Arterial Stiffness and Incidence of Diabetes: A Population-Based Cohort Study

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OBJECTIVE

Diabetes is known to be associated with increased arterial stiffness. However, the temporal association between increased carotid-femoral pulse wave velocity (c-f PWV) and diabetes is unclear. The aim of this study is to explore the relationship between arterial stiffness, as determined by c-f PWV, and incidence of diabetes.

RESEARCH DESIGN AND METHODS

The study population included participants from the Malmö Diet and Cancer cardiovascular cohort, using measurements from the 2007–2012 reexamination as baseline. Arterial stiffness was evaluated by measuring c-f PWV (SphygmoCor). After excluding participants with prevalent diabetes (according to measurements of fasting glucose, oral glucose tolerance tests, and physician's diagnoses), the final study population consisted of 2,450 individuals (mean age = 71.9 ± 5.6 years). Incidence of diabetes was followed by linkage to local and national diabetes registers. Cox proportional hazards regression was used to assess the incidence of diabetes in relation to the tertiles of c-f PWV, adjusted for potential confounders.

RESULTS

During a mean follow-up of 4.43 ± 1.40 years, 68 (2.8%) participants developed diabetes. Crude incidence of diabetes (per 1,000 person-years) was 3.5, 5.7, and 9.5, respectively, for subjects in the first, second, and third tertiles of c-f PWV. After adjustment for potential confounders, the hazard ratio of diabetes was 1.00 (reference), 1.83 (95% CI 0.88–3.8), and 3.24 (95% CI 1.51–6.97), respectively, for the tertiles of c-f PWV (*P* for trend = 0.002).

CONCLUSIONS

Increased c-f PWV is associated with increased incidence of diabetes, independent of other risk factors. These results suggest that increased arterial stiffness is an early risk marker for developing diabetes.

With an estimated 422 million people living with diabetes worldwide, the prevalence of diabetes is rising and is clearly a major global health problem (1). Diabetes and its accompanying complications not only affect quality of life but also impose a substantial health and economic burden. The risk of developing vascular disease increases by twofold in individuals who have diabetes as compared with those without (2). Many risk factors, such as age, obesity, lifestyle, and familial background, including genetics, have been attributed to the development of diabetes (3). Moreover, various risk factors have been suggested as predictors of the development of diabetes (4). Early detection and management of diabetes are needed in order to combat the burden of disease

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complications. This requires the need for identifying risk markers beyond the established ones for early risk stratification.

Arterial stiffness manifests as a result of adverse structural and functional changes in the vessel wall of elastic arteries over time. It is strongly associated with age (5) and hypertension (6). Other risk factors that have shown to be associated with arterial stiffness include abdominal obesity, hyperglycemia, and dyslipidemia (7,8). Several indices are used to determine arterial stiffness, but carotid-femoral pulse wave velocity (c-f PWV) is the most widely validated and universally accepted and is considered the gold standard measurement (9).

Arterial stiffness has been shown to be associated with diabetes. Woolam et al. (10) demonstrated that diabetes is associated with increased PWV and, hence, arterial stiffness. Many other studies have also shown increased stiffening of arteries in diabetes (11–14). The proposed pathological pathways explaining this link include endothelial dysfunction, low-grade inflammation, and oxidative stress (13), as well as the formation of advanced glycation end products in the vessel wall resulting in cross-linking of collagen molecules and loss of elasticity (15). These studies demonstrate that increased arterial stiffening develops in the presence of diabetes and contributes to the explanation of the cardiovascular complications accompanying it. However, some findings have recently suggested the concept that arterial stiffness can be a possible risk marker for diabetes itself. The relationship between risk of development of diabetes and various hemodynamic parameters of large artery stiffness, such as pulse pressure and central aortic pressure, has been assessed in previous studies (16,17). However, whether c-f PWV, a direct measurement of arterial stiffness, has any predictive value for the risk of developing diabetes has not yet been prospectively explored. The aim of this present cohort study was to explore the association between arterial stiffness, as determined by c-f PWV, and incidence of diabetes.

