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Genetic Risk, Muscle Strength, and Incident Stroke: Findings From the UK Biobank Study

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Abstract

Objective: To examine the associations of muscle strength and genetic risk for stroke with stroke incidence.

Participants and Methods: We included 284,767 white British participants of UK Biobank without genetic relatedness and stroke or myocardial infarction at baseline between March 13, 2006, and October 1, 2010. Genetic risk was assessed with polygenic risk scores, calculated by summing the risk-increasing alleles, weighted by the effect estimates. Muscle strength was assessed through grip strength tests by hand dynamometers. Incidence of overall (n= 4008), ischemic (n= 3031), and hemorrhagic (n=1073) stroke was adjudicated during 11.5-year follow-up.

Results: Compared with the bottom muscle strength tertile, hazard ratios (95% CI) of stroke were 0.81 (0.75 to 0.87) and 0.76 (0.71 to 0.82) for the middle and top muscle strength tertiles, respectively, after adjustment for confounders and genetic risk; higher genetic risk was independently associated with higher stroke incidence. Stroke hazards for the top muscle strength tertile were consistently lower across genetic risk strata, with no evidence of interaction. Compared with individuals with high muscle strength and low genetic risk, stroke hazards were higher for individuals who had medium or high genetic risk combined with low or medium muscle strength but not for those who had medium genetic risk but high muscle strength. Associations were similar for ischemic and hemorrhagic stroke (although CIs were inconclusive for some of the associations).

Conclusion: Higher muscle strength was associated with lower stroke incidence in all individuals, including those with high genetic susceptibility. The increased genetic risk of overall and ischemic stroke was partly attenuated through increased muscle strength.

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Stroke, a contemporary public health burden across the globe,[1] is characterized by a combination of both genetic and modifiable risk factors.[2,3] The contribution of genetic factors to stroke has been demonstrated through genome-wide association study research providing single-nucleotide polymorphisms (SNPs) significantly associated with stroke risk.[4] On the basis of the established list of SNPs, a polygenic risk score can be calculated as an indicator of inherited risk for stroke, making it possible to stratify individuals by genetic susceptibility to stroke. In addition to the genetic contribution to stroke, there is compelling evidence that muscle strength, an independent modifiable physical fitness component, is inversely associated with stroke risk,[5-7] calling for public health and clinical action to improve muscle strength as a stroke prevention strategy.

However, a fundamental gap in the literature is a paucity of evidence on the favorable impacts of increased muscle strength on stroke risk in the context of genetics. All previous research[5-7] examined the associations between muscle strength and stroke risk without taking into account individuals' unique genetic susceptibility to stroke. This methodology is predicated on an assumption that the benefits of improved muscle strength are consistent across all levels of genetic predispositions, including individuals at high genetic risk. Little is currently known

about the interplay between muscle strength and genetic predispositions to stroke in relation to stroke risk. The purpose of this study was therefore to examine whether the associations between muscle strength and stroke are independent of or vary by genetic risk for stroke.

PARTICIPANTS AND METHODS

Study Design and Participants

The study used data from UK Biobank, an ongoing UK national prospective cohort of more than 500,000 UK adults aged between 40 and 69 years at recruitment. Specific details about the methodology of the UK Biobank project are provided elsewhere.[8] In brief, the eligibility criteria for the UK Biobank project included individuals who resided less than 25 miles away from 1 of 22 assessment centers across Great Britain and were registered with the National Health Service. The baseline measurement was carried out between March 13, 2006, and October 1, 2010, collecting an expansive series of variables obtained through physical measurements, biologic samples, and touch-screen questionnaires (sociodemographic factors, early-life exposures, family history, general health and disabilities, cognitive and psychological state, and lifestyle risk markers). The present research was based on a subset of 284,767 individuals who self-reported as white British, with verification from the principal component analysis using genotype data; they had no self-reported or diagnosis of stroke or myocardial infarction at baseline, had no second-degree genetic relatedness (defined as kinship coefficients between 0.0442 and 0.0884),[9] and had full information for all covariates (Figure 1).

The protocol of the UK Biobank project was approved by the North West Multicentre Research Ethics Committee (11/NW/0382). Each participant provided signed informed written consent before participation.

