Arterial Stiffness, Genetic Risk, and Type 2 Diabetes: A Prospective Cohort Study

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OBJECTIVE

We aimed to investigate prospective associations of pulse wave arterial stiffness index (ASI) and pulse pressure (PP) with type 2 diabetes (T2D) and assess the modifying effect of genetics.

RESEARCH DESIGN AND METHODS

We included 152,611 participants free of diabetes and cardiovascular disease in the UK Biobank. All participants had ASI and blood pressure measurements collected at baseline visit. In total, 37 single nucleotide polymorphisms were used to calculate the genetic risk score (GRS) of T2D.

RESULTS

During a median follow-up of 9.5 years, 3,000 participants developed T2D. Per-SD increase in ASI was associated with a 3% higher T2D risk (95% CI 2–4%). The hazard ratio (HR) (95% CI) of T2D was 1.58 (1.39–1.80) in the highest quintile group compared with the lowest quintile group of ASI. However, the association between PP and T2D was nonlinear. Compared with the lowest quintile group, the risk of T2D in higher quintile groups of PP was 0.91 (0.79–1.04), 0.98 (0.86–1.11), 1.15 (1.01–1.30), and 1.24 (1.10–1.41), respectively. Furthermore, we observed an interaction between ASI and genetic susceptibility to T2D, because the elevated HR of T2D associated with high ASI was more evident among participants with higher GRS of T2D (P interaction = 0.008), whereas the interaction between PP and GRS was nonsignificant (P interaction = 0.55).

CONCLUSIONS

ASI was associated with an elevated risk of T2D in a dose-response fashion, whereas PP and T2D showed a nonlinear J-shaped association. Additionally, the association between ASI and T2D was partially strengthened by higher genetic susceptibility to T2D.

Type 2 diabetes (T2D) and its complications have contributed to an enormous global burden of mortality and disability (1). It is estimated that 693 million people will have diabetes by 2045 worldwide (2). Notably, cardiovascular disease (CVD) complications are the primary cause of morbidity and mortality in patients with T2D (1). Therefore, cardiovascular risk management might be essential for better prevention and management of T2D (3). As a subclinical marker of cardiovascular risk, arterial stiffness has been suggested as an independent predictor of vascular ageing, CVD, and mortality (4–6). In addition, arterial stiffness has been linked to diabetes through pathological pathways, including chronic inflammation, oxidant

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stress, endothelial dysfunction, and advanced glycation end products (7). However, investigations of the association between arterial stiffness and T2D have been relatively limited, and the results have been inconsistent (8–10).

Pulse wave velocity (PWV) is the reference standard measurement of arterial stiffness (11,12). Of note, arterial stiffness index (ASI) can be measured noninvasively and conveniently using the pulse waveforms obtained at the finger with photoplethysmography. ASI has shown close correlation and agreement with PWV (13–15). Moreover, pulse pressure (PP) is another marker for arterial stiffness, which showed the strongest association with PWV among various blood pressure parameters (16). In particular, a recent cohort study showed that ASI was associated with CVD and mortality risk (17). However, to our knowledge, the prospective association between ASI and T2D has not been evaluated in large-scale population-based cohort studies. In addition, several studies have assessed the association between PP and T2D in patients with hypertension or kidney dysfunction (18,19), but the results have been limited among generally healthy populations.

Importantly, T2D is a complex disorder, with both genetic and nongenetic factors contributing to its etiology (20). The unexplored heritability of T2D could be partially explained by interactions between genetic variations and nongenetic exposures, where the impact of a given nongenetic determinant might be modified by genes (1). A previous study showed that the genetic variant might interact with PWV in relation to T2D risk (21). However, the interaction between arterial stiffness and genetic variations associated with T2D at the genome-wide significance level remains unknown.

UK Biobank is a large prospective cohort study with arterial stiffness assessments as well as genetic variations. In the current study, we aimed to evaluate the association of arterial stiffness, as indicated by ASI and PP, with the risk of incident T2D and further investigate whether the associations might be modified by genetic susceptibility to T2D.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The UK Biobank study is a national population-based prospective cohort study for investigations of genetic and environmental determinants of diseases. A detailed description of the cohort design and populations is provided elsewhere (22). Briefly, >500,000 adults aged 37–73 years were recruited from 22 assessment centers across England, Scotland, and Wales between 2006 and 2010. All participants provided a wealth of information, including demographics, lifestyles, medical records, physical measurements, and biological samples. The UK Biobank study has obtained approval from the North West Multicenter Research Ethics Committee in the U.K., the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. All participants gave written informed consent.

