Honigberg MC, Ye Y, Dattilo L, et al. Polygenic Risk, Frequency of Depressed Mood, and Cardiometabolic Disease.

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Supplementary Table 1. Baseline characteristics of included vs. excluded individuals.

Characteristic	Excluded	
	(n=32,316)	(N=328,152)
Age, years	59.0 (7.6)	56.8 (7.9)
Female sex	19,228 (59.5%)	173,333 (52.8%)
Townsend deprivation index (median [IQR])	-1.6 [-3.3, 1.6]	-2.4 [-3.8, -0.1]
Smoking status		
Current	4,690 (15.0%)	31,441 (9.6%)
• Former	10,924 (35.0%)	116,041 (35.4%)
Never	15,597 (50.0%)	180,670 (55.1%)
Body mass index, kg/m ²	28.5 (5.3)	27.3 (4.6)
Systolic blood pressure	142.8 (20.1)	140 (19.6)
Antihypertensive medication use	9,231 (28.6%)	65,869 (20.1%)
Cholesterol-lowering medication use	7,717 (23.9%)	55,075 (16.8%)
Non-HDL cholesterol, mg/dL	165.7 (44.0)	164.9 (41.5)
C-reactive protein, mg/L (median [IQR])	1.8 [0.9, 3.8]	1.3 [0.6, 2.6]
Coronary artery disease	2,109 (6.5%)	13,259 (4.0%)
Type 2 diabetes mellitus	1,245 (3.9%)	6,903 (2.1%)
Atrial fibrillation	702 (2.2%)	5,671 (1.7%)
Values are displayed as mean (SD) or n	(%) unloss other	vise specified

Values are displayed as mean (SD) or n (%) unless otherwise specified.

Supplementary Table 2. Absolute incidence rates for coronary artery disease, type 2 diabetes mellitus, and atrial fibrillation by polygenic risk and frequency of depressed mood.

Polygenic risk category	Frequency of depressed mood	Number of participants at risk	Events / person-years	Incidence rate per 1,000 person-years (95% CI)	Incidence rate difference (vs. highest frequency of depressed mood) (95% CI)	P-value
				Coronary artery dise	ease	
High	High	2,510	260 / 26,747	9.72 (8.54-10.90)	Reference	
High	Moderate	11,305	882 / 121,624	7.25 (6.77-7.73)	-2.47 (-3.74 to -1.19)	1.5x10 ⁻⁴
High	Low	47,034	3,849 / 505,565	7.61 (7.37-7.85)	-2.11 (-3.31 to -0.90)	6.1x10 ⁻⁴
Intermediate	High	7,441	565 / 80,185	7.05 (6.47-7.63)	Reference	
Intermediate	Moderate	34,561	1,909 / 376,361	5.07 (4.84-5.30)	-1.97 (-2.60 to -1.35)	5.6x10 ⁻¹⁰
Intermediate	Low	147,593	7,972 / 1,609,235	4.95 (4.85-5.06)	-2.09 (-2.68 to -1.50)	4.0x10 ⁻¹²
Low	High	2,449	143 / 26,623	5.37 (4.49-6.25)	Reference	
Low	Moderate	11,707	452 / 128,460	3.52 (3.19-3.84)	-1.85 (-2.79 to -0.91)	1.1x10 ⁻⁴
Low	Low	50,292	1,848 / 552,728	3.34 (3.19-3.50)	-2.03 (-2.92 to -1.13)	8.6x10 ⁻⁶
				Type 2 diabetes mel	litus	
High	High	2,520	314 / 26,517	11.84 (10.53-13.15)	Reference	
High	Moderate	11,622	916 / 124,939	7.33 (6.86-7.81)	-4.51 (-5.90 to -3.12)	2.2x10 ⁻¹⁰
High	Low	48,832	3,597 / 526,273	6.83 (6.61-7.05)	-5.01 (-6.34 to -3.68)	1.5x10 ⁻¹³
Intermediate	High	7,575	523 / 81,770	6.40 (5.85-6.94)	Reference	
Intermediate	Moderate	35,118	1,594 / 383,993	4.15 (3.94-4.35)	-2.25 (-2.83 to -1.66)	5.3x10 ⁻¹⁴
Intermediate	Low	150,472	6,022 / 1,651,081	3.65 (3.56-3.74)	-2.75 (-3.30 to -2.19)	<2.2x10 ⁻¹⁶
Low	High	2,528	100 / 27,818	3.59 (2.89-4.30)	Reference	
Low	Moderate	11,813	259 / 130,651	1.98 (1.74-2.22)	-1.61 (-2.36 to -0.87)	2.2x10 ⁻⁵
Low	Low	50,768	1,020 / 562,424	1.81 (1.70-1.92)	-1.78 (-2.49 to -1.07)	9.9x10 ⁻⁷

