Higher Hospital Frailty Risk Score is Associated with Increased Risk of Stroke: Observational and Genetic Analyses

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Abstract

Background: Frailty is a prevalent state associated with several aging-related traits and conditions. The relationship between frailty and stroke remains understudied. Here we aim to investigate whether the Hospital Frailty Risk Score (HFRS) is associated with the risk of stroke and determine whether a significant association between genetically determined frailty and stroke exists.

Design: Observational study using data from *All of Us* research program and Mendelian Randomization (MR) analyses.

Methods: Participants from *All of Us* with available electronic health records were selected for analysis. *All of Us* began national enrollment in 2018 and is expected to continue for at least 10 years. *All of Us* is recruiting members of groups that have traditionally been underrepresented in research. All participants provided informed consent at the time of enrollment, and the date of consent was recorded for each participant. Incident stroke was defined as stroke event happening on or after the date of consent to the *All of Us* study HFRS was measured with a 3-year look-back period before the date of consent for stroke risk. The HFRS was stratified into four categories: No-frailty (HFRS = 0), Low (HFRS ≥ 1 and < 5), Intermediate (≥ 5 and <15) and High (HFRS ≥ 15). Lastly, we implemented MR analyses to evaluate whether genetically determined frailty is associated with stroke risk.

Results: 253,226 participants were at risk of stroke. In multivariable analyses frailty status was significantly associated with risk of any (ischemic or hemorrhagic) stroke following a dose-response way: not-frail versus low HFRS (HR 4.9; CI 3.5–6.8; p< 0.001, not-frail versus

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CONFLICTS OF INTEREST
We report no conflict of interest.

intermediate HFRS (HR 11.4; CI 8.3–15.7; p< 0.001) and not-frail versus high HFRS (HR 42.8; CI 31.2–58.6; p< 0.001). We found similar associations when evaluating ischemic and hemorrhagic stroke separately (p-value for all comparisons <0.05). MR confirmed this association by indicating that genetically determined frailty was independently associated with risk of any stroke (OR, 1.45; 95% CI, 1.15–1.84; p=0.002).

Conclusions: Frailty, based on the HFRS was associated with higher risk of any stroke. MR analyses confirmed this association providing evidence to support a causal relationship.

Graphical Abstract

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- Frailty status was significantly associated with risk of any (ischemic or hemorrhagic) stroke following a dose-response way (p< 0.001).
- Genetically determined frailty was independently associated with risk of any stroke (p=0.002).
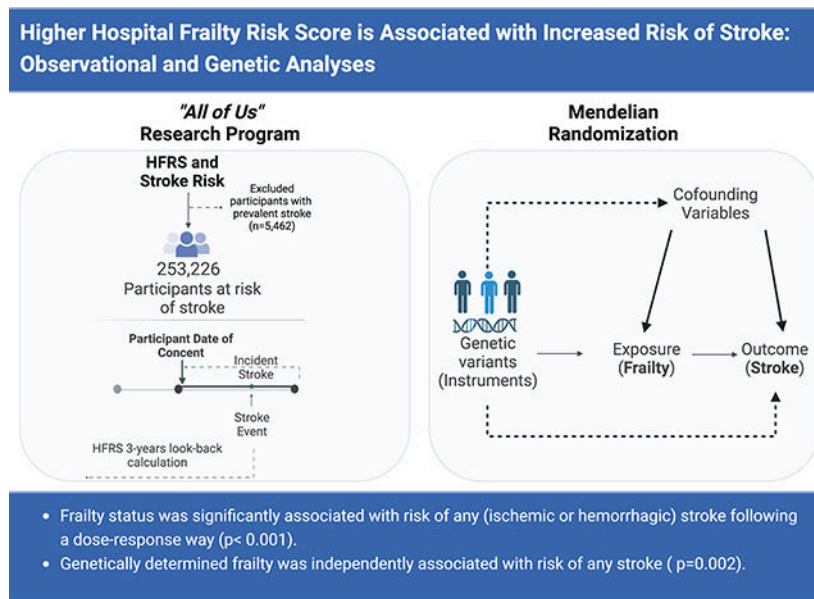
Keywords

Hospital Frailty Risk Score; Stroke; All of Us; Mendelian randomization

INTRODUCTION

Frailty is a state characterized by progressive decline in normal physiology of several systems.[1] Frailty constitutes an emerging global health problem as its prevalence continues to rise alongside an aging population.[2] The prevalence of frailty is estimated to increase in the following decades associated with changing demographics making it an important issue for stroke research.[3–5]

Mounting evidence indicates that frailty is an important predictor of higher risk and worse outcomes for different conditions, [6,7,8,9] including stroke.[10,11,12,13,14]

A frailty-based consideration of how the multisystem decline in physiological reserves modifies the natural history of stroke is important for future stroke research. Identification of frailty as a causal factor for higher risk of ischemic and hemorrhagic stroke would lay the foundation for important follow-up research focused on using frailty scores to identify high-

risk individuals, selecting patients for clinical trials, and discovering new pathophysiological insights.

