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Altered Blood Pressure Progression in the Community and its Relation to Clinical Events

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Abstract

Background—Long-term blood pressure (BP) progression and its importance as a predictor of clinical outcome have not been well characterized across different time periods.

Methods—We evaluated time-period trends for three BP variables (long-term slope and mean during a baseline period of 16 years, and last baseline value) in an earlier (1953–1971; n=1644, mean age 61 years) and later (1971–1990; n=1040, mean age 58 years) time period among initially non-hypertensive participants in the Framingham Heart Study. In addition, we explored the relations of BP to cardiovascular disease incidence and all-cause mortality in the two time periods, each with up to 16 years of follow up.

Results—Long-term slope, mean, and last baseline BPs were significantly lower in the later time period ($P<0.001$). Rates of hypertension control (BP<140/90 mm Hg) were higher in the later vs. earlier period (32% vs. 23%; $P<0.001$). Multivariable hazard ratios (HR) for the relations of BP to outcomes were generally lower in the later period; this was statistically significant for the relations of last baseline BP to all-cause mortality (HR for 1-SD-increase in systolic BP, 1.02 vs. 1.25, $P=0.032$; HR for diastolic BP 1.00 vs. 1.23, $P=0.036$).

Conclusions—We found evidence that BP levels in the community have changed over time, coinciding with improved rates of hypertension control and attenuation of BP-mortality relations. These findings are consistent with the hypothesis that hypertension treatment in the community has altered the natural history of BP progression and its relation to clinical outcome.

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INTRODUCTION

Elevated blood pressure (BP) is a major risk factor for cardiovascular disease (CVD), with a doubled risk for each increment of 20 mm Hg systolic or 10 mm Hg diastolic BP above 115/75 mm Hg.¹ Rates of hypertension awareness, treatment, and control have increased steadily over the past few decades,² leading to reduced prevalence of high BP and target organ damage,³ as well as lower mortality from hypertension.⁴ Some recent studies, however, have reported increasing prevalence and inadequate control of hypertension, especially in certain population groups.^{5–7}

The majority of etiologic studies have focused on single occasion BP without accounting for prior or subsequent readings. Some prior investigations, however, have highlighted the importance of BP levels over time vis-à-vis CVD risk,^{8–16} often considering the contribution of antecedent BPs as compared to a single baseline measurement, without assessing the impact of within-individual BP progression (i.e. long-term slope). Further, studies that assessed BP progression are from the era before widespread introduction of effective antihypertensive treatment. To our knowledge, there are no investigations of the impact of BP progression on CVD incidence in the contemporary era. The Framingham Heart Study, with over 50 years of repeated BP measurements and follow-up data, provides a unique opportunity to examine BP progression as in relation to CVD incidence and all-cause mortality in two different time periods.

Thus, the aims of the present study were to determine if there have been changes in BP progression and the relation of BP to risk of clinical events in the community. To do so, we examined several BP measures and their relations to CVD incidence and all-cause mortality comparing time periods before and after widespread introduction of anti-hypertensive treatment.

METHODS

Study Samples

We utilized long-term follow up in the Framingham Heart Study original cohort for the earlier time period and the offspring cohort for the later time period. The selection of examinations, follow-up periods, and exclusion criteria for the two time periods (referred to as the earlier and later time periods) was done *a priori* to make them comparable and all analyses were conducted separately in these two study samples. All study protocols were approved by the Boston University Medical Center Institutional Review Board.

Earlier Time Period—The design of the Framingham Heart Study has been described previously.¹⁷ Original cohort participants have been examined approximately every two years. Only participants who attended the third (1953–56), seventh (1960–64), ninth (1964–68), and eleventh (1968–71) examination cycles (1953 to 1971; used for slope and mean BP calculations) were eligible for the present study (n=2605). Participants were excluded for the following reasons: age <50 years at the last baseline examination (n=10), major CVD at or prior to the last baseline examination (n=162), systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg at the first baseline examination (n=600), and anti-hypertensive treatment at any of the baseline examinations (n=189). After these exclusions, 1644 individuals (mean age, 61 years; 57% women) remained eligible for this investigation.

