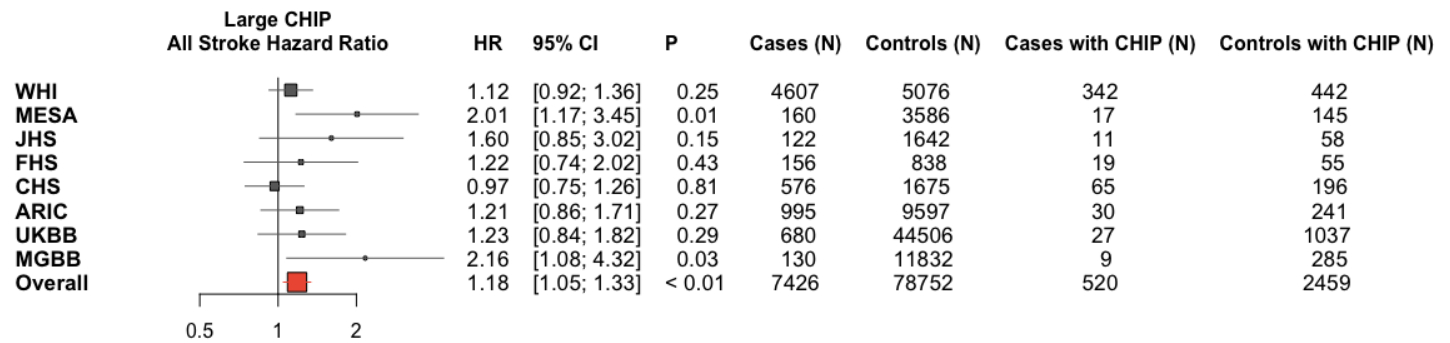
<i>WHI Cohort</i>	<i>HR</i>	<i>lower 95% CI</i>	<i>upper 95% CI</i>	<i>P</i>
<i>ICH age ≤ 80 years</i>	1.14	0.79	1.63	0.49
<i>ICH age &gt; 80 years</i>	1.84	1.15	2.92	0.010



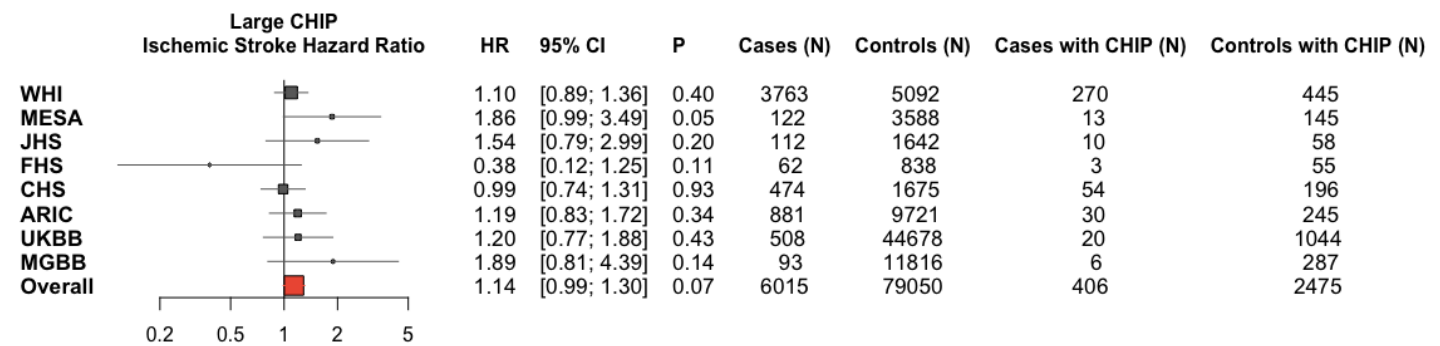
**SUPPLEMENTAL FIGURES:**

**Supplemental Figure I. Forest plot of meta-analyzed hazard ratio for the association between large CHIP (VAF  $\geq 10\%$ ) and Stroke.** Cox proportional hazards models were fitted, adjusted for age, sex, and the first 10 principal components of genetic ancestry. Here forest plots are used to show the HR, 95% CI and numerical events for each study. (CHIP, Clonal Hematopoiesis of Indeterminate Potential; VAF, variant allele fraction; HR, hazard ratio; CI, confidence interval; WHI, Women’s Health Initiative; MESA, Multi Ethnic Study of Atherosclerosis; JHS, Jackson Heart Study; FHS, Framingham Heart Study; CHS, Cardiovascular Health Study; ARIC, Atherosclerosis Risk In Communities study; MGGB, Mass General Brigham Biobank; UKBB, United Kingdom BioBank).