The most well validated and widely accepted tools to measure frailty are the phenotypic definition of frailty and the accumulation of deficits definition of frailty. The accumulation of deficits definition of frailty, often termed as the frailty index (FI) is based on the cumulative effect of medical, functional, and psychosocial age-related deficits. The greater the number of deficits one has, the higher the likelihood of adverse health outcomes. The FI, developed by Rockwood and colleagues, is a count of 70 clinical deficits from the Canadian Study of Health and Aging. Each deficit is mapped to the interval 0–1 to represent the severity of the problem.[15]

The Hospital Frailty Risk Score (HFRS) is an increasingly used and a well-validated risk score developed to measure frailty utilizing the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes.[16] This score is based on the cumulative deficit definition of frailty and is based entirely on ICD-10, which facilitates the ascertainment of frailty in national and international registries that primarily use ICD-10 codes. The HFRS was developed from a cluster analysis assessing ICD-10 diagnoses, bed-days, and hospital costs. For this analysis they previously identified a small set of ICD-10 codes as candidate markers of frailty. In the initial cluster analysis, they found a group that had a higher incidence of ICD-10 codes indicative of frailty. From this group, HFRS was derived using over-represented ICD-10 codes and further validated in different cohorts. [16]

HFRS has been showed to predict adverse events across difference conditions. [8,17–19] In recent studies from Kilkenny et, al. and Pinho et, al. frailty ascertained using HFRS was associated with worse outcomes following stroke/transient ischemic attack.[10,20]

Given that these previous studies demonstrated an important role of frailty in stroke we aimed to investigate whether HFRS-calculated frailty is associated with an increased risk of stroke in a large and diverse population-based study, the All of Us Research program (*All of Us*). In addition, we sought to determine whether this association was partially independent of classical cardiovascular risk factors and age. We determined the average mediated effects of the HFRS going through known risk factors for stroke including hypertension, hyperlipidemia, diabetes and smoking status. We subsequently pursued Mendelian Randomization (MR) analyses to investigate a causal relationship between frailty and stroke.

Although observational studies have shown a strong association between frailty and stroke, it is challenging to establish a causal relationship due to potential confounding and reverse causation. Mendelian Randomization (MR) is a statistical approach that can help to address these limitations by using genetic variants as instrumental variables to test for causal relationships. In the current study, we use MR to investigate the causal relationship between frailty and stroke, providing a more robust understanding of the potential causal relationship between these two variables.

METHODS

Data availability

All of Us, supported by the National Institutes of Health, aims to enroll 1 million Americans aged 18 or older from demographically, geographically, and medically diverse groups across the United States, with open enrollment to all who choose to participate. The program began national enrollment in 2018 and is expected to continue for at least 10 years.[21] *All of Us* is recruiting members of groups that have traditionally been underrepresented in research. All participants provided informed consent at the time of enrollment, and the date of consent was recorded for each participant. Exclusion criteria include inability to provide informed consent, inability to speak and understand English or Spanish, and residency outside the United States. Data from the *All of* are available at allofus.nih.gov. Data were extracted using standardized procedures and were de-identified to protect participant privacy.

At baseline, participants undergo a comprehensive assessment that includes collection of demographic information, medical history, medication use, lifestyle factors, and physical measurements. Participants also provide blood and urine samples for biobanking and undergo genomic testing. Follow-up assessments are conducted at regular intervals, with participants providing updates on their medical history and health outcomes. *All of U* includes more than 340 recruitment sites across the United States, including academic medical centers, community health centers, and other healthcare organizations.

Study Design and Participants

We conducted a two-stage study that combined observational and genetic analyses.

First, we tested for associations between frailty and stroke risk. Second, we implemented summary statistics-based MR analyses to evaluate whether genetically-determined frailty is associated with stroke risk.

Exposure ascertainment

We calculated the HFRS using the 109 ICD-10 diagnostic codes over-represented in frail individuals, described elsewhere.[16] We ascertained conditions that happened within a 3-year look-back period before the date of consent to the *All of Us* study. Specific values were applied to each condition and an aggregated score per patient was determined. The frailty score was stratified into four categories: No-frailty (HFRS= 0), Low (HFRS ≥ 1 and < 5), Intermediate (≥ 5 and <15) and High (HFRS ≥ 15), as previously described by Gilbert et, al.[16]

Stroke ascertainment

We identified stroke patients using validated ICD-9 and ICD-10 codes from participants with available EHR (Supplementary Table 1). Due to the longitudinal nature of *All of Us*, we used the date of consent (previously described) to identify patients with prevalent stroke (stroke event happening before the date of consent to the *All of Us* study) and with incident stroke (stroke event happening on or after the date of consent to the *All of Us* study).

