Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study

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Objective **Type 2 diabetic patients have an increased arterial stiffness and a very high risk of cardiovascular death. The present study investigated the relationship between pulse pressure, an indicator of vascular stiffness, and risk of cardiovascular mortality among type 2 diabetic and non-diabetic individuals. Second, we determined the relationship between pulse pressure and its main determinant (i.e. age), and the influence of diabetes and mean arterial pressure on this relationship.**

Design and methods **We studied a cohort of 2484 individuals including 208 type 2 diabetic patients. Mean age and median follow-up for non-diabetic and diabetic individuals, respectively, were 61 and 66 years, and 8.8 and 8.6 years. One-hundred and sixteen non-diabetic and 34 diabetic individuals died of cardiovascular causes. Relative risks of cardiovascular mortality were estimated by Cox proportional hazards regression adjusted for age, gender and mean arterial pressure.**

Results **Pulse pressure was associated with cardiovascular mortality among the diabetic, but not among the non-diabetic individuals [adjusted relative risk (95% confidence interval) per 10 mmHg increase, 1.27 (1.00–1.61) and 0.98 (0.85–1.13), *P* interaction = 0.07]. Further adjustment for other risk factors gave similar results. The association, at baseline, between age and pulse pressure was dependent on the presence of diabetes (*P* interaction = 0.03) and on the mean arterial pressure (*P* interaction < 0.001) (i.e. there was a stronger association when diabetes was present and when mean arterial pressure was higher).**

Conclusions **We conclude that, in type 2 diabetes, pulse pressure is positively associated with cardiovascular mortality. The association between age and pulse pressure is influenced by the presence of type 2 diabetes and by the height of the mean arterial pressure. These findings support the concept of accelerated vascular aging in type 2 diabetes. *J Hypertens* 20:1743–1751 © 2002 Lippincott Williams & Wilkins.**

Journal of Hypertension 2002, **20**:1743–1751

Keywords: pulse pressure, type 2 diabetes mellitus, cardiovascular mortality, vascular aging, mean arterial pressure

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Received 21 January 2002 **Revised** 2 April 2002
Accepted 24 May 2002

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Introduction

Vascular stiffness is associated with cardiovascular disease and mortality [1–10]. Vascular stiffness increases myocardial afterload and oxygen demand, leads to left ventricular hypertrophy, and limits coronary filling during diastole [11]. Over 50 years of age, pulse pressure is regarded as a manifestation of arterial stiffness, and several studies have shown a relationship between pulse pressure and cardiovascular mortality [6,12–16].

Type 2 diabetic patients are at very high risk of cardiovascular death [17–22] and are thought to have an increased arterial stiffness [23] and increased pulse pressure [15,24–26]. However, it is not known whether pulse pressure is positively associated with cardiovascular mortality in these patients, nor whether any such relationship is similar in diabetic and non-diabetic individuals. In addition, it is not known whether the increase of pulse pressure in diabetes is related to the accelerated vascular aging that is thought to occur in diabetes [27], in which case one would expect a stronger association between age and pulse pressure than in non-diabetic individuals.

Therefore, we investigated these issues among type 2 diabetic and non-diabetic individuals in a prospective, population-based cohort study.

Subjects and methods

The Hoorn Study is a population-based cohort study on glucose intolerance in a Dutch population conducted from 1989 until 1992. We invited a random sample of

3553 50- to 74-year-old individuals taken from the population register of the town of Hoorn, The Netherlands; 2484 participated (response rate, 71%). The study cohort and baseline measurement have been described in detail previously [28]. All subjects, except previously diagnosed diabetic individuals treated with oral glucose-lowering agents or insulin, underwent an oral glucose tolerance test according to the guidelines of the World Health Organization [29]. On the basis of this test, glucose tolerance was divided into two categories: normal and impaired glucose tolerance ($n = 2260$), and type 2 diabetes ($n = 208$). In 16 subjects, no data on glucose tolerance were available. Blood pressure was measured twice on the right arm of seated subjects, after at least 5 min of rest, with a random-zero sphygmomanometer (Hawksley-Gelman Ltd, Lancing, Sussex, UK). Hypertension was defined as diastolic blood pressure $\geqslant 95$ mmHg, systolic blood pressure $\geqslant 160$ mmHg and/or treatment with antihypertensive drugs, in accordance with clinical practice at the time the baseline data for this study were collected. Mean arterial pressure was defined as two-thirds of diastolic blood pressure plus one-third of systolic blood pressure. Pulse pressure was defined as systolic blood pressure minus diastolic blood pressure. The average of duplicate measurements was used for analysis. Body mass index, waist-to-hip ratio, specific fasting insulin, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, smoking habits, and prior cardiovascular disease were determined as previously described [28].