		Atrial fibrillation						
High	High	2,573	195 / 27,804	7.01 (6.03-8.00)	Reference			
High	Moderate	11,683	741 / 127,107	5.83 (5.41-6.25)	-1.18 (-2.25 to -0.11)	0.03		
High	Low	49,158	3,843 / 531,231	7.23 (7.01-7.46)	+0.22 (-0.79 to +1.23)	0.67		
Intermediate	High	7,796	378 / 85,468	4.42 (3.98-4.87)	Reference			
Intermediate	Moderate	35,418	1,393 / 389,586	3.58 (3.39-3.76)	-0.85 (-1.33 to -0.36)	6.0x10 ⁻⁴		
Intermediate	Low	150,722	7,004 / 1,652,523	4.24 (4.14-4.34)	-0.18 (-0.64 to +0.27)	0.43		
Low	High	2,558	68 / 28,232	2.41 (1.84-2.98)	Reference			
Low	Moderate	11,899	336 / 131,201	2.56 (2.29-2.83)	+0.15 (-0.48 to +0.79)	0.64		
Low	Low	50,673	1,439 / 559,929	2.57 (2.44-2.70)	+0.16 (-0.42 to +0.75)	0.59		

Two-sided P-values (unadjusted for multiple comparisons) were calculated from the chi-squared statistic for the difference in incidence rates using the 'fmsb' package in R version 3.6.0.

Supplementary Table 3. Hazard ratios for incident cardiometabolic disease associated with frequency of depression among individuals at high polygenic risk (i.e., individuals in the top quintile of polygenic risk).

			Model 1		Model 2	
	Frequency of depressed	No. at	Hazard ratio (95%		Hazard ratio (95%	
Condition	mood	risk	CI)	P-value	CI)	P-value
	High	2 5 1 0	1.00		1.00	
	High	2,510	(reference)		(reference)	
Coronany artony disease	Modorato	11 305	0.73	1 0×10 ⁻⁵	0.77	9.5×10^{-4}
Coronary artery disease	Woderale	11,305	(0.64-0.84)	1.0010	(0.66-0.90)	9.5710
		47.034	0.62	7 2×10 ⁻¹⁴	0.70	1.2×10^{-6}
	EOW	47,034	(0.54-0.70)	7.2810	(0.61-0.81)	1.2×10
	High	2,520	1.00		1.00	
			(reference)		(reference)	
Type 2 diabetes	Modorato	11 622	0.63	7 8x10 ⁻¹³	0.78	7.6x10 ⁻⁴
mellitus	Moderate	11,022	(0.55-0.71)	7.0710	(0.68-0.90)	
		18 832	0.50	$< 2.2 \times 10^{-16}$	0.66	3.0x10 ⁻¹⁰
	EGW	+0,002	(0.44-0.56)	~2.2710	(0.57-0.75)	
	High	2 573	1.00		1.00	
Atrial fibrillation	- Ingri	2,575	(reference)		(reference)	
	Moderate	11 683	0.83	0.02	0.88	0.16
	Moderate	11,000	(0.71-0.97)	0.02	(0.74-1.05)	0.10
		49 158	0.79	0.001	0.87	0.10
	200	+5,150	(0.68-0.91)	0.001	(0.74-1.02)	0.10

