

Supplementary Material
**Genetic predisposition, modifiable lifestyles, and their joint effects on
human lifespan: evidence from multiple cohort studies**

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Supplementary methods

Study population and data collection

US NHANES enrolled a representative sample of the total noninstitutionalized civilian U.S. population with demographic, examination, dietary, questionnaire and laboratory data using a complex, multi-stage sample design. We retrieved and preprocess publicly available data sets from the NHANES 2005 to 2018 surveys (seven cycles: 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016 and 2017-2018) according to our research purpose. US NHANES received approval from the National Centre for Health Statistics Research Ethics Review Board.

UK Biobank is a large population-based cohort study including approximately half a million individuals aged 40 to 69 years between 2006 and 2010¹. Briefly, the UK Biobank recruited participants from 22 assessment centers, largely in urban areas of England, Wales, and Scotland at baseline. Participants provided information on lifestyle and other potentially health-related information through extensive baseline questionnaires, interviews, and physical measurements. Blood samples were also collected for genotyping. The UK Biobank was approved by the North West Multi-centre Research Ethics Committee (MREC). Access to UK Biobank data was granted through the UK Biobank application number 66354.

Healthy lifestyle score

NHANES and UK biobank cohorts are largely identical, except for healthy diet. Smoking status was defined as never or ever smoking. Participants who never smoked and those who previously smoked occasionally or just tried once or twice but did not smoke 100 times in lifetime were categorized into “never smoking” group.² Regular physical activity was referred to those exercised at least ≥ 150 minutes moderate activity per week or ≥ 75 minutes vigorous activity per week (or an equivalent

combination) or engaged in moderate physical activity at least 5 days a week or vigorous activity once a week, as recommended by the American Heart Association.³In UK biobank, dietary intake information was collected by a food frequency questionnaire at baseline. Considering those who consumed an adequate amount of fruits, vegetables, whole grains, fish, and a reduced amount of red meats and processed meats following recommendations on dietary priorities for cardiometabolic health, healthy diet was referred as meeting consumption guidelines of at least 4 of 7 food groups⁴. In US NHANES, dietary quality was obtained from 24 hour dietary recalls and was assessed by healthy eating index 2015 (HEI-2015) scores.⁵ A healthy diet was defined as the health eating index in the top one fourths of the distribution. A meta-analysis about the correlation between alcohol consumption and all-cause mortality suggested a U-shaped relationship, with moderate consumption associated with lower risk.⁶ Therefore, moderate consumption was defined as 0 to 14 g for female and 0 to 28g for male per day. Healthy body shape was defined as 18.5-30.0 kg/m² according to World Health Organization standards for the European population. Sleep duration was defined as normal (7.0-8.0 hours/day) and abnormal sleep duration (<7 or >8 hours/day).⁷

Covariates

In US NHANES, models were adjusted by age (continuous in years), age square, sex (men and women), race (white and non-white), education (college or university degree and above, and high school and below), poverty to income ratio (low (≤ 1), middle (1-4), and high (≥ 4))⁸ and history of hypertension, diabetes, CVD and cancer.

Life expectancy

The flexible parametric survival models with age as timescale were applied to estimate life expectancy. The calculation of years of life gained (difference in average life expectancy) involved a two-step process. First, residual life expectancy was estimated

as the area under the survival curve up to 100 years old, conditional on surviving at ages 40–100 years old (1-year intervals); survival curves were predicted for each individual and averaged over individuals. Second, years of life gained were calculated as the difference between the areas under two survival curves.

Reference

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Supplementary table 1. Genetic variants associated with lifespan

