

# Blood pressure and risk of developing type 2 diabetes mellitus: The Women's Health Study

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## KEYWORDS

Blood pressure;  
Hypertension;  
Diabetes mellitus;  
Metabolic syndrome;  
Obesity

**Aims** To examine the relationship of blood pressure (BP) and BP progression with the subsequent development of type 2 diabetes.

**Methods and results** We performed a prospective cohort study among 38 172 women free of diabetes and cardiovascular disease at baseline. Women were classified into four categories according to self-reported baseline BP (<120/75 mmHg, 120–129/75–84 mmHg, 130–139/85–89 mmHg and hypertension) and were further classified according to progression to a higher BP category during the first 48 months of follow-up. The main outcome measure was time to incident type 2 diabetes. During 10.2 years of follow-up, 1672 women developed type 2 diabetes. The multivariable adjusted hazard ratios (HRs) (95% confidence interval) for incident diabetes across BP categories were 0.66 (0.55–0.80), 1.0 (referent), 1.45 (1.23–1.71), and 2.03 (1.77–2.32) (*P*-value for trend <0.0001). Stratification by body mass index revealed similar results. Adjusted HRs (95% confidence intervals) for incident diabetes after 48 months among women who had no BP progression, women with BP progression but remaining normotensive, and women who developed hypertension during the first 48 months were 1.0, 1.26 (0.97–1.64), and 1.64 (1.33–2.02) compared with 2.39 (1.95–2.93) in women with baseline hypertension (*P*-value for trend <0.0001).

**Conclusion** Baseline BP and BP progression are strong and independent predictors of incident type 2 diabetes among initially healthy women.

## Introduction

The incidence of type 2 diabetes is increasing rapidly,<sup>1</sup> and a recent study suggested that elevated blood glucose levels are a leading cause of cardiovascular morbidity and mortality worldwide.<sup>2</sup> Similar findings have been reported for blood pressure (BP) and hypertension.<sup>3</sup> As part of the metabolic syndrome, hypertension and diabetes are closely associated with obesity and frequently occur together in an individual.<sup>4–6</sup>

Despite this close relationship between hypertension and type 2 diabetes, little information exists on the relationship of BP levels with the subsequent development of type 2 diabetes. The metabolic syndrome itself is a major risk factor for incident type 2 diabetes.<sup>7,8</sup> One study of men found that the risk of developing type 2 diabetes increases with increasing number of metabolic abnormalities, but that BP *per se* was not independently associated with new-onset diabetes.<sup>7</sup> Data in women are more limited.<sup>8</sup>

Finding an independent association between BP or BP progression and new-onset diabetes may be important, as it could imply close surveillance of blood glucose levels in individuals with increasing BP levels. We therefore evaluated the relationship of BP and BP progression with incident type 2 diabetes in a large cohort of initially healthy women.

## Methods

### Participants

All study subjects were participants of the Women's Health Study, a completed randomized trial evaluating the risks and benefits of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. Details of the study design have been described previously.<sup>9–11</sup>

Briefly, beginning in 1993, 39 876 female health professionals in the USA who were 45 years or older and free of cardiovascular disease, cancer, or other major illnesses were randomized to receive 100 mg aspirin every other day, 600 IU vitamin E every other day, both agents, or placebo. The trial initially had a beta-carotene arm that was terminated early.<sup>12</sup> Information on baseline variables was collected using mailed questionnaires. Follow-up

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questionnaires asking participants about study outcomes and other information were sent every 6 months during the first year and every 12 months thereafter.

Follow-up information from randomization through the end of the trial, 31 March 2004, was used for the present analysis. As of this date, follow-up was 97.2% complete for morbidity and 99.4% for mortality. For the present analysis, the study population consisted of 38 172 women without a history of diabetes at randomization and with complete information about BP, personal history of hypertension, and antihypertensive therapy at baseline.