Exposures

Polygenic Risk Score for Stroke. In UK Biobank, all participants were genotyped using the UK Biobank Axiom Array and UK BiLEVE Axiom Array; genotypes were then imputed to a reference panel of the Haplotype Reference Consortium combined with UK10K.[10] For this study, genetic risk for stroke was estimated through polygenic risk scores that were calculated on the basis of 87 SNPs[4] (significant at a P value $<1\times10^{-5}$ and in low linkage disequilibrium according to $r^2<0.05$) known to be associated with stroke risk (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org), a

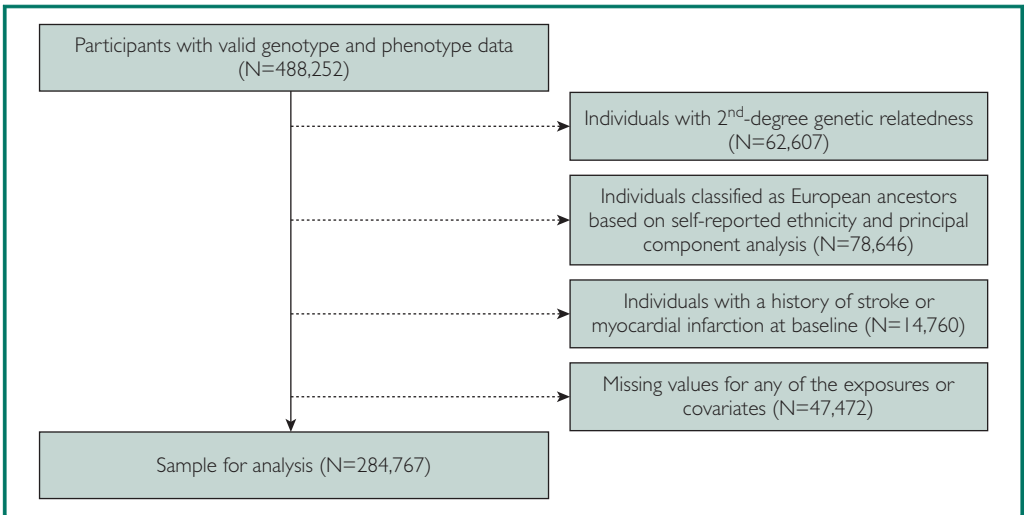

FIGURE 1. A flow diagram.

methodology used in previous research[11]; polygenic risk scores calculated with this methodology were shown to predict stroke outcomes.[11] More specifically, a weighted polygenic risk score was calculated by summing the number of risk-increasing alleles at each of the known loci, multiplied by effect estimates for that locus identified on the basis of an independent sample of European ancestors from the MEGASTROKE Consortium,[4] a methodology used to avoid overestimation of effect size of genetic variants.[12,13] The correlations between variants (r^2<0.05) were based on participants of European ancestry from the 1000 Genomes Project, phase 3.[14] The calculated continuous polygenic risk score followed a normal distribution (Supplemental Figure, available online at http://www.mayoclinicproceedings.org) and was categorized into low, middle, and high genetic risk for stroke on the basis of the tertiles. There was no ambiguous palindromic variant in the list of SNPs used in our analyses.

Muscle Strength. In UK Biobank, muscle strength of each participant was evaluated through measurements of grip strength, which is a strong predictor of overall muscle strength[15-17] as well as of mortality.[18,19] Each participant's grip strength was measured with a hydraulic hand dynamometer (Jamar J00105), which is capable of assessing isometric hand grip force up to 90 kg. Participants were asked to squeeze the handle of the hand dynamometer as strongly as possible for about 3 seconds while maintaining a 90-degree angle of the elbow and sitting upright on a chair; the test protocol was performed in both hands. The same procedure was used following a standard grip strength measurement protocol across all 22 assessment centers.[20] For this study, an indicator of muscle strength was estimated by dividing grip strength values from both hands by fat-free mass (measured with a bioimpedance analyzer [Tanita BC-418MA]) to adjust for differences in grip strength attributable to lean mass (which is known to be more strongly associated with muscle strength than total body mass or body mass index[21-23]). Previous research documented no material differences in mortality risk between different ways of quantifying relative grip strength measures.[24] Tertiles of muscle strength were created according to participants' age- and sex-specific cut points of grip strength (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).

