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Association between arterial stiffness/remodeling and new-onset type 2 diabetes mellitus in general population

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ABSTRACT

Objective: We studied if large artery stiffness is involved in type 2 diabetes pathogenesis. We also investigated the effect of genetic risk for type 2 diabetes in these associations and the causality.
Research design and Methods: In the prospective population-based Rotterdam Study (n = 3,055; mean age, 67.2 years), markers of aortic and carotid stiffnesses and measures of arterial remodeling were assessed. Cox proportional hazard regression analysis estimated the associations between arterial stiffness measures with incident type 2 diabetes. We used 403 single nucleotide polymorphisms to calculate the genetic risk score (GRS) for type 2 diabetes. We adopted Mendelian randomization (MR) analysis to evaluate the causal associations.
Results: Over a median follow-up of 14.0 years, higher carotid-femoral pulse wave velocity (hazard ratio,1.18; 95 %CI: 1.04–1.35), carotid distensibility coefficient (1.17; 1.04–1.32), and carotid intima-media thickness (1.15; 1.01–1.32) were independently associated with incident diabetes. The associations were stronger among individuals with a higher GRS for type 2 diabetes. MR analysis did not support the causality of the observed associations.
Conclusions: Elevated arterial stiffness is independently associated with incident type 2 diabetes. For most arterial stiffness markers, the associations with incident type 2 diabetes were more robust in individuals with a higher GRS for diabetes.

1. Introduction

Type 2 diabetes mellitus has become one of the major challenges to human health in the 21st century. The number of individuals with diabetes is projected to rise from 415 million in 2015 to 700 million by 2045[1]. Arterial stiffness is a subclinical measurement of cardiovascular diseases (CVD) and an independent predictor of vascular dysfunction that leads to altered central hemodynamics[2,3]. A sustained increase in blood pressure due to increased arterial stiffness may induce structural changes in the arteries, known as arterial remodeling, leading to atherosclerotic plaques[4,5].

Although evidence suggests that arterial stiffness increases in patients with type 2 diabetes and is closely associated with type 2 diabetes complications[6], knowledge regarding arterial stiffness before developing type 2 diabetes is limited[7–10]. Recent evidence suggests that increased arterial stiffness could be evident before the onset of type 2 diabetes and among individuals in a prediabetes state[11]. Findings in this regard, however, remain inconclusive. Notably, abnormal glucose metabolism is the key factor driving increased arterial stiffness stepwise from normal to prediabetes to type 2 diabetes[12]. Increased pulse pressure has been shown to independently identify subjects at risk for developing type 2 diabetes in a study that included 2,685 Japanese hypertensive patients[13]. However, it remains unclear whether large artery stiffness and its associated hemodynamic changes are involved in the pathogenesis of type 2 diabetes.

Type 2 diabetes is a multifactorial disease resulting from multiple genetic and environmental risk factors. A recent study included 152,611 participants in the UK Biobank and showed that the association between arterial stiffness index (ASI) and type 2 diabetes was partially modified by genetic susceptibility to type 2 diabetes [7]. However, this study was

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limited by using a few arterial stiffness measurements, i.e., ASI as a proxy of pulse wave velocity (PWV)/arterial stiffness.

Using data from the large population-based Rotterdam Study, we examined the association of markers of arterial stiffness and remodeling with new-onset type 2 diabetes. We also studied whether associations were modified by age, sex, blood glucose levels, or mean arterial pressure (MAP). As the association between vascular dysfunction and incident type 2 diabetes might be driven by changes in distinct metabolic parameters, insulin resistance, and β-cell function, we tested the associations only among the population with prediabetes. Our study investigated whether the associations might be modified by type 2 diabetes genetic susceptibility. Complementary to our genetic approach, we studied the associations between genetic variants for arterial stiffness and risk of type 2 diabetes by performing i) a Mendelian randomization (MR) analysis, using summary statistics from large-scale genome-wide association studies and ii) a weighted genetic risk score (GRS) analysis.

2. Methods

2.1. Study design and population

This study is embedded within the Rotterdam Study (RS), a prospective cohort study of the community-dwelling population aged 55 years and older in Rotterdam, the Netherlands. Briefly, in 1990 all inhabitants (n = 10,215) aged 55 years or over were invited; 7,983 invitees agreed to participate (RS-I). In 2000, 3,011 participants who had reached the age of 55 years (out of 4,472 invitees) were invited to participate in the second cohort (RS-II). There were no eligibility criteria to enter the Rotterdam Study apart from the minimum age and residential area based on postal codes. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 020.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study entered into the Netherlands National Trial Register (NTR; https://www.trialregister.nl) and the WHO International Clinical Trials Registry Platform (ICTRP; https://www.who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. 98 % of participants provided written informed consent to participate in the study and obtain their information from treating physicians. The complete design and rationale behind the Rotterdam Study have been described previously[14].

