

Supplemental Materials

Polygenic risk for type 2 diabetes, lifestyle, metabolic health, and cardiovascular
disease: a prospective UK Biobank study

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Supplemental Table 1. Detailed definitions of baseline major comorbidities and outcomes.

Disease	Path	Field ID	Code
Baseline dyslipidemia	Verbal interview	Non-cancer illness, self-report (20002)	High cholesterol (1473)
	First occurrence before enrollment	First reported of disorders of lipoprotein metabolism and other lipidemia (130815, 130816)	E78.x
	Medication	Medication for cholesterol, blood pressure or diabetes (6177)	Cholesterol lowering medication
Baseline hypertension	Verbal interview	Non-cancer illness, self-report (20002)	1065, 1072
	Touchscreen	Vascular/heart problems diagnosed by doctor (6150)	High blood pressure
		First reported of essential hypertension (131286, 131287)	I10.x
		First reported of hypertensive heart disease (131288, 131289)	I11.x
		First reported of hypertensive renal disease (131290, 131291)	I12.x
	First occurrence before enrollment	First reported of hypertensive heart and renal disease (131292, 131293)	I13.x
		First reported of secondary hypertension (131294, 131295)	I15.x
		Medication for cholesterol, blood pressure or diabetes (6177)	Blood pressure medication
Baseline type 2 diabetes mellitus	Verbal interview	Non-cancer illness, self-report (20002)	Diabetes (1220)
	Touchscreen	Diabetes diagnosed by doctor (2443)	Type 2 diabetes (1223)
		First reported of non-insulin-dependent diabetes mellitus (130708, 130709)	Yes
		First reported of unspecified diabetes mellitus (130714, 130715)	E11.x
	Medication	Treatment/medication code (20003)	E14.x
			Insulin (1140883066)
			Metformin (1140884600, 1141189090)
			Sulfonylurea (1141152590, 1140874744, 1140874718, 1141156984)
	HbA1c at baseline	Glycated hemoglobin (HbA1c) (30750)	Acarbose (1140868902)
			Thiazolidinedione (1141171646)
			Meglitinide (1141168660, 1141173882)
	Verbal interview for exclusion type 1 diabetes	Non-cancer illness, self-report (20002)	≥6.5%
	First occurrence for exclusion type 1 diabetes	First reported of insulin-dependent diabetes mellitus (130706, 130707)	Type 1 diabetes (1222)
			E10.x
Baseline coronary artery disease	Verbal interview	Non-cancer illness, self-report (20002)	1074 (angina)
	Touchscreen	Vascular/heart problems diagnosed by doctor (6150)	1075 (heart attack/myocardial infarction)
		First reported of angina pectoris (131296, 131297)	Heart attack, angina
		First reported of acute myocardial infarction (131298, 131299)	I20.x
	First occurrence before enrollment		I21.x

		First reported of subsequent myocardial infarction (131300, 131301)	I22.x
		First reported of certain current complications following acute myocardial infarction (131302, 131303)	I23.x
		First reported of other acute ischemic heart diseases (131304, 131305)	I24.x
		First reported of chronic ischemic heart disease (131306, 131307)	I25.x
Baseline peripheral artery disease	Verbal interview	Non-cancer illness, self-report (20002)	Peripheral vascular disease (1067)
	Hospital inpatient data	Summary Diagnosis (ICD10, 41270)	I70.0, I70.00, I70.01, I70.2, I70.21, I70.8, I70.80, I70.9, I70.90, I73.8, I73.9
		Summary Diagnosis (ICD9, 41271)	4400, 4402, 4438, 4439
Baseline heart failure	Verbal interview	Non-cancer illness, self-report (20002)	Heart failure (1076, 1079)
	Hospital inpatient data	Summary Diagnosis (ICD10, 41270)	I50, I50.0, I50.1, I50.9
		Summary Diagnosis (ICD9, 41271)	4254, 4280, 4281, 4289
Baseline heart arrhythmia	Verbal interview	Non-cancer illness, self-report (20002)	Heart arrhythmia (1094)
	First occurrence before enrollment	First reported of atrial fibrillation/flutter (131350, 131351)	I48.x
		First reported of other cardiac arrhythmias (131352, 131353)	I49.x
Baseline ischemic stroke	Verbal interview	Non-cancer illness, self-report (20002)	Stroke (1081,1082,1583)
	First occurrence before enrollment	First reported of cerebral infarction (131366, 131367)	I63.x
Baseline hemorrhagic stroke	Verbal interview	Non-cancer illness, self-report (20002)	Stroke (1081)
	First occurrence before enrollment	First reported of subarachnoid hemorrhage (131360, 131361)	I60.x
		First reported of intracerebral hemorrhage (131362, 131363)	I61.x
		First reported of other nontraumatic intracranial hemorrhage (131364, 131365)	I62.x
Baseline chronic lung disease	Verbal interview	Non-cancer illness, self-report (20002)	Asthma (1111)
			Chronic obstructive airway disease/COPD (1112)
			Emphysema/chronic bronchitis (1113)
			Bronchiectasis (1114)
			Interstitial lung disease (1115)
	First occurrence before enrollment	First reported of bronchitis, not specified as acute or chronic (131484, 131485)	J40.x
		First reported of simple and mucopurulent chronic bronchitis (131486, 131487)	J41.x
		First reported of unspecified chronic bronchitis (131488, 131489)	J42.x
		First reported of emphysema (131490, 131491)	J43.x
		First reported of other chronic obstructive pulmonary disease (131492, 131493)	J44.x
		First reported of asthma (131494, 131495)	J45.x
		First reported of status asthmaticus (131496, 131497)	J46.x