Incidence of Stroke

Three incident stroke outcome variables of the study included overall stroke, ischemic stroke, and hemorrhagic stroke (intracerebral and subarachnoid hemorrhagic stroke combined), all of which were quantified according to a set of algorithms recommended by the UK Biobank Outcome Adjudication Group; detailed descriptions about the algorithms are provided elsewhere.[25] Briefly, the stroke variables were generated through linkage with national death registry and hospital admission records. Codes of *International Classification of Diseases* were used to adjudicate overall (*Ninth Revision*, 430-431, 434, 436; *Tenth Revision*, I60-I61, I63-I64), ischemic (*Ninth Revision*, 434, 436; *Tenth Revision*, I63-I64), and hemorrhagic (*Ninth Revision*, 430-431; *Tenth Revision*, I60-I61) stroke cases accrued until August 16, 2020, for individuals in England and Wales and July 19, 2020, for individuals in Scotland. Incidence of each stroke type was determined on the basis of the first occurrence of its type regardless of the data source used. The positive predictive value (point estimate; 95% CI) of the codes (ie, probability that code-identified candidate stroke cases are truly stroke cases) was acceptably high for overall stroke (79%; 73% to 84%) and ischemic stroke (83%; 74% to 90%) but relatively lower (albeit more inconclusive with larger CIs) for hemorrhagic stroke (intracerebral [42%; 23% to 63%] and subarachnoid [71%; 49% to 87%] hemorrhagic stroke), as verified through validation by stroke physicians relative to full electronic patient records including formal scan reports in a regional subsample of 17,249 UK Biobank participants.[26] The median follow-up was 11.5 years (interquartile range, 10.8 to 12.1

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TABLE 1. Characteristics of Individuals Overall and Within Tertiles of Muscle Strength at Baseline (N=284,767)

Variables	All	Tertiles of muscle strength		
		Low	Middle	High
Age (y)	56.7 (7.9)	57.0 (7.9)	56.8 (7.9)	56.5 (7.8)
Sex				
Men	130,419 (45.8)	43,449 (45.8)	43,478 (45.8)	43,492 (45.8)
Women	154,348 (54.2)	51,428 (54.2)	51,443 (54.2)	51,477 (54.2)
Body mass index (kg/m^2)	27.3 (4.7)	29.0 (5.3)	27.1 (4.3)	25.7 (3.6)
Smoking status				
Never	55.5	54.9	55.5	56.0
Previous	34.9	35.5	35.2	34.0
Current	9.6	9.6	9.4	9.9
Employment				
Unemployed	41.6	44.5	40.8	39.6
Employed	58.4	55.5	59.2	60.4
Townsend Deprivation Index	−1.7 (2.9)	−1.4 (3.0)	−1.7 (2.8)	−1.9 (2.7)
Alcohol consumption				
Never	2.9	3.5	2.6	2.5
Previous	3.2	4.0	2.9	2.6
Current (<3 times/wk)	47.3	50.9	46.8	44.2
Current (≥3 times/wk)	46.7	41.6	47.6	50.8
Red meat intake (d/wk, average)	0.9 (0.5)	0.9 (0.6)	0.9 (0.5)	0.9 (0.5)
Resting pulse rate (beats/min)	69.3 (11.2)	70.2 (11.4)	69.0 (11.0)	68.7 (11.0)
Systolic blood pressure (mm Hg)	138.3 (18.6)	137.9 (18.3)	138.2 (18.5)	138.7 (18.8)
Low-density lipoproteins (mmol/L)	3.6 (0.9)	3.6 (0.9)	3.6 (0.9)	3.6 (0.8)
Hypertension medication use (%)	18.7	23.4	18.0	14.6
Moderate to vigorous physical activity (min/d)	45.0 (54.6)	40.6 (52.3)	45.3 (54.5)	49.1 (56.7)
Polygenic risk score for stroke	4.7 (0.3)	4.6 (0.3)	4.6 (0.3)	4.7 (0.3)
Fat-free mass (kg)	53.4 (11.5)	55.1 (12.3)	53.5 (11.4)	51.8 (10.6)
Grip strength (kg)	31.0 (11.0)	24.3 (9.1)	31.3 (9.3)	37.3 (10.5)
Grip strength/fat-free mass (kg)	0.6 (0.1)	0.4 (0.1)	0.6 (0.1)	0.7 (0.1)

Continuous variables are presented as means (standard deviation). Categorical variables are presented as number (percentage) or percentage.

years for overall stroke, 10.9 to 12.1 years for ischemic stroke, and 10.9 to 12.2 years for hemorrhagic stroke).

Confounders

The following variables that may confound the associations between genetic risk, muscle strength, and stroke were included as confounders in all models: sex, body mass index (weight in kilograms/height in meters squared), smoking status (never, previous, current), employment (unemployed, employed), Townsend Deprivation Index (a composite score of employment, car ownership, home ownership, and household overcrowding; based on postcode, with higher values indicating a higher degree of deprivation), alcohol consumption (never, previous, currently <3 times/wk, currently ≥3 times/wk), processed/red meat consumption (times/wk), resting pulse rate (beats/min; as a proxy measure for cardiorespiratory fitness[27]), systolic blood pressure (mm Hg), low-density lipoproteins (mmol/L), hypertension medication use, and moderate to vigorous physical activity (min/d).