Gene	SNP	Chr	Position	Effect allele	Freq1	Beta	SE	P	SSE P	Disease
GBX2/ASB18	rs10211471	2	237081854	C	0.8	0.2401	0.0493	1.10E-06	2.30E-08	Education
LPA	rs10455872	6	161010118	A	0.92	0.7639	0.0743	8.50E-25	3.10E-24	Cardiometabolic
ATXN2/BRAP	rs11065979	12	112059557	C	0.56	0.2798	0.0393	1.00E-12	6.20E-13	Autoimmune/Cardiometabolic
IGF2R	rs111333005	6	160487196	G	0.98	0.8665	0.1577	3.90E-08	6.60E-09	LDL/CAD
POM121C	rs113160991	7	75094329	G	0.78	0.2541	0.0495	2.80E-07	7.50E-09	BMI/Insulin
MAGI3	rs1230666	1	114173410	G	0.85	0.3224	0.0555	6.40E-09	6.10E-08	Autoimmune
KCNK3	rs1275922	2	26932887	G	0.74	0.2579	0.0443	6.00E-09	2.70E-07	Cardiometabolic
HP	rs12924886	16	72075593	A	0.8	0.2798	0.0493	1.40E-08	9.10E-08	Cardiometabolic
LDLR	rs142158911	19	11190534	A	0.12	0.355	0.0616	8.10E-09	3.30E-08	Cardiometabolic
CDKN2B-AS1	rs1556516	9	22100176	G	0.5	0.251	0.0386	7.50E-11	6.40E-12	Cardiometabolic
ABO	rs2519093	9	136141870	C	0.81	0.2244	0.0497	6.30E-06	1.90E-08	LDL/CAD
HLA-DQA1	rs34967069	6	32591248	T	0.07	0.5613	0.0956	4.30E-09	3.60E-09	Autoimmune
APOE	rs429358	19	45411941	T	0.85	1.0561	0.0546	3.10E-83	1.80E-85	Cardiometabolic/Neuropsychiatric
CELSR2/PSRC1	rs4970836	1	109821797	G	0.23	0.2234	0.0463	1.40E-06	1.60E-09	LDL/HDL/CAD
ZC3HC1	rs56179563	7	129685597	A	0.39	0.2107	0.0406	2.10E-07	5.60E-09	CAD
HTT	rs61348208	4	3089564	T	0.39	0.2299	0.0395	5.80E-09	1.20E-07	-
FURIN/FES	rs6224	15	91423543	G	0.52	0.2507	0.039	1.30E-10	1.80E-09	Cardiometabolic
TMEM18	rs6744653	2	628524	A	0.17	0.2772	0.0511	5.80E-08	7.00E-10	BMI
CHRNA3/5	rs8042849	15	78817929	T	0.65	0.4368	0.041	1.60E-26	1.90E-30	Smoking-related

Chr – Chromosome; Position – Base-pair position on chromosome (GRCh37); A1 – the effect allele, increasing lifespan; Freq1 – Frequency of the A1 allele; Years1 – Years of life gained for carrying one copy of the A1 allele; SE – Standard Error; P – the P value for the Wald test of association between imputed dosage and cox model residual; SSE P -The index SNP with the lowest P value in the standard or sex-specific effect (SSE) analysis

Supplementary table 2. Healthy lifestyle factor definitions

Healthy lifestyle factor	Source and definition	Self-reported UK Biobank field code
Never smoking	UK Biobank Touchscreen questionnaire at baseline; Smoking status was defined as current, previous, never smoker. participants who never smoked and those who previously smoked occasionally or just tried once or twice but did not smoke 100 times in lifetime were categorized into “never smoking” group. Others with no missing information on smoking would be viewed as ever smokers.	20116, 2897
Regular physical activity	UK Biobank Touchscreen questionnaire at baseline; ≥ 150 minutes moderate activity per week OR ≥ 75 minutes vigorous activity per week OR equivalent combination OR moderate physical activity at least 5 days a week and vigorous activity once a week	884, 894, 904, 914
Healthy diet	UK Biobank Food Frequency Questionnaire at baseline; At least 4 of the following 7 food groups: 1. Fruits: ≥ 3 servings/day 2. Vegetables: ≥ 3 servings/day 3. Fish: ≥ 2 times/week 4. Processed meats: ≤ 1 times/week 5. Unprocessed red meats: ≤ 2 times/week 6. Whole grains: ≥ 3 servings/day 7. Refined grains: ≤ 2 servings/day	1309, 1319, 1289, 1299, 1329, 1339, 1349, 1369, 1379, 1389, 1438, 1448, 1458, 1468
Moderate alcohol consumption	UK Biobank Touchscreen questionnaire at baseline; UK Biobank Touchscreen questionnaire on whether the participant reported drinking alcohol, frequency of intake, beverage type, whether they usually drink with meals. US Dietary Guidelines for Americans 2015-2020 of up to 1 drink/day for women and up to 2 drinks/day for men. To calculate drink-equivalents as per guidelines, multiply the volume in ounces by the alcohol content in percent and divide by 0.6 ounces of alcohol per drink-equivalent; then convert to grams: 1 drink-equivalent described as containing 14g of pure alcohol. 125ml wine=0.85 drink-equivalents, 4% ABV pint beer = 1.28 drink-equivalents, 25ml spirits=0.57 drink-equivalents, 50ml fortified wine= 0.56 drink-equivalents	20117, 1558, 1568, 1578, 1588, 1598, 1608, 5364, 4407, 4418, 4429, 4440, 4451, 4462
Healthy body shape	UK Biobank Physical measures at baseline;	21001

	UK Biobank measured body composition manually at baseline, and BMI was constructed from height and weight measured (weight/height-square, Kg/m ²), 18.5-30	
Adequate sleep	UK Biobank Touchscreen questionnaire at baseline; UK Biobank Touchscreen question 'About how many hours sleep do you get in every 24 hours? (Please include naps)' 1-Sleep duration ≥ 7 and ≤ 8	1160

Supplementary table 3. ICD-9-CM and ICD-10 Coding Algorithms for Charlson Comorbidities