In the current study, participants with a history of diabetes (n = 26,736) or CVD (coronary heart diseases or stroke) (n = 21,652) at baseline were excluded. The final analysis was restricted to participants with measured ASI and blood pressure at baseline (N = 152,611).

Arterial Stiffness and Blood Pressure Assessments

Data on ASI were collected at the baseline visit using PulseTrace PCA2 (CareFusion, San Diego, CA). Photoplethysmography was used to obtain pulse waveforms by clipping the infrared sensor to an index finger in a seated position over 10–15 s. The shape of the volume waveforms in the finger is directly related to the time it takes for the pulse wave to pass through the arterial tree of the lower body and reflect back to the finger. Height (meters) was divided by the time between peaks of the waveforms to obtain ASI (meters per second). Detailed information about the ASI measurement is available on the UK Biobank website (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/Pulsewave.pdf). The validity of ASI has been reported previously (13,14).

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice using the automatic Omron Digital blood pressure monitor (OMRON Healthcare Europe, Hoofddorp, the Netherlands). If the largest cuff size was too small for the participant or if the electronic blood pressure monitor failed to measure the blood pressure, a sphygmomanometer with an inflatable cuff together with a stethoscope was used for measurements. Full details on blood pressure measurements are available on the UK Biobank website (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/Bloodpressure.pdf). Mean values for multiple blood pressure measurements were adopted in the analysis. PP was calculated using the following formula: PP = SBP (mmHg) − DBP (mmHg). We calculated PP from each blood pressure measurement separately and then averaged the PP from each blood pressure reading. In addition, mean arterial pressure (MAP) was obtained as follows: PP/3+DBP.

Ascertainment of Outcomes

Incident T2D cases were ascertained using the first occurrence variables in UK Biobank. UK Biobank provided multiple reports resources, including self-report information, medical history, hospital admissions, and death register for extracting the earliest occurrence dates. Incident T2D cases were identified using the ICD-10 code of E11 in combination with comparisons between first occurrence dates and baseline visit dates.

Covariate Assessment

Data on covariates, including age, sex, race, Townsend deprivation index, smoking status, habitual alcohol drinking, physical activity, and diet, were collected through touchscreen questionnaires at the baseline visit. The healthy diet score was adapted according to American Heart Association guidelines (23,24). We defined five favorable diet factors based on the corresponding median consumption (vegetable intake at least 4 tbsp/day, fruit intake at least 3 pieces/day, fish intake at least twice per week, unprocessed red meat intake no more than twice per week, and processed meat intake less than twice per week). One point was given for each favorable diet factor, and a healthy diet score ranging from 0 to 5 was calculated by adding the corresponding score of each diet factor. Metabolic equivalent of task (minutes) obtained from the short International Physical Activity Questionnaire were used to measure physical activity.

In addition, BMI was calculated using weight (kilograms) divided by height squared (meters). Information

on cholesterol-lowering medication and antihypertensive drug use was collected through the touchscreen question, "Do you regularly take any of the following medications?" Furthermore, blood samples were collected from all participants at recruitment. Serum LDL cholesterol concentrations were determined by the enzymatic selective protection method (Beckman Coulter [U.K.], Ltd). In addition, serum triglycerides, cholesterol, and glucose were measured with the enzymatic method (Beckman Coulter [U.K.], Ltd). Hemoglobin A_{1c} (HbA_{1c}) was measured by the high-performance liquid chromatography method on a Bio-Rad VARIANT II Turbo (Bio-Rad Laboratories, Inc.).

Genetic Risk Score

The genotyping, quality control, and imputation procedures used in UK Biobank have been published elsewhere (25). A recent genome-wide association study identified 128 single nucleotide polymorphisms (SNPs) associated with T2D in Europeans (26), among which 42 SNPs reached the genome-wide significance level ($P < 5 \times 10^{-8}$). We calculated the genetic risk score (GRS) for T2D based on the 37 of 42 SNPs that passed quality control in UK Biobank. Detailed information about the selected SNPs is provided in Supplementary Table 1. In the genetic analysis, we only included 113,927 unrelated individuals of European descent. The GRS of T2D was calculated using a weighted method: $GRS = (\beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \ldots + \beta_n \times SNP_n) \times (N/\text{sum of the } \beta \text{ coefficients})$. SNP_n referred to the number of risk alleles (0, 1, 2), and β_n was the risk estimate between the SNP and T2D. In the current analysis, the GRS of T2D ranged from 26.6 to 61.2, with higher GRS indicating a higher genetic risk of T2D. We divided participants into three groups of low (score 26.6–42.4), intermediate (42.5–45.8), and high (45.9–61.2) genetic risk of T2D according to the tertile of the GRS.

