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## IMPACT OF HIGH-NORMAL BLOOD PRESSURE ON THE RISK OF CARDIOVASCULAR DISEASE

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### ABSTRACT

**Background** Information is limited regarding the risk of cardiovascular disease in persons with high-normal blood pressure (systolic pressure of 130 to 139 mm Hg, diastolic pressure of 85 to 89 mm Hg, or both).

**Methods** We investigated the association between blood-pressure category at base line and the incidence of cardiovascular disease on follow-up among 6859 participants in the Framingham Heart Study who were initially free of hypertension and cardiovascular disease.

**Results** A stepwise increase in cardiovascular event rates was noted in persons with higher baseline blood-pressure categories. The 10-year cumulative incidence of cardiovascular disease in subjects 35 to 64 years of age who had high-normal blood pressure was 4 percent (95 percent confidence interval, 2 to 5 percent) for women and 8 percent (95 percent confidence interval, 6 to 10 percent) for men; in older subjects (those 65 to 90 years old), the incidence was 18 percent (95 percent confidence interval, 12 to 23 percent) for women and 25 percent (95 percent confidence interval, 17 to 34 percent) for men. As compared with optimal blood pressure, high-normal blood pressure was associated with a risk-factor-adjusted hazard ratio for cardiovascular disease of 2.5 (95 percent confidence interval, 1.6 to 4.1) in women and 1.6 (95 percent confidence interval, 1.1 to 2.2) in men.

**Conclusions** High-normal blood pressure is associated with an increased risk of cardiovascular disease. Our findings emphasize the need to determine whether lowering high-normal blood pressure can reduce the risk of cardiovascular disease. (N Engl J Med 2001;345:1291-7.)

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SEVERAL epidemiologic studies<sup>1-7</sup> have demonstrated that systolic and diastolic blood pressures have a “strong, continuous, graded and etiologically significant” positive association with cardiovascular-disease outcomes.<sup>1</sup> These relations are consistent in both men and women, in young, middle-aged, and older subjects, among different racial and ethnic groups,<sup>1-5</sup> and within and between countries.<sup>6,7</sup> Although there is a continuum of cardiovascular risk across levels of blood pressure,<sup>1-7</sup> the classification of adults according to blood pressure provides a framework for differentiating levels of risk associated with various blood-pressure categories and for defining treatment thresholds and therapeutic goals.

According to the classification approaches developed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)<sup>8</sup> and the World Health Organization and the International Society of Hypertension (WHO-ISH),<sup>9</sup> nonhypertensive subjects with a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg are categorized as having high-normal blood pressure. Although subjects with high-normal blood pressure are likely to have an elevated risk of cardiovascular disease (given the continuum of risk), there is a paucity of information regarding the absolute and relative risks of cardiovascular disease in these persons. Although data on fatal coronary events and strokes in persons with

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high-normal blood pressure are available,<sup>10,11</sup> information on the risk of nonfatal cardiovascular events among people in this blood-pressure category is limited. We undertook a prospective examination of the risk of cardiovascular disease in men and women with high-normal blood pressure.

## METHODS

### Study Sample

The selection criteria and study design of the Framingham Heart Study have been described previously.<sup>12,13</sup> Subjects in the original cohort who attended examinations 4 (1956 to 1958, 4541 subjects), 12 (1972 to 1974, 3261 subjects), or 18 (1984 to 1986, 1825 subjects) and participants in the offspring study who attended examination 2 (1978 to 1982, 3863 participants) were eligible for this investigation. These examinations are referred to as the "base-line" examinations. Of the 13,490 attendees, subjects were excluded if they had hypertension (defined as systolic pressure of at least 140 mm Hg, diastolic pressure of at least 90 mm Hg, or use of antihypertensive drugs<sup>8,9</sup>; 5745 subjects [43 percent] were excluded for that reason) or prevalent cardiovascular disease (478 subjects [3.5 percent]) at the base-line examinations. Another 408 subjects (3 percent) were excluded because information on the covariates used in the multivariable analyses detailed below was incomplete. After the exclusions, 6859 subjects (3892 women and 2967 men) remained eligible for this investigation. Original cohort subjects who were eligible at any examination remained eligible at the next qualifying examination if they reached that examination free of cardiovascular disease and hypertension.