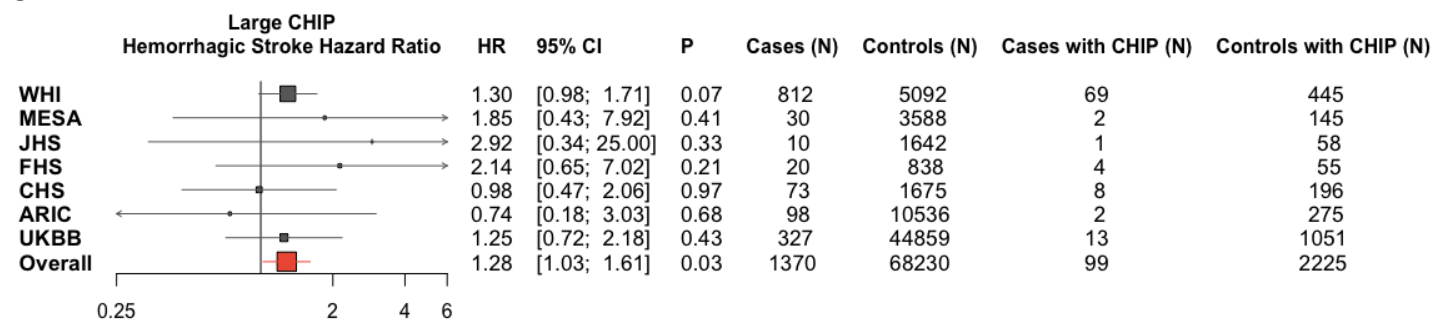
**A**



**B**

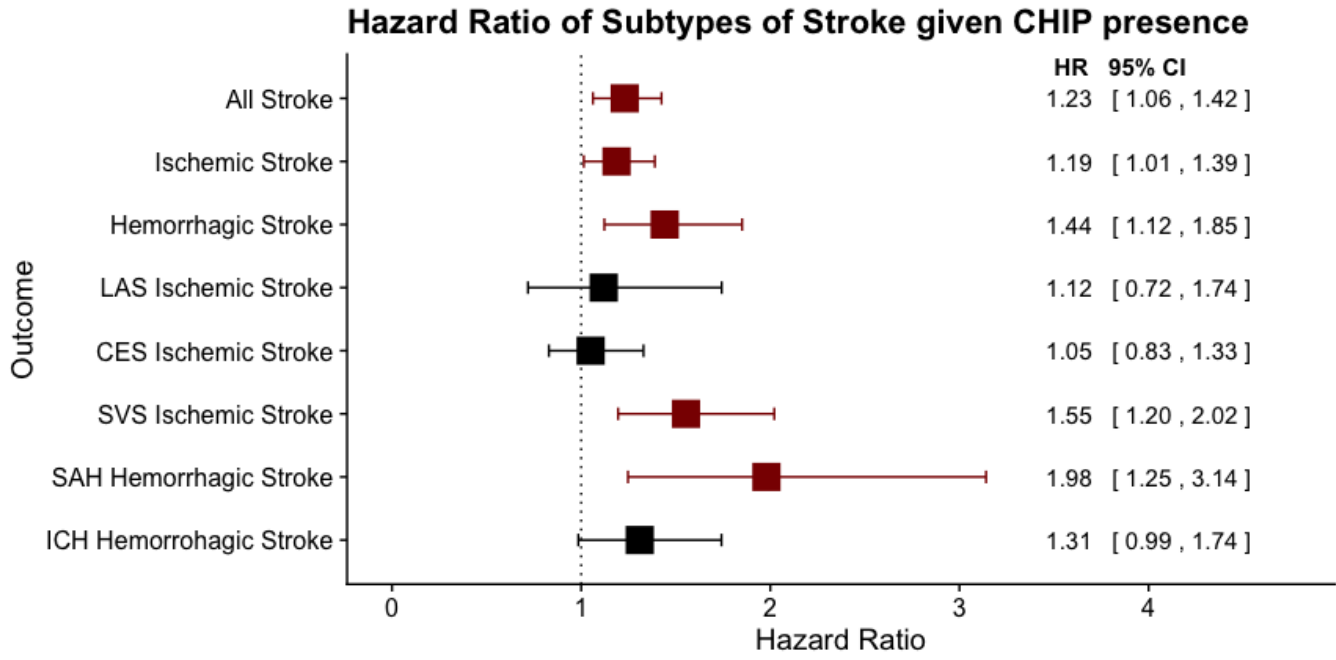


**C**



**Supplemental Figure II. Forest Plot of hazard ratios for subtypes of stroke among the WHI cohort.**

Compared to individuals without CHIP, individuals with CHIP demonstrate higher hazard for incident stroke, which varies by TOAST stroke subtype as shown here. Red indicates statistical significance. HR and 95% CI are also shown. (CHIP, Clonal Hematopoiesis of Indeterminate Potential; WHI, Women’s Health Initiative; TOAST, Trial of Org 10172 in Acute Stroke Treatment; HR, hazard ratio; CI, confidence interval; SE, standard error; LAS, Large Artery Stroke; CES, Cardioembolic Stroke; SVS, Small Vessel Stroke; SAH, Subarachnoid Hemorrhage; ICH, intracerebral hemorrhage)