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted Cox proportional hazard models. Model 1: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index

Model 2: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, prevalent type 2 diabetes mellitus (models for coronary artery disease and atrial fibrillation only), body-mass index, C-reactive protein

Supplementary Table 4. Hazard ratios for incident cardiometabolic and cardiovascular disease associated with frequency of depression, excluding individuals (n=25,092) with prevalent coronary artery disease, type 2 diabetes, atrial fibrillation, ischemic stroke, peripheral artery disease, and/or heart failure from all models.

			Model 1		Model 2		
			Hazard ratio		Hazard ratio		
Condition	Frequency of depressed mood	No. at risk	(95% CI)	P-value	(95% CI)	P-value	
	High	11 760	1.00		1.00		
	Tign	11,703	(reference)		(reference)		
Coronary artery	Moderate	55 361	0.72	<2.2×10 ⁻¹⁶	0.78	1.8×10 ⁻⁸	
disease	Widderate	55,501	(0.67-0.78)	~2.2810	(0.71-0.85)	1.0/10	
	Low	225 020	0.56	<2 2×10 ⁻¹⁶	0.66	<2 2×10 ⁻¹⁶	
	LOW	235,930	(0.52-0.61)	~2.2X10	(0.61-0.72)	~2.2X10	
	High	11 760	1.00		1.00		
	riigii	11,703	(reference)		(reference)		
Type 2 diabetes	Modorato	55,361	0.64	<2.2×10 ⁻¹⁶	0.79	8.7x10 ⁻⁹	
mellitus	Woderate		(0.59-0.70)	~2.2810	(0.72-0.86)		
		225 020	0.49	<2 2×10 ⁻¹⁶	0.66	$< 2.2 \times 10^{-16}$	
	LOW	233,930	(0.46-0.53)	~2.2810	(0.61-0.72)	~Z.ZX10	
	High	11 760	1.00		1.00		
Atrial fibrillation	Tiigit	11,703	(reference)		(reference)		
	Moderate	55 261	0.82	0.1v10 ⁻⁵	0.86	0.01	
	Woderate	55,501	(0.74-0.91)	9.1710	(0.77-0.96)	0.01	
	Low	225 020	0.77	1 4×10-8	0.83	2 2×10 ⁻⁴	
	LOW	235,930	(0.70-0.84)	1.4X10	(0.75-0.92)	3.3X10	

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted Cox proportional hazard models. Model 1: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index Model 2: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, body-mass index, C-reactive protein, and polygenic risk Supplementary Table 5. Hazard ratios for incident cardiometabolic disease associated with frequency of depression, accounting for antidepressant medication use.

		Further adjusted for antidepressant			Excludi	ng those (n=21,180) using
			medication use		antic	lepressant medicat	ions
	Frequency of		Hazard ratio			Hazard ratio	
Condition	depressed mood	No. at risk	(95% CI)	P-value	No. at risk	(95% CI)	P-value
	High	12 400	1.00		0 161	1.00	
	ніўн	12,400	(reference)		9,101	(reference)	
Coronary artery	Modorato	57 574	0.79	2 0×10 ⁻⁸	50.262	0.78	5.0v10 ⁻⁷
disease	Moderate	57,574	(0.73-0.86)	2.9710	50,202	(0.71-0.86)	5.0210
		244 010	0.69	$< 2.2 \times 10^{-16}$	235 470	0.68	<2 2×10 ⁻¹⁶
	LOW	244,919	(0.64-0.74)	~2.2X10	233,479	(0.62-0.74)	~2.2X10
	High	12 623	1.00		9 337	1.00	
	- I light	12,025	(reference)		5,001	(reference)	
Type 2 diabetes	Moderate	58,554	0.82	4 9x10⁻ ⁶	51 172	0.83	4 2×10⁻⁴
mellitus	moderate		(0.75-0.89)	4.0710	01,172	(0.75-0.92)	4.2710
	Low	250 072	0.72	8 6x10 ⁻¹⁶	240 498	0.69	6 8x10 ⁻¹⁴
		200,072	(0.67-0.78)	0.0710	240,400	(0.63-0.76)	0.0710
	High	12 927	1.00		9 503	1.00	
	i ngri	12,021	(reference)		0,000	(reference)	
Atrial fibrillation	Moderate	59 001	0.86	0.002	51 392	0.86	0.006
		00,001	(0.78-0.94)	0.002	01,002	(0.77-0.96)	0.000
	Low	250 553	0.81	4 0x10 ⁻⁶	240 770	0.80	3 8x10⁻⁵
	2011	200,000	(0.74-0.89)	1.0/10	240,770	(0.72-0.89)	0.0/10