Statistical Analysis

Distributions of the baseline characteristics are described by incident T2D status, where continuous and categorical variables are presented as means (SDs) and percentages, respectively.

Survival time for each participant was calculated as the duration from the time of baseline visit to the date of diagnosis of T2D, death, loss to follow-up, or 31 July 2019, whichever occurred first. The Cox proportional hazards regression model was used to assess associations of ASI and PP with incident T2D. Hazard ratios (HRs) and 95% CIs were calculated using the lowest quintile of ASI or PP as the reference group. The Schoenfeld residuals method was adopted to test the proportional hazards assumption. In addition, we modeled the variables continuously to test for linear trends.

We constructed two multivariable models. In model 1, we adjusted for age (continuous) (years) and sex (male and female). In model 2, we further adjusted for UK Biobank assessment center, race (White European, mixed, South Asian, Black, or other), Townsend deprivation index (continuous), alcohol consumption (current, former, never, or missing), smoking status (current, former, never, or missing), BMI (continuous) (kg/m^2), physical activity (continuous) (metabolic equivalent of task [minutes]), healthy diet score (0, 1, 2, 3, 4, or 5), use of antihypertensive drugs (yes or no), use of lipid-lowering drugs (yes or no), LDL cholesterol (continuous) (mmol/L), and family history of diabetes (yes, no, or missing). SBP was only included in the model assessing the association between ASI and T2D. In the genetic analysis, we further adjusted for genotyping batch and the first 10 genetic principal components. For missing data, a missing indicator category was coded for categorical variables, such as alcohol consumption, and mean values were imputed for continuous variables.

After assessing main associations of ASI and PP with the risk of incident T2D, we further evaluated whether genetic predisposition to T2D may modify the associations. We conducted a stratified analysis according to the tertile of T2D GRS and explored the potential interactions with T2D risk. We tested gene-ASI and gene-PP interactions by setting variable cross-product terms of GRS with ASI or PP in the models.

We also conducted several sensitivity analyses to determine the robustness of our findings. Because kidney function might influence arterial stiffness (27), we first further adjusted for serum creatinine level (μmol/L), MAP, or waist circumference (cm) in the models. Various antihypertensive medications might have different effects on the risk of T2D (28,29); therefore, we also conducted a sensitivity analysis with further adjustment for antihypertensive drug types, namely drugs that might increase the risk of diabetes (thiazide diuretics or β-blockers) and those that might not increase the risk of diabetes (angiotensin-converting enzyme inhibitors, calcium channel blockers, or angiotensin receptor blockers) in the models. In addition, to confirm the temporal relationship between arterial stiffness and T2D, we only included participants with serum glucose levels ≤6.1 mmol/L. We also further adjusted for serum glucose and HbA_{1c} levels in the multivariable models. Then, we conducted analyses among the participants with >2 years of follow-up to minimize the reverse causality of the observed associations. Furthermore, we also conducted a sensitivity analysis excluding participants with imputed data.

All analyses were performed using SAS software (version 9.4) (SAS Institute, Inc., Cary, NC). All tests were two sided, and $P < 0.05$ was considered statistically significant.

RESULTS

The baseline characteristics of the participants by incident T2D status are shown in Table 1. Participants who had incident T2D were older, and a higher percentage were men, compared with those without incident T2D. In addition, those with incident T2D had higher BMI and Townsend deprivation index values. They were also more likely to be current smokers but less likely to be current drinkers or have a healthy diet. We also observed that participants with incident T2D had a higher prevalence of hypertension, antihypertensive drug use, and cholesterol-lowering drug use. In addition, blood pressure and serum triglyceride levels among those with incident T2D were higher than the levels in T2D-free participants. We observed higher mean (SD) estimates of serum glucose (5.8 [2.0] mmol/L) and HbA_{1c} (43.4 [11.8] mmol/mol) among those with incident T2D compared with those without incident T2D (5.1 [0.6] and 35.1 [4.0], respectively). In addition, mean (SD) estimates of ASI and PP were 10.2 (4.2) m/s and 59.0 (14.9) mmHg among participants with incident T2D, and the corresponding values were 9.2 (3.7) and