Assembly of Analytic Sample

After excluding participants without EHR data (113,692), 258,688 participants were available for complete-case analysis. In our study sample (253,226 participants), we excluded participants with prevalent stroke to evaluate the relationship between HFRS and stroke risk. (Figure 1).

Genetic instruments and summary statistics

We used publicly available summary statistics from published genome-wide association studies (GWASs) of frailty[22] and stroke.[23,24] In the GWAS for frailty, Atkins et. al, identified 14 genetic loci associated with frailty (as measured by the FI) in 164,610 UK community-based individuals aged 60 to 70 years of European ancestry, with meta-analysis of data from similarly aged Swedish individuals in TwinGene.[22] As the genetic instrument for frailty, we used independent (R^2 <0.1) single nucleotide polymorphisms (SNPs) associated with the frailty index[25] at genome-wide levels (p < 5e−8). (Supplementary Table 2) All selected SNPs were aligned to the GRCh37 assembly of the human genome. Palindromic SNPs were excluded and the effect alleles were aligned to model increases in frailty. We used the MEGASTROKE GWAS, for all types of stroke, all ischemic stroke, cardioembolic stroke, small vessel stroke and large artery stroke. MEGASTROKE GWAS is a large-scale international collaboration launched by the International Stroke Genetics Consortium, that releases summary statistics from the 2018 meta-analysis of Genome-wide Association (GWA) data in stroke and stroke subtypes.[24] For ICH, we used the latest ICH GWAS for all ICH, lobar ICH, and non-lobar ICH.[23,24] Finally for subarachnoid hemorrhage (SAH) we used the intracranial aneurysmal and subarachnoid hemorrhage (aSAH) latest GWAS. [26]

We adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and STROBE Mendelian Randomization statement to ensure transparent and complete reporting of our study. To this end, we used the checklists to guide the reporting of our study design, methods, results, and conclusions.[27,28]

Statistical Analysis

Discrete variables are presented as counts (percentages [%]) and continuous variables as means (standard deviation [SD]).

Stage 1. Longitudinal association between frailty and stroke risk. A) Primary analysis.—Our primary hypothesis was that frail persons, identified by a high HFRS, have a higher risk of stroke. To test this hypothesis, we constructed univariable and multivariable Cox proportional hazard regression models adjusted by sex, race/ethnicity, and cardiovascular risk factors. We adjusted for cardiovascular conditions to evaluate the proportion of the association between frailty and stroke risk that is not mediated by cardiovascular conditions. We evaluated associations between HFRS categories (no-frailty, low HFRS, intermediate and high HFRS) and risk of all strokes. Because the underlying biology differs according to the specific type of stroke, our secondary analyses evaluated ischemic and hemorrhagic stroke separately. B) *Effect modification*. We tested for interactions between HFRS and potential effect modifiers including age, sex, and

race/ethnicity by introducing a product term in the regression models. Additionally, we performed stratified analyses across subgroups defined by these variables to determine the point estimates among each of these subgroups. C) *Mediation analysis.* We utilized the R package Mediation to determine the average mediated effects of the HFRS going through known risk factors for stroke, including hypertension, hyperlipidemia, diabetes and smoking status.[29]

Stage 2. Summary statistics based Mendelian Randomization.—MR constitutes a special case of instrumental variable analysis, a widely used analytical framework for causal inference. When the MR assumptions are met, it is possible to identify and quantify causal relationships between exposures and outcomes of interest.[30,31]

We conducted a 2-sample MR study, where the genetic information for the exposure (frailty) and the outcome (risk of stroke) come from various studies.[22–25] Our primary analysis was the inverse variance weighted (IVW) method. In sensitivity analyses, we used the Weighted median (WM), MR-Egger, and MR-PRESSO methods. Additionally, we tested for the presence of pleiotropy (effect of the genetic instruments going through other pathways not related to frailty) using the MR-Egger intercept and MR-PRESSO global test.

Software—To analyzed data from *All of Us* we used The Researcher Workbench, a cloud-based platform where registered researchers can access Registered and Controlled Tier data. Jupiter notebooks with both Python for data cleaning and R for statistical analysis were employed. [32]

For MR analysis we used MendelianRandomization package and R (version 4.1.3) for association testing, and MR analysis. [33]

RESULTS

The Controlled Tier Dataset V6 of All of Us included data from 372,380 participants, including 258,688 with electronic health records (EHR) information that was harmonized using the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM). [34] After excluding 113,692 participants without electronic health record (EHR) data and 5,462 with prevalent stroke, 253,226 were included in the first stage of this study. (Figure 1, Supplementary Table 3) Mean age was 51.83 years (SD 16.91) and 152,139 participants were female (60%). Race/ethnic groups included 51,641 Black (20.4%), 47,559 Hispanic (18.8%), 130,099 White (51.4%) and 6,995 Asian (2.8%) participants. The number of participants with high, intermediate, low HFRS and no-frailty were 34,581 (13.7%), 68,341 (27.0%) 69,083 (27.3%) and 81,221 (32.1%) respectively (Table 1).