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted Cox proportional hazard models. Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, prevalent type 2 diabetes mellitus (models for coronary artery disease and atrial fibrillation only), body-mass index, C-reactive protein, and polygenic risk Supplementary Table 6. Hazard ratios for incident cardiometabolic and cardiovascular disease, with follow-up truncated at December 31, 2019.

			Model 1		Model 2	
	Frequency of depressed		Hazard ratio (95%		Hazard ratio (95%	
Condition	mood	No. at risk	CI)	P-value	CI)	P-value
	High	11 760	1.00		1.00	
	i ligit	11,709	(reference)		(reference)	
Coronary artery	Modorato	55 361	0.70	<2 2×10 ⁻¹⁶	0.77	1 1×10-10
disease	Moderate	55,501	(0.65-0.75)	~2.2810	(0.71-0.84)	4.4710
		235 030	0.55	<2 2×10 ⁻¹⁶	0.66	<2 2×10 ⁻¹⁶
	LOW	233,930	(0.51-0.59)	~2.2810	(0.61-0.71)	~2.2810
	High	11 760	1.00		1.00	
	Tigri	11,703	(reference)		(reference)	
Type 2 diabetes	Moderate	55 361	0.65	<2.2×10 ⁻¹⁶	0.79	2 5×10 ⁻⁸
mellitus	INIOGETALE	33,301	(0.60-0.70)	-2.2710	(0.72-0.86)	2.0/10
	Low	235 030	0.50	<2.2x10 ⁻¹⁶	0.67	<2 2×10 ⁻¹⁶
	LOW	200,000	(0.46-0.53)		(0.62-0.72)	\$2.2710
	High	11 769	1.00		1.00	
	- Ingri	11,700	(reference)		(reference)	
Atrial fibrillation	Moderate	55 361	0.80	1 4x10 ⁻⁶	0.85	0.002
		30,001	(0.74-0.88)	1.4710	(0.77-0.94)	0.002
	Low	235 030	0.72	2 3×10 ⁻¹⁵	0.80	2 /v10 ⁻⁶
	200	200,900	(0.66-0.78)	2.5710	(0.73-0.88)	2.4710

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted Cox proportional hazard models.

Model 1: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index Model 2: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, body-mass index, C-reactive protein, and polygenic risk