Follow-up

Data on the vital status of the subjects on 1 January 2000 were collected from the mortality register of the municipality of Hoorn as previously described [30]. For all subjects who died, the cause of death was extracted from the medical records of the general practitioner and the hospital of Hoorn, and classified according to the ninth edition of the International Classification of Diseases (ICD-9) [31]. Cardiovascular mortality was defined as codes 390–459, ('Diseases of the circulatory system') or code 798 ('Sudden death, cause unknown'), because sudden death in general is of cardiovascular origin [30]. Seventeen subjects (0.7% of the study cohort) were lost to follow-up. All participants gave informed consent for this study, which was approved by the Ethics Committee of the Vrije Universiteit Medical Centre, Amsterdam.

Statistical analysis

All analyses were performed with SPSS 9.0 for Windows 95 (SPSS Inc., Chicago, Illinois, USA). The associations between pulse pressure and cardiovascular risk factors were investigated by multiple linear regression analyses, with pulse pressure as the dependent variable and risk factors as independent variables. Survival over the follow-up period was calculated by Kaplan–Meier curves for different groups. Differences were tested by the log-rank test for trend. Cox proportional hazards multiple regression analysis was performed to assess the associations of pulse pressure and risk factors with cardiovascular and all-cause mortality. Results are described as relative risks (RR) (hazard ratios) with 95% confidence intervals (95% CI). The analyses were adjusted for all variables that were significantly associated with cardiovascular mortality, that were significantly associated with pulse pressure, or that were of pathophysiological interest. To evaluate possible interaction between pulse pressure and risk factors of interest, their product term, and age, gender and mean arterial pressure were added to the model. Risk factors measured on a continuous scale were used as such in the regression model, except for levels of fasting specific insulin, body mass index, HDL cholesterol, and triglycerides because the association of these variables with mortality was non-linear (see footnote to Table 1 for cut-off points).

Pulse pressure was entered into the regression model as a continuous variable, since the association with all-cause and cardiovascular mortality appeared to be linear. The proportional hazards assumption was checked by use of a hazard function plot. To examine the relationship of pulse, systolic, diastolic and mean arterial pressure with age, multiple linear regression was used with adjustment for gender and the presence of type 2 diabetes. Possible interactions between age and diabetes or age and mean arterial pressure in the associations of age with the measures of blood pressure were assessed with interaction terms in multiple regression. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

Table 1 shows the baseline characteristics of the study population and RR (95% CI) of mortality associated with risk factors after adjustment for age and gender (columns on the right). Median duration of follow-up was 8.6 years (range, 0.5–10.2 years) for diabetic and 8.8 years (range, 0.2–10.2 years) for non-diabetic individuals. During follow-up, 65 of 208 diabetic individuals died [34 of cardiovascular disease, five of whom died of cerebrovascular disease (ICD-9 codes 431–436)] compared with 265 of 2260 non-diabetic individuals (116 of cardiovascular disease, 16 of whom died of cerebrovascular disease). Of three patients who died, all of non-cardiovascular causes, glucose tolerance data were missing. Fifty-five diabetic individuals had prior cardiovascular disease (acute myocardial infarction in 17, angina pectoris in 21, coronary bypass or angioplasty in 11, intermittent claudication in 10, cerebrovascular disease in 14 and nitrate treatment in 15). Three

Table 1 **Baseline characteristics and relative risk of cardiovascular and all-cause mortality with risk factors**