HFRS and risk of any stroke

Higher frailty, modeled via HFRS, was significantly associated with increased risk of stroke. When looking at participants with no-frailty, low, intermediate and high HFRS we found 49 (0.1%), 236 (0.3%), 743 (1.1%) and 1,963 (5.7%) participants with any stroke respectively; 42 (0.1%), 212 (0.3%), 659 (1.0 %) and 1,620 (4.7%) participants

with ischemic stroke respectively; and 7 (0.0%), 24 (0.0%), 84 (0.1%) and 343 (1.0%) participants with hemorrhagic stroke respectively (unadjusted p<0.001) (Table 2).

Similar statistically significant differences were observed in multivariable analyses adjusted by cardiovascular risk factors. Study participants with low, intermediate and high HFRS versus no-frailty had HR 4.7 (CI 3.4–6.4; p< 0.001), HR 11.5 (11.5; CI, 8.60– 15.5; p< 0.001) and HR 45.7 (CI, 34.1– 61.2; p< 0.001 of any stroke, respectively (Table 3). Our primary analysis focusing exclusively on ischemic stroke indicated that study participants with low, intermediate, and high HFRS had HR 4.9 (CI 3.5– 6.8; p<0.001), HR 11.4 (CI, 8.33– 15.7; p< 0.001) and HR 42.8 (CI, 31.2– 58.6; p< 0.001) of ischemic stroke versus no-frailty study participants. Frailty was also associated with the risk of hemorrhagic stroke. Compared with participants with no-frailty, participants with low, intermediate and high HFRS had HR 4 (CI 1.74–9.47, p=0.001), HR 13.2 (CI, 6.0– 28.9; p< 0.001) and HR 98.2 (CI, 45.0–211.6; p< 0.001) of hemorrhagic stroke, respectively (Table 3). Multivariable analyses adjusted by only age, sex, and race/ethnicity remain significant. (Supplementary table 4)

Effect modification

We tested for interaction by introducing product terms to the regression models. Results were different across age groups for any type of stroke (interaction p<0.001), ischemic stroke (interaction p=<0.001) and intracerebral hemorrhage (interaction p=<0.001). No significant interactions were found among sex and race/ethnicity groups for any type of stroke, ischemic and hemorrhagic stroke (all interactions p>0.05) (Supplementary Table 5).

Mediation analysis

We tested whether known vascular risk factors for stroke mediated the association between frailty and stroke. We found that part of this effect was mediated through hypertension for any stroke (23.6%), ischemic stroke (24.8%), and hemorrhagic stroke (17.8%) (p<0.001); diabetes for any stroke 2.5%, and ischemic stroke 3.1% (p<0.001); and hyperlipidemia in 14.2% for any stroke and 15.6% for ischemic stroke respectively (p<0.001). Diabetes and hyperlipidemia were not significant mediators for hemorrhagic stroke. Smoking was not a significant mediator (all p>0.05). However, the HFRS remained significant after accounting for these classical cardiovascular risk factors suggesting an independent effect of the score.

Mendelian randomization

Several different MR techniques indicated that the association between frailty and risk of stroke could be causal. Our primary MR analyses using the inverse variance weighted approach indicated that genetically-determined frailty was associated with 45% higher estimates of any stroke (OR, 1.45; 95% CI, 1.15–1.84; p=0.002), 39% higher estimates of ischemic stroke (OR, 1.39; 95% CI, 1.07–1.70; p=0.012) and 6-fold higher estimates of ICH (OR, 6.33; 95% CI, 1.59–25.27; p=0.008), without evidence of horizontal pleiotropy. (Figure 2, Table 4) In additional analyses we evaluated ischemic stroke subtypes and hemorrhagic stroke subtypes obtaining consistent results (Supplementary Table 6).

We explored traits associated to the GWAS of frailty, we found that SNP rs3959554 is associated with coronary artery disease (Supplementary table 2); we did a secondary MRization summary statistics excluding this SNP and we still found significant association between genetically determined frailty and stroke. (Supplementary table 7)

DISCUSSION

We report the results of a combined observational and genetic study that evaluated the role of frailty in different types of strokes. We used data from the All of Us Research Program, the largest population-based open-access study conducted in the United States.[21] We found that higher frailty scores were independently associated with higher risk of any stroke, ischemic stroke, and hemorrhagic stroke, and that these associations were consistent across several race/ethnic groups. MR analyses demonstrated a significant association between genetically-determined frailty and risk of any type of stroke, any ischemic stroke and all ICH supporting a causal link between these conditions.

