Supplementary Material

Zhu, Qian, et al. Modifiable Lifestyle Factors, Genetic Risk, and Incident Peripheral Artery Disease among Individuals with Type 2 Diabetes: A Prospective Study

Supplementary Method

S1 Figure. Flowchart of participants included in the analysis

S2 Figure. Distribution of the genetic risk score (GRS) for PAD using 19 SNPs

S3 Figure. Dose-response relationship of weighted healthy lifestyle score with risk of PAD among 14,543 participants with T2D

S4 Figure. Stratified analyses of the associations of the weighted healthy lifestyle score with risks of PAD among participants with T2D

S1 Table. Information of 19 peripheral arterial disease-associated SNPs used in this study

S2 Table. HRs (95% CIs) of PAD according to individual healthy lifestyle factor in 14,543 participants with T2D

S3 Table. HRs (95% CIs) of PAD according to genetic risk among 10,836 participants with T2D

S4 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories within each genetic risk group among 10,836 participants with T2D

S5 Table. Multivariable-adjusted linear regression models for the association between the weighted healthy lifestyle score and biomarker levels among participants with T2D

S6 Table. Risk estimates of PAD associated with the selected biomarkers (1-SD increment) among participants with T2D

S7 Table. HRs (95% CIs) of PAD according to different combinations of healthy lifestyle factors among 14,543 participants with T2D

S8 Table. HRs (95% CIs) of PAD according to unweighted healthy lifestyle score among 14,543 participants with T2D

S9 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories among participants with T2D after excluding the cases occurred within the first two-years of follow-up

S10 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories using moderate drinking and non-drinking as the healthy behavior in participants with T2D

S11 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories using optimal BMI or optimal waist circumstance as the healthy behavior in participants with T2D

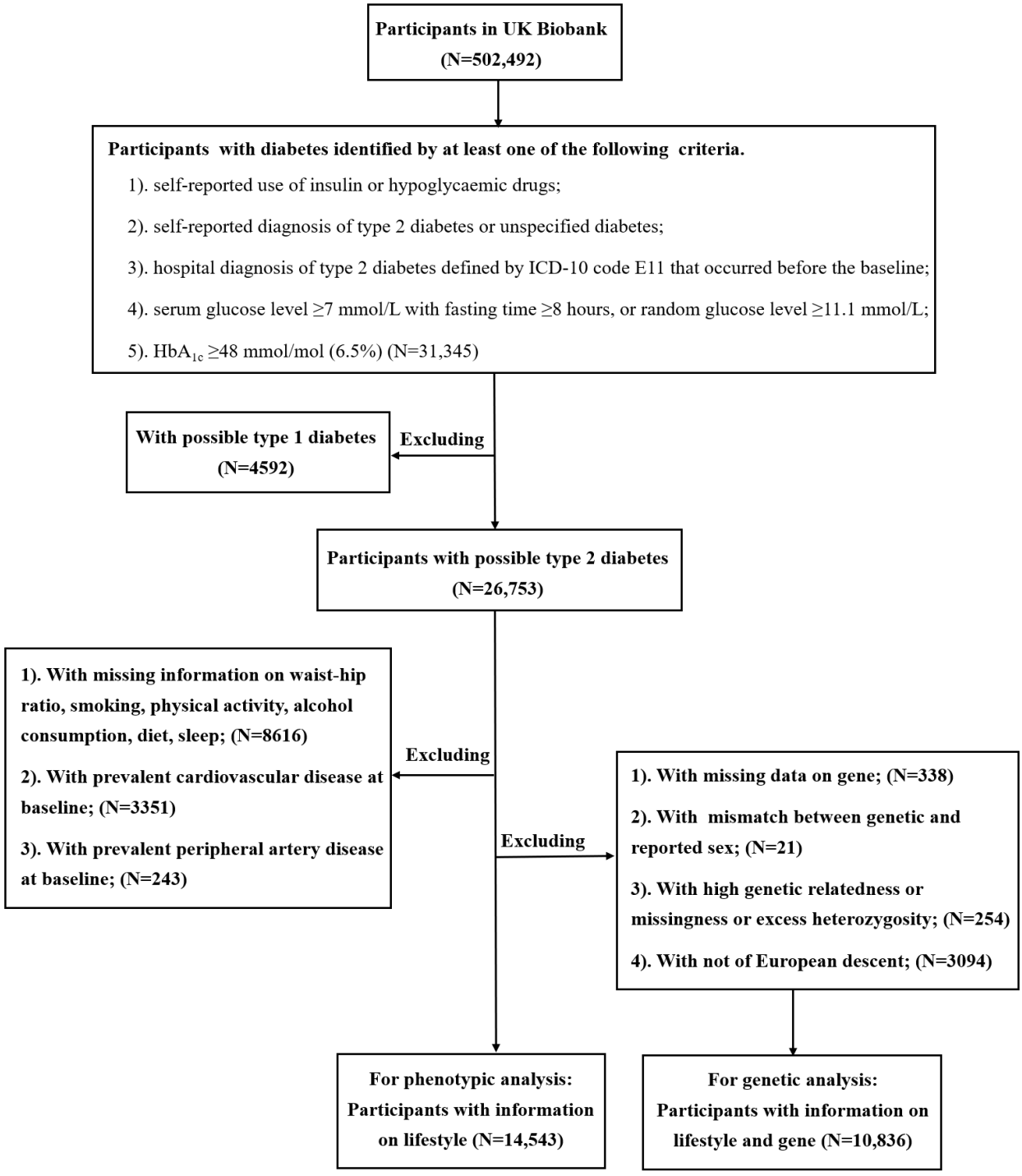
S12 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories using optimal pack years of smoking instead of non-smoking status as the healthy behavior in participants with T2D