				Cardiovascular mortality [RR (95% CI)][a]		All-cause mortality [RR (95% CI)][a]	
Risk factor	Diabetic individuals ($n = 208$)	Non-diabetic individuals ($n = 2260$)	Difference in risk factor or indicator	Diabetic individuals (34 cases)	Non-diabetic individuals (116 cases)	Diabetic individuals (65 cases)	Non-diabetic individuals (265 cases)
Male gender (%)	43	46	Yes vs. no	0.95 (0.47–1.95)[b]	2.77 (1.87–4.09)[b]	1.61 (0.98–2.65)[b]	2.05 (1.59–2.62)[b]
Age (years)	65.6 ± 6.8	61.3 ± 7.3	Per 5-year increase	1.68 (1.24–2.28)[b]	1.75 (1.53–2.00)[b]	1.75 (1.41–2.19)[b]	1.63 (1.49–1.77)[b]
Fasting insulin (pmol/l)	108 (75–143)	76 (60–97)	High vs. low[c]	0.82 (0.40–1.69)	1.45 (1.00–2.09)	1.01 (0.60–1.71)	1.15 (0.89–1.48)
Waist-to-hip ratio	0.95 ± 0.08	0.89 ± 0.09	Per 0.1 increase	1.09 (0.67–1.79)	1.50 (1.14–1.98)	1.38 (0.97–1.98)	1.38 (1.14–1.66)
Body mass index (kg/m^2)	28.6 ± 4.5	26.3 ± 3.4	High vs. low[d]	1.37 (0.62–3.02)	1.17 (0.80–1.72)	1.11 (0.65–1.90)	1.12 (0.87–1.44)
Total cholesterol (mmol/l)	6.6 ± 1.3	6.7 ± 1.2	Per 1.0 mmol/l increase	1.20 (0.95–1.51)	1.20 (1.03–1.40)	1.11 (0.93–1.33)	1.08 (0.97–1.20)
High-density lipoprotein cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.4	Low vs. high[e]	1.57 (0.66–3.75)	2.02 (1.22–3.36)	1.06 (0.55–2.03)	1.70 (1.19–2.45)
Low-density lipoprotein cholesterol (mmol/l)	4.4 ± 1.2	4.6 ± 1.1	Per 1.0 mmol/l increase	1.17 (0.90–1.53)	1.25 (1.06–1.46)	1.06 (0.87–1.29)	1.07 (0.95–1.19)
Triglycerides (mmol/l)	1.9 (1.3–2.8)	1.3 (1.0–1.8)	High vs. low[f]	2.21 (1.10–4.44)	1.40 (0.93–2.11)	2.23 (1.34–3.71)	1.15 (0.87–1.53)
Current smokers (%)	25.0	32.1	Yes vs. no	1.27 (0.57–2.84)	2.08 (1.42–3.03)	1.35 (0.77–2.37)	1.73 (1.34–2.23)
Prior cardiovascular disease (%)	26.4	14.8	Yes vs. no[g]	1.92 (0.97–3.83)	3.08 (2.11–4.48)	1.38 (0.83–2.31)	2.12 (1.63–2.76)
Hypertension (%)	60.6	29.1	Yes vs. no	3.44 (1.32–8.98)	2.62 (1.81–3.81)	1.37 (0.80–2.34)	1.95 (1.53–2.50)
Use of anti-hypertensive drugs (%)	40.9	18.2	Yes vs. no	2.29 (1.11–4.71)	2.58 (1.77–3.77)	1.27 (0.77–2.10)	1.91 (1.47–2.48)
Pulse pressure (mmHg)	62 ± 17	52 ± 15	Per 10 mmHg	1.27 (1.04–1.55)	1.08 (0.96–1.22)	1.13 (0.97–1.32)	1.08 (0.99–1.17)
Systolic blood pressure (mmHg)	146 ± 20	134 ± 20	Per 10 mmHg	1.18 (1.00–1.40)	1.11 (1.01–1.21)	1.09 (0.96–1.24)	1.08 (1.02–1.15)
Diastolic blood pressure (mmHg)	84 ± 10	82 ± 10	Per 10 mmHg	1.05 (0.74–1.47)	1.23 (1.05–1.45)	1.05 (0.82–1.33)	1.14 (1.02–1.27)
Mean arterial pressure (mmHg)	104 ± 12	99 ± 12	Per 10 mmHg	1.20 (0.90–1.60)	1.20 (1.05–1.38)	1.11 (0.90–1.36)	1.13 (1.03–1.24)

[a]Relative Risk (RR) with 95% confidence intervals (95% CI) obtained with Cox regression analyses of cardiovascular and all-cause mortality associated with continuous or dichotomous variables after adjustment for age and gender. [b]The effects of age and gender were only adjusted for each other. [c]$>$ 90 pmol/l versus $\leqslant$ 90 pmol/l. [d]$>$ 27 kg/m^2 versus $\leqslant$ 27 kg/m^2 for males and $>$ 26kg/m^2 versus $\leqslant$ 26 kg/m^2 for females. [e]$>$ 0.9 mmol/l versus $\geqslant$ 0.9 mmol/l. [f]$>$ 2.0 mmol/l versus $\leqslant$ 2.0 mmol/l. [g]A history of cardiovascular disease according to the Rose questionnaire [48].

hundred and thirty-four non-diabetic individuals had prior cardiovascular disease (acute myocardial infarction in 117, angina pectoris in 112, coronary bypass or angioplasty in 68, intermittent claudication in 15, cerebrovascular disease in 94, and nitrate treatment in 77).