RESEARCH DESIGN AND METHODS

Study Population

The Malmö Diet and Cancer cohort is a large, prospective, population-based cohort comprising men and women from the city of Malmö in southern Sweden (18). From this cohort, a random sample of participants was invited during 1991–1994 to study the epidemiology of carotid artery atherosclerosis. This subcohort, consisting of 6,103 individuals, comprised the Malmö Diet and Cancer cardiovascular cohort (MDC-CC) (19).

Between May 2007 and September 2012, in all, 3,734 individuals from the MDC-CC participated in a reexamination (76% attendance of the eligible population). This forms the baseline for our study. The number of nonparticipating individuals along with their reasons are schematically presented in Supplementary Fig. 1. The characteristics of the nonattendees from this examination have been described in detail elsewhere (20). The c-f PWV measurements were completed in 3,056 participants. All the participants with a history of prevalent diabetes (n = 532) before the measurements of c-f PWV were excluded. Furthermore, participants with missing laboratory data and anthropometric measurements were also excluded, leading to a final study population of 2,450 subjects (mean age = 71.9 $\pm$ 5.6 years) (Supplementary Fig. 1).

Baseline Examinations

The 2007–2012 examination consisted of a self-administered questionnaire, physical examination, and laboratory tests. Blood pressure was measured after 10 min of rest in supine position. Waist circumference was measured midway between the lowest rib margin and iliac crest. Information regarding smoking habits, use of antidiabetic medications, antihypertensive treatment, and family history of diabetes (mother and father) was obtained from the questionnaire. Smokers were categorized into two categories: nonsmokers and current smokers. Blood samples were collected after an overnight fast (20). Fasting plasma glucose (FPG) was determined using HemoCue (HemoCue AB, Ängelholm, Sweden). The examination also consisted of an oral glucose tolerance test (OGTT) after an overnight fast, with a measurement of plasma glucose before and 120 min after intake of 75 g glucose. Total cholesterol and HDL cholesterol were measured by standard procedures at the Department of Clinical Chemistry, Skåne University Hospital. LDL cholesterol was calculated by using the Friedewald formula (21).

c-f PWV

The measurements for c-f PWV were carried out by using applanation tonometry (SphygmoCor; AtCor Medical, West Ryde, New South Wales, Australia) according to a specific study protocol. These measurements were done an average of 261 days after the first visit in the 2007–2012 examination for logistic reasons. With patients in a supine position after 5 min resting, pulse curves from the carotid and femoral arteries were obtained with a pressure-sensitive probe. The distance was measured from the suprasternal notch to the umbilicus and the umbilicus to the measuring point at the femoral artery subtracting the distance between the suprasternal notch and the measuring point at the carotid artery. The time from the peak of the R wave on the electrocardiogram to the foot of the pulse wave at the carotid and femoral arteries was automatically calculated by using the simultaneously registered electrocardiogram. Each participant had a varying number of successful measurements, ranging between one and five. The goal was to achieve three measurements per individual. This was possible in 86.7% of the case subjects but not in subjects with arrhythmias or anatomical variants of the neck. Mean c-f PWV was calculated from these measurements (7). Heart rate was defined as average heart rate (beats per minute [bpm]) at registration of the carotid artery. Blood pressure measurements were also performed just before measuring the c-f PWV using the OMRON M5-1 IntelliSense device. Mean arterial pressure (MAP) was calculated by the following formula: (2 $\times$ diastolic pressure + systolic pressure)/3.

End Point Ascertainment and Incidence of Diabetes

All individuals with diabetes at the baseline examination were excluded from the analysis of incidence of diabetes. Prevalent diabetes was identified by FPG $\geq$7.0 mmol/L or a 2-h post-OGTT plasma glucose $\geq$11.1 mmol/L, which was subsequently verified by a repeated FPG level, self-report of a physician diagnosis, or use of antidiabetic medication according to a questionnaire. In addition, all individuals with a diagnosis of diabetes according to national or local registers prior to the c-f PWV examination in 2007–2012 were excluded, together with individuals who had diabetes at previous examinations of the MDC-CC cohort. The characteristics of case subjects with prevalent diabetes are presented in Table 1.