Statistical Analyses

Cox regression with age as the underlying timescale was used to estimate associations

TABLE 2. Associations of the Polygenic Risk Score for Stroke and Muscle Strength With Incident Stroke, Ischemic Stroke, and Hemorrhagic Stroke

Stroke outcome	Comparisons	No. of participants	No. of cases	Crude incident rate per 100,000 person-years	Hazard ratio (95% CI)		
					Model 1[a]	Model 2[b]	Model 3[c]
Overall stroke		284,767	4008	122.8			
	Tertiles of polygenic risk score for stroke						
	Low (Reference)	94,921	1184	108.7	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Middle	94,923	1309	120.3	1.11 (1.03-1.20)	1.10 (1.02-1.20)	1.11 (1.02-1.20)
	High	94,923	1515	139.4	1.29 (1.20-1.39)	1.28 (1.19-1.38)	1.28 (1.19-1.38)
	P for linear trend				<.001	<.001	<.001
	Per 1-SD increment in polygenic risk score for stroke				1.11 (1.08-1.15)	1.11 (1.08-1.14)	1.11 (1.08-1.15)
	Tertiles of muscle strength						
	Low (Reference)	94,877	1617	150.1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Middle	94,921	1242	114.3	0.78 (0.72-0.84)	0.81 (0.75-0.87)	0.81 (0.75-0.87)
	High	94,969	1149	104.4	0.72 (0.67-0.78)	0.77 (0.71-0.83)	0.76 (0.71-0.82)
	P for linear trend				<.001	<.001	<.001
	Per 1-SD increment in muscle strength				0.94 (0.91-0.97)	0.88 (0.85-0.91)	0.88 (0.85-0.91)
Ischemic stroke		284,767	3031	92.7			
	Tertiles of polygenic risk score for stroke						
	Low (Reference)	94,921	872	80.0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Middle	94,923	978	89.7	1.13 (1.03-1.24)	1.12 (1.03-1.23)	1.12 (1.02-1.23)
	High	94,923	1181	108.5	1.36 (1.25-1.49)	1.35 (1.24-1.48)	1.36 (1.24-1.48)
	P for linear trend				<.001	<.001	<.001
	Per 1-SD increment in polygenic risk score for stroke				1.14 (1.10-1.18)	1.14 (1.10-1.18)	1.14 (1.10-1.18)
	Tertiles of muscle strength						
	Low (Reference)	94,877	1243	115.2	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Middle	94,921	942	86.6	0.77 (0.71-0.84)	0.81 (0.75-0.89)	0.81 (0.74-0.88)
	High	94,969	846	76.8	0.70 (0.64-0.76)	0.76 (0.69-0.83)	0.75 (0.69-0.82)
	P for linear trend				<.001	<.001	<.001
	Per 1-SD increment in muscle strength				0.96 (0.92-0.99)	0.88 (0.85-0.92)	0.88 (0.84-0.91)
Hemorrhagic stroke		284,767	1073	32.7			
	Tertiles of polygenic risk score for stroke						
	Low (Reference)	94,921	338	30.9	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Middle	94,923	364	33.3	1.08 (0.93-1.25)	1.07 (0.93-1.24)	1.07 (0.93-1.24)
	High	94,923	371	34.0	1.10 (0.95-1.28)	1.09 (0.94-1.27)	1.09 (0.94-1.27)
	P for linear trend				.63	<.001	<.001
	Per 1-SD increment in polygenic risk score for stroke				1.05 (0.99-1.11)	1.04 (0.98-1.11)	1.04 (0.98-1.11)

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TABLE 2. Continued

Stroke outcome	Comparisons	No. of participants	No. of cases	Crude incident rate per 100,000 person-years	Hazard ratio (95% CI) Model 1[a]	Model 2[b]	Model 3[c]
Hemorrhagic stroke, continued							
	Tertiles of muscle strength						
	Low (Reference)	94,877	419	38.7	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Middle	94,921	328	30.1	0.79 (0.68-0.91)	0.79 (0.68-0.92)	0.79 (0.68-0.91)
	High	94,969	326	29.5	0.79 (0.68-0.91)	0.77 (0.66-0.90)	0.77 (0.66-0.90)
	P for linear trend				<.001	<.001	<.001
	Per 1-SD increment in muscle strength				0.89 (0.83-0.94)	0.87 (0.81-0.93)	0.87 (0.81-0.92)

[a]Model 1: adjusted for the genotype array type (UK Biobank Axiom Array, UK BiLEVE Axiom Array) and first 10 principal components of genetic variant in models for polygenic risk scores and no confounders in models for muscle strength.