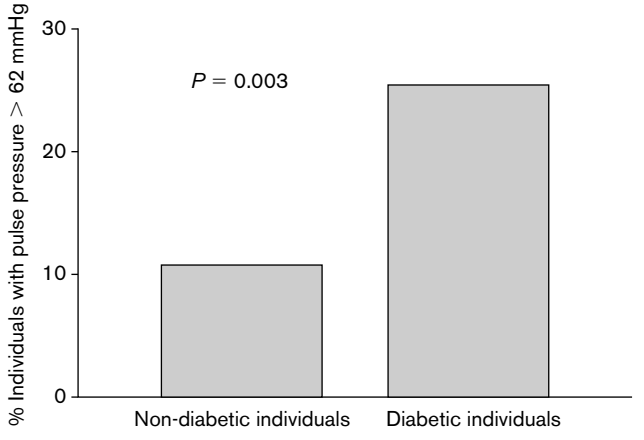
Mortality and pulse pressure

The mean ± SD pulse pressure at baseline in the subjects who died was higher than in those who survived (60 ± 17 versus 52 ± 15 mmHg, $P = 0.003$). Figure 1 shows the percentage of subjects with a pulse pressure above 62 mmHg (the upper quartile of the distribution) in type 2 diabetic and non-diabetic individuals. Figure 2 shows cardiovascular survival according to quartiles of pulse pressure. Table 2 presents the RR of cardiovascular and all-cause mortality associated with a 10 mmHg increase of pulse pressure.

Among diabetic individuals, pulse pressure was positively associated with cardiovascular mortality (crude RR, 1.40; 95% CI, 1.16–1.68). After adjustment for age, gender and mean arterial pressure, the RR was 1.27 (95% CI, 1.00–1.61). The crude and adjusted RR for the association of pulse pressure with all-cause mortality were 1.26 (95% CI, 1.09–1.45) and 1.12 (95% CI, 0.93–1.34). Adjustment for systolic blood pressure instead of mean arterial pressure did not materially change the RR (Table 2).

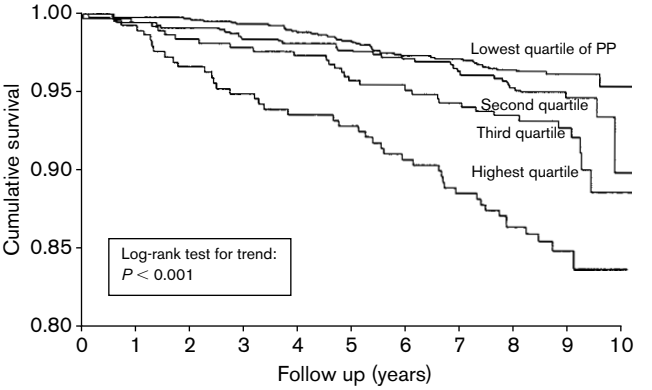
Among non-diabetic individuals, pulse pressure was significantly associated with cardiovascular and all-cause mortality in crude analyses. However, these associations were confounded by age and, to a lesser extent, by mean arterial pressure and gender [adjusted RR, 0.98 (95% CI, 0.85–1.13) and 1.02 (95% CI, 0.92–1.12)].

Fig. 1



Percentage of individuals with pulse pressure in the upper quartile (> 62 mmHg) of the entire cohort, according to the presence of diabetes.

Fig. 2



Cardiovascular survival (Kaplan–Meier curves) according to pulse pressure (PP) in the lowest (< 42 mmHg), second (42–50 mmHg), third (51–61 mmHg) and highest (⩾ 62 mmHg) quartile of the entire cohort.

The associations of cardiovascular and all-cause mortality with pulse pressure were somewhat, but not significantly, stronger than those with systolic blood pressure in both diabetic and non-diabetic individuals (data not shown).

The associations between pulse pressure and mortality were not importantly affected by further adjustment for prior cardiovascular disease, current smoking, HDL cholesterol, LDL cholesterol and total cholesterol, triglycerides, waist-to-hip ratio, body mass index, and the use of antihypertensive drugs (Table 2).