S13 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories among participants with T2D using two competing risk models

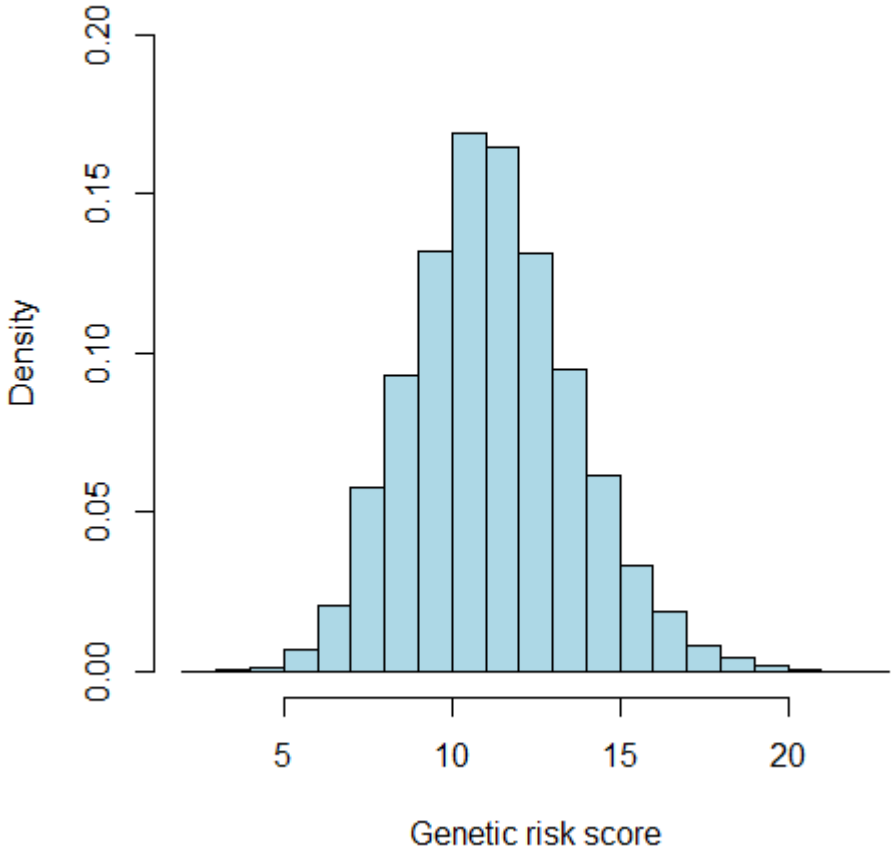
Supplementary Method

Selection and Measurement of the circulating biomarkers

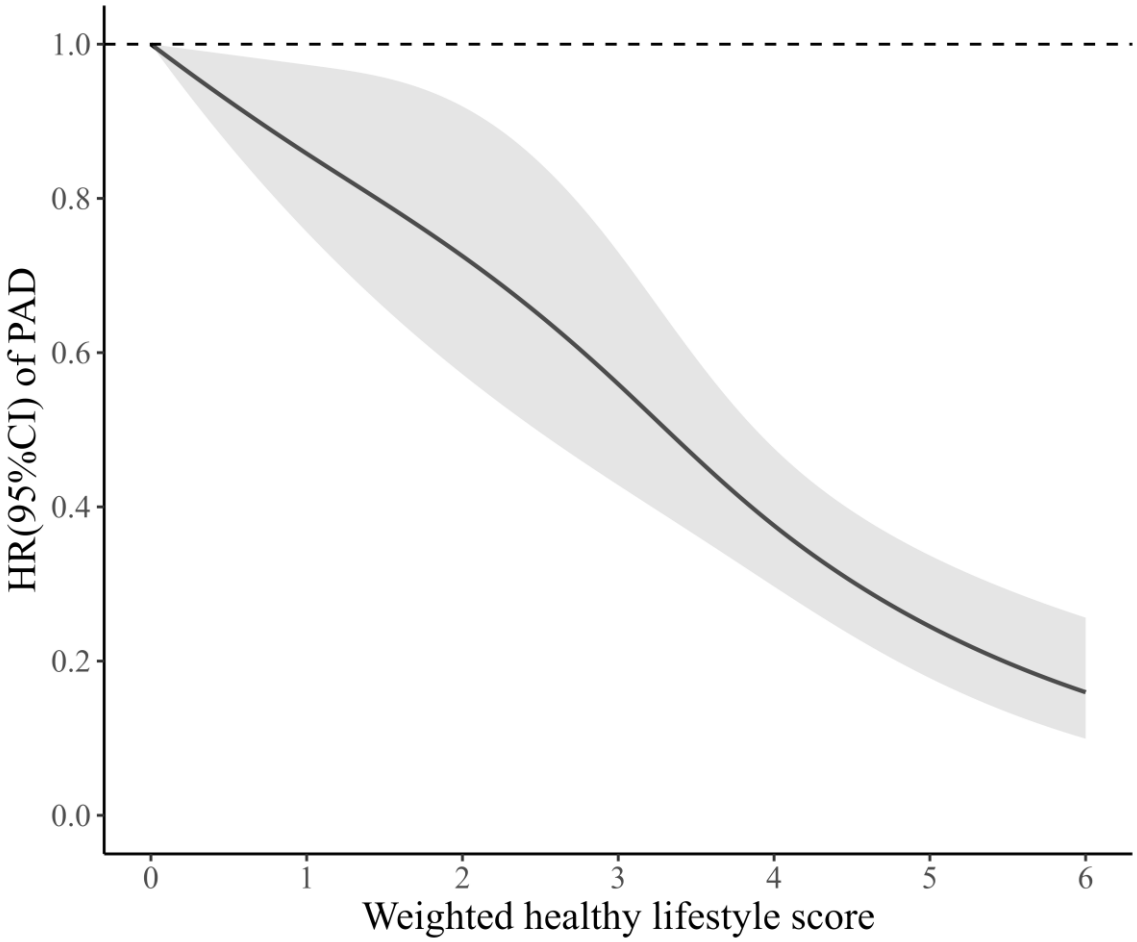
In detail, potential biological biomarkers included hepatic function [albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, total bilirubin, and total protein], renal function [cystatin C, creatinine, urea, and urate], inflammation [C-reactive protein and white blood cell count], lipid profiles [high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), total cholesterol, triglycerides, apolipoprotein A, apolipoprotein B, and lipoprotein (a) [Lp(a)]], and blood pressure [diastolic blood pressure (DBP) and systolic blood pressure (SBP)], and glycated hemoglobin (HbA_{1c}). The measurement of abovementioned blood biomarkers in UK Biobank was externally validated using strict quality control.