Later Time Period—The Framingham Heart Study offspring has been described previously.¹⁸ There were eight years between the first and second examination, and thereafter examinations were conducted approximately every four years. Only participants who attended the first (1971–75), second (1979–82), third (1984–87), and fourth (1987–90)

examination cycles (1971 to 1990; used for slope and mean BP calculations) were eligible for the present study (n=3214). Participants were excluded for the following reasons: age <50 years at the last baseline examination (n=1391), major CVD at or prior to the last baseline examination (n=96), systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg at the first baseline examination (n=397), and anti-hypertensive treatment at any of the baseline examinations (n=290). After these exclusions, 1040 individuals (mean age, 58 years; 57% women) remained eligible for this investigation.

Measurement of Blood Pressure and Covariates

At each examination, participants underwent routine medical history, physical examination, anthropometry, and laboratory assessment of CVD risk factors. Systolic BP and diastolic BP were obtained in the supported left arm of the resting seated participant, using a mercury-column sphygmomanometer, and recorded to the nearest even number using standardized methods.¹¹ The average of two separate readings by the examining physician was taken as the examination BP.

Body mass index (BMI) was calculated as weight divided by height² (kg/m²). Cigarette smoking was defined as self-report of smoking at least 1 cigarette daily within the preceding year. Diabetes was defined as a non-fasting blood glucose ≥ 200 mg/dL (earlier time period) or a fasting plasma glucose ≥ 126 mg/dL (later time period) or use of insulin or oral hypoglycemic agents (both time periods). Prior non-major CVD was defined as angina pectoris, coronary insufficiency, myocardial infarction (unrecognized or questionable), transient ischemic attack, questionable congestive heart failure, and intermittent claudication.

Follow Up and Outcome Events

All study participants were under continuous surveillance for CVD events and death, through review of Framingham Heart Study clinic visits, outside medical records, hospitalization records, and communication with personal physicians. A panel of three experienced investigators reviewed all suspected CVD events. Follow up extended up to 16 years following the last (through 1984 in the earlier, 2003 in the later time period). The primary outcome was incidence of a first major CVD event, defined as fatal/nonfatal recognized acute myocardial infarction, fatal/nonfatal stroke, definite congestive heart failure, or cardiovascular death. Diagnostic criteria have been detailed elsewhere.¹⁹ The secondary outcome was all-cause mortality.

Statistical Methods

Long-term systolic and diastolic BP slope (in mm Hg per year) was calculated from the four baseline examinations using linear regression. Mean systolic and diastolic BPs were calculated as the average of the BP recordings at these examinations (Figure). Means of BP variables in the earlier versus later period were compared using Student's t-tests. Pair-wise Pearson correlation coefficients were estimated for the interrelations between the BP measurements. The proportions of individuals with hypertension (defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of anti-hypertensive treatment), individuals receiving anti-hypertensive treatment among those with hypertension, and individuals with controlled hypertension (defined as systolic BP <140 mm Hg and diastolic BP <90 mm Hg in individuals with hypertension) were calculated from the last available clinic examination during follow up for the two time periods separately. The proportions were compared using chi-square tests.

Multivariable-adjusted (age, sex, total cholesterol, BMI, smoking, diabetes, prior non-major CVD, and atrial fibrillation at baseline) Cox proportional hazards analyses were used to

investigate associations of various BP variables with outcome, separately for the two time periods. We estimated hazards ratios (HR) and their 95 percent confidence intervals (CI) for a 1-standard deviation increment of each BP variable. The standardization of variables was done in a sex-specific manner. Likelihood ratio chi-square statistics for the models were calculated to indicate overall model fit. Non-linear associations were excluded by examining incidence rates for tertiles of BP variables. The assumption of proportionality of hazards was confirmed by examining interactions of BP variables and survival time in Cox models. We used three sets of models in a hierarchical fashion: A) including each BP variable separately; B) paired systolic and diastolic BP components jointly entered; and C) multivariable models with backwards elimination including all significant BP variables with an individual threshold of $p < 0.05$ for retention. The clinical covariates were forced into this model. HRs in the earlier versus later time period were compared using Z-statistics.

We repeated the analyses after excluding participants with non-major CVD or atrial fibrillation at or prior to the last baseline examination (eligible sample, $n=1499$ in the earlier, and $n=1032$ in the later time period); and excluding participants on anti-hypertensive treatment following the first baseline visit (eligible sample, $n=1833$ in the earlier, and $n=1278$ in the later time period).

