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Risk of Progression to Hypertension in a Low-Income Mexican Population with Pre-hypertension and Normal Blood Pressure

Aida Jimenez-Corona, MD, PhD[a], **Ruy Lopez-Ridaura, MD, MSc**[a], **Michael P Stern, MD**[b], and **Clicerio Gonzalez-Villalpando, MD**[a,c,d]

[a] Centro de Investigacion en Salud Poblacional, Instituto Nacional de Salud Publica, Cuernavaca, Morelos, Mexico.

[b] Division of Clinical Epidemiology, Department of Medicine, The University of Texas Health Science Center, San Antonio, Texas, USA.

[c] Centro de Estudios en Diabetes A. C., Mexico City. American British Cowdray Hospital, Mexico City, Mexico.

[d] Investigacion en Epidemiologia Clinica, Hospital General Gabriel Mancera, Mexico City, Mexico.

Abstract

BACKGROUND—Blood pressure (BP) levels below the pre-hypertension category may be associated with the risk of developing hypertension. We estimated the incidence rates of hypertension in low-income Mexican population according to several subcategories of baseline BP within normal and pre-hypertension categories.

METHODS—A total of 1572 nonhypertensive men (n=632) and non-pregnant women (n=940), aged 35 to 64 years at baseline, were followed for a median of 5.8 years. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, or self-reported physician diagnosis with anti-hypertensive medications.

RESULTS—During follow-up, 267 subjects developed hypertension, of whom 83 were men and 184 were women. Age-adjusted incidence rate was higher in women (37.1 per 1000 person-years) than in men (23.7 per 1000 person-years). There was a significant association between BP levels at baseline and hypertension incidence even within the normal category. For the upper levels of normal SBP (110-119 mm Hg), the HR (95%CI) was 2.43 (1.50-3.93) in women and 2.44 (1.05-5.69) in men, compared with SBP <110 mm Hg. For the upper levels of normal DBP (70-79 mm Hg), the HR (95%CI) was 2.33 (1.65-3.31) in women and 1.80 (0.92-3.52) in men, compared with DBP <70 mm Hg, after adjustment for recognized predictors.

CONCLUSIONS—High risk of hypertension incidence was associated with levels of BP even within the normal category. This information could help define a population at high risk of progression to hypertension, in order to establish preventive measures.

Keywords

Blood pressure; Hypertension; Cardiovascular risk

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Corresponding author: Ruy Lopez-Ridaura, Avenida Universidad # 655, Col. Santa Maria Ahuacatitlan, C.P. 62508, Cuernavaca, Morelos, Mexico Telephone: 52 (777) 311 2343, Facsimile: 52 (777) 329 3000-3204 E-mail: rlridaura@correo.insp.mx.

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Introduction

Hypertension substantially increases the morbidity and mortality associated with stroke, [1,2] cardiovascular disease, [3,4,5] peripheral vascular disease, retinopathy, and nephropathy. [2] Worldwide, hypertension affects 8% to 14% of the population, [6] and its prevalence is especially high (20% to 60%) in people with diabetes or metabolic syndrome. (7) In Mexico, the National Survey of 2006 (ENSANUT2006) reported a hypertension prevalence of 30.8% in adults 20 years and older. [8] The high prevalence of diabetes and metabolic syndrome observed in the same survey suggests that hypertension and cardiovascular complication may increase considerably for the next decades.

Repeated screening of blood pressure (BP) has been widely recommended by international and Mexican guidelines [9,10,11] to promote an early detection of hypertension and therapeutic interventions. However, the definition of categories below the cutoff points of hypertension diagnosis that may justify a modification in surveillance or intervention is still controversial. [12] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) [10] combined the previously known categories of “normal BP” (SBP 120-129 mm Hg or DBP 80-84 mm Hg) and “high normal BP” (SBP 130-139 mm Hg or DBP 85-89 mm Hg) into a category called “pre-hypertension”. Additionally, this report recommended lifestyle modifications and frequent follow-up evaluations starting at the pre-hypertension category. On the other hand, several international societies such as the World Health Organization, the International Society of Hypertension, and the European Society of Cardiology, have not agreed on the use of the term “pre-hypertension” yet. They recommend that people with high normal BP levels undergo early lifestyle modifications only in case of concurrent risk factors. [13,14] Current Mexican guidelines follow the definition of BP categories from the previous US Joint Commission report (JNC 6). This report classifies BP levels into 4 categories: optimum BP (SBP<120 mm Hg or DBP<80 mm Hg); normal BP (SBP 120-129 mm Hg or DBP 80-84 mm Hg); high normal BP (SBP 130-139 mm Hg or DBP 85-89 mm Hg); and hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg). [15] Mexican guidelines do not make any specific recommendation of an early intervention or closer surveillance on those people with normal or high normal BP levels.