S1 Figure. Flowchart of participants included in the analysis

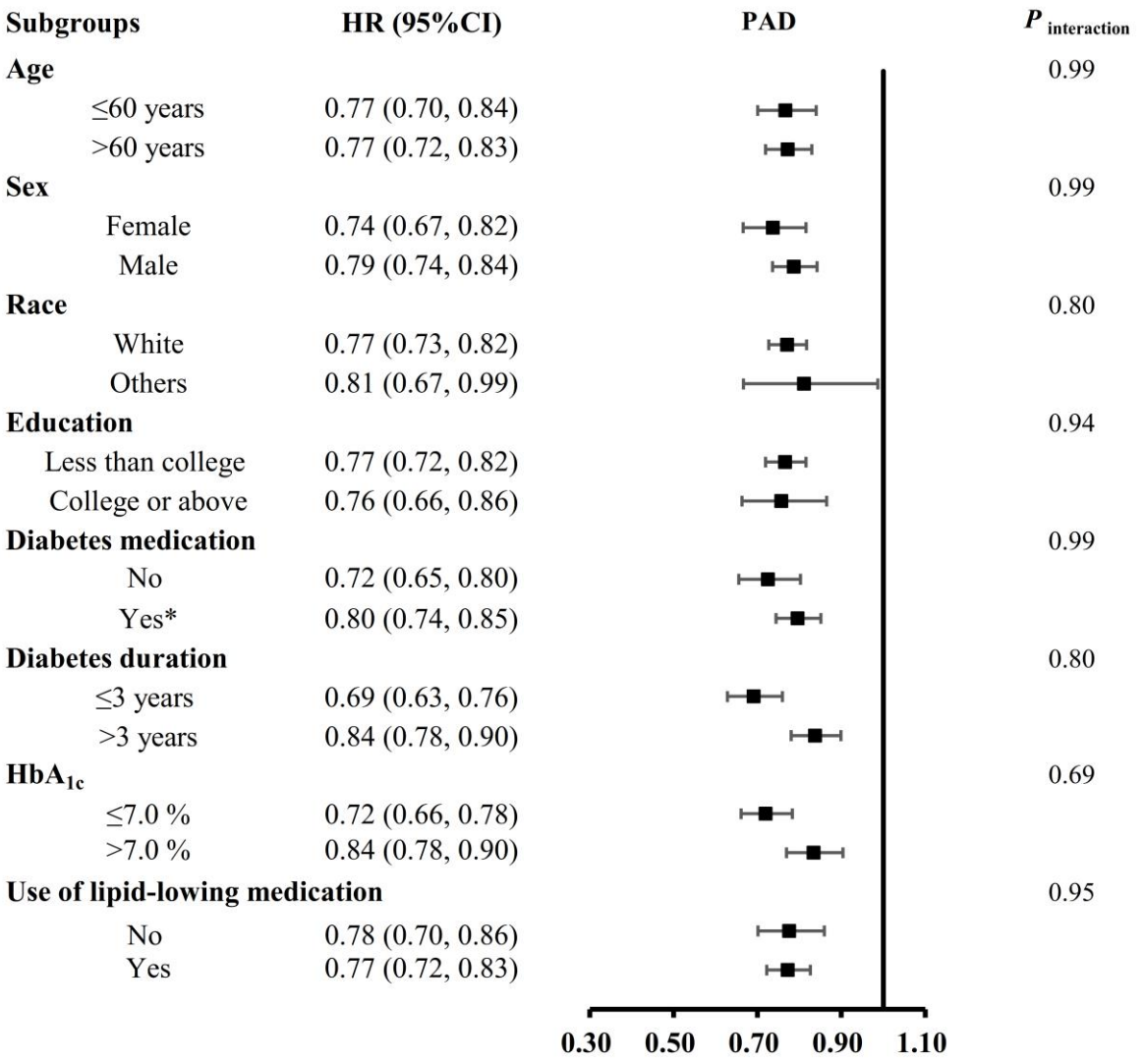


S2 Figure. Distribution of the genetic risk score (GRS) for PAD using 19 SNPs



S3 Figure. Dose-response relationship of weighted healthy lifestyle score with risk of PAD among 14,543 participants with T2D

Models were adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin). $P_{nonlinearity}$=0.07 and *P* for overall association were <0.0001.



S4 Figure. Stratified analyses of the associations of the weighted healthy lifestyle score[†] with risks of PAD among participants with T2D

Models were adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin) except for the stratifying factors.

