Supplementary Material

Hyunsuk Lee et al

Earlier Age at Type 2 Diabetes Diagnosis is Associated with Increased Genetic Risk for Cardiovascular Disease

Table of Contents

Supplementary Method

Study Population

UK Biobank is a large population-based prospective cohort based in the United Kingdom. Between 2007 and 2010, approximately half a million people aged 40-69 years across England, Scotland, and Wales were recruited. Details of UK Biobank study have been previously described (1). Participants with type 2 diabetes (T2D) and their age at diagnosis were algorithmically defined using self-reported medical history and medication (2). Participants who answered that they had been diagnosed with type 1 diabetes (T1D) in self-reported questionnaires or nurse interviews, along with participants who started insulin treatment within one year of diabetes diagnosis, were presumed to have T1D and were therefore excluded. Additionally, participants with an age at T2D diagnosis under 30 were excluded due to the possibility of misdiagnosis of T1D.

The Seoul National University Hospital (SNUH) T2D cohort is a hospital-based prospective cohort based in South Korea and has been described in detail previously (3). People with T2D were enrolled between January 2001 and September 2018, and T2D was diagnosed according to American Diabetes Association guidelines (4). The institutional review board of the Biomedical Research Institute at SNUH approved the study protocol (H-1603-079-749), and written informed consent was obtained from all participants. All clinical investigations were conducted according to the Declaration of Helsinki.

Ascertainment of Outcomes

An incident cardiovascular disease (CVD) event was defined as the first CVD event that occurred at least 1 year after T2D diagnosis. Based on the definition of incident CVD event, participants with CVD events prior to or within 1 year after T2D diagnosis were excluded. In UK Biobank, CVD events were defined as nonfatal myocardial infarction, nonfatal stroke and cardiovascular death using an algorithm developed by UK Biobank (5). Briefly, UK Biobank identified the date of the first known CVD event with questionnaires, hospital admission data and death registry information using the 10^{th} edition of the International Classification of Diseases (ICD) codes (Table S1). Information was collected until February 2018. In the SNUH T2D cohort, CVD events were defined as nonfatal myocardial infarction, ischemic heart disease requiring revascularization, nonfatal stroke and cardiovascular death. CVD events were identified from the cohort follow-up records and SNUH electronic health records. Death registry information was obtained by linking the Korean national database for the cause of death registered at

the Korean National Statistics Office. CVD death was defined as death caused by diseases coded as I20-I82. Information was collected until December 2020. CVD events were divided into coronary artery disease (CAD) and stroke in both cohorts.

Genotype Data and Calculation of PRS

Participants in UK Biobank were genotyped centrally by the UK Biobank team (1). Unrelated participants of European ancestry with high-quality genotyping data were used to derive individual-level polygenic risk score (PRS). PRSs for T2D, CAD and stroke were calculated by PRS via Bayesian regression using continuous shrinkage priors (PRS-CS) (6). The PRSs for T2D, CAD and stroke were calculated using 1.1 million SNPs each based on the summary statistics of DIAGRAM, CARDIoGRAMplusC4D Consortium (C4D) and MEGASTROKE, respectively (7-9).

Genetic data of the SNUH T2D cohort were previously described in detail (3). Briefly, genotyping was performed using the Affymetrix Axiom Biobank Plus Genotyping Array by DNA Link, Inc. (Seoul, Republic of Korea). After standard genotype quality control, imputation was performed using the 1000 Genomes Project reference panel. The PRS for T2D was calculated using precalculated 1,259,754 SNPs with weights derived by trans-ancestry PRS-CS (PRS-CSx) in trans-ancestry meta-analysis of DIAGRAM, MEDIA consortium and Biobank Japan (10). The PRS for CAD was calculated using precalculated 75,028 SNPs with weights that had been derived by p-value thresholding in trans-ancestry random-effect meta-analysis of Biobank Japan, UK Biobank, and C4D (11). In the SNUH T2D cohort, we preferentially used the above-mentioned CAD PRS calculation because its performance in predicting CAD was superior to that of PRS-CS, calculated by Nagelkerke's pseudo R^2. PRSs were standardized to have a mean of zero and standard deviation (SD) of one in UK Biobank and the SNUH T2D cohort

Assessment of Lifestyle Factors and Covariates

To assess lifestyle factors, we adapted four components associated with primary prevention of ASCVD from the strategic goals of the American Heart Association: 1) no current smoking, 2) no obesity (BMI < 30 kg/m^2), 3) healthy diet pattern and 4) physical activity at goal levels (12,13). Information about lifestyle factors was collected at baseline, and details can be found in Table S2. An ideal diet was defined as adequate intake of at least one-half of 10 food groups recommended for cardiometabolic health: increased intake of fruits, vegetables, whole grains, fish, dairy and vegetable oils and reduced intake of refined grains, processed/unprocessed meats and

sugar-sweetened beverages (14,15). Physical activity goals were defined as at least 150 min/week of moderate activity or 75 min/week of vigorous activity. Participants were categorized as having a favorable lifestyle (satisfying the goals of at least two lifestyle factors) or an unfavorable lifestyle (satisfying the goals of fewer than two lifestyle factors).