[b]Model 2: adjusted for all confounders in model 1 plus sex, body mass index, smoking status (never, previous, current), employment (unemployed, employed), Townsend Deprivation Index, alcohol consumption (never, previous, currently <3 times/wk, currently ≥3 times/wk), processed/red meat consumption (d/wk), resting pulse rate (beats/min), systolic blood pressure (mm Hg), low-density lipoproteins (mmol/L), hypertension medication use, and moderate to vigorous physical activity (min/d); no adjustment for the genotype array type (UK Biobank Axiom Array, UK BiLEVE Axiom Array) and first 10 principal components of genetic variant in models for muscle strength.

[c]Model 3: adjusted for all confounders in model 2 plus muscle strength in models for polygenic risk scores or polygenic risk scores in models for muscle strength.

of muscle strength and polygenic risk scores with each of the 3 incident stroke outcomes. Models using muscle strength as the main exposure were unadjusted (model 1), adjusted for potential confounders (model 2), and additionally adjusted for the polygenic risk score along with the genotyping array type (UK Biobank Axiom Array, UK BiLEVE Axiom Array) and the first 10 principal components of ancestry (to control for population stratification[28]; model 3). Models using the polygenic risk score as the main exposure were adjusted for the array type and first 10 principal components of ancestry (model 1), potential confounders (model 2), and muscle strength (model 3). Similar sets of models were fit using standardized continuous variables of muscle strength and polygenic risk score (ie, per 1-SD increment; through a calculation of *z*-scores), given the log-linear association observed from cubic spline regression. Models were also fit to estimate associations of muscle strength with each stroke outcome within 3 strata of genetic predisposition to stroke; multiplicative and additive interaction (relative excess risk due to interaction[29]) between tertiles of polygenic risk score and muscle strength were tested. To examine the extent to which the increased genetic risk for development of stroke is attenuated through increased muscle strength, we fit joint association models whereby a total of 9 comparison groups were generated on the basis of the combination of tertiles of polygenic risk scores and muscle strength. Visual inspections of log-log plots revealed that the proportional hazard assumption for each exposure was reasonable. The following 4 sets of sensitivity analyses were performed: an analysis excluding incident stroke events in the first year of follow-up to address potential for reverse causality; an analysis including individuals with second-degree genetic relatedness but adjusting for genetic relatedness by estimating cluster-robust standard errors; an analysis using polygenic risk scores calculated on the basis of 82 SNPs (significant at a *P* value $<1\times10^{-5}$ and in low linkage disequilibrium according to $r^2<0.05$) associated with ischemic stroke (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org) in examining

the associations between muscle strength and incident ischemic stroke; and an analysis using polygenic risk scores calculated on the basis of 8 SNPs significant for stroke at a *P* value $<5\times10^{-8}$ (combined with the low linkage disequilibrium cutoff, $r^2<0.05$). There was no evidence of interaction with sex, so sex-combined analyses were performed. All polygenic risk scores were derived using PLINK 2.0. All statistical analyses were performed using Stata/MP version 16.0 software (StataCorp LLC).

RESULTS

Participants' characteristics at baseline are summarized for all and each muscle strength category in Table 1. A total of 4008 overall stroke cases was accrued during 3,264,054 person-years of follow-up: 3031 ischemic stroke cases during 3,269,070 person-years of follow-up and 1073 hemorrhagic stroke cases during 3,277,812 person-years of follow-up (Table 2). Compared with the lowest genetic risk tertile (model 3), the middle and highest tertiles had higher hazards of overall and ischemic stroke after adjustment for confounders and muscle strength (inconclusive evidence of association for hemorrhagic stroke). Hazard ratios of overall, ischemic, and hemorrhagic stroke were lower for the middle and highest tertiles of muscle strength compared with the lowest tertile of muscle strength after adjustment for confounders, polygenic risk scores, array type, and the first 10 principal components of ancestry (model 3). Every 1-SD increment in the polygenic risk score and muscle strength was associated with higher and lower hazard of each stroke type, respectively (an exception for the association between the polygenic risk score and hemorrhagic stroke). Similar trends of associations were observed in the sensitivity analyses (Supplemental Tables 4-7, available online at http://www.mayoclinicproceedings.org).