Comorbidities	ICD-10	Deyo's ICD-9-CM
Myocardial infarction	I21.x, I22.x, I25.2	410.x, 412.x
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0	428.x
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	443.9, 441.x, 785.4, V43.4, Procedure 38.48
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x	430.x–438.x
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1	290.x
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3	490.x–505.x, 506.4
Rheumatic disease	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0	710.0, 710.1, 710.4, 714.0–714.2, 714.81, 725.x
Peptic ulcer disease	K25.x–K28.x	531.x–534.x
Mild liver disease	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4	571.2, 571.4–571.6
Diabetes without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	250.0–250.3, 250.7
Diabetes with chronic complication	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7	250.4–250.6
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9	344.1, 342.x
Renal disease	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2	582.x, 583–583.7, 585.x, 586.x, 588.x

Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x	140.x–172.x, 174.x.–195.8, 200.x–208.x
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	456.0–456.21, 572.2–572.8
Metastatic solid tumor	C77.x–C80.x	196.x–199.1
AIDS/HIV	B20.x–B22.x, B24.x	042.x–044.x

Supplementary table 4. Associations Between the Polygenic Risk Score and Healthy lifestyle factors

Healthy lifestyle Factors	Polygenic risk score of death	
	OR (95% CI)	P value
Never smoking	1 (0.99-1.01)	8.74E-01
Moderate alcohol consumption	1 (0.99-1.01)	5.77E-01
Healthy body shape	1.01 (1-1.01)	1.13E-01
Moderate sleep duration (7-8h)	0.99 (0.99-1)	5.29E-02
Healthy diet	1.02 (1.01-1.03)	4.29E-07
Regular physical activity	1.01 (1-1.01)	5.20E-02

Adjusted for age, age-square, sex, socioeconomic status quintile, education, CCI, first 20 principal components of ancestry, and other healthy lifestyle factors.

Supplementary table 5. Baseline characteristics of eligible participants in US NHANES.

Characteristic	All (No. (%) ^a)	
	Alive (n=17885)	Death (n=1599)
Age (mean (SD))	45.09 (0.25)	66.79 (0.47)
Gender (%)		
Male	8587 (48.4)	905 (53.26)
Female	9298 (51.6)	694 (46.74)
Race (%)		
Mexican American	2812 (8.22)	114 (3.34)
Other Hispanic	1706 (5.25)	83 (2.26)
Non-Hispanic White	7824 (69.71)	1038 (81.57)
Non-Hispanic Black	3628 (10.09)	302 (9.85)
Other Race - Including Multi-	1915 (6.72)	62 (2.98)
Racial		
Marital status		
Married	9475 (57.09)	752 (48.44)
Unmarried	8410 (42.91)	847 (51.56)
Education (%)		
College or above	10290 (64.75)	667 (47.53)
High school or equivalent	4077 (22.91)	431 (27.97)
Less than high school	3518 (12.34)	501 (24.5)
PIR ^b (%)		
High	5125 (39.74)	290 (24.57)
Low	3394 (12.37)	317 (15.29)
Medium	9366 (47.89)	992 (60.14)
Healthy lifestyle factors		
No current smoking	10328 (57.27)	665 (42.62)
Moderate alcohol consumption	10018 (54.14)	1182 (71.93)
No obesity	4783 (27.96)	429 (26.28)
Adequate sleep duration (7-8h)	9047 (53.7)	796 (50.96)
Healthy diet	3803 (21.57)	369 (23.3)
Regular physical activity	7872 (47)	466 (32.24)
No. of healthy lifestyle factors (%)		
0	643 (3.24)	76 (4.24)
1	2799 (15.09)	256 (16.13)
2	5345 (29.4)	524 (31.96)
3	5139 (28.52)	449 (28.85)
4	2968 (17.46)	223 (14.06)
5	873 (5.39)	62 (4.07)
6	118 (0.9)	9 (0.69)

Supplementary table 6. Associations Between the Healthy lifestyle factors and lifespan in US NHANES.

Healthy lifestyle factors	coefficients	HR (95%CI)^a	P value
Never smoking	-0.31	0.73 (0.64-0.84)	9.38E-06
Moderate alcohol consumption	-0.19	0.83 (0.7-0.98)	3.15E-02
Healthy body shape	-0.05	0.95 (0.83-1.09)	4.66E-01
Moderate sleep duration (7-8h)	-0.21	0.81 (0.73-0.9)	8.77E-05
Healthy diet	-0.25	0.78 (0.66-0.93)	5.09E-03
Regular physical activity	-0.25	0.78 (0.68-0.89)	3.17E-04

a Adjusted for age, age-square, sex, race, education, poverty to income ratio and history of CVD, cancer, diabetes or hypertension.

Supplementary table 7. Association of risk of death with lifestyle categories by genetic risk level.