At least 2 previous reports [12,16] have evaluated the need for a better definition of early stages of risk in the clinical continuous of BP by evaluating the association between pre-hypertension categories and progression to hypertension. In this investigation, we analyzed the incidence of hypertension associated with BP subcategories even at lower levels of the cutoff points defining pre-hypertension.

Methods

Study population

The Mexico City Diabetes Study is a prospective population-based study started in 1989, aimed at describing the prevalence, incidence and natural history of cardiovascular risk factors in a low-income population of Mexico City. The detailed methodology has been reported elsewhere. [19] Briefly, a population-based sample of 2282 men and non-pregnant women aged 35 to 64 years completed baseline interview and physical examination in 1989. Two follow-up visits have been carried out approximately every 3.5 years with 83% of follow-up success at the last visit. Baseline and follow-up evaluations included medical history, physical examination, electrocardiogram, and blood samples. For this analysis, we included 1572 participants (632 men and 940 women), who were free of hypertension at

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baseline, and who had at least 1 follow-up visit. Of 1572 subjects, 1305 attended both follow-up exams; 131 attended only the first one, and 136 attended only the second one.

The Institutional Review Boards of both The University of Texas Health Science Center and the Centro de Estudios en Diabetes approved the study protocol. Each subject gave informed consent.

Blood pressure assessment

At baseline and follow-up visits, BP was measured 3 times (after resting for at least 5 min) using a random zero sphygmomanometer (Hawksley, London). We used the average of the last 2 readings to classify the BP levels into predefined categories. Based on the JNC 7 criteria, we defined normal BP as SBP<120 mm Hg or DBP<80 mm Hg, and pre-hypertension as SBP 120-139 mm Hg or DBP 80-89 mm Hg. We further subdivided the normal and the pre-hypertension categories into 4 independent subcategories of SBP (<110, 110-119, 120-129, and 130-139 mm Hg) and into 4 independent subcategories of DBP (<70, 70-79, 80-84, and 85-89 mm Hg).

At follow-up visits, incidence cases of hypertension included individuals with SBP≥140 mm Hg or DBP≥90 mm Hg, who were not taking antihypertensive drugs, and those individuals with self-reported physician diagnosis of hypertension between visits, who were taking anti-hypertensive drugs regardless of BP levels. [10]

Other covariates

At baseline and follow-up, physical examination included an anthropometric evaluation in which weight, height, and waist circumference were measured. Body mass index (BMI) was calculated as weight/height^2 in kg/m^2. Participants reported their smoking habits and other lifestyle factors. In every visit, participants completed a glucose tolerance test with a 75-g oral carbohydrate load. Diabetes was defined in accordance with the World Health Organization criteria [20] as fasting glucose concentration≥126 mg/dl, 2-hour glucose ≥200 mg/dl, or treatment with hypoglucemiant drugs. Serum cholesterol, LDL-cholesterol, and HDL-cholesterol were determined by cholesterol-esterase, and triglycerides by glycerol-kinase. Additionally, non-HDL cholesterol was calculated as the difference between total serum cholesterol and HDL-cholesterol levels.

Statistical Analysis

We compared clinical and laboratory characteristics at baseline across BP categories (normal and pre-hypertension) among men and women separately. Subjects were followed from baseline up to the development of hypertension, lost to follow-up, or end of the study period (1998), with a median follow-up of 5.8 years (ranged 0.4-8.9 years). In subjects diagnosed during a follow-up visit the period of risk finished at the date of the visit, whereas in subjects with self-reported physician-diagnosed hypertension, the period of risk ended at the mid-point between the previous visit without hypertension and the first visit in which subjects were taking anti-hypertensive medication already. Age-adjusted incidence rates (per 1000 person-years) and their 95% confidence interval (CI) were estimated using the direct method, taking the 2000 world population as standard population.