Compared with the lowest muscle strength tertile (Figure 2), the highest and middle tertiles had 15% to 29% lower hazards of incident overall and ischemic stroke across all strata of genetic risk. The hazard of incident hemorrhagic stroke was 29% and 37% lower for the middle and high muscle strength tertiles, respectively, at high genetic risk (inconclusive evidence of associations observed at low and middle genetic risk). *P* values for multiplicative and additive interactions between muscle strength and genetic risk were .94 and .43 for overall stroke, .77 and .60 for ischemic stroke, and .72 and .64 for hemorrhagic stroke, respectively.

The joint association analyses (Figure 3) showed that compared with the reference category of low genetic risk and high muscle strength, the lowest tertile of muscle strength combined with any level of genetic risk was associated with increased hazards of overall stroke. In the highest muscle strength tertile, however, the hazard ratio of incident overall stroke was not higher for the middle genetic risk tertile but higher only for the highest genetic risk tertile, suggesting that the increased genetic risk of overall stroke is partly attenuated (albeit not completely eliminated) by high muscle strength. A nearly identical pattern of associations was identified for incident ischemic stroke. Hazards of hemorrhagic stroke were higher only for high genetic risk combined with either the lowest or highest muscle strength tertile in comparison with the reference category of low genetic risk and high muscle strength.

DISCUSSION

This study is the first investigating the associations between genetic predispositions to stroke, muscle strength, and incident stroke. Using the full genotype and phenotype data from UK Biobank, we found that lower muscle strength and higher genetic predispositions to stroke were both independently associated with increased incidence of overall, ischemic, and hemorrhagic stroke (not for genetic risk). Moreover, at each stratum of genetic risk including more genetically predisposed individuals, higher muscle strength tertiles were associated with lower incidence of all stroke types (except for hemorrhagic stroke at low and middle genetic risk). However, highest muscle strength did

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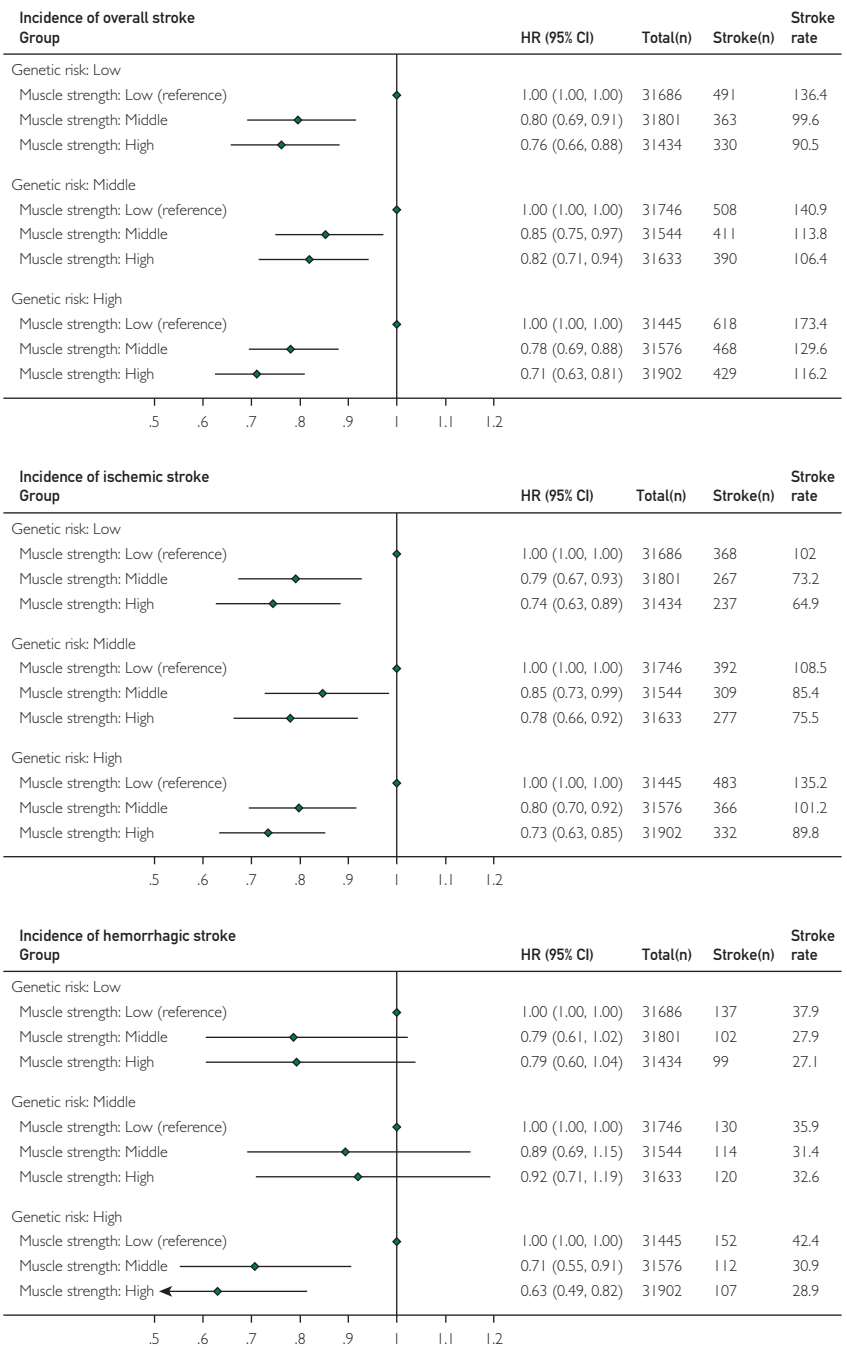