We had statistical power of 90% and 96% to detect a HR of 1.20 (per BP SD) for CVD and all-cause mortality, respectively, in the earlier time period (at an alpha of 0.05). In the later time period, our power to detect a HR of 1.35 was 90% for CVD and 96% for all-cause mortality. We evaluated two-way interaction terms for sex and the different BP variables for both outcomes. Two-sided p -values of < 0.05 were considered statistically significant. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the study samples are shown in Table 1. The systolic and diastolic BP slope, as well as the mean and last baseline BP were lower in the later time period ($P < 0.001$ for all comparisons). The proportion of individuals with hypertension at the last clinic visit during follow up was 40% in the later and 59% in the earlier time period ($P < 0.001$). Of those with hypertension, 55% were receiving anti-hypertensive treatment in the later time period, and 49% in the earlier time period ($P = 0.08$). Among all participants with hypertension, 32% in the later, and 23% in the earlier time period were controlled ($P < 0.001$). Many of the BP variables demonstrated high pair-wise correlations (Table 2). The correlations were very similar in the two study samples.

In the earlier time period, 308 participants (15.8/1000 person-years at risk [PYARs]) had a first major CVD event and 414 (20.0/1000 PYARs) died during follow up (median 13.9 and 14.0 years, respectively). In the later time period, 105 individuals (10.5/1000 PYARs) had a first major CVD event and 138 (13.2/1000 PYARs) died during follow up (median 10.4 years for both endpoints).

Out of 24 examined interaction terms, two were significant ($P < 0.05$): systolic BP slope-sex and last baseline systolic BP-sex (both in relation to CVD incidence in the later time period). The interaction terms indicated a slightly weaker association of these BP variables in women than in men; the number of CVD events in women was too low ($n=42$) to allow sex-specific analyses. The directions of effect were the same in men and women.

CVD Incidence

In multivariable-adjusted analyses, all BP variables except diastolic BP slope were significant predictors of incident CVD in the earlier time period (Table 3, left panel). When

considering paired systolic and diastolic BP components in the same model, systolic BP was highly significant for all three BP components; diastolic BP was not significantly associated with incident CVD. When examining the relative contribution of the BP variables to CVD incidence in a multivariable model with backwards elimination, only mean systolic BP remained significant in the earlier time period (HR, 1.51; 95 % CI, 1.35–1.69; $P<0.001$).

All systolic BP variables were highly significant predictors of incident CVD in the later time period (Table 3, right panel). When including pairs of systolic and diastolic BP components in the same models, all three systolic BP components were significant predictors of incident CVD, whereas the diastolic BP variables were not significantly associated with outcome. In a multivariable model with backwards elimination, only mean systolic BP remained significant in the later time period (HR, 1.38; 95 % CI, 1.14–1.67; $P<0.001$).

Although the point estimates generally were lower in the later time period, there were no significant differences in hazard ratios for CVD between the later and earlier time periods.

All-Cause Mortality

In multivariable-adjusted analyses, all variables were significant predictors of all-cause mortality in the earlier time period (Table 4, left panel). When including pairs of systolic and diastolic BP components in the same models, all three systolic BP components were significant predictors of mortality, whereas the diastolic BP variables were not. When examining the relative importance of the significant BP variables to all-cause mortality in a multivariable model with backwards elimination, only mean systolic BP remained significant in the earlier time period (HR, 1.29; 95 % CI, 1.17–1.42; $P<0.001$).

None of the BP variables was significantly associated with all-cause mortality when examining them separately or in pairs in the later time period (Table 4, right panel). Since there were no significant associations in the single BP variable models, we did not proceed with a multivariable stepwise selection model.

The hazard ratios for all-cause mortality associated with last baseline systolic and diastolic BP were significantly lower in the later versus earlier time period ($P=0.033$ and $P=0.036$, for comparisons of last baseline systolic and diastolic BP, respectively), while there were no significant differences for the other comparisons.

Additional Analyses

The results for analyses following exclusion of participants with non-major CVD or atrial fibrillation at or prior to the last baseline examination were similar as for the main analyses, although the point estimates were generally slightly higher (Supplementary Tables 1 and 2). In analyses including participants taking anti-hypertensive treatment after the first baseline examination (Supplementary Tables 3 and 4), results for the earlier time period were very similar to the main results. In the later time period, the associations of BP slope to outcome were no longer apparent, presumably due to treatment effects during the baseline slope calculation period. Also the relations of the other BP variables to outcome were slightly weaker in the later time period.