We included 3,055 participants with available data for carotid assessment and type 2 diabetes from the third examination of the first cohort (RS-I-3: 1997–1999) and the first examination of the second cohort (RS-II-1: 2000–2001). We included participants with information on prevalent and incident type 2 diabetes status with at least one baseline interview or clinical examination. We excluded those who did not provide or withdrew informed consent for the collection of follow-up data (n = 313), participants with a history of type 2 diabetes (n = 501) or insufficient baseline screening for type 2 diabetes /non-fasting glucose (n = 1,232), and participants with a history of cardiovascular disease (n = 492). Fig. 1 shows the flowchart of the study population.

2.2. Baseline measurements

At baseline, information was obtained on individuals' characteristics, health status, medical and medication history, and lifestyle factors.

2.3. Measures of arterial stiffness and arterial remodeling

Functional arterial stiffness and remodeling measures were measured with subjects in the supine position[15]. ***Carotid-femoral pulse wave velocity (cf_PWV)*** is a non-invasive gold standard of arterial stiffness. Cf_PWV was assessed with an automatic device (Complior, Colson) by measuring the time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid and the femoral arteries[16]. PWV index was calculated as the ratio between the distance and the foot-to-foot time delay expressed in meters per second. ***Carotid distensibility coefficient (carDC)*** as a measure of carotid artery elasticity and was assessed with the subject's head tilted slightly to the contralateral side. The vessel wall motion of the right common carotid artery was measured through a duplex scanner (ATL Ultramark IV, operating frequency 7.5 MHz) connected to a vessel wall movement detector system. ***CarDC*** was calculated according to the following equation: $(2\Delta D \times D + \Delta D^2)/(\text{pulse pressure (PP)} \times D^2)$, 10^{-3}/ kPa, where D is arterial diameter, ΔD is distension or the absolute stroke change in diameter during systole, and PP is brachial PP (calculated as systolic minus diastolic blood pressure). Lower carotid distensibility represents greater carotid stiffness. ***cf_PWV*** and ***carDC***, are pressure-dependent and require blood pressure adjustment. Arterial remodeling refers to the structural and functional changes of the vessel wall and reflects an adaptation of the vessel wall to biochemical or biomechanical causes. ***Carotid intima-media thickness (cIMT)*** measures carotid atherosclerotic vascular disease that shows the thickness of the inner

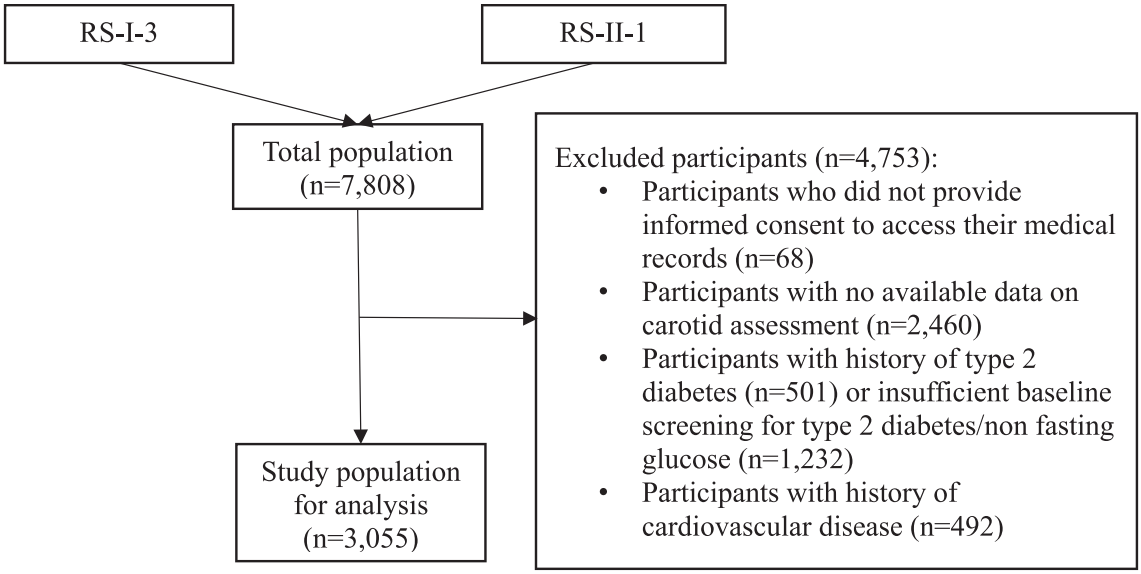

Fig. 1. Flow-chart of the study population.

two layers of the carotid artery—the intima and media. cIMT was calculated as the average of left and right common carotid IMT[17]. ***Carotid artery lumen diameter (carDi)*** was calculated as D−(2 × cIMT), mm. ***Mean (CWS$_{mean}$) circumferential wall stress*** was calculated as mean arterial pressure×([lumen diameter/2]/IMT), kPa[18]. ***Pulsatile (CWS$_{puls}$) circumferential wall stress*** calculated as PP×(lumen diameter/2/cIMT), kPa.