### Measurement of Blood Pressure and Covariates

At the base-line examination, all participants underwent a physical examination with a medical history taking, laboratory assessment of risk factors for cardiovascular disease, and routine electrocardiography. The average of two readings of systolic and diastolic pressure, measured with a mercury-column sphygmomanometer by a physician while the subject was seated, was recorded as the base-line blood pressure. At the base-line examination, the subjects were classified into one of the three nonhypertensive blood-pressure categories on the basis of the criteria of JNC VI and WHO-ISH: optimal (systolic pressure of less than 120 mm Hg and diastolic pressure of less than 80 mm Hg), normal (systolic pressure of 120 to 129 mm Hg or diastolic pressure of 80 to 84 mm Hg), or high-normal (systolic pressure of 130 to 139 mm Hg or diastolic pressure of 85 to 89 mm Hg).<sup>8,9</sup> If the systolic and diastolic pressure readings belonged to different categories, the higher of the two readings was used to assign the blood-pressure category.<sup>8,9</sup>

### Follow-up and Outcome Events

All study participants were monitored for cardiovascular events and death. Information about cardiovascular events on follow-up was obtained with the aid of the medical history, physical examination as part of the Framingham Heart Study (every two years for the original cohort and every four years for the offspring cohort), hospitalization records, and communication with the subjects' personal physicians. All suspected events were reviewed by a panel of three experienced investigators, who evaluated all pertinent medical records. The primary outcome of interest was the time to the occurrence of any of the following major cardiovascular events during 12 years of follow-up: death due to cardiovascular disease, recognized myocardial infarction, stroke, or congestive heart failure. These end points were chosen because they have been used as major outcome events in clinical trials demonstrating that treatment of hypertension reduces the risk of cardiovascular events.<sup>14-16</sup> The criteria for these end points have been described previously.<sup>17</sup> A diagnosis of recognized myocardial infarction required the presence of at least two of the following three criteria: a history of

prolonged chest pain, electrocardiographic changes consistent with myocardial injury, and elevated cardiac-enzyme levels.

### Statistical Analysis

Cardiovascular-event rates for each blood-pressure category were calculated by dividing the number of subjects who had such events by the number of person-years of observation contributed by subjects within a blood-pressure category. The Kaplan–Meier product-limit estimator was used to determine the cumulative incidence of cardiovascular disease in men and women according to their blood-pressure category at base line. Sex-specific multivariable Cox proportional-hazards regression models,<sup>18</sup> stratified according to the time of the base-line examination (in four categories, corresponding to offspring-cohort examination 2 and original-cohort examinations 4, 12, and 18), were constructed to evaluate the association of the base-line blood-pressure category with the occurrence of a first cardiovascular event during follow-up, after adjustment for age, body-mass index, smoking status, total cholesterol level, and presence or absence of diabetes mellitus. In addition, trend models were fitted to investigate whether there was an increase in risk from one blood-pressure category to the next higher category.

To examine whether the association of a given blood-pressure level at base line with the risk of future cardiovascular disease was mediated by progression to higher levels of blood pressure over time,<sup>19</sup> the blood-pressure category and all covariates were included in Cox models as time-dependent variables during follow-up. For this purpose, the subjects were reclassified according to their blood pressure at each follow-up examination, with the inclusion of hypertension<sup>8,9</sup> as an additional category. Cox models incorporating change in blood-pressure category on follow-up were also examined. Hazard ratios for cardiovascular disease, with 95 percent confidence intervals, were calculated for subjects with normal blood pressure, high-normal blood pressure, and hypertension; persons with optimal blood pressure served as the reference group.

Additional analyses that included interaction terms (age with blood-pressure category and calendar decade of examination with blood-pressure category) were also performed. The number needed to treat (i.e., the number of patients who would need to have their blood pressure lowered) for five years to prevent one major cardiovascular event was estimated for subjects with high-normal blood pressure by taking the reciprocal of the absolute reduction in event rates (assuming a range of reductions in event rates with treatment).<sup>20,21</sup> All analyses were performed with SAS software (SAS Institute, Cary, N.C.), primarily Proc Phreg<sup>22</sup> on an UltraSparc workstation (Sun Microsystems, Palo Alto, Calif.). All reported P values are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### Characteristics of the Study Subjects

At base line, a quarter of the study subjects had high-normal blood pressure, a third had normal blood pressure, and the remainder had optimal blood pressure (Table 1). A higher proportion of women than men in our study sample had optimal blood pressure. Subjects with high-normal blood pressure were older, had a higher body-mass index, and had higher serum cholesterol levels than those with optimal blood pressure.