		First reported of bronchiectasis (131498, 131499)	J47.x
		First reported of coalworker's pneumoconiosis (131500, 131501)	J60.x
		First reported of pneumoconiosis due to asbestos and other mineral fibers (131502, 131503)	J61.x
		First reported of pneumoconiosis due to dust containing silica (131504, 131505)	J62.x
		First reported of pneumoconiosis due to other inorganic dusts (131506, 131507)	J63.x
		First reported of unspecified pneumoconiosis (131508, 131509)	J64.x
		First reported of airway disease due to specific organic dust (131512, 131513)	J66.x
		First reported of hypersensitivity pneumonitis due to organic dust (131514, 131515)	J67.x
Baseline chronic liver disease	Verbal interview		Hepatitis (1155)
		Non-cancer illness, self-report (20002)	Infective/viral hepatitis (1156) Non-infective hepatitis (1157) Liver failure/cirrhosis (1158)
	First occurrence before enrollment	First reported of chronic viral hepatitis (130200, 130201)	B18.x
		First reported of esophageal varices (131406, 131407)	I85.x
		First reported of alcoholic liver disease (131658, 131659)	K70.x
		First reported of toxic liver disease (131660, 131661)	K71.x
		First reported of hepatic failure, not elsewhere classified (131662, 131663)	K72.x
		First reported of chronic hepatitis, not elsewhere classified (131664, 131665)	K73.x
		First reported of other diseases of liver (131670, 131671)	K76.x
Baseline chronic kidney disease	Verbal interview		Renal/kidney failure (1192)
		Non-cancer illness, self-report (20002)	Renal failure requiring dialysis (1193) Renal failure not requiring dialysis (1194)
	First occurrence before enrollment	First reported of chronic renal failure (132030, 132031)	N18.x
		First reported of unspecified renal failure (132032, 132033)	N19.x
Baseline cancer	Verbal interview	Cancer, self-report (20001)	1001-1012, 1015-1048, 1050-1053, 1055,1056, 1058-1068, 1070-1082, 1084-1088
	First occurrence before enrollment	Cancer register (40006)	C00-C97
Coronary artery disease outcome	First occurrence before enrollment	First reported of angina pectoris (131296, 131297)	I20.x
		First reported of acute myocardial infarction (131298, 131299)	I21.x
		First reported of subsequent myocardial infarction (131300, 131301)	I22.x

		First reported of certain current complications following acute myocardial infarction (131302, 131303)	I23.x
		First reported of other acute ischemic heart diseases (131304, 131305)	I24.x
		First reported of chronic ischemic heart disease (131306, 131307)	I25.x
Peripheral artery disease outcome	Hospital inpatient data	Summary Diagnosis (ICD10, 41270)	I70.0, I70.00, I70.01, I70.2, I70.21, I70.8, I70.80, I70.9, I70.90, I73.8, I73.9
Heart failure outcome	Hospital inpatient data	Summary Diagnosis (ICD9, 41271)	4400, 4402, 4438, 4439
		Summary Diagnosis (ICD10, 41270)	I50, I50.0, I50.1, I50.9
		Summary Diagnosis (ICD9, 41271)	4254, 4280, 4281, 4289
Atrial fibrillation/atrial flutter outcome	First occurrence before enrollment	First reported of atrial fibrillation/flutter (131350, 131351)	I48.x
Ischemic stroke	First occurrence before enrollment	First reported of cerebral infarction (131366, 131367)	I63.x
Hemorrhagic stroke	First occurrence before enrollment	First reported of subarachnoid hemorrhage (131360, 131361)	I60.x
		First reported of intracerebral hemorrhage (131362, 131363)	I61.x
		First reported of other nontraumatic intracranial hemorrhage (131364, 131365)	I62.x

Supplemental Table 2. Detailed definitions of lifestyle factors, lifestyle behavior and metabolic health.

Lifestyle factors	Component	Healthy lifestyle or metabolic status	Field ID of UK biobank
Current smoking	Current smoking at baseline	Absence	20116
Obesity	BMI at baseline	<30 kg/m ²	21001
Physical activity	Number of days per week of physical activity 10+ minutes	Participating in moderate activity ≥5 days a week or vigorous activity ≥3 days a week	884 (Moderate physical activity 10+ minutes) 904 (Vigorous physical activity 10+ minutes)
Eating habits	At least half of all following diet components was considered as a healthy lifestyle, less than half was considered as an unhealthy lifestyle		
	Fruit	≥ 3 serving/day	1309 (Fresh fruit) 1319 (Dried fruit)
	Vegetable	≥ 3 serving/day	1289 (Cooked vegetables) 1299 (Salad or raw vegetables)
	Whole grains	≥ 3 serving/day	1438, 1448 (Wholemeal or wholegrain bread) 1458, 1468 (Bran, oat, muesli cereal)
	Fish	≥ 2 serving/week	1329 (Oily fish) 1339 (Non-oily fish)
	Dairy	≥ 2.5 serving/week	1408 (Cheese) 1418 (Milk)
	Refined grains	≤ 1.5 serving/week	1438, 1448 (Wholemeal or wholegrain bread) 1458, 1468 (Bran, oat, muesli cereal)
	Processed meats	≤ 1 serving/week	1349 (Processed meat) 3680 (Age when last ate any kind of meat, 0 if indicated having never eaten meat)
	Unprocessed meats	≤ 1.5 serving/week	1359 (Poultry) 1369 (Beef) 1379 (Lamb) 1389 (Pork)
			3680 (Age when last ate any kind of meat, 0 if indicated having never eaten meat) 6144 (Never eats sugar or foods/drinks containing sugar)
Lifestyle behavior	Favorable	Having at least three healthy lifestyle factors	
	Intermediate	Having two healthy lifestyle factors	
	Unfavorable	Having one or fewer healthy lifestyle factor	
Components of metabolic syndrome	Waist circumference	Men <102 cm Women <88 cm	48
	Triglyceride	<1.70 mmol/L	30870
	HDL cholesterol	≥1.03 mmol/L	30760
	Glucose (or having diabetes)	≥5.6 mmol/L	30740
	Systolic blood pressure or diastolic blood pressure	≥130 mmHg or	4080
		≥ 85 mmHg	4079

Supplemental Table 3. Number of cases with missing data for each variable.

Variable	n (%)
Total	345217
Systolic blood pressure	294 (0.1)
Diastolic blood pressure	292 (0.1)
Height	648 (0.2)
Weight	844 (0.3)
Body mass index	942 (0.3)
Waist circumference	521 (0.2)
Lifestyle behavior	12550 (3.6)
Total cholesterol	16011 (4.6)
Triglyceride	16274 (4.7)
HDL-cholesterol	43959 (12.7)
LDL-cholesterol	16626 (4.8)
Creatinine	16190 (4.7)
HbA1c	16237 (4.7)
Income	47173 (13.7)
Townsend deprivation index	415 (0.1)

Supplemental Table 4. Hazard ratios and 95% confidential intervals for the cardiovascular disease using Cox proportional regression model.

		No. of Events/ Total No.	Incidence rate per 1000 person-yr (95% CI)	Absolute risk (%)	Crude		Model 1		Model 2		Model 3	
					HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
T2D PRS	Low risk	4045/70210	6.74 (6.53-6.95)	5.86	Ref		Ref		Ref		Ref	
	Intermediate risk	13115/210634	7.30 (7.28-7.43)	6.33	1.08 (1.05-1.12)	<0.001	1.10 (1.06-1.14)	<0.001	1.09 (1.05-1.13)	<0.001	1.09 (1.05-1.13)	<0.001
	High risk	4443/66608	7.84 (7.62-8.08)	6.78	1.16 (1.12-1.21)	<0.001	1.19 (1.14-1.24)	<0.001	1.17 (1.11-1.22)	<0.001	1.16 (1.11-1.21)	<0.001
	Very high risk	262/3510	8.81 (7.78-9.94)	7.59	1.30 (1.15-1.48)	<0.001	1.35 (1.19-1.53)	<0.001	1.27 (1.10-1.46)	<0.001	1.30 (1.15-1.48)	<0.001
	<i>P</i> for trend					<0.001		<0.001				<0.001

Model 1 was adjusted for age, sex, genotyping array, first ten principal components.