2.4. Follow-up measurements and type 2 diabetes assessment

Follow-up data on vital status and incident type 2 diabetes for all individuals included in the study were available. Outpatient clinic reports and hospital discharge letters were collected from general practitioners and hospital records. Information on vital status was obtained from the central registry of the municipality of the city of Rotterdam.

Incident type 2 diabetes was defined based on the World Health Organization (WHO) guideline as a fasting blood glucose concentration of 7.0 mmol/L or higher, a non-fasting blood glucose concentration of 11.1 mmol/L or higher (when fasting samples were unavailable), or the use of blood glucose-lowering medications[19]. Type 2 diabetes cases were ascertained at baseline and follow-up using general practitioners' records, hospital discharge letters, medication data, and serum glucose measurements collected from center visits every 3–5 years. Blood glucose-lowering medications were obtained from structured home interviews and pharmacy dispensing records (95 %). Two physicians independently adjudicated all potential events of type 2 diabetes. In the case of disagreement, a consensus was achieved by a diabetologist. Follow-up started at baseline, and individuals were followed until the incident type 2 diabetes or death or the end of follow-up, January 1st, 2015.

2.5. Genotyping

Genotyping in Rotterdam Study has been performed using the Illumina 550 K and 610 K quad array (Illumina Inc., San Diego, CA, USA) and was imputed to the Haplotype Reference Consortium reference panel (version 1.0) with Minimac 3.

2.6. Covariables

Body mass index (BMI) was calculated as body weight (in kg) divided by the square of length (in meters). Mean arterial pressure (MAP) was defined as 1/3 systolic blood pressure plus 2/3 diastolic blood pressure. All biochemical variables were assessed in serum samples taken after overnight fasting. Serum total cholesterol (TC) (mmol/L) and high-density lipoprotein-cholesterol (HDL-c) (mmol/L) were both measured on the COBAS 8000 Modular Analyzer (Roche Diagnostics GmbH, Germany). Non-HDL cholesterol was defined as total cholesterol minus HDL cholesterol. Smoking behavior was assessed using a computerized questionnaire and categorized into three groups: current, former (former smoker, or stopped cigarettes $\leq$ 12 months), and never (never smoker, or stopped cigarettes $>$ 12 months).

2.7. Statistical analysis

Data were assessed visually for normality. We performed descriptive statistics by reporting mean (standard deviation (SD)) or median (interquartile range (IQR)) for continuous variables and numbers (percentage) for categorical variables. We first investigated the multicollinearity between different arterial stiffness/remodeling markers by calculating the variance inflation factor (VIF). The association between markers of arterial stiffness and remodeling at baseline with incident type 2 diabetes was evaluated using Cox proportional hazard regression models. The associations were adjusted for age, sex, and cohort (**Model 1**) and additionally adjusted for BMI, MAP, antihypertensive medications, heart rate, non-HDL-cholesterol[20], lipid-lowering medications, and smoking (**Model 2**). To test the proportional hazards assumption, the Schoenfeld residuals method was applied. We modeled all arterial stiffness and remodeling measurements on a continuous scale (per SD). To detect possible non-linear associations between arterial stiffness and remodeling measurements with incident type 2 diabetes, we performed a non-linear spline analysis. We applied P-Splines (penalized cubic B-Splines) in the Cox models[21]. Many central knots were taken, followed by a penalty term optimized via generalized cross-validation to avoid over-fitting. This is a data-driven and explorative approach to detecting any non-linear relationship. We also included interaction terms in model 2 to study whether any significant associations were modified by age, sex, or MAP[22]. In a linear regression analysis, we also examined the associations between arterial stiffness/remodeling markers at baseline with follow-up measurements of fasting blood glucose.

