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ORIGINAL RESEARCH

Polygenic Risk, Midlife Life's Simple 7, and Lifetime Risk of Stroke

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BACKGROUND: Recent genetic discoveries in stroke have unleashed the potential of using genetic information for risk prediction and health interventions aimed at disease prevention. We sought to estimate the lifetime risk of stroke (LTRS) by levels of genetic risk and to investigate whether optimal cardiovascular health can offset the negative impact of high genetic risk on lifetime risk of stroke.

METHODS AND RESULTS: Study participants were 11 568 middle-aged adults (56% women, 23% Black adults), who were free of stroke at baseline and were followed up for a median of 28 years. The remaining LTRS was estimated according to levels of genetic risk based on a validated stroke polygenic risk score, and to levels of cardiovascular health based on the American Heart Association Life's Simple 7 recommendations. At age 45, individuals with high, intermediate, and low polygenic risk score had a remaining LTRS of 23.2% (95% CI, 20.8%–25.5%), 13.8% (95% CI, 11.7%–15.8%), and 9.6% (95% CI, 7.3%–11.8%), respectively. Those with both a high genetic risk and an inadequate Life's Simple 7 experienced the highest LTRS: 24.8% (95% CI, 22.0%–27.6%). Across all polygenic risk score categories, those with an optimal Life's Simple 7 had a ≈30% to 43% lower LTRS than those with an inadequate Life's Simple 7. This corresponded to almost 6 additional years lived free of stroke.

CONCLUSIONS: The LTRS varies by levels of polygenic risk and cardiovascular health. Maintaining an optimal cardiovascular health can partially offset a high genetic risk, emphasizing the importance of modifiable risk factors and illustrating the potential of personalizing genetic risk information to motivate lifestyle changes for stroke prevention.

Key Words: epidemiology ■ modifiable risk factors ■ polygenic risk ■ stroke

Stroke is the second leading cause of death and a major cause of disability and dementia worldwide. It is a significant public health burden with enormous financial and human costs that are projected to rise over the next decades due to demographic shifts in populations around the globe.[1] In the United States, the lifetime risk of stroke (LTRS) in adults from age 25 is estimated at 21%[2] and the average lifetime cost of stroke per person, including in-patient care, rehabilitation, and follow-up care, is estimated at $140 048.[3]

Identifying people at high risk of developing stroke over their lifetime represents a cornerstone of effective prevention strategies.[4] Both genetic and environmental risk factors, including lifestyle, influence the risk of developing stroke. The effect of a healthy lifestyle on reducing stroke risk is well documented.[5–7] Indeed, managing cardiometabolic risk factors and promoting healthy lifestyle behaviors remain the first-line strategy to improve cardiovascular health and decrease incident stroke risk.[8]

Recent genome-wide association studies have identified multiple risk variants for stroke[9] and have enabled the development of genetic risk scores that predict stroke incidence.[10–12] However, it is unclear whether a favorable cardiovascular health might attenuate a high genetic risk or whether genetic

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CLINICAL PERSPECTIVE

What Is New?

- Estimates of lifetime risk of stroke and years lived free of the disease according to levels of polygenic risk and of cardiovascular health (based on the American Heart Association's Life's Simple 7 (LS7) recommendations) in White and Black men and women have not been reported previously.
- Depending on race, the lifetime risk of stroke varies substantially by levels of polygenic risk and cardiovascular health.
- Maintaining an optimal midlife cardiovascular health offsets the lifetime risk of stroke by 30% to 43% and lengthens the years lived free of stroke by 5 to 6 years.

What Are the Clinical Implications?

- Communicating the impact of cardiovascular health and polygenic risk on long-term absolute probabilities of stroke (lifetime risk of stroke) may be more easily interpreted by both physicians and patients.
- The benefit of maintaining an optimal cardiovascular health on lifetime risk of stroke across all levels of genetic risk emphasizes the importance of modifiable risk factors in prevention efforts to reduce stroke risk for all.
- Improved polygenic risk scores for stroke are needed before clinical utility can be achieved, especially in Black adults for whom the predictive strength of the current score is poor.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk In Communities
LS7	Life's Simple 7
LTRS	lifetime risk of stroke
PRS	polygenic risk score

factors and lifestyle factors contribute independently to the LTRS. Because they account for competing causes of death, lifetime risk estimates provide more accurate assessments of the long-term probabilities of stroke.[13]

Here, we aimed to estimate the LTRS according to levels of genetic risk based on a previously described stroke polygenic risk score (PRS)[11] and to levels of cardiovascular health based on the American Heart Association Life's Simple 7 (LS7) recommendations.[8] We hypothesized that optimal cardiovascular health possibly mitigates the effect of high genetic risk on the LTRS.

METHODS

Study Sample

The data that support the findings of this study are available from the ARIC (Atherosclerosis Risk in Communities) study in accordance with its data sharing policy described in https://sites.cscc.unc.edu/aric/node/10303. The ARIC study is a prospective, population-based study of atherosclerosis and cardiovascular diseases in 15 792 adults (11 478 non-Hispanic White adults; 8710 women) aged between 45 and 64 years at the baseline examination from 1987 to 1989. Participants were randomly selected and recruited from suburban Minneapolis, Minnesota; Washington County, Maryland; and Forsyth County, North Carolina. In Jackson, Mississippi, only Black residents were enrolled. Details about the ARIC study design and examination procedures have been previously published.[14,15] The ARIC study has been reviewed and approved by the institutional review boards at all participating institutions. All participants provided written informed consent.

Our primary analysis was conducted on 11 568 ARIC participants (8917 White participants, 2651 Black participants) who had available genetic and LS7 data and were free of stroke or transient ischemic attack at baseline. In addition, because the stroke PRS used in this study was developed and validated in the UK Biobank on participants of European ancestry, a sensitivity analysis was conducted in the subsample of White participants free of stroke or transient ischemic attack at baseline and with available genetic and LS7 data. Because of the limited sample size of the Black cohort, we estimated LTRS at age 45 by PRS only and by LS7 only, but not jointly. We also examined the association of the PRS with incident stroke by race.

Stroke Ascertainment

The study included hospitalized strokes that occurred by December 31, 2018. Participants' hospitalizations and deaths were identified via annual telephone contacts and by reviewing hospital records and lists of stroke discharges (*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 430 to 438). Details on quality assurance for ascertainment and classification of stroke are described elsewhere.[16,17] Briefly, stroke diagnosis was assigned via a computer algorithm and an expert reviewer, based on criteria adapted from the National Survey of Stroke.[18] Disagreements between the computer algorithm and the reviewer were adjudicated by a second physician. Strokes were classified as hemorrhagic stroke (subarachnoid and intracerebral hemorrhage) or ischemic stroke (thrombotic and embolic

brain infarction) based on available data including neuroimaging, autopsy, and review of the medical records.

Genome-Wide Genotyping and Genetic Risk Score Calculation

Participants were genotyped with the Affymetrix 6.0 array (Affymetrix, Santa Clara, CA). After quality control, over 800 000 variants were used to perform imputation to the 1000G Phase3 v5 reference panel using the Michigan imputation server.[19] Abraham et al.[11] developed a PRS for stroke in individuals of European ancestry from the UK Biobank using genome-wide association study summary statistics for 19 stroke and stroke-related traits. They first derived distinct PRSs for each trait and then combined them into a single meta-genetic risk score that was further validated and converted to a set of 3.2 million single-nucleotide variants weights made publicly available. Based on these weights, we calculated, for each ARIC participant, an additive stroke PRS as the weighted sum of the number of risk alleles (ranging from 0 to 2) at each single-nucleotide variant with imputation quality R^2>0.3. The total number of single-nucleotide variants included in the PRS was 2 759 739 for ARIC White participants and 2 236 753 for ARIC Black participants. Within each racial group, the PRS was standardized by dividing by the SD and participants were categorized into low (<25th percentile), intermediate (25th–75th percentile), and high (>75th percentile) genetic risk strata. White and Black participants were then combined within each genetic risk stratum. The intermediate genetic risk category was used as the reference to examine the effects of low and high genetic risk.

Life's Simple 7 Scores

LS7 scores were derived according to the American Heart Association definitions,[8] which are based on 7 modifiable risk factors: total cholesterol, blood pressure, blood glucose, physical activity, diet, smoking status, and body mass index. For each component, participants were categorized into 3 groups—poor, intermediate, and ideal. Details about the definitions used for classification are provided in Table S1. A total LS7 score was computed for each participant as the sum of the participant's numbers of ideal cardiovascular health components (Range 0–7). In these analyses, participants were further categorized into 3 classes of cardiovascular health: inadequate (0–2 ideal components), average (3–4 ideal components), or optimal (5–7 ideal components). The average category was used as the reference to examine the effects of both inadequate and optimal cardiovascular health.

All data for calculating LS7 scores were collected by trained staff using standardized protocols at the baseline visit (1987–1989). Glucose and total cholesterol were measured from fasting blood samples using standard laboratory assays. Sitting systolic and diastolic blood pressure was measured with a random zero sphygmomanometer 3 times after a 5-minute rest and the average of the second and third measurements was used. Physical activity was measured with the Baecke questionnaire. Diet was assessed by a modified 66-item Harvard food frequency questionnaire. Smoking status was self-reported. Body mass index was calculated from height and weight measures at the study visit. Use of blood pressure-, cholesterol-, and glucose-lowering medications was ascertained by asking participants to bring to the visit all medications they had been using over the previous 2 weeks.

Statistical Analysis

Baseline characteristics were computed within each racial group and in the overall sample according to PRS categories or LS7 categories. Differences among PRS and LS7 groups were estimated using Kruskal-Wallis tests for continuous variables and Pearson's χ^2 test for categorical variables.

The remaining lifetime risk of first-ever stroke was calculated using a modified technique of survival analysis that adjusts for the competing risk of death and thus provides an estimate of the actual risk of stroke during one's lifetime.[13] Participants were followed from the baseline examination (1987–1989) until they developed a first-ever stroke, died, or were censored due to withdrawal or end of follow-up for the present study (December 31, 2018). The remaining lifetime risk estimates for stroke were calculated at each index age (45, 55, 65, 75, and 85) stratified by PRS category and by LS7 category, separately. In addition, at index age 45, LTRS was calculated for PRS and LS7 categories, jointly. Differences in overall survival time and stroke-free survival time between PRS categories and LS7 categories were investigated using Irwin's restricted mean.

The association of the PRS and LS7 with incident stroke was also assessed using Fine and Gray proportional hazards models accounting for competing risk of death.[20] Age was used as the timescale and ages were left-truncated at time of entry into the ARIC study. Model 1 analyzed the effects of the PRS and LS7 separately. Model 2 examined the effects of the PRS and LS7 in the same model. Model 3 further included a multiplicative interaction term between PRS and LS7. All models were adjusted for sex, race (except in the race-stratified analyses), field center, education level, and parental history of stroke. Hazard ratios (HR) and 95% CIs were reported for each model. Departure from the proportional hazard assumption was assessed by calculating the Schoenfeld residuals and implementing graphical diagnostics. All *P* values are 2 sided and a significance threshold of P<0.05 was used. All statistical analyses were performed using SAS software v. 9.4 (SAS Institute, Cary, NC). Analyses were performed for all strokes and ischemic strokes.

We also evaluated the predictive value of the PRS in our cohort using the same methodology as we previously described.[12] Briefly, we derived receiver-operated characteristic curves with corresponding areas under the curve (AUC) and 95% CI from Cox regression models. The partial model adjusted for sex, race (except in the race-stratified analyses), field center, education level, parental history of stroke, and LS7 (or the conventional risk factors individually). The full model additionally adjusted for the PRS. The statistical significance of the change in the AUC between models was tested with the method of Hanley and McNeil,[21] which accounts for the correlation between both models.