### Relation of Blood-Pressure Category to the Risk of Cardiovascular Disease

During follow-up (mean, 11.1 years; 75,980 person-years), 397 study subjects (138 women and 259 men) had a first cardiovascular event, including 72 deaths from cardiovascular disease (24 women and

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE STUDY SUBJECTS, ACCORDING TO BLOOD-PRESSURE CATEGORY AT BASE LINE.\*

CHARACTERISTIC†	WOMEN			MEN		
	OPTIMAL (N=1875)	NORMAL (N=1126)	HIGH NORMAL (N=891)	OPTIMAL (N=1005)	NORMAL (N=1059)	HIGH NORMAL (N=903)
Age (yr)	45±11	51±11	55±11	46±12	49±12	51±12
Blood pressure (mm Hg)						
Systolic	108±7	122±5	132±5	111±6	122±5	131±6
Diastolic	70±6	77±6	81±6	71±5	78±5	83±6
Cholesterol (mg/dl)	206±43	226±43	236±45	208±40	217±41	223±40
Current smoker (%)	44	36	31	49	42	44
Diabetes mellitus (%)	1	2	2	1	2	4
Body-mass index	23.3±3.3	24.7±4.0	25.6±4.5	25.0±3.1	26.0±3.3	26.7±3.5

\*Optimal blood pressure is a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg. Normal blood pressure is a systolic pressure of 120 to 129 mm Hg or a diastolic pressure of 80 to 84 mm Hg. High-normal blood pressure is a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used. Plus-minus values are means ±SD.

†To convert cholesterol values to millimoles per liter, multiply by 0.02586. The body-mass index is the weight in kilograms divided by the square of the height in meters.

48 men), 190 recognized myocardial infarctions (35 women and 155 men), 85 strokes (46 women and 39 men), and 50 cases of congestive heart failure (33 women and 17 men). Cardiovascular-event rates increased in a stepwise manner across the three blood-pressure categories (Table 2 and Fig. 1). Among younger subjects (35 to 64 years old) with high-normal blood pressure, the 10-year cumulative incidence of cardiovascular disease was 4 percent (95 percent confidence interval, 2 to 5 percent) among women and 8 percent (95 percent confidence interval, 6 to 10 percent) among men. The 10-year cumulative incidence of cardiovascular disease was particularly high among older subjects (65 to 90 years old) of both sexes with high-normal blood pressure (women: 18 percent; 95 percent confidence interval, 12 to 23 percent; men: 25 percent; 95 percent confidence interval, 17 to 34 percent).

As compared with optimal blood pressure, high-normal blood pressure was associated with a risk-factor-adjusted hazard ratio for cardiovascular disease of 2.5 (95 percent confidence interval, 1.6 to 4.1) among women and 1.6 (95 percent confidence interval, 1.1 to 2.2) among men (Table 3). The hazard ratios associated with high-normal blood pressure for the two sexes were not significantly different (P=0.10). Normal blood pressure was associated with a risk-factor-adjusted hazard ratio for cardiovascular disease of 1.5 (95 percent confidence interval, 0.9 to 2.5) among women and 1.3 (95 percent confidence interval, 1.0 to 1.9) among men. In the trend models, a stepwise increase in the risk of cardiovascular

disease was noted with an increase in blood-pressure category (Table 3).

In analyses in which blood pressure and other risk factors during follow-up were modeled as time-dependent variables, the association of high-normal blood pressure with an increased risk of cardiovascular disease remained significant for men but was attenuated for women (Table 3). An increase in blood-pressure category during follow-up was associated with an increased risk of cardiovascular disease (for men, the hazard ratio associated with an increase of one category was 1.2 [95 percent confidence interval, 1.1 to 1.4], P=0.006; for women, it was 1.4 [95 percent confidence interval, 1.1 to 1.6], P=0.002). The subject's age and the time of the base-line examination had no significant interaction with high-normal blood pressure (P>0.41 for all analyses).