Table 1—Baseline characteristics of participants by incident T2D

Characteristic	Incident T2D	
	Yes (n = 3,000)	No (n = 149,611)
Age, years	58.9 (7.4)	56.3 (8.2)
Male sex	53.9	43.5
White race	83.0	91.6
BMI, kg/m^2	31.5 (5.6)	27.1 (4.6)
Townsend deprivation index	−0.3 (3.2)	−1.2 (2.9)
Current drinker	84.8	91.7
Current smoker	13.0	9.9
MET, min per week	2,461.1 (2,457.5)	2,748.0 (2,480.4)
Healthy diet score		
0–1	14.1	11.5
2–3	52.8	48.6
4–5	33.1	39.9
SBP, mmHg	144.9 (18.7)	137.5 (18.6)
DBP, mmHg	85.9 (10.2)	82.2 (10.0)
PP, mmHg	59.0 (14.9)	55.2 (13.5)
MAP, mmHg	105.6 (11.7)	100.6 (11.9)
Prevalent hypertension	49.9	23.8
Triglycerides, mmol/L	2.4 (1.3)	1.7 (0.9)
LDL cholesterol, mmol/L	3.6 (0.9)	3.6 (0.8)
HDL cholesterol, mmol/L	1.3 (0.3)	1.5 (0.4)
Antihypertensive drug use	39.3	16.3
Cholesterol-lowering drug use	28.9	11.9
Family history of diabetes	36.6	21.2
Serum glucose, mmol/L	5.8 (2.0)	5.1 (0.6)
HbA_{1c}, mmol/mol	43.4 (11.8)	35.1 (4.0)
Pulse wave ASI, m/s	10.2 (4.2)	9.2 (3.7)

Continuous and categorical variables are presented as means (SDs) and percentages (%), respectively. MET, metabolic equivalent of task.

55.2 (13.5), respectively, for those without incident T2D.

During a median follow-up of 9.5 years (1,422,810 person-years), we documented 3,000 incident T2D cases. We found that ASI was significantly associated with a higher risk of incident T2D in a dose-response fashion (Table 2). In the age- and sex-adjusted model, per-SD higher ASI was associated with a 4% elevation in the risk of incident T2D (95% CI 3–5%). After further adjustment for race, UK Biobank assessment center, Townsend deprivation index, alcohol consumption, smoking, BMI, physical activity, healthy diet score, SBP, LDL cholesterol, antihypertensive medication use, cholesterol-lowering medication use, and family history of diabetes, ASI was positively associated with the risk of incident T2D in a dose-response fashion. The HR (95% CI) of T2D was 1.03 (1.02–1.04) for per-SD increase in ASI. In addition, the HRs (95% CIs) of T2D were 1.23 (1.07–1.41), 1.33 (1.16–1.52), 1.45 (1.27–1.65), and 1.58 (1.39–1.80), respectively, in higher quintiles compared with the lowest quintile of ASI (P trend < 0.001).

In the age- and sex-adjusted model, the HR (95% CI) of T2D for per-SD higher PP was 1.15 (1.11–1.19). In model 2, with further adjustment for race, UK Biobank assessment center, Townsend deprivation index, alcohol consumption, smoking, BMI, physical activity, diet, LDL cholesterol, antihypertensive medication use, cholesterol-lowering medication use, and family history of diabetes, per-SD increase in PP was associated with a 11% elevation in the risk of incident T2D (95% CI 7–15%). When compared with the lowest quintile group of PP, the risk of T2D (HR [95% CI]) in higher quintile groups was 0.91 (0.79–1.04), 0.98 (0.86–1.11), 1.15 (1.01–1.30), and 1.24 (1.10–1.41), respectively (Table 3). We observed a J-shaped association between PP and T2D, where the risk increased markedly with PP >45 mmHg (Fig. 1).

In the models adjusting for age, sex, assessment center, genotyping batch, and the first 10 genetic principal components, we observed a significant association of T2D GRS with the risk of incident T2D. The T2D GRS was associated with a 98% higher risk of incident T2D (95% CI 78–121%). The association remained significant in the multivariable-adjusted model; the HR (95% CI) of T2D was 2.01 (1.80–2.25) for per-unit increase in T2D GRS (Supplementary Table 2). We further assessed the interaction between arterial stiffness and genetic variations and the risk of T2D. The results showed that there was a significant interaction between ASI and the GRS of T2D (P interaction = 0.008), where the elevated HR of T2D associated with higher ASI was more evident among participants with higher GRS compared with lower GRS. The HR (95% CI) of T2D in the highest quintile group compared with the lowest quintile group of ASI was 1.66 (1.29–2.15) among participants with high genetic risk, 1.48 (1.13–1.95) among participants with intermediate genetic risk, and 1.23 (0.88–1.71) among those with low genetic risk (Fig. 2). However, there was no statistically significant interaction between PP and genetic susceptibility to T2D (P interaction = 0.55).