In a series of sensitivity analyses, to further study the role of glycemic traits, we evaluated the associations between measurements of arterial stiffness and remodeling at baseline with incident type 2 diabetes by i) adding baseline fasting glucose level to model 2, ii) adding baseline fasting insulin level and homeostatic model assessment for insulin resistance (HOMA-IR) to model 2, iii) excluding individuals with prediabetes at baseline, and iv) testing the associations between various markers of arterial stiffness and remodeling with incident type 2 diabetes among the population with prediabetes at baseline. To account for reverse causality bias, we excluded incident type 2 diabetes cases (n = 109) in the first 5 years of follow-up[23].

We also examined cross-sectional associations between arterial stiffness and remodeling with fasting serum glucose, HOMA-IR (a proxy of insulin resistance), and HOMA- β-cell function (***methods and the corresponding results and discussion are shown in supplementary materials***).

All measures of association are presented with 95 % confidence intervals. We used $P < 0.05$ as the significance level. Missing values on covariates were imputed using single imputation, the expectation–maximization method. All analyses were conducted in SPSS version 26 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R statistical software version 3.6.3.

2.8. Genetic studies

Association of type 2 diabetes genetic variants and arterial stiffness: In a set of genetic analyses, we further evaluated whether genetic predisposition to type 2 diabetes modifies the associations between arterial stiffness/remodeling and the risk of type 2 diabetes. We explored this effect modification through stratification by GRS tertiles. For type 2 diabetes GRS analysis, we included 403 independent type 2 diabetes genetic variants in 243 loci reported by a recent genome-wide association study (GWAS) in European ancestry; a *meta*-analysis of 32 GWAS included almost 900,000 individuals in the DIAMANTE Consortium[24]. We calculated the weighted GRS as b1 × SNP1 + b2 × SNP2 +.. + bn × SNPn, where b is the beta coefficient for each SNP, and n is the number of risk alleles (0, 1, 2). We rescaled the weighted score using the following equation to reflect the number of type 2 diabetes risk alleles: weighted GRS = weighted score × (total number of SNPs/sum of the b coefficients). In our analysis, and among 2,647 individuals with available genetic data, the GRS for type 2 diabetes ranged from 24.24 to 29.41, with higher GRS indicating a higher genetic risk of type 2 diabetes. We divided individuals into three groups, including low (24.24–26.43), intermediate (26.44–27.03), and high (27.04–29.41) GRS according to the GRS tertile.

2.9. Association of arterial stiffness genetic variants and type 2 diabetes

Mendelian Randomization (MR): We first performed an MR analysis using publicly available summary-level data[25] from a GWAS for ASI in 127,121 UK Biobank participants of European ancestry that

identified three genome-wide significant loci. This study showed three SNPs associated with ASI (**Table S1**). The calculated estimates were expressed as odds ratios (ORs) on type 2 diabetes per unit difference in an ASI. Inverse-variance weighted (IVW) regression was used, which assumes no invalid genetic instruments, such as pleiotropic (affecting multiple exposures) SNPs[26]. When the intercept of this regression deviates from zero, this indicates a bias in the IVW estimates. MR Egger regression was further used to ensure that the IVW estimates were not biased by directional pleiotropy[26].

Weighted genetic risk score for arterial stiffness index: We calculated the weighted GRS based on the three SNPs for ASI from the UK Biobank study[25], as described earlier. We studied the associations of GRS for ASI (continuous variable) and fasting glucose, insulin and HOMA-IR at baseline (linear regression analyses) and incident type 2 diabetes (Cox regression analysis).

All analyses were performed using the R-based package" TwoSampleMR" (https://mrcieu.github.io/TwoSampleMR/).

3. Results

We used data from 3,055 participants of the Rotterdam Study. The baseline characteristics of the total population are shown in Table 1. The population's mean age was 67.2 years (SD 7.9), and 1,816 (59.4 %) participants were women. During a median follow-up of 14.0 (IQR 10.1–14.9) years, 395 (12.9) type 2 diabetes cases were identified (incidence rate: 10.5 per 1000 person-years).

Fig. 2**A** shows the association between arterial stiffness and remodeling measurements with incident type 2 diabetes. Increased (per SD) arterial stiffness and remodeling were associated with an incident type 2 diabetes after additional adjustment in model 2; hazard ratios (HR) and 95 % confidence intervals (CI) were 1.18 (1.04–1.35) for cf_PWV, 1.17 (1.04–1.32) for carDi, 1.15 (1.01–1.32) for cIMT, and 1.28 (1.12–1.47) for CWS_{puls}. The association between CWS_{mean} and new-onset type 2 diabetes did not remain statistically significant after further adjustment in model 2. An increase in carDC (lower carotid stiffness) was associated with a lower risk of incident type 2 diabetes (0.96; 0.93–0.99) in model 2. Spline analyses for model 2 did not show any non-linear relationship between arterial stiffness/remodeling markers with incident type 2 diabetes (**Figure S1**). Age, sex, and MAP did not modify the associations between arterial stiffness/remodeling measurements and incident type 2 diabetes; the *p*-values for interaction were not statistically significant. Our results investigating the associations between markers of arterial stiffness/remodeling with follow-up measurements of fasting blood glucose showed statistically significant associations even after adjusting for confounders in all except for cf_PWV, carotid artery lumen diameter and CWS_{mean} in model 2 (**Table S2**).