Anthropometric measures and nonfasting venous blood sampling were performed during initial assessment visit between 2007 and 2010. Detailed protocol for collection and archiving samples for the study is described elsewhere (16).

Statistical Analysis

All variables used in the analysis had missing rates below 10%, and missing data were imputed using multiple imputation by chained equation method (17). The variables of baseline characteristics are shown as n (%) for categorical variables and mean (SD) for continuous variables. The distribution of baseline characteristics was compared using the χ^2 test and ANOVA, respectively. Age at T2D diagnosis was stratified by decades, and participants were divided into four groups (age at T2D diagnosis from 30-39, 40-49, 50-59 and 60-69 years).

The risk for incident CVD in each age at T2D diagnosis group compared to the reference group (age at T2D diagnosis from 60-69) was estimated using Cox proportional hazards models. The follow-up time for each participant was calculated as age, which from the date of birth to the date at first incident CVD event, death, or end of follow-up—whichever came first. Model 1 was adjusted for age at enrollment and sex, and model 2 was additionally adjusted for ASCVD risk factors: ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol and smoking status at baseline enrollment (18).

The genetic risk for incident CVD was estimated by calculating hazard ratio (HR) with 95% confidence interval (CI) for a 1 SD increment of PRS using Cox proportional hazard model, with additional adjustment for the first ten principal components that reflect ancestry in the aforementioned two models. Interaction analysis between age at T2D diagnosis and PRS was performed using the same models to investigate whether the association between genetic predisposition and CVD incidence was modified by age at T2D diagnosis. Since the effect of CAD PRS becomes larger as the age at T2D diagnosis gets earlier, age at T2D diagnosis was converted to negative numbers to show an increased effect of PRS for earlier diagnosis in the interaction analysis (for example, if a person's age at T2D diagnosis was 52, it was converted to -52 in the interaction analysis). The association

between genetic risk and lifestyle in the development of CVD was examined by categorizing genetic risk as high risk (PRS ≥ 0) and low risk (PRS < 0), and calculating HRs with 95% CIs in groups divided by genetic risk and lifestyle compared to the reference group (favorable lifestyle with low genetic risk). Log-minus-log plots and Schoenfeld residuals were used to assess the proportional hazard assumptions. Statistical analysis was performed with Python version 2.7.5 and R software version 4.1.0.

Sensitivity Analysis

The two sensitivity analyses in the manuscript are performed as follows. First, we performed a sensitivity analysis including those who were excluded for having CVD events prior to T2D diagnosis, as excluding anyone with a prior CVD event may induce a selection bias. In the original analysis, 1,112 participants were excluded for having CVD events prior to T2D diagnosis. After including the 1,112 participants with CVD prior to diagnosis of T2D, the increased genetic effect of CAD PRS was still seen in people with earlier age at T2D diagnosis, which are in line with our main findings. Second, we performed another sensitivity analysis by changing the start of the observation period from birth to age at cohort entrance. Since the acquisition point of the information about lifestyle and covariates is measured at the point of enrollment and not measured at the time of either T2D diagnosis or outcome assessment, it could lead to measurement bias. To overcome this limitation, we performed a sensitivity analysis by changing the start of observation to age at cohort entrance and found that the results are in line with the main findings. Follow-up time was calculated as the duration of enrollment, which is from the date of enrollment of the UK Biobank to the date of first incident CVD event, death, or end of follow-up – whichever came first. Events only included incident CVD events that occurred after enrollment and participants with CVD events before enrollment were excluded from the analysis. This could reduce measurement bias, as this sensitivity analysis utilizes covariates acquired at the time of enrollment. Also, it would exclude those who had their information acquired after the diagnosis of T2D and CVD, as this subpopulation could have had a major change in lifestyle or medication compliance (leading to change in covariates such as LDL cholesterol) after a major health event such as CVD.

Data and Resource Availability Statement

The datasets generated during and/or analyzed in the current study are available from the corresponding

author upon reasonable request.

Supplementary Table 1

ICD codes used for defining coronary artery disease and stroke in UK Biobank.