Table 1—Characteristics of individuals with no diabetes, incident diabetes, and prevalent diabetes

	Included in the study population		
	Diabetes free	Incident diabetes	Prevalent diabetes (excluded)
Number (*n*)	2,382	68	532
c-f PWV* (m/s)	9.90 (8.63–11.46)	10.95 (9.76–12.70)***	11.23 (9.63–13.05)
Age (years)	71.94 (±5.54)	70.96 (±6.05)	72.66 (±5.30)
Heart rate (bpm)	62.58 (±9.82)	62.11 (±9.10)	64.32 (±10.82)
MAP (mmHg)	95.57 (±10.51)	99.46 (±12.24)**	95.84 (±10.76)
Waist (cm)	90.24 (±11.62)	96.21 (±11.85)***	97.65 (±12.40)†
Smokers, *n* (%)	234 (9.8)	7 (10.3)	45 (8.5)†
Use of antihypertensive drugs, *n* (%)	1,151 (48.3)	49 (72.1)***	422 (79.3)
FPG (mmol/L)	5.71 (±0.60)	6.39 (±0.70)***	7.75 (±2.07)†
2-h post-OGTT plasma glucose (mmol/L)	6.68 (±1.87)†	9.09 (±2.59)†***	10.46 (±3.71)† (*n* = 235)
LDL cholesterol (mmol/L)	3.43 (±0.90)	3.29 (±0.87)	2.84 (±0.92)†
HDL cholesterol (mmol/L)	1.47 (±0.44)	1.27 (±0.39)***	1.28 (±0.38)†
Triglycerides* (mmol/L)	0.90 (0.70–1.20)	1.20 (0.90–1.60)***	1.10 (0.80–1.5)†
FH^+ father, *n* (%)	174 (7.3)	9 (13.2)	73 (13.7)
FH^+ mother, *n* (%)	223 (9.4)	14 (20.6)**	111 (20.9)

Values expressed are means (±SD) unless specified otherwise. *Median (25–75%). **$P < 0.01$; ***$P < 0.001$, statistically significant difference in incident group with diabetes from group without diabetes. †Some individuals have missing data regarding these covariates. FH^+, family history–positive.

All individuals without diabetes were followed from the date of the c-f PWV measurement until first diagnosis of diabetes, emigration from Sweden, death, or end of follow-up (31 December 2014)—whichever came first. Incident diabetes during follow-up was retrieved from several local and national registers, which have previously been described in detail (22). In short, new cases of diabetes were identified in the Malmö HbA_{1c} register (MHR), the Swedish National Diabetes Register (NDR), the Swedish inpatient register, the Swedish outpatient register, the nationwide Swedish drug prescription register, and the regional Diabetes 2000 register of the Scania region. At least two independent sources confirmed the diagnosis for 74% of the cases. NDR and the Diabetes 2000 register required a physician diagnosis according to established diagnostic criteria (FPG concentration ≥7.0 mmol/L, measured on two different occasions). In the Swedish inpatient register and outpatient register, diabetes was defined as diagnosis of the decision by a senior physician. A filled prescription of insulin or antidiabetic medication (Anatomical Therapeutic Chemical Classification code A10) was required for diagnosis in the nationwide prescription register. The MHR at the Department of Clinical Chemistry, Skåne University Hospital, analyzed and recorded HbA_{1c} samples taken in institutional and noninstitutional care in the greater Malmö area from 1988 onwards. Individuals who had at least two HbA_{1c} recordings ≥6.0% in the MHR with the Swedish Mono-S standardization system (corresponding to 7.0% [53 mmol/mol] according to the U.S. National Glycohemoglobin Standardization Program) after the baseline examination were defined as incident diabetes case subjects.

Written informed consent was given by all participants. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committee at Lund University.