DISCUSSION

Principal Findings

Our study provides an opportunity to examine time-period changes in BP progression and the relations of BP to major clinical outcomes in the community. Our data support the hypothesis that treatment has altered the natural history of BP progression. First, the results

are consistent with an important effect of treatment on the long-term consequences of hypertension. The HRs of BP variables, both for CVD incidence and all-cause mortality, were generally lower in the later versus the earlier time period; the attenuation was statistically significant for the relation of last baseline BPs to all-cause mortality. Additionally, while there were strong associations between all systolic BP variables and all-cause mortality in the earlier time period, there were no significant associations in the later time period. Judging from the effect sizes and the power calculations, this change does not seem to be due to inadequate statistical power. Second, a significantly higher proportion of hypertensive individuals in the later time period were treated and achieved BP control (<140/90 mm Hg). Finally, the BP slope was significantly less steep in the later time period compared to the earlier period. Taken together, these observations support the hypothesis that the widespread introduction and adoption of anti-hypertensive treatment has altered the natural history of BP progression and the relations of BP to outcome in the community. The lower hazards associated with BP in the later time period should not be interpreted to mean that BP is no longer an important contributor to outcome, but rather, that effective treatment has had a measurable impact on BP progression and consequently also on morbidity and mortality due to hypertension in the community.

Additional Findings

In accord with most prior studies of individuals over age 50,^{2,20,21} we found that the systolic BP variables were consistently better predictors of CVD incidence than the diastolic BP variables. We also extended these previous studies by observing the superiority of systolic BP variables for all-cause mortality. The different systolic BP components (last baseline, mean, and long-term slope), demonstrated fairly similar associations with outcome. When including all three systolic BP variables in the same models, only mean systolic BP was consistently retained, indicating the superiority of repeated measures.

Comparison with Previous Studies

In the earlier time period of our study, the proportion of participants achieving BP control at the last clinic visit during follow up (1980–84 for most participants) was 23%. The corresponding BP control rates in the National Health and Nutrition Examination Surveys (NHANES) were 10% in NHANES II (1976–80) and 29% in the first phase of NHANES III (1988–91).²² In the later time period of our study, the proportion achieving BP control during follow up (1999–2003 for most participants) was 32%. This estimate is similar to the BP control rate of 31% reported from NHANES for 1999–2000.²³ BP control rates have been reported to be lower in European countries, ranging from 5% in Spain to 10% in England during the 1990s.²⁴

To our knowledge, there are few prior studies examining whether BP slope over time adds predictive information above and beyond a single baseline measurement of BP. Hofman and co-workers using follow-up data in the Framingham original cohort,¹¹ concluded that BP slope (assessed over 12 years) did not add predictive value above a baseline BP level. Those results were supported by another Framingham report also using data from the original cohort, showing that BP slope before age 65 was a borderline significant predictor of CVD when entered into a bivariate model including baseline BP at age 65.¹⁰ Reports from the Seven Countries Study have demonstrated that systolic BP slope over 10 years adds significant predictive value to models including BP at the start of the 10 year baseline, both for incident CVD and all-cause mortality.^{12–14} Consistent with that finding, the BP slope predicted outcome above and beyond the BP at the start of the slope calculation period also in the study by Hofman *et al.*¹¹ These studies were conducted using BP data from several decades ago, which makes them potentially less relevant to current practice. In addition, these studies were limited by evaluation in men only,¹⁴ restriction to systolic BP parameters,

^{10,11,14} lack of multivariable models,¹⁰ or by not excluding or adjusting for important confounders, such as prior CVD or prior antihypertensive treatment.¹⁴

Sytkowski *et al* used data from the Framingham original cohort to assess secular trends in long-term hypertension treatment and its relation to clinical outcome.⁴ They did not examine the progression of BP in the same individuals over time, but used three different cohorts of hypertensive individuals and found decreasing mortality rates in treated individuals with long-term hypertension.

Clinical Implications

Even though the results for systolic BP slope were comparable to those of mean or last baseline systolic BP, BP slope did not have an incremental predictive value over and beyond that of mean or last baseline BP. Thus, the conclusion from the 1983 study by Hofman *et al* still holds: “For the clinician this suggests that the decision to treat high BP is best guided by the actual level of pressure and not by its long term trend in the past.”¹¹

An observation in the present study that might have importance for planning of future randomized clinical trials is that none of the BP variables predicted all-cause mortality in the later time period. This result suggests that all-cause mortality might not be the best choice of a primary endpoint in future treatment trials in hypertensive patients.