Polygenic risk score (quintiles)	Events/Person-years	Model 1 ^a		Model 2 ^b	
		HR (95% CI)	P value	HR (95% CI)	P value
1 (the Longest)	4510/4944075	1 [Reference]		1 [Reference]	
2	4660/4943487	1 (0.96-1.05)	0.865933	1.01 (0.97-1.05)	0.6574
3	4839/4940643	1.09 (1.04-1.13)	6.87E-05	1.09 (1.04-1.13)	4.52E-05
4	4834/4937289	1.08 (1.03-1.12)	0.000445	1.08 (1.04-1.13)	0.000128
5 (the Shortest)	5396/4933241	1.21 (1.16-1.26)	5.17E-21	1.21 (1.17-1.26)	1.45E-21
<i>p</i> value for trend ^c			1.53E-29		4.64E-30

a Adjusted for age, age-square, sex, socioeconomic status quintile, education, CCI, and first 20 principal components of ancestry.

b Adjusted for Model 1 and weighted lifestyle category or genetic risk category

c The P value for trend was calculated using genetic risk or healthy lifestyle scores as continuous variables.

Supplementary table 8. Association of risk of death with unweighted lifestyle score.

Number of healthy lifestyle factors	Events/Person-years	Model 1 ^a		Model 2 ^b	
		HR (95% CI)	P value	HR (95% CI)	P value
6	788/1461633	Reference	Reference	Reference	Reference
5	3225/4729158	1.16 (1.07-1.25)	2.75E-04	1.15 (1.07-1.25)	3.14E-04
4	6076/7153088	1.34 (1.24-1.44)	1.49E-14	1.34 (1.24-1.44)	1.27E-14
3	6946/6438598	1.58 (1.47-1.7)	1.72E-33	1.58 (1.47-1.7)	9.79E-34
2	4901/3576508	1.95 (1.81-2.1)	2.33E-66	1.95 (1.81-2.1)	1.50E-66
1	1949/1176002	2.2 (2.02-2.39)	7.58E-76	2.2 (2.02-2.39)	8.22E-76
0	354/163748	2.91 (2.57-3.3)	9.42E-62	2.91 (2.57-3.31)	7.95E-62
<i>p</i> value for trend ^c			<0.001		<0.001

^a Adjusted for age, age-square, sex, socioeconomic status quintile, education, CCI, and first 20 principal components of ancestry.

^b Adjusted for Model 1 and weighted lifestyle category or genetic risk category

Supplementary table 9. Cox proportional-hazards models investigating the association between lifestyle and lifespan by APOE ϵ 4 carrier status

APOE ϵ4 carrier status	Events/Person-years	HR (95% CI)	P value
Non-APOE ϵ4 carrier			
Favorable lifestyle	2272/3320221	1 [Reference]	
Intermediate lifestyle	6950/7959792	1.18 (1.12-1.24)	1.31E-11
Unfavorable lifestyle	4458/3098645	1.78 (1.69-1.88)	7.45E-107
<i>p</i> value for trend ^a			1.70E-167
APOE ϵ4 carrier			
Favorable lifestyle	1767/2398434	1 [Reference]	
Intermediate lifestyle	5420/5756799	1.21 (1.15-1.28)	2.35E-12
Unfavorable lifestyle	3372/2164845	1.76 (1.66-1.87)	1.29E-79
<i>p</i> value for trend ^a			2.89E-113

^a The P value for trend was calculated using genetic risk or healthy lifestyle scores as continuous variables.

Supplementary table 10. Risk of death According to Genetic and Lifestyle Risk with Unweighted and Weighted Lifestyle Score before and After Excluding Participants with Incomplete Data of Covariables

Subgroup	All participants (n=353742)			Participants with incomplete data of covariables excluded (n=353,170)					
	Unweighted lifestyle categories (n=424,533)			Unweighted lifestyle categories			Weighted lifestyle categories		
	Events/Person-years	HR (95%CI)	P value	Events/Person-years	HR (95%CI)	P value	Events/Person-years	HR (95%CI)	P value
Long genetic risk									
Favorable lifestyle	735/1234933	Reference	Reference	725/1226646	Reference	Reference	713/1248649	Reference	Reference
Intermediate lifestyle	3351/3431280	1.4 (1.3-1.52)	9.69E-17	3321/3404364	1.41 (1.3-1.53)	6.09E-17	3257/3377387	1.48 (1.37-1.61)	1.82E-21
Unfavorable lifestyle	424/277862	1.95 (1.73-2.19)	1.56E-27	419/276632	1.94 (1.72-2.19)	6.17E-27	495/281606	2.29 (2.04-2.57)	3.76E-45
Intermediate genetic risk									
Favorable lifestyle	2358/3703484	1.07 (0.99-1.17)	9.44E-02	2330/3679574	1.07 (0.99-1.17)	8.96E-02	2344/3727759	1.1 (1.01-1.19)	3.08E-02
Intermediate lifestyle	10582/10318349	1.46 (1.36-1.58)	3.70E-23	10474/10244576	1.46 (1.36-1.58)	4.30E-23	10345/10185482	1.55 (1.44-1.67)	1.36E-29
Unfavorable lifestyle	1393/799587	2.24 (2.05-2.45)	6.59E-69	1380/795216	2.24 (2.04-2.45)	4.90E-68	1495/806125	2.45 (2.24-2.68)	2.53E-85
Short genetic risk									
Favorable lifestyle	920/1252375	1.19 (1.08-1.31)	3.58E-04	913/1244370	1.2 (1.09-1.32)	2.60E-04	888/1243201	1.26 (1.14-1.39)	3.63E-06
Intermediate lifestyle	3990/3418565	1.72 (1.59-1.87)	9.09E-42	3953/3394116	1.73 (1.6-1.87)	7.07E-42	3917/3390494	1.81 (1.67-1.96)	1.23E-47
Unfavorable lifestyle	486/262301	2.22 (1.98-2.49)	9.44E-42	481/260367	2.35 (2.1-2.64)	1.60E-47	542/265158	2.61 (2.33-2.92)	4.43E-63