Statistical Analysis

The variables c-f PWV and triglycerides were natural log transformed due to their skewed distribution. Participants were categorized into tertiles of c-f PWV. The characteristics of the study population and of the participants in each of the tertiles were described as means ± SD, median (25–75%) for skewed distribution, or percentages. The differences between characteristics of individuals without diabetes and individuals with incident diabetes were tested with independent-sample Student *t* test and Mann-Whitney *U* test for statistical significance. For categorical variables, χ^2 test was used. ANOVA for continuous variables and χ^2 test for categorical variables were used to compare the characteristics of the participants across the tertiles of c-f PWV. Cox proportional hazards regression was used to compare incidence of diabetes in the tertiles of c-f PWV. Hazard ratios (HRs) with 95% CIs were calculated, with the lowest tertile (tertile 1) as the reference category. Adjustments were done for potential confounders in the Cox regression models. Model 1 was adjusted for age, sex, MAP, and average heart rate measured at the carotid artery. In model 2, further adjustments were done for waist circumference, smoking habits, FPG, LDL cholesterol, and use of antihypertensive medications. In addition, several other potential confounders were explored in a sensitivity analysis. The Kaplan-Meier curve was used to plot the incidence of diabetes across the different tertiles of c-f PWV.

In a sensitivity analysis, we also analyzed c-f PWV after adjustments for age and MAP, according to published reference equations (23). The predicted PWV was calculated separately for age-groups 60–69 years (PWV = 0.0715 × MAP + 3.16) and ≥70 years (PWV = 0.0676 × MAP + 5.46), and PWV in percent of the predicted values was calculated by dividing the actual PWV by the predicted value and multiplying by 100. Those in the 90th percentile of the distribution were considered to have high c-f PWV.

All analyses were performed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY). A *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A comparison of characteristics of the individuals included in the study populations with and without diabetes is presented in

Table 1. Case subjects with incident diabetes had significantly higher c-f PWV, MAP, FPG, and waist circumference. This group also had higher usage of antihypertensive medications as compared with the individuals without diabetes. The corresponding values for the excluded case subjects with prevalent diabetes are also presented in Table 1. c-f PWV was somewhat higher in subjects who were excluded because of prevalent diabetes, compared with subjects who developed diabetes during follow-up.

The characteristics of the study population are presented in Table 2. The mean age of the population is 71.9 ± 5.6 years. The table also shows the distribution and comparison of risk factors across the different tertiles of c-f PWV. The participants in the highest tertile of c-f PWV were significantly older and had a higher heart rate and MAP and increased waist circumference. The FPG level and usage of antihypertensive medication were also higher in the top tertile. However, there were significantly fewer smokers and lower LDL cholesterol levels among the participants in the highest tertile.

PWV and Incidence of Diabetes

During a mean follow-up period of 4.4 ± 1.4 years, 68 (2.8%) participants developed diabetes. The incidence of diabetes was 6.27 per 1,000 person-years in the whole study population, 7.06 per 1,000 person-years in men, and 5.82 per 1,000 person-years in women. The diabetes-free survival of the study population in relation to the different tertiles of c-f PWV is shown in Fig. 1.

The participants in the third tertile (T3) had a significantly higher risk of diabetes (HR 3.41 [95% CI 1.63–7.14]) as compared with those in the first tertile (T1) with adjustment for age, sex, MAP, and average heart rate in model 1, as shown in Table 3. The risk remained significantly higher after adjustments for additional covariates in model 2 (HR 3.24 [95% CI 1.51–6.97]).

For assessment of the effect of other classical risk factors associated with diabetes, a subanalysis was performed with additional adjustments for the following risk factors: HDL cholesterol, triglycerides, 2-h post-OGTT plasma glucose (in place of fasting glucose), and family history of diabetes (mother and father). The HR decreased, but remained significant, for participants in the third tertile versus the first tertile (reference category) of c-f PWV (HR 2.18 [95% CI 1.003–4.719]).

We also calculated c-f PWV in percentage of the predicted value according to age-group and MAP. Those above the 90th percentile of the distribution (n = 245) had a significantly higher incidence of diabetes than those below this cutoff (HR 2.97 [95% CI 1.64–5.38], adjusted for covariates in model 2).