The crude event rates per 1000 person-years in subjects with high-normal blood pressure who were 65 years of age or older were 19.5 in women and 28.1 in men. The crude event rates per 1000 person-years in subjects with high-normal blood pressure who were below the age of 65 years were 4.7 in women and 9.2 in men. On the basis of these absolute cardiovascular-event rates in subjects with high-normal blood pressure, and assuming risk reductions of 10 to 30 percent with blood-pressure lowering, we estimate that for subjects with high-normal blood pressure who are 65 or older, the numbers needed to treat for five years to prevent one cardiovascular event range from 24 to 71 in men and from 34 to 102 in women. The corresponding numbers are consider-

**TABLE 2.** CUMULATIVE INCIDENCE OF A FIRST CARDIOVASCULAR EVENT AMONG STUDY SUBJECTS, ACCORDING TO BLOOD-PRESSURE CATEGORY AT BASE LINE.\*

CATEGORY	WOMEN			MEN		
	NO. OF EVENTS/ NO. AT RISK	10-YR CUMULATIVE INCIDENCE (95% CI)		NO. OF EVENTS/ NO. AT RISK	10-YR CUMULATIVE INCIDENCE (95% CI)	
		Crude	Age-Adjusted†		Crude	Age-Adjusted†
		percent			percent	
Optimal	26/1875	1.3 (0.8–1.8)	1.9 (1.1–2.7)	55/1005	4.9 (3.5–6.2)	5.8 (4.2–7.4)
Normal	40/1126	2.9 (1.9–3.9)	2.8 (1.9–3.8)	96/1059	7.8 (6.1–9.4)	7.6 (6.0–9.1)
High-normal	72/891	6.4 (4.8–8.0)	4.4 (3.2–5.5)	108/903	10.3 (8.3–12.3)	10.1 (8.1–12.1)

\*Optimal blood pressure is a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg. Normal blood pressure is a systolic pressure of 120 to 129 mm Hg or a diastolic pressure of 80 to 84 mm Hg. High-normal blood pressure is a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used. CI denotes confidence interval.

†The numbers have been adjusted by direct standardization to the overall age distribution of the subjects in the study sample in four age groups (<50 years, 50 to 59 years, 60 to 69 years, and ≥70 years).

ably higher in younger subjects, ranging from 73 to 218 in men and from 143 to 429 in women.

## DISCUSSION

Although numerous investigators have reported cardiovascular risks associated with elevated blood pressure,<sup>1-7</sup> few have presented the absolute and relative risks of cardiovascular disease according to the blood-pressure categories used in clinical practice. High-normal blood pressure rivals mild hypertension in prevalence in the U.S. adult population.<sup>23</sup> Yet, information regarding the risk of cardiovascular disease associated with this blood-pressure category is limited to fatal cardiovascular events.<sup>10,11</sup>

Our results extend prior reports in several respects. We determined absolute cardiovascular-event rates (in addition to relative risks) for subjects in the three nonhypertensive blood-pressure categories. We calculated the incidence of major cardiovascular events, not just fatal events. We have provided data on the cardiovascular risk associated with high-normal blood pressure separately for middle-aged and elderly subjects and for men and women. Finally, blood-pressure category and risk factors during follow-up were used as time-dependent variables in the multivariable analyses.