Adjusted for age, age-square, sex, TDI, education, CCI, and first 20 principal components of ancestry

Supplementary table 11. Risk of death according to genetic and lifestyle risk with additional adjustment for depressive symptoms and family history of cancer, CVD or diabetes

Subgroup	Family history ^a			Depressive symptoms ^b		
	Events/Person-years	HR (95%CI)	P value	Events/Person-years	HR (95%CI)	P value
Long genetic risk						
Favorable lifestyle	734/1140555	1 [Reference]		1 [Reference]		Reference
Intermediate lifestyle	2284/2732093	1.21 (1.11-1.31)	9.10E-06	1.22 (1.12-1.33)	5.02E-06	1.82E-21
Unfavorable lifestyle	1492/1071428	1.79 (1.64-1.96)	4.02E-38	1.78 (1.62-1.95)	9.84E-35	3.77E-45
Intermediate genetic risk						
Favorable lifestyle	2381/3431436	1.06 (0.98-1.15)	0.151626	1.08 (0.99-1.18)	0.078509	3.08E-02
Intermediate lifestyle	7257/8236031	1.26 (1.16-1.36)	3.83E-09	1.26 (1.17-1.37)	4.25E-09	1.36E-29
Unfavorable lifestyle	4695/3153952	1.95 (1.8-2.11)	6.95E-63	1.96 (1.81-2.12)	5.25E-60	2.57E-85
Short genetic risk						
Favorable lifestyle	924/1146664	1.26 (1.14-1.39)	3.15E-06	1.28 (1.16-1.41)	1.22E-06	3.63E-06
Intermediate lifestyle	2829/2748468	1.5 (1.39-1.63)	7.18E-23	1.5 (1.38-1.63)	1.81E-21	1.23E-47
Unfavorable lifestyle	1643/1038110	2.04 (1.86-2.22)	4.47E-57	2.02 (1.84-2.21)	1.35E-52	4.51E-63

^a Self-reported family history of cancer, CVD or diabetes

^b Depression symptoms, assessed using a 2-item depression scale (PHQ-2)

Supplementary table 12. Risk of death According to Genetic and Lifestyle Risk Stratified by Covariates