As part of the sensitivity analysis, another index of arterial stiffness, peripheral pulse pressure (24), was also explored. The association across the tertiles of peripheral pulse pressure and incidence of diabetes was assessed, but no significant association was found.

Impaired Fasting Glucose and Impaired Glucose Tolerance

The study population was stratified into those with a normal fasting glucose (FPG <6.1 mmol/L) and impaired fasting glucose (IFG) (FPG ≥6.1 and ≤6.9 mmol/L) and those with normal glucose tolerance (OGTT <7.8 mmol/L) and impaired glucose tolerance (IGT) (OGTT ≥7.8 and ≤11.0 mmol/L). After adjusting for age, sex, MAP, and average heart rate, the risk of developing diabetes was significantly higher in both the prediabetes categories in participants with higher c-f PWV. The HRs for participants in the highest tertile of c-f PWV for the groups with IFG and IGT were 4.03 (95% CI 1.47–11.10) and 9.95 (95% CI 1.22–12.77), respectively. The association between c-f PWV and incidence of diabetes was not significant in those with normal fasting glucose or glucose tolerance.

CONCLUSIONS

The results of this observational, population-based study demonstrate that c-f PWV, as a marker of arterial stiffness, is associated with increased risk of developing diabetes. This risk remained significantly increased even after adjusting for the established risk factors and plasma glucose at baseline.

It is already known that the process of arterial stiffness is accelerated in the presence of diabetes (25,26). However, the notion of arterial stiffness as a possible predictor for diabetes development has

Table 2—Characteristics of study population at follow-up in relation to tertiles (T1–T3) of c-f PWV (n = 2,450)

	Whole study population	T1	T2	T3	P value
n	2,450	808	831	811	—
c-f PWV* (m/s)	9.93 (8.67–11.53)	8.17 (7.57–8.65)	9.93 (9.47–10.37)	12.30 (11.53–13.90)	—
Age (years)	71.92 (±5.55)	69.43 (±4.92)	71.72 (±5.32)	74.59 (±5.17)	<0.001
Heart rate (bpm)	62.57 (±9.80)	60.29 (±9.12)	62.64 (±9.86)	64.77 (±9.90)	<0.001
MAP (mmHg)	95.68 (±10.58)	91.09 (±9.47)	96.15 (±9.63)	99.78 (±10.76)	<0.001
Waist (cm)	90.40 (±11.66)	88.11 (±11.17)	90.49 (±11.64)	92.59 (±11.75)	<0.001
Smokers, n (%)	241 (9.8)	93 (11.5)	87 (10.5)	61 (7.5)	0.020
Use of antihypertensive drugs, n (%)	1,200 (49)	323 (40)	411 (49.5)	466 (57.5)	<0.001
FPG (mmol/L)	5.73 (±0.61)	5.66 (±0.63)	5.72 (±0.59)	5.81 (±0.61)	<0.001
2-h post-OGTT plasma glucose (mmol/L) (n = 2,424)	6.73 (±1.92)	6.30 (±1.82)	6.71 (±1.87)	7.19 (±1.99)	<0.001
LDL cholesterol (mmol/L)	3.43 (±0.90)	3.51 (±0.91)	3.41 (±0.88)	3.38 (±0.91)	0.008
HDL cholesterol (mmol/L)	1.47 (±0.44)	1.50 (±0.43)	1.47 (±0.44)	1.43 (±0.43)	0.002
Triglycerides* (mmol/L) (n = 2,448)	0.90 (0.70–1.20)	0.90 (0.70–1.10)	0.90 (0.70–1.30)	1.00 (0.80–1.30)	<0.001
FH$^+$ father, n (%)	183 (7.5)	52 (6.4)	68 (8.2)	63 (7.8)	0.374
FH$^+$ mother, n (%)	237 (9.7)	77 (9.5)	84 (10.1)	76 (9.4)	0.868

Values expressed are means (±SD) unless specified otherwise. *Median (25–75%). FH$^+$, family history–positive.