Model 2 was adjusted for model 1 components, income level, and Townsend deprivation index.

Model 3 was adjusted for model 1 components, and CAD PRS.

Abbreviations: T2D, type 2 diabetes; CAD, coronary artery disease; PRS, polygenic risk score; HR, hazard ratio; CI, confidence interval.

Supplemental Table 5. Hazard ratios and 95% confidential intervals for the cardiovascular disease using Cox proportional regression model.

		No. of Events/ Total No.	Incidence rate per 1000 person-yr (95% CI)	Absolute risk (%)	Model 1		Model 2		Model 3		
					HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	
T2D PRS	Low risk	4045/70210	6.74 (6.53-6.95)	5.86	Ref		Ref		Ref		
	Intermediate risk	13115/210634	7.30 (7.28-7.43)	6.33	1.07 (1.03-1.11)	0.002	1.06 (1.02-1.10)	0.002	1.10 (1.06-1.13)	<0.001	
	High risk	4443/66608	7.84 (7.62-8.08)	6.78	1.13 (1.08-1.19)	<0.001	1.11 (1.06-1.16)	<0.001	1.18 (1.13-1.23)	<0.001	
	Very high risk	262/3510	8.81 (7.78-9.94)	7.59	1.20 (1.03-1.39)	0.019	1.17 (1.02-1.35)	0.022	1.33 (1.18-1.51)	<0.001	
<i>P</i> for trend						<0.001		<0.001		<0.001	

Model 1 was adjusted for age, sex, genotyping array, first ten principal components, BMI, current smoking, alcohol frequency, physical activity, and eating habits.

Model 2 was adjusted for Model 1 components, systolic BP, diastolic BP, HbA1c, triglyceride, HDL cholesterol, LDL cholesterol, and estimated GFR.

Model 3 was adjusted for Model 1 components, cancer, chronic lung disease, chronic liver disease, and chronic kidney disease.

Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score; BP, blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

Supplemental Table 6. Participant distribution according to the risk group of type 2 diabetes and coronary artery disease polygenic risk scores.

LDpred* Khera <i>et al.</i> , 2018		T2D PRS			
		Low risk 0-20 th	Intermediate 21-80 th	High 79-98 th	Very high 99 th
CAD PRS	Low risk 0-20 th	15401	41613	11462	581
	Intermediate 21-79 th	41277	124293	39553	1997
	High 80-98 th	11817	39164	13793	814
	Very high 99 th	562	2050	780	60

*The PRSs for T2D and CAD respectively derived from the DIAGRAM consortium and CARDIOGRAMplusC4D consortium, which were based on the pre-calculated weights for SNPs provided by Khera et al. 2018.

Abbreviations: T2D, type 2 diabetes; CAD, coronary artery disease; PRS, polygenic risk score.

Supplemental Table 7. Study outcome summarization.

	Total	T2D PRS				<i>P</i> value
		Low	Intermediate	High	Very high	
		0-19 th percentile	20-79 th percentile	80-98 th percentile	99 th percentile	
	(n=345217)	(n=69070)	(n=207192)	(n=65505)	(n=3450)	
Cardiovascular events during follow-up periods	21865 (6.3)	4045 (5.9)	13115 (6.3)	4443 (6.8)	262 (7.6)	<0.001
Coronary artery disease	14307 (4.1)	2597 (3.8)	8580 (4.1)	2947 (4.5)	183 (5.3)	<0.001
Peripheral artery disease	2054 (0.6)	366 (0.5)	1198 (0.6)	468 (0.7)	22 (0.7)	<0.001
Heart failure	2954 (0.9)	528 (0.8)	1803 (0.9)	579 (0.9)	44 (1.3)	0.002
Atrial fibrillation/Atrial flutter	5677 (1.6)	1092 (1.6)	3396 (1.6)	1116 (1.7)	73 (2.1)	0.048
Ischemic stroke	2328 (0.7)	444 (0.6)	1421 (0.7)	440 (0.7)	23 (0.7)	0.696
Hemorrhagic stroke	1117 (0.3)	209 (0.3)	675 (0.3)	225 (0.3)	8 (0.2)	0.444
Cardiovascular death during follow-up periods	1963 (0.6)	351 (0.5)	1177 (0.6)	408 (0.6)	27 (0.8)	0.014

Data are n (%) or mean (SD).

Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score.

Supplemental Table 8. Hazard ratios and 95% confidential intervals for the cardiovascular mortality using Cox proportional regression model.

		Cardiovascular mortality				
		No. of Events/ Total No.	Incidence rate per 1000 person-yr (95% CI)	Absolute risk (%)	Model 1	
					HR (95% CI)	P value
T2D PRS	Low risk	351/69070	0.57 (0.51-0.63)	0.51	Ref	
	Intermediate risk	1177/207192	0.64 (0.60-0.67)	0.57	1.14 (1.01-1.29)	0.03
	High risk	408/65505	0.70 (0.63-0.77)	0.62	1.27 (1.10-1.46)	0.001
	Very high risk	27/3450	0.88 (0.58-1.28)	0.78	1.63 (1.10-2.41)	0.015

Model 1 was adjusted for age, sex, genotyping array, and first ten principal components.

Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score; HR, hazard ratio; CI, confidence interval.

Supplemental Table 9. Hazard ratios and 95% confidential intervals for increased cardiovascular disease risk according to genetic risk for type 2 diabetes, metabolic health status, and lifestyle behavior.