We calculated the Kaplan Meier survival function to evaluate the association between baseline BP categories and the incidence of hypertension at follow up. For this analysis, we subdivided the normal and pre-hypertension categories into 4 subcategories for SBP and into 4 subcategories for DBP, as previously mentioned. We used the log-rank test to contrast the survival function of each subcategory vs. the BP reference subcategory (SBP <110 mm Hg and DBP <70 mm Hg). To evaluate the independent association between baseline BP

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subcategories and hypertension incidence we used a Cox proportional hazards model including age, diabetes, BMI and cholesterol levels as potential confounders in multivariate models. Additional analysis using the BP subcategories as time dependent variables did not modify significantly our results and conclusions (data not shown). We used the likelihood ratio test in order to test potential interactions between BP subcategories and sex, BMI, or diabetes. The proportionality assumption was evaluated by scaled Schoenfeld residuals and the global fit of the models by graphically examining the cumulative hazard function relative to the Cox-Snell residuals. We also used stratified proportional hazards models when the proportionality assumption was violated. All analyses were conducted using Stata 9.0 (Stata Corporation, Tex) and SAS 9.1 (SAS Institute Inc., Cary, NC).

Results

At baseline, 273 (43.2%) men and 274 (29.3%) women had pre-hypertension. Mean age was 46.8 years (s.d. 8.2 years) in men and 47.2 years (s.d. 8.1 years) in women. Table 1 shows baseline characteristics according to sex and BP categories. In contrast to participants with normal BP, men and women with pre-hypertension were older, more obese, and had higher levels of serum cholesterol, non-HDL cholesterol, and triglycerides. In addition, the proportion of men and women with diabetes was higher in people with pre-hypertension than in people with normal BP, especially among women.

During follow-up, 83 (13.1%) men and 184 (19.6%) women developed hypertension. The percentage of subjects who progressed from either normal BP or pre-hypertension to hypertension was higher in women (10.5% and 41.5%, respectively) than in men (4.7% and 24.2%, respectively) (Table 2). Among incident cases of hypertension, 163 cases (69 men and 94 women) were diagnosed during follow-up evaluation, whereas 104 cases (14 men and 90 women) were defined as hypertensive by self-reported physician diagnosis between follow-up visits, and were already taking anti-hypertensive medication at follow-up visit. Regarding the type of hypertension among those who were diagnosed during follow-up examination, 109 (66.9%) had isolated systolic hypertension, 23 (14.1%) had isolated diastolic hypertension, and 31 (19.0%) had both.

Age-adjusted incidence of hypertension was 37.1 per 1000 person-years (95% CI 31.6-42.7) in women and 23.7 per 1000 person-years (95% CI 18.4-29.0) in men. In both sexes, the incidence rates of hypertension increased with age and were higher in women in all age categories, except for 40-44 years (Table 3). Among participants who were classified as having normal BP at baseline, age-adjusted incidence of hypertension was 19.7 per 1000 person-years (14.9-24.6) in women and 10.6 per 1000 person-years (95% CI 5.8-15.4) in men. In comparison, the incidence of hypertension among subjects with pre-hypertension was 63.9 per 1000 person-years (95% CI 53.6-74.3) in women and 43.5 per 1000 person-years (95% CI 32.5-54.6) in men.

Figure 1 shows survival function according to subcategories of SBP and DBP at baseline. In general, survival function begins to differentiate from the reference subcategory after 2 years of follow-up for the subcategory immediately below the hypertension cutoff, and after 4 to 6 years for the other subcategories.

Multiple Cox Proportional Hazards models, including 4 subcategories of baseline SBP and 4 subcategories of DBP, are displayed in tables 4 and 5, respectively. The risk of developing hypertension increased as SBP and DBP increased in both men and women. In comparison to the reference subcategory (SBP <110 mmHg), in men, the HR associated with SBP subcategories ranged from 2.44 (95%CI 1.05-5.69) (110-119 mm Hg subcategory) to 6.90 (95%CI 2.95-16.14) (130-139 mm Hg subcategory). As for women, the HR ranged from

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2.43 (95%CI 1.50-3.93) to 6.93 (95%CI 4.14-11.60) for the same SBP subcategories, after adjustment for other covariates (Table 4). Concerning DBP, in men, the HR ranged from 1.80 (95%CI 0.92-3.52) (70-79 mm Hg subcategory) to 6.31 (95%CI 2.90-13.71) (85-89 mm Hg subcategory), and in women, the HR ranged from 2.33 (95%CI 1.65-3.31) to 3.90 (95%CI 2.13-7.16) for the same DBP subcategories (Table 5). Models excluding cases diagnosed between follow-up visits did not change significantly our results.