Cardiovascular risk factors such as hypertension, hyperlipidemia, obesity, smoking and diabetes are the strongest contributors to stroke risk. In fact, around 87% of strokes are estimated to result from these factors.[35] However, in the past few years, several non-conventional risk factors have been suggested to increase the risk of stroke.[35,36] Examples of these are kidney disease, pregnancy, migraine with aura, obstructive sleep apnea and chronic inflammatory diseases.[36–43] These observations highlight the complex pathophysiology underlying stroke risk, and the probable synergistic effects among risk factors. In this setting, there is increasing interest in physiological states like frailty that capture the combined contribution of several of these risk factors due to their downstream location in the causal pathway.[44]

Frailty is a state of increased vulnerability with impaired physiological function across multiple systems of the body. [1] The HFRS is the only score based entirely on ICD-10 codes which allows us to measure frailty in national and international registries. It constitutes a risk score with established benefit in the prediction of complications in the hospitalized elderly and in an increasing number of pathological states including stroke.[81016]In our study, we demonstrated that, compared to patients with no-frailty, those with low, intermediate and high HFRS had 4.7, 11.5 and 45.7 times higher risk of any stroke. Importantly, while a proportion of this effect was mediated by cardiovascular risk factors, the association between HFRS and stroke risk remained significant after adjusting for these factors, suggesting that the overall vulnerability present in frail patients is independently associated with stroke risk.

Our study also provides new information on two other important matters. First, the majority of studies assessed frailty at the time of stroke. We were able to calculate it before the stoke episode thanks to the longitudinal nature of All of us. Second, we evaluated the association between HFRS and stroke risk across several subgroups represented in All of Us and showed that this relationship becomes stronger in older persons. These findings suggest that the role of frailty in stroke may grow as age increases, a finding that has been observed for other diseases.[45,46] Importantly, these stratified analyses also indicated that the

relationship between frailty and stroke is equally strong for women and men, and across different race/ethnic groups. Third, we performed MR analyses using known genetic risk factors for frailty. These genetic analyses confirmed the observed association and provided evidence for a causal role of frailty in stroke. Genetic variants constitute an excellent tool to assess causality due to their random assortment during meiosis that makes them relatively immune to post-partum confounders.

In combination, our findings point to a number of interesting and practical applications. First, the utilization of formal tools to quantify frailty (HFRS and other similar frailty metrics) could be helpful in the everyday clinical care of stroke patients providing a consistent way of determining the overall "functional age" of the patient, that may or may not reflect the chronological age. Medical data naturally generated by routine clinical work in inpatients or outpatient settings, like symptoms, signs, diagnoses, laboratory tests results, or even lifestyle factors indicators are stored in electronic health records (EHRs). These data could be used in frailty assessment tools, especially in frailty based cumulative deficit model methods. Using frailty assessment tools based on EHRs may bridge the gap between frailty research and clinical frailty assessment.[47–49]

Similarly, a formal quantification of frailty in stroke patients could be helpful in the design, execution and analysis of clinical trials evaluating novel treatments for stroke, complementing the notion of chronological age with information about the clinical status of patients.

Our study has a number of limitations. First, there are limitations inherent to all EHR-based observational studies, which may contain coding and reporting biases, and data may be misclassified or incomplete. Second, there are some limitations based on the cluster analysis methods used to define HFRS. The HFRS was validated to screen frail individuals older than 75 years in secondary care, which is much older than the population of All of Us.[50] Arguably, population specific risk scores could be developed to better capture conditions that lead to frailty in this younger age group. Negative perceptions linked to the term "frail" have been previously described and are associated with administrations of treatments that do not follow standard of care. [51,52] It is therefore possible the observed risk of stroke could be due to less intensive prevention efforts in these patients. We would like to note that genetic analysis overcomes these limitations of observational studies.[30,31]

CONCLUSION

Higher HFRS was associated with an increased risk for any stroke as well as ischemic and hemorrhagic stroke subtypes. HFRS remained significant after accounting for vascular risk factors suggesting an independent effect of the score. MR analyses revealed a significant association between genetically-determined frailty and risk of any type of stroke, all ischemic stroke and all ICH supporting a causal link between these conditions. Further research is needed to understand the potential value of the HFRS for risk stratification with the goal of providing personalized preventive strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Non-Standard Abbreviations and Acronyms:

HFRS	Hospital Frailty Risk Score
ICD-10	International Classification of Diseases, Tenth Revision
All of Us	All of Us Research program
MR	Mendelian Randomization
EHR	Electronic Health Records
GWAS	Genome-wide association Studies

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"All of Us" Research Program

372,380 Participants

Excluded participants without Electronic Health Records(n= 113,692)

258,688 Participants

HFRS and Stroke Risk

Excluded participants with prevalent stroke (n=5,462)