RESULTS

Study Sample Description

Table 1 presents participants' baseline characteristics for the overall sample and stratified by low, intermediate, and high genetic risk. At baseline, participants had a median age of 54 years and were followed up for a median of 28 years (interquartile range: 19–30 years). Compared with participants with intermediate and low PRS, those with a high PRS had a higher prevalence of parental history of stroke, hypertension, and diabetes, and had a higher body mass index and total plasma cholesterol level (P<0.001). This is not unexpected given that the PRS was developed based on genetic factors associated with stroke and stroke-related traits, including systolic and diastolic blood pressure, total cholesterol, body mass index, and type 2 diabetes. Those with a high PRS also had the lowest prevalence of optimal LS7 and the highest prevalence of inadequate LS7 (P<0.001). During a total of 274 432 person-years of follow-up, 1138 participants were diagnosed with a stroke (incidence rate: 4.15 per 1000 person-years): 159 (14%) in the low genetic risk category, 475 (41.7%) in the intermediate genetic category, and 504 (44.3%) in the high genetic risk category (Table 1). In addition, participants with an inadequate LS7 experienced 646 stroke events (56.8%), whereas those with an optimal LS7 experienced 71 stroke events (6.2%).

Genetic Risk Score, LS7, and Relative Risk of Stroke

Compared with an intermediate PRS, a high PRS was associated with a 2.2-fold greater risk of developing a stroke (P<0.0001, Table 2), and a low PRS was associated with a ≈40% lower risk of developing a stroke (P<0.0001, Table 2). Results were similar after adjusting for LS7. Adjusting for established risk factors individually also showed similarly strong associations (High PRS: HR, 2.2, P<0.0001; Low PRS: HR, 0.68; P<0.0001) (Table S2). The differences in HR for incident

Table 1. Baseline Characteristics of ARIC Participants by Genetic Risk Score Category and Overall

	Overall	High PRS	Intermediate PRS	Low PRS	
	N=11 568	N=2892	N=5783	N=2893	*P* value*
Age, y, median (Q1, Q3)	54 (49, 59)	54 (49, 59)	54 (49, 59)	54 (49, 59)	0.002
Female sex, n (%)	6425 (56)	1587 (55)	3260 (56)	1578 (55)	0.20
Education category					<0.001
Less than high school	2447 (21)	650 (22)	1215 (21)	582 (20)	
High school graduate or vocational school	4779 (41)	1263 (44)	2417 (42)	1099 (38)	
At least some college or professional school	4342 (38)	979 (34)	2151 (37)	1212 (42)	
Parental history of stroke, n (%)	3372 (29)	917 (32)	1662 (29)	793 (27)	<0.001
Body mass index, median (Q1, Q3)	26.8 (24.0, 30.3)	27.5 (24.5, 31.0)	26.7 (24.0, 30.2)	26.3 (23.5, 29.6)	<0.001
Hypertension, n (%)	3795 (33)	1202 (42)	1851 (32)	742 (26)	<0.001
Diabetes, n (%)	1226 (11)	363 (13)	598 (10)	265 (9.2)	<0.001
Total cholesterol (mmol/L), median (Q1, Q3)	5.48 (4.81, 6.21)	5.69 (4.97, 6.39)	5.48 (4.86, 6.18)	5.30 (4.63, 5.97)	<0.001
Current smoking, n (%)	2940 (25)	746 (26)	1492 (26)	702 (24)	0.3
Systolic blood pressure (mm Hg), median (Q1, Q3)	118 (108, 131)	121 (111, 134)	118 (108, 130)	115 (105, 127)	<0.001
Life's Simple 7, n (%)					<0.001
Optimal	1302 (11)	209 (7.2)	638 (11)	455 (16)	
Average	5073 (44)	1188 (41)	2516 (44)	1369 (47)	
Inadequate	5193 (45)	1495 (52)	2629 (45)	1069 (37)	
Total stroke events, n (%)	1138 (9.8)	504 (17)	475 (8.2)	159 (5.5)	<0.001
Ischemic stroke events, n (%)	999 (8.6)	451 (16)	410 (7.1)	138 (4.8)	<0.001

ARIC indicates Atherosclerosis Risk In Communities; PRS, Polygenic risk score; Q1, 25th percentile; and Q3, 75th percentile.
*Kruskal-Wallis rank-sum test; Pearson's chi-square test.

Table 2. Relative Risk of All Stroke and Ischemic Stroke Among Genetic Risk and Life's Simple 7 Categories

	Stroke events	Median year to event	Model 1		Model 2	
			HR* (95% CI)	*P* value	HR* (95% CI)	*P* value
All stroke						
PRS						
High	504/2892	14	2.23 (1.97–2.53)	<0.0001	2.19 (1.93–2.49)	<0.0001
Intermediate	475/5783	18	Ref		Ref	
Low	159/2893	22	0.66 (0.55–0.79)	<0.0001	0.68 (0.56–0.81)	<0.0001
LS7						
Optimal	71/1302	22	0.76 (0.59–0.98)	0.0347	0.84 (0.65–1.08)	0.1734
Average	421/5073	19	Ref		Ref	
Inadequate	646/5193	14	1.37 (1.21–1.55)	<0.0001	1.29 (1.13–1.46)	<0.0001
Ischemic stroke						
PRS						
High	352/2229	14	2.30 (2.01–2.63)	<0.0001	2.25 (1.97–2.58)	<0.0001
Intermediate	264/4458	19	Ref		Ref	
Low	63/2230	22	0.66 (0.55–0.81)	<0.0001	0.68 (0.56–0.83)	<0.0001
LS7						
Optimal	54/1211	21	0.77 (0.59–1.02)	0.0663	0.85 (0.65–1.12)	0.2519
Average	284/4187	19	Ref		Ref	
Inadequate	341/3519	14	1.45 (1.27–1.66)	<0.0001	1.35 (1.18–1.55)	<0.0001

Model 1: adjusted for center, race, sex, education category, family history; Model 2: adjusted for center, race, sex, education category, family history and included both PRS and LS7. All models account for the competing risk of death. HR indicates hazard ratio; LS7, Life's simple 7; PRS, polygenic risk score; and Ref, reference.

*HR (95% CI) were calculated using Fine and Gray subdistribution hazard regression.

stroke across the LS7 categories were similar for all PRS categories (Figure 1) and there was no evidence of multiplicative interaction between the PRS and LS7 (*P*=0.37). When PRS was modeled as a continuous variable, it was associated with stroke with an HR of 1.6 (95% CI, 1.3–1.8) per SD (Table S3). Association analyses of PRS and LS7 with ischemic stroke produced slightly stronger effects but overall similar results to those for all stroke (Table 2; Figure 1).

Compared with an average LS7, an optimal LS7 was associated with a ≈25% lower risk of developing a stroke, whereas an inadequate LS7 was associated with a 30% higher risk (Table 2). Among individual LS7 factors, blood pressure and fasting blood glucose were most significantly associated with incident stroke. For example, compared with those in the intermediate blood pressure category, those in the ideal blood pressure category had a 21% lower risk of developing a stroke, and those in the poor blood pressure category had a 31% higher risk (Table S4). The associations of LS7 with ischemic stroke were similar to those with all stroke (Tables 2, S3 and S4).

Genetic Risk Score, LS7, and Remaining LTRS

The remaining LTRS at age 45 was 15% (95% CI, 13.7%–16.3%). Starting at age 45, participants with a high, intermediate, and low PRS had a remaining LTRS of 23.2% (95% CI, 20.8%–25.5%), 13.8% (95% CI, 11.7%–15.8%), and 9.6% (95% CI, 7.3%–11.8%), respectively (Figure 2A, Table S5). The remaining LTRS for participants with low and intermediate PRS stayed relatively constant throughout life. Although the remaining LTRS of participants with high PRS attenuated with advancing age, it remains higher than that of participants with intermediate and low PRS up to age 85. (Figure 2A).

Starting at age 45, participants with an inadequate, average, and optimal LS7 had a remaining LTRS of 17.6% (95% CI, 15.6%–19.6%), 13.4% (95% CI, 11.8%–15.1%), and 9.8% (95% CI, 7.1%–12.5%), respectively (Figure 2B, Table S6). The remaining LTRS stratified by LS7 decreased slightly with advancing age, but across all ages, the remaining LTRS was lowest for participants with optimal LS7 and highest among those with

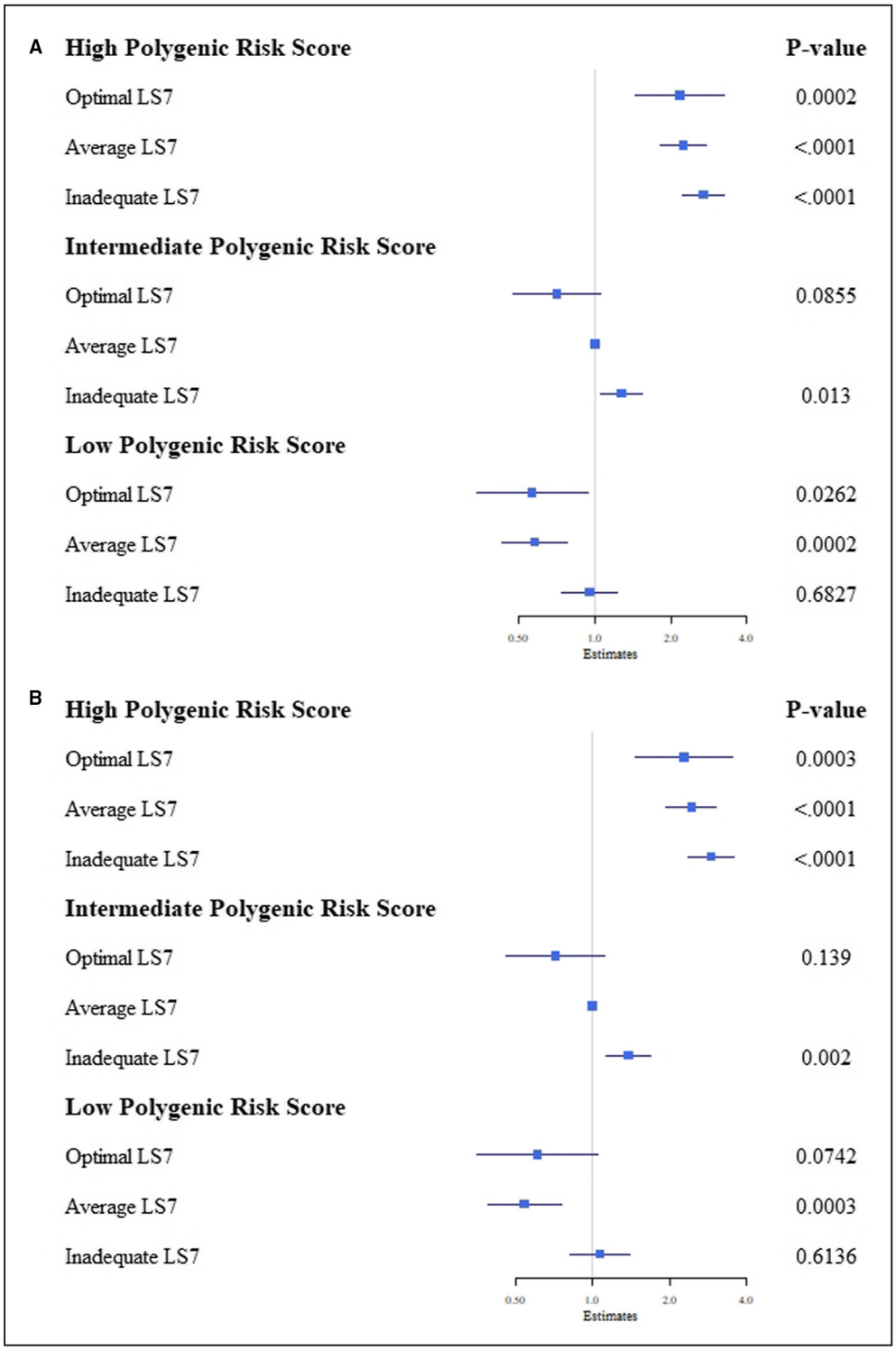

Figure 1. Relative risk of incident stroke by PRS and LS7 scores in the ARIC study.
Shown are the hazard ratios (95% CIs) for the incident stroke by PRS and LS7 categories, calculated accounting for the competing risk of death and adjusting for sex, race, center, and parental history of stroke. Intermediate PRS and average LS7 was used as the reference. (**A**) All stroke; (**B**) Ischemic stroke. ARIC indicates Atherosclerosis Risk In Communities; LS7, Life's Simple 7; and PRS, polygenic risk score.