Subgroup	Age ≤ 60		Age >60		Female		Male		College/University degree		No college/university degree	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Long genetic risk												
Favorable lifestyle	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Intermediate lifestyle	1.12 (0.96-1.32)	0.151802	1.24 (1.12-1.37)	1.93E-05	1.15 (1.03-1.29)	0.016988	1.27 (1.12-1.43)	0.000115	1.21 (1.05-1.39)	0.007536	1.22 (1.1-1.35)	0.0002
Unfavorable lifestyle	1.65 (1.39-1.95)	5.76E-09	1.86 (1.67-2.06)	3.75E-31	1.64 (1.43-1.87)	8.27E-13	1.93 (1.71-2.19)	2.10E-25	1.63 (1.39-1.91)	1.55E-09	1.89 (1.69-2.1)	3.40E-30
Intermediate genetic risk												
Favorable lifestyle	0.98 (0.84-1.15)	0.82781	1.09 (0.99-1.2)	0.073151	1.05 (0.94-1.17)	0.396471	1.07 (0.95-1.22)	0.254318	1.02 (0.89-1.17)	0.764103	1.09 (0.98-1.21)	0.104975
Intermediate lifestyle	1.14 (0.98-1.31)	0.082464	1.32 (1.2-1.44)	1.70E-09	1.18 (1.06-1.31)	0.002026	1.35 (1.2-1.51)	1.89E-07	1.16 (1.02-1.31)	0.023176	1.33 (1.2-1.46)	8.39E-09
Unfavorable lifestyle	1.72 (1.48-2)	7.83E-13	2 (1.83-2.2)	1.57E-49	1.78 (1.59-1.99)	2.72E-24	2.09 (1.87-2.34)	2.41E-37	1.75 (1.54-2)	6.68E-17	2.05 (1.86-2.27)	3.23E-47
Short genetic risk												
Favorable lifestyle	1.11 (0.92-1.34)	0.278682	1.32 (1.18-1.48)	1.50E-06	1.21 (1.06-1.38)	0.004016	1.31 (1.13-1.51)	0.000233	1.24 (1.06-1.46)	0.007254	1.27 (1.13-1.44)	0.000109
Intermediate lifestyle	1.29 (1.1-1.51)	0.001316	1.59 (1.44-1.75)	2.16E-21	1.33 (1.18-1.49)	1.12E-06	1.66 (1.48-1.87)	3.34E-17	1.5 (1.31-1.72)	3.11E-09	1.52 (1.37-1.68)	1.40E-15
Unfavorable lifestyle	1.98 (1.68-2.33)	4.00E-16	2.05 (1.85-2.28)	1.82E-42	1.99 (1.74-2.27)	9.14E-25	2.13 (1.88-2.41)	1.43E-33	1.83 (1.57-2.14)	2.68E-14	2.12 (1.91-2.36)	6.06E-43
Subgroup	T1		T2		T3		Charlson comorbidities index = 0		Charlson comorbidities index > 0			
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value		
Long genetic risk												
Favorable lifestyle	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference		
Intermediate lifestyle	1.15 (0.96-1.38)	0.117651	1.19 (1.07-1.33)	0.001268	1.35 (1.1-1.64)	0.003262	1.16 (1.05-1.28)	0.003287	1.36 (1.16-1.58)	0.000106		
Unfavorable lifestyle	1.5 (1.22-1.85)	0.000127	1.75 (1.56-1.97)	5.29E-21	2.24 (1.84-2.73)	1.53E-15	1.75 (1.57-1.94)	2.59E-24	1.82 (1.55-2.14)	1.67E-13		
Intermediate genetic risk												
Favorable lifestyle	1.08 (0.91-1.29)	0.397684	1.07 (0.96-1.19)	0.231847	1.06 (0.86-1.3)	0.581926	1.06 (0.96-1.17)	0.21395	1.09 (0.94-1.28)	0.255491		
Intermediate lifestyle	1.2 (1.02-1.41)	0.028372	1.22 (1.11-1.35)	4.85E-05	1.5 (1.25-1.81)	1.35E-05	1.27 (1.16-1.39)	2.44E-07	1.34 (1.16-1.55)	5.30E-05		
Unfavorable lifestyle	1.64 (1.38-1.96)	1.75E-08	1.83 (1.66-2.03)	7.89E-32	2.53 (2.1-3.04)	5.92E-23	1.86 (1.7-2.04)	6.56E-39	1.94 (1.68-2.24)	2.98E-19		
Short genetic risk												
Favorable lifestyle	1.31 (1.07-1.61)	0.010045	1.29 (1.14-1.47)	4.11E-05	1.11 (0.87-1.42)	0.392407	1.29 (1.15-1.45)	1.23E-05	1.19 (0.99-1.43)	0.061173		
Intermediate lifestyle	1.4 (1.17-1.67)	0.000215	1.43 (1.29-1.59)	2.32E-11	1.9 (1.57-2.31)	4.72E-11	1.52 (1.38-1.68)	9.30E-18	1.44 (1.24-1.68)	2.14E-06		
Unfavorable lifestyle	1.65 (1.35-2.03)	1.61E-06	1.93 (1.72-2.16)	6.17E-29	2.67 (2.2-3.25)	7.05E-23	2.04 (1.84-2.27)	6.64E-40	1.92 (1.64-2.25)	4.09E-16		

Supplementary table 13. Life expectancy at different years old according to genetic risk and lifestyle categories