253,226 Participants at risk of stroke

Participant Date of Concent

Incident Stroke

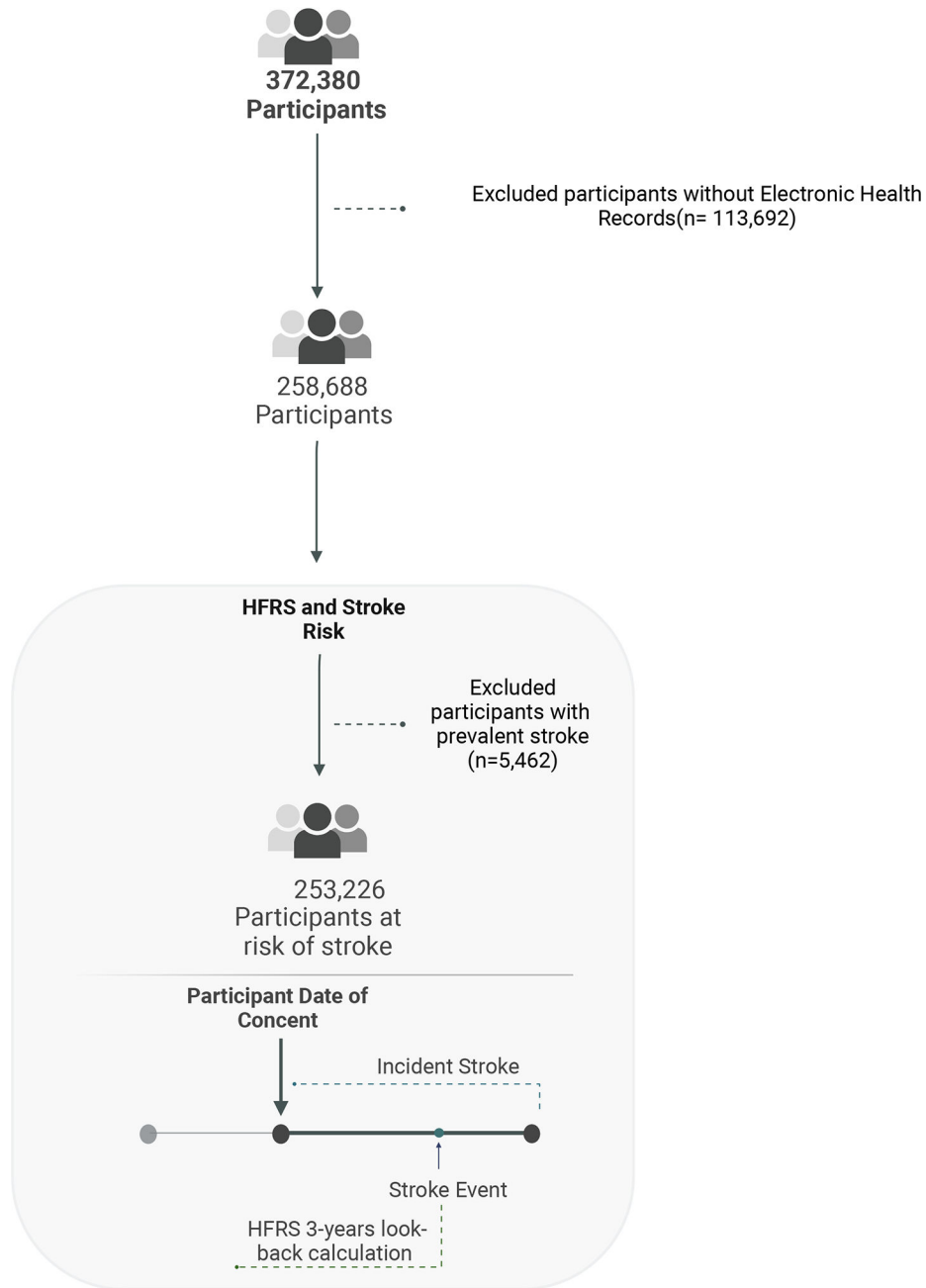Stroke Event

HFRS 3-years look-back calculation

Figure 1. Assembly of Analytic Sample
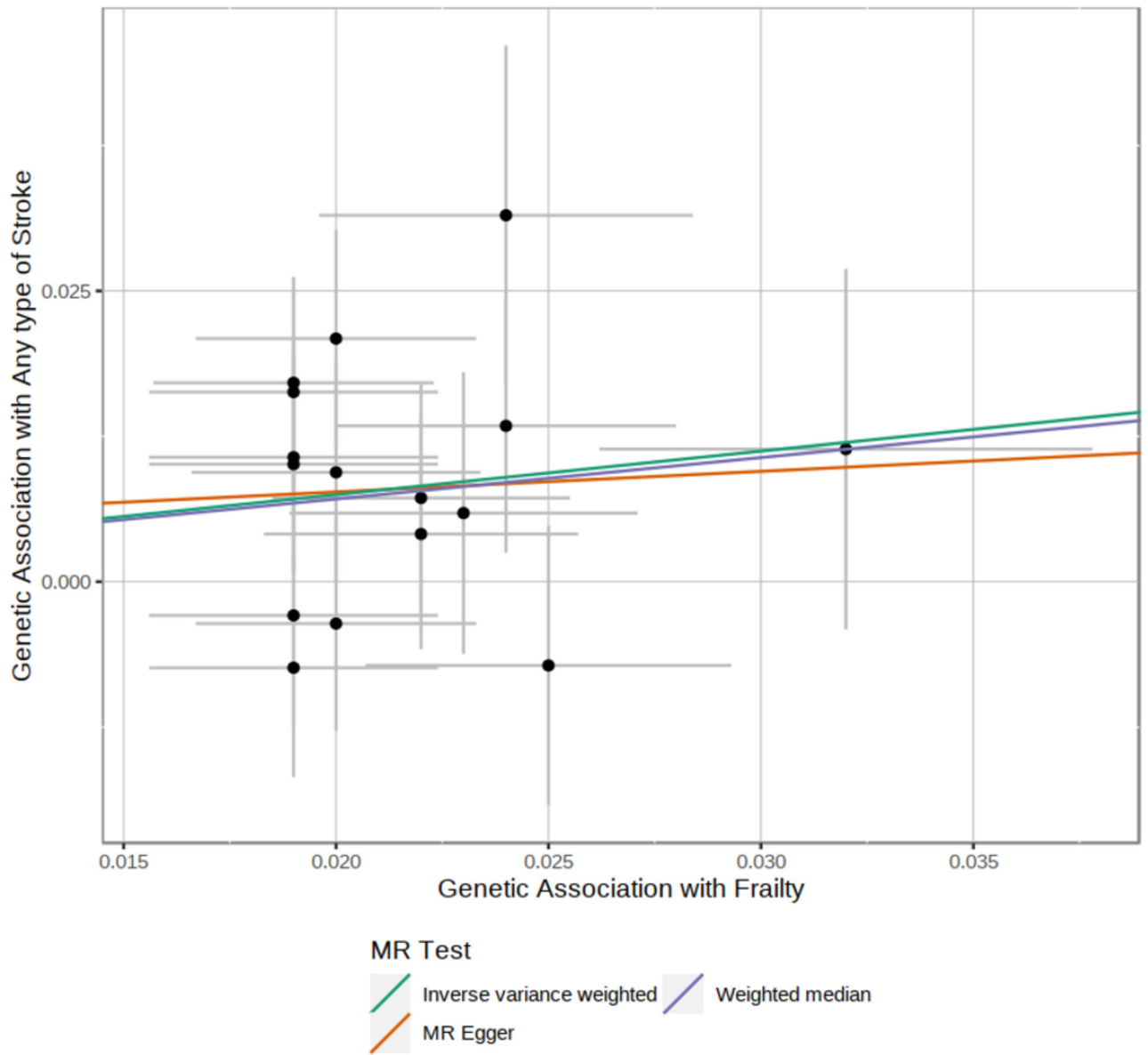• HFRS = Hospital Frailty Risk Score

Figure 2.
Mendelian randomization results for genetically determined frailty and risk of any type of stroke.

- IVW = Inverse-variance weighted
- WM = Weighted-median
- MR-Egger = Mendelian randomization-Egger

Table 1.

Baseline of participants at risk of stroke.

Variable	Overall	High HFRS	Intermediate HFRS	Low HFRS	No-Frailty
	253,226	34,581	68,341	69,083	81,221
Age, y; mean (SD)	51.83 (16.91)	60.11 (15.37)	55.09 (16.03)	48.81 (16.79)	48.12 (16.58)
Sex					
Female	152,139 (60.1%)	21,413 (61.9%)	43,010 (62.9%)	41,926 (60.7%)	45,790 (56.4%)
Male	93,941 (37.1%)	12,163 (35.2%)	23,461 (34.3%)	25,293 (36.6%)	33,024 (40.7%)