Coronary artery disease and stroke events were obtained using baseline assessment data collection, along with linked data from hospital admissions and death registries. Cardiovascular death was the sum of fatal coronary artery disease and fatal stroke.

Disease	UK Biobank Self Report	ICD 9 code	ICD 10 code
Coronary artery disease	20002 (1075)	410, 410.0-410.9, 411.0, 412.X[4], 429.79	I21, I21.0-I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0-I23.6, I23.8, I24.1, I25.2
Stroke	20002 (1081, 1086, 1491, 1583)	430.X, 431.X, 434.X, 434.0, 434.1, 434.9, 436.X[5,6]	I60, I60.0-I60.9, I61, I61.0-I61.6, I61.8, I61.9, I63, I63.0-I63.6, I63.8, I63.9, I63.X[4]

Supplementary Table 2

Assessment of lifestyle factors in UK Biobank.

Individual lifestyle information was collected at baseline enrollment (2006-2010) by touchscreen questionnaires. Detailed information about questionnaires can be obtained in the UK Biobank website (https://biobank.npdh.ox.ac.uk/showcase/).

- Smoking: Individuals were asked about their smoking status with the following questions: “Do you smoke tobacco now? i. yes, on most or all days, ii. only occasionally, iii. no, or iv. prefer not to answer”. The smoking status was then categorized into two groups (current smoking and no current smoking).

- Physical activity: Individuals were asked of moderate/vigorous physical activity through questionnaires: “In a typical week, on how many days did you do 10 minutes or more of moderate physical activities like carrying light loads, cycling at a normal pace? (not include walking)” and “In a typical week, how many days did you do 10 minutes or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)”. Individuals were further asked about the time spent on moderate/vigorous physical activity with the following questions: “How many minutes did you usually spend doing moderate activities on a typical day?” and “How many minutes did you usually spend doing vigorous activities on a typical day?”. Total amount of moderate or vigorous physical activity in a week were calculated by multiplying the number of days and the duration per day, respectively.

- Obesity: Physical measurements of height and weight was done by nurses at baseline and body-mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Individuals were categorized as two groups for having BMI below and above 30kg/m^2 (not obese and obese).

- Diet: Ten food groups were selected as dietary priorities for cardiometabolic health (14), as in previous UK Biobank study (15). Ideal diet was defined as adequate intake of at least one-half of 10 recommended food groups. Details are shown below:

Diet Component	Intake Goal	Field IDs
Fruits	≥3 servings/day	1309-"About how many pieces of FRESH fruit would you eat per DAY?"

		1319-"About how many pieces of DRIED fruit would you eat per DAY?"
Vegetables	≥3 servings/day	1289-"On average how many heaped tablespoons of COOKED vegetables would you eat per DAY?” 1299-"On average how many heaped tablespoons of SALAD or RAW vegetables would you eat per DAY?"
Whole grains	≥3 servings/day	1438-"How many slices of bread do you eat each WEEK?" 1448-"What type of bread do you mainly eat?" 1458-"How many bowls of cereal do you eat a WEEK?" 1468-"What type of cereal do you mainly eat?"
(Shell)fish	≥2 servings/week	1329-"How often do you eat oily fish? (e.g. sardines, salmon, mackerel, herring)" 1339-"How often do you eat other types of fish? (e.g. cod, tinned tuna, haddock)"
Dairy	≥2 servings/day	1408-"How often do you eat cheese? (Include cheese in pizzas, quiches, cheese sauce etc.)" 1418-"What type of milk do you mainly use?"
Vegetable oils	≥2 servings/day	1428-"What type of spread do you mainly use?" (Spread type) 2654-"What type of spread do you mainly use?" (Non-butter spread type details) 1438-"How many slices of bread do you eat each WEEK?"
Refined grains	≤2 servings/day	1438-"How many slices of bread do you eat each WEEK?" 1448-"What type of bread do you mainly eat?" 1458-"How many bowls of cereal do you eat a WEEK?" 1468-"What type of cereal do you mainly eat?"
Processed meats	≤1 serving/week	1349-"How often do you eat processed meats (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets)"
Unprocessed meats	≤2 serving/week	1359-"How often do you eat chicken, turkey or other poultry? (Do not count processed meats)" 1369-"How often do you eat beef? (Do not count processed meats)" 1379-"How often do you eat lamb/mutton? (Do not count processed meats)" 1389-"How often do you eat pork? (Do not count processed meats such as bacon or ham)"
Sugar-sweetened beverages	Don’t drink	6144-"Which of the following do you NEVER eat?"

Supplementary Table 3

Risk of cardiovascular disease, according to age at T2D diagnosis in UK Biobank, ASCVD risk factors adjusted (time=age, event=incident CVD event).