As shown in **Table S3**, additional adjustments for baseline blood glucose attenuated the associations in a sensitivity analysis. However, the associations remained statistically significant except for cf_PWV (1.11; 0.97–1.28). We further adjusted the associations by adding fasting insulin and HOMA-IR to model 2, and the results did not substantially change (**Table S3**). Besides, after excluding individuals with prediabetes at baseline, results did remain statistically significant except for carDC (0.97; 0.93–1.00) and cIMT (1.09; 0.92–1.29) (Fig. 2**B**). As shown in Fig. 2**C** and **Table S4**, when we further studied the longitudinal associations between markers of arterial stiffness and remodeling with incident type 2 diabetes among the population with prediabetes at baseline (n = 513), our results did not change substantially. However, it remained statistically significant only for the associations of carDC (0.96; 0.92–0.99) and cIMT (1.39; 1.12–1.73). Excluding incident cases during the first five years of follow-up did not significantly change the associations observed in model 2.

Our results showed multicollinearity (VIF around 5 or below) between arterial stiffness/remodeling markers. Still, it was not strong enough to warrant further adjustments in our statistical models (data not shown).

Table 1
Baseline Characteristics of the study population.

	Total (n = 3,055)
Age, years	67.2 ± 7.9
Sex, Female, n (%)	1,816 (59.4)
BMI, kg/m^2	26.6 (3.8)
MAP	98.5 ± 12.6
Antihypertensive medication, n (%)	835 (27.3)
Heart rate bpm	70.4 ± 10.8
Total cholesterol, mmol/L	5.9 ± 0.96
HDL-cholesterol, mmol/L	1.4 ± 0.38
Non-HDL-cholesterol, mmol/L	4.5 ± 0.98
Lipid-lowering medication, n (%)	311 (10.2)
Smoking (ever), n (%)	2,023 (66.2)
[q1]	7.1 (0.86–15.1)
Physical activity, median, MET hour	88.3 ± 43.6
Prevalent prediabetes, n (%)	513 (16.8)
Fasting glucose levels, mmol/L	5.5 ± 0.54
*Fasting insulin levels, mmol/L	66.0 (47.0–92.0)
*HOMA-IR	2.3 (1.6–3.3)
*HOMA-B	95.6 (69.1–130.9)
cf_PWV, m/s	12.6 ± 2.8
carDC, 10–3/kPa	12.2 ± 4.8
carDi, mm	7.6 ± 0.93
cIMT, mm	0.82 ± 0.14
CWS_{mean}, kPa	44.6 ± 10.1
CWS_{puls}, kPa	29.5 ± 8.2

Abbreviations: BMI, body mass index; MAP, mean arterial pressure; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-B, Homeostatic model assessment of beta-cell function; cf_PWV, carotid-femoral pulse wave velocity; carDC, carotid distensibility; carDi, carotid diameter; cIMT, carotid intima-media thickness; CWSmean, Mean carotid wall stress; CWSpuls, Pulsatile carotid wall stress.
Plus-minus values are means ± standard deviation.
HOMA-IR = (fasting plasma insulin × fasting plasma glucose)/22.5.
HOMA-B = (20 × fasting plasma insulin)/(fasting plasma glucose − 3.5).
* Median (inter-quartile range).

4. Genetic studies

Among 2,647 individuals with genetic data (87 % of the total population), in the multivariable-adjusted model, the associations between cf_PWV (1.34 (1.08–1.66)), carDC (0.93 (0.89–0.98)), CWS_{mean} (1.27 (1.01–1.58)) and CWS_{puls} (1.30 (1.04–1.63)) with type 2 diabetes remained statistically significant only among individuals with a high GRS for type 2 diabetes (Table 2).

The results of the IVW analysis showed no causal association between ASI and type 2 diabetes (OR: 1.37; 95 %CI: 0.42–2.31). There was no evidence for horizontal pleiotropy (p-value for intercept: 0.60). We tested the associations between GRS for ASI and glycemic traits (baseline fasting blood glucose and insulin levels and HOMA-IR) and incident type 2 diabetes among 2,647 individuals with genetic data. Our finding showed statistically significant associations between GRS for ASI and fasting insulin (β: 0.001; p value = 0.01) and HOMA-IR (β: 0.001; p value = 0.03) at baseline, even after adjusting for potential confounders (model 2 of adjustment) but not with incident type 2 diabetes.

5. Discussion

Our study showed that arterial stiffness and remodeling markers were associated with new-onset type 2 diabetes among women and men from the general population, free of cardiovascular disease and diabetes at baseline. The associations were not due to reverse causation. The associations were independent of established diabetes risk factors and baseline blood glucose levels. Besides, the associations between markers of arterial stiffness and remodeling with type 2 diabetes were not modified by age, sex, and hypertension status. We also investigated the associations between arterial stiffness/remodeling markers with follow-up measurements of fasting blood glucose. Our results showed

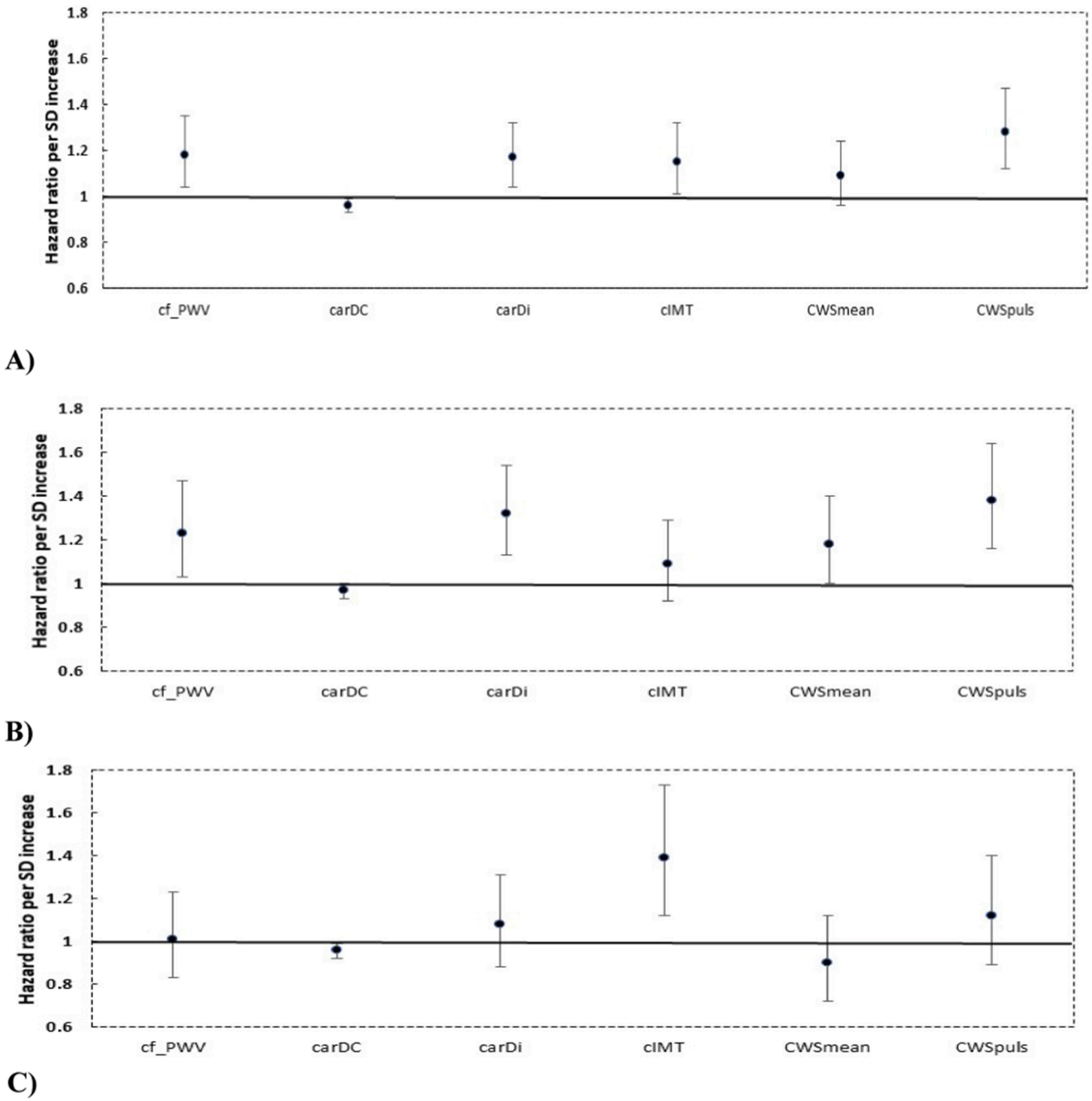

Fig. 2. Association between markers of arterial stiffness and arterial remodeling with incident type 2 diabetes among the general population free of diabetes (**A**), among the general population free of diabetes and prediabetes (**B**), and among high-risk individuals with prediabetes at baseline (**C**).