## STROBE-STREGA CHECKLIST

	Reporting Item	Page Number
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	<b>Title Pg</b>
Abstract	<a href="#">#1b</a> Provide in the abstract an informative and balanced summary of what was done and what was found	<b>1</b>
<b>Background/rationale</b>		
	<a href="#">#2</a> Explain the scientific background and rationale for the investigation being reported	<b>4-5</b>
<b>Objectives</b>		
	<a href="#">#3</a> State specific objectives, including any prespecified hypotheses. State if the study is the first report of a genetic association, a replication effort, or both.	<b>5</b>
<b>Study design</b>		
	<a href="#">#4</a> Present key elements of study design early in the paper	<b>6</b>
<b>Setting</b>		
	<a href="#">#5</a> Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	<b>6, S2-S5</b>
<b>Eligibility criteria</b>		
	<a href="#">#6a</a> Cohort study – Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study – Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross-sectional study – Give the eligibility criteria, and the sources and methods of selection of participants. Give information on the criteria and methods for selection of subsets of participants from a larger study, when relevant.	<b>S2-S5</b>
	<a href="#">#6b</a> Cohort study – For matched studies, give matching criteria and number of exposed and unexposed. Case-control study – For matched studies, give matching criteria and the number of controls per case.	<b>NA</b>
<b>Variables</b>		
	<a href="#">#7a</a> Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	<b>7-9</b>
	<a href="#">#7b</a> Clearly define genetic exposures (genetic variants) using a widely-used nomenclature system. Identify variables likely to be associated with population stratification (confounding by ethnic origin).	<b>7</b>
<b>Data sources/measurement</b>		
	<a href="#">#8a</a> For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment	<b>6</b>

methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.

[#8b](#) Describe laboratory methods, including source and storage of DNA, genotyping methods and platforms (including the allele calling algorithm used, and its version), error rates and call rates. State the laboratory / centre where genotyping was done. Describe comparability of laboratory methods if there is more than one group. Specify whether genotypes were assigned using all of the data from the study simultaneously or in smaller batches. 7

## Bias

[#9a](#) Describe any efforts to address potential sources of bias 8-9

[#9b](#) Describe any efforts to address potential sources of bias

## Study size

[#10](#) Explain how the study size was arrived at 6-7

## Quantitative variables

[#11](#) Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why. If applicable, describe how effects of treatment were dealt with. 8-9

## Statistical methods

[#12a](#) Describe all statistical methods, including those used to control for confounding. State software version used and options (or settings) chosen. 9-10

[#12b](#) Describe any methods used to examine subgroups and interactions 9-10

[#12c](#) Explain how missing data were addressed 6

[#12d](#) If applicable, explain how loss to follow-up was addressed NA

[#12e](#) Describe any sensitivity analyses 9

[#12f](#) State whether Hardy-Weinberg equilibrium was considered and, if so, how. NA

[#12g](#) Describe any methods used for inferring genotypes or haplotypes Refs 3,7

[#12h](#) Describe any methods used to assess or address population stratification. NA

[#12i](#) Describe any methods used to address multiple comparisons or to control risk of false positive findings. NA

[#12j](#) Describe any methods used to address and correct for relatedness among subjects 6

## Participants

[#13a](#) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable. Report numbers of individuals in whom genotyping was attempted and numbers of individuals in whom genotyping was successful. 6-7

	<a href="#">#13b</a>	Give reasons for non-participation at each stage	NA
	<a href="#">#13c</a>	Consider use of a flow diagram	NA
<b>Descriptive data</b>			
	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable. Consider giving information by genotype	6, 26
	<a href="#">#14b</a>	Indicate number of participants with missing data for each variable of interest	NA
	<a href="#">#14c</a>	Cohort study – Summarize follow-up time, e.g. average and total amount.	26
<b>Outcome data</b>			
	<a href="#">#15</a>	Cohort study Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable. Report outcomes (phenotypes) for each genotype category over time Case-control study – Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls . Report numbers in each genotype category. Cross-sectional study – Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable. Report outcomes (phenotypes) for each genotype category	11, S18
<b>Main results</b>			
	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
	<a href="#">#16b</a>	Report category boundaries when continuous variables were categorized	NA
	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
	<a href="#">#16d</a>	Report results of any adjustments for multiple comparisons	NA
<b>Other analyses</b>			
	<a href="#">#17a</a>	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	12-13
	<a href="#">#17b</a>	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	12-13
	<a href="#">#17c</a>	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	12-13
<b>Key results</b>			
	<a href="#">#18</a>	Summarise key results with reference to study objectives	13-14
<b>Limitations</b>			

	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	<b>16-17</b>
<b>Interpretation</b>			
	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	<b>17</b>
<b>Generalisability</b>			
	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study results	<b>17</b>
<b>Funding</b>			
	<a href="#">#22</a>	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	<b>18-20</b>