Age at T2D diagnosis (years)	Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*
30-39	**6.01 (4.32-8.35)**	$<2.0\times10^{-16}$	**5.88 (4.21-8.20)**	$<2.0\times10^{-16}$
40-49	**4.15 (3.43-5.00)**	$<2.0\times10^{-16}$	**3.94 (3.26-4.77)**	$<2.0\times10^{-16}$
50-59	**1.63 (1.42-1.88)**	5.0×10^{-12}	**1.59 (1.38-1.83)**	1.1×10^{-10}
60-69	**1.00 (Ref)**		**1.00 (Ref)**	
	P_{trend} $<2.0\times10^{-16}$		P_{trend} $<2.0\times10^{-16}$	

Shown are adjusted hazard ratios for cardiovascular disease in each group divided by age at T2D diagnosis. Participants diagnosed with T2D between age 60 to 69 served as the reference group in these comparisons. Model 1 was adjusted for age at enrollment and sex. Model 2 was additionally adjusted for atherosclerotic cardiovascular disease (ASCVD) risk factors: ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol and smoking status.

Supplementary Table 4

Risk of cardiovascular disease, according to age at T2D diagnosis in UK Biobank, ASCVD risk factors adjusted. (time=years after enrollment, event=incident CVD event after enrollment).

Age at T2D diagnosis (years)	Model 1		Model 2	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
30-39	**1.93 (1.16-3.22)**	0.0113	**1.90 (1.14-3.18)**	0.014
40-49	**1.87 (1.45-2.42)**	1.54×10^{-6}	**1.82 (1.40-2.35)**	5.88×10^{-6}
50-59	**1.06 (0.90-1.26)**	0.460	**1.05 (0.89-1.24)**	0.594
60-69	**1.00 (Ref)**		**1.00 (Ref)**	
	$P_{trend} = 4.62 \times 10^{-5}$		$P_{trend} < 2.0 \times 10^{-16}$	

Shown are adjusted hazard ratios for cardiovascular disease in each group divided by age at T2D diagnosis. Participants diagnosed with T2D between age 60 to 69 served as the reference group in these comparisons. Follow-up time was calculated as duration of enrollment, which is from the date of enrollment of UK Biobank to the date of first incident CVD event, death, or end of follow-up – whichever came first. Events only included incident CVD events that occurred after enrollment and those with CVD events before enrollment were excluded. Model 1 was adjusted for age at enrollment and sex. Model 2 was additionally adjusted for atherosclerotic cardiovascular disease (ASCVD) risk factors: ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol and smoking status.

Supplementary Table 5

Baseline characteristics of SNUH T2D cohort.

Age at T2D diagnosis	30-39 (N=196)	40-49 (N=374)	50-59 (N=400)	60-69 (N=195)	*P**	P_{trend}†
Age at enrollment, years, mean (SD)	49.7 (10.4)	56.0 (8.5)	61.5 (6.8)	67.7 (5.2)	<0.001	<0.001
Male, no. (%)	114 (58.2)	189 (50.5)	174 (43.5)	70 (35.9)	<0.001	<0.001
Duration of T2D, years, mean (SD)	23.6 (11.0)	19.1 (9.3)	16.1 (7.3)	13.0 (5.9)	<0.001	<0.001
Family history of T2D, no. (%)	137 (69.9)	209 (55.9)	185 (46.2)	66 (33.8)	<0.001	<0.001
HbA1c, %, mean (SD)	8.13 (1.73)	7.96 (2.50)	7.60 (1.52)	7.39 (1.54)	<0.001	<0.001
C-peptide, ng/ml, mean (SD)	1.91 (1.06)	2.00 (1.14)	2.25 (1.52)	2.37 (2.04)	0.004	<0.001
Insulin use, no. (%)	81 (41.3)	130 (34.8)	61 (15.2)	22 (11.3)	<0.001	<0.001
BMI, kg/m², mean (SD)	24.4 (3.6)	24.4 (2.9)	24.5 (3.0)	24.8 (3.1)	0.461	0.143
Current smoking, no. (%)	42 (21.4)	58 (15.5)	47 (11.8)	10 (5.2)	<0.001	<0.001
Blood Pressure, mmHg, mean (SD)						
Systolic blood pressure	124 (15)	127 (17)	129 (17)	131 (17)	<0.001	<0.001
Diastolic blood pressure	76 (10)	78 (11)	78 (10)	78 (11)	0.059	0.058
Lipid levels, mg/dl, mean (SD)						
Total cholesterol	182 (46)	184 (41)	185 (41)	185 (38)	0.81	0.401
HDL cholesterol	46 (15)	48 (14)	49 (13)	50 (14)	0.041	0.0059
LDL cholesterol	106 (36)	104 (37)	106 (36)	108 (35)	0.722	0.47
Use of antihypertensive medication, no. (%)	78 (39.8)	176 (47.1)	183 (45.8)	96 (49.2)	0.260	0.122
Incident event - no. (%)						
Cardiovascular disease	36 (18.4)	85 (22.7)	75 (18.8)	40 (20.5)	0.491	0.920
Coronary artery disease	22 (11.2)	53 (14.2)	46 (11.5)	21 (10.8)	0.554	0.550
Stroke	19 (9.7)	51 (13.6)	44 (11.0)	29 (14.9)	0.298	0.348
Polygenic risk score, mean (SD)						
T2D PRS	0.40 (1.04)	0.09 (0.94)	-0.12 (0.97)	-0.32 (0.99)	<0.001	<0.001
CAD PRS	0.10 (1.04)	0.01 (0.99)	-0.02 (1.01)	-0.08 (0.95)	0.338	0.079