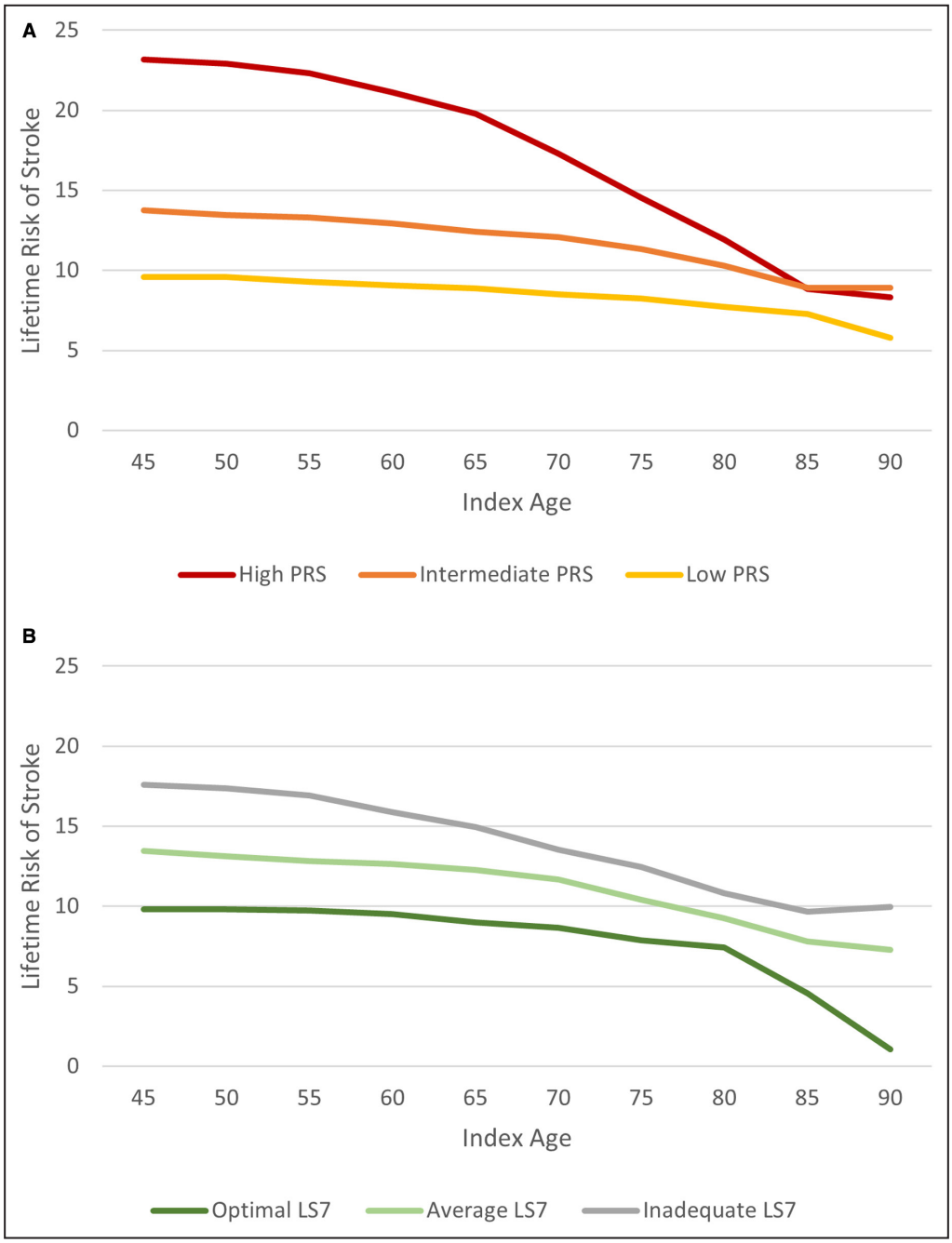

Figure 2. Remaining lifetime risk of stroke by PRS categories (A) and LS7 categories (B) conditional on surviving free of stroke to index age and adjusting for competing risk of death.
LS7 indicates Life's Simple 7; and PRS, polygenic risk score.

inadequate LS7 (Figure 2B). Among the 7 individual cardiovascular health factors, remaining LTRS was highest among individuals with hypertension (20.3%; 95% CI, 18.1%–22.4%) or diabetes (15.6%; 95% CI, 13.0%–18.3%) (Table S7). Stratification of individuals at low, intermediate, and high genetic risk by LS7 category revealed the highest remaining LTRS for individuals with an inadequate LS7 and a high genetic risk: 24.8% (95% CI, 22.0%–27.6%). Across all PRS categories, those with an optimal LS7 had a ≈30% to 43% lower LTRS than those with an inadequate LS7. For ischemic stroke, this reduction in lifetime risk was between 40% and 46% (Table 3). Stratification of individuals at low, intermediate, and high genetic risk by blood pressure category alone or blood glucose alone showed that for those with a high genetic risk, adherence to an optimal blood pressure or blood glucose reduced the LTRS by 43% and 28%, respectively. Overall, similar findings were observed for ischemic stroke (Table 3, Figure S1, Tables S6 and S7).

Table 3. Remaining Lifetime Risk of Stroke Across Genetic Risk and Life's Simple 7 Categories Conditional on Survival Free of Stroke to Age 45 Years

LS7	High PRS		Intermediate PRS		Low PRS	
	N event/total	CIF% (95% CI)	N event/total	CIF% (95% CI)	N event/total	CIF% (95% CI)
All stroke						
Optimal	27/209	17.27 (10.88–23.66)	28/638	9.00 (5.13–12.87)	16/455	7.48 (3.09–11.87)
Average	181/1188	21.93 (17.56–26.30)	182/2516	13.15 (10.59–15.71)	58/1369	7.06 (4.92–9.20)
Inadequate	296/1495	24.82 (22.05–27.59)	265/2629	14.99 (12.16–17.81)	85/1069	13.19 (8.91–17.48)
Ischemic stroke						
Optimal	23/209	13.78 (8.29–19.28)	23/638	7.15 (3.65–10.65)	14/455	6.79 (2.47–11.10)
Average	162/1188	19.45 (15.22–23.69)	150/2516	10.60 (8.41–12.79)	45/1369	5.89 (3.85–7.94)
Inadequate	266/1495	22.62 (19.89–25.34)	237/2629	13.33 (10.59–16.07)	79/1069	12.53 (8.25–16.82)

CIF indicates cumulative incidence function; LS7, Life's Simple 7; and PRS, polygenic risk score.

Genetic Risk Score, LS7, and Remaining LTRS by Sex

There were sex differences in LTRS by PRS category: In the high PRS category, men had a higher LTRS than women (25.1% versus 21.5%), whereas in the low PRS category, women had a higher LTRS than men (11.4% versus 7.3%). In the intermediate PRS category, men and women had a similar LTRS (14.0% and 13.9%, respectively). There were only minimal sex differences in LTRS by LS7 category. Similar findings were observed for ischemic stroke (Table S8).

Genetic Risk Score, LS7, and Mean Stroke-Free Years and Overall Survival

Participants with low PRS or optimal LS7 lived the longest and had the most years lived free of stroke or ischemic stroke. For example, starting from age 45, those with a high PRS lived ≈3 years less free of stroke than those with low PRS and those with inadequate LS7 lived ≈5 years less free of stroke than those with optimal LS7 (Table S9). In addition, those with a high PRS and an inadequate LS7 had the shortest overall survival (72.7±0.23 years) and the shortest survival free of stroke (66.7±0.24 years), whereas those with a low PRS and an optimal LS7 had the most extended overall survival and survival free of stroke (76.7±0.09 years and 74.1±0.27, respectively) (Table 4 and Figure S2).

Secondary Analyses on White Participants Only

Baseline characteristics are shown for White participants in Table S10. These differ significantly by genetic risk categories, except for current smoking. In this subsample, 770 experienced a stroke during the 215 375 person-years of follow-up: 77 (10%) in the low PRS group, 305 (39.6%) in the intermediate PRS group, and

Table 4. Overall Survival and Years Free of Stroke Across Genetic Risk and Life's Simple 7 Categories From Age 45 Years

LS7	PRS	All stroke		Ischemic stroke	
		Years free of stroke (RMST±SE)	Overall survival (RMST±SE)	Years free of stroke (RMST±SE)	Overall survival (RMST±SE)
Optimal	High	72.50±0.54	74.78±0.42	72.69±0.52	75.10±0.39
	Intermediate	73.98±0.24	76.47±0.12	74.01±0.24	76.54±0.11
	Low	74.12±0.27	76.68±0.09	74.14±0.27	76.71±0.08
Average	High	69.80±0.26	74.08±0.21	69.99±0.26	74.39±0.20
	Intermediate	71.53±0.16	75.89±0.09	71.61±0.16	76.10±0.08
	Low	71.92±0.20	76.41±0.08	71.96±0.20	76.54±0.07
Inadequate	High	66.75±0.24	72.67±0.23	66.92±0.24	73.12±0.22
	Intermediate	68.72±0.17	74.99±0.12	68.77±0.17	75.22±0.11
	Low	68.86±0.27	75.52±0.16	68.89±0.27	75.62±0.16

LS7 indicates Life's Simple 7; PRS, polygenic risk score; and RMST, restricted mean survival time.

388 (50.4%) in the high PRS group. In addition, participants with an inadequate LS7 experienced 377 stroke events (49%), and those with an optimal LS7 experienced 65 stroke events (8.4%).

The remaining LTRS at age 45 in White participants was 13.6% (95% CI, 12.1%–15.0%). Remaining lifetime risk estimates in White participants only were similar to those in the overall sample both across categories of PRS and across categories of LS7 (Table S11 and S12). As in the primary analysis, participants with an inadequate LS7 and a high genetic risk experienced the highest lifetime risk from age 45: 24.1% (95% CI, 20.9%–27.3%). Adhering to an optimal LS7 reduced this estimate to 17.6% (95% CI, 10.9%–24.3%) (Table S13), which corresponded to almost 6 additional years lived free of stroke or 2 additional years lived. Similar differences in years lived free of stroke and overall survival between optimal and inadequate LS7 were also observed for intermediate and low genetic risk categories (Table S14). Analyses of ischemic stroke showed similar results (Tables S11 through S14). As in the overall sample, we observed sex differences in LTRS by PRS category but not LS7 category. Similar results were observed for ischemic stroke (Table S15).

Genetic Risk Score and LTRS in Black Participants

Baseline characteristics are shown for Black participants in Table S16. In contrast to White participants, characteristics of Black participants did not significantly differ by genetic risk categories. Moreover, few Black participants experienced an optimal LS7 (3.4%) and the majority (63.1%) had an inadequate LS7. In Black participants, the remaining LTRS at age 45 was 19.7% (95% CI, 17.1%–22.3%). Participants with a high PRS had a remaining LTRS of 22.9% (95% CI, 18.4%–27.3%), similar to that of White participants with a high PRS. However, the LTRS did not differ markedly across PRS categories in this subgroup (Table S17). Similar results were observed for ischemic stroke.

Association of the PRS With Incident Stroke by Race

Compared with participants with an intermediate PRS, Black participants with a high PRS had a 1.4-fold greater risk of developing a stroke (P=0.01), whereas there was no significant difference in stroke incidence for those with a low PRS. In contrast, White participants with a high PRS had a 2.7-fold greater risk of developing a stroke (P<0.0001), whereas those with a low PRS had half the risk of developing a stroke (HR, 0.50; P<0.0001) (Table S18). Adjusting for established risk factors individually also showed similar associations (Table S19). For all PRS categories, the differences in HR for incident stroke across the LS7 categories were similar in Black and White participants (Figures S3 and S4), and there was no evidence of multiplicative interaction between the PRS and LS7 in either group (Black participants: P=0.63; White participants: P=0.83). When PRS was modeled as a continuous variable, it was associated with stroke with an HR of 1.14 (95% CI, 1.01–1.27) per SD in Black participants and 1.67 (95% CI, 1.57–1.79) in White participants (Table S20). Association analyses of PRS with ischemic stroke produced similar results (Tables S18 through S20).