Non-binary/Not answered	7,093 (2.8%)	996 (2.9%)	1,858 (2.7%)	1,854 (2.7%)	2,385 (2.9%)
Race/Ethnicity					
Asian	6,995 (2.8%)	402 (1.2%)	1,350 (2.0%)	2,207 (3.2%)	3,036 (3.7%)
Black or African American	51,641 (20.4%)	5,658 (16.4%)	11,150 (16.3%)	11,919 (17.3%)	22,914 (28.2%)
Hispanic or Latino	47,559 (18.8%)	5,457 (15.8%)	11,707 (17.1%)	13,978 (20.2%)	16,417 (20.2%)
Other	16,932 (6.7%)	2,369 (6.9%)	4,423 (6.5%)	4,614 (6.7%)	5,526 (6.8%)
White	130,099 (51.4%)	20,695 (59.8%)	39,711 (58.1%)	36,365 (52.6%)	33,328 (41.0%)
Cardiovascular Risk Factors					
Hypertension	106,870 (42.2%)	27,414 (79.3%)	38,499 (56.3%)	24,985 (36.2%)	15,972 (19.7%)
Hyperlipidemia	101,146 (39.9%)	25,263 (73.1%)	38,072 (55.7%)	24,150 (35.0%)	13,661 (16.8%)
Diabetes	44,904 (17.7%)	14,573 (42.1%)	16,047 (23.5%)	9,052 (13.1%)	5,232 (6.4%)
Ever smoked	101,055 (39.9%)	16,469 (47.6%)	28,147 (41.2%)	24,842 (36.0%)	31,597 (38.9%)

• HFRS = Hospital Frailty Risk Score

• SD = Standard deviation

Table 2.

Distribution of stroke types and outcomes across HFRS.

Variable	Overall	High	Intermediate	Low	No-frailty	Unadjusted p-value
Risk analyses						
n	253,226	34,609	68,322	69,074	81,221	-
Any Stroke	2,991 (1.2%)	1,963 (5.7%)	743 (1.1%)	236 (0.3%)	49 (0.1%)	< 0.001
Ischemic Stroke	2,533 (1.0%)	1,620 (4.7%)	659 (1.0%)	212 (0.3%)	42 (0.1%)	< 0.001
Hemorrhagic Stroke	458 (0.2%)	343 (1.0%)	84 (0.1%)	24 (0.0%)	7 (0.0%)	< 0.001

Table 3.

Cox proportional hazard regression models for HFRS and stroke risk.

Variable	Univariate HR (95% CI)	Multivariate HR (95% CI)
Any Stroke		
HFRS		
No-frailty	REFERENCE	
Low	5.5 (4.1–7.6)	4.7 (3.4–6.4)
Intermediate	17.8 (13.3–23.7)	11.5 (8.6–15.5)
High	90.0 (67.7–119.5)	45.7 (34.1–61.2)
Ischemic Stroke		
HFRS		
No-frailty	REFERENCE	
Low	5.9 (4.2–8.3)	4.9 (3.5–6.8)
Intermediate	18.7 (13.7–25.6)	11.4 (8.3–15.7)
High	91.9 (67.6–124.9)	42.8 (31.2–58.6)
Hemorrhagic Stroke		
HFRS		
No-frailty	REFERENCE	
Low	4.0 (1.7–9.4)	4.0 (1.74–9.47)
Intermediate	14.2 (6.6–30.8)	13.2 (6.0–28.9)
High	114.2 (54.0–241.5)	98.2 (45.0–211.6)

Adjusted by age, sex, race/ethnicity, and cardiovascular risk factors (smoking, hypertension, hyperlipidemia, type 2 diabetes). All p-values were <0.001.

• HFRS = Hospital Frailty Risk Score

• HR = Hazard ratio

Table 4.

Mendelian randomization summary statistics.

MR Method	SNIPS N	OR	CI	p-value
Any Stroke				
IVW	16	1.45	(95%CI 1.1–1.8)	0.002
WM	16	1.43	(95%CI 1.0–2.0)	0.038
MR-Egger	16	1.19	(95%CI 0.1–7.8)	0.85
MR-PRESSO	16	1.45	(95%CI 1.15–1.8)	0.006
MR-Egger Intercept	16	1	(95%CI 0.9–1.0)	0.83
Global Test	16	-	-	0.53
Any Ischemic Stroke				
IVW	16	1.39	(95%CI 1.0–1.7)	0.012
WM	16	1.29	(95%CI 0.9–1.8)	0.13
MR-Egger	16	0.96	(95%CI 0.1–7.4)	0.97
MR-PRESSO	16	1.39	(95%CI 1.1–1.6)	0.003
MR-Egger Intercept	16	1.01	(95%CI 0.9–1.0)	0.730
Global Test	16	-	-	0.945
All ICH				
IVW	14	6.33	(95%CI 1.5–25.2)	0.008
WM	14	11.83	(95%CI 1.7–78.3)	0.010
MR-Egger	14	1782.24	(95%CI 0.0–66882234.1)	0.18
MR-PRESSO	14	6.33	(95%CI 1.7–22.4)	0.013
MR-Egger Intercept	14	0.89	(95%CI 0.7–1.1)	0.31
Global Test	14	-	-	0.65

- MR = Mendelian randomization

- SNP = Single-nucleotide polymorphisms

- OR = Odds ratio

- CI = Confident interval

- IVW = Inverse-variance weighted

- WM = Weighted-median

- MR-PRESSO= Mendelian randomization pleiotropy residual sum and outlier

- MR-Egger = Mendelian randomization-Egger