Exclusion of individuals with prior cardiovascular disease did not materially change the results (data not shown).

We considered that the association between pulse pressure and mortality might be confounded by impaired renal function. Data on serum creatinine and urinary albumin excretion were available in a subgroup [32], which included all diabetic individuals. Analyses adjusted for Cockroft–Gault-estimated glomerular filtration [33] ($n = 631$) were similar to those without such adjustment (data not shown). Analyses adjusted for the presence of microalbuminuria and macroalbuminuria among those in whom such data were available ($n = 575$) did not materially change the association between pulse pressure and cardiovascular mortality (data not shown), but decreased the association of pulse pressure with all-cause mortality among diabetic individuals

Table 2 Relative risk of cardiovascular and all-cause mortality associated with pulse pressure increase after adjustment for potentially confounding risk factors

		Cardiovascular mortality [RR (95% CI)][a]		All-cause mortality [RR (95% CI)][a]	
Model	Determinants in the model	Non-diabetic subjects (116 cases)	Diabetic subjects (34 cases)	Non-diabetic subjects (265 cases)	Diabetic subjects (65 cases)
1	Pulse pressure per 10 mmHg	1.27 (1.14–1.41)	1.40 (1.16–1.68)	1.25 (1.17–1.34)	1.26 (1.09–1.45)
2	Model 1 and age	1.05 (0.93–1.18)	1.27 (1.03–1.55)	1.05 (0.97–1.14)	1.11 (0.95–1.30)
3	Model 2 and gender	1.08 (0.96–1.22)	1.27 (1.04–1.55)	1.08 (0.99–1.17)	1.13 (0.97–1.32)
4	Model 3 and mean arterial pressure	0.98 (0.85–1.13)	1.27 (1.00–1.61)	1.02 (0.92–1.12)	1.12 (0.93–1.34)
5	Model 3 and systolic blood pressure	0.86 (0.69–1.08)	1.26 (0.84–1.90)	0.95 (0.81–1.10)	1.10 (0.81–1.48)
6	Model 4 and prior cardiovascular disease[b]	0.98 (0.85–1.14)	1.25 (0.98–1.59)	1.02 (0.93–1.13)	1.10 (0.91–1.33)
7	Model 4 and current smoking	0.96 (0.83–1.11)	1.26 (1.00–1.63)	1.01 (0.91–1.11)	1.11 (0.92–1.34)
8	Model 4 and high-density lipoprotein cholesterol[b]	0.98 (0.85–1.14)	1.28 (1.01–1.63)	1.02 (0.93–1.12)	1.12 (0.93–1.35)
9	Model 4 and low-density lipoprotein cholesterol	0.98 (0.85–1.13)	1.30 (1.02–1.66)	1.02 (0.92–1.12)	1.13 (0.94–1.36)
10	Model 4 and total cholesterol	0.98 (0.85–1.13)	1.26 (1.00–1.60)	1.02 (0.92–1.12)	1.12 (0.93–1.34)
11	Model 4 and triglycerides[b]	0.98 (0.85–1.14)	1.25 (0.99–1.58)	1.02 (0.93–1.12)	1.11 (0.93–1.33)
12	Model 4 and waist-to-hip ratio	0.98 (0.85–1.14)	1.28 (1.01–1.63)	1.02 (0.92–1.12)	1.13 (0.94–1.35)
13	Model 4 and body mass index	0.97 (0.84–1.13)	1.28 (1.01–1.64)	1.02 (0.92–1.12)	1.13 (0.94–1.36)
14	Model 4 and use of anti-hypertensive drugs	0.97 (0.84–1.12)	1.29 (1.02–1.63)	1.01 (0.92–1.12)	1.12 (0.94–1.35)

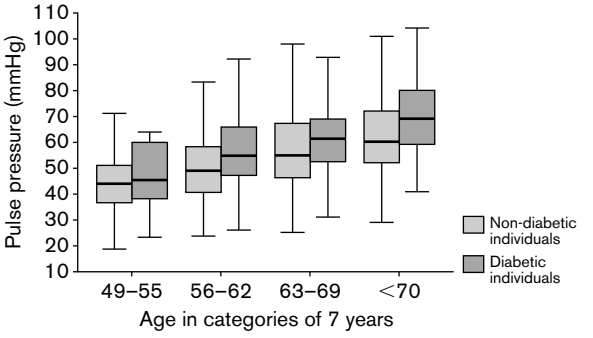
[a]Relative risk (RR) with 95% confidence interval (95% CI) obtained with Cox regression analyses of cardiovascular and all-cause mortality adjusted for several risk factors. [b]Defined footnote to Table 1.

(RR, 1.00), but the confidence interval was wide (95% CI, 0.79–1.27).

The association between pulse pressure and cardiovascular mortality differed between diabetic and non-diabetic individuals ($P = 0.07$ for pulse pressure-by-diabetes interaction in a model adjusted for age, gender and mean arterial pressure that included the whole population).

All analyses presented in Table 2 were also performed with the exclusion of hypertensive subjects and users of antihypertensive drugs. The results of these analyses were similar to the results presented here. Analyses stratified for gender showed similar RR for men and women (data not shown). Analyses in individuals with impaired glucose tolerance ($n = 252$) indicated that RR were similar to those in individuals with normal glucose tolerance (data not shown).

Fig. 3



The association between pulse pressure and age. The association is stronger in diabetic than in non-diabetic individuals and was tested statistically by the interaction term of age with the presence of type 2 diabetes (P interaction = 0.03).

Cross-sectional associations of measures of blood pressure with age and diabetes at baseline

Pulse pressure among diabetic individuals was 3.2 mmHg (95% CI, 1.6–4.9) higher than among non-diabetic individuals after adjustment for age, gender and mean arterial pressure. Age was associated with pulse pressure both among diabetic and non-diabetic individuals, but the association was stronger among diabetic individuals. Pulse pressure increased by 0.98 mmHg per year of age in diabetic and by 0.71 mmHg per year of age in non-diabetic individuals. This difference was statistically significant as tested by the interaction term of age with the presence of type 2 diabetes (P interaction = 0.03; Fig. 3). Exclusion of individuals with impaired glucose tolerance did not change the results.

Mean arterial pressure is an additional important determinant of pulse pressure. Pulse pressure increased with 6.37 mmHg per 10 mmHg increase in mean arterial pressure after adjustment for age and gender (Table 3). The association between pulse pressure and mean arterial pressure was similar among diabetic and non-diabetic individuals (7.09 versus 6.27 mmHg, P interaction = 0.219).

The association between age and systolic blood pressure also increased more with age in diabetic compared with non-diabetic individuals. Systolic blood pressure increased by 0.67 mmHg per year of age in the diabetic and by 0.48 mmHg per year of age in the non-diabetic individuals (P interaction = 0.03; Table 4). In addition,

Table 3 **Cross-sectional associations of pulse pressure with cardiovascular risk factors[a]**

	Regression coefficient	Standard error	*P* value
Crude			
Mean arterial pressure (per 1 mmHg increase)	0.713	0.021	< 0.001
Adjusted for age and gender			
Mean arterial pressure (per 1 mmHg increase)	0.637	0.019	< 0.001
Gender (male versus female)	−1.862	0.557	0.001
Age (per 5 year increase)	4.834	0.188	< 0.001
Adjusted for age, gender and mean arterial pressure			
Gender (male versus female)	−3.219	0.463	< 0.001
Age (per 5 year increase)	3.778	0.159	< 0.001
Diabetes mellitus type 2 (yes versus no)	3.238	0.838	< 0.001
Fasting insulin (high versus low)[b]	1.139	0.503	0.024
Hypertension (yes versus no)	2.000	0.596	0.001
Current smoking (yes versus no)	2.028	0.504	< 0.001

[a]Regression coefficient, standard error and *P* value obtained by linear regression analyses with pulse pressure as dependent and risk factors as independent variable. [b]Defined in footnote to Table 1. A regression coefficient of 0.713 (top left) indicates that, for each 1 mmHg increase in mean arterial pressure, pulse pressure increases by 0.713 mmHg.

diastolic blood pressure decreased more with age in diabetic than in non-diabetic individuals. Diastolic blood pressure decreased by 0.34 mmHg per year of age in the diabetic and by 0.24 mmHg per year of age in the non-diabetic individuals (P interaction = 0.03; Table 4). Mean arterial pressure also decreased more with age in diabetic compared with non-diabetic subjects (P interaction = 0.03; Table 4).

Age and mean arterial pressure interacted in their relationship with pulse, systolic and diastolic pressure (P interaction < 0.001). The complete model for pulse

Table 4. **Cross-sectional associations of systolic, diastolic and mean arterial pressure with age**

	Regression coefficient	Standard error	*P*-value
Systolic blood pressure			
Crude			
Age (per 5 year increase)	0.502	0.027	<0.0001
Adjusted for age, gender, mean arterial pressure, diabetes and interactions			
Age (per 5 year increase)	−0.563	0.838	0.502
Mean arterial pressure (per 1 mmHg)	1.053	0.105	<0.0001
Diabetes mellitus type 2 (yes vs no)	−9.308	5.322	0.080
Age × diabetes	0.879	0.405	0.030
Age × mean arterial pressure	0.030	0.008	<0.001
Diastolic blood pressure			
Crude			
Age (per 5 year increase)	0.000	0.015	0.991
Adjusted for age, gender, mean arterial pressure, diabetes and interactions			
Age (per 5 year increase)	0.282	0.419	0.502
Mean arterial pressure (per 1 mmHg)	0.973	0.052	<0.0001
Diabetes mellitus type 2 (yes versus no)	4.654	2.661	0.080
Age × diabetes	−0.439	0.203	0.030
Age × mean arterial pressure	−0.015	0.004	<0.001
Mean arterial pressure			
Crude			
Age (per 5 year increase)	1.672	0.175	<0.0001
Adjusted for age, gender, diabetes and age × diabetes			
Age (per 5 year increase)	1.620	0.175	<0.0001
Diabetes mellitus type 2 (yes versus no)	22.410	8.508	0.008
Age × diabetes	−1.434	0.648	0.027

Regression coefficient, standard error and *P*-value obtained by linear regression analyses with systolic, diastolic or mean arterial pressure as dependent variables. A regression coefficient of 0.502 (top left) indicates that, for each 5 year increase in age, systolic pressure increases by 0.502 mmHg. Note that the full effect of age, mean arterial pressure and diabetes can be calculated in a manner analogous to that shown in the text for pulse pressure.

pressure, including the interactions of age with diabetes and age with mean arterial pressure (MAP), was:

$$\text{pulse pressure} = 2.023 - 0.169\ \text{age} + 0.080\ \text{MAP} + 0.009\ \text{age} \times \text{MAP} - 13.962\ \text{diabetes} + 0.264\ \text{diabetes} \times \text{age} - 3.067\ \text{gender}.$$

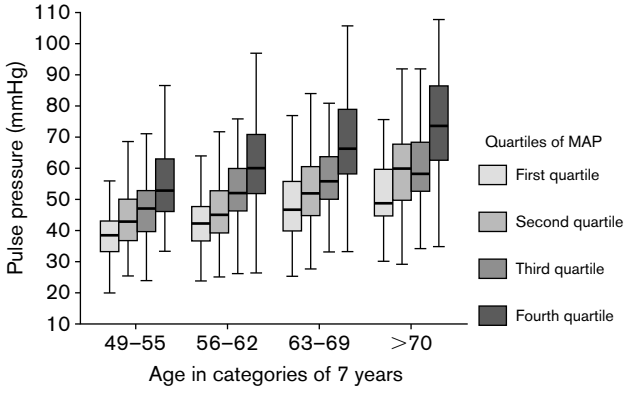
The interaction of age with mean arterial pressure means that the association between, in this case, pulse pressure and age is stronger at a higher mean arterial pressure (Fig. 4). Thus, for non-diabetic women with a mean arterial pressure of 90 mmHg, pulse pressure increased by 0.64 mmHg per year, while for non-diabetic women with a mean arterial pressure of 110 mmHg, the increase was 0.82 mmHg per year. The interaction between age and mean arterial pressure with regard to pulse pressure was similar among diabetic and non-diabetic individuals.

Discussion

The present study demonstrates, to our knowledge for the first time, that pulse pressure is independently associated with cardiovascular mortality in individuals with type 2 diabetes. These patients have a 27% increased risk of cardiovascular death per 10 mmHg increase of pulse pressure. In addition, we show that the pulse pressure increase typically observed in type 2 diabetes is, in part, related to a stronger association of pulse pressure with age compared with non-diabetic individuals. This finding supports the concept that type 2 diabetes can be regarded as a state of accelerated vascular aging.

Among non-diabetic individuals, pulse pressure was significantly associated with cardiovascular mortality in crude analysis. After adjustment for age, gender and mean arterial pressure, the relationship disappeared. These findings differ from those reported by others [12,13,16,34]. The explanation for this discrepancy is unclear and may be multifactorial. First, many studies did not adjust the association between pulse pressure and mortality for the influence of mean arterial pressure [12,13,16,34], which is an important confounder of this association (Table 2). Failure to adjust for mean arterial pressure leads to higher estimated levels of RR, and thus to an overestimation of the influence of pulse pressure on mortality risk. Second, our study had a relatively short follow-up and very low mortality rate compared with other population-based studies, whereas studies with a longer follow-up and higher mortality rates generally report stronger associations between pulse pressure and mortality (7.2 per 1000 person-years for cardiovascular mortality in our study, compared with 1.7–48.6 per 1000 person-years in other studies) [12–16]. The association between pulse pressure and cardiovascular mortality may thus be more prominent among populations with higher mortality risk than our population. In this regard, it should be noted that we cannot exclude that our findings among the diabetic individuals were related to their high-risk status rather than to the diabetic state *per se*.

Fig. 4



The association between pulse pressure and age. The association is stronger at higher mean arterial pressure (MAP) and was tested statistically by the interaction term of age with MAP (P interaction $<$ 0.001).

Vascular aging encloses a broad spectrum of changes in the arterial vessel wall, including increased stiffening. Our data support the concept of accelerated vascular aging in diabetic individuals. First, we found that, among diabetic individuals, both the age-related increase of systolic blood pressure and the age-related decrease of diastolic blood pressure were more pronounced than among non-diabetic individuals (Table 4) [3,35–37]. Therefore, it is likely that the increase in pulse pressure among diabetic individuals reflects increased arterial stiffness rather than alterations in ventricular ejection. Second, accelerated vascular aging in diabetes is biologically plausible. During aging, collagen in large arteries becomes more prominent, while elastin fibers become disrupted, leading to stiffer vessel walls. In diabetes, increases in oxidative stress, carbonyl stress and advanced glycation endproducts may combine to exaggerate these alterations in collagen and elastin structure and function, with resultant loss of vascular elasticity [27,35,36].

The rise of pulse pressure with age was, in addition, stronger at higher mean arterial pressure (Fig. 4) [37–39]. The Framingham study [38] reported an interaction between age and hypertension in the association with pulse pressure, which is comparable with the interaction between mean arterial pressure and age we report, because mean arterial pressure is an indicator of hypertension. One interpretation of the interaction of age with mean arterial pressure is that it, too, may

represent accelerated arterial aging at higher mean arterial pressure. Static wall stress increases with mean arterial pressure, which will cause tissue fatigue characterized by alterations in collagen and elastin, and increased arterial stiffness [37,40].

The elevated pulse pressure observed in the type 2 diabetic patients, and the associated elevation in cardiovascular risk, may imply that pulse pressure, in addition to mean arterial pressure, is a target for therapeutic intervention in these patients. However, it is not clear how pulse pressure or arterial stiffness can be reduced. Current antihypertensive treatments often focus on reduction of the extracellular volume or smooth muscle cell tone, thereby reducing both systolic and diastolic blood pressure. When both pressures are reduced, pulse pressure may not have changed. Some non-pharmacological efforts may be able to reduce arterial stiffness; for instance, physical exercise [41,42], reduction of salt intake [43] and the intake of n-3 fatty acids [44]. Furthermore, some evidence exists that angiotensin-converting enzyme inhibitors may have a direct effect on large artery wall properties, thereby reducing arterial stiffness [45]. They particularly reduce stiffness in combination with small doses of diuretics [46]. Novel therapeutic drugs, such as ALT-711 [47], which breaks down established advanced glycation endproduct cross-links between proteins, have been demonstrated to reduce arterial stiffness, but more evidence is necessary to establish the impact of such drugs.

The present study had several limitations. First, there were only 34 cardiovascular deaths among the diabetic individuals, which limits the precision of the risk estimates. However, we tested a pre-specified hypothesis and the results are biologically plausible. Second, we were not able to show a difference in the association between pulse pressure and cardiovascular mortality in the subgroup of impaired glucose tolerance compared with the group with normal glucose tolerance, which may be due to the small number of deaths in this subgroup ($n = 20$). Both limitations may be related to the relatively short follow-up period and the apparently healthy state of our population.

In summary, our data provide the first evidence that pulse pressure is independently associated with cardiovascular mortality in type 2 diabetic individuals. Furthermore, the presence of diabetes and a high mean arterial pressure increase the (normal) rise of pulse pressure with age. This may represent accelerated vascular aging in diabetes and hypertension.

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