FIGURE 2. Associations of muscle strength with incidence of overall stroke, ischemic stroke, and hemorrhagic stroke across 3 levels of genetic risk for stroke. Cox regression models using age as the underlying timescale were adjusted for sex, body mass index, smoking status (never, previous, current), employment (unemployed, employed), Townsend Deprivation Index, alcohol consumption (never, previous, currently <3 times/wk, currently ≥3 times/wk), processed/red meat consumption (d/wk), resting pulse rate (beats/min), systolic blood pressure (mm Hg), low-density lipoproteins (mmol/L), hypertension medication use, and moderate to vigorous physical activity (min/d); genotyping array type (UK Biobank Axiom Array, UK BiLEVE Axiom Array); and the first 10 principal components of genetic variant. *P* values for multiplicative and additive interactions between muscle strength and genetic risk were .94 and .43 for overall stroke, .77 and .60 for ischemic stroke, and .72 and .64 for hemorrhagic stroke, respectively. Rates are per 100,000 person-years. HR, hazard ratio.

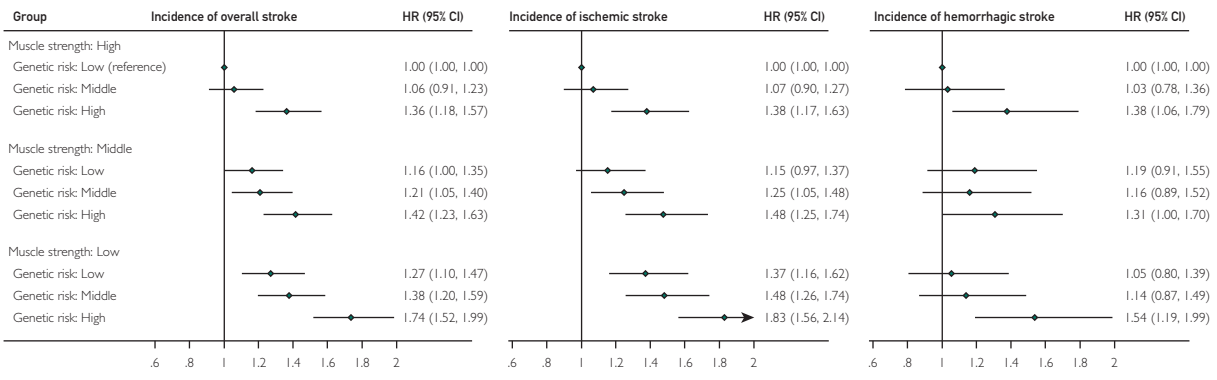

FIGURE 3. Joint associations of muscle strength and genetic risk with incidence of overall stroke, ischemic stroke, and hemorrhagic stroke. Cox regression models using age as the underlying timescale were adjusted for sex, body mass index, smoking status (never, previous, current), employment (unemployed, employed), Townsend Deprivation Index, alcohol consumption (never, previous, currently <3 times/wk, currently ≥3 times/wk), processed/red meat consumption (d/wk), resting pulse rate (beats/min), systolic blood pressure (mm Hg), low-density lipoproteins (mmol/L), hypertension medication use, and moderate to vigorous physical activity (min/d); genotyping array type (UK Biobank Axiom Array, UK BiLEVE Axiom Array); and the first 10 principal components of genetic variant. HR, hazard ratio.

not eliminate but partially attenuated the increased genetic risk of overall and ischemic stroke. In addition, there was no evidence of interactions between muscle strength and genetic risk, which may suggest that increased muscle strength has similar levels of stroke risk reduction in individuals at low genetic risk and high genetic risk.