T2D PRS subgroup	MS subgroup	Lifestyle subgroup	No. of Events/ Total No.	Absolute risk (%)	Model 1	
					HR (95% CI)	P value
Low genetic risk	0 component of MetS	Favorable lifestyle	143/6685	2.14	Ref	
		Nonfavorable lifestyle	408/17519	2.33	1.07 (0.72-1.61)	0.729
	1 component of MetS	Favorable lifestyle	117/4770	2.45	0.91 (0.52-1.59)	0.734
		Nonfavorable lifestyle	3/198	1.52	2.16 (0.52-9.00)	0.292
	2 components of MetS	Favorable lifestyle	657/13382	4.91	2.34 (1.61-3.40)	<0.001
		Nonfavorable lifestyle	1689/36998	4.57	2.38 (1.66-3.40)	<0.001
	3 or more components of MetS	Favorable lifestyle	553/10653	5.19	2.86 (1.96-4.16)	<0.001
		Nonfavorable lifestyle	22/499	4.41	1.76 (0.69-4.52)	0.239
Intermediate genetic risk	0 component of MetS	Favorable lifestyle	471/8470	5.56	2.83 (1.93-4.14)	<0.001
		Nonfavorable lifestyle	1611/25412	6.34	3.51 (2.31-4.92)	<0.001
	1 component of MetS	Favorable lifestyle	503/8028	6.27	3.37 (2.31-4.92)	<0.001
		Nonfavorable lifestyle	30/403	7.44	3.61 (1.72-7.56)	<0.001
	2 components of MetS	Favorable lifestyle	348/4652	7.48	4.08 (2.77-6.01)	<0.001
		Nonfavorable lifestyle	1210/15509	7.80	4.14 (2.89-5.93)	<0.001
	3 or more components of MetS	Favorable lifestyle	470/5719	8.22	3.76 (2.56-5.51)	<0.001
		Nonfavorable lifestyle	33/335	9.85	5.48 (3.86-7.79)	<0.001
High genetic risk	0 component of MetS	Favorable lifestyle	92/2744	3.35	1.76 (1.03-3.01)	0.039
		Nonfavorable lifestyle	220/7088	3.10	1.85 (1.21-2.84)	0.005
	1 component of MetS	Favorable lifestyle	63/1952	3.23	2.09 (1.19-3.69)	0.011
		Nonfavorable lifestyle	3/89	3.37	4.76 (1.14-19.88)	0.032
	2 components of MetS	Favorable lifestyle	362/6204	5.84	3.21 (2.17-4.75)	<0.001
		Nonfavorable lifestyle	1024/17405	5.88	3.22 92.24-4.63)	<0.001
	3 or more components of MetS	Favorable lifestyle	319/5201	6.13	3.81 (2.57-5.65)	<0.001
		Nonfavorable lifestyle	11/263	4.18	3.48 (1.36-8.94)	0.009
Very high genetic risk	0 component of MetS	Favorable lifestyle	472/6938	6.80	3.83 (2.62-5.59)	<0.001
		Nonfavorable lifestyle	1538/21796	7.06	3.79 (2.65-5.42)	<0.001
	1 component of MetS	Favorable lifestyle	559/7079	7.90	4.11 (2.82-6.00)	<0.001
		Nonfavorable lifestyle	32/332	9.64	4.50 (2.15-9.43)	<0.001
	2 components of MetS	Favorable lifestyle	846/9090	9.31	4.89 (3.39-7.04)	<0.001
		Nonfavorable lifestyle	3106/32080	9.68	5.31 (3.73-7.54)	<0.001
	3 or more components of MetS	Favorable lifestyle	1125/11627	9.68	5.43 (3.79-7.79)	<0.001
		Nonfavorable lifestyle	79/754	10.48	6.54 (3.96-10.82)	<0.001

Model 1 was adjusted for age, sex, genotyping array, and first ten principal components.

Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score; MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval.

Supplemental Table 10. Hazard ratios and 95% confidential intervals for the cardiovascular disease according to lifestyle behavior.

		Cardiovascular disease			
		No. of Events/ Total No.	Absolute risk (%)	Model 1	
				HR (95% CI)	P value
Lifestyle behavior	Unfavorable lifestyle	3838/39232	9.78	Ref	
	Intermediate lifestyle	7997/113231	7.06	0.71 (0.67-0.74)	<0.001
	Favorable lifestyle	9780/185728	5.27	0.53 (0.51-0.55)	<0.001

Model 1 was adjusted for age, sex, genotyping array, and first ten principal components.

Abbreviations: HR, hazard ratio; CI, confidence interval.

Supplemental Table 11. Hazard ratios and 95% confidential intervals for the cardiovascular disease according to T2D genetic risk and lifestyle behavior.

T2D PRS subgroup	Lifestyle subgroup	No. of Events/ Total No.	Cardiovascular disease		
			Absolute risk (%)	Model 1	
				HR (95% CI)	P value
All participants	Unfavorable lifestyle	3643/38450	9.48	Ref	
	Intermediate lifestyle	7619/111276	6.85	0.70 (0.67-0.73)	<0.001
	Favorable lifestyle	9414/182991	5.15	0.52 (0.50-0.54)	<0.001
Very high genetic risk	Unfavorable lifestyle	54/466	11.59	Ref	
	Intermediate lifestyle	91/1183	7.69	0.65 (0.46-0.91)	0.012
	Favorable lifestyle	103/1660	6.21	0.50 (0.36-0.69)	<0.001
High genetic risk	Unfavorable lifestyle	775/8069	9.61	Ref	
	Intermediate lifestyle	1578/21512	7.34	0.74 (0.68-0.81)	<0.001
	Favorable lifestyle	1856/33562	5.53	0.55 (0.51-0.60)	<0.001
Intermediate genetic risk	Unfavorable lifestyle	2178/23110	9.42	Ref	
	Intermediate lifestyle	4564/66812	6.83	0.70 (0.68-0.74)	<0.001
	Favorable lifestyle	5625/109760	5.13	0.52 (0.49-0.54)	<0.001
Low genetic risk	Unfavorable lifestyle	636/6805	9.35	Ref	
	Intermediate lifestyle	1386/21769	6.37	0.65 (0.59-0.72)	<0.001
	Favorable lifestyle	1830/38009	4.82	0.49 (0.44-0.53)	<0.001

Model 1 was adjusted for age, sex, genotyping array, and first ten principal components.

Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score; HR, hazard ratio; CI, confidence interval.

Supplemental Table 12. Hazard ratios and 95% confidential intervals for the cardiovascular disease according to T2D genetic risk and metabolic health status.

T2D PRS subgroup	MetS subgroup	No. of Events/ Total No.	Cardiovascular disease		
			Absolute risk (%)	Model 1	
				HR (95% CI)	P value
All participants	3 or more components	7673/83448	9.20	Ref	
	2 components	5473/81314	6.73	0.74 (0.72-0.77)	<0.001
	0 or 1 component	5961/135345	4.40	0.55 (0.53-0.57)	<0.001
Very high genetic risk	3 or more components	121/1155	10.48	Ref	
	2 components	64/760	8.42	0.79 (0.58-1.07)	0.125
	0 or 1 component	43/1081	3.98	0.42 (0.30-0.60)	<0.001
High genetic risk	3 or more components	1694/18142	9.34	Ref	
	2 components	1104/15619	7.07	0.77 (0.71-0.83)	<0.001
	0 or 1 component	1100/23215	4.74	0.57 (0.53-0.62)	<0.001
Intermediate genetic risk	3 or more components	4608/49761	9.26	Ref	
	2 components	3315/48955	6.77	0.74 (0.71-0.78)	<0.001
	0 or 1 component	3509/81240	4.32	0.53 (0.51-0.56)	<0.001
Low genetic risk	3 or more components	1250/14390	8.69	Ref	
	2 components	990/15980	6.20	0.72 (0.66-0.78)	<0.001
	0 or 1 component	1309/29809	4.39	0.58 (0.54-0.63)	<0.001

Model 1 was adjusted for age, sex, genotyping array, and first ten principal components.

Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score; MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval.

Supplemental Table 13. Sensitivity analysis of the interaction between high/low genetic risk (top 10 percentile vs. bottom 90 percentile), metabolic health, and lifestyle.

T2D PRS subgroup	MetS subgroup	Lifestyle subgroup	No. of Events/ Total No.	Absolute risk (%)	Model 1		<i>P</i> for interaction
					HR (95% CI)	<i>P</i> value	
							0.399
High genetic risk (Top 10 percentile)	3 or more components	Nonfavorable lifestyle	288/2769	10.40	Ref		
		Favorable lifestyle	120/1295	9.27	0.81 (0.65-0.99)	0.049	
	2 components	Nonfavorable lifestyle	120/1471	8.16	0.80 (0.65-0.99)	0.042	
		Favorable lifestyle	108/1666	6.48	0.59 (0.47-0.74)	<0.001	
	0-1 component	Nonfavorable lifestyle	74/1462	5.06	0.53 (0.41-0.69)	<0.001	
		Favorable lifestyle	128/3049	4.20	0.43 (0.35-0.54)	<0.001	
Low genetic risk (Bottom 90 percentile)	3 or more components	Nonfavorable lifestyle	4868/50782	9.59	Ref		
		Favorable lifestyle	1944/24920	7.80	0.73 (0.69-0.77)	<0.001	
	2 components	Nonfavorable lifestyle	2481/34674	7.16	0.76 (0.72-0.79)	<0.001	
		Favorable lifestyle	2507/40647	6.17	0.61 (0.58-0.64)	<0.001	
	0-1 component	Nonfavorable lifestyle	2020/39484	5.12	0.60 (0.57-0.64)	<0.001	
		Favorable lifestyle	3464/87655	3.95	0.45 (0.43-0.47)	<0.001	

Model 1 was adjusted for age, sex, genotyping array, and first ten principal components.

Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score; MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval.

Supplemental Table 14. Sensitivity analysis of the interaction between high/low genetic risk (top 30 percentile vs. bottom 70 percentile), metabolic health, and lifestyle.

T2D PRS subgroup	MetS subgroup	Lifestyle subgroup	No. of Events/ Total No.	Absolute risk (%)	Model 1		<i>P</i> for interaction
					HR (95% CI)	<i>P</i> value	
							0.223
High genetic risk (Top 30 percentile)	3 or more components	Nonfavorable lifestyle	921/9545	9.65	Ref		
		Favorable lifestyle	395/4624	8.54	0.81 (0.72-0.91)	<0.001	
	2 components	Nonfavorable lifestyle	446/5614	7.94	0.84 (0.75-0.94)	0.002	
		Favorable lifestyle	399/6345	6.29	0.62 (0.56-0.70)	<0.001	
	0-1 component	Nonfavorable lifestyle	300/5655	5.31	0.61 (0.54-0.70)	<0.001	
		Favorable lifestyle	523/12071	4.33	0.49 (0.44-0.54)	<0.001	
Low genetic risk (Bottom 70 percentile)	3 or more components	Nonfavorable lifestyle	4235/44006	9.62	Ref		
		Favorable lifestyle	1669/21591	7.73	0.72 (0.68-0.76)	<0.001	
	2 components	Nonfavorable lifestyle	2155/30531	7.06	0.74 (0.71-0.78)	<0.001	
		Favorable lifestyle	2216/35968	6.16	0.61 (0.58-0.64)	<0.001	
	0-1 component	Nonfavorable lifestyle	1794/35291	5.08	0.60 (0.57-0.63)	<0.001	
		Favorable lifestyle	3069/78633	3.90	0.44 (0.42-0.47)	<0.001	

Model 1 was adjusted for age, sex, genotyping array, and first ten principal components.

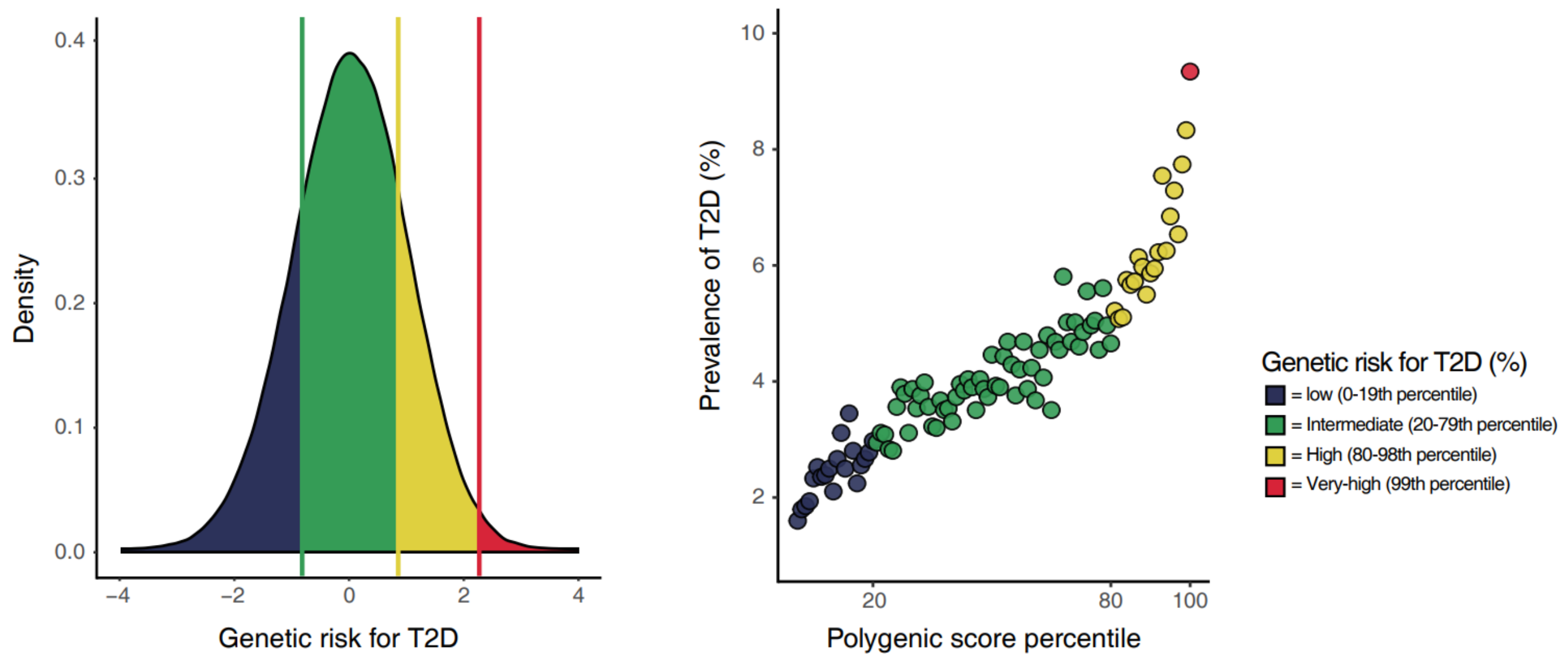
Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score; MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval.