T2D, type 2 diabetes; HbA1c, hemoglobin A1C; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRS, polygenic risk score; CAD, coronary artery disease. Information was collected at baseline enrollment.

*P values for the difference between groups divided by age at T2D diagnosis groups were calculated with an ANOVA and χ^2 test for continuous and categorical variables, respectively.

†P values for trend between groups divided by age at T2D diagnosis were calculated with a linear regression test and Cochran-Armitage test for continuous and categorical variables, respectively.

Supplementary Table 6

Risk of cardiovascular disease, according to age at T2D diagnosis in SNUH T2D cohort, ASCVD risk factors adjusted (time=age, event=incident CVD event).

Age at T2D diagnosis (years)	Model 1		Model 2	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
30-39	**3.64 (2.24-5.89)**	1.6×10^{-7}	**3.30 (2.02-5.40)**	2.1×10^{-6}
40-49	**3.05 (2.04-4.54)**	4.9×10^{-8}	**2.92 (1.95-4.37)**	2.0×10^{-7}
50-59	**1.49 (1.01-2.22)**	0.046	**1.44 (0.97-2.13)**	0.072
60-69	**1.00 (Ref)**		**1.00 (Ref)**	
	$P_{trend} = 3.77 \times 10^{-11}$		$P_{trend} = 1.24 \times 10^{-9}$	

Shown are adjusted hazard ratios for cardiovascular disease in each group divided by age at T2D diagnosis. Participants diagnosed with T2D between age 60 to 69 served as the reference group in these comparisons. Model 1 was adjusted for age at enrollment and sex. Model 2 was additionally adjusted for atherosclerotic cardiovascular disease (ASCVD) risk factors: ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol and smoking status.

Supplementary Table 7

Genetic risk of coronary artery disease, according to age at T2D diagnosis in UK Biobank, ASCVD risk factors adjusted (time=age, event=incident CAD event).

Age at T2D diagnosis (years)	HR of CAD polygenic risk score (Model 1)		HR of CAD polygenic risk score (Model 2)	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
30-39	**2.25 (1.56-3.26)**	$1.6x10^{-5}$	**2.20 (1.53-3.18)**	$2.4x10^{-5}$
40-49	**1.51 (1.30-1.75)**	$7.5x10^{-8}$	**1.48 (1.27-1.72)**	$4.6x10^{-7}$
50-59	**1.36 (1.24-1.50)**	$4.9x10^{-10}$	**1.35 (1.22-1.49)**	$2.2x10^{-9}$
60-69	**1.30 (1.14-1.48)**	$6.9x10^{-5}$	**1.27 (1.11-1.44)**	$3.5x10^{-4}$

Interaction term	Model 1		Model 2	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age at T2D diagnosis X CAD PRS	1.01 (1.00-1.02)	0.0031	1.01 (1.00-1.02)	0.0028

Shown are adjusted hazard ratios for coronary artery disease in each group divided by age at T2D diagnosis. Follow-up time was calculated as age in UK Biobank which is from the date of birth to the date of first incident CAD event, death, or end of follow-up – whichever came first. Hazard ratios were calculated for 1 SD increment of CAD PRS. Model 1 was adjusted for age at enrollment, sex and the first 10 principal components that reflect ancestry. Model 2 was adjusted for variables in model 1 plus ASCVD risk factors: ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol and smoking status.

The interaction analysis translates to an additional 14% increase (1.14, 1.05-1.25) in the effect of CAD PRS as age

at T2D diagnosis decreased by 10 years after adjustment for ASCVD risk factors.