statistically significant associations even after adjusting for confounders for most markers. In addition, we found stronger associations between arterial stiffness and remodeling markers and type 2 diabetes in individuals with a higher GRS for type 2 diabetes. Our MR approach indicated that the relationship between arterial stiffness and type 2 diabetes is not causal. However, GRS for arterial stiffness index showed significant associations with fasting insulin and HOMA-IR as a proxy for insulin resistance.

We showed that increased aortic and carotid stiffnesses are associated with an increased risk of incident type 2 diabetes. Higher aortic stiffness is an independent predictor of incident type 2 diabetes in the general population[7–10,27] or high-risk hypertensive individuals [13,28]. A recent study evaluated the association between large artery stiffness (LAS) and the risk of type 2 diabetes in 5,676 participants of the Framingham Heart Study (FHS) over 7 years of follow-up. Applying the MR approach in the UK Biobank, this study found evidence supporting that greater LAS is associated with an increased risk of type 2 diabetes. This study showed that cf_PWV (HR: 1.36) and central pulse pressure (HR:1.26) were associated with an increased risk of incident diabetes [29]. We proved that increased carotid stiffness is associated with an increased risk of incident type 2 diabetes. An increase in the markers of arterial remodeling, including carDi, cIMT, and CWS_{puls} was associated with a greater risk for incident type 2 diabetes. Arterial remodeling is a homeostatic response to changes in the flow and circumferential stretch to restore normal shear stress and wall tension within certain operation limits[4], which means remodeling is closely related to hemodynamic stimuli. All these changes in the arterial structure suggest potential preclinical vascular dysfunction, which in turn may relate to future events related to diabetes[30].

Besides considering arterial stiffness as a marker of hypertension

Table 2
The association between arterial stiffness and incident type 2 diabetes, stratified by GRS for type 2 diabetes.

	Low GRS	Intermediate GRS	High GRS
	HR (95 %CI)	HR (95 %CI)	HR (95 %CI)
Carotid-femoral pulse wave velocity	0.86 (0.67–1.10)	0.99 (0.72–1.36)	**1.34 (1.08–1.66)**
Carotid distensibility	1.01 (0.95–1.08)	0.97 (0.92–1.01)	**0.93 (0.89–0.98)**
Carotid diameter	1.11 (0.84–1.47)	1.18 (0.94–1.48)	1.21 (1.00–1.47)
Carotid intima-media thickness	1.05 (0.77–1.44)	**1.41 (1.04–1.65)**	1.12 (0.90–1.40)
Mean carotid wall stress	1.14 (0.83–1.56)	0.91 (0.73–1.13)	**1.27 (1.01–1.58)**
Pulsatile carotid wall stress	1.22 (0.88–1.68)	**1.33 (1.03–1.72)**	**1.30 (1.04–1.63)**

Abbreviations: GRS, genetic risk score; HR, hazard ratio; CI, confidence interval.
The models were adjusted for age, sex, cohort, body mass index, mean arterial pressure, antihypertensive medications, heart rate, non-HDL-cholesterol, lipid-lowering medications, and smoking.

end-organ damage, arterial stiffness can directly induce metabolic dysregulations by dramatically slowing blood flow that accelerates hyperglycemia[30]. Blood flow is an essential factor that regulates the metabolic function of muscles. It is speculated that enhancing blood flow may induce insulin and glucose delivery to peripheral tissues and contribute to overall glucose disposal[30]. It has been suggested that, even before the onset of type 2 diabetes, altered arterial stiffness are evident in individuals with prediabetes[6]. Hyperinsulinemia induced by insulin resistance and impaired fasting glucose causes vascular dysfunction, leading to the increased renin-angiotensin-aldosterone system, impaired vascular reactivity/resistance, and abnormal glucose metabolism[31]. This suggests that the link between arterial stiffness and remodeling with type 2 diabetes can be through hyperglycemia. To examine this, we studied the associations between arterial stiffness/remodeling and incident type 2 diabetes in the presence of hyperglycemia. Our stratified analyses among individuals with prediabetes remained the same as the general population for most markers except for cIMT. The involvement of cIMT, a marker of arterial remodeling and a measure of atherosclerosis, in developing type 2 diabetes was stronger in the prediabetes stage than in the normoglycemic general population. Our result may suggest that early insulin resistance and impaired fasting glucose may enhance the impact of atherosclerosis on type 2 diabetes development. In a previous study, Ronald et al.[11] concluded that arterial stiffness and remodeling are increased with deteriorating glucose tolerance[32]. In this concept, an increase in cIMT could, at least partially, be viewed as a compensatory response to counteract the increased wall stress induced by the diameter enlargement.