Supplemental Table 15. Papulation attributable fraction of lifestyle modification and metabolic health for cardiovascular disease.

Lifestyle	Nonfavorable to favorable	All participants	17.2% (16.0 to 18.4%)
		40 to 50 years	27.1% (23.4 to 30.6%)
		51 to 69 years	15.9% (14.6 to 17.1%)
Metabolic syndrome	MetS 2 or 3 to MetS 0 or 1	All participants	31.1% (29.7 to 32.5%)
		40 to 50 years	34.5% (30.8 to 38.0%)
		51 to 69 years	26.1% (24.5 to 27.7%)

Abbreviation: MetS, metabolic syndrome.

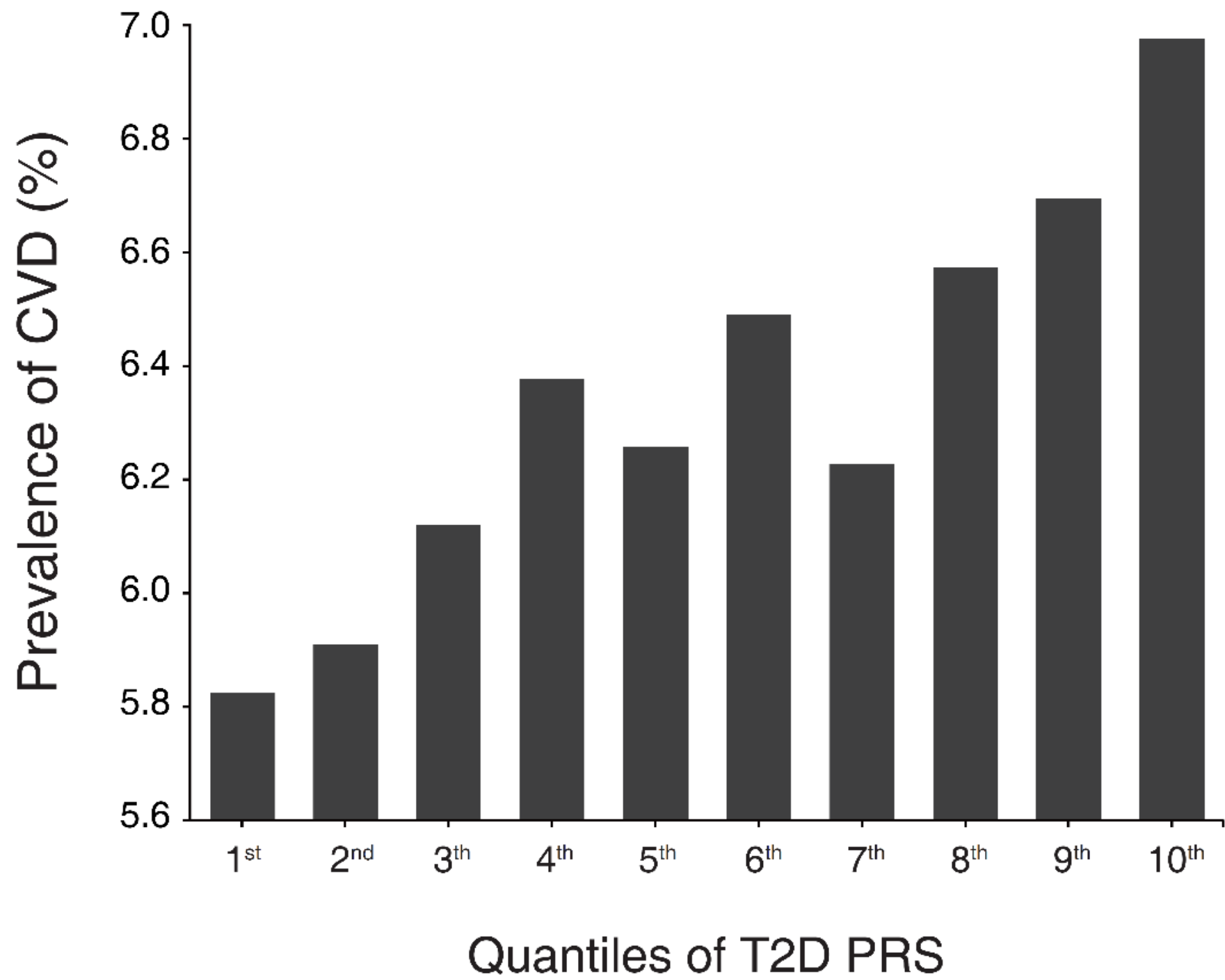
Supplemental Figure 1. Density and prevalence plot according to genetic risk for type 2 diabetes distribution.



T2D PRS risk groups: low (0–19th percentile), intermediate (20–79th percentile), high (80–98th percentile), and very high (99th percentile).