We also evaluated the PRS's predictive strength by comparing the improvement in c-statistics from a model including the PRS (full model) over that including covariates only (partial model). A comparable AUC for the partial model was observed for Black and White participants ($AUC_{partial}$=60.9% and 58.7%, respectively). However, there was a significant improvement in the c-statistic (ΔAUC) for the PRS in White (AUC_{full}=69.1%, ΔAUC=10.4%; P=1.4×10^{-23}) but not in Black participants (AUC_{full}=61.9%, ΔAUC=1.0%; P=0.09) (Figure S5). Similar results were obtained for ischemic stroke (Table S21) and with a partial model that included established risk factors individually instead of LS7 (not shown). For all stroke, the AUC of the PRS only was 54.5% in Black and 66.7% in White participants. For ischemic stroke, it was 53.7% and 67.4%, respectively.

DISCUSSION

In this community-based study of middle-aged White and Black adults over the age of 45 years, we estimated that almost 1 in 7 individuals will experience a stroke event in their lifetime. However, for those with high genetic risk and inadequate cardiovascular health, this estimate rose to 1 in 4. These individuals also had the shortest overall survival and survival free of stroke, and those with a low genetic risk and an optimal cardiovascular health had the longest. Maintenance of a healthy lifestyle through adherence to the LS7 recommendations mitigated a high PRS-associated LTRS by up to 43%, which corresponds to up to almost 6 more years lived free of stroke.

Communicating risk is a key component of primary prevention of cardiovascular disease, including stroke. By accounting for competing causes of death, lifetime risk estimates provide more accurate evaluations of long-term absolute probabilities of disease, which are more easily interpreted by both physicians and patients.[22] Our estimate of overall LTRS was similar to that of other studies,[2,23] but, for the first time, we also investigated whether genetic information and cardiovascular health has an impact on LTRS and years lived free of the disease. Our data show that a high genetic burden

and a poor cardiovascular health negatively influence stroke risk. The benefit of a healthy lifestyle in reducing stroke risk is well documented.[7,24–26] Maintaining an optimal cardiovascular health was associated with a substantially lower relative risk and lower LTRS from midlife. Maintaining an ideal blood pressure and an ideal blood glucose level had the strongest association with relative risk and LTRS. Although the LTRS was higher for those with high genetic risk than those with low genetic risk, a reduction in lifetime risk associated with adhering to an optimal midlife LS7 was observed across all genetic risk categories. This finding underscores the benefit of maintaining an optimal cardiovascular health for all, independent of genetic risk. It also strengthens the notion, also demonstrated by others, that intervention on modifiable risk factors can mitigate the increased genetic risk of stroke and other cardiovascular disease.[10,27,28]

It further illustrates the potential of genetic information to identify high-risk individuals, who would most benefit from intensive lifestyle modification, presumably early in life, when conventional clinical risk factors are not yet informative.

Our findings are also broadly consistent with multiple studies of varying study design that reported polygenic risk scores as independent risk factors for stroke beyond clinical risk factors.[10,11,29] For example, in the UK Biobank, the PRS was associated with a 26% greater risk of incident ischemic stroke per SD.[11] In a population of older healthy individuals, this estimate was 41%.[29] Both studies included individuals of European ancestry only, and, to date, there is little information about the predictive value of the PRS in populations of diverse ancestry. In our cohort of Black and White participants, the PRS was significantly associated with a higher risk of incident ischemic stroke in both groups, but the magnitude of the association was far weaker in Black than in White participants (13% versus 55% per SD). This may be explained by a difference in the performance of the PRS between the 2 groups. Indeed, contrary to White participants, in Black participants, the PRS did not improve stroke prediction over conventional risk factors. Previous studies have consistently reported a poorer predictive power of polygenic risk scores in non-European populations, particularly among individuals of African ancestry.[30,31] In addition, the performance of the PRS has been shown to vary among stroke subtypes with a poorer performance for small vessel stroke. Racial and ethnic differences in stroke subtype distribution are also well documented, with individuals of African ancestry having an excess of small vessel strokes.[32,33] The disparity in the stroke PRS performance between White and Black participants highlights the need for genetic investigations in diverse and underrepresented populations. Although efforts to expand gene discovery for stroke in more diverse populations are increasing,[9,34] additional progress must be made to achieve an equitable deployment and use of genetic risk scores in clinical applications so as not to exacerbate existing health disparities.[31]

Our study has several limitations. First, as previously discussed, the performance of the stroke polygenic risk score used here remains suboptimal, owing to the lack of diversity and rather limited sample size of current genome-wide association studies for stroke and stroke subtypes. It is likely that as stroke genetic discoveries progress, the predictive power of the next generation of PRS will increase. Second, the stroke PRS implemented in this study was defined based on genetic factors associated with stroke and stroke-related traits, some of which likely also influence LS7 status. Hence, ideal cardiovascular health may have been harder to achieve in people with high PRS, thereby possibly dampening the estimated effects of maintaining an optimal cardiovascular health on remaining lifetime risk in those at high genetic risk. Third, our sample size did not allow us to examine more extreme thresholds of the PRS where the risk of disease is the greatest.[11] Moreover, although we describe sex differences in remaining LTRS by PRS category, these results will need to be independently confirmed given the small number of events in the sex-stratified sample. Fourth, our study included adults followed from middle age and lifetime risk were estimated for individuals aged 45 to 85 years. Although most strokes occur after age 45, the value of genetic information for lifetime risk estimation may be at earlier ages when clinical risk factors are not yet apparent. Finally, LS7 was measured at the baseline examination only. Changes in lifestyle or vascular health that may have occurred in the follow-up period have not been considered and may have affected the precision of risk estimates.

CONCLUSIONS

In conclusion, in this prospective diverse cohort of middle-aged adults, the LTRS varied substantially by levels of polygenic risk and cardiovascular health based on the American Heart Association's LS7 recommendations. Maintaining an optimal cardiovascular health was associated with the lowest lifetime risk estimates, emphasizing the importance of modifiable risk factors in prevention efforts to reduce stroke risk for all. Considerable improvements to the stroke PRS are needed before clinical utility can be achieved, especially for minority populations, which are typically underrepresented in genome-wide association studies. However, studies such as ours lay the groundwork toward realizing the potential of personalizing genetic risk information to motivate lifestyle and vascular health changes and prevent stroke.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S21
Figures S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Definition of LS7 categories assessed at the baseline exam.

Component	Category	Points	Definition
Total cholesterol			
	Ideal	2	<200 mg/dl, without lipid lowering medication
	Intermediate	1	200-239 mg/dl or treated to goal
	Poor	0	≥240 mg/dl
Blood Pressure			
	Ideal	2	<120/<80 mm Hg, without antihypertensive medication
	Intermediate	1	SBP 120 – 139 or DBP 80 – 89 mm Hg or treated with antihypertensive to goal
	Poor	0	SBP ≥140 or DBP ≥90 mm Hg
Glucose			
	Ideal	2	<100 mg/dl, without anti-diabetes treatment
	Intermediate	1	100 – 125 mg/dl or treated with anti-diabetes to goal
	Poor	0	≥126 mg/d
Smoking			
	Ideal	2	Never or quit >12 months
	Intermediate	1	Former smoker and quit ≤12 months ago
	Poor	0	Current
Body Mass Index			
	Ideal	2	<25 kg/m 2
	Intermediate	1	25 – <30 kg/m 2
	Poor	0	≥30 kg/m 2
Diet[#]			
	Ideal	2	4 – 5 components
	Intermediate	1	2 -3 components
	Poor	0	0-1 components
Physical Activity			
	Ideal	2	≥150 minutes/week
	Intermediate	1	1 to 149 minutes/week
	Poor	0	None

[#] Derived from the food frequency questionnaire based on 5 healthy diet components, each worth 1 point: (1) fruits and vegetables: ≥4.5 servings per day; (2) fish: ≥2 3.5 oz of servings per week; (3) fiber-rich whole grains (>1 g of fiber per 10 g of carbohydrate): ≥3 1 oz equivalent servings per day; (4) sodium: <1500 mg per day; and (5) sugar-sweetened foods and beverages: ≤450 kcal (36 oz) per week.

Table S2. Association of PRS categories with incident all strokes and ischemic stroke adjusting for conventional risk factors

		Model 1 adjusted for individual conventional risk factors	
	PRS	**HR[#]**	**P- value**
All Stroke	**High**	2.17 (1.91-2.47)	<.0001
	Low	0.68 (0.56-0.81)	<.0001
	Intermediate	Ref	Ref
Ischemic Stroke	**High**	2.23 (1.95-2.56)	<.0001
	Low	0.68 (0.56-0.83)	0.0002
	Intermediate	Ref	Ref

[#] Adjusted for Center, Race, Sex, Education category, Family history, BMI, Smoking, SBP, Total cholesterol, Diabetes, Hypertension. Model accounts for the competing risk of death.

HR (95% CI) were calculated using Fine and Gray sub-distribution hazard

HR: Hazard ratio; CI: Confidence interval; PRS: Polygenic risk score; Ref: Reference

Table S3. Association of incident all stroke and ischemic stroke with PRS, LS7 score, and their interaction. PRS and LS7 are modeled on the continuous scale

		Model 1		Model 2	
		HR*	**P- value**	**HR***	**P- value**
All stroke	**LS7 score**	0.88 (0.84-0.92)	<.0001	0.87 (0.82-0.92)	<.0001
	PRS	1.67 (1.57-1.79)	<.0001	1.56 (1.35-1.80)	<.0001
	LS7 score × PRS	-	-	1.03 (0.98-1.09)	0.28
Ischemic stroke	**LS7 score**	0.87 (0.82-0.91)	<.0001	0.85 (0.80-0.90)	<.0001
	PRS	1.72 (1.60-1.84)	<.0001	1.55 (1.33-1.81)	<.0001
	LS7 score × PRS	-	-	1.04 (0.98-1.11)	0.15

Model 1: adjusted for center, race, sex, education category, family history; Model 2: adjusted for center, race, sex, education category, family history and included both PRS and LS7. All models account for the competing risk of death.

* HR (95% CI) were calculated using Fine and Gray sub-distribution hazard regression

HR: Hazard ratio; CI: Confidence interval; PRS: Polygenic risk score; LS7: Life's simple 7; Ref: Reference

Table S4. Association of individual LS7 health factors with Incident stroke and ischemic stroke

	All-stroke		Ischemic stroke	
LS7 Health factor	**HR[#]**	**P- value**	**HR[#]**	**P- value**
Glucose				
Ideal	0.97 (0.84-1.10)	0.61	0.92 (0.80-1.07)	0.27
Intermediate	Ref	Ref	Ref	Ref
Poor	1.56 (1.31-1.86)	<.0001	1.64 (1.36-1.97)	<.0001
Total Cholesterol				
Ideal	0.99 (0.86-1.14)	0.89	1.01 (0.86-1.17)	0.94
Intermediate	Ref	Ref	Ref	Ref
Poor	1.00 (0.87-1.16)	0.98	1.04 (0.89-1.21)	0.62
Blood Pressure				
Ideal	0.79 (0.68-0.92)	0.003	0.80 (0.68-0.94)	0.008
Intermediate	Ref	Ref	Ref	Ref
Poor	1.31 (1.14-1.51)	0.0002	1.32 (1.14-1.53)	0.0003
BMI				
Ideal	0.93 (0.80-1.08)	0.32	0.88 (0.75-1.03)	0.11
Intermediate	Ref	Ref	Ref	Ref
Poor	0.96 (0.83-1.10)	0.53	0.99 (0.85-1.15)	0.88
Physical activity				
Ideal	0.96 (0.82-1.12)	0.58	0.97 (0.82-1.15)	0.76
Intermediate	Ref	Ref	Ref	Ref
Poor	0.98 (0.83-1.14)	0.76	0.97 (0.82-1.15)	0.73
Diet				
Ideal	1.10 (0.84-1.44)	0.47	1.11 (0.84-1.48)	0.46
Intermediate	Ref	Ref	Ref	Ref
Poor	1.08 (0.95-1.24)	0.23	1.04 (0.90-1.20)	0.59
Smoking				
Ideal	0.88 (0.62-1.24)	0.47	1.04 (0.70-1.54)	0.84
Intermediate	Ref	Ref	Ref	Ref
Poor	1.17 (0.82-1.67)	0.38	1.40 (0.94-2.09)	0.1

