SUPPLEMENTAL MATERIALS

Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle:

follow-up of 306,473 UK Biobank participants

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Content

Text S1 Diet score extended information

During the baseline assessment all UK Biobank participants completed an extensive questionnaire that included dietary habits ("Touchscreen Questionnaire", available from http://www.ukbiobank.ac.uk/resources/). Supplemental table S1 lists the questions corresponding to the data used in the current analysis.

Healthy diet patterns were adapted from the American Heart Association Guidelines[1] and defined as follows:

Total fruit and vegetable intake: $\geq$ 4.5 pieces or servings a week. 3 Tablespoons of vegetables were considered one serving

Total fish intake: $\geq$ 2 per week

Processed and red meat intake: 2 or fewer times intake of processed meat per week & 5 or fewer times intake of red meat per week

The healthy diet score was dichotomised as 1 = at least two of the healthy food items, 0 = fewer than 2 of the healthy food items.

Text S2 MEGASTROKE extended information and acknowledgements

Stroke genome-wide association summary statistics were obtained from the MEGASTROKE study.[2] In this study ~8 million single nucleotide polymorphisms (SNPs) and InDels with minor allele frequency (MAF) > 0.01 were tested for association in up to 67,162 stroke cases and 454,450 controls. Participants were drawn from 29 studies, that were genotyped with GWAS arrays and imputed to 1000 Genomes phase 1v3 or similar. Two main analysis were performed, one of European participants only (40,585 cases; 406,111 controls) and a second transethnic analysis which involved participants of European, East Asian (17,369; 28,195), African (5,541; 15,154), South Asian (2,437; 6,707), mixed Asian (365; 333), and Latin American (865; 692) ancestry.

In the current analysis we only used the results of the European-only analysis.

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230 Department of Medicine I, Ludwig-Maximilians-Universität, Munich, Germany
231 DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
232 Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico “Carlo Besta”, Milano, Italy
233 Karolinska Institutet, MEB, Stockholm, Sweden
234 University of Tartu, Estonian Genome Center, Tartu, Estonia, Tartu, Estonia
235 Department of Clinical and Experimental Sciences, Neurology Clinic, University of Brescia, Italy
236 Translational Genomics Unit, Department of Oncology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy
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239 Department of Neurology, IMIM-Hospital del Mar, and Universitat Autònoma de Barcelona, Spain
240 IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
241 National Institute for Health Research Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust and King's College London, London, UK
242 Division of Health and Social Care Research, King's College London, London, UK
243 FIMM-Institute for Molecular Medicine Finland, Helsinki, Finland
244 THL-National Institute for Health and Welfare, Helsinki, Finland
245 Iwate Tohoku Medical Megabank Organization, Iwate Medical University, Iwate, Japan
246 BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, Glasgow, UK
247 deCODE Genetics/Amgen, Inc., Reykjavik, Iceland
248 Icelandic Heart Association, Reykjavik, Iceland
249 Institute of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Goteborg, Sweden
250 Department of Epidemiology, University of Maryland School of Medicine, Baltimore, MD, USA
251 Institute of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow, Glasgow, UK
252 Chair of Genetic Epidemiology, IBE, Faculty of Medicine, LMU Munich, Germany
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254 Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
255 University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany
256 Department of Neurology, Caen University Hospital, Caen, France
257 University of Caen Normandy, Caen, France

258 Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands
259 Landspitali University Hospital, Reykjavik, Iceland
260 Survey Research Center, University of Michigan, Ann Arbor, MI, USA
261 University of Virginia Department of Neurology, Charlottesville, VA, USA

Table S1 Dietary questions used in the current analysis

Questions	Response	Hints
About how many pieces of FRESH fruit would you eat per DAY? (Count one apple, one banana, 10 grapes etc as one piece; put '0' if you do not eat any)	Enter INTEGER OR -10: Less than 1 OR -1: Do not know OR -3: Prefer not to answer	Please provide an average considering your intake over the last year. If you are unsure, please provide an estimate or select Do not know.
On average how many heaped tablespoons of COOKED vegetables would you eat per DAY? (Do not include potatoes; put '0' if you do not eat any)	Enter INTEGER OR -10: Less than 1 OR -1: Do not know OR -3: Prefer not to answer	Please provide an average considering your intake over the last year. If you are unsure, please provide an estimate or select Do not know. If you have less than one tablespoon a day select Less than one.
On average how many heaped tablespoons of SALAD or RAW vegetables would you eat per DAY? (Include lettuce, tomato in sandwiches; put '0' if you do not eat any)	Enter INTEGER OR -10: Less than 1 OR -1: Do not know OR -3: Prefer not to answer	Please provide an average considering your intake over the last year. If you are unsure, please provide an estimate or select Do not know. If you have less than one tablespoon a day select Less than one.
How often do you eat oily fish? (e.g. sardines, salmon, mackerel, herring)	SELECT one of 8 from 0: Never 1: Less than once a week 2: Once a week 3: 2-4 times a week 4: 5-6 times a week 5: Once or more daily -1: Do not know -3: Prefer not to answer	Please provide an average considering your intake over the last year. If you are unsure, please provide an estimate or select Do not know. Oily fish include: Salmon, Anchovies, Trout, Swordfish, Mackerel, Bloater, Herring, Cacha, Sardines, Carp, Pilchards, Hilsa, Kipper, Jack fish, Eel, Katla,Whitebait, Orange roughy, Tuna (fresh only), Pangas, Sprats.
How often do you eat other types of fish? (e.g. cod, tinned tuna, haddock)	SELECT one of 8 from 0: Never 1: Less than once a week 2: Once a week 3: 2-4 times a week 4: 5-6 times a week 5: Once or more daily -1: Do not know -3: Prefer not to answer	Please provide an average considering your intake over the last year. If you are unsure, please provide an estimate or select Do not know