[*]The group of diabetes medications (yes) included participants taking insulin and/or oral medications. [†]Per one-point increment of the weighted healthy lifestyle score

S1 Table. Information of 19 peripheral arterial disease-associated SNPs used in this study

rsID	Chr	Risk/reference allele	OR (95% CI)	*P*-value
rs7528419	1	A/G	1.07 (1.05, 1.09)	2.54×10^{-11}
rs6025	1	T/C	1.20 (1.14, 1.26)	1.63×10^{-12}
rs118039278	6	A/G	1.26 (1.22, 1.30)	1.57×10^{-43}
rs3130968	6	T/C	1.07 (1.05, 1.10)	3.16×10^{-10}
rs2107595	7	A/G	1.08 (1.05, 1.10)	2.49×10^{-11}
rs4722172	7	G/A	1.08 (1.05, 1.10)	3.65×10^{-11}
rs322	8	A/C	1.06 (1.04, 1.07)	2.53×10^{-9}
rs505922	9	C/T	1.06 (1.04, 1.07)	7.10×10^{-11}
rs1537372	9	T/G	1.12 (1.10, 1.14)	4.32×10^{-39}
rs7903146	10	T/C	1.06 (1.04, 1.08)	3.76×10^{-11}
rs566125	11	T/C	1.08 (1.05, 1.11)	4.37×10^{-9}
rs7476	11	C/A	1.06 (1.04, 1.08)	8.33×10^{-10}
rs11066301	12	G/A	1.06 (1.04, 1.08)	2.96×10^{-11}
rs4842266	12	G/A	1.06 (1.04, 1.08)	1.01×10^{-9}
rs1975514	13	C/T	1.05 (1.04, 1.07)	8.32×10^{-10}
rs55784307	14	A/C	1.06 (1.04, 1.09)	2.93×10^{-8}
rs10851907	15	A/G	1.06 (1.05, 1.08)	1.49×10^{-13}
rs62084752	17	C/G	1.07 (1.05, 1.09)	1.58×10^{-10}
rs138294113	19	C/T	1.09 (1.06, 1.11)	1.20×10^{-10}

S2 Table. HRs (95% CIs) of PAD according to individual healthy lifestyle factor in 14,543 participants with T2D

	PAD		
	Person-years	**Cases**	**HR (95% CI)** *
Smoking			
Ever smoking (>0 smoking pack-year)	91,475	450	1.00
Non-smoking (0 smoking pack-year)	94,915	178	0.49 (0.41, 0.59)
Physical activity*			
Irregular	100,392	362	1.00
Regular	85,998	266	0.90 (0.76, 1.05)
Dietary score			
< 5 ideal components	149,566	518	1.00
≥5 ideal components	36,824	110	0.92 (0.75, 1.13)
Alcohol intake			
Others	66,440	249	1.00
1-28 g/day (men) or 1-14 g/day (women)	119,950	379	0.81 (0.69, 0.95)
Waist-hip ratio			
≥0.90 (men) or ≥0.85 (women)	152,520	576	1.00
< 0.90 (men) or < 0.85 (women)	33,869	52	0.68 (0.50, 0.91)
Sleep duration			
<7 or >8hours/day	72,583	260	1.00
7-8 hours/day	113,806	368	0.97 (0.83, 1.14)

Model was adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin). Individual lifestyle factors were mutually adjusted in model.

* Regular physical activity was defined as ≥150 min/week of moderate activity, ≥75 min/week of vigorous activity, or an equivalent combination.

S3 Table. HRs (95% CIs) of PAD according to genetic risk among 10,836 participants* with T2D

	Genetic risk				Per SD increment in genetic risk
	Low (lowest tertile)	Intermediate (middle tertile)	High (highest tertile)	P_{trend}	
No of Cases/person-years	168/62,286	211/62,289	234/62,009	-	-
Model 1	1	1.22 (0.98, 1.53)	1.38 (1.11, 1.72)	0.004	1.13 (1.03, 1.23)
Model 2	1	1.22 (0.98, 1.53)	1.37 (1.10, 1.71)	0.005	1.13 (1.03, 1.23)

Model 1: age (continuous, years), sex (male, female), Townsend Deprivation Index (continuous), race/ethnicity (White, others)**,** education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin), genotype measurement batch, and the first 10 principal components of ancestry.

Model 2: Model 1 + weighted healthy lifestyle scores (continuous).

*The genetic analyses were conducted among 10,836 participants with T2D who had the genetic information available.

S4 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories within each genetic risk group among 10,836 participants* with T2D

	Low Genetic risk			Intermediate Genetic risk			High Genetic risk		
Healthy lifestyle categories	**Unfavorable**	**Intermediate**	**Favorable**	**Unfavorable**	**Intermediate**	**Favorable**	**Unfavorable**	**Intermediate**	**Favorable**
Cases/N	31/596	98/2185	13/831	47/572	110/2228	14/813	55/595	117/2206	14/810
HR (95% CI)	1	0.92 (0.61, 1.39)	0.38 (0.20, 0.73)	1	0.58 (0.41, 0.81)	0.25 (0.13, 0.45)	1	0.64 (0.46, 0.89)	0.26 (0.14, 0.47)
P value for trend		0.002			<0.0001			<0.0001	
$P_{interaction}$					0.97				

Model was adjusted for age (continuous, years), sex (male, female), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin), genotype measurement batch, and the first 10 principal components of ancestry.

*The genetic analyses were conducted among 10,836 participants with T2D who had the genetic information available

S5 Table. Multivariable-adjusted linear regression models for the association between the weighted healthy lifestyle score and biomarker levels among participants with T2D*

Risk factors	β	Lower 95%CI	Upper 95%CI	*P*- value
Biomarkers of renal function				
Cystatin C (mg/L)	-0.0927	-0.1208	-0.0645	<0.0001
Creatinine (μmol/L)	0.0982	0.0676	0.1287	<0.0001
Urate (μmol/L)	-0.0938	-0.1217	-0.0659	<0.0001
Urea (mmol/L)	0.1074	0.0796	0.1352	<0.0001
Biomarkers of liver function				
Alanine aminotransferase (U/L)	-0.1112	-0.1391	-0.0832	<0.0001
Alkaline phosphatase (U/L)	-0.0922	-0.1194	-0.0650	<0.0001
Aspartate aminotransferase (U/L)	-0.0541	-0.0810	-0.0273	<0.0001
Gamma glutamyltransferase (U/L)	-0.2392	-0.2668	-0.2116	<0.0001
Total bilirubin (μmol/L)	0.1333	0.1056	0.1609	<0.0001
Total protein (g/L)	0.0395	0.0113	0.0676	0.01
Albumin (g/L)	0.0609	0.0328	0.0890	<0.0001
Biomarkers of lipid profile				
Total blood cholesterol (mmol/L)	-0.0740	-0.1057	-0.0423	<0.0001
HDL-C (mmol/L)	0.1345	0.1048	0.1641	<0.0001
LDL-C (mmol/L)	-0.0831	-0.1149	-0.0512	<0.0001
Triglycerides (mmol/L)	-0.2127	-0.2399	-0.1855	<0.0001
Apolipoprotein A (g/L)	0.0920	0.0625	0.1214	<0.0001
Apolipoprotein B (g/L)	-0.1304	-0.1612	-0.0996	<0.0001
Lipoprotein (a) (nmol/L)	0.0184	-0.0118	0.0485	0.23
Inflammatory biomarkers				
C-reactive protein (mg/L)	-0.2474	-0.2752	-0.2196	<0.0001
White blood cell count (x10^9/L)	-0.2134	-0.2396	-0.1873	<0.0001
Blood pressure indices				
SBP (mmHg)	0.0034	-0.0172	0.0240	0.75
DBP (mmHg)	-0.0384	-0.0589	-0.0179	0.0002
Biomarkers of glucose metabolism				
HbA_{1c} (%)	-0.0777	-0.0976	-0.0579	<0.0001

Model was adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication, use of lipid-lowing medication, use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin).

For biomarkers of systolic blood pressure and diastolic blood pressure, model was not adjusted for prevalence of hypertension (yes, no). HbA_{1c} (continuous, %) levels were not adjusted when HbA_{1c} was analyzed as a biomarker in model.

[*] The levels of biomarkers were nature log transformed except for systolic blood pressure and diastolic blood pressure

S6 Table. Risk estimates of PAD associated with the selected biomarkers (1-SD increment) among participants with T2D*

Biomarkers	HR	Lower	Upper	*P*
Biomarkers of renal function				
Cystatin C (mg/L)	1.43	1.34	1.52	<0.0001
Creatinine (μmol/L)	1.25	1.15	1.35	<0.0001
Urate (μmol/L)	1.09	1.00	1.19	0.04
Urea (mmol/L)	1.17	1.08	1.28	0.0001
Biomarkers of liver function				
Alanine aminotransferase (U/L)	0.81	0.74	0.89	<0.0001
Alkaline phosphatase (U/L)	1.18	1.09	1.28	<0.0001
Aspartate aminotransferase (U/L)	0.89	0.81	0.97	0.01
Gamma glutamyltransferase (U/L)	1.06	0.98	1.16	0.16
Total bilirubin (μmol/L)	0.86	0.79	0.95	0.001
Total protein (g/L)	0.95	0.87	1.04	0.28
Albumin (g/L)	0.82	0.76	0.88	<0.0001
Biomarkers of lipid profile				
Total blood cholesterol (mmol/L)	1.10	0.99	1.21	0.07
HDL-C (mmol/L)	0.84	0.76	0.92	0.0002
LDL-C (mmol/L)	1.14	1.03	1.26	0.01
Triglycerides (mmol/L)	1.15	1.06	1.25	0.001
Apolipoprotein A (g/L)	0.84	0.77	0.92	0.0002
Apolipoprotein B (g/L)	1.16	1.05	1.27	0.003
Inflammatory biomarkers				
C-reactive protein (mg/L)	1.31	1.20	1.43	<0.0001
White blood cell count (x10^9/L)	1.27	1.17	1.38	<0.0001
Blood pressure indices				
DBP (mmHg)	0.90	0.83	0.98	0.02
Biomarkers of glucose metabolism				
HbA_{1c} (%)	1.23	1.13	1.33	<0.0001

Model were adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication, use of lipid-lowing medication, use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin), and weighted healthy lifestyle scores (continuous).

For biomarker of diastolic blood pressure, model was not adjusted for prevalence of hypertension (yes, no). HbA_{1c} (continuous, %) levels were not adjusted when HbA_{1c} was analyzed as a biomarker in model.

*The levels of biomarkers were nature log-transformed before analyses except for diastolic blood pressure.

S7 Table. HRs (95% CIs) of PAD according to different combinations of healthy lifestyle factors among 14,543 participants with T2D

	PAD		
	Person-years	**Cases**	**HR (95% CI)** *
Two healthy factors (physical activity, alcohol consumption)			
0	36,254	147	1.00
1-2	150,136	481	0.77 (0.64, 0.93)
P-trend			0.01
Three healthy factors (above two plus sleep duration)			
0	15,591	67	1.00
1	57,286	210	0.89 (0.68, 1.18)
2-3	113,512	351	0.75 (0.57, 0.97)
P-trend			0.01
Four healthy factors (above three plus waist-hip ratio)			
0	13,424	64	1.00
1	49,948	199	0.87 (0.66, 1.16)
2	73,578	244	0.72 (0.55, 0.95)
3-4	49,440	121	0.64 (0.47, 0.87)
P-trend			0.001
Five healthy factors (above four plus diet)			
0	11,402	52	1.00
1	43,265	185	0.98 (0.72, 1.34)
2	67,406	222	0.74 (0.55, 1.01)
3	47,044	132	0.73 (0.53, 1.00)
4 -5	17,272	37	0.62 (0.41, 0.95)
P-trend			0.001
Six healthy factors (above five plus smoking)			
0-1	33,873	182	1.00
2	55,199	220	0.78 (0.64, 0.94)
3	54,500	150	0.60 (0.48, 0.74)
4	31,819	66	0.49 (0.37, 0.65)
5-6	10,999	10	0.24 (0.12, 0.45)
P-trend			<0.0001

Model was adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin), with the individual healthy factor mutual adjustment.

S8 Table. HRs (95% CIs) of PAD according to unweighted healthy lifestyle score among 14,543 participants with T2D

	Unweighted healthy lifestyle score						Per 1-unit increment in unweighted lifestyle score
	0-1	**2**	**3**	**4**	**5-6**	***P*-trend**	
HRs (95% CIs)	1	0.78 (0.64, 0.94)	0.60 (0.48, 0.74)	0.49 (0.37, 0.65)	0.24 (0.12, 0.45)	<0.0001	0.79 (0.73, 0.84)

Model was adjusted for age (years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin).

S9 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories among participants with T2D after excluding the cases occurred within the first two-years of follow-up

	Healthy lifestyle categories*				Per 1- point in weighted lifestyle score
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	*P*-trend	
Cases/person-years	188/37,315	346/107,813	47/41,210		
HRs (95% CIs)	1	0.72 (0.60, 0.86)	0.31 (0.22, 0.43)	<0.0001	0.78 (0.74, 0.83)

Model was adjusted for age (years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin).