HR (95% CI) were calculated using Fine and Gray sub-distribution hazard regression
Model accounts for the competing risk of death and adjusts for Center, Race, Sex, Education category, Family history, PRS, and all other LS7 factors

Table S5. Lifetime risk estimates for all stroke and ischemic stroke by PRS category at selected index age*

	Index age	% (95% CI)		
		High PRS	**Intermediate PRS**	**Low PRS**
All stroke	45	23.17 (20.82-25.53)	13.77 (11.71-15.84)	9.57 (7.34-11.79)
	55	22.33 (19.99-24.67)	13.30 (11.25-15.34)	9.29 (7.07-11.51)
	65	19.80 (17.31-22.29)	12.43 (10.28-14.58)	8.89 (6.57-11.21)
	75	14.55 (11.59-17.51)	11.32 (8.80-13.84)	8.26 (5.65-10.88)
	85	8.83 (4.56-13.10)	8.91 (5.30-12.52)	7.29 (3.70-10.87)
Ischemic stroke	45	20.80 (18.50-23.10)	11.77 (9.80-13.74)	8.67 (6.46-10.87)
	55	20.12 (17.82-22.41)	11.74 (9.75-13.73)	8.39 (6.19-10.59)
	65	18.08 (15.65-20.51)	11.07 (8.98-13.17)	8.03 (5.73-10.33)
	75	13.27 (10.38-16.15)	10.10 (7.65-12.55)	7.64 (5.05-10.24)
	85	8.13 (3.97-12.29)	8.13 (4.61-11.65)	7.00 (3.43-10.57)

* Lifetime risk estimates represent the percentage of participants who would experience a stroke from the index age to the end of follow-up if the last participant in the cohort were to die at the last age of follow-up (90 years)

PRS: Polygenic risk score; CI: confidence interval

Table S6. Remaining lifetime risk estimates for all stroke and ischemic stroke by LS7 category at selected index age*

	Index age	% (95% CI)		
		Optimal LS7	**Average LS7**	**Inadequate LS7**
All stroke	45	9.82 (7.13-12.51)	13.44 (11.76-15.11)	17.58 (15.60-19.57)
	55	9.73 (7.04-12.43)	12.84 (11.22-14.46)	16.93 (14.95-18.90)
	65	8.99 (6.28-11.70)	12.26 (10.59-13.94)	14.93 (12.80-17.06)
	75	7.87 (5.04-10.71)	10.42 (8.55-12.29)	12.45 (9.81-15.10)
	85	4.55 (1.51-7.60)	7.81 (5.36-10.26)	9.65 (5.41-13.89)
Ischemic stroke	45	8.15 (5.64-10.67)	11.28 (9.76-12.81)	15.96 (14.01-17.91)
	55	8.06 (5.55-10.57)	11.04 (9.52-12.56)	15.59 (13.63-17.55)
	65	7.46 (4.94-9.99)	10.69 (9.11-12.26)	13.92 (11.80-16.04)
	75	6.24 (3.60-8.87)	9.07 (7.32-10.82)	11.85 (9.22-14.49)
	85	3.79 (0.93-6.66)	6.87 (4.58-9.16)	9.53 (5.30-13.76)

* Lifetime risk estimates represent the percentage of participants who would experience a stroke from the index age
LS7: Life's Simple 7; CI: confidence interval

Table S7. Remaining lifetime risk estimate of stroke and ischemic stroke by individual LS7 factor

	Lifetime Risk (%) (95% CI)*	
Life's simple 7 factors	**All stroke**	**Ischemic stroke**
Blood glucose		
Ideal	13.35 (11.80-14.89)	11.22 (9.77-12.66)
Intermediate	15.69 (13.04-18.34)	14.09 (11.50-16.68)
Poor	21.77 (18.74-24.80)	20.62 (17.64-23.61)
Total Cholesterol		
Ideal	13.58 (11.83-15.33)	11.98 (10.27-13.69)
Intermediate	15.77 (13.34-18.20)	13.45 (11.17-15.73)
Poor	15.57 (13.50-17.65)	14.18 (12.14-16.22)
Blood Pressure		
Ideal	11.20 (9.41-12.98)	9.67 (7.97-11.36)
Intermediate	15.81 (13.31-18.31)	14.13 (11.64-16.62)
Poor	20.27 (18.13-22.40)	17.65 (15.79-19.51)
BMI		
Ideal	12.34 (10.00-14.68)	10.36 (8.07-12.66)
Intermediate	16.10 (13.99-18.20)	14.04 (12.07-16.00)
Poor	16.62 (14.63-18.61)	15.35 (13.39-17.30)
Physical activity		
Ideal	13.96 (12.16-15.77)	12.12 (10.49-13.75)
Intermediate	14.45 (11.79-17.12)	12.78 (10.16-15.41)
Poor	16.36 (14.16-18.57)	14.50 (12.33-16.66)
Diet		
Ideal	13.50 (10.07-16.93)	11.78 (8.54-15.02)
Intermediate	14.22 (12.91-15.52)	12.49 (11.29-13.69)
Poor	18.11 (14.02-22.19)	16.13 (12.03-20.23)
Smoking		
Ideal	14.71 (13.20-16.21)	12.96 (11.53-14.39)
Intermediate	12.63 (8.42-16.83)	9.61 (5.89-13.33)
Poor	16.30 (13.28-19.32)	14.44 (11.43-17.44)

*from age 45

Table S8. Remaining lifetime risk estimates* for all stroke and ischemic stroke by PRS category or by LS7 category in men and women. Shown are cumulative incidence function (%) and 95% confidence intervals

	All stroke				Ischemic stroke			
	N events/total	Men	N events/total	Women	N events/total	Men	N events/total	Women
High PRS	262/1305	25.13 (21.61-28.65)	242/1587	21.47 (18.53-24.40)	239/1211	23.06 (19.60-26.53)	212/1587	18.86 (16.04-21.69)
Intermediate PRS	219/2523	14.03 (11.48-16.58)	256/3260	13.89 (10.34-17.44)	200/2036	11.75 (9.64-13.86)	210/3260	12.08 (8.54-15.63)
Low PRS	58/1315	7.28 (5.18-9.39)	101/1578	11.37 (7.76-14.98)	53/2013	6.72 (4.66-8.77)	85/1578	10.23 (6.64-13.82)
Optimal LS7	27/454	9.44 (5.57-13.31)	44/848	10.16 (6.40-13.91)	23/454	7.57 (4.14-11.01)	36/848	8.65 (5.05-12.25)
Average LS7	204/2235	14.64 (11.87-17.41)	217/2838	12.24 (10.40-14.09)	179/2235	12.17 (9.77-14.56)	178/2838	10.38 (8.62-12.13)
Inadequate LS7	308/2454	16.43 (14.44-18.41)	338/2739	18.50 (15.31-21.68)	290/2571	15.25 (13.39-17.11)	292/2739	16.49 (13.32-19.65)

*from age 45

Table S9. Restricted mean survival time for all stroke and ischemic stroke by PRS or LS7 categories

	All stroke		Ischemic stroke	
	Years free of stroke (RMST±SE) *	**Overall Survival (RMST±SE) ***	**Years free of stroke (RMST±SE) ***	**Overall Survival (RMST±SE) ***
PRS				
High	68.45 ± 0.17	73.49 ± 0.15	68.63 ± 0.17	73.87 ± 0.14
Intermediate	70.56 ± 0.11	75.63 ± 0.07	70.62 ± 0.11	75.84 ± 0.06
Low	71.19 ± 0.15	76.23 ± 0.07	71.22 ± 0.15	76.33 ± 0.07
LS7				
Optimal	73.84 ± 0.17	76.33 ± 0.10	73.89 ± 0.17	76.43 ± 0.09
Average	71.26 ± 0.11	75.66 ± 0.07	71.35 ± 0.11	75.88 ± 0.06
Inadequate	68.20 ± 0.13	74.49 ± 0.10	68.28 ± 0.13	74.75 ± 0.09

* from age 45 years

RMST: Restricted mean survival time; SE: Standard error; PRS: Polygenic risk score; LS7: Life's simple 7

Table S10. Baseline characteristics of ARIC white participants by genetic risk score category and overall

Baseline Characteristics	Overall	High PRS	Intermediate PRS	Low PRS	p-value*
	N = 8,917	N = 2,229	N = 4,458	N = 2,230	
Age, median (Q1, Q3)	54 (49, 59)	54 (50, 59)	54 (49, 59)	55 (49, 60)	<0.001
Female, n (%)	4,738 (53)	1,174 (53)	2,421 (54)	1,143 (51)	0.055
Education Category					<0.001
Less than high school	1,384 (16)	359 (16)	684 (15)	341 (15)	
High school graduate or vocational school	4,043 (45)	1,089 (49)	2,046 (46)	908 (41)	
At least some college or professional school	3,490 (39)	781 (35)	1,728 (39)	981 (44)	
Parental History of stroke, n (%)	2,651 (30)	734 (33)	1,300 (29)	617 (28)	<0.001
BMI, median (Q1, Q3)	26.3 (23.6, 29.5)	27.1 (24.2, 30.5)	26.2 (23.6, 29.4)	25.7 (23.1, 28.5)	<0.001
Hypertension, n (%)	2,327 (26)	836 (38)	1,107 (25)	384 (17)	<0.001
Diabetes, n (%)	739 (8.3)	240 (11)	351 (7.9)	148 (6.7)	<0.001
Total cholesterol (mmol/L), median (Q1, Q3)	5.48 (4.84, 6.18)	5.72 (5.02, 6.41)	5.51 (4.89, 6.15)	5.25 (4.58, 5.90)	<0.001
Current Smoking, n (%)	2,182 (24)	549 (25)	1,105 (25)	528 (24)	0.6
Systolic BP (mm Hg), median (Q1, Q3)	116 (106, 128)	121 (110, 133)	117 (106, 128)	112 (103, 124)	<0.001
Life's simple 7, n (%)					<0.001
Optimal	1,211 (14)	192 (8.6)	591 (13)	428 (19)	
Average	4,187 (47)	965 (43)	2,080 (47)	1,142 (51)	
Inadequate	3,519 (39)	1,072 (48)	1,787 (40)	660 (30)	
Total stroke events, n (%)	770 (8.6)	388 (17)	305 (6.8)	77 (3.5)	<0.001
Ischemic stroke events, n (%)	679 (7.6)	352 (16)	264 (5.9)	63 (2.8)	<0.001

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test; PRS: Polygenic risk score; Q1: 25th percentile; Q3: 75th percentile; BMI: Body mass index; BP: Blood pressure

Table S11. Lifetime risk estimates for all stroke and ischemic stroke by PRS category at selected index age in the subgroup of white participants*

	Index Age	High PRS	Intermediate PRS	Low PRS
All Strokes	45	23.32 (20.55-26.09)	12.21 (9.88-14.53)	6.72 (4.50-8.93)
	55	22.24 (19.51-24.97)	12.16 (9.82-14.50)	6.73 (4.51-8.95)
	65	20.30 (17.42-23.19)	11.92 (9.47-14.36)	6.85 (4.54-9.16)
	75	14.99 (11.56-18.43)	11.33 (8.52-14.14)	6.96 (4.39-9.53)
	85	8.49 (3.62-13.36)	9.32 (5.33-13.30)	6.34 (2.87-9.82)
Ischemic Strokes	45	21.17 (18.47-23.87)	10.64 (8.39-12.90)	5.90 (3.71-8.08)
	55	20.34 (17.66-23.02)	10.67 (8.40-12.94)	5.91 (3.72-8.10)
	65	18.66 (15.84-21.49)	10.54 (8.16-12.92)	6.05 (3.77-8.33)
	75	13.81 (10.47-17.16)	9.94 (7.22-12.67)	6.26 (3.72-8.80)
	85	7.89 (3.15-12.64)	8.42 (4.55-12.29)	6.00 (2.56-9.45)

* Lifetime risk estimates represent the percentage of participants who would experience a stroke from the index age to the end of follow-up if the last participant in the cohort were to die at the last age of follow-up (90 years)

PRS: Polygenic risk score; CI: confidence interval

Table S12. Lifetime risk estimates for all stroke and ischemic stroke by LS7 category at selected index age in the subgroup of white participants*