A model including men and women together showed that women had 1.66 (95% CI 1.26-2.17) times the risk of developing hypertension of men. However, the interaction between BP and sex was not significantly different (data not shown). Lastly, separate models for diabetic and non-diabetic subjects showed that the association between BP and the incidence of hypertension was stronger among non-diabetic subjects. Nonetheless, the test for interaction was not significant.

Discussion

The results of our analysis support the concept that pre-hypertension increases the risk of progression to hypertension independently of other recognized risk factors. [12,16] Moreover, we were able to extend this observation by showing an independent effect of BP subcategories even at levels lower than that of the pre-hypertension category, usually considered as normal and without any therapeutic or surveillance implication.

The longitudinal characteristic of our study, with repeated evaluations and a long and relatively successful (>80%) follow-up, supports the validity and strengths of our observations. Furthermore, the prospective and standardized assessment of BP increases the precision of the measurement and reduces a potential misclassification of the outcome. [21] Because of the gap of approximately 3.5 years between evaluations, from 184 women and 83 men who had incident hypertension, 90 (48.9%) and 14 (16.9%), respectively, were defined by self-reported physician diagnosis and medication intake. However, a secondary analysis excluding these cases did not change our conclusion.

Previous studies have evaluated a similar hypothesis through the association between BP levels below the cutoff point to diagnose hypertension (pre-hypertension) and other cardiovascular risk factors, [22,23] and have consistently shown a strong relationship. Other researches have evaluated whether these levels of BP are associated with an increased risk of mortality or morbidity from cardiovascular disease. [2,4,24-26] Most of these studies showed that these borderline levels of BP increased the risk of cardiovascular diseases in the age-adjusted models. However, after adjustment for several risk factors, the association lost their significance. [2] The lack of power or short follow-up of these investigations might partially explain the non-significant effect on cardiovascular outcomes after the multivariate adjustment for risk factors.

Some other studies have explored the same question as our study, evaluating the possible association of non-hypertensive levels of BP and the progression to hypertension in the short or long term. [12,16,27,28] Two previous reports [12,16] specifically evaluated the category of pre-hypertension and found results similar to those of our study. In the Framingham Heart Study, Vasan et al. [16] evaluated the progression to hypertension in participants with BP in the JNC6 categories of optimum (<120/80 mm Hg), normal (between 120-129/80-84 mm Hg) and high normal (between 130-139/85-90 mm Hg). After 4 years of follow up, 5.3% (95%CI 4.4-6.3) of the participants in the optimum level progressed to hypertension, whereas the progression among individuals in the normal category was more than 3 times higher (17.6%, 95%CI 15.2-20.3), and in the high normal category, it was more than 7 times higher (37.4%, 95%CI 33.3-41.5). The multivariate analyses in this study showed and

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independent difference in the effect of normal and high normal BP, compared with the optimum levels. In the second study, Winegarden et al. [12] analyzed 2 surveys conducted 7 years apart in the same population, and showed the same independent effect of the pre-hypertension categories, with more conservative estimates. To our knowledge, our study is the first that reported an independent association using lower subcategories of BP, below the cutoff point of pre-hypertension. The repeated follow-up visits in our study made it possible to evaluate the rates of progression within each subcategory, which other studies were not able to do as they only had baseline information and 1 follow-up at 4 years [16] or 7 years. [12]

It should not be a surprise that BP levels close to the lowest cutoff point of the pre-hypertension category be predictive of future hypertension. The pre-hypertension category comprises a set of subjects who clearly have a high cardiovascular risk profile already. However, after adjusting for some risk factors, we found the effect of these categories still significant. Furthermore, in a recent placebo controlled clinical trial, Julius et al. [29] demonstrated that a pharmacological treatment of pre-hypertension decreased the onset of hypertension at 4 years on almost two thirds in contrast to placebo. This is evidence that independently of other risk factors, lowering levels of BP in the pre-hypertensive subcategories will have an impact on hypertension incidence.