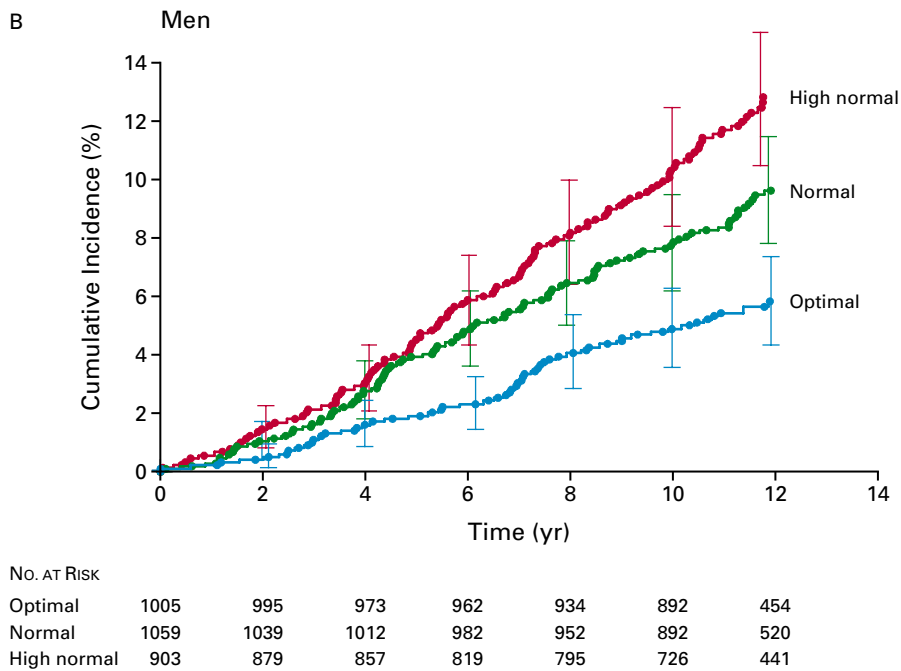
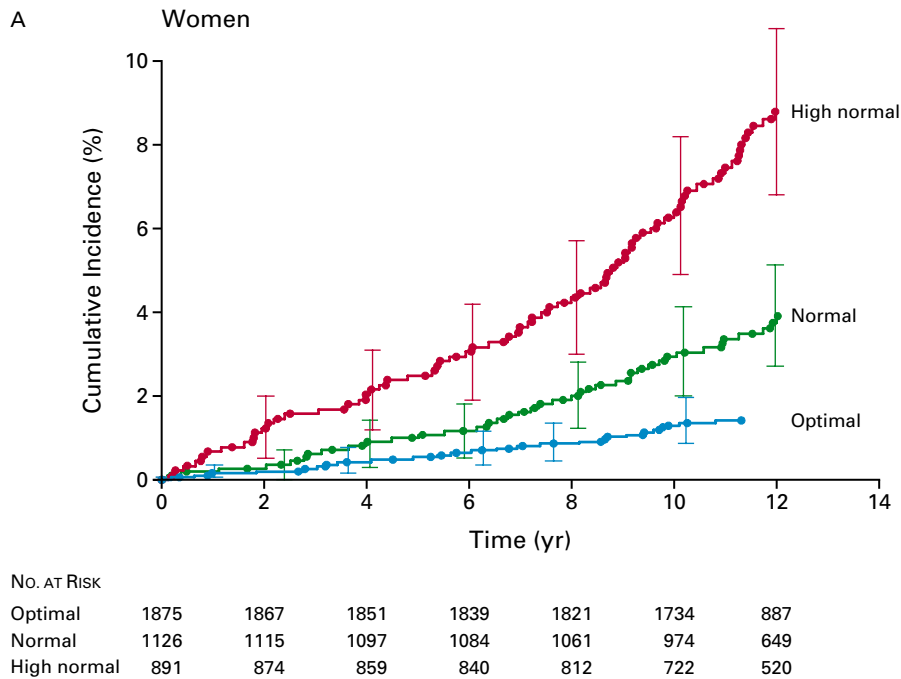
Men and women with high-normal blood pressure at base-line examination had a higher incidence of cardiovascular disease on follow-up than those with optimal blood pressure. These relations were consistent in both men and women and in both age groups, and they persisted after adjustment for multiple cardiovascular risk factors. The rate of cardiovascular events was low among men and women with optimal blood pressure, as has been emphasized by other investigators.<sup>24</sup> Furthermore, a continuous gradient

of increasing risk across the three nonhypertensive blood-pressure categories was observed. This finding was further confirmed by tests for trend. In analyses accounting for blood-pressure category during follow-up, the association of high-normal blood pressure with an increased risk of cardiovascular events persisted in men but was attenuated in women.

A 20 percent overall absolute risk of all cardiovascular events (not just major events) at 10 years is considered high and defines the current threshold for pharmacologic lowering of blood pressure in patients with hypertension, according to some international guidelines.<sup>9,25,26</sup> In subjects 65 years of age or older in the present study, the 10-year absolute rates of major cardiovascular events associated with high-normal blood pressure exceeded 20 percent in men and approached that threshold in women.

If lowering of blood pressure could reduce the five-year absolute risk of cardiovascular disease by 25 percent in elderly persons with high-normal blood pressure — an assumption based on the efficacy of blood-pressure lowering in clinical trials involving subjects with hypertension<sup>27</sup> — we estimate that only 28 men or 41 women would have to have their blood pressure lowered for five years to prevent one major cardiovascular event. These numbers may vary according to the JNC VI risk category.<sup>28</sup> These estimates are speculative, because there is no evidence that lowering blood pressure will reduce the risk of cardiovascular disease in this blood-pressure category. A clinical trial would be needed to determine whether pharmacologic treatment of high-normal blood pressure is beneficial. Our estimates of the number needed to treat could provide a framework for designing such a trial.