## Study variables

BP at randomization was self-reported by the female health professionals, a group where self-report of BP has proved highly accurate.<sup>13,14</sup> Women were classified into four pre-defined BP categories: below 120 mmHg for systolic and 75 mmHg for diastolic BP (subsequently called optimal BP); 120–129 mmHg for systolic or 75–84 mmHg for diastolic BP (subsequently called normal BP); 130–139 mmHg for systolic or 85–89 mmHg for diastolic BP (subsequently called high normal BP); and established hypertension. Established hypertension was defined as self-reported history of hypertension, self-report of taking antihypertensive treatment, or self-reported BP of at least 140 mmHg for systolic or 90 mmHg for diastolic BP. Women with discordant systolic and diastolic BP categories were classified into the higher category.

Covariates of interest were collected at baseline and included age, smoking, ethnicity, history of hypercholesterolaemia [self-reported cholesterol of at least 6.22 mmol/L (240 mg/dL)], body mass index (BMI) (weight in kilograms divided by the square of height in metres), family history of diabetes, exercise, alcohol consumption, and highest education level achieved. We used categorized BMI in all analyses: normal (<25 kg/m<sup>2</sup>), overweight (≥25 and <30 kg/m<sup>2</sup>), and obese (≥30 kg/m<sup>2</sup>).

## Ascertainment of incident type 2 diabetes

Details regarding the ascertainment of incident type 2 diabetes in the Women's Health Study have been reported previously.<sup>15</sup> Briefly, participants were asked annually whether and when they had been diagnosed with diabetes since randomization. Screening rates for diabetes were high, with at least 85–90% of all participants reporting a recent blood glucose screening on their annual questionnaire. Using the diagnostic criteria recommended by the American Diabetes Association,<sup>16</sup> all self-reported cases of type 2 diabetes required confirmation by a supplemental questionnaire, which was validated by medical record review. Only confirmed cases of incident type 2 diabetes are included in this report. We also conducted validation studies by using three complementary approaches, confirming the validity of self-reported incident type 2 diabetes.<sup>15</sup>

## Statistical analysis

The primary outcome variable was incident type 2 diabetes during follow-up. We calculated age-adjusted incidence rates per 1000 person-years according to BP category. Subsequently, Cox proportional-hazards models were constructed to calculate the hazard ratio (HR) and 95% confidence intervals for the comparison of event rates in the four BP categories. Women with normal BP at baseline were chosen as the reference group. This allowed direct contrast between the optimal, normal, and high normal BP groups.

In a first step, the crude models were adjusted for age. Thereafter, we fitted a multivariable model adjusting for age, ethnicity, smoking, BMI category, history of hypercholesterolaemia, exercise, alcohol consumption, highest education level, family history of diabetes, and randomized treatment assignments (aspirin, vitamin E, and beta-carotene).

To address the possibility that some women had undiagnosed type 2 diabetes at randomization, we repeated all analyses after the

exclusion of 242 women who either developed type 2 diabetes or died during the first 2 years of follow-up.

To further explore the independent relationship between BP and incident diabetes, we performed another series of Cox proportional-hazards models among women with no more than one out of the following three metabolic syndrome components, as defined by the Adult Treatment Panel III: BMI >26.7 kg/m<sup>2</sup>, high density lipoprotein (HDL) cholesterol levels <1.29 mmol/L (50 mg/dL) or triglycerides ≥1.69 mmol/L (150 mg/dL).<sup>5,17</sup> BMI rather than waist circumference was used as an indicator of central obesity, because waist circumference was unavailable at baseline.<sup>17</sup> We considered for this analysis those 26 318 women who provided a blood sample and reported BMI at baseline.

We then stratified the total sample into three groups of BMI as described earlier (normal, overweight, and obese). The same analyses described earlier were performed separately for each stratum of BMI. To further minimize the effect of obesity, we included the level of BMI in the multivariable models.

To analyse whether the effect of BP in predicting diabetes differs among the three categories of BMI, we included BP category by BMI category interaction terms into the non-stratified Cox model. The significance of the interaction term was assessed by comparing the likelihood ratio  $\chi^2$  statistic with and without the interaction terms in the model.

To assess the effect of BP progression on incident diabetes, we categorized women into the following categories: women without hypertension at baseline and not progressing to a higher BP category during the first 48 months of follow-up; women without hypertension at baseline and progressing by at least one BP category, but remaining normotensive (systolic BP <140 mmHg and diastolic BP <90 mmHg) during the first 48 months of follow-up; women without hypertension at baseline who developed hypertension during the first 48 months of follow-up; and women with hypertension at baseline. Cox proportional hazards models were constructed to compare the crude and adjusted HRs for incident type 2 diabetes among these newly created categories. Women who developed type 2 diabetes or died during the first 48 months of follow-up were excluded from these analyses. In addition to the variables described earlier, the multivariable model was also adjusted for baseline BP category.

Categorical variables were entered in the models using binary indicator variables. Tests for trend were performed using integer scores across categories. The proportional hazards assumption was examined by including a logarithm of time by BP category interaction term in the models.<sup>18</sup> No violation of this assumption was detected. All analyses were carried out using SAS version 9 (SAS Institute Inc., Cary, NC, USA). A two-tailed  $P < 0.05$  was considered to indicate statistical significance.

## Results

*Table 1* shows the baseline characteristics across BP categories. At randomization, 25.5% of the study participants had hypertension, 12.7% had high normal, 29.2% had normal, and 32.7% had optimal BP. Higher BP levels were associated with older age, higher BMI, and a higher prevalence of hypercholesterolaemia and parental history of diabetes. Current smoking, moderate alcohol consumption, exercise, and a higher education level were more prevalent in women with lower BP levels.

## Blood pressure categories and incident type 2 diabetes

During median follow-up of 10.2 years (inter-quartile range 9.6–10.6 years), 1672 out of 38 172 women developed type 2 diabetes. After 10 years of follow-up, 1.4, 2.9, 5.7, and

**Table 1** Baseline characteristics according to blood pressure category

Characteristics	Baseline blood pressure level, systolic/diastolic (mmHg)			
	<120/75 (n = 12462)	120–129/75–84 (n = 11147)	130–139/85–89 (n=4835)	Hypertension <sup>a</sup> (n = 9728)
Age (years)	53 ± 6	54 ± 7	56 ± 7	57 ± 8
Body mass index category (%)				
Normal	8468 (69)	5848 (53)	1830 (39)	3228 (34)
Overweight	2968 (24)	3540 (32)	1705 (36)	3339 (35)
Obese	800 (7)	1558 (14)	1184 (25)	2933 (31)
History of hypercholesterolaemia (%)	2681 (21.5)	2824 (25.3)	1481 (30.7)	4119 (42.4)
Family history of diabetes (%)	2754 (22.1)	2737 (24.6)	1286 (26.6)	2699 (27.7)
Smoking (%)				
Current	1710 (13.7)	1444 (13.0)	661 (13.7)	1182 (12.2)
Former	4483 (36.0)	3942 (35.4)	1727 (35.8)	3501 (36.0)
Never	6259 (50.3)	5756 (51.7)	2440 (50.5)	5033 (51.8)
Hormone replacement therapy (%)				
Never or former	7312 (58.8)	6533 (58.7)	2894 (59.9)	5566 (57.3)
Current	5122 (41.2)	4598 (41.3)	1934 (40.1)	4142 (42.7)
Exercise (times/week)				
Rarely/never	4060 (32.6)	4160 (37.3)	1981 (41.0)	4305 (44.3)
<1	2478 (19.9)	2279 (20.5)	986 (20.4)	1850 (19.0)
1–3	4228 (34.0)	3565 (32.0)	1481 (30.7)	2705 (27.8)
>3	1688 (13.6)	1141 (10.2)	383 (7.9)	864 (8.9)
Alcohol consumption				
Rarely/never	5187 (41.6)	4766 (42.8)	2179 (45.1)	4810 (49.5)
1–3 drinks/month	1731 (13.9)	1448 (13.0)	611 (12.6)	1245 (12.8)
1–6 drinks/week	4310 (34.6)	3763 (33.8)	1504 (31.1)	2661 (27.4)
≥1 drink/day	1231 (9.9)	1166 (10.5)	540 (11.2)	1010 (10.4)
Highest education level				
Less than a bachelor's degree	6533 (53.2)	6013 (54.8)	2865 (60.2)	6049 (63.3)
Bachelor's degree	3114 (25.4)	2599 (23.7)	1039 (21.8)	1940 (20.3)
Master's degree or doctorate	2623 (21.4)	2354 (21.5)	854 (18.0)	1567 (16.4)

Data are mean ± standard deviation or counts (percentages).

<sup>a</sup>Hypertension was defined as previous diagnosis of hypertension, systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or receiving blood pressure lowering therapy.

9.4% of women across the four baseline BP categories developed type 2 diabetes. The overall incidence rate for type 2 diabetes was 4.5 events per 1000 person-years. Age-adjusted incidence rates according to BP category are shown in *Table 2*. Women with baseline hypertension had a seven-fold increased risk of developing diabetes compared with women with optimal BP.

After multivariable adjustment, these risk differences were attenuated but remained statistically significant. As shown in *Table 2*, the adjusted HRs for incident type 2 diabetes across baseline BP categories were 0.66, 1.0 (reference group), 1.45, and 2.03 (*P*-value for trend <0.0001). Thus, there was still a three-fold increased risk among women with hypertension compared with women with optimal BP.

As shown in *Table 3*, the results were very similar when women who had an event during the first 2 years of follow-up were excluded. There was again a three-fold increased risk of developing type 2 diabetes among women with hypertension compared with those with optimal BP.

In our cohort, 17 313 women who provided a baseline blood sample had not more than one of the three metabolic syndrome components considered: BMI >26.7 kg/m<sup>2</sup>, HDL cholesterol <1.29 mmol/L (50 mg/dL), or triglycerides ≥1.69 mmol/L (150 mg/dL). During follow-up, 222 incident

events occurred. After multivariable adjustment, we found the following HRs (95% confidence intervals) across the four BP categories: 0.73 (0.49–1.10), 1 (reference group), 1.49 (0.96–2.34), 1.96 (1.37–2.81) (*P*-value for trend <0.0001).

### Incident type 2 diabetes stratified by body mass index

Among 37 401 women with available BMI at baseline, 51.8% had a normal BMI, 30.9% were overweight, and 17.3% were obese (*Table 4*). Although obese women had the highest absolute event rates across all BP categories, BP was a strong predictor of incident type 2 diabetes within each category of BMI. Age-adjusted incidence rates and Cox proportional hazards models demonstrated a similar rise in risk across BP categories among women with normal BMI compared with overweight and obese women (*Figure 1*).

After multivariable adjustment, there was a three-fold increase in risk from the lowest to the highest category among women with normal BMI compared with a 2.5-fold increase among women with overweight or obesity. Adding BP category by BMI category interaction terms to the non-stratified Cox model had no significant effect

**Table 2** Risk of incident type 2 diabetes according to blood pressure category

<i>n</i> = 38172	Baseline blood pressure level, systolic/diastolic (mmHg)				
	<120/75	120–129/75–84	130–139/85–89	Hypertension	
	Absolute risk of developing diabetes				
Number of events/person-years	180/124 425	329/110 416	270/47 133	893/92 775	
Age-adjusted incidence rate per 1000 person-years	1.47	2.97	5.79	10.00	
	Hazard ratio (95% confidence interval)				<i>P</i> <sub>trend</sub>
Crude	0.49 (0.40–0.58)	1.0 <sup>a</sup>	1.93 (1.64–2.27)	3.25 (2.87–3.69)	<0.0001
Age-adjusted	0.48 (0.40–0.57)	1.0	1.98 (1.68–2.32)	3.39 (2.99–3.86)	<0.0001
Multivariable-adjusted <sup>b</sup>	0.66 (0.55–0.80)	1.0	1.45 (1.23–1.71)	2.03 (1.77–2.32)	<0.0001

<sup>a</sup>Reference category.<sup>b</sup>Adjusted for age, ethnicity, smoking, history of hypercholesterolaemia, body mass index category, exercise, alcohol consumption, highest education level, family history of diabetes, and randomized treatment assignments (aspirin, vitamin E, and beta-carotene); due to missing covariates, the multivariable (crude) analysis was based on 1566 (1672) incident events in 36 432 (38 172) women.**Table 3** Risk of incident type 2 diabetes according to blood pressure category after exclusion of incident diabetes cases during the first 2 years of follow-up

<i>n</i> = 37 930	Baseline blood pressure level, systolic/diastolic (mmHg)				
	<120/75	120–129/75–84	130–139/85–89	Hypertension	
	Absolute risk of developing diabetes				
Number of events/person-years	166/99 527	300/88 157	252/37 490	783/73 420	
Age-adjusted incidence rate per 1000 person-years	1.69	3.40	6.78	11.10	
	Hazard ratio (95% confidence interval)				<i>P</i> <sub>trend</sub>
Crude	0.49 (0.41–0.59)	1.0 <sup>a</sup>	1.98 (1.67–2.34)	3.14 (2.75–3.59)	<0.0001
Age-adjusted	0.48 (0.40–0.58)	1.0	2.03 (1.72–2.40)	3.29 (2.87–3.76)	<0.0001
Multivariable-adjusted <sup>b</sup>	0.66 (0.54–0.81)	1.0	1.49 (1.25–1.77)	1.96 (1.70–2.26)	<0.0001

<sup>a</sup>Reference category.<sup>b</sup>Adjusted for age, ethnicity, smoking, history of hypercholesterolaemia, body mass index category, exercise, alcohol consumption, highest education level, family history of diabetes, and randomized treatment assignments (aspirin, vitamin E and beta-carotene); due to missing covariates, the multivariable (crude) analysis was based on 1406 (1501) incident events in 36 204 (37 930) women.

(*P* = 0.7), confirming a similar relative effect across BP categories within all BMI categories.

### Blood pressure progression and incident type 2 diabetes

After exclusion of women with incident diabetes or death during the first 48 months of follow-up, 34 281 women had a self-reported BP measurement available at 48 months. Among these women, 1101 developed type 2 diabetes after the 48-months follow-up questionnaire.

There was a highly significant trend of increasing type 2 diabetes across the categories of BP change (Table 5). After multivariable adjustment, women who had an increase in BP but remaining normotensive at 48 months had an HR (95% confidence intervals) of 1.26 (0.97–1.64) compared with women who had stable or decreasing BP (*P* = 0.08). Women progressing to hypertension had a 64% increased risk of incident diabetes and this risk more than doubled in those with baseline hypertension (Table 5 and Figure 2). The HR of women with baseline hypertension compared with those progressing to hypertension was 1.46 (95% confidence interval 1.18–1.80).

### Discussion

In the present study of initially healthy, middle-aged women, BP and BP progression were strong predictors of incident type 2 diabetes. This effect was independent of BMI and other components of the metabolic syndrome. Compared with an overall rate of 4.5 events per 1000 person-years, the age-adjusted incidence rates in the optimal BP category was 1.47 events per 1000 person-years, showing that women with optimal BP had a very low risk of developing type 2 diabetes during follow-up.

On the other hand, women with high normal BP had a much higher risk compared with women with normal BP, and the risk among those with established hypertension was substantial. After 10 years of follow-up, almost 10% of these women had type 2 diabetes (10.0 events per 1000 person-years). Interestingly, women with BP progression during the first 48 months of follow-up had a higher risk of developing type 2 diabetes compared with women without BP progression. The risk among women progressing to hypertension approached the risk of those with established hypertension.

These associations were attenuated but remained highly significant after adjustment for other variables and persisted after stratification by BMI. Although the absolute risk of



**Table 4** Risk of incident type 2 diabetes according to blood pressure category, stratified by baseline body mass index

	Baseline blood pressure level, systolic/diastolic (mmHg)				
	<120/75	120–129/75–84	130–139/85–89	Hypertension	
Absolute risk of developing diabetes					
Number of events/person-years					
Normal ( <i>n</i> = 19 374) <sup>a</sup>	49/84 831	56/58 439	33/18 169	80/31 680	
Overweight ( <i>n</i> = 11 552) <sup>b</sup>	69/29 562	118/35 047	84/16 658	238/32 284	
Obese ( <i>n</i> = 6475) <sup>c</sup>	55/7780	145/14 963	148/11 184	547/26 666	
Age-adjusted incidence rate per 1000 person-years					
Normal ( <i>n</i> = 19 374) <sup>a</sup>	0.63	0.96	1.79	2.30	
Overweight ( <i>n</i> = 11 552) <sup>b</sup>	2.33	3.38	4.94	7.48	
Obese ( <i>n</i> = 6475) <sup>c</sup>	7.58	9.85	13.27	20.53	
Hazard ratio (95% confidence interval)					<i>P</i> <sub>trend</sub>
Crude					
Normal ( <i>n</i> = 19 374) <sup>a</sup>	0.60 (0.41–0.88)	1.0 <sup>d</sup>	1.90 (1.24–2.92)	2.65 (1.88–3.73)	<0.0001
Overweight ( <i>n</i> = 11 552) <sup>b</sup>	0.69 (0.51–0.93)	1.0	1.50 (1.14–1.99)	2.21 (1.77–2.75)	<0.0001
Obese ( <i>n</i> = 6475) <sup>c</sup>	0.73 (0.53–0.99)	1.0	1.37 (1.09–1.72)	2.13 (1.78–2.56)	<0.0001
Age-adjusted					
Normal ( <i>n</i> = 19 374) <sup>a</sup>	0.62 (0.42–0.91)	1.0	1.81 (1.18–2.79)	2.46 (1.73–3.49)	<0.0001
Overweight ( <i>n</i> = 11 552) <sup>b</sup>	0.69 (0.51–0.93)	1.0	1.51 (1.14–1.99)	2.21 (1.77–2.77)	<0.0001
Obese ( <i>n</i> = 6475) <sup>c</sup>	0.73 (0.53–0.99)	1.0	1.37 (1.09–1.72)	2.13 (1.77–2.56)	<0.0001
Multivariable-adjusted <sup>e</sup>					
Normal ( <i>n</i> = 18 904) <sup>a</sup>	0.72 (0.49–1.07)	1.0	1.80 (1.16–2.80)	1.92 (1.33–2.77)	<0.0001
Overweight ( <i>n</i> = 11 242) <sup>b</sup>	0.69 (0.51–0.94)	1.0	1.36 (1.03–1.81)	1.74 (1.38–2.19)	<0.0001
Obese ( <i>n</i> = 6286) <sup>c</sup>	0.74 (0.54–1.02)	1.0	1.30 (1.03–1.64)	1.89 (1.56–2.28)	<0.0001

<sup>a</sup>Defined as body mass index <25 kg/m<sup>2</sup>.<sup>b</sup>Defined as body mass index ≥25 kg/m<sup>2</sup> and body mass index <30 kg/m<sup>2</sup>.<sup>c</sup>Defined as body mass index ≥30 kg/m<sup>2</sup>.<sup>d</sup>Reference category.<sup>e</sup>Adjusted for age, ethnicity, smoking, history of hypercholesterolaemia, body mass index, exercise, alcohol consumption, highest education level, family history of diabetes, and randomized treatment assignments (aspirin, vitamin E, and beta-carotene); due to missing covariates, the multivariable (crude) analysis was based on 209 (218) incident events in 18 904 (19 374) women with normal weight; 487 (509) incident events in 11 242 (11 552) overweight women; and 870 (895) incident events in 6286 (6475) obese women.

developing type 2 diabetes was highest among overweight and obese women, we nonetheless observed a strong association between BP and incident type 2 diabetes in women with normal weight. Among women with no more than one out of three components of the metabolic syndrome excluding glucose or BP, we found the same strong trend across BP categories and very similar HR estimates compared with the entire study population. Taken together, our findings suggest that obesity or the metabolic syndrome do not explain the entire association between BP and incident diabetes.

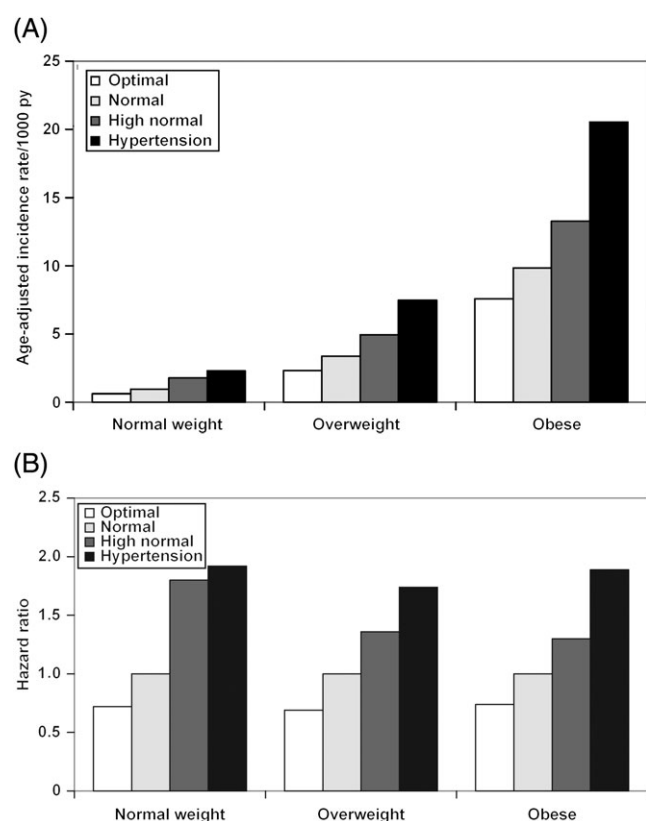
Few studies analysed the precise relationship between BP and incident type 2 diabetes.<sup>19,20</sup> Gress *et al.*<sup>19</sup> found that individuals with hypertension had a relative risk of 2.34 (95% confidence interval 2.16–2.73) of developing type 2 diabetes compared with individuals without hypertension. However, no multivariable adjustment of this association was performed in their study. Our study further expands these findings by demonstrating that the increased risk of new-onset type 2 diabetes is not confined to subjects with hypertension, and women with BP progression have an increased risk of incident type 2 diabetes.

One study in men did not find an independent relationship between BP and new-onset diabetes.<sup>7</sup> These differential findings may be explained by a lack of power due to the low number of events in this study (139 new cases of type 2 diabetes). Whether gender modifies this relationship deserves further study.

Endothelial dysfunction could be one of the common pathophysiological pathways explaining the strong association between BP and incident type 2 diabetes. Several studies have shown that markers of endothelial dysfunction are associated with new-onset diabetes,<sup>21,22</sup> and endothelial dysfunction is closely related to BP and hypertension.<sup>23</sup> Markers of inflammation such as C-reactive protein have been consistently related to incident type 2 diabetes<sup>24–26</sup> and to increasing BP levels,<sup>27,28</sup> suggesting that inflammation might be another explanatory factor for the association between BP, the metabolic syndrome, and incident type 2 diabetes.<sup>17</sup> Finally, insulin resistance<sup>29</sup> and low birth weight<sup>30,31</sup> are other potential links between BP levels and the incidence of type 2 diabetes.

### Strengths and limitations

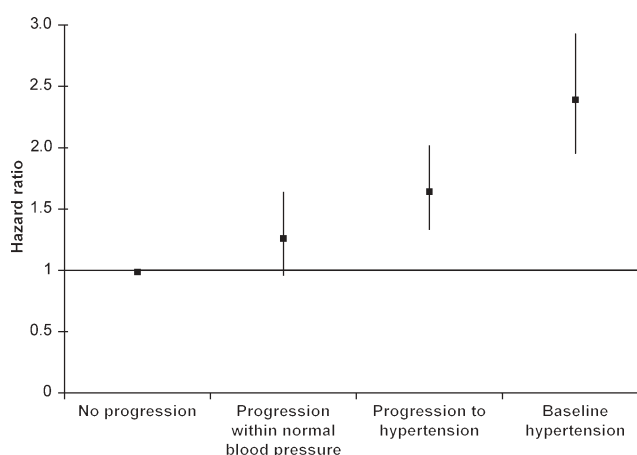
Strengths of the present study are the large sample size, the prospective design, and the complete long-term follow-up with a large number of incident events. A possible limitation is the use of self-reported BP. However, the validity of this approach has been examined in the comparable Nurses' Health Study, where 99% of the women who reported high BP levels had their diagnosis confirmed based on medical record review.<sup>13</sup> Furthermore, the prognostic value of self-reported BP in cohort studies involving US health professionals was similar compared with directly measured BP



**Figure 1** Age-adjusted incidence rates (A) and multivariable adjusted hazard ratios (B) of incident type 2 diabetes according to blood pressure category, stratified by baseline body mass index. Blood pressure categories are <120/75 mmHg (optimal), 120–129/75–84 mmHg (normal), 130–139/85–89 mmHg (high normal), and hypertension. Normal weight was defined as body mass index <25 kg/m<sup>2</sup>, overweight as body mass index ≥25 kg/m<sup>2</sup> and <30 kg/m<sup>2</sup>, and obese as body mass index ≥30 kg/m<sup>2</sup>. The hazard ratio for incident diabetes was adjusted for age, ethnicity, smoking, history of hypercholesterolaemia, body mass index, exercise, alcohol consumption, highest education level, family history of diabetes, and randomized treatment assignments. The normal blood pressure category was chosen as the referent. py, person-years.

values in participants of other cohort studies.<sup>14</sup> Finally, self-reported BP, total cholesterol, and BMI have previously been shown in the Women's Health Study to be strong predictor of cardiovascular risk, with relative risks consistent in magnitude with those observed in other major studies.<sup>32–35</sup>

We used BMI rather than waist circumference as an indicator of central obesity. However, previous studies showed that BMI and waist circumference have a similar ability to predict type 2 diabetes.<sup>36</sup> The present study included predominantly Caucasian women, and our findings may not be generalizable to other populations. Finally, residual confounding is a concern in all epidemiological studies. Given the strength of the association and the consistent dose-response relationship, it is unlikely that more extensive adjustments would have completely eliminated the



**Figure 2** Hazard ratios for a first diagnosis of type 2 diabetes in women with no progression of blood pressure during the first 48 months of follow-up (referent), women with blood pressure progression but without developing hypertension, women with progression to hypertension, and women with hypertension at baseline (identical categories as in Table 5). Squares indicate hazard ratio adjusted for age at 48 months, ethnicity, baseline blood pressure category, smoking, history of hypercholesterolaemia, body mass index category, exercise, alcohol consumption, highest education level, family history of diabetes, and randomized treatment assignments. Lines represent 95% confidence intervals.

**Table 5** Risk of incident type 2 diabetes according to blood pressure evolution during the first 48 months of follow-up

<i>n</i> = 34 281	Hazard ratio (95% confidence interval)				<i>P</i> <sub>trend</sub>
	No progression <sup>a</sup> ( <i>n</i> = 12 970)	Progression within normal BP <sup>a</sup> ( <i>n</i> = 6396)	Progression to hypertension <sup>a</sup> ( <i>n</i> = 5577)	Baseline hypertension <sup>a</sup> ( <i>n</i> = 9338)	
Events/person-years	185/78 202	103/38 556	223/32 883	590/54 110	
Crude	1.0 <sup>b</sup>	1.53 (1.19–1.97)	2.09 (1.70–2.57)	4.17 (3.45–5.05)	<0.0001
Age-adjusted <sup>c</sup>	1.0	1.57 (1.22–2.02)	2.14 (1.74–2.63)	4.45 (3.67–5.39)	<0.0001
Multivariable-adjusted <sup>d</sup>	1.0	1.26 (0.97–1.64)	1.64 (1.33–2.02)	2.39 (1.95–2.93)	<0.0001

BP, blood pressure.

<sup>a</sup>No progression was defined as a BP < 140/90 mmHg at baseline and being within the same or a lower BP category during the first 48 months of follow-up; progression within normal BP was defined as BP < 140/90 mmHg at baseline and progressing by at least one BP category during the first 48 months of follow-up, but without developing hypertension; progression to hypertension was defined as BP < 140/90 mmHg at baseline and progression to hypertension during the first 48 months of follow-up; baseline hypertension was defined as previous diagnosis of hypertension, systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg or receiving BP lowering therapy at baseline.

<sup>b</sup>Reference category.

<sup>c</sup>Age at 48 months of follow-up was used for adjustment.

<sup>d</sup>Adjusted for age at 48 months, ethnicity, baseline BP category, smoking, history of hypercholesterolaemia, body mass index category, exercise, alcohol consumption, highest education level, family history of diabetes, and randomized treatment assignments (aspirin, vitamin E, and beta-carotene); due to missing covariates, the multivariable analysis was based on 1027 (1101) incident events among 32 757 (34 281) women.

significant relationship between BP and incident type 2 diabetes.

## Conclusion

Our study provides strong evidence that baseline BP and BP progression are associated with an increased risk of incident type 2 diabetes. Clinicians should be aware of these relationships to optimize the management of patients at increased risk for cardiovascular disease.

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