Strengths and Limitations

The strengths of the present study include the large community-based samples of men and women from two different time periods, the standardized BP measurements, and the long-term, continuous surveillance for outcome events. However, several limitations should be recognized. Our sample consists of middle-aged whites, limiting the generalizability of our findings to other age groups and ethnicities. Prior studies have shown that the proportion of treated hypertensive patients who achieved BP control differed between whites and blacks.²⁵ Further, the study sample could reflect selection bias, due to the exclusion of individuals with prior major CVD or anti-hypertensive treatment, which might have influenced the comparisons of the two time periods; However, results from additional analyses indicate that differential exclusion rates do not account for our findings. Further, the observed temporal differences in BP-outcome relations may have had explanations other than the wide-spread introduction of anti-hypertensive treatment, such as birth-cohort effects, residual confounding due to differential use of aspirin or lipid-lowering therapy in the two time periods, or general reductions in CVD risk factors in the population.²⁶ By the very nature of our observational study design, we cannot establish a causal role of anti-hypertensive treatment for the time trends observed in our study. Finally, the statistical power to detect associations was lower in the later time period, although we had 90% and 96% power to detect a HR of 1.35 for CVD and all-cause mortality, respectively.

Conclusions

In our large community-based sample, we explored long-term BP progression and its importance for prediction of CVD and all-cause mortality in time periods before and after the widespread introduction and more aggressive adoption of antihypertensive treatment. Our study demonstrates a striking temporal change in the course of blood pressure progression and its relation to outcome in the general population. Taken as a whole, our findings are consistent with the hypothesis that hypertension treatment has had a profound effect on outcome at the community level. Given the low rates of BP control worldwide, our findings underscore the opportunity to improve public health by applying existing recommendations on hypertension treatment. This may be especially true in Europe and other regions of the world where BP control rates lag behind those of the US.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913. [PubMed: 12493255]
2. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–1252. [PubMed: 14656957]
3. Mosterd A, D'Agostino RB, Silbershatz H, et al. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. *N Engl J Med* 1999;340:1221–1227. [PubMed: 10210704]
4. Sytkowski PA, D'Agostino RB, Belanger AJ, Kannel WB. Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality. The Framingham Heart Study 1950 to 1990. *Circulation* 1996;93:697–703. [PubMed: 8640998]
5. Ostchega Y, Dillon CF, Hughes JP, Carroll M, Yoon S. Trends in hypertension prevalence, awareness, treatment, and control in older U.S. adults: data from the National Health and Nutrition Examination Survey 1988 to 2004. *J Am Geriatr Soc* 2007;55:1056–1065. [PubMed: 17608879]
6. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004;291:335–342. [PubMed: 14734596]
7. Wong ND, Lopez VA, L'italien G, Chen R, Kline SE, Franklin SS. Inadequate Control of Hypertension in US Adults With Cardiovascular Disease Comorbidities in 2003–2004. *Arch Intern Med* 2007;167:2431–2436. [PubMed: 18071164]
8. de Vries CL, Feskens EJ, de Lezenne CC, Kromhout D. Repeated measurements of serum cholesterol and blood pressure in relation to long-term incidence of myocardial infarction. The Zutphen Study. *Cardiology* 1993;82:89–99. [PubMed: 8324782]
9. Gordon T, Sorlie P, Kannel WB. Problems in the assessment of blood pressure: the Framingham Study. *Int J Epidemiol* 1976;5:327–334. [PubMed: 1010660]
10. Harris T, Cook EF, Kannel W, Schatzkin A, Goldman L. Blood pressure experience and risk of cardiovascular disease in the elderly. *Hypertension* 1985;7:118–124. [PubMed: 3980054]
11. Hofman A, Feinleib M, Garrison RJ, van Laar A. Does change in blood pressure predict heart disease? *Br Med J (Clin Res Ed)* 1983;287:267–269.
12. Menotti A, Seccareccia F. Spontaneous changes of systolic blood pressure as predictors of future fatal events. Italian Research Group of the Seven Countries Study. *Am J Hypertens* 1990;3:549–554. [PubMed: 2363894]
13. Menotti A, Keys A, Blackburn H, et al. Blood pressure changes as predictors of future mortality in the seven countries study. *J Hum Hypertens* 1991;5:137–144. [PubMed: 1920337]
14. Menotti A, Lanti M, Kafatos A, et al. The role of a baseline casual blood pressure measurement and of blood pressure changes in middle age in prediction of cardiovascular and all-cause mortality occurring late in life: a cross-cultural comparison among the European cohorts of the Seven Countries Study. *J Hypertens* 2004;22:1683–1690. [PubMed: 15311095]