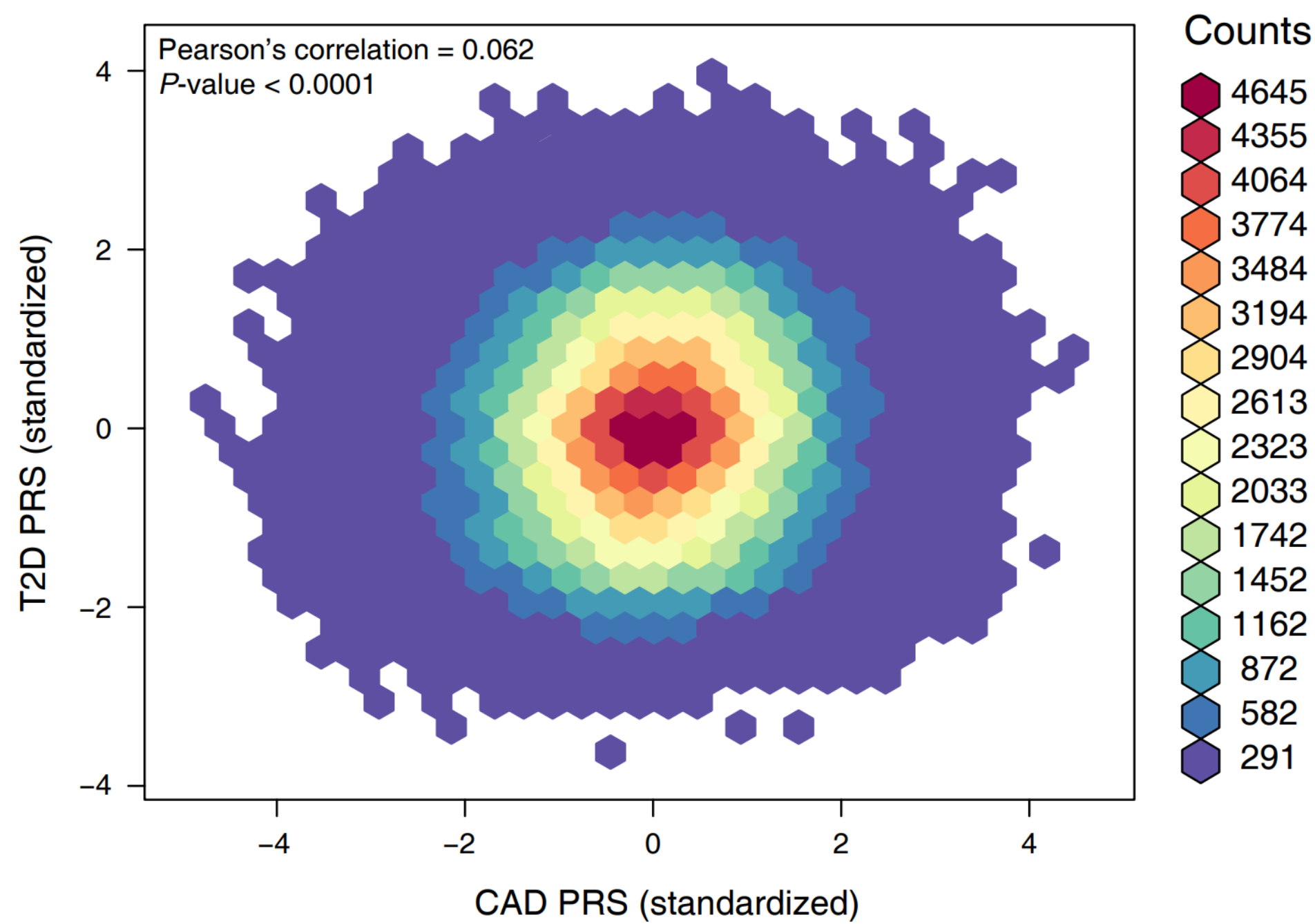
Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score.

Supplemental Figure 2. Prevalence plot for CVD according to the Quantile groups for genetic risk for type 2 diabetes.



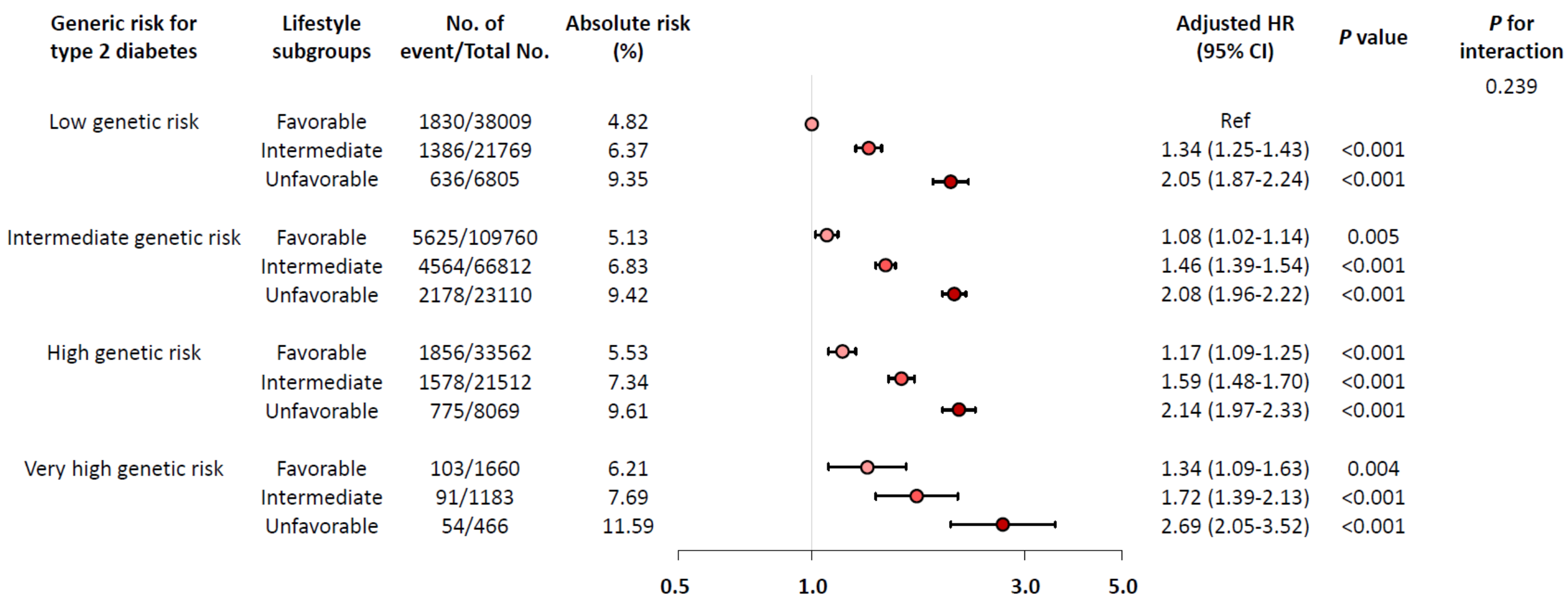
Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes; PRS, polygenic risk score.

Supplemental Figure 3. Scatterplot of the relationship between type 2 diabetes and coronary artery disease polygenic risk scores.



Abbreviations: T2D, type 2 diabetes; CAD, coronary artery disease; PRS, polygenic risk score.

Supplemental Figure 4. Forest plot for cardiovascular disease according to genetic risk for type 2 diabetes and lifestyle behavior.

