

**Supplementary Table 1.** Codes uses to ascertain conditions.

Coding standard	Stroke
ICD-9 CM	430, 431, 434.0, 434.1, 434.9, 436.X
ICD-10 CM	I60, I60.0 , I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0 , I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63, I63.0 , I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I63.X, I64, I64.X

**Supplementary Table 2.** Genetic instruments for frailty

<b>SNP</b>	<b>CHR</b>	<b>BP</b>	<b>Reported trait besides Frailty index</b>
rs12789243	1	210128698	-
rs4952693	2	43924669	-
rs2071207	3	50122411	-
rs583514	3	173396377	-
rs82334	4	3223644	-
rs1363103	5	104582136	Subjective well-being, Neuropsychiatric disorders, Insomnia
rs9275160	6	32684843	complement C4 measurement, prostate carcinoma
rs2396766	7	114678016	-
rs56299474	8	22135291	-
rs4146140	10	60125604	-
rs10891490	11	113014805	-
rs3959554	15	41151726	coronary artery disease, body height
rs17612102	15	51971897	-
rs8089807	18	41742675	-
rs111432129	2	207175279	-
rs758591652	3	136419233	-
rs796921150	8	113025459	-
rs7219015	17	2652298	Brain shape (segment 41), Depression, cortical thickness
rs77338984	17	30815796	-
rs10625032	17	49395505	-

**Supplementary Table 3.** Baseline characteristics between participants excluded (without electronic health in *All of us*) and participants included in the analysis.

<b>Participant Characteristics</b>	<b>Excluded</b>	<b>Included</b>
<b>n</b>	114,266	258,688
Age (Mean, SD)	48.7 (17.1)	52.0 (16.9)
<b>Sex</b>		
Female	67,766 (59.3%)	155,118 (60.0%)
Male	42,742 (37.4%)	96,248 (37.2%)
Non-binary/Not answered	3,731 (3.3%)	7,269 (2.8%)
<b>Race/Ethnicity</b>		
Asian	5,089 (4.5%)	7,067 (2.7%)
Black or African American	19,184 (16.8%)	52,962 (20.5%)
Hispanic or Latino	18,255 (16.0%)	48,538 (18.8%)
Other	8,679 (7.6%)	17,295 (6.7%)
White	63,059 (55.2%)	132,826 (51.3%)

**Supplementary Table 4.** Cox proportional hazard regression models for HFERS and stroke risk.

<b>Variable</b>	<b>HR (95% CI)</b>
<b>Any Stroke</b>	
<b>HFERS</b>	
No-frailty	REFERENCE
Low	6.0 (4.4-8.1)
Intermediate	17.2 (12.8-22.9)
High	78.3 (58.8-104.2)
<b>Ischemic Stroke</b>	
<b>HFERS</b>	
No-frailty	REFERENCE
Low	6.4 (4.6-8.9)
Intermediate	17.9 (13.1-24.6)
High	78.6 (57.8-107.0)
<b>Hemorrhagic Stroke</b>	
<b>HFERS</b>	
No-frailty	REFERENCE
Low	4.2 (1.8-9.8)
Intermediate	14.3 (6.6-30.9)
High	98.2 (51.6-232.43)

Adjusted by age, sex and race/ethnicity. All p-values were <0.001.

- HFERS = Hospital Frailty Risk Score
- HR = Hazard ratio

**Supplementary Table 5. Stratified analysis.**

<b>HFRS</b>	<b>Any Stroke</b>	
	<b>Age</b>	
	<b>Interaction p-value &lt;0.001</b>	
	<b>&lt;65</b>	<b>&gt;65</b>
No-Frailty	REFERENCE	
Low	4.0 (2.8-5.8)	7.3 (3.8-14.2)
Intermediate	10.2 (7.35-14.3)	16.4 (8.6-30.9)
High	40.8 (29.2-56.9)	64.4 (34.2-121.2)
	<b>Ischemic Stroke</b>	
	<b>Age</b>	
	<b>Interaction p-value &lt;0.001</b>	
	<b>&lt;65</b>	<b>&gt;65</b>
No-Frailty	REFERENCE	
Low	3.9 (2.7-5.7)	9.7 (4.5-21.2)
Intermediate	9.5 (6.7-13.6)	2.0 (9.7-44)
High	35.1 (24.7-49.9)	79.4 (37.4-168.5)
	<b>Hemorrhagic Stroke</b>	
	<b>Age</b>	
	<b>Interaction p-value &lt;0.001</b>	
	<b>&lt;65</b>	<b>&gt;65</b>
No-Frailty	REFERENCE	
Low	5.4 (6.6-51.7)	2.2 (0.5-8.6)
Intermediate	18.5 (6.6-51.7)	6.7 (2.0-22.4)
High	144.2 (52.4-396.9)	45.3 (13.9-146.6)

**Supplementary Table 6.** Mendelian randomization summary statistics.

MR Method	SNIPS N	OR	CI	p-
<b>Large artery stroke</b>				
IVW	16	2.67	(95%CI 1.4-5.0)	0.002
WM	16	3.15	(95%CI 1.3-7.1)	0.006
MR-Egger	16	2.42	(95%CI 0.02-387.2)	0.73
MR-PRESSO	16	2.67	(95%CI 1.7-4.0)	0.0003
MR-Egger Intercept	16	1	(95%CI 0.9-1.1)	0.97
Global Test	16	-	-	0.9723
<b>Small vessel stroke</b>				
IVW	16	1.9	(95%CI 1.0-3.4)	0.03
WM	16	1.97	(95%CI 0.8-4.4)	0.09
MR-Egger	16	0.37	(95%CI 0-38.3)	0.67
MR-PRESSO	16	1.9	(95%CI 1.1-3.2)	0.034
MR-Egger Intercept	16	1.04	(95%CI 0.9-1.1)	0.49
Global Test	16	-	-	0.64
<b>Cardioembolic stroke</b>				
IVW	16	1	(95%CI 0.5-1.9)	0.47
WM	16	1.21	(95%CI 0.7-2.0)	0.99
MR-Egger	16	0.19	(95%CI 0-10.8)	0.43
MR-PRESSO	16	1.21	(95%CI 0.7-2.0)	0.48
MR-Egger Intercept	16	1.04	(95%CI 0.9-1.1)	0.37
Global Test	16	-	-	0.39
<b>Deep ICH</b>				
IVW	14	9.9	(95%CI 1.9-51.3)	0.006
WM	14	8.07	(95%CI 0.8-78.2)	0.07
MR-Egger	14	5.06	(95%CI 0-1310581.5)	0.80
MR-PRESSO	14	2.19	(95%CI 0.01-676.5)	0.011
MR-Egger Intercept	14	9.9	(95%CI 2.1-46)	0.91
Global Test	14	-	-	0.61
<b>Lobar ICH</b>				
IVW	14	3.58	(95%CI 0.5-21.8)	0.16
WM	14	4.81	(95%CI 0.4-52.7)	0.19
MR-Egger	14	84475.01	(95%CI 0.08-87158162771.7)	0.13
MR-PRESSO	14	3.58	(95%CI 0.8-15.3)	0.10
MR-Egger Intercept	14	0.81	(95%CI 0.6-1.0)	0.17
Global Test	14	-	-	0.82
<b>aSAH</b>				
IVW	14	2.27	(95%CI 1.2-4.1)	0.006
WM	14	2.31	(95%CI 1.0-5.1)	0.04
MR-Egger	14	63.15	(95%CI 0.6-6217.8)	0.10
MR-PRESSO	14	2.27	(95%CI 1.4-3.5)	0.003
MR-Egger Intercept	14	1.07	(95%CI 0.9-1.1)	0.177
Global Test	14	-	-	0.87

**Supplementary Table 7.** Secondary Mendelian randomization summary statistics.

<b>MR Method</b>	<b>SNIPS N</b>	<b>OR</b>	<b>CI</b>	<b>p-value</b>
<b>Any Stroke</b>				
IVW	15	1.5	(95%CI 1.1-1.9)	0.001
<b>Any Ischemic Stroke</b>				
IVW	16	1.34	(95%CI 1.04-5.1)	0.009
<b>All ICH</b>				
IVW	14	8.29	(95%CI 1.9-34.6)	0.003

- MR = Mendelian randomization
- SNP = Single-nucleotide polymorphisms
- OR = Odds ratio
- CI = Confident interval
- IVW = Inverse-variance weighted