			Model 1		Model 2	
Condition	PHQ-2 score	No. at risk	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
	3-6	14,364	1.00 (reference)		1.00 (reference)	
	1-2	69,955	0.74 (0.69-0.79)	<2.2x10 ⁻¹⁶	0.82 (0.76-0.89)	3.6x10 ⁻⁷
Coronary artery disease	0	225,787	0.58 (0.54-0.61)	<2.2x10 ⁻¹⁶	0.70 (0.65-0.75)	<2.2x10 ⁻¹⁶
	3-6	14,364	1.00 (reference)		1.00 (reference)	
	0-1	261,985	0.59 (0.55-0.63)	<2.2x10 ⁻¹⁶	0.71 (0.66-0.77)	<2.2x10 ⁻¹⁶
	3-6	14,639	1.00 (reference)		1.00 (reference)	
Type 2 diabetes mellitus	1-2	71,239	0.63 (0.59-0.67)	<2.2x10 ⁻¹⁶	0.77 (0.72-0.83)	2.3x10 ⁻¹¹
	0	230,507	0.47 (0.44-0.50)	<2.2x10 ⁻¹⁶	0.66 (0.61-0.71)	<2.2x10 ⁻¹⁶
	3-6	14,639	1.00 (reference)		1.00 (reference)	
	0-1	267,361	0.48 (0.45-0.51)	<2.2x10 ⁻¹⁶	0.66 (0.62-0.71)	<2.2x10 ⁻¹⁶
	3-6	14,980	1.00 (reference)		1.00 (reference)	
	1-2	71,771	0.83 (0.76-0.89)	2.3x10 ⁻⁶	0.85 (0.78-0.93)	4.3x10 ⁻⁴
Atrial fibrillation	0	230,792	0.72 (0.67-0.78)	<2.2x10 ⁻¹⁶	0.81 (0.74-0.88)	3.5x10 ⁻⁷
	3-6	14,980	1.00 (reference)		1.00 (reference)	
	0-1	267,804	0.73 (0.68-0.79)	<2.2x10 ⁻¹⁶	0.81 (0.74-0.88)	5.8x10 ⁻⁷

Supplementary Table 7. Hazard ratios for incident cardiometabolic disease associated with Patient Health Questionnaire-2 (PHQ-2) score.

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted Cox proportional hazard models. Model 1: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index Model 2: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol

intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, prevalent type 2 diabetes mellitus (models for coronary artery disease and atrial fibrillation models only), body-mass index, C-reactive protein, and polygenic risk

	Hazard ratio for interaction between polygenic risk	Darsha fan internation
Condition	and frequency of depressed mood (95% CI)	P-value for interaction
Coronary artery disease	0.95 (0.93-0.98)	0.002
Type 2 diabetes mellitus	1.00 (0.97-1.04)	0.85
Atrial fibrillation	0.97 (0.94-1.01)	0.12

Supplementary Table 8. Interactions between polygenic risk and frequency of depressed mood.

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted Cox proportional hazard models. Polygenic risk is modeled as a quantitative trait. Frequency of depressed mood is modeled as an ordinal variable.

Models are adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, prevalent type 2 diabetes mellitus (models for coronary artery disease and atrial fibrillation models only), body-mass index, C-reactive protein, polygenic risk, frequency of depressed mood, and interaction terms between frequency of depressed mood and each covariate.

Supplementary Table 9. Hazard ratios for incident coronary artery disease associated with frequency of depressed mood, stratified by polygenic risk tier.

			Model 1		Model 2	
Polygenic risk	Frequency of depressed mood	No. at risk	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
	High	2,510	1.00 (reference)		1.00 (reference)	
High	Moderate	11,305	0.73 (0.64-0.84)	1.0x10⁻⁵	0.77 (0.66-0.90)	9.5x10 ⁻⁴
	Low	47,034	0.62 (0.54-0.70)	7.2x10 ⁻¹⁴	0.70 (0.61-0.81)	1.2x10 ⁻⁶
	High	7,441	1.00 (reference)		1.00 (reference)	
Intermediate	Moderate	34,561	0.70 (0.64-0.78)	3.7x10 ⁻¹³	0.79 (0.71-0.88)	1.5x10⁻⁵
	Low	147,593	0.54 (0.49-0.59)	<2.2x10 ⁻¹⁶	0.66 (0.60-0.73)	<2.2x10 ⁻¹⁶
	High	2,449	1.00 (reference)		1.00 (reference)	
Low	Moderate	11,707	0.64 (0.53-0.77)	3.7x10⁻ ⁶	0.73 (0.59-0.90)	0.003
	Low	50,292	0.47 (0.40-0.56)	<2.2x10 ⁻¹⁶	0.57 (0.47-0.69)	1.7x10 ⁻⁸

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted Cox proportional hazard models. Model 1: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index

Model 2: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, prevalent type 2 diabetes mellitus, body-mass index, and C-reactive protein

Supplementary Table 10. Interactions between polygenic risk and frequency of depressed mood for total coronary artery disease (prevalent and incident).