	Index Age	Optimal LS7	Average LS7	Inadequate LS7
All Strokes	45	9.60 (6.87-12.34)	12.86 (11.09-14.64)	15.13 (12.94-17.33)
	55	9.49 (6.76-12.23)	12.43 (10.68-14.19)	14.78 (12.59-16.97)
	65	8.73 (5.98-11.48)	12.05 (10.24-13.86)	13.82 (11.48-16.16)
	75	7.71 (4.84-10.58)	10.57 (8.56-12.58)	11.68 (8.84-14.52)
	85	4.34 (1.29-7.39)	7.99 (5.37-10.61)	9.00 (4.49-13.50)
Ischemic Strokes	45	7.86 (5.31-10.40)	11.07 (9.41-12.72)	13.94 (11.76-16.12)
	55	7.74 (5.20-10.28)	10.84 (9.19-12.49)	13.64 (11.46-15.81)
	65	7.15 (4.59-9.70)	10.55 (8.85-12.25)	12.87 (10.55-15.20)
	75	6.01 (3.37-8.66)	9.17 (7.29-11.05)	11.06 (8.24-13.88)
	85	3.56 (0.70-6.42)	7.04 (4.60-9.48)	8.85 (4.36-13.34)

* Lifetime risk estimates represent the percentage of participants who would experience a stroke from the index age to the end of follow-up if the last participant in the cohort were to die at the last age of follow-up (90 years)

LS7: Life's Simple 7; CI: confidence interval

Table S13. Remaining lifetime risk of stroke across genetic risk and Life's Simple 7 categories conditional on survival free of stroke to age 45 in the subgroup of white participants

	LS7	High PRS		Intermediate PRS		Low PRS	
		N event/total	CIF% (95% CI)	N event/total	CIF% (95% CI)	N event/total	CIF% (95% CI)
All strokes	Optimal	25/192	17.6 (10.89-24.31)	26/591	8.82 (4.87-12.78)	14/428	7.05 (2.65-11.44)
	Average	154/965	23.16 (18.26-28.05)	137/2080	12.35 (9.64-15.06)	37/1142	5.7 (3.64-7.76)
	Inadequate	209/1072	24.15 (20.95-27.34)	142/1787	12.22 (9.02-15.43)	26/660	7.13 (3.22-11.05)
Ischemic strokes	Optimal	21/192	13.89 (8.12-19.65)	21/591	6.88 (3.33-10.42)	12/428	6.33 (2.02-10.64)
	Average	139/965	20.67 (15.93-25.40)	117/2080	10.42 (7.99-12.86)	28/1142	4.67 (2.72-6.62)
	Inadequate	192/1072	22.49 (19.34-25.65)	126/1787	11.08 (7.91-14.25)	23/660	6.6 (2.71-10.49)

CIF: Cumulative incidence function; CI: Confidence interval; PRS: Polygenic risk score; LS7: Life's simple 7

Table S14. Overall survival and years free of stroke across genetic risk and Life's Simple 7 categories from age 45 in the subgroup of white participants

		All stroke		Ischemic stroke	
LS7	**PRS**	**Years free of stroke (RMST±SE)**	**Overall Survival (RMST±SE)**	**Years free of stroke (RMST±SE)**	**Overall Survival (RMST±SE)**
Optimal	**High**	75.77 ± 0.54	77.77 ± 0.45	75.97 ± 0.52	78.12 ± 0.41
	Intermediate	76.99 ± 0.25	79.46 ± 0.12	77.02 ± 0.25	79.55 ± 0.11
	Low	77.20 ± 0.27	79.71 ± 0.08	77.23 ± 0.27	79.74 ± 0.08
Average	**High**	72.58 ± 0.29	76.91 ± 0.24	72.78 ± 0.29	77.21 ± 0.23
	Intermediate	74.84 ± 0.17	79.09 ± 0.08	74.88 ± 0.17	79.22 ± 0.08
	Low	75.06 ± 0.21	79.63 ± 0.06	75.11 ± 0.21	79.73 ± 0.05
Inadequate	**High**	69.90 ± 0.29	75.79 ± 0.27	70.01 ± 0.28	76.15 ± 0.26
	Intermediate	72.25 ± 0.20	78.54 ± 0.12	72.29 ± 0.20	78.71 ± 0.12
	Low	72.31 ± 0.34	79.45 ± 0.10	72.33 ± 0.34	79.52 ± 0.09

RMST: Restricted mean survival time; SE: Standard error; PRS: Polygenic risk score; LS7: Life's simple 7

Table S15. Remaining lifetime risk estimates* for all stroke and ischemic stroke by PRS category or by LS7 category in white men and women. Shown are cumulative incidence function (%) and 95% confidence intervals

	All stroke				Ischemic stroke			
	N events/total	Men	N events/total	Women	N events/total	Men	N events/total	Women
High PRS	216/1055	25.92 (21.95-29.90)	172/1174	20.84 (17.43-24.25)	196/1055	23.66 (19.75-27.56)	156/1174	18.81 (15.54-22.09)
Intermediate PRS	142/2037	11.74 (9.13-14.35)	163/2461	12.92 (8.71-17.13)	132/2037	10.38 (8.02-12.74)	132/2421	11.23 (7.02-15.43)
Low PRS	35/1087	5.15 (3.34-6.95)	42/1143	8.08 (4.29-11.88)	30/1087	4.46 (2.76-6.17)	33/1143	7.17 (3.40-10.93)
Optimal LS7	25/422	9.22 (5.28-13.15)	40/789	9.97 (6.14-13.79)	21/422	7.24 (3.79-10.69)	33/789	8.38 (4.73-12.04)
Average LS7	163/1893	13.73 (10.94-16.51)	165/2294	11.91 (9.85-13.96)	145/1893	11.84 (9.26-14.42)	139/2294	10.29 (8.32-12.25)
Inadequate LS7	205/1864	14.11 (12.05-16.17)	172/1655	15.86 (12.21-19.51)	192/1864	13.35 (11.32-15.38)	149/1655	14.20 (10.58-17.82)

*from age 45

Table S16. Baseline characteristics of ARIC African-American participants by genetic risk score category and overall

Baseline Characteristics	Overall	High PRS	Intermediate PRS	Low PRS	p-value*
	N=2,651	N = 663	N = 1,325	N = 663	
Age, median (Q1, Q3)	53 (48, 58)	52 (48, 58)	53 (48, 58)	53 (48, 58)	0.4
Female, n (%)	1,687 (64)	413 (62)	839 (63)	435 (66)	0.4
Education Category					0.087
Less than high school	1,063 (40)	291 (44)	531 (40)	241 (36)	
High school graduate or vocational school	736 (28)	174 (26)	371 (28)	191 (29)	
At least some college or professional school	852 (32)	198 (30)	423 (32)	231 (35)	
Parental History of stroke, n (%)	721 (27)	183 (28)	362 (27)	176 (27)	>0.9
BMI, median (Q1, Q3)	28.8 (25.6, 32.8)	29 (25.5, 33.3)	28.8 (25.6, 32.6)	28.8 (25.7, 32.6)	0.8
Hypertension, n (%)	1,468 (55)	366 (55)	744 (56)	358 (54)	0.6
Diabetes, n (%)	487 (19)	123 (19)	247 (19)	117 (18)	0.9
Total cholesterol (mmol/L), median (Q1, Q3)	5.48 (4.78, 6.28)	5.56 (4.78, 6.26)	5.4 (4.78, 6.31)	5.48 (4.78, 6.31)	0.7
Current Smoking, n (%)	758 (29)	197 (30)	387 (29)	174 (26)	0.3
SBP (mm Hg), median (Q1, Q3)	125 (114, 139)	126 (114, 140)	125 (113, 140)	125 (114, 138)	0.7
Life's simple 7, n (%)					0.6
Optimal	91 (3.4)	17 (2.6)	47 (3.5)	27 (4.1)	
Average	886 (33)	223 (34)	436 (33)	227 (34)	
Inadequate	1,674 (63)	423 (64)	842 (64)	409 (62)	
Total stroke events, n (%)	368 (14)	116 (17)	170 (13)	82 (12)	0.008
Ischemic stroke events, n (%)	320 (12)	99 (15)	146 (11)	75 (11)	0.032

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test; PRS: Polygenic risk score; Q1: 25th percentile; Q3: 75th percentile; BMI: Body mass index; BP: Blood pressure

Table S17. Remaining lifetime risk of stroke and ischemic stroke by polygenic risk score categories, conditional on survival free of stroke to age 45, in African-Americans.

PRS	All stroke		Ischemic stroke	
	N event/ total	CIF% (95% CI)	N event/ total	CIF% (95% CI)
High	99/663	22.87 (18.40-27.35)	116/663	19.74 (15.39-24.10)
Intermediate	146/1325	18.24 (14.38-22.10)	170/1325	15.20 (11.65-18.75)
Low	75/663	19.29 (14.05-24.53)	82/663	18.20 (12.98-23.41)

Table S18. Relative risk of all stroke and ischemic stroke among genetic risk and Life's Simple 7 categories in African-Americans and white participants

				Stroke Events	Median Year to Event	Model 1		Model 2	
						HR* (95% CI)	P- value	HR* (95% CI)	P- value
African-Americans	All stroke	PRS	High	116/663	12	1.37 (1.07-1.74)	0.0108	1.37 (1.08-1.74)	0.0106
			Low	82/663	16	0.98 (0.75-1.27)	0.8738	0.98 (0.76-1.28)	0.9
			Intermediate	170/1325	13	Ref		Ref	
		LS7	Optimal	6/91	20	0.68 (0.30-1.54)	0.3571	0.69 (0.31-1.56)	0.376
			Inadequate	269/1674	12	1.49 (1.17-1.89)	0.001	1.49 (1.18-1.89)	0.001
			Average	93/886	15	Ref		Ref	
	Ischemic stroke	PRS	High	99/663	13	1.35 (1.04-1.75)	0.0219	1.35 (1.04-1.75)	0.0225
			Low	75/663	16	1.05 (0.80-1.39)	0.724	1.06 (0.80-1.40)	0.6935
			Intermediate	146/1325	14	Ref		Ref	
		LS7	Optimal	6/91	20	0.9 (0.40-2.04)	0.7964	0.91 (0.40-2.06)	0.816
			Inadequate	241/1674	13	1.69 (1.30-2.21)	<.0001	1.69 (1.30-2.21)	<.0001
			Average	73/886	16	Ref		Ref	
Whites	All stroke	PRS	High	388/2229	14	2.75 (2.36-3.19)	<.0001	2.7 (2.32-3.14)	<.0001
			Low	77/2230	26	0.49 (0.38-0.62)	<.0001	0.5 (0.39-0.64)	<.0001
			Intermediate	305/4458	21	Ref		Ref	
		LS7	Optimal	65/1211	23	0.76 (0.58-1.00)	0.0464	0.87 (0.66-1.14)	0.3059
			Inadequate	377/3519	15	1.33 (1.14-1.54)	0.0002	1.17 (1.00-1.36)	0.0474
			Average	328/4187	20	Ref		Ref	
	Ischemic stroke	PRS	High	352/2229	14	2.86 (2.43-3.35)	<.0001	2.8 (2.39-3.29)	<.0001
			Low	63/2230	26	0.46 (0.35-0.60)	<.0001	0.47 (0.36-0.62)	<.0001
			Intermediate	264/4458	22	Ref		Ref	
		LS7	Optimal	54/1211	21	0.74 (0.55-0.99)	0.0461	0.85 (0.63-1.14)	0.2856
			Inadequate	341/3519	16	1.37 (1.17-1.61)	<.0001	1.2 (1.02-1.41)	0.0282
			Average	284/4187	20	Ref		Ref	

Model 1: adjusted for center, sex, education category, family history; Model 2: adjusted for center, sex, education category, family history and included both PRS and LS7. All models account for the competing risk of death.