Supplementary Table 8

Genetic risk of coronary artery disease, according to age at T2D diagnosis in UK Biobank, ASCVD risk adjusted (time=age, event=CAD event including events prior to diagnosis of T2D).

Age at T2D diagnosis (years)	HR of CAD polygenic risk score (Model 1)		HR of CAD polygenic risk score (Model 2)	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
30-39	**2.15 (1.52-3.03)**	$1.4x10^{-5}$	**2.13 (1.51-3.00)**	$1.7x10^{-5}$
40-49	**1.52 (1.34-1.73)**	$1.9x10^{-10}$	**1.49 (1.31-1.70)**	$2.1x10^{-9}$
50-59	**1.49 (1.39-1.60)**	$<2.0x10^{-16}$	**1.46 (1.36-1.57)**	$<2.0x10^{-16}$
60-69	**1.51 (1.40-1.63)**	$<2.0x10^{-16}$	**1.45 (1.35-1.57)**	$<2.0x10^{-16}$

Interaction term	Model 1		Model 2	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age at T2D diagnosis X CAD PRS	1.01 (1.00-1.02)	0.0030	1.01 (1.00-1.02)	0.0028

Shown are adjusted hazard ratios for coronary artery disease in each group divided by age at T2D diagnosis. Follow-up time was calculated as age in UK Biobank which is from the date of birth to the date of first CAD event (including CAD events prior to diagnosis of T2D), death, or end of follow-up – whichever came first. Hazard ratios were calculated for 1 SD increment of CAD PRS. Model 1 was adjusted for age at enrollment, sex and the first 10 principal components that reflect ancestry. Model 2 was adjusted for variables in model 1 plus ASCVD risk factors: ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol and smoking status.

The interaction analysis translates to an additional 15% increase (1.15, 1.05-1.25) in the effect of CAD PRS as age

at T2D diagnosis decreased by 10 years after including CAD events prior to T2D diagnosis and adjustment for ASCVD risk factors.

Supplementary Table 9

Genetic risk of coronary artery disease, according to age at T2D diagnosis in UK Biobank, ASCVD risk adjusted (time=years after enrollment, event=incident CAD event after enrollment).

Age at T2D diagnosis (years)	HR of CAD polygenic risk score (Model 1)		HR of CAD polygenic risk score (Model 2)	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
30-39	**1.80 (1.08-2.99)**	0.024	**1.73 (1.05-2.86)**	0.032
40-49	**1.65 (1.35-2.02)**	$1.2x10^{-6}$	**1.62 (1.32-1.99)**	$4.2x10^{-6}$
50-59	**1.35 (1.19-1.52)**	$2.0x10^{-6}$	**1.33 (1.17-1.50)**	$6.1x10^{-6}$
60-69	**1.36 (1.19-1.57)**	$1.5x10^{-5}$	**1.32 (1.15-1.52)**	$8.7x10^{-5}$

Interaction term	Model 1		Model 2	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age at T2D diagnosis X CAD PRS	1.01 (1.00-1.03)	0.022	1.01 (1.00-1.03)	0.019

Shown are adjusted hazard ratios for coronary artery disease analyzed after changing the start of the observation in each group divided by age at T2D diagnosis. Follow-up time was calculated as duration of enrollment, which is from the date of enrollment of UK Biobank to the date of first incident CAD event, death, or end of follow-up – whichever came first. Events only included incident CAD events that occurred after enrollment and participants with CAD events before enrollment were excluded from the analysis. Hazard ratios were calculated for 1 SD increment of CAD PRS. Model 1 was adjusted for age at enrollment, sex, duration of type 2 diabetes and the first 10 principal components that reflect ancestry. Model 2 was adjusted for variables in model 1 plus ASCVD risk factors: ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total

cholesterol, HDL cholesterol and smoking status.

Supplementary Table 10

Genetic risk of coronary artery disease, according to age at T2D diagnosis in SNUH T2D cohort, ASCVD risk factors adjusted (time=age, event=incident CAD event).

Age at T2D diagnosis (years)	HR of CAD polygenic risk score (Model 1)		HR of CAD polygenic risk score (Model 2)	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
30-39	**1.75 (1.18-2.62)**	0.0059	**1.77 (1.19-2.61)**	0.0046
40-49	**1.71 (1.30-2.24)**	0.00013	**1.75 (1.33-2.31)**	6.0×10^{-5}
50-59	**1.54 (1.16-2.03)**	0.0025	**1.55 (1.17-2.05)**	0.0025
60-69	**1.48 (0.93-2.36)**	0.098	**1.51 (0.94-2.40)**	0.087

Interaction term	Model 1		Model 2	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age at T2D diagnosis X CAD PRS	1.01 (0.99-1.02)	0.47	1.01 (0.99-1.02)	0.43

Meta-analysis of SNUH T2D cohort and UK Biobank

Interaction term	Model 1		Model 2	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age at T2D diagnosis X CAD PRS	1.01 (1.00-1.02)	0.0030	1.01 (1.00-1.02)	0.0025

Shown are adjusted hazard ratios for coronary artery disease in each group divided by age at T2D diagnosis.