How often do you eat processed meats (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets)?	SELECT one of 8 from 0: Never 1: Less than once a week 2: Once a week 3: 2-4 times a week 4: 5-6 times a week 5: Once or more daily -1: Do not know -3: Prefer not to answer	Please provide an average considering your intake over the last year If you are unsure, please provide an estimate or select Do not know.
How often do you eat beef? (Do not count processed meats)	SELECT one of 8 from 0: Never 1: Less than once a week 2: Once a week 3: 2-4 times a week 4: 5-6 times a week 5: Once or more daily -1: Do not know -3: Prefer not to answer	Please provide an average considering your intake over the last year If you are unsure, please provide an estimate or select Do not know.
How often do you eat lamb/mutton? (Do not count processed meats)	SELECT one of 8 from 0: Never 1: Less than once a week 2: Once a week 3: 2-4 times a week 4: 5-6 times a week 5: Once or more daily -1: Do not know -3: Prefer not to answer	Please provide an average considering your intake over the last year If you are unsure, please provide an estimate or select Do not know.
How often do you eat pork? (Do not count processed meats such as bacon or ham)	SELECT one of 8 from 0: Never 1: Less than once a week 2: Once a week 3: 2-4 times a week 4: 5-6 times a week 5: Once or more daily -1: Do not know -3: Prefer not to answer	Please provide an average considering your intake over the last year If you are unsure, please provide an estimate or select Do not know.

Table S2 UK Biobank data fields used to derive the outcome variables and follow-up duration

Data field ID	Description
53	Date of attending assessment centre
40000	Date of death
42000	Date of first myocardial infarction
42001	Source of first myocardial infarction report
42006	Date of first stroke
42007	Source of first stroke report
42008	Date of first ischaemic stroke
42009	Source of first ischaemic stroke report
42010	Date of first intracerebral haemorrhage
42011	Source of first intracerebral haemorrhage report
42012	Date of first subarachnoid haemorrhage
42013	Source of first subarachnoid haemorrhage report

Table S4 Impact of cardiometabolic risk factors on the association of the genetic risk score with incident stroke

	Model 1 (No cardiometabolic risk factors)		**Model 2** (Cardiometabolic risk factors included)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Genetic risk category				
High	**1.35 (1.21-1.50)**	**3.9×10^{-08}**	**1.36 (1.22-1.53)**	**9.9×10^{-08}**
Intermediate	**1.20 (1.08-1.34)**	**0.001**	**1.22 (1.09-1.38)**	**6.7×10^{-04}**
Low	**1**		**1**	
Blood pressure				
SBP, per 10mmHg			1.08 (1.05-1.12)	1.0×10^{-06}
DBP, per 10mmHg			1.09 (1.03-1.16)	0.004
Diabetes			1.93 (1.63-2.29)	3.9×10^{-14}
Lipid lowering medication			1.03 (0.91-1-15)	0.72

Table S5 Association of genetic risk and lifestyle with incident stroke

	Model 1		Model 2		Model 3	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Genetic risk category	1.35 (1.21-1.50)	3.90×10^{-08}			1.35 (1.21-1.50)	3.72×10^{-08}
High	1.20 (1.08-1.34)	0.001	x		1.20 (1.08-1.34)	0.001
Intermediate			x			
Low	1		x		1	
Lifestyle						
Unfavourable	x		1.66 (1.45-1.89)	1.19×10^{-13}	1.62 (1.42-1.85)	1.48×10^{-12}
Intermediate	x		1.27 (1.16-1.40)	8.59×10^{-07}	1.26 (1.15-1.39)	1.96×10^{-06}
Favourable	x		1		1	

Model 1 includes age, sex, first 10 principal components of ancestry, genotyping batch and genetic risk; model 2 includes age, sex and lifestyle profile; model 3 includes all variables of model 1 with the addition of lifestyle profile.

Table S6 Association of lifestyle with incident stroke in genetic risk strata

	Low genetic risk		Intermediate genetic risk		High genetic risk	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Lifestyle						
Unfavourable	1.88 (1.47-2.39)	3.90×10^{-07}	1.49 (1.17-1.88)	0.001	1.66 (1.34-2.06)	4.12×10^{-06}
Intermediate	1.37 (1.15-1.64)	5.70×10^{-04}	1.28 (1.09-1.51)	0.003	1.20 (1.02-1.40)	0.03
Favourable	1		1		1	

Abbreviations: HR, hazard ratio; CI, confidence interval

Hazard ratios were calculated using Cox proportional hazards models, adjusted for age and sex.

Table S7 Association of genetic risk with incident stroke and incident ischaemic stroke using Cox proportional hazards regression and incident stroke using competing risk regression (Fine and Gray)

	All-Stroke		**Ischaemic stroke**		**All-Stroke CRR**	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**	**SHR (95%CI)**	**p**
Genetic risk category						
High	1.35 (1.21-1.50)	3.9×10^{-08}	1.30 (1.16-1.47)	1.8×10^{-05}	1.35 (1.21-1.50)	4.0×10^{-08}
Intermediate	1.20 (1.08-1.34)	$9.7\times10\text{-}^{04}$	1.13 (1.00-1.28)	0.06	1.20 (1-08-1.34)	0.001
Low	1		1		1	

Abbreviations: HR, hazard ratio; CI, confidence interval; SHR, subdistribution hazard ratio
Hazard ratios were calculated using Cox proportional hazards models. Subdistribution hazard ratio was calculated using proportional subdistribution hazards regression models (Fine and Gray) as implemented in the R-package 'cmprsk'
All models were adjusted for age, sex, first 10 principal components of ancestry and genotyping batch

Table S8 Association of lifestyle with incident stroke and incident ischaemic stroke using Cox proportional hazards regression and incident stroke using competing risk regression (Fine and Gray)

	All-Stroke		**Ischaemic stroke**		**All-Stroke CRR**	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**	**SHR (95%CI)**	**p**
Lifestyle						
Unfavourable	1.66 (1.45-1.89)	1.2×10^{-13}	1.72 (1.48-2.00)	1.8×10^{-12}	1.63 (1.42-1.86)	7.4×10^{-13}
Intermediate	1.27 (1.16-1.40)	8.6×10^{-07}	1.30 (1.16-1.45)	3.5×10^{-06}	1.26 (1.15-1.39)	1.9×10^{-06}
Favourable	1		1		1	

Abbreviations: HR, hazard ratio; CI, confidence interval; SHR, subdistribution hazard ratio
Hazard ratios were calculated using Cox proportional hazards models. Subdistribution hazard ratio was calculated using proportional subdistribution hazards regression models (Fine and Gray) as implemented in the R-package 'cmprsk'
All models were adjusted for age and sex

Table S9 Association of lifestyle and genetic risk score with incident stroke and incident ischaemic stroke using Cox proportional hazards regression and incident stroke using competing risk regression (Fine and Gray)

	All-Stroke		Ischaemic stroke		All-Stroke CRR	
	HR (95%CI)	p	HR (95%CI)	P	SHR (95%CI)	p
HG-UL	2.30 (1.84-2.87)	3.3×10^{-13}	2.52 (1.95-3.24)	8.8×10^{-13}	2.25 (1.80-2-81)	1.4×10^{-12}
HG-IL	1.70 (1.44-2.01)	8.1×10^{-10}	1.93 (1.59-2.34)	2.0×10^{-11}	1.68 (1.42-2.00)	1.7×10^{-09}
HG-FL	1.44 (1.25-1.66)	7.0×10^{-07}	1.36 (1.15-1.61)	4.4×10^{-4}	1.44 (1.25-1-66)	7.2×10^{-07}
IG-UL	1.85 (1.46-2.37)	5.4×10^{-07}	1.62 (1.20-2.19)	0.002	1.82 (1.43-2-32)	1.2×10^{-06}
IG-IL	1.62 (1.37-1.92)	3.2×10^{-08}	1.36 (1.10-1.68)	0.004	1.60 (1.35-1.90)	6.7×10^{-08}
IG-FL	1.26 (1.09-1.46)	0.002	1.36 (1.15-1.62)	3.9×10^{-4}	1.26 (1.09-1.46)	0.002
LG-UL	1.84 (1.44-2.35)	8.0×10^{-07}	2.18 (1.67-2.85)	8.9×10^{-9}	1.81 (1.42-2.30)	1.6×10^{-06}
LG-IL	1.36 (1.14-1.63)	7.3×10^{-04}	1.47 (1.20-1.80)	2.5×10^{-4}	1.35 (1.13-1.62)	0.001
LG-FL	1		1		1	

Abbreviations: HR, hazard ratio; CI, confidence interval; SHR, subdistribution hazard ratio; HG, high genetic risk; IG, intermediate genetic risk; LG, low genetic risk; UL, unfavourable lifestyle; IL, intermediate lifestyle; FL, favourable lifestyle

Hazard ratios were calculated using Cox proportional hazards models. Subdistribution hazard ratio was calculated using proportional subdistribution hazards regression models (Fine and Gray) as implemented in the R-package 'cmprsk'

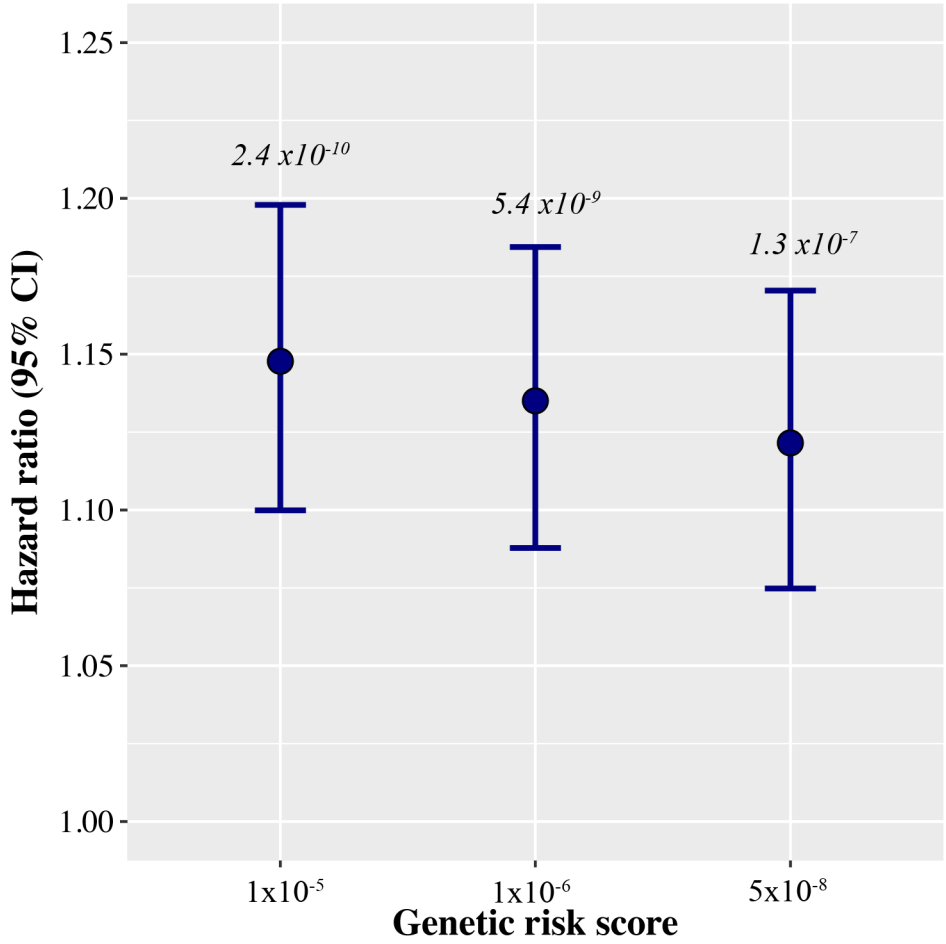
All models were adjusted for age, sex, first 10 principal components of ancestry and genotyping batch.

Table S10 Relative and absolute risk of incident stroke according to genetic and lifestyle profiles including double weighting for smoking

		Lifestyle		
Genetic risk		**Favourable**	**Intermediate**	**Unfavourable**
Low	Hazard Ratio (95% CI)	1	1.31 (1.09-1.58) p=0.005	1.96 (1.58-2.44) $p=1.3\times10^{-9}$
	8-year cumulative incidence (95% CI)	0.53% (0.47%-0.59%)	0.69% (0.58%-0.80%)	1.00% (0.80%-1.20%)
Intermediate	Hazard Ratio (95% CI)	1.24 (1.07-1.45) p=0.005	1.52 (1.27-1.82) $p=4.0\times10^{-6}$	2.25 (1.83-2.76) $p=2.1\times10^{-14}$
	8-year cumulative incidence (95% CI)	0.66% (0.59%-0.73%)	0.76% (0.65%-0.87%)	1.09% (0.89%-1.28%)
High	Hazard Ratio (95% CI)	1.45 (1.25-1.68) $p=6.7\times10^{-7}$	1.62 (1.36-1.94) $p=6.6\times10^{-8}$	2.45 (2.00-3.00) $p=<2\times10^{-16}$
	8-year cumulative incidence (95% CI)	0.78% (0.70%-0.85%)	0.87% (0.74%-1.00%)	1.16% (0.97%-1.36%)

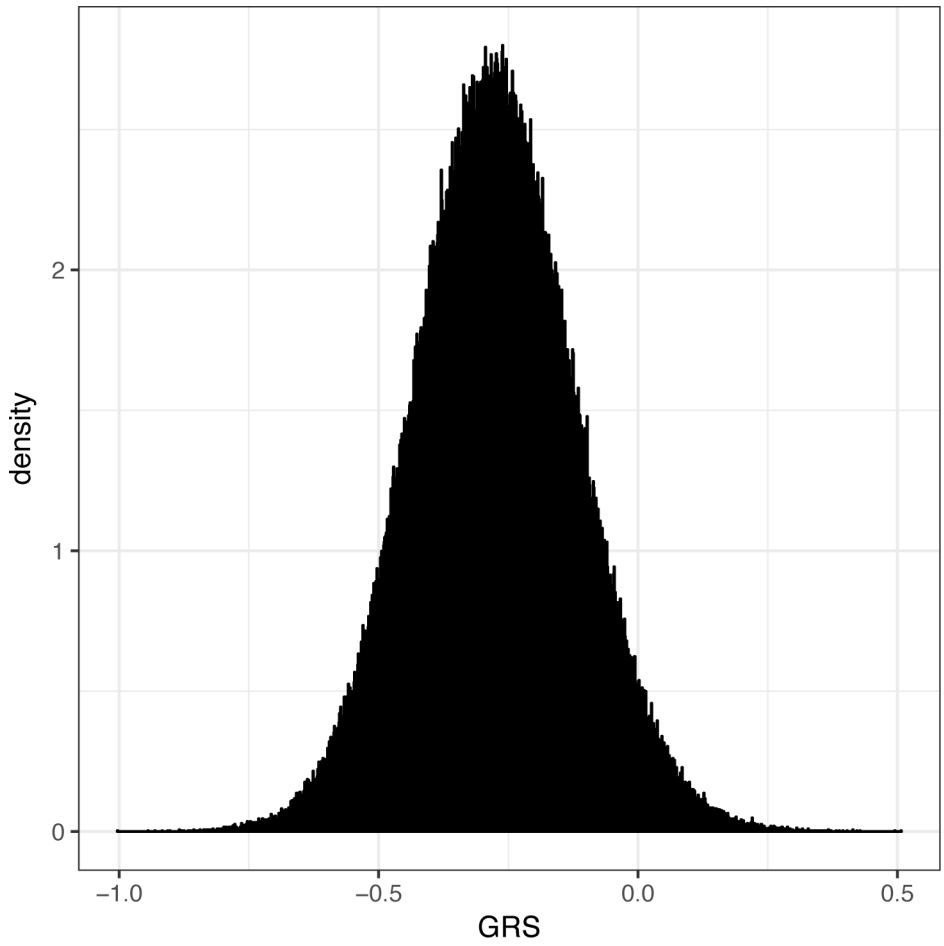
Hazard Ratios were calculated using Cox proportional hazards models, adjusted for age, sex, first 10 principal components of ancestry and genotyping batch. 8-year cumulative incidence was calculated using the cumulative incidence function as implemented in the 'cmprsk' R-package.

Figure S1 Association of genetic risk score at varying significance thresholds with incident stroke



P-values above the bars are the p-values for the association of the specific risk score with incident stroke.

Figure S2 Distribution of all stroke genetic risk score derived from MEGASTROKE $p<1\times10^{-5}$



Abbreviations: GRS, genetic risk score

Figure S3 Distribution of genetic risk across lifestyle categories

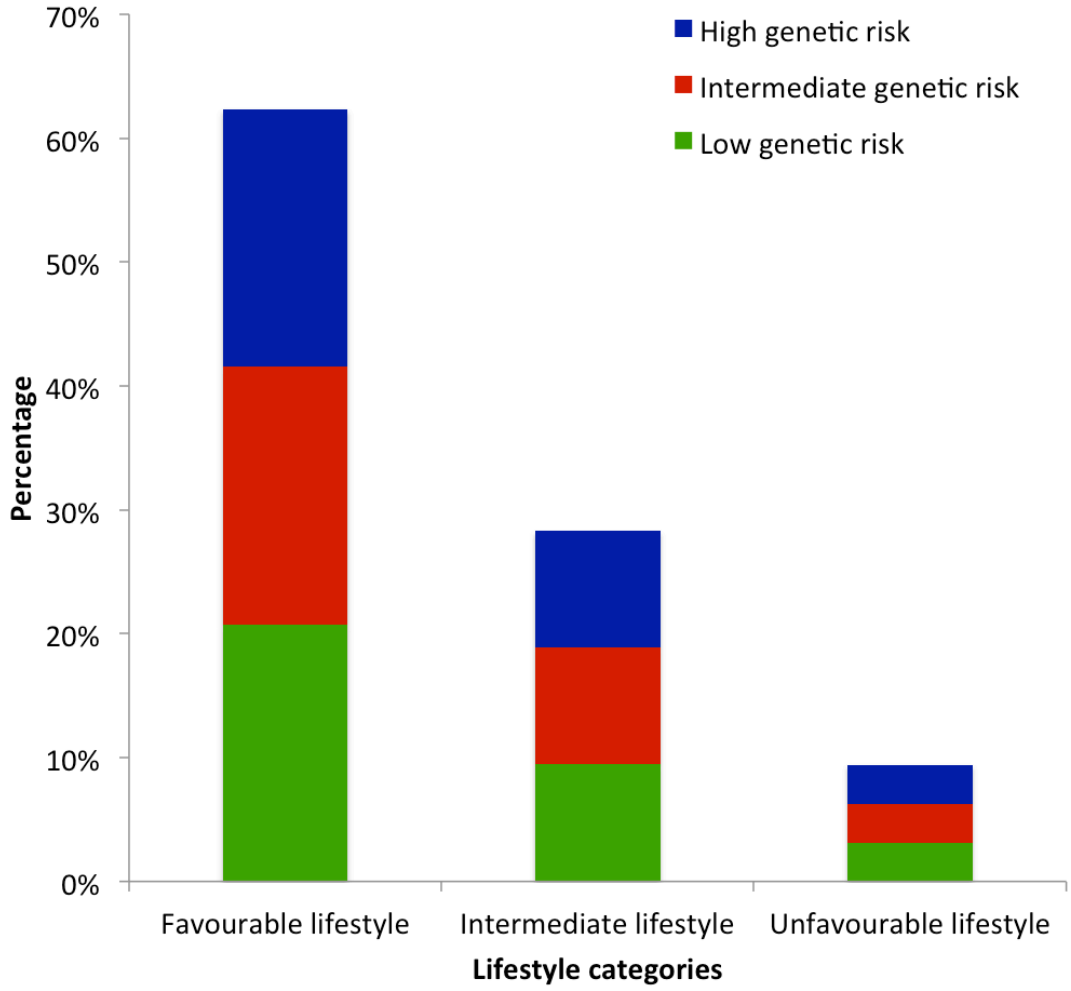
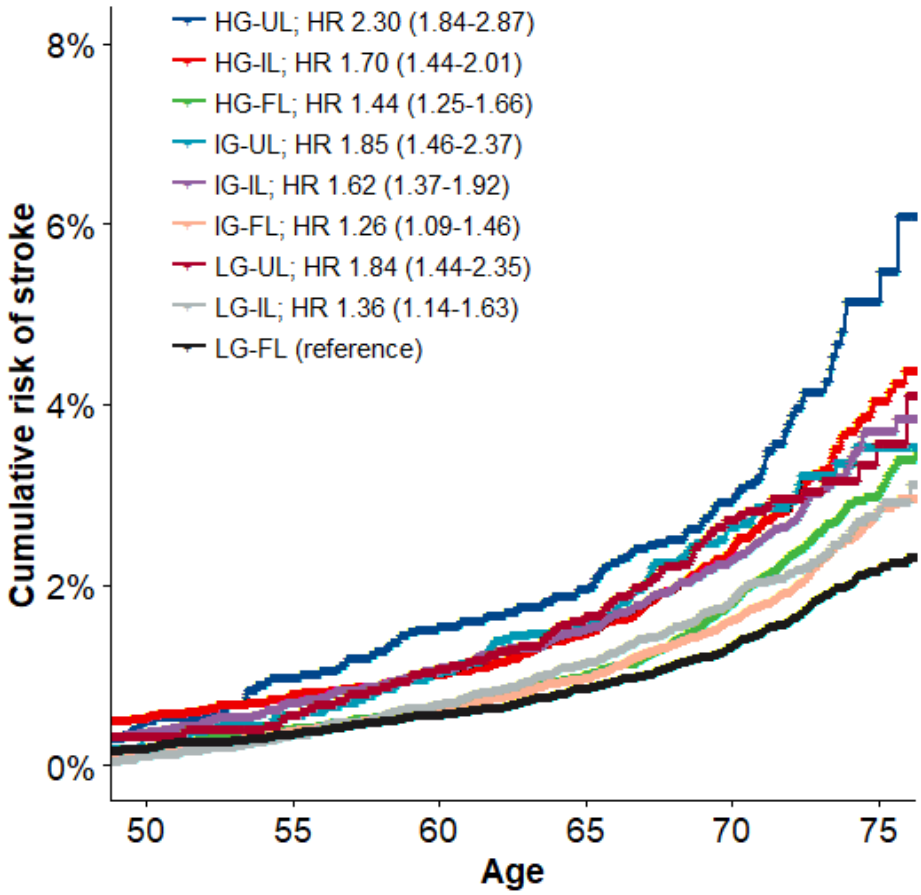
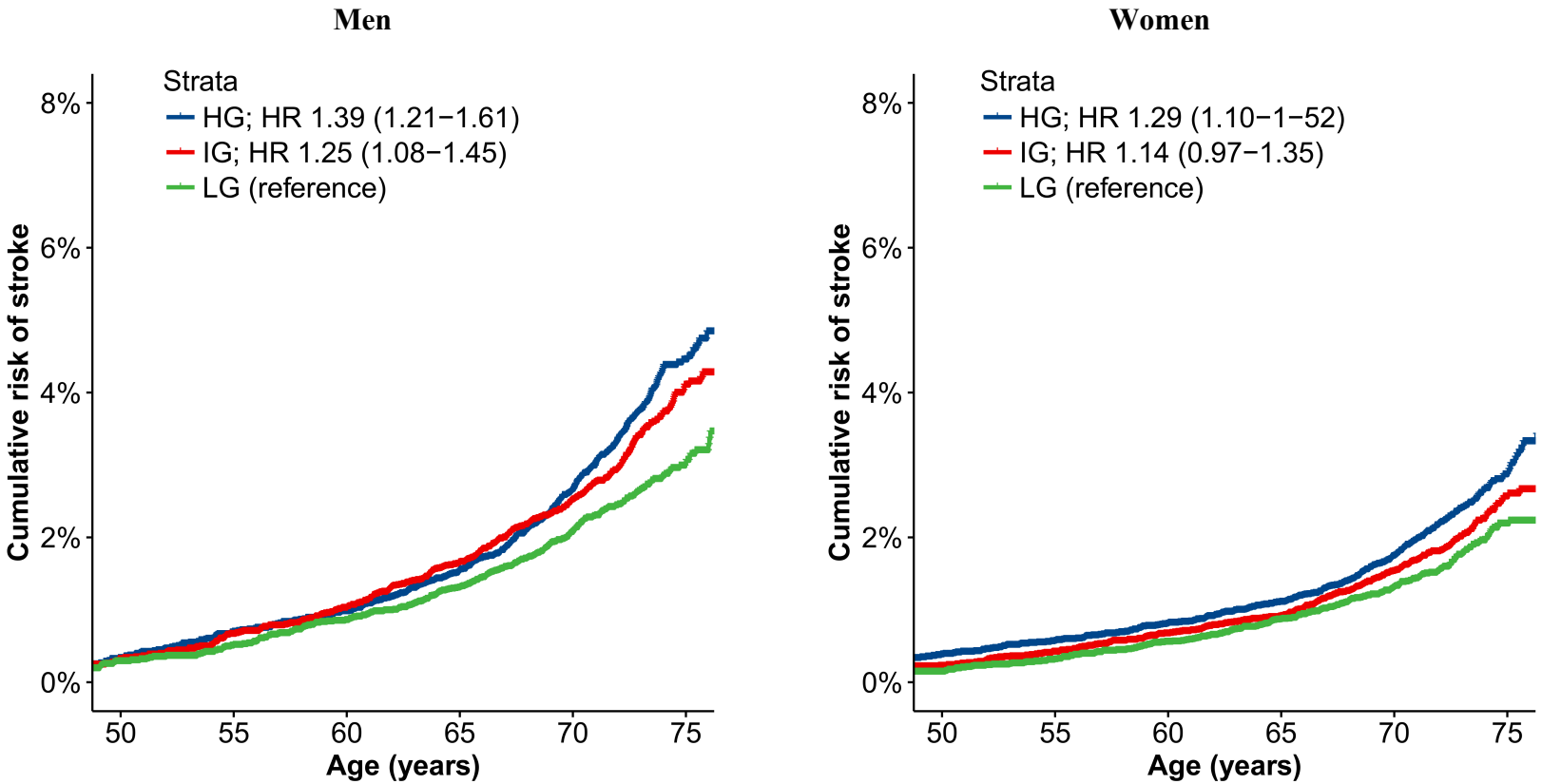


Figure S4 Standardized risk of incident stroke according to genetic risk and lifestyle



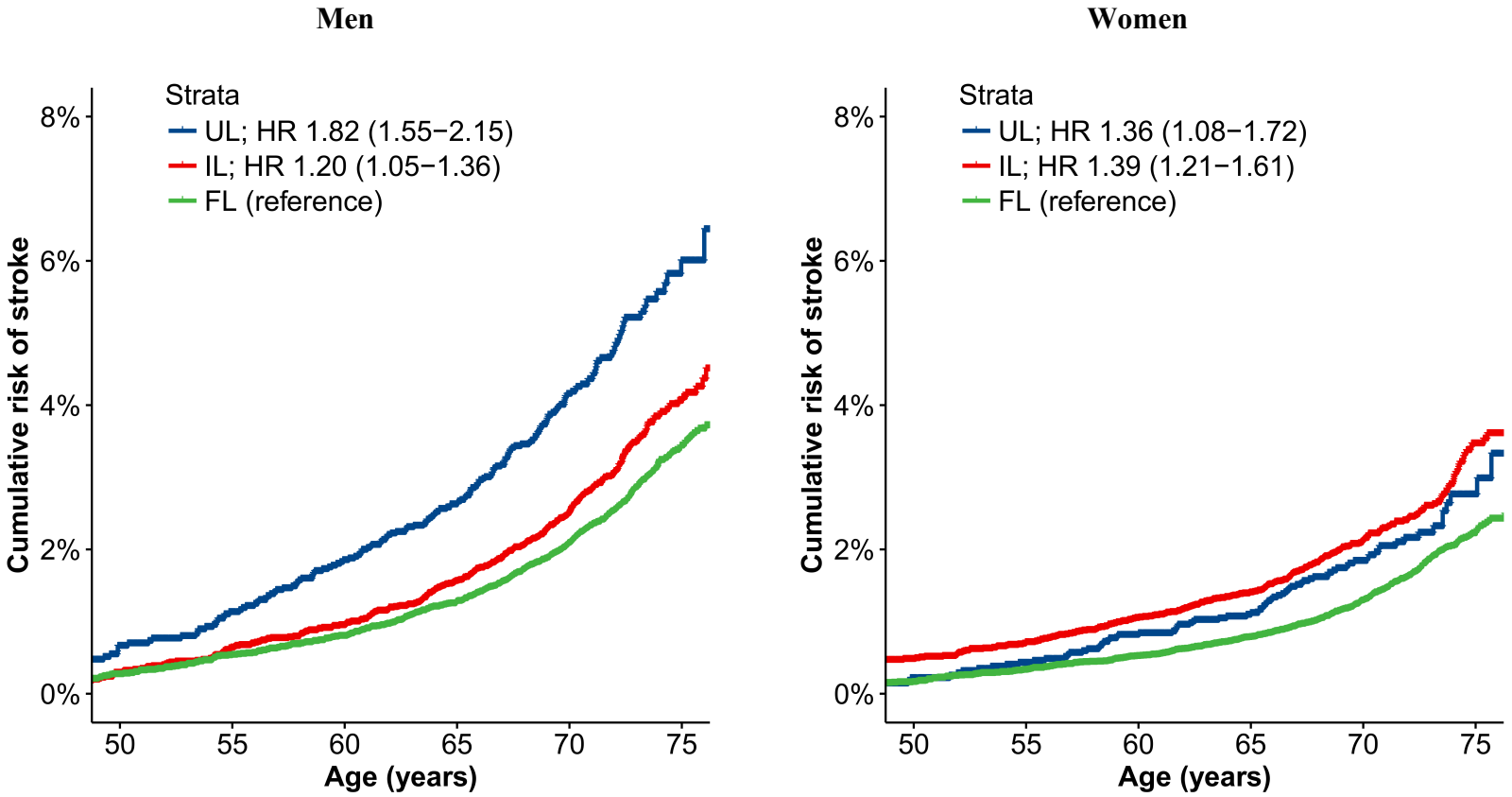
Abbreviations: HG. high genetic risk; IG, intermediate genetic risk; LG, low genetic risk; UL, unfavourable lifestyle; IL, intermediate lifestyle; FL, favourable lifestyle

Figure S5 Standardized risk of incident stroke according to genetic risk stratified by sex



Abbreviations: HG, high genetic risk; IG, intermediate genetic risk; LG, low genetic risk

Figure S6 Standardized risk of incident stroke according to lifestyle profile stratified by sex



Abbreviations: UL, unfavourable lifestyle; IL, intermediate lifestyle; FL, favourable lifestyle

Supplemental References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017;135(10):e146-e603. doi: 10.1161/CIR.0000000000000485
2. Malik R, Chauhan G, Traylor M, et al. Multi-ancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet.* 2018 Apr;50(4):524-537. 10.1038/s41588-018-0058-3