These findings expand the existing evidence base that examined muscle strength[5-7] and genetic risk for stroke[4] separately in relation to stroke risk. Previous research[11] using UK Biobank data found that individuals who adhered to a healthy lifestyle (a combination of nonsmoking, healthy diet, body mass index below 30 kg/m^2, and regular physical activity) had reduced risk for development of stroke, independent of their genetic predispositions to stroke. That research[11] reported on associations for each of the 4 separate healthy lifestyle variables but found no associations between stroke risk and achieving 150 min/wk or more of moderate-intensity activity or 75 min/wk or more of vigorous-intensity activity at any stratum of genetic risk for stroke, and more important, it did not attempt to explore the gene—muscle strength interactions concerning stroke risk. Nonetheless, both that research[11] and this study detected no evidence of gene-environment interactions, suggesting that the benefits of the behavior-related trait may be similar to individuals of different genetic susceptibility to stroke. A few other studies[30,31] have also attempted to determine the gene-environment interaction, with health behavior as an environmental component, for cardiovascular outcomes, but they used a polygenic risk score for coronary heart disease rather than for stroke, making direct comparison with this study challenging. However, adhering to a healthy lifestyle[31] and favorable levels of behavior-related traits (eg, muscle strength, aerobic fitness, physical activity)[30] were associated with reduced risk of cardiovascular outcomes independent of genetic predispositions to coronary heart disease.

The joint models provided unique insights into the extent to which the increased inherited risk of stroke is attenuated through improved muscle strength. We observed that high muscle strength partly attenuated the increased genetic risk for development of overall and ischemic stroke. This finding corroborates the existing knowledge that improved muscle strength through resistance exercise or muscle-strengthening activities[32-34] leads to favorable changes in

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intermediate traits of stroke[35-39] and potential subclinical symptoms related to stroke.[40-43] To the best of our knowledge, however, there has been no research that takes into account individuals' different genetic predispositions to stroke in determining the effects of muscle-strengthening activities on stroke incidence and markers of stroke as well as the effects of an exercise dose on increasing muscle strength. Therefore, clinical trials using individuals' genetic susceptibility are needed to provide causal evidence on the degree to which the elevated genetic risk for development of stroke is reduced by improving muscle strength and engaging in resistance training or muscle-strengthening activities.

Several strengths of this research are worth noting. First, we used a combined data set of full genotype, phenotype, and health outcome records from the UK Biobank database, which enabled us to explore the complex interplay between muscle strength and genetic risk for stroke in relation to incidence of stroke including stroke subtypes. In addition, we used a total of 87 SNPs[4] that are genome-wide significant and in low linkage disequilibrium for stroke risk and followed a standard procedure[10] to calculate a polygenic risk score for stroke. Moreover, we adjusted all our analyses for potential differences in muscle strength due to differences in age, sex, and fat-free mass.

However, several limitations should be considered in interpreting the findings of this study. First, given that this study included only White British individuals, our results may not be generalizable to other ethnicity groups. Another limitation is that no strong evidence on causality and physiologic mechanisms can be drawn because of the use of data from observational research. Future research is warranted to explore the specific biologic mechanism through which increased muscle strength leads to reductions in stroke risk attributable to increased genetic risk. It is also possible that subclinical stroke-related conditions were associated with lower muscle strength, thereby resulting in higher risk of stroke; however, the sensitivity analysis after exclusion of stroke events accrued within the first-year follow-up revealed an identical trend of associations as in the main analyses. There is a possibility that residual confounding may have occurred because of measurement error in some of the self-reported confounders and that some unmeasured variables may have acted as confounders in the associations. Another limitation is the relatively smaller number of hemorrhagic stroke cases (n=1073), which is reflected in the wider CIs around the estimates of association for this outcome.

CONCLUSION

Higher muscle strength was associated with lower incidence of overall, ischemic, and hemorrhagic stroke, independent of genetic risk for stroke. The increased genetic risk of overall and ischemic stroke was partly attenuated through increased muscle strength. Improving muscle strength has great potential to serve as a behavior-based stroke prevention strategy in all individuals, including those at increased genetic risk for stroke.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **SNP** = single-nucleotide polymorphism

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