Subgroup	Age					
	40	45	50	55	60	65
Long						
Favorable lifestyle	52.52 (52-53.01)	47.52 (47-48.01)	42.52 (42-43.01)	37.52 (37.01-38.02)	32.54 (32.02-33.03)	27.57 (27.06-28.06)
Intermediate lifestyle	50.7 (50.29-51.11)	45.7 (45.29-46.11)	40.71 (40.29-41.11)	35.71 (35.3-36.12)	30.73 (30.32-31.14)	25.78 (25.37-26.18)
Unfavorable lifestyle	47.05 (46.55-47.55)	42.05 (41.55-42.55)	37.05 (36.55-37.55)	32.06 (31.57-32.56)	27.09 (26.6-27.59)	22.17 (21.68-22.67)
Intermediate						
Favorable lifestyle	52.11 (51.73-52.48)	47.11 (46.73-47.48)	42.11 (41.74-42.48)	37.12 (36.74-37.49)	32.13 (31.76-32.5)	27.17 (26.8-27.54)
Intermediate lifestyle	50.27 (49.92-50.61)	45.27 (44.92-45.61)	40.27 (39.93-40.61)	35.28 (34.93-35.62)	30.3 (29.95-30.63)	25.35 (25.01-25.68)
Unfavorable lifestyle	46.43 (46.06-46.81)	41.43 (41.06-41.81)	36.44 (36.06-36.81)	31.45 (31.08-31.83)	26.48 (26.11-26.86)	21.57 (21.2-21.94)
Short						
Favorable lifestyle	51.05 (50.53-51.56)	46.05 (45.53-46.56)	41.05 (40.53-41.56)	36.06 (35.54-36.57)	31.08 (30.56-31.59)	26.12 (25.6-26.63)
Intermediate lifestyle	49.11 (48.7-49.52)	44.11 (43.7-44.52)	39.11 (38.7-39.53)	34.12 (33.71-34.53)	29.14 (28.73-29.55)	24.21 (23.8-24.61)
Unfavorable lifestyle	45.83 (45.35-46.32)	40.83 (40.35-41.32)	35.83 (35.35-36.32)	30.85 (30.36-31.33)	25.88 (25.4-26.37)	20.97 (20.5-21.46)
Subgroup	Age					
	70	75	80	85	90	95
Long						
Favorable lifestyle	22.66 (22.15-23.14)	17.85 (17.36-18.32)	13.24 (12.78-13.68)	8.96 (8.54-9.35)	5.19 (4.86-5.5)	2.14 (1.96-2.33)
Intermediate lifestyle	20.89 (20.49-21.29)	16.15 (15.75-16.53)	11.66 (11.29-12.03)	7.6 (7.27-7.93)	4.18 (3.91-4.44)	1.61 (1.46-1.76)
Unfavorable lifestyle	17.36 (16.88-17.85)	12.78 (12.32-13.24)	8.61 (8.19-9.04)	5.08 (4.72-5.44)	2.42 (2.16-2.68)	0.76 (0.64-0.89)
Intermediate						
Favorable lifestyle	22.26 (21.89-22.63)	17.47 (17.1-17.82)	12.88 (12.54-13.22)	8.65 (8.33-8.96)	4.95 (4.7-5.21)	2.02 (1.87-2.17)

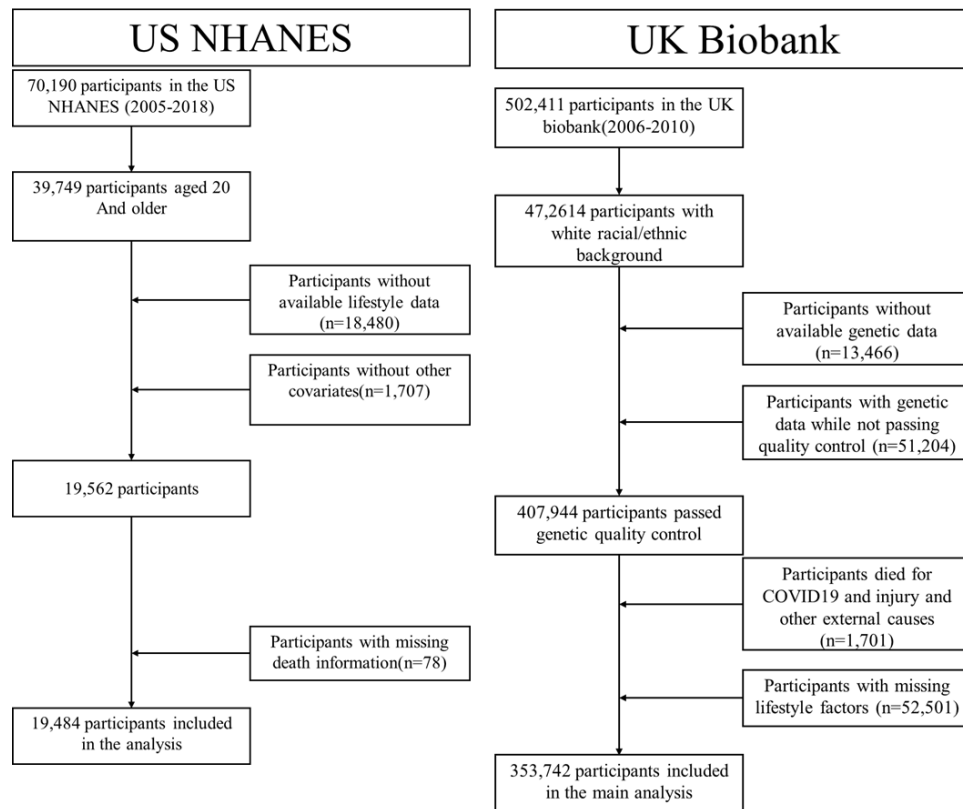
Intermediate lifestyle	20.47 (20.13-20.8)	15.74 (15.41-16.07)	11.29 (10.97-11.6)	7.28 (6.99-7.57)	3.95 (3.71-4.18)	1.49 (1.36-1.63)
Unfavorable lifestyle	16.77 (16.41-17.14)	12.22 (11.87-12.58)	8.11 (7.79-8.45)	4.68 (4.4-4.97)	2.16 (1.96-2.37)	0.65 (0.56-0.76)
Short						
Favorable lifestyle	21.23 (20.72-21.73)	16.47 (15.98-16.96)	11.96 (11.5-12.42)	7.86 (7.45-8.26)	4.37 (4.05-4.68)	1.71 (1.53-1.88)
Intermediate lifestyle	19.35 (18.95-19.75)	14.67 (14.28-15.06)	10.31 (9.94-10.68)	6.46 (6.14-6.79)	3.36 (3.11-3.62)	1.2 (1.07-1.34)
Unfavorable lifestyle	16.2 (15.73-16.67)	11.68 (11.24-12.13)	7.64 (7.24-8.05)	4.31 (3.98-4.65)	1.92 (1.7-2.16)	0.56 (0.46-0.66)