Follow-up time was calculated as age in the SNUH T2D cohort which is from the date of birth to the date of first incident CAD event, death, or end of follow-up – whichever came first. Hazard ratios were calculated for 1 SD increment of CAD PRS. Model 1 was adjusted for age at enrollment, sex and the first 10 principal components that reflect ancestry. Model 2 was adjusted for variables in model 1 plus ASCVD risk factors: ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol and smoking status.

Supplementary Table 11

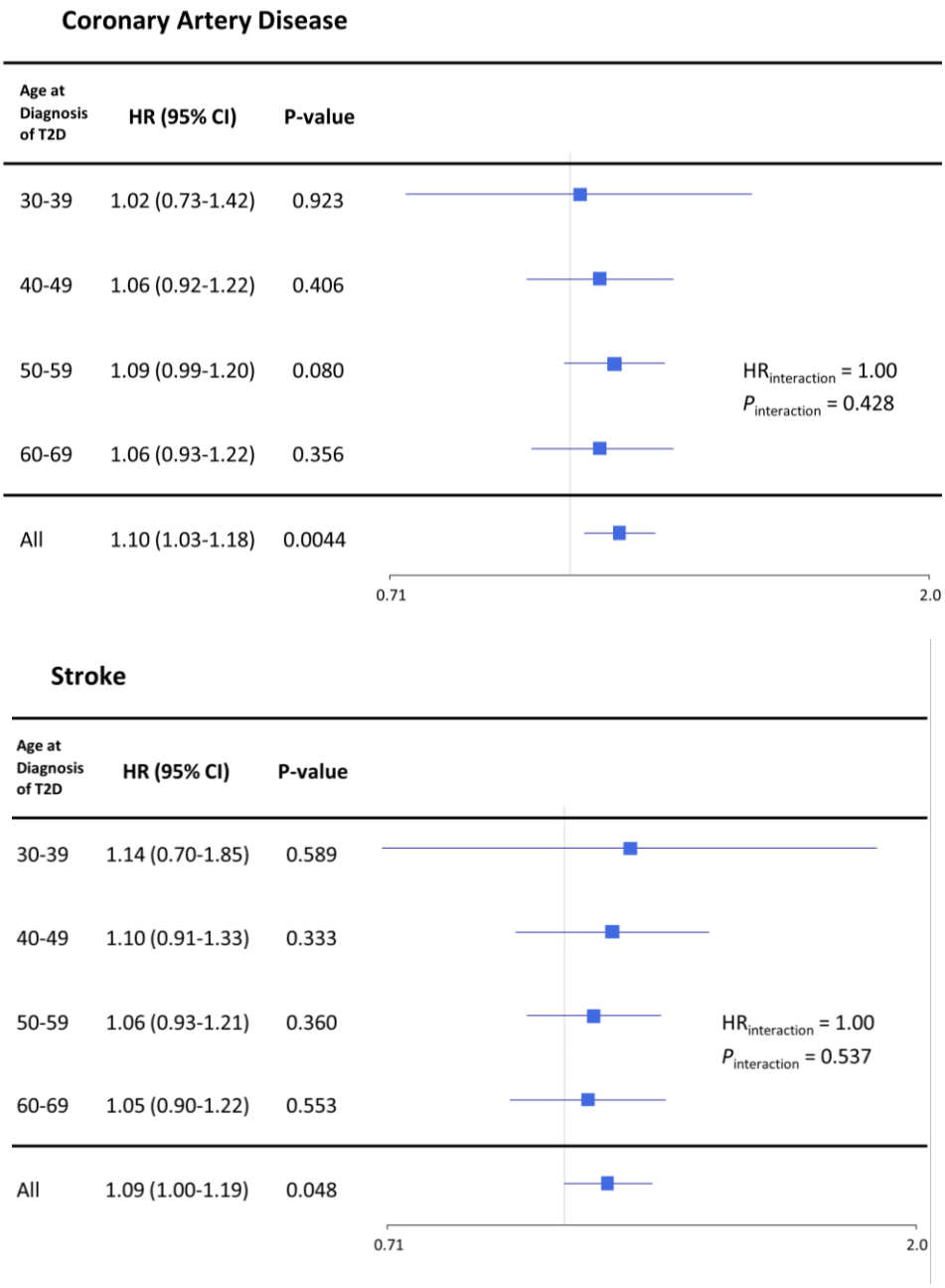
Risk of coronary artery disease, according to age at T2D diagnosis, lifestyle and genetic risk in UK Biobank.