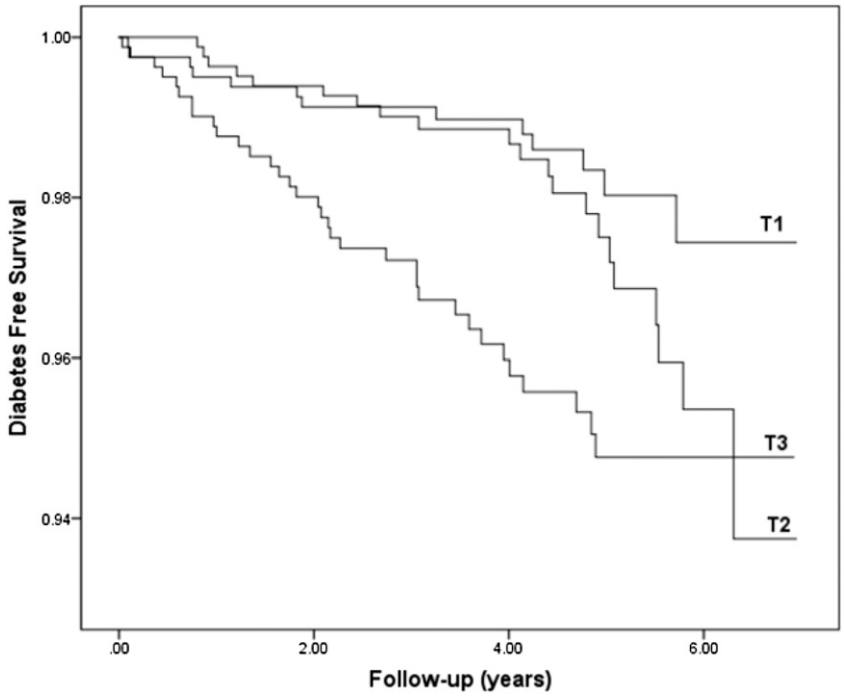

Figure 1—Diabetes-free survival in relation to the tertiles (T1–T3) of c-f PWV.

not been widely studied. Some studies have looked at the association between different indices of measurement of large artery stiffness and incidence of diabetes, although they have explored these parameters and their association with new-onset diabetes in high-risk hypertensive individuals only (16,17). To our knowledge, this is the first study that has explored the association between baseline arterial stiffness using c-f PWV measurement and incidence of diabetes in an apparently healthy elderly population.

In the previously mentioned studies (16,17), various indices reflective of arterial stiffness have been used. Nevertheless, the results do lend support to our study. Yasuno et al. (16) conducted a subanalysis in the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial. Their results showed that pulse pressure was an independent predictor of diabetes in high-risk Japanese hypertensive patients (16). However, it should be noted that pulse pressure is a crude surrogate index of arterial stiffness (24). In contrast, no association was found between peripheral pulse pressure and incident diabetes in our study.

Chen et al. (17) conducted a study consisting of 178 individuals with diabetes and hypertension. They concluded that measures of central aortic pressure, namely, central systolic blood pressure and augmentation index corrected at heart rate 75 bpm, were independent predictors for new-onset diabetes after adjusting for age, sex, mean blood pressure, glucose, and β-receptor blocker use (17). It is interesting to note that in their study, however, no association between pulse pressure and new-onset diabetes was demonstrated. Besides the small sample size and low number of end points, one of the other limitations of the study was the use of measurement of carotid-radial PWV, mainly reflecting muscular arteries, and not c-f PWV, reflecting large elastic arteries, as mentioned by the authors.

In the current study, diabetes at the baseline examination was carefully assessed by measurements of FPG at two separate visits, a 2-h OGTT, questionnaires about medical history and treatment for diabetes, as well as data linkage to several hospital and diabetes registers. Hence, it seems unlikely that the results are explained by preexisting diabetes. One question is whether blood glucose elevations in the prediabetic range could

Table 3—Incidence of diabetes in relation to tertiles (T1–T3) of c-f PWV (n = 2,450)