	Mode	11	Model 2		
	Odds ratio for interaction		Odds ratio for interaction		
Condition	(95% CI)	P-value for interaction	(95% CI)	P-value for interaction	
Coronary artery disease	0.96 (0.94-0.98)	6.4x10 ⁻⁴	0.95 (0.92-0.97)	6.6x10⁻⁵	

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted logistic regression models. Polygenic risk is modeled as a quantitative trait. Frequency of depressed mood is modeled as an ordinal variable.

Model 1: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, polygenic risk, frequency of depressed mood

Model 2: Adjusted for age, age², sex, PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, prevalent type 2 diabetes mellitus, body-mass index, C-reactive protein, polygenic risk, frequency of depressed mood, and interaction terms between frequency of depressed mood and each covariate

Supplementary Table 11	 Sex-stratified models f 	for incident coror	ary artery	/ disease.
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	Men			Women		
Frequency of depressed mood	Number at risk	Hazard ratio (95% CI)	P-value	Number at risk	Hazard ratio (95% CI)	P-value
High	4,844	1.00 (reference)		7,556	1.00 (reference)	
Moderate	22,339	0.84 (0.75-0.94)	0.002	35,235	0.70 (0.62-0.79)	1.0x10 ⁻⁸
Low	117,201	0.74 (0.67-0.81)	3.1x10 ⁻⁹	127,718	0.57 (0.51-0.63)	<2.2x10 ⁻¹⁶

Two-sided P-values (unadjusted for multiple comparisons) were calculated using multivariable-adjusted Cox proportional hazard models. Model adjusted for age, age², PC 1-20, genotyping array, country, Townsend deprivation index, smoking status, pack-year smoking history, alcohol intake, vegetable + fresh fruit intake, days per week of moderate and vigorous exercise, sleep duration, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, antiplatelet medication use, antihyperglycemic medication use, prevalent type 2 diabetes mellitus, body-mass index, C-reactive protein, and polygenic risk Online Appendix. *International Classification of Diseases* and procedure codes used to ascertain incident coronary artery disease, type 2 diabetes mellitus, and atrial fibrillation in the UK Biobank.

Diagnosis	ICD codes
Coronary artery disease	ICD 9: 410, 4109, 411, 4119, 412, 4129, 4140, 4148, 4149
	ICD 10: I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3,
	123.4, 123.5, 123.6, 123.8, 124, 124.0, 124.1, 124.8, 124.9, 125.1, 125.2, 125.5, 125.6, 125.8, 125.9
	OPCS-4: K40, K40.1, K40.2, K40.3, K40.4, K40.8, K40.9, K41, K41.1, K41.2, K41.3, K41.4, K41.8, K41.9, K42,
	K42.1, K42.2, K42.3, K42.4, K42.8, K42.9, K43, K43.1, K43.2, K43.3, K43.4, K43.8, K43.9, K44, K44.1, K44.2,
	K44.8, K44.9, K45.1, K45.2, K45.3, K45.4, K45.5, K45.6, K45.8, K45.9, K46.1, K46.2, K46.3, K46.4, K46.5,
	K46.8, K46.9, K49.1, K49.2, K49.3, K49.4, K49.8, K49.9, K50.1, K50.2 K50.4, K75.1, K75.2, K75.3, K75.4,
	K75.8, K75.9
Type 2 diabetes mellitus	ICD-10: E11, E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.9, E11.9
Atrial fibrillation	ICD 9: 4273
	ICD 10: I48.0, I48.1, I48.2, I48.3, I48.4, I48.9