Age at T2D diagnosis (years)	Lifestyle	Genetic Risk for CAD	N	Risk of Coronary Artery Disease	
				HR (95% CI)	*P*
30-39	Unfavorable	High	99	8.55 (2.76-26.5)	$2.0x10^{-4}$
		Low	65	4.43 (1.13-17.3)	0.032
	Favorable	High	88	3.56 (1.07-11.8)	0.038
		Low	103	1.00	Ref
40-49	Unfavorable	High	542	2.93 (1.90-4.53)	$6.5x10^{-7}$
		Low	485	1.62 (0.97-2.70)	0.064
	Favorable	High	623	2.13 (1.38-3.29)	0.00068
		Low	591	1.00	Ref
50-59	Unfavorable	High	1085	1.92 (1.43-2.57)	$1.2x10^{-5}$
		Low	1092	1.07 (0.77-1.50)	0.685
	Favorable	High	1880	1.76 (1.36-2.27)	$1.3x10^{-5}$
		Low	1869	1.00	Ref
60-69	Unfavorable	High	552	2.20 (1.44-3.36)	$2.6x10^{-4}$
		Low	600	2.17 (1.44-3.26)	$2.2x10^{-4}$
	Favorable	High	1354	2.18 (1.55-3.05)	$6.0x10^{-6}$
		Low	1520	1.00	Ref

Shown are adjusted hazard ratios for coronary artery disease in each group divided by age at T2D diagnosis, lifestyle and genetic risk. In these comparisons, participants with a favorable lifestyle and low genetic risk for CAD served as the reference group. Model was adjusted for age at enrollment, sex and the first 10 principal components that reflect ancestry.

Supplementary Figure 1

Genetic risk of type 2 diabetes and risk for coronary artery disease and stroke, according to age at T2D diagnosis in UK Biobank



Shown are adjusted hazard ratios of PRS for coronary artery disease and stroke in each group divided by age at T2D diagnosis. Hazard ratios were calculated for 1 SD increment of T2D PRS, and coronary artery disease or stroke as outcome. Model was adjusted for age at enrollment, sex and the first 10 principal components that reflect ancestry. Hazard ratio for the interaction term between age at T2D diagnosis and T2D PRS was estimated to

express increased effect of PRS for earlier diagnosis of T2D.

1. Bycroft C, Freeman C, Petkova D, et al. The UK biobank resource with deep phenotyping and genomic data. Nature 2018;562:203–209
2. Eastwood SV, Mathur R, Atkinson M, et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK biobank. PLoS One 2016;11:e0162388
3. Kwak SH, Chae J, Lee S, et al. Nonsynonymous variants in PAX4 and GLP1R are associated with type 2 diabetes in an East Asian population. Diabetes 2018;67:1892–1902
4. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44:S15–S33
5. UK Biobank Outcome Adjudication Group. *UK Biobank Algorithmically-Defined Outcomes*. Greater Manchester, UK, UK Biobank, 2022
6. Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun 2019;10:1776
7. Scott RA, Scott LJ, Mägi R, et al. An expanded genome-wide association study of type 2 diabetes in Europeans. Diabetes 2017;66:2888–2902
8. Nikpay M, Goel A, Won HH, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015;47:1121–1130
9. Malik R, Chauhan G, Traylor M, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. Nat Genet 2018;50:524–537
10. Ge T, Irvin MR, Patki A, et al. Development and validation of a trans-ancestry polygenic risk score for type 2 diabetes in diverse populations. Genome Med 2022;14:70
11. Koyama S, Ito K, Terao C, et al. Population-specific and trans-ancestry genome-wide analyses identify distinct and shared genetic risk loci for coronary artery disease. Nat Genet 2020;52:1169–1177
12. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010;121:586–613
13. Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med 2016;375:2349-2358
14. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. Circulation 2016;133:187–225
15. Han H, Cao Y, Feng C, et al. Association of a healthy lifestyle with all-cause and cause-specific mortality among individuals with type 2 diabetes: a prospective study in UK biobank. Diabetes Care 2022;45:319–329
16. Elliott P, Peakman TC; UK Biobank. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. Int J Epidemiol. 2008;37(2):234-244
17. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219–242
18. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2019;140:e563–e595