Although our results demonstrate that high-normal



**Figure 1.** Cumulative Incidence of Cardiovascular Events in Women (Panel A) and Men (Panel B) without Hypertension, According to Blood-Pressure Category at the Base-Line Examination.

Vertical bars indicate 95 percent confidence intervals. Optimal blood pressure is a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg. Normal blood pressure is a systolic pressure of 120 to 129 mm Hg or a diastolic pressure of 80 to 84 mm Hg. High-normal blood pressure is a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used.

**TABLE 3.** RESULTS OF SEX-SPECIFIC MULTIVARIABLE COX PROPORTIONAL-HAZARDS REGRESSION MODELS EXAMINING THE RELATION OF BLOOD-PRESSURE CATEGORY TO THE RISK OF A FIRST MAJOR CARDIOVASCULAR EVENT.

TYPE OF MODEL AND BLOOD-PRESSURE CATEGORY*	HAZARD RATIO (95% CONFIDENCE INTERVAL)	
	WOMEN (N=3892)	MEN (N=2967)
Models with blood pressure defined at base line†		
Optimal (2880 subjects)	1.0	1.0
Normal (2185 subjects)	1.5 (0.9–2.5)‡	1.3 (1.0–1.9)§
High normal (1794 subjects)	2.5 (1.6–4.1)¶	1.6 (1.1–2.2)¶
P for trend across categories	<0.001	0.01
Models with blood-pressure category and covariates defined as time-dependent variables**		
Optimal	1.0	1.0
Normal	1.1 (0.6–2.0)‡	1.3 (0.8–1.9)‡
High normal	1.8 (1.0–3.1)§	1.6 (1.1–2.3)¶
Hypertension	2.9 (1.7–5.2)¶	2.0 (1.3–2.9)¶
P for trend across categories	<0.001	<0.001

\*Optimal blood pressure (the reference category) is a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg. Normal blood pressure is a systolic pressure of 120 to 129 mm Hg or a diastolic pressure of 80 to 84 mm Hg. High-normal blood pressure is a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used. Hypertension was defined as a systolic pressure of 140 mm Hg or more, a diastolic pressure of 90 mm Hg or more, or the use of antihypertensive medication.

†Models were stratified according to examination and adjusted for age, body-mass index, total cholesterol level, presence or absence of diabetes mellitus, and smoking status.

‡P≥0.10.

§P>0.05 but <0.10.

¶P<0.001.

||P<0.05.

\*\*Models were stratified according to examination and adjusted for base-line age and the following as time-dependent covariates: body-mass index, total cholesterol level, presence or absence of diabetes mellitus, smoking status, and blood-pressure category.

blood pressure is a marker of an elevated risk of cardiovascular disease, it is uncertain whether the increased risk is attributable solely to subjects' blood-pressure levels. High-normal blood pressure has been associated with increased thickness of the carotid intima and media, altered cardiac morphologic features, and diastolic ventricular dysfunction,<sup>29-31</sup> which may be precursors of cardiovascular events. Furthermore, persons in our sample with high-normal blood pressure frequently had other risk factors for cardiovascular disease, as has been reported previously.<sup>32</sup> The additive effect of more than one risk factor on the risk of cardiovascular disease has been well established.<sup>2,11</sup>

The prospective study design, the large, community-based sample, and the comprehensive longitudinal surveillance for cardiovascular events are strengths of the present study. The use of blood-pressure values measured on a single occasion is a possible limitation, because it may result in underestimation of the strength of the relation between high-normal blood pressure and the incidence of cardiovascular disease.<sup>4,33</sup> Because our study spanned more than four decades of observation, the absolute event rates reported may not be valid for a contemporary cohort. However,

when we stratified our analyses according to the date of the examination and tested for an interaction between time period and blood pressure, we found no interaction, probably because during the period of our study, subjects with high-normal blood pressure were not treated with antihypertensive medication. The fact that our sample was predominantly white limits the generalizability of our findings. Moreover, we did not adjust for levels of physical activity and high-density lipoprotein cholesterol, because information regarding these risk factors was not available at the base-line examinations.

The recent WHO-ISH report<sup>9</sup> emphasized the "rationale for expecting high-risk subjects without hypertension to benefit from blood pressure lowering and the need for clinical trials to investigate this possibility." Our observational data underscore the need for additional research to determine whether persons with high-normal blood pressure who are at high risk for cardiovascular disease, such as elderly persons or those with diabetes or multiple risk factors, will benefit from blood-pressure lowering.

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