* HR (95% CI) were calculated using Fine and Gray sub-distribution hazard regression

HR: Hazard ratio; CI: Confidence interval; PRS: Polygenic risk score; LS7: Life's simple 7; Ref: Reference

Table S19. Association of PRS categories with incident all strokes and ischemic stroke adjusting for conventional risk factors in African-American and white participants

			Model 1 adjusted for individual conventional risk factors	
		PRS category	**HR[1]**	**P- value**
African-Americans	**All Stroke**	**High**	1.40 (1.10-1.79)	0.0072
		Low	0.95 (0.72-1.25)	0.7125
		Intermediate	Ref	Ref
	Ischemic Stroke	**High**	1.39 (1.06-1.82)	0.016
		Low	1.02 (0.76-1.37)	0.8789
		Intermediate	Ref	Ref
Whites	**All Stroke**	**High**	2.67 (2.29-3.11)	<.0001
		Low	0.51 (0.40-0.66)	<.0001
		Intermediate	Ref	Ref
	Ischemic Stroke	**High**	2.77 (2.35-3.26)	<.0001
		Low	0.49 (0.37-0.64)	<.0001
		Intermediate	Ref	Ref

[1] Adjusted for Center, Sex, Education category, Family history, BMI, Smoking, SBP, Total cholesterol, Diabetes, Hypertension. Model accounts for the competing risk of death.

HR (95% CI) were calculated using Fine and Gray sub-distribution hazard regression

HR: Hazard ratio; CI: Confidence interval; PRS: Polygenic risk score; Ref: Reference

Table S20. Association of incident all stroke and ischemic stroke with PRS, LS7 score, and their interaction in African-Americans and whites. PRS and LS7 are modeled on the continuous scale

			Model 1		Model 2	
			HR*	**P- value**	**HR***	**P- value**
African-Americans	**All stroke**	**LS7 score**	0.79 (0.71-0.87)	<.0001	0.79 (0.71-0.87)	<.0001
		PRS	1.14 (1.01-1.27)	0.0271	1.19 (0.96-1.47)	0.116
		LS7 score × PRS	-	-	0.98 (0.89-1.07)	0.6327
	Ischemic stroke	**LS7 score**	0.76 (0.68-0.84)	<.0001	0.75 (0.68-0.84)	<.0001
		PRS	1.14 (1.01-1.28)	0.0317	1.13 (0.89-1.42)	0.313
		LS7 score × PRS	-	-	1.01 (0.91-1.12)	0.9041
Whites	**All stroke**	**LS7 score**	0.88 (0.84-0.92)	<.0001	0.87 (0.82-0.91)	<.0001
		PRS	1.67 (1.57-1.79)	<.0001	1.56 (1.35-1.79)	<.0001
		LS7 score × PRS	-	-	1.03 (0.98-1.09)	0.2753
	Ischemic stroke	**LS7 score**	0.86 (0.82-0.91)	<.0001	0.85 (0.80-0.90)	<.0001
		PRS	1.72 (1.60-1.84)	<.0001	1.55 (1.32-1.81)	<.0001
		LS7 score × PRS	-	-	1.05 (0.98-1.11)	0.1455

Model 1: adjusted for center, sex, education category, family history; Model 2: adjusted for center, sex, education category, family history and included both PRS and LS7. All models account for the competing risk of death.

Table S21. Area Under the Curve (AUC) estimates for all stroke and ischemic stroke in African-Americans, in whites, and in the overall sample

		Model	AUC	LCI	UCI	P value compared with null model	P value Full vs. Partial model
African-Americans	All stroke	Full model	0.619	0.589	0.65	3.31E-11	0.092
		Partial model	0.609	0.578	0.639	3.64E-13	
	Ischemic stroke	Full model	0.636	0.604	0.668	5.65E-14	0.376
		Partial model	0.631	0.599	0.664	8.61E-15	
Whites	All stroke	Full model	0.691	0.671	0.71	6.57E-16	1.38E-23
		Partial model	0.587	0.566	0.608	6.72E-69	
	Ischemic stroke	Full model	0.701	0.681	0.722	1.99E-17	2.72E-22
		Partial model	0.597	0.575	0.619	1.67E-68	
Overall	All stroke	Full model	0.686	0.67	0.702	1.17E-42	1.81E-17
		Partial model	0.624	0.607	0.641	2.65E-93	
	Ischemic stroke	Full model	0.693	0.677	0.71	8.28E-43	5.73E-16
		Partial model	0.632	0.614	0.65	2.72E-89	

Partial model: Adjusted for center, sex, education, race (except in race-stratified analyses), family history, and LS7

Full model: Same as partial model + PRS

LCI: lower 95% confidence interval; UPI: Upper 95% confidence interval

Figure S1. Remaining lifetime risk of ischemic stroke by PRS categories (A) and LS7 categories (B) conditional on surviving free of ischemic stroke to index age and adjusting for competing risk of death.

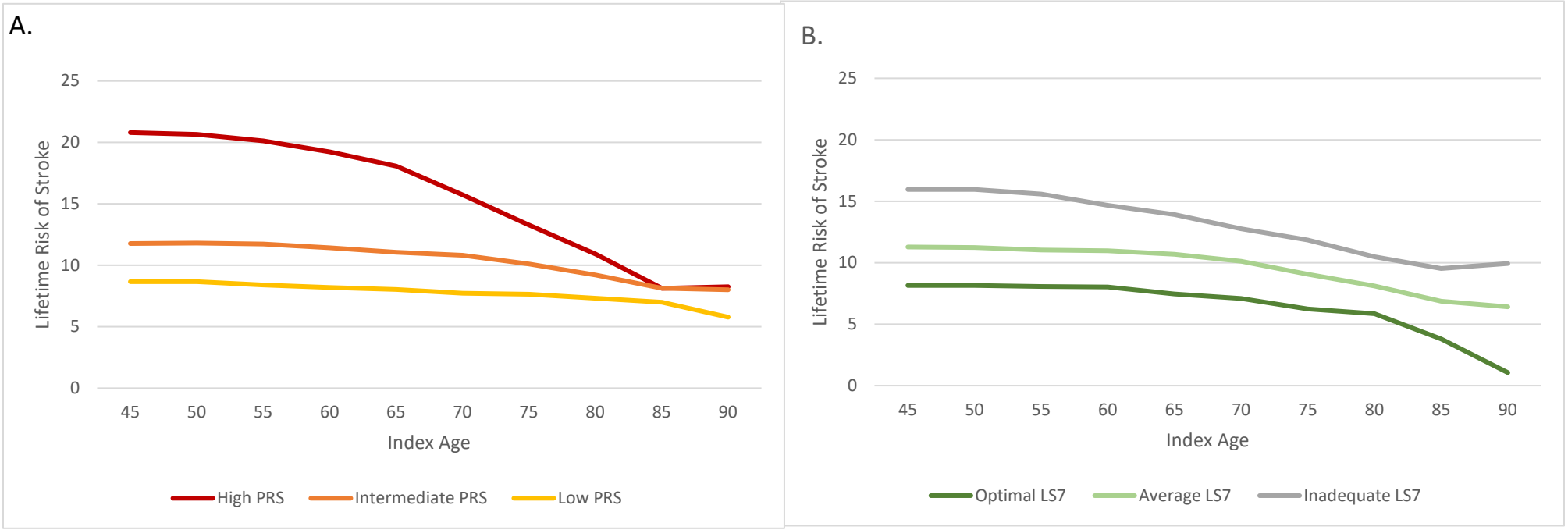
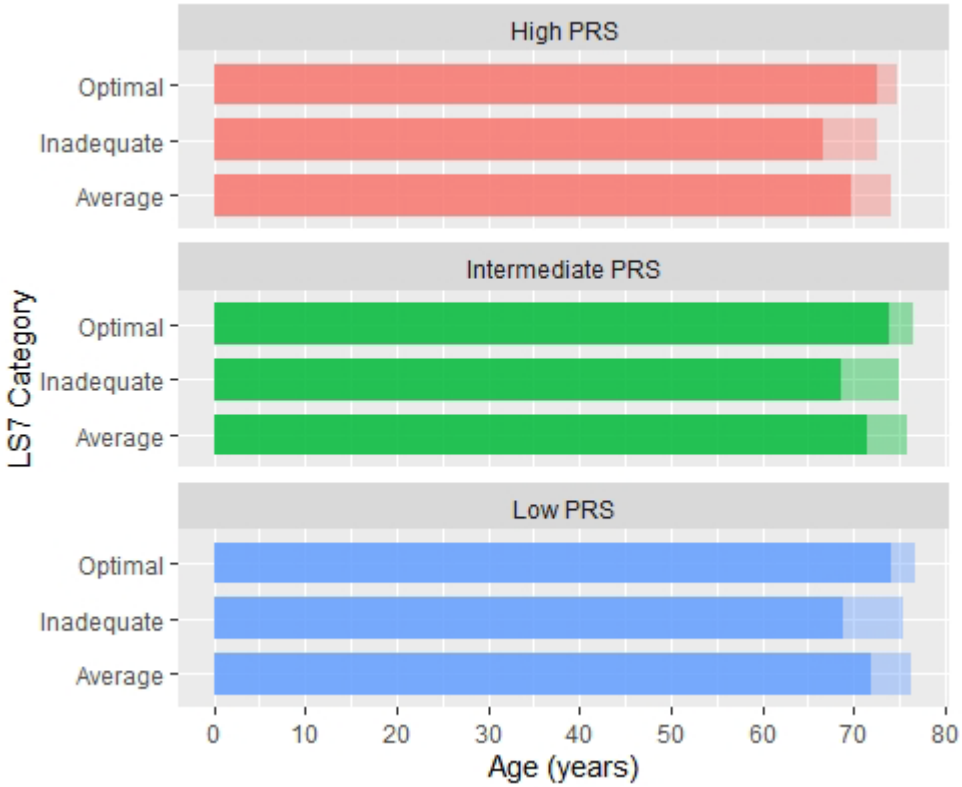


Figure S2. Years lived free of stroke and overall survival by PRS and LS7 categories.

Each bar represents Irwin's restricted mean survival time (RMST) for incident stroke (years free of stroke) and overall survival for the participants in each of the PRS and LS7 categories. Stroke-free years (solid bars) and overall survival (transparent bars) are shown for All Stroke (A) and Ischemic Stroke (B).