In sensitivity analyses, we found that the results were appreciably unchanged with further adjustment for serum creatinine (Supplementary Table 3). Moreover, the HR of T2D for ASI was stable with further adjustment for MAP, while the association between PP and T2D was weakened after further adjusting for MAP in the models (Supplementary Table 4). Furthermore, the results were largely unchanged with further adjustment for waist circumference (Supplementary Table 5) or antihypertensive drug type (Supplementary Table 6). The sensitivity analyses also showed that the associations of ASI and PP with the risk of

Table 2—ASI with incident T2D

	Pulse wave ASI						
	Q1	Q2	Q3	Q4	Q5	Per SD	*P* trend
Mean (SD)	5.57 (0.78)	7.23 (0.46)	8.91 (0.49)	10.65 (0.53)	13.97 (5.11)		
n/*N*	343/30,511	459/30,529	619/30,507	734/30,508	845/30,556		
Model 1[a]	1.00	1.28 (1.11–1.48)	1.62 (1.42–1.85)	1.79 (1.57–2.04)	1.93 (1.69–2.19)	1.04 (1.03–1.05)	<0.001
Model 2[b]	1.00	1.23 (1.07–1.41)	1.33 (1.16–1.52)	1.45 (1.27–1.65)	1.58 (1.39–1.80)	1.03 (1.02–1.04)	<0.001

Data for models given as HR (95% CI). Q, quintile. [a]Adjusted for age (continuous) (years) and sex (male or female). [b]Adjusted for age (continuous) (years), sex (male or female), UK Biobank assessment center, race (White European, mixed, South Asian, Black, or other), Townsend deprivation index (continuous), alcohol consumption (current, former, never, or missing), smoking status (current, former, never, or missing), BMI (continuous) (kg/m^2), physical activity (continuous) (metabolic equivalent of task [minutes]), healthy diet score (0, 1, 2, 3, 4, or 5), use of antihypertensive drugs (yes or no), use of lipid-lowering drugs (yes or no), SBP (continuous) (mmHg), LDL cholesterol (continuous) (mmol/L), and family history of diabetes (yes, no, or missing).

incident T2D were robust by including participants with serum glucose levels ≤6.1 mmol/L (Supplementary Table 7). The associations of ASI and PP with the risk of incident T2D remained robust if we further adjusted for serum glucose and HbA_{1c} (Supplementary Table 8). In addition, the results were almost unchanged after excluding the participants with <2 years of follow-up (Supplementary Table 9) or those with imputed data (Supplementary Table 10).

CONCLUSIONS

In this large-scale prospective cohort study, we evaluated the associations between two arterial stiffness indicators, ASI and PP, and the risk of incident T2D. The results showed that ASI was associated with an elevated risk of T2D in a dose-response fashion, whereas PP and T2D had a nonlinear J-shaped relationship. In addition, a significant interaction between ASI and genetic variations was observed; the association between ASI and T2D was stronger among participants with higher genetic susceptibility to T2D.

Several previous studies have assessed the association between arterial stiffness and T2D. However, most of these studies have had cross-sectional designs, although their results are supportive of our analysis (30–33). Furthermore, limited prospective studies on the association between arterial stiffness and T2D have had relatively small sample sizes or short follow-up times (9,34). The current study included >150,000 participants and found that elevation in ASI was associated with a higher risk of T2D during a comparatively longer follow-up time. The direction of our estimate for ASI and T2D is in line with several prospective population-based cohorts despite different markers being used in those studies. For example, a cohort study of 14,159 participants with 3.7 years of follow-up found that the HR of diabetes was 1.59 for the borderline brachial-ankle PWV (baPWV) group and 2.11 for the elevated baPWV group when compared with the normal baPWV group (35). Another cohort study showed that the HR was 1.66 for the third tertile group of baPWV compared with the lowest tertile group (34). However, the magnitude of the association between ASI and T2D in the current study was relatively smaller than that of the abovementioned association between baPWV and diabetes. PWV reflects the velocity of the travel time of pulse waves between two arterial points and is the gold standard of arterial stiffness measurement. Because of the methodological concern about the measurement of ASI, the clinical significance of the marker in predicting T2D still needs to be explored in future studies. More importantly, the results were unchanged after excluding participants with prediabetes at baseline or those with incident T2D in the first 2 years of follow-up in our analysis. Therefore, ASI should be considered a predictor for the development of T2D. The finding