	T1	T2	T3	*P* for trend	*P*/SD
Number of participants	808	831	811	—	—
Incidence of diabetes, *n* (*n* per 1,000 person-years)	13 (3.54)	21 (5.70)	34 (9.47)	—	—
Model 1	1	1.73 (0.85–3.54)	3.41** (1.63–7.14)	0.001	<0.001
Model 2	1	1.83 (0.88–3.80)	3.24** (1.51–6.97)	0.002	0.001
Men					
Number of participants	263	295	347	—	—
Incidence of diabetes, *n* (*n* per 1,000 person-years)	4 (3.39)	8 (6.18)	16 (10.73)	—	—
Model 1	1	1.78 (0.52–6.10)	3.16 (0.90–11.06)	0.059	0.027
Model 2	1	1.38 (0.39–4.80)	2.37 (0.65–8.62)	0.151	0.089
Women					
Number of participants	545	536	464	—	—
Incidence of diabetes, *n* (*n* per 1,000 person-years)	9 (3.62)	13 (5.44)	18 (9.01)	—	—
Model 1	1	1.74 (0.72–4.18)	3.61** (1.44–9.09)	0.006	<0.001
Model 2	1	2.05 (0.83–5.05)	3.44* (1.30–9.10)	0.012	0.004

Model 1 is adjusted for age, sex, MAP, and average heart rate measured at the carotid artery. Model 2 is adjusted for age, sex, MAP, average heart rate measured at the carotid artery, waist circumference, smoking habits, FPG, LDL cholesterol, and antihypertensive drug medication. *$P < 0.05$; **$P < 0.01$. *P* for trend, *P* value for trend across tertiles; *P*/SD, *P* value per one SD increment of c-f PWV.

explain the increased incidence of diabetes associated with c-f PWV. This possibility cannot be excluded. It has been observed that there is increased central artery stiffness in subjects with impaired glucose metabolism, although the changes are less pronounced than those observed in diabetes (27). In our study, the relationship between c-f PWV and incident diabetes was mainly seen in participants with IFG or IGT. Since the results were also adjusted for plasma glucose levels (fasting and 2-h post-OGTT at the baseline examination), differences in glucose in the prediabetic range have been taken into account in the analysis. However, it is still possible that temporal glucose variations in the prediabetic range could affect the arterial stiffness.

Weber (28) discussed the plausibility of a bidirectional relationship between arterial stiffness and development of diabetes, supported by various studies. These studies and our results together indicate that it is worthwhile to explore if the hemodynamic changes accompanying the stiffening of large arteries have a potential role in the pathophysiologic process of diabetes development. One possible explanation for the association between arterial stiffness and incidence of diabetes could be offered by considering the cross-talk between arterial stiffness and endothelial dysfunction. It has been suggested that endothelial dysfunction can facilitate the development of diabetes (29), and endothelial dysfunction has been shown to be associated with arterial stiffness (30). Therefore, it could be speculated that a common pathway may be linking arterial stiffness and endothelial dysfunction to the development of diabetes, or it may be so that the two potentiate each other. Interestingly, results from a cross-sectional study demonstrated that both endothelial dysfunction and increased arterial stiffness were present in normoglycemic, normotensive first-degree relatives of individuals with type 2 diabetes (31).

Another potential pathophysiologic mechanism that can be suggested is the perturbed microvascular function resulting from arterial stiffness. This may cause impaired tissue perfusion and ultimately contribute to the development of diabetes (32).

There are many strengths of the study. It has a population-based prospective design. The study population was carefully screened to exclude all prevalent cases of diabetes. Because of the gradual development of diabetes, it can go undetected for a long time. However, the addition of the OGTT at the baseline examination helps to ensure that no undiagnosed case of diabetes was included. Some limitations, however, also need to be considered. Having a longer follow-up time and possibly a greater number of incidents would have allowed a subgroup analysis to be performed. Also, the current study did not include any established inflammatory biomarkers, which would have been interesting to analyze, as both arterial stiffness and diabetes are associated with chronic inflammation (33,34).

In conclusion, the results of this prospective population-based study suggest that there is an association between c-f PWV and risk of incident diabetes. Certainly, this is an interesting finding and requires further epidemiological and mechanistic research in this direction to understand the elusive mechanism connecting these two entities.

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