The possibility of sex differences on the risk of hypertension is still unclear. As our analysis, some studies have found higher hypertension rates in women compared with men. However, these differences decrease with age, and may disappear at older ages. [30,31,32] In our study, women had a worse cardiovascular profile at baseline and a greater risk of developing hypertension from early ages than men had. Nevertheless, sex differences were still significant after adjustment for some cardiovascular risk factors. In addition, ascertainment bias could partially explain sex differences. A secondary analysis using only cases of hypertension diagnosed prospectively during the study follow-up visit showed that the risk of developing hypertension for women vs. men was lower and non-significant (HR=1.13, 95%CI 0.81-1.58) compared with the original results (HR=1.66, 95%CI 1.26-2.17). Further analysis is required to evaluate sex differences in the progression to hypertension.

Using the age-adjusted progression rate, we found that 4%-6% of pre-hypertensive subjects developed hypertension after 1 year of follow-up, compared with 1%-2% of subjects with normal BP. This supports the recommendation of a repeated screening of BP in adults, even at younger ages, especially among those who are at or closer to the pre-hypertension category. Finally, our results will incorporate empirical information to assess the need for a re-evaluation of the BP categories that define the population at high risk of developing hypertension, in order to establish preventive measures. These data suggest that at least in Mexican population the high-risk group likely to progress to hypertension is identifiable at BP levels lower than that established by the JNC7. There is a need for further investigation to estimate the public health benefits of this information.

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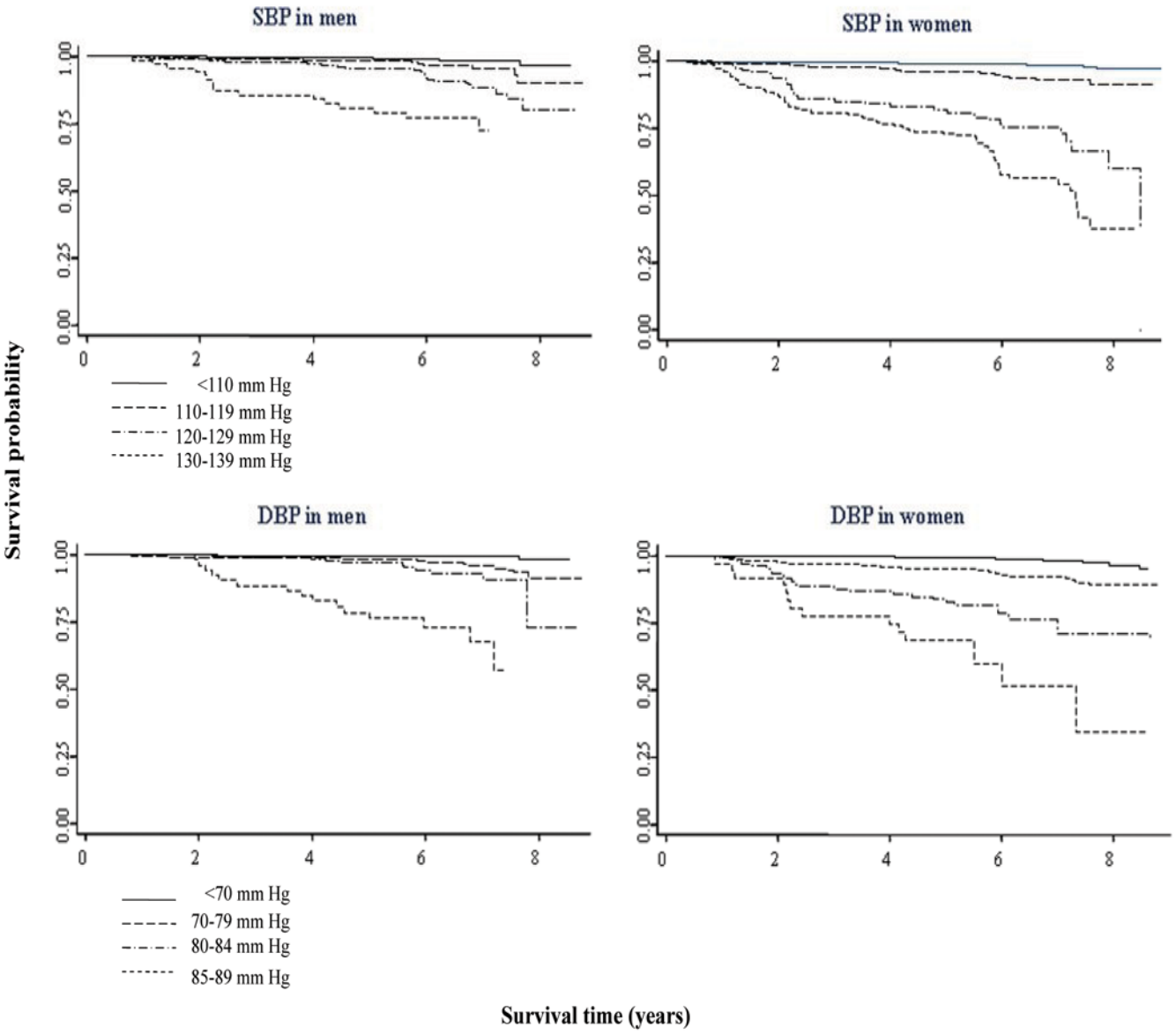

Figure 1.

Kaplan-Meier survival functions* for hypertension by SBP and DBP subcategories in men and women

*P value <0.05 for pair-wise comparisons between each survival function vs. its respective reference group.

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Table 1

Baseline characteristics according to sex and blood pressure category

Variables	Men (n=632)		Women (n=940)	
	Normal* n=359	Pre-hypertension* n=273	Normal* n=665	Pre-hypertension* n=275
Age (years)	45.5 (7.6)	48.6 (8.6)§	45.8 (7.7)	50.6 (8.1)§
Body mass index (kg/m^2)	26.1 (3.2)	27.8 (3.7)§	28.1 (4.5)	29.9 (4.5)§
Obesity (BMI≥30)	33 (9.2)	69 (25.3)§	192 (28.9)	121 (44.0)§
Waist circumference (m)	0.91 (0.08)	0.96 (0.09)§	0.96 (0.12)	1.03 (0.14)§
SBP (mm Hg)	107.7 (7.6)	124.6 (6.5)§	105.6 (8.3)	125.0 (7.1)§
DBP (mm Hg)	68.9 (6.6)	78.1 (7.1)§	66.6 (6.8)	76.3 (7.2)§
Serum cholesterol (mg/dl)	187.2 (41.0)	199.0 (42.0)§	188.2 (41.8)	199.1 (44.0)§
HDL cholesterol (mg/dl)	30.0 (8.5)	30.2 (8.1)	35.2 (8.7)	34.1 (8.7)
Non-HDL cholesterol (mg/dl)	157.4 (40.0)	169.0 (41.8)§	153.0 (41.7)	165.0 (43.0)§
LDL cholesterol (mg/dl)	122.4 (36.1)	130.4 (37.9)‡	122.1 (36.7)	128.4 (39.4)‡
Triglycerides (mg/dl) median (25th and 75th)	184.8 (131.4-274.2)	209.4 (142.6-326.8)‡	146.4 (106.7-198.4)	181.1 (133.4-253.7)§
Diabetes (no, %)	42 (11.7)	44 (16.1)	73 (11.0)	56 (20.4)§
Current smoking (no, %)	167 (46.5)	107 (39.2)	139 (20.9)	35 (12.7)‡

Mean and s.d. are shown except where noted.

Normal vs. pre-hypertension

*Normal BP was defined as SBP<120 mm Hg and DBP<80 mm Hg. Pre-hypertension was defined as SBP 120-139 mm Hg, or DBP 80-89 mm Hg. Normal and pre-hypertension categories were defined for subjects not taking anti-hypertensive drugs.

‡p<0.05

§p<0.001

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Table 2

Change on BP category at the end of follow-up according to BP category at baseline

BP at baseline	Blood pressure at the end of follow-up		
	Normal (n, %)	**Pre-hypertension (n, %)**	**Hypertension (n, %)**
Men			
Normal BP* (n=359)	263 (73.3)	79 (22.0)	17 (4.7)
Pre-hypertension* (n=273)	102 (37.3)	105 (38.5)	66 (24.2)
Total (n=632)	365(57.8)	184 (29.1)	83 (13.1)
Women			
Normal BP* (n=665)	474 (71.3)	121 (18.2)	70 (10.5)
Pre-hypertension* (n=275)	71 (25.8)	90 (32.7)	114 (41.5)
Total (n=940)	545 (58.0)	211 (22.5)	184 (19.5)

*Normal BP was defined as SBP<120 mm Hg and DBP<80 mm Hg. Pre-hypertension was defined as SBP 120-139 mm Hg or DBP 80-89 mm Hg. Normal and pre-hypertension categories were defined for subjects not taking anti-hypertensive drugs. Hypertension was defined as SBP≥140 mm Hg, DBP≥90 mm Hg or as taking anti-hypertensive medication regardless of BP values.

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Table 3

Number of cases and age-specific incidence of hypertension in men and women

	Men			Women		
Age at baseline (years)	**Case (n)**	**Person-years**	**Incidence per 1000/year (95%CI)**	**Case (n)**	**Person-years**	**Incidence per 1000/year (95%CI)**
35-39	9	969.2	9.3 (4.8-17.8)	15	1361.3	11.0 (6.6-18.3)
40-44	17	813.4	20.9 (13.0-33.6)	28	1082.8	25.9 (17.9-37.5)
45-49	12	686.2	17.5 (9.9-30.8)	37	980.1	37.8 (27.4-52.1)
50-54	13	478.8	27.1 (15.8-46.8)	31	802.6	38.6 (27.2-54.9)
>=55	32	657.7	48.7 (34.4-68.8)	73	891.0	81.9 (65.1-103.1)
Crude	83	3605.3	23.0 (18.6-28.5)	184	5117.8	35.9 (31.1-41.5)
Age-adjusted	83	-	23.7 (18.4-29.0)	184	-	37.1 (31.6-42.7)

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Table 4

Adjusted hazards ratio for hypertension in men and women, using subcategories of systolic blood pressure

	Men			Women		
Variables	**Cases n=82**	**HR (CI 95%)**	**p value**	**Cases n=181**	**HR (CI 95%)**	**p value**
Age (per 10 years)		1.57 (1.20-2.06)	0.001		1.55 (1.26-1.90)	<0.001
SBP (mm Hg)						
<110	8	1.0	-	28	1.0	-
110 to 119	17	2.44 (1.05-5.69)	0.038	42	2.43 (1.50-3.93)	<0.001
120 to 129 (pre-hypertension)	39	5.55 (2.55-12.08)	<0.001	72	5.98 (3.78-9.45)	<0.001
130 to 139 (pre-hypertension)	19	6.90 (2.95-16.14)	<0.001	39	6.93 (4.14-11.60)	<0.001
BMI (per 5 kg/m^2)		0.97 (0.71-1.32)	0.846		1.25 (1.07-1.473)	0.006
Serum cholesterol (per 50 mg/dl)		1.31 (1.02-1.68)	0.036	-	-	-
Diabetes		1.88 (1.12-3.16)	0.017	-	-	-

For women, diabetes and serum cholesterol violated the proportionality assumption; therefore, a stratified Cox Proportional Hazards model was employed.

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Table 5

Adjusted hazards ratio for hypertension in men and women, using subcategories of diastolic blood pressure

	Men			Women		
Variables	**Cases n=82**	**HR (CI 95%)**	**p value**	**Cases n=180**	**HR (CI 95%)**	**p value**
Age (per 10 years)		1.90 (1.46-2.46)	<0.001		2.11 (1.74-2.56)	<0.001
DBP (mm Hg)						
<70	12	1.0	-	53	1.0	-
70 to 79	35	1.80 (0.92-3.52)	0.085	93	2.33 (1.65-3.31)	<0.001
80 to 84 (pre-hypertension)	19	5.17 (2.47-10.83)	<0.001	23	3.15 (1.89-5.25)	<0.001
85 to 89 (pre-hypertension)	16	6.31 (2.90-13.71)	<0.001	15	3.90 (2.13-7.16)	<0.001
BMI (per 5 kg/m^2)		0.93 (0.68-1.28)	0.665		1.28 (1.09-1.49)	0.003
Serum cholesterol (per 50 mg/dl)		1.38 (1.08-1.77)	0.009		-	-
Diabetes		1.71 (1.02-2.88)	0.043		-	-

In women, diabetes and serum cholesterol violated the proportionality assumption; therefore, a stratified Cox Proportional Hazards model was employed.