*The weighted healthy lifestyle score was categorized as unfavorable, intermediate, and favorable lifestyle based on the distribution of the unweighted lifestyle score.

S10 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories using moderate drinking and non-drinking as the healthy behavior in participants with T2D

	Healthy lifestyle categories*				Per 1-point increment in weighted lifestyle score
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	$P_{\text{-trend}}$	
Using moderate drinking and non-drinking† as the healthy behavior					
Cases/person-years	152/27,652	418/111,326	58/47,411		
HRs (95% CIs)	1	0.78 (0.65, 0.94)	0.32 (0.23, 0.43)	<0.0001	0.78 (0.74, 0.82)

Model was adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no) diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin).

*The weighted healthy lifestyle score was categorized as unfavorable, intermediate, and favorable lifestyle based on the distribution of the unweighted lifestyle score.

†Healthy alcohol drinking was defined as <28 g/d for men and <14 g/d of ethanol intakes for women.

S11 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories using optimal BMI or optimal waist circumstance as the healthy behavior in participants with T2D

	Healthy lifestyle categories*				Per 1-point increment in weighted lifestyle score
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	*P*-trend	
Using optimal BMI† instead of waist-hip ratio as the healthy behavior					
Cases/person-years	230/42,130	315/96,247	82/47,447		
HRs (95% CIs)	1	0.68 (0.57, 0.80)	0.39 (0.30, 0.50)	<0.0001	0.83 (0.80, 0.87)
Using optimal waist circumstance‡ instead of waist-hip ratio as the healthy behavior					
Cases/person-years	193/33,052	351/105,360	84/48,044		
HRs (95% CIs)	1	0.63 (0.53, 0.75)	0.37 (0.29, 0.48)	<0.0001	0.83 (0.79, 0.86)

Model was adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin).

*The weighted healthy lifestyle score was categorized as unfavorable, intermediate, and favorable lifestyle based on the distribution of the unweighted lifestyle score.

†Optimal BMI was defined as 18.5-24.9 kg/m^2 in 14,496 participants with T2D who have BMI data.

‡Optimal waist circumstance was defined as <94 cm for men or <80 cm for women in 14,548 participants with T2D who have waist circumstance data.

S12 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories using optimal pack years of smoking instead of non-smoking status as the healthy behavior in 19,356 participants with T2D

	Healthy lifestyle categories*				Per 1-point increment in weighted lifestyle score
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	*P*-trend	
Using non-smoking status† instead of pack years of smoking as the healthy behavior					
Cases/person-years	195/34,626	500/166,848	72/47,326		
HRs (95% CIs)	1	0.58 (0.49, 0.69)	0.33 (0.25, 0.44)	<0.0001	0.82 (0.79, 0.86)

Model was adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin).

*The weighted healthy lifestyle score was categorized as unfavorable, intermediate, and favorable lifestyle based on the distribution of the unweighted lifestyle score.

†Non-smoking status was defined as never smoking.

S13 Table. HRs (95% CIs) of PAD according to healthy lifestyle categories among participants with T2D using two competing risk models

	Healthy lifestyle categories*				Per 1-point increment in weighted lifestyle score
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	*P*-trend	
Fine-Gray subdistribution hazards model					
HRs (95% CIs)	1	0.68 (0.57, 0.82)	0.28 (0.20, 0.40)	<0.0001	0.78 (0.74, 0.83)
Cause-specific hazards model					
HRs (95% CIs)	1	0.66 (0.55, 0.79)	0.27 (0.19, 0.37)	<0.0001	0.77 (0.73, 0.82)

Model was adjusted for age (continuous, years), sex (male, female), ethnicity (White, others), education attainment (college or university degree, A/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, or none of the above), Townsend Deprivation Index (continuous), family history of CVD (yes, no), prevalence of hypertension (yes, no), use of antihypertensive medication (yes, no), use of lipid-lowing medication (yes, no), use of aspirin (yes, no), diabetes duration (continuous, years), HbA_{1c} (continuous, %), and use of diabetes medication (none, only oral medication pills, or only insulin or combination of oral medications and insulin).

*The weighted healthy lifestyle score was categorized as unfavorable, intermediate, and favorable lifestyle based on the distribution of the unweighted lifestyle score.