Supplementary table 14. The reconstruction of weighted healthy lifestyle score by eliminating one of healthy lifestyle factors

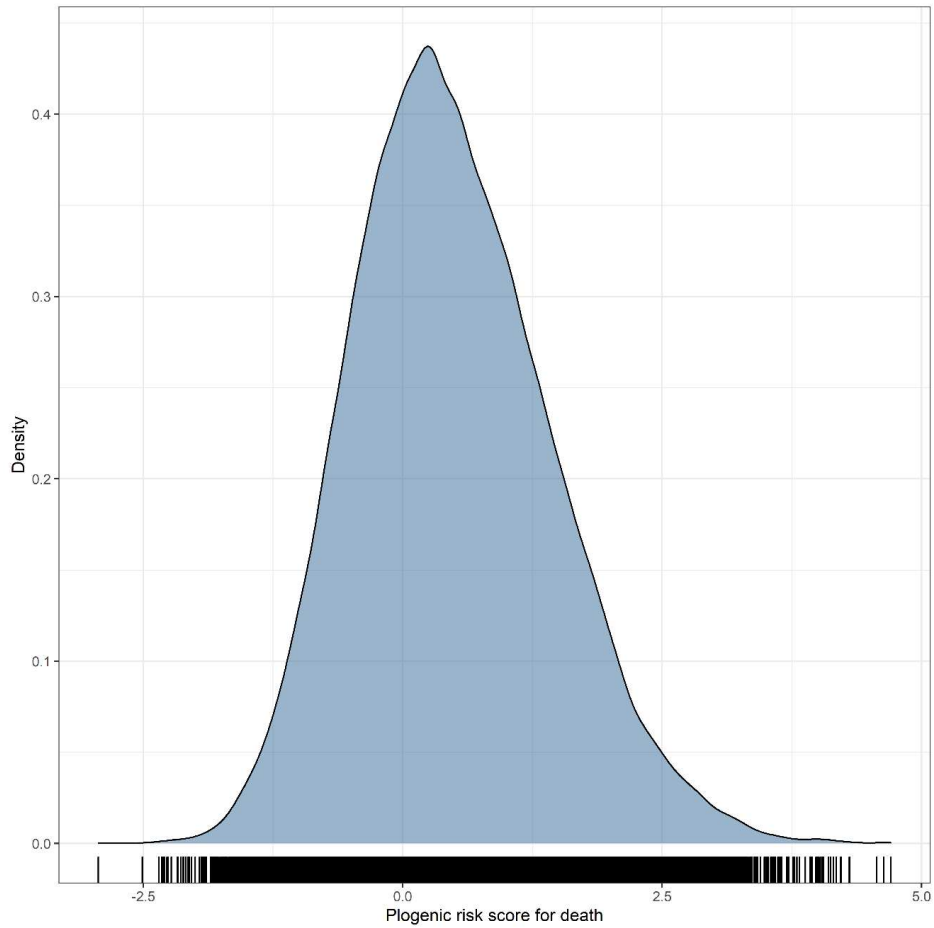
The elimination of factor	coefficients	HR	HR (95%CI)	P value
None	-9.55E-03	0.990493	0.99 (0.99-0.99)	0.00E+00
alcohol	-9.54E-03	0.990506151	0.99 (0.99-0.99)	0.00E+00
BMI	-9.41E-03	0.990629267	0.99 (0.99-0.99)	0.00E+00
diet	-8.24E-03	0.99179134	0.99 (0.99-0.99)	7.21e-310
sleep	-8.06E-03	0.991976259	0.99 (0.99-0.99)	2.25E-305
Physical activity	-7.76E-03	0.992271928	0.99 (0.99-0.99)	6.12E-278
smoking	-6.69E-03	0.993329442	0.99 (0.99-0.99)	3.38E-153

Adjusted for age, age-square, sex, socioeconomic status quintile, education, CCI, first 20 principal components of ancestry, and genetic risk categor

Supplementary figure 1. Flowchart of study population selection in the US NHANES and UK Biobank study.



Supplementary figure 2. Distribution of the polygenic risk score for the participants of death.



Supplementary figure 3. Cumulative probability plot of the risk of death by polygenic risk score categories and healthy lifestyle categories.