Table 3—PP with incident T2D

	PP						
	Q1	Q2	Q3	Q4	Q5	Per SD	*P* trend
Mean (SD)	39.02 (3.69)	46.84 (1.72)	52.91 (1.86)	60.34 (2.57)	75.87 (9.67)		
n/*N*	428/29,371	432/29,341	538/31,421	710/30,950	892/31,528		
Model 1[a]	1.00	0.89 (0.77–1.01)	0.94 (0.83–1.07)	1.17 (1.03–1.32)	1.34 (1.18–1.52)	1.15 (1.11–1.19)	<0.001
Model 2[b]	1.00	0.91 (0.79–1.04)	0.98 (0.86–1.11)	1.15 (1.01–1.30)	1.24 (1.10–1.41)	1.11 (1.07–1.15)	<0.001

Data for models given as HR (95% CI). Q, quintile. [a]Adjusted for age (continuous) (years) and sex (male or female). [b]Adjusted for age (continuous) (years), sex (male or female), UK Biobank assessment center, race (White European, mixed, South Asian, Black, or other), Townsend deprivation index (continuous), alcohol consumption (current, former, never, or missing), smoking status (current, former, never, or missing), BMI (continuous) (kg/m^2), physical activity (continuous) (metabolic equivalent of task [minutes]), healthy diet score (0, 1, 2, 3, 4, or 5), use of antihypertensive drugs (yes or no), use of cholesterol-lowering drugs (yes or no), LDL cholesterol (continuous) (mmol/L), and family history of diabetes (yes, no, or missing).

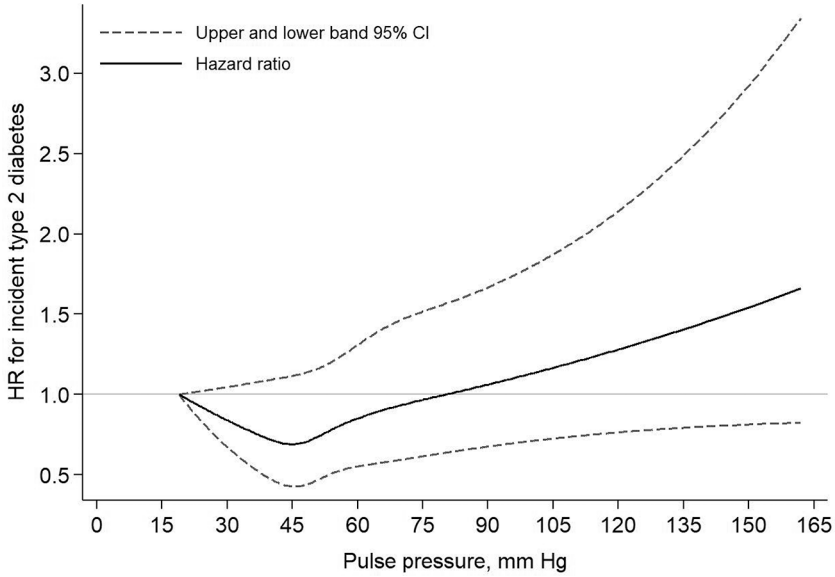

Figure 1—The association between PP and incident T2D. The model was adjusted for age (continuous) (years), sex (male or female), UK Biobank assessment center, race (White European, mixed, South Asian, Black, or other), Townsend deprivation index (continuous), alcohol consumption (current, former, never, or missing), smoking status (current, former, never, or missing), BMI (continuous) (kg/m^2), physical activity (continuous) (metabolic equivalent of task [minutes]), healthy diet score (0, 1, 2, 3, 4, or 5), use of antihypertensive drugs (yes or no), use of lipid-lowering drugs (yes or no), LDL cholesterol (continuous) (mmol/L), and family history of diabetes (yes, no, or missing).

was similar to that of a previous cohort study showing arterial stiffness might precede the change in blood fasting glucose levels (35).

PP has influence on wave reflections and is considered a surrogate marker for arterial stiffness (36). Several studies have evaluated the association between PP and diabetes. For example, the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial showed that per-SD increase in PP was associated with a 44% higher risk of incident diabetes among patients with hypertension (18). In addition, the HR of new-onset diabetes for PP was 1.26 in a cohort of participants after kidney transplantation (19). In the current analysis, we assessed the association between PP and incident T2D among general populations. The results showed a J-shaped association between PP and T2D, with the lowest HR observed at ∼45 mmHg of PP. Similarly, a previous cohort also observed a J-shaped association between baPWV and T2D risk (34).

There are several potential underlying mechanisms for the association between arterial stiffness and T2D. First, endothelial dysfunction may result in a decrease in the elasticity of arteries, causing arterial stiffness, which could further aggravate the impairment of vessels (37,38). Previous studies have shown that endothelial dysfunction is the common pathophysiology of arterial stiffness and T2D and is involved in the development of T2D (39). Second, arterial stiffness is associated with liver dysfunction (40). Hepatic damage might affect insulin resistance in

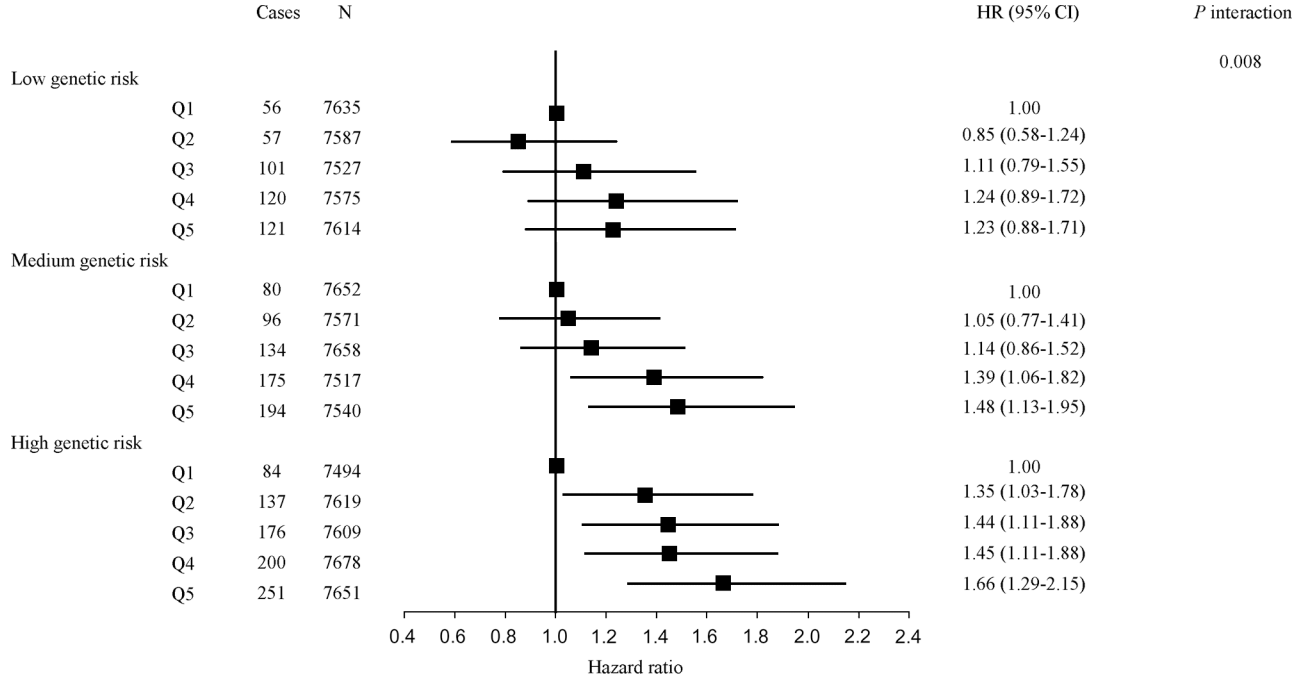

Figure 2—The association between ASI and incident T2D stratified by genetic risk factors. The model was adjusted for age (continuous) (years), sex (male or female), UK Biobank assessment center, race (White European, mixed, South Asian, Black, or other), Townsend deprivation index (continuous), alcohol consumption (current, former, never, or missing), smoking status (current, former, never, or missing), BMI (continuous) (kg/m^2), physical activity (continuous) (metabolic equivalent of task [minutes]), healthy diet score (0, 1, 2, 3, 4, or 5), use of antihypertensive drugs (yes or no), use of lipid-lowering drugs (yes or no), SBP (continuous) (mmHg), LDL cholesterol (continuous) (mmol/L), family history of diabetes (yes, no, or missing), genotyping batch, and the first 10 genetic principal components.

the liver, leading to the development of T2D (41). Third, arterial stiffness could cause rarefaction of capillaries, which might affect glucose metabolism and insulin resistance (42,43). In addition, oxidative stress and inflammation are risk factors for both arterial stiffness and T2D (44,45). Furthermore, arterial stiffness is an important pathophysiological mechanism for the development of CVD (46) and is a well-recognized risk factor for and predictor of CVD (6,47). Meanwhile, CVD is an important comorbidity and risk factor for T2D (48,49). Therefore, CVD might provide more insight into potential mechanisms of the impact of arterial stiffness on T2D. Future work is needed to confirm the role of arterial stiffness in the pathogenesis of T2D.

We also examined interactions of ASI and PP with genetic susceptibility to T2D in regard to the risk of incident T2D. The results showed that genetic variations of T2D might modify the association between ASI and T2D, because the elevated risk of T2D associated with higher ASI was stronger among participants with higher genetic risk compared with lower genetic risk of T2D. Existing evidence has indicated potential mechanisms for the significant interaction between ASI and genetic susceptibility to T2D. The genetic loci included for calculating the GRS of T2D in the current analysis were related to traits influencing the risk of T2D, such as adiponectin levels, lipids, obesity, blood pressure, inflammatory factors, and liver function (26). Notably, these traits were also associated with arterial stiffness (50). Therefore, we assumed that ASI and genetic variations of T2D might have additive effects on the risk of T2D through overlapped biological mechanisms related to these aforementioned traits to a certain extent. Furthermore, previous studies have suggested that arterial stiffness and T2D might share the same genetic background. For instance, a Mendelian randomization study showed a causal association between genetically determined decrease in insulin secretion and arterial stiffness (51), which might also partially explain the interaction between ASI and genetic susceptibility to T2D. The findings from the current study are in line with prior evidence indicating that genetic risk factors might interact with nongenetic exposures on cardiometabolic outcomes (52,53).

The current cohort study included a large sample size and a wide range of information on lifestyles, diets, genetic variations, and biomarkers, which enabled us to explore the independent prospective association between arterial stiffness and T2D. In addition, we conducted several sensitivity analyses and found the results were largely unchanged, suggesting the robustness of our findings. Moreover, we newly assessed the interaction between arterial stiffness and genetic variations of T2D at the genome-wide significance level. The novel finding on the interaction between ASI and genetic risk of T2D might prompt the development of prevention strategies by considering genetic susceptibility to the disease. However, limitations of the study should also be noted. First, there are methodological differences between the reference arterial stiffness measurement and indicators used in the current study (17). However, both ASI and PP have shown good agreement with PWV. Furthermore, ASI and PP could be measured conveniently and are relatively suitable for large-scale epidemiological studies such as UK Biobank. Nevertheless, the results should be interpreted with caution, and further investigations are warranted to validate our findings.

Furthermore, older participants or those with hypertension might be more likely to be diagnosed with T2D because of more frequent medical treatments. Therefore, the association between arterial stiffness and T2D might not be accurately estimated, although we carefully adjusted for confounders, including age, blood pressure levels, and use of antihypertensive drugs in the models. Future studies are needed to verify our findings. Another important limitation is that our analyses relied on single ASI and PP assessments at baseline while failing to consider changes in these markers over the follow-up period. In addition, confounders such as serum glucose and HbA_{1c} were unavailable during follow-up; therefore, residual confounding could still exist despite our careful adjustment for these variables at baseline in the analyses. Moreover, the nature of the observational study might limit the causality of the findings. Therefore, the causality of the observed associations must be confirmed with additional clinical trials. Finally, we only included participants of European descent in the genetic analysis; the observed interactions should be validated in other populations.

In conclusion, our data indicate that ASI, a marker of arterial stiffness, is an independent risk factor for incident T2D, and the association was modified by genetic risk factors. Unlike ASI, PP was associated with the risk of T2D in a J-like shape. Our findings suggest that arterial stiffness might be an important risk factor for T2D, especially among those with high genetic risk of the disease. Additional studies are warranted to confirm our findings for the better prevention of T2D.

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