A. All Stroke



B. Ischemic Stroke

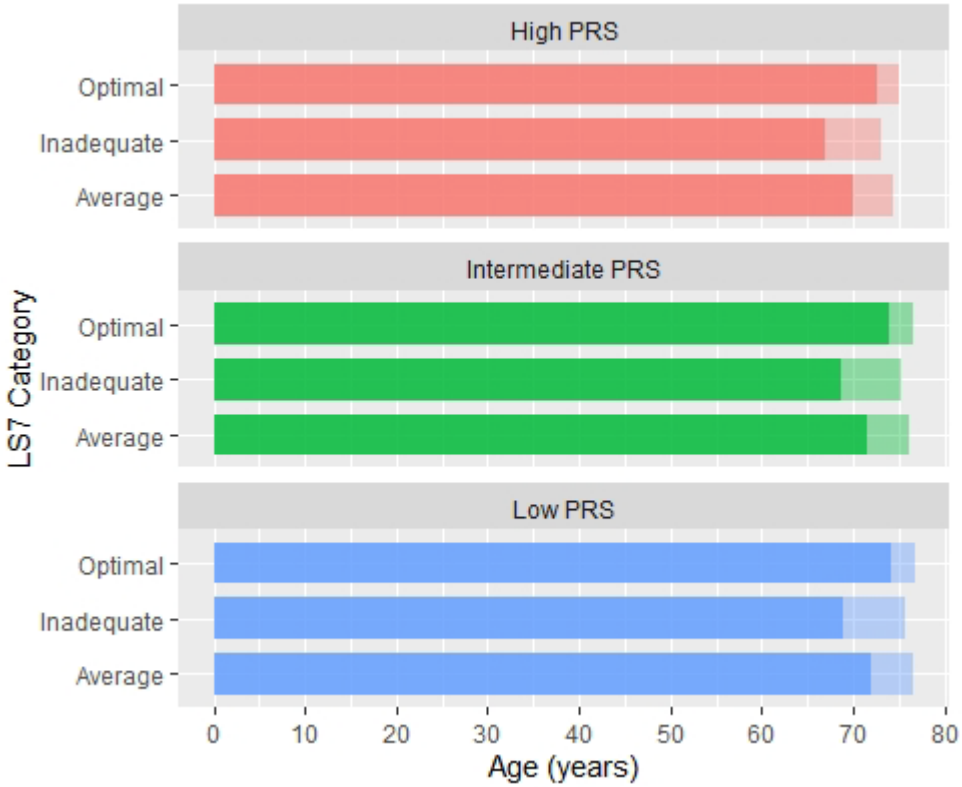
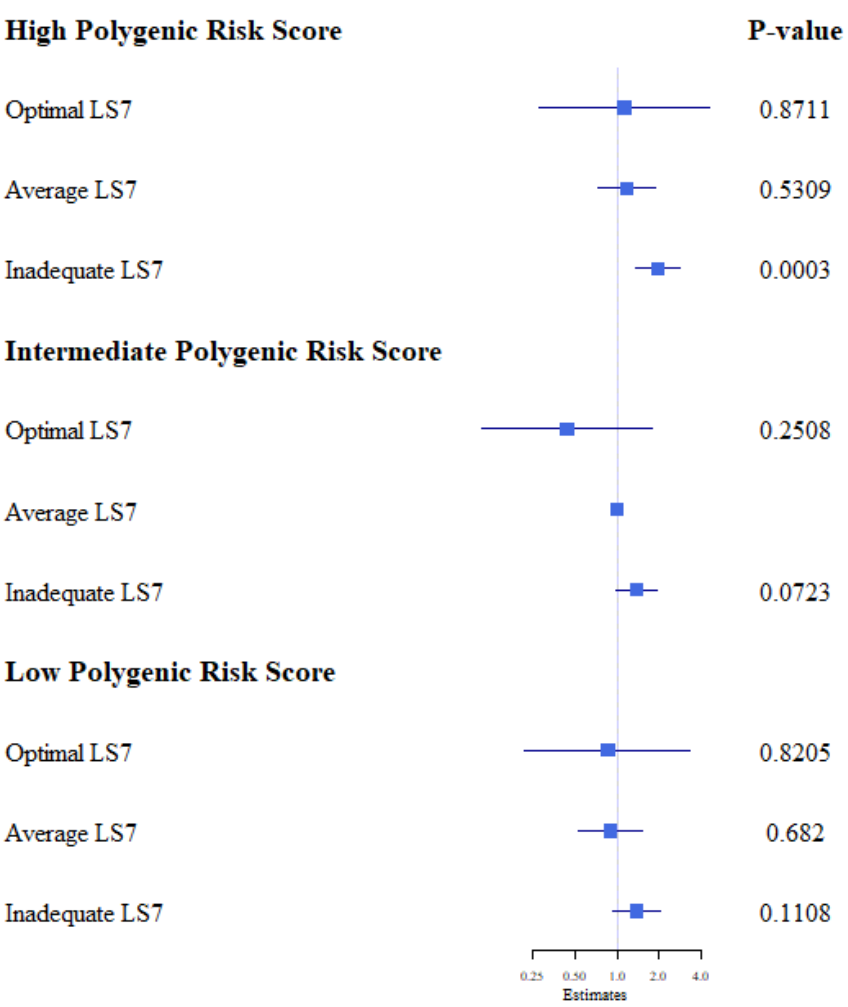


Figure S3. Relative risk of incident stroke by PRS and LS7 scores in ARIC African-Americans. Shown are the hazard ratios (95% confidence intervals) for the incident stroke by PRS and LS7 categories, calculated accounting for the competing risk of death and adjusting for sex, race, center, and family history. Intermediate PRS and average LS7 was used as the reference.

A. All Stroke



B. Ischemic Stroke

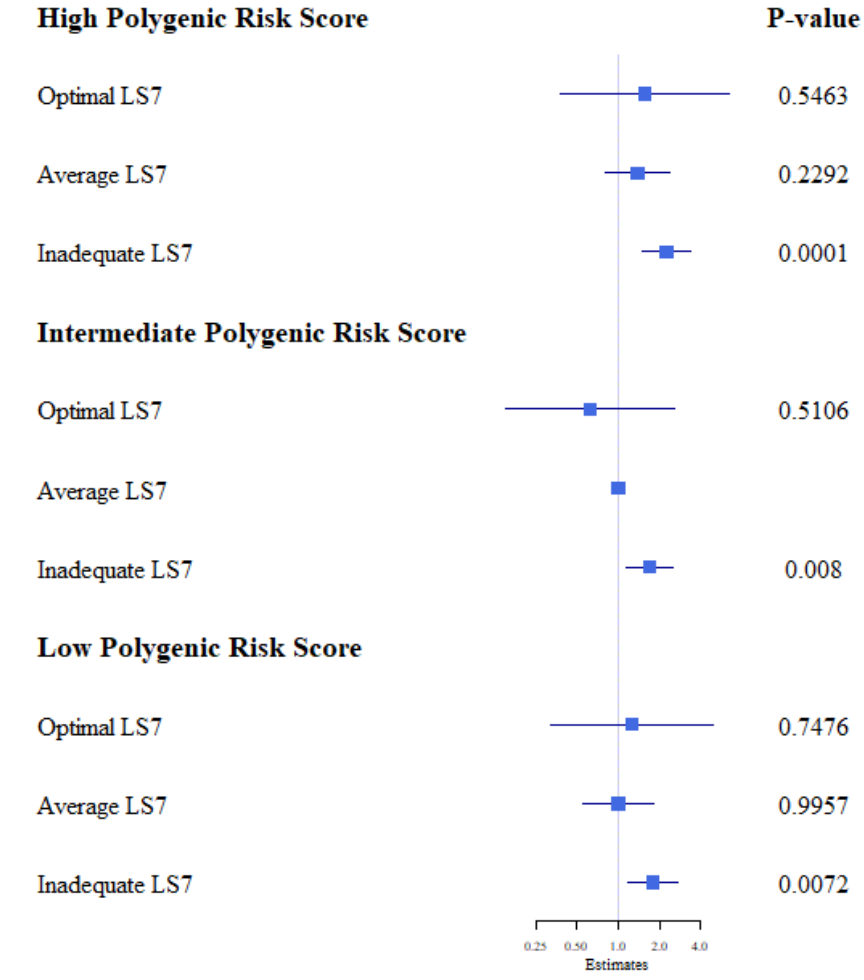
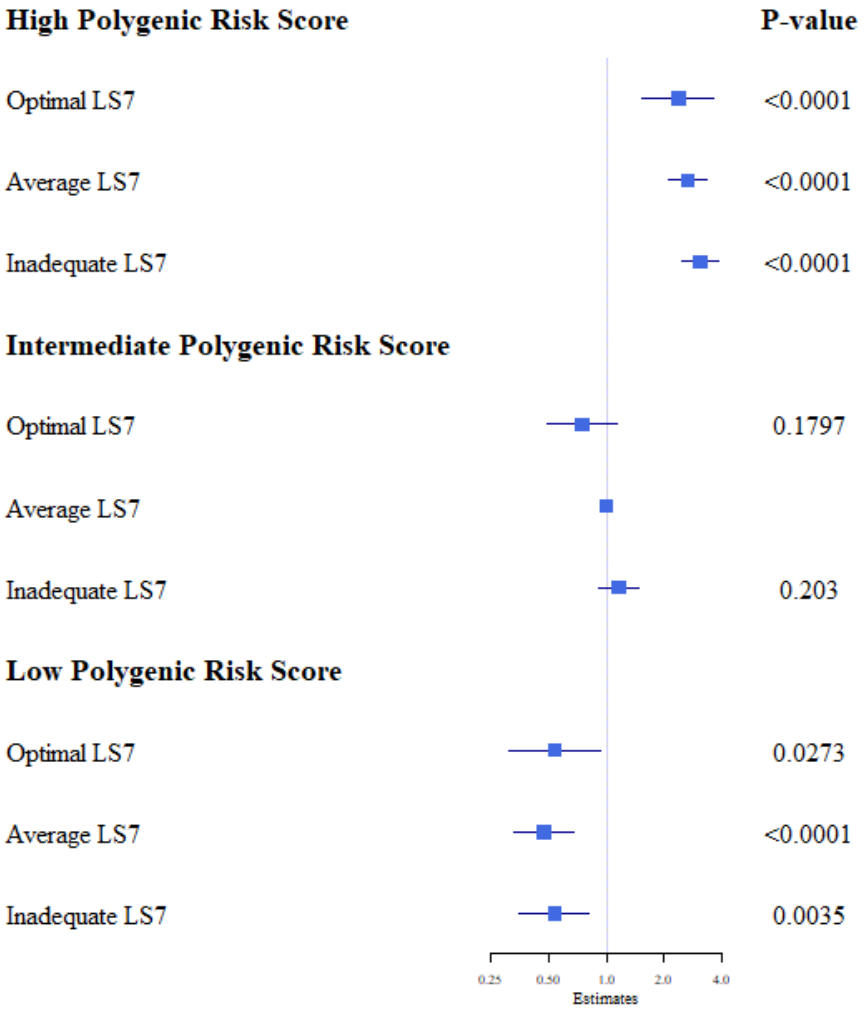


Figure S4. Relative risk of incident stroke by PRS and LS7 scores in ARIC whites. Shown are the hazard ratios (95% confidence intervals) for the incident stroke by PRS and LS7 categories, calculated accounting for the competing risk of death and adjusting for sex, race, center, and family history. Intermediate PRS and average LS7 was used as the reference.

A. All Stroke



B. Ischemic Stroke

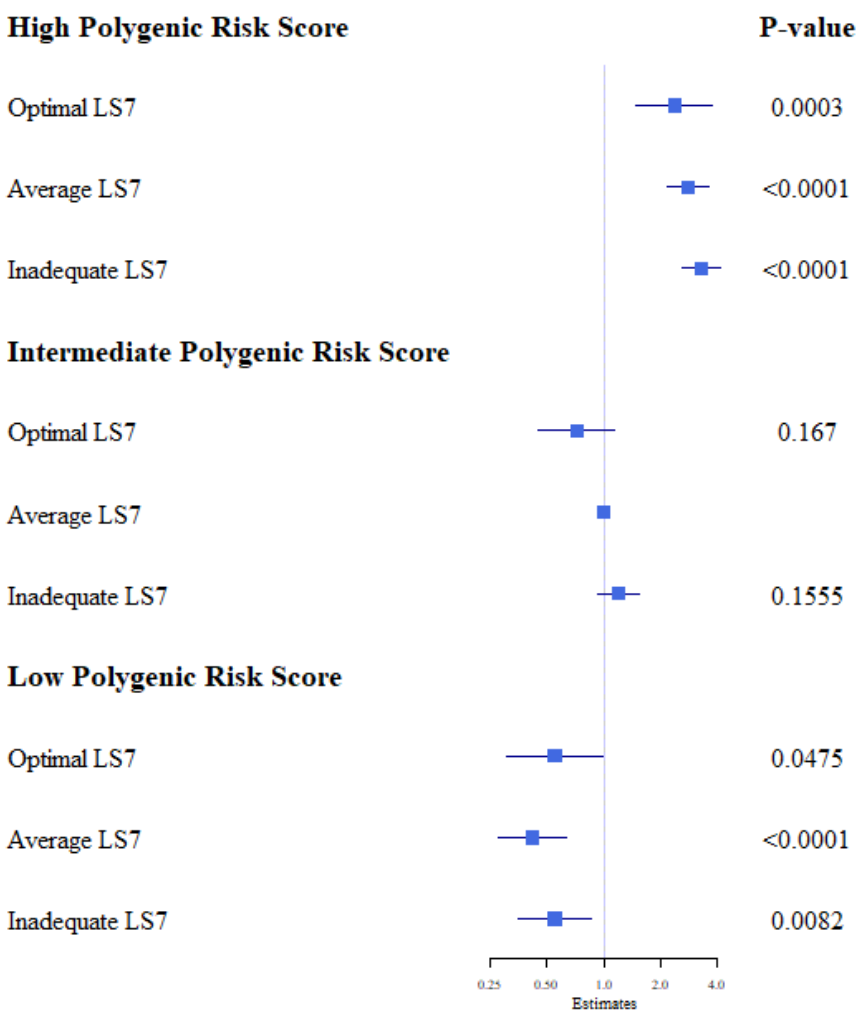


Figure S5. Receiver operating characteristic curves for models predicting all stroke in African-Americans (A) and in whites (B). The corresponding models for ischemic stroke are shown in (C) and (D). The partial model of only covariates is shown in black, the full model including the PRS is shown in red. The grey diagonal line represents a random prediction.