Increased vascular stiffness is associated with increased MAP[22,33] as a potential reciprocal risk factor for type 2 diabetes. Type 2 diabetes and hypertension are closely linked due to shared risk factors, e.g., endothelial dysfunction, vascular inflammation, and obesity[34]. Therefore, we hypothesized that the associations between arterial stiffness and remodeling might be modified by MAP. However, our study did not provide evidence for effect modification by MAP values on the associations between arterial stiffness and remodeling with new-onset type 2 diabetes. These together suggest that additional mechanisms such as oxidative stress, inflammation, or endothelial dysfunction might play a role in this association[35].

A major contributor to arterial stiffening is ageing, a dominant risk factor for type 2 diabetes and cardiovascular diseases, decreasing vascular elasticity[36]. So far, several studies have investigated the effect of age on arterial stiffness[36]. The age-associated increased stiffness of the aorta is greater than the carotid artery[37]. However, in our study, the associations between aortic and carotid stiffness and remodeling markers with new-onset type 2 diabetes were independent of age.

It is known that type 2 diabetes is often diagnosed with a delay of several years[38]. Hence, a degree of asymptomatic type 2 diabetes sufficient to cause vascular damage may be present long before the clinical diagnosis of diabetes. Therefore, diabetes-associated increased arterial stiffness and remodeling could occur long before the clinical diagnosis of diabetes. The associations were not due to the reverse causation as we had excluded incident cases of diabetes during the first five years of follow-up, and the results did not change. However, the mechanisms through which arterial stiffness and remodeling affect type 2 diabetes require additional investigation.

We examined the role of GRS for type 2 diabetes in the associations between markers of arterial stiffness and remodeling and incident type 2 diabetes. The results showed that type 2 diabetes genetic variations might modify the associations, in line with the previous study[7]. This might be explained by overlapped biological mechanisms involved in diabetes-related traits, e.g., obesity and arterial stiffness/remodeling, or similar genetic backgrounds between arterial stiffness/remodeling and type 2 diabetes. Although our MR analysis did not support the causality for diabetes, we showed that genetic variants of ASI are associated with insulin resistance in our population. Insulin resistance has been proposed as a pathway interacting with an individual's genetic background to cause type 2 diabetes[39]. However, our study looked at continuous measures of HOMA-IR as a proxy for insulin resistance and showed a causal association. There is great variability in the HOMA-IR threshold levels to define insulin resistance which might explain why the causal association observed for insulin resistance did not translate into the same causality for incident type 2 diabetes in our study.

Strengths of this study include the prospective cohort design, relatively long follow-up time, meticulous adjudication of incident diabetes, availability of several measures of arterial stiffness and remodeling within the same population, and access to a wide range of cardiovascular and diabetes risk factors, genetic information, and MR analysis. Some limitations, however, also need to be considered. Our dataset only includes baseline measurements of arterial stiffness, and we could not investigate the changes in arterial stiffness/remodeling markers over time concerning diabetes incidence. Our study mainly included individuals of European ancestry, limiting the generalizability of our findings to other populations. As pertinent to all prospective cohort studies with long follow-up times, loss of follow-up could have underestimated the observed effect. In MR analysis, we only had summary statistics available for ASI (a marker of arterial stiffness) with few SNPs.

An essential point regarding arterial stiffness (cf_PWV) is that strategies that may lead to aortic de-stiffening still need to be demonstrated in future interventions and prospective studies. Over the last two decades, there has been increasing knowledge of the importance of arterial stiffness for the pathogenesis of age-related cardiovascular diseases. In the last decade, it demonstrated its predictive importance for cardiovascular outcomes in various clinical conditions, including type 2 diabetes. Up to now, most prospective studies have evaluated the effects of pharmacological or non-pharmacological (lifestyle) interventions in hypertension in the short term of a few months up to a year. The most potent therapy for reducing arterial stiffness is vigorously treating hypertension using pharmacological agents. Though, new pharmacological strategies to reduce arterial stiffness are still warranted.

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Contributor's statement.

F.A. and M.K. are responsible for the study concept and design; F.A. composed the statistical dataset, performed the statistical analyses, and

wrote the manuscript; All authors revised/edited the manuscript for intellectual content.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110237.

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