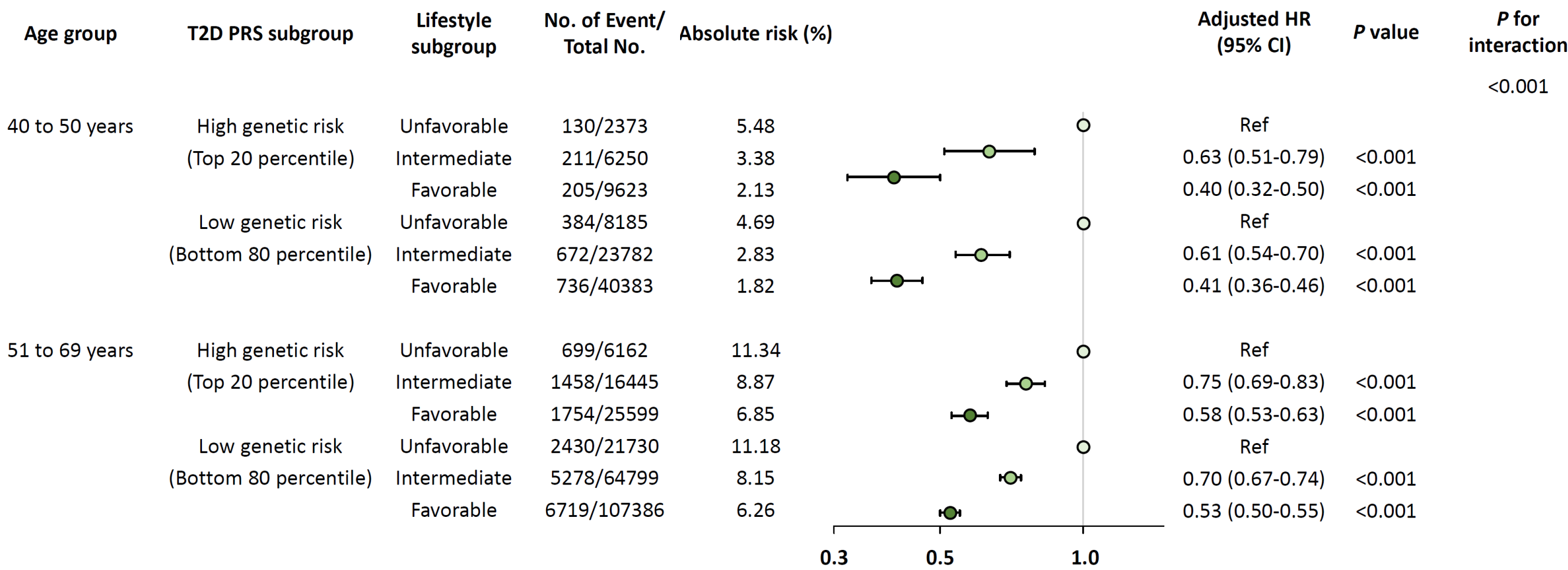


Cox regression model were adjusted for age, sex, genotyping array, first ten principal components of ancestry.

P for interaction is for testing the interaction between four genetic risk groups and three lifestyle categories.

Abbreviations: HR, hazard ratio; CI, confidence interval.

Supplemental Figure 5. Forest plot for cardiovascular disease of age interaction according to genetic risk for type 2 diabetes and lifestyle behavior using reference group as unfavorable lifestyle.

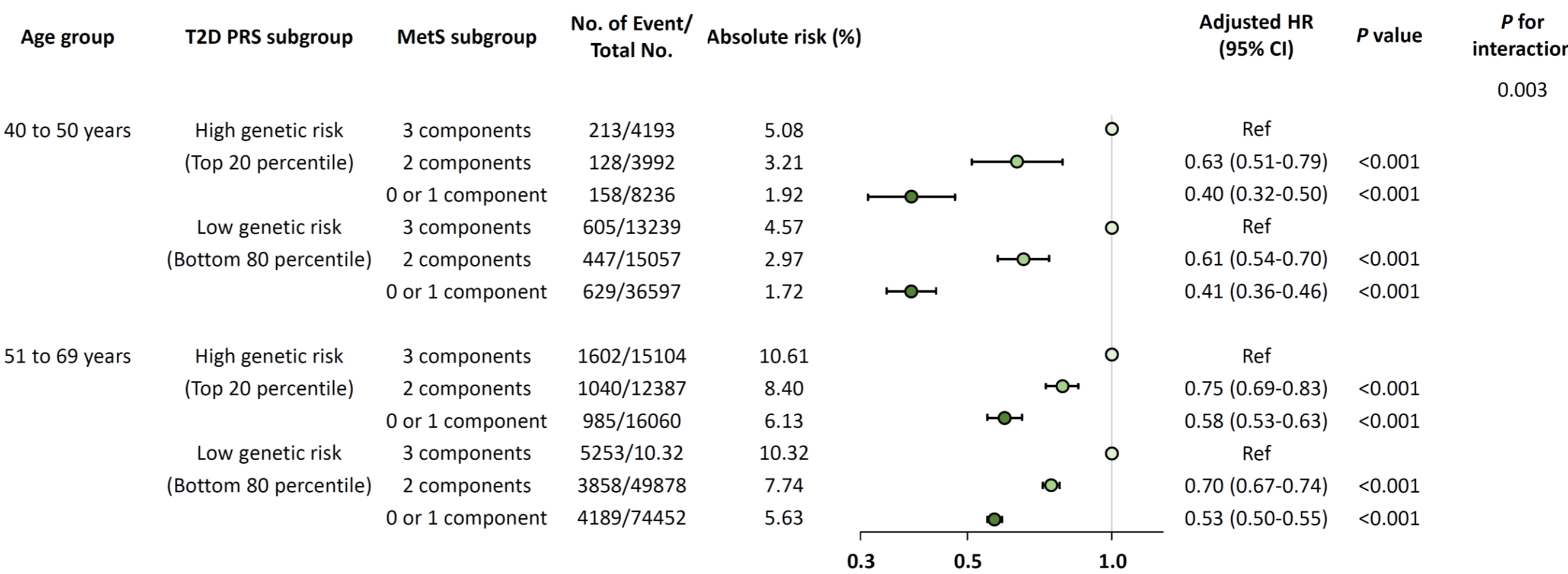


Cox regression model were adjusted for age, sex, genotyping array, first ten principal components of ancestry.

P for interaction is for testing the interaction between each genetic risk by lifestyle category and age subgroups.

Abbreviations: HR, hazard ratio; CI, confidence interval.

Supplemental Figure 6. Forest plot for cardiovascular disease of age interaction according to genetic risk for type 2 diabetes and metabolic health status using reference group as metabolically unhealthy subgroup.



Cox regression model were adjusted for age, sex, genotyping array, first ten principal components of ancestry.

P for interaction is for testing the interaction between genetic risk by metabolic health category and age subgroups.

Abbreviations: T2D, type 2 diabetes; PRS, polygenic risk score; MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval.