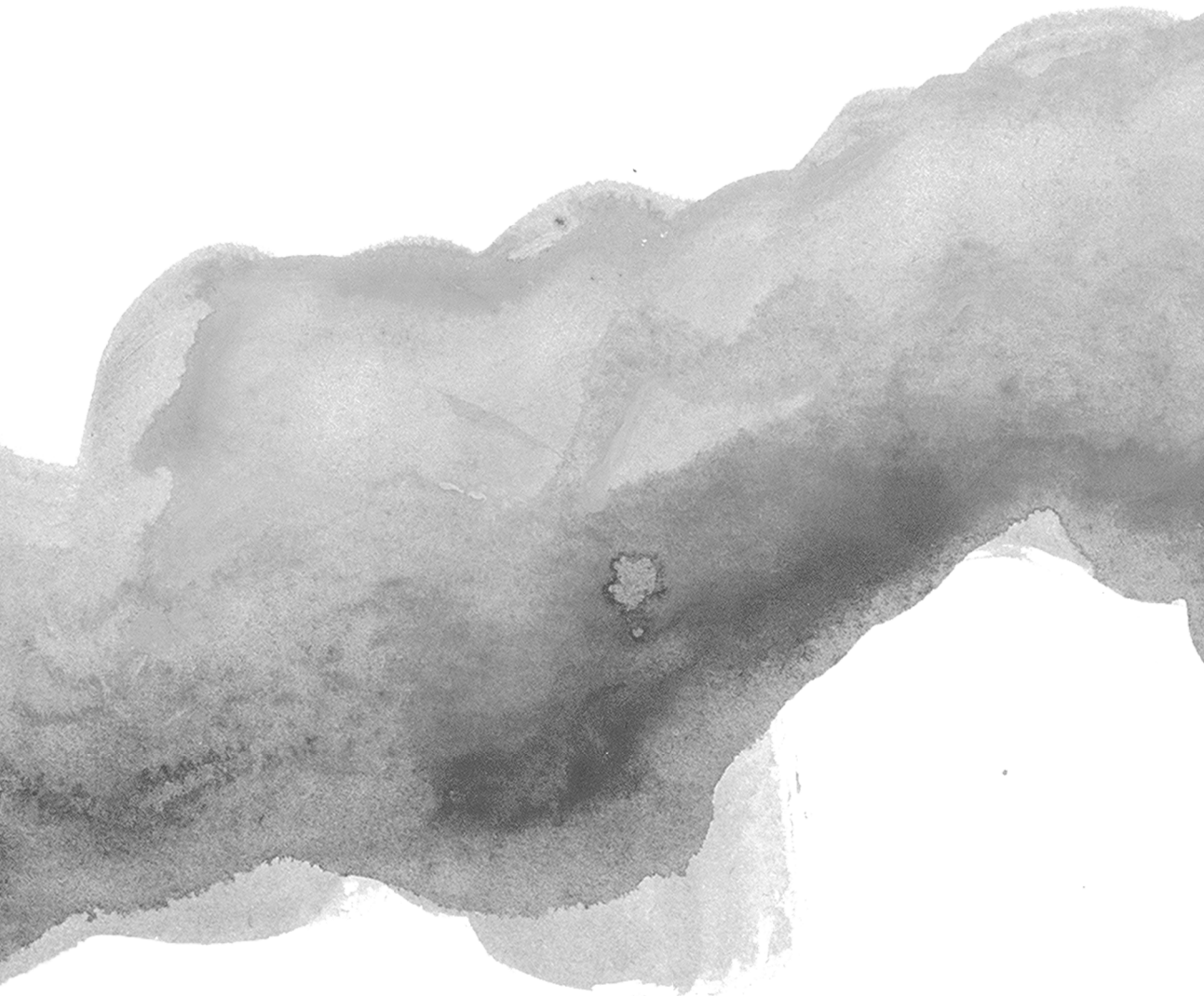

Part I

Blood pressure, cognitive function and mortality

Chapter 2

Association of diastolic blood pressure with cardiovascular events in older people varies upon cardiovascular history

Liselotte W Wijsman, Majon Muller, Anton JM de Craen, J Wouter Jukema,
Rudi GJ Westendorp, Simon P Mooijaart

Submitted

Abstract

Background In older age, a low diastolic blood pressure (DBP) has been associated with increased risk of cardiovascular events, especially in frail older people. A potential mechanism might be that low DBP leads to inadequate perfusion of vital organs. Here, we tested the hypothesis that low DBP is associated with a high risk of cardiovascular events in people with a previous history of cardiovascular disease, as a proxy of vascular impairment.

Methods We included 5,804 participants (mean age 75 years) from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) who as part of the trial were intensively monitored for an average period of 3.2 years. Baseline DBP was categorized in low (<70 mmHg), normal (70-90 mmHg) or high (>90 mmHg). Cox proportional hazards analyses were used to estimate hazard ratio (HR) with 95% confidence intervals (CI) for the association of DBP with cardiovascular events. Analyses were stratified for cardiovascular history.

Results We show that participants with low DBP had an 1.24-fold (95% CI 1.04; 1.49) increased risk of cardiovascular events compared to those with normal DBP. After further adjusting for cardiovascular factors, this association attenuated to 1.05 (95% CI 0.86; 1.28). A previous history of cardiovascular disease significantly modified the relation between DBP and risk of cardiovascular events (p for interaction=0.042). In participants without a history of cardiovascular disease, DBP was marginally significant associated with an increased event risk (HR (95% CI) per 10 mmHg increase in DBP 1.08 (0.99; 1.18), p-value=0.07), whereas in participants with a history of cardiovascular disease higher DBP was associated with a decreased risk of cardiovascular events (HR (95% CI) per 10 mmHg increase in DBP 0.92 (0.85; 0.99, p-value=0.018). These risk estimates were independent of potential confounders, including classical cardiovascular risk factors.

Conclusion The association of DBP with cardiovascular events in older people varies upon their previous history, showing that in participants with pre-existing cardiovascular disease a higher DBP associates with a decreased risk of future cardiovascular events.

Introduction

The association between blood pressure and cardiovascular events has been studied in numerous observational studies.(1-11) Despite a large body of evidence showing that high systolic and diastolic blood pressure are risk factors for cardiovascular disease in middle-aged people, the association is less evident in older age.(10, 12) Several studies in older people showed an attenuating relation between blood pressure and occurrence of myocardial infarction, stroke, and vascular and all-cause mortality.(2, 3, 5, 9, 12)

Recent data found that the risk associated with lower levels of blood pressure was even reversed in frail older people.(6, 8, 10, 13, 14) A population-based study including 599 of the oldest old (85 years or older) showed that blood pressure values below 140/90 mmHg were associated with excess mortality.(10) Furthermore, observational studies found that low blood pressure was associated with higher risk of cardiovascular events, but only in people with impaired physical and cognitive function, used as a marker of vascular impairment.(6, 8, 14) This finding was in particular the case for low diastolic blood pressure. (6, 8) This poses the hypothesis that instead of chronological age, it might be vascular impairment that explains that the association between low diastolic blood pressure and cardiovascular risk reverses.

We therefore hypothesized that low diastolic blood pressure, independent of systolic blood pressure, is associated with an increased risk of cardiovascular events in people with a previous history of cardiovascular disease, as a proxy of vascular impairment. The aims of this study were 1) to investigate the association of diastolic blood pressure with cardiovascular events, and 2) to study whether this association differed in people with and without a previous cardiovascular history. We used data of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), which included older participants (70-82 years) with a cardiovascular history and participants without a cardiovascular history, but with one or more risk factors defined as hypertension, cigarette smoking or diabetes mellitus.

Methods

Study design and participants

We used data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized, placebo-controlled trial designed to investigate whether treatment with pravastatin would diminish the occurrence of vascular events in participants with pre-existing cardiovascular diseases or risk factors thereof. PROSPER included 5,804 participants, aged 70-82 years, from three collaborating centers in Ireland, Scotland and the Netherlands.15 Approximately 50% of all participants had a history of cardiovascular diseases, including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, and vascular surgery. The rest of the participants had one or more major cardiovascular risk factors, defined as hypertension, cigarette smoking, or diabetes mellitus. Primary outcome of the trial is the composite outcome of coronary heart disease death, non-fatal myocardial infarction, and fatal or non-fatal stroke. Details of the design and outcome of the PROSPER have been published elsewhere.(15)

Blood pressure measurements

Blood pressure was measured at two consecutive moments at baseline, in sitting position, with a fully automatic electronic sphygmomanometer (Omron M4H) by trained research nurses. Baseline blood pressure was defined as the mean value of the two blood pressure measurements. Diastolic blood pressure was categorized based on three clinically relevant cutoff level: low (<70 mmHg), normal (70-90 mmHg) and high (>90 mmHg).

Outcomes

Information on the occurrence of cardiovascular events was collected during the course of PROSPER, which had a mean follow-up period of 3.2 years. Cardiovascular events were defined as definite or suspect death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal stroke / transient ischemic attack, coronary artery bypass graft or percutaneous transluminal coronary angioplasty or peripheral arterial surgery or angioplasty.(16)

Statistical analysis

Baseline characteristics were calculated for all participants and for participants with low, normal and high diastolic blood pressure at baseline. Baseline differences in continuous variables were tested with linear regression models; Chi-squared tests were used to test differences in categorical variables.

We used Cox proportional hazards analyses to estimate hazard ratio's (HR) with 95% confidence intervals (CI) for the association of diastolic blood pressure with risk of cardiovascular events. Participants with normal diastolic blood pressure (70-90 mmHg) were taken as reference category. To investigate the association of diastolic blood pressure with cardiovascular events in participants with and without a cardiovascular history, we stratified our analyses for history of cardiovascular disease. To study whether the trend for cardiovascular events among the diastolic blood pressure groups was significant, we calculated a probability (p) value by using diastolic blood pressure as a continuous variable. Furthermore, we analysed whether the association between diastolic blood pressure and cardiovascular events differed in participants with and without cardiovascular history. For this, we calculated the interaction term between diastolic blood pressure (as a continuous variable) and history of cardiovascular disease; and included this interaction term together with diastolic blood pressure (as a continuous variable) and history of cardiovascular disease in the Cox proportional hazards analyses. All Cox regression analyses were adjusted for the following sociodemographic variables: sex, age, country and treatment during follow-up of the study (pravastatin or placebo). We additionally adjusted the analyses for potential cardiovascular confounders, including systolic blood pressure, histories of hypertension, diabetes, smoking, body mass index (BMI), estimated glomerular filtration rate (eGFR), N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac troponin T, and high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride levels at baseline.

In addition, we explored the association between systolic blood pressure with cardiovascular events. Again, participants with normal systolic blood pressure (120-140 mmHg) were taking as a reference category. All Cox regression analyses were adjusted for sociodemographic variables (sex, age, country and treatment during follow-up of the study) and additionally for potential cardiovascular confounders, including diastolic blood pressure, histories of hypertension, diabetes, smoking, body mass index (BMI), estimated glomerular filtration rate (eGFR), N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac troponin T, and high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride levels at baseline.

All analyses were performed using SPSS software (version 20.0.0, SPSS Inc., Chicago, IL). Supplemental tables are available on request.

Results

Table 1 shows the baseline characteristics for all 5,804 study participants and in groups of diastolic blood pressure at baseline. Mean age of all participants was 75.3 years; participants with higher diastolic blood pressure were younger; 3,000 participants (51.7%) were female. Participants with a higher diastolic blood pressure had higher systolic blood pressure, higher pulse pressure, and a higher prevalence of hypertension. Participants with lower diastolic blood pressure had a higher prevalence of cardiovascular disease, history of

Table 1. Baseline characteristics in categories of diastolic blood pressure

	Diastolic blood pressure			
	Low <70 mmHg N=698	Normal 70-90 mmHg N=3701	High ≥90 mmHg N=1405	P-value[1]
Blood pressure (mmHg)				
Systolic blood pressure	133.2 (0.7)	153.0 (0.3)	169.6 (0.5)	<0.001
Diastolic blood pressure	65.5 (0.2)	81.7 (0.1)	98.3 (0.2)	
Pulse pressure	67.7 (0.7)	71.3 (0.3)	71.3 (0.5)	0.023
Demographics				
Age (years)	75.6 (0.1)	75.4 (0.1)	75.1 (0.1)	0.024
Female, n (%)	344 (49.3%)	1958 (52.9%)	698 (49.7%)	0.048
Vascular risk factors				
History of hypertension, n (%)	292 (41.8%)	2275 (61.5%)	1025 (73.0%)	<0.001
History of diabetes mellitus, n (%)	73 (10.5%)	375 (10.1%)	175 (12.5%)	0.055
History of stroke or TIA, n (%)	69 (9.9%)	428 (11.6%)	152 (10.8%)	0.384
History of MI, n (%)	150 (21.5%)	491 (13.3%)	135 (9.6%)	<0.001
History of vascular disease, n (%)	412 (59.0%)	1647 (44.5%)	506 (36.0%)	<0.001
Current smoker, n (%)	221 (31.7%)	1001 (27.0%)	336 (23.9%)	0.001
Body mass index (kg/m^2)	25.7 (0.2)	26.8 (0.1)	27.6 (0.1)	<0.001
LDL cholesterol (mmol/L)	3.8 (0.0)	3.8 (0.0)	3.8 (0.0)	0.581
HDL cholesterol (mmolL)	1.3 (0.0)	1.3 (0.0)	1.3 (0.0)	0.482
Triglycerides (mmol/L)	1.5 (0.0)	1.5 (0.0)	1.6 (0.0)	0.247
Blood pressure lowering medication, n (%)				
Diuretics	251 (36.0%)	1517 (41.0%)	590 (42.0%)	0.022
Ace-inhibitors	105 (15.0%)	562 (15.2%)	284 (20.2%)	<0.001
Beta-blockers	199 (28.5%)	947 (25.6%)	356 (25.3%)	0.235
Calcium channel blockers	218 (31.2%)	947 (25.6%)	293 (20.9%)	<0.001
Biochemistry				
eGFR (ml/min/1.73m^2)	59.5 (0.6)	59.8 (0.2)	60.8 (0.4)	0.025
NT-proBNP (ng/L)	375.7 (21.5)	279.1 (9.3)	293.7 (15.1)	0.547
Cardiac troponin T (ng/L)	10.1 (1.4)	9.2 (0.6)	13.4 (1.0)	0.021

Data represent mean (standard error), unless stated otherwise. Abbreviations: TIA, transient ischemic attack; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide. [1]P-value for continuous variables was calculated by using DBP as continuous variable.

myocardial infarction and smoking. No differences existed in prevalence of diabetes mellitus and stroke or transient ischemic attack between the diastolic blood pressure groups.

A total number of 977 participants (16.8%) experienced a cardiovascular event during the mean follow-up period of 3.2 years. Across the total population, participants with low diastolic blood pressure (<70 mmHg) had a 1.24-fold (1.04; 1.49) increased risk of cardiovascular events (HR (95% CI) compared to those with normal diastolic blood pressure). After adjusting for cardiovascular risk factors, the association between diastolic blood pressure and cardiovascular events attenuated to 1.11 (0.90; 1.37). When compared to normal diastolic blood pressure, high diastolic blood pressure (>90 mmHg) was not associated with an increased cardiovascular event risk (0.91 (0.76; 1.107)).

To further study the association between diastolic blood pressure and cardiovascular events, we investigated whether the association differed in participants with and without a previous history of cardiovascular disease as a marker of vascular impairment. History of cardiovascular disease significantly modified the relation between diastolic blood pressure and risk of cardiovascular events (p for interaction=0.042) (table 3 and figure 1). In participants without a history of cardiovascular disease, DBP was marginally significant associated with an increased event risk (HR (95%) per 10 mmHg increase in DBP 1.08 (0.99; 1.18), p-value=0.07), whereas in participants with a history of cardiovascular disease higher DBP was associated with a decreased risk of cardiovascular events (HR (95%) per 10 mmHg increase in DBP 0.92 (0.85; 0.99, p-value=0.018). Associations were independent of potential confounders, including classical cardiovascular risk factors.

Table 2. Association of diastolic blood pressure with cardiovascular events in all participants

Cardiovascular events	Diastolic blood pressure							
	Low <70 mmHg N=698		Normal 70-90 mmHg N=3701		High ≥90 mmHg N=1405		Change per 10 mmHg DBP[1]	
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	HR (95% CI)	P-value
Adjusted for sociodemographic factors	143	1.24 (1.04; 1.49)*	609	1 (ref)	225	0.98 (0.84; 1.14)	0.95 (0.90; 1.01)	0.077
Additionally adjusted for cardiovascular factors	143	1.11 (0.90; 1.37)	609	1 (ref)	225	0.91 (0.76; 1.12)	0.93 (0.87; 1.00)	0.049

Abbreviations: HR, Hazard Ratio; CI, confidence interval. *p-value <0.05 [1]value represents the change in log-hazard per 10 mmHg increase in DBP. Sociodemographic factors included sex, age, country and treatment during follow-up of the study (pravastatin or placebo). Cardiovascular factors included systolic blood pressure, histories of hypertension, diabetes, smoking, BMI, eGFR, NT-proBNP, cardiac troponin T, HDL, LDL and triglyceride levels at baseline.

Table 3. Association of diastolic blood pressure with cardiovascular events stratified by cardiovascular history

	Diastolic blood pressure								
	Low <70 mmHg N=698		Normal 70-90 mmHg N=3701		High ≥90 mmHg N=1405		Change per 10 mmHg DBP[1]		
Cardiovascular events	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	HR (95% CI)	P-value	P for interaction
Adjusted for sociodemographic factors									
No cardiovascular history	40	1.19 (0.85; 1.66)	246	1 (ref)	126	1.19 (0.96; 1.47)	1.08 (0.99; 1.18)	0.074	0.008
Cardiovascular history	103	1.14 (0.91; 1.42)	363	1 (ref)	99	0.89 (0.71; 1.11)	0.92 (0.85; 0.99)	0.018	
Additionally adjusted for cardiovascular factors									
No cardiovascular history	40	0.97 (0.67; 1.41)	246	1 (ref)	126	1.12 (0.89; 1.41)	1.03 (0.93; 1.15)	0.541	0.042
Cardiovascular history	103	1.05 (0.83; 1.34)	363	1 (ref)	99	0.84 (0.66; 1.07)	0.87 (0.79; 0.96)	0.004	

Abbreviations: HR, Hazard Ratio; CI, confidence interval.

*p-value <0.05 [1]value represents the change in log-hazard per 10 mmHg increase in DBP. Sociodemographic factors included sex, age, country and treatment during follow-up of the study (pravastatin or placebo). Cardiovascular factors included systolic blood pressure, histories of hypertension, diabetes, smoking, BMI, eGFR, NT-proBNP, cardiac troponin T, HDL, LDL and triglyceride levels at baseline.

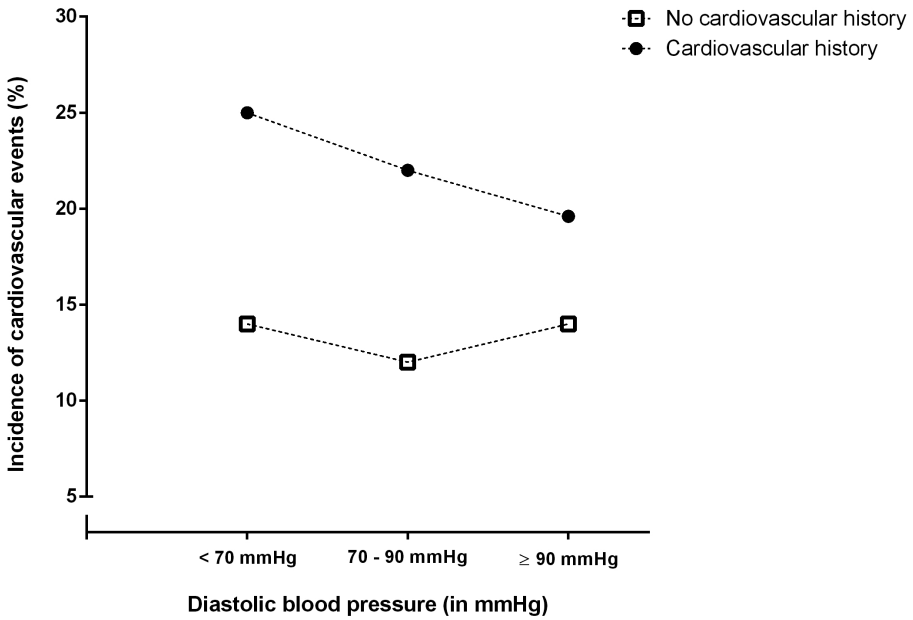

Figure 1. Incidence of cardiovascular events in different diastolic blood pressure groups, stratified by cardiovascular history. Data represent point estimates of incidence (in percentage) of cardiovascular events.

Furthermore, we performed additional analyses in which we explored the association between systolic blood pressure with cardiovascular events. Participants with a higher systolic blood pressure had an increased risk of cardiovascular events, independent of sociodemographic and cardiovascular factors (change in log-hazard per 10 mmHg systolic blood pressure (95% CI)=1.04 (1.00;1.08) (supplemental table 1). When stratifying for cardiovascular history, the same trend as for diastolic blood pressure was seen, showing that higher systolic blood pressure was associated with an increased risk of cardiovascular events in participants with and without a previous history of cardiovascular disease (p for interaction=0.490) (supplemental table 2).

Discussion

In this prospective cohort study including 5,804 participants with a mean age of 75 years, we show that history of cardiovascular disease modified the relation between diastolic blood pressure and cardiovascular event risk: in participants without a history of cardiovascular disease, there was no association between diastolic blood pressure and cardiovascular

events, whereas participants with a history of cardiovascular disease showed a decreased risk of cardiovascular events with higher diastolic blood pressure.

Previous studies that showed an association between high diastolic blood pressure and decreased cardiovascular risk have predominantly been performed in frail older populations in which all participants suffered from cardiovascular disease.(1-3, 5, 7, 9-11) Only few have studied whether biological age might determine the association between diastolic blood pressure and worse outcomes.(6, 8, 17) Recently, a population-based cohort study including 4,057 people investigated if the association of late-life blood pressure with brain atrophy and brain functioning differed in people with and without chronic hypertension. They found that in participants with a history of midlife hypertension, lower late-life diastolic blood pressure was associated with increased brain atrophy and worse cognitive function.(17) Furthermore, two prospective studies including 2340 and 1466 participants showed that the association of blood pressure with mortality risk was higher in biologically older people, defined as those with decreased psychical and cognitive function.(6, 8) To our knowledge, we are the first to investigate whether cardiovascular history as a proxy of vascular impairment could modulate the association between low diastolic blood pressure and cardiovascular risk in older people.

There are several pathophysiological mechanisms that can explain our finding that history of cardiovascular disease modified the relation between diastolic blood pressure and cardiovascular event risk. First, low diastolic blood pressure might be a reflection of deteriorating health status, leading to increased cardiovascular events and mortality.(18) Previous studies have demonstrated that a decreasing trend in blood pressure independently predicts cardiovascular events and mortality in older people.(4, 7) This is in line with results from a community based study of 835 subjects of 85 years and older, showing that the relation of low blood pressure with mortality disappeared after adjusting for indicators of poor health.(1) Indeed, our results demonstrate that risk factors for cardiovascular events and mortality such as older age, history of myocardial infarction and smoking status were more present in participants with lower diastolic blood pressure. However, adjusting our results for these indicators did not essentially change our findings. A second explanation is that both low diastolic blood pressure and cardiovascular events share a common cause, which most likely would be aging of the arterial system including atherosclerosis. Previous studies showed that progression of atherosclerosis is accompanied by a decrease in diastolic blood pressure.(19, 20) Instead of being causally related, low diastolic blood pressure might therefore be a reflection of widespread atherosclerosis, which itself associates

with increased risk of cardiovascular disease and mortality.(21) However, this might not be true for the population under study since pulse pressure, which reflects arterial aging and atherosclerosis best, was lower instead of higher in participants with low diastolic blood pressure.(22) Finally, there might be a causal relation between low diastolic blood pressure and cardiovascular events and mortality rates. In this scenario, low diastolic blood pressure, which is an important contributor of the perfusion pressure of an organ, might predispose to vascular hypoperfusion of vital organs, particularly in people who already suffer from increased arterial stiffness.(23, 24) It has been shown that diastolic blood pressure is more important than systolic blood pressure with respect to adequate perfusion of an organ. (5) Therefore, low perfusion pressure could also explain why we did not find a consistent association between systolic blood pressure with cardiovascular events. Furthermore, it suggests that excessive reduction of diastolic blood pressure in these people should be avoided, and has an experimental underpinning.(5)

Major strengths of the current study include the large sample size and the detailed monitoring during a mean follow-up period of 3.2 years. Furthermore, because of the inclusion criteria of PROSPER, all participants had cardiovascular disease or were at risk thereof, which provided us the unique opportunity to investigate the hypothesis whether people with a vascular impairment would suffer more from a lower diastolic blood pressure. However, this study also has several weaknesses. First, the study population consisted of older participants at risk of cardiovascular diseases with relatively preserved cognitive function (MMSE≥24 points), which might limit the extrapolation of our findings to the elderly population in general. A second limitation is that the design of the study is observational. Future trials investigating whether people with a cardiovascular history benefit from discontinuation of blood pressure lowering therapy are needed to provide definite answers.(25)

In conclusion, our study demonstrates that the association of diastolic blood pressure with cardiovascular events in older people varies upon previous cardiovascular history, showing that in participants with cardiovascular history higher diastolic blood pressure associates with a decreased risk of cardiovascular events. Randomized controlled trials are needed to investigate whether increasing diastolic blood pressure levels by discontinuation of blood pressure lowering therapy will lead to less recurrent events in people with a cardiovascular history. Eventually, this may result in moving from a 'one size fits all' concept of achieving normal blood pressure to an individualized approach and specific guidelines in blood pressure management for older people.

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