15. Prentice RL, Shimizu Y, Lin CH, et al. Serial blood pressure measurements and cardiovascular disease in a Japanese cohort. *Am J Epidemiol* 1982;116:1–28. [PubMed: 7102645]
16. Vasan RS, Massaro JM, Wilson PW, et al. Antecedent blood pressure and risk of cardiovascular disease: the Framingham Heart Study. *Circulation* 2002;105:48–53. [PubMed: 11772875]
17. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951;41:279–281.
18. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol* 1979;110:281–290. [PubMed: 474565]
19. Kannel, WB.; Wolf, PA.; Garrison, RJ. Framingham Heart Study: 30 Year Follow-Up. Bethesda, Md: US Department of Health and Human Services; 1987. Some risk factors related to the annual incidence of cardiovascular disease and death in pooled repeated biennial measurements.
20. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001;103:1245–1249. [PubMed: 11238268]
21. Lichtenstein MJ, Shipley MJ, Rose G. Systolic and diastolic blood pressures as predictors of coronary heart disease mortality in the Whitehall study. *Br Med J (Clin Res Ed)* 1985;291:243–245.
22. Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. *Hypertension* 1995;26:60–69. [PubMed: 7607734]
23. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA* 2003;290:199–206. [PubMed: 12851274]
24. Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 2004;43:10–17. [PubMed: 14638619]
25. Hertz RP, Unger AN, Cornell JA, Saunders E. Racial disparities in hypertension prevalence, awareness, and management. *Arch Intern Med* 2005;165:2098–2104. [PubMed: 16216999]
26. Kabir Z, Bennett K, Shelley E, et al. Life-years-gained from population risk factor changes and modern cardiology treatments in Ireland. *Eur J Public Health* 2007;17:193–198. [PubMed: 16798782]

Figure.

Definitions of blood pressure variables with hypothetical values and a schematic overview of the timeline of the study. Examination BPs for original cohort participants (earlier time period) are shown in blue and those for the offspring cohort (later time period) in red.

Table 1

Baseline Characteristics of the Study Samples*

	Earlier time period (N=1644)	Later time period (N=1040)
<i>Clinical features</i>		
Age, years	61±8	58±6
Women, %	57	57
Total cholesterol, mg/dL	233±43	214±38
Body mass index, kg/m ²	25.5±3.7	26.2±4.1
Smokers, %	41	24
Diabetes [†] , %	3.9	5.0
Prior non-major CVD [‡] , %	7.9	4.1
Atrial fibrillation, %	1.0	0.8
First baseline exam systolic BP [§] , mm Hg	118±10	117±9
First baseline exam diastolic BP [§] , mm Hg	76±7	76±7
<i>BP variables used in the study[¶]</i>		
Systolic BP slope, mm Hg/year	1.0±1.0	0.6±1.0
Diastolic BP slope, mm Hg/year	0.2±0.6	0.1±0.6
Mean systolic BP, mm Hg	127±12	122±11
Mean diastolic BP, mm Hg	79±6	77±6
Last baseline exam systolic BP, mm Hg	134±18	127±17
Last baseline exam diastolic BP, mm Hg	80±10	78±9

* Values are means ± standard deviations or percentages.

[†] Non-fasting blood glucose ≥200 mg/dL or use of insulin or oral hypoglycemic agents in the earlier time period; Fasting plasma glucose ≥126 mg/dL or use of insulin or oral hypoglycemic agents in the later time period.

[‡] Unrecognized or questionable myocardial infarction, coronary insufficiency, angina pectoris, transient ischemic attack, questionable congestive heart failure and intermittent claudication.

[§] The BP at the first baseline exam (exam 3 for the earlier time period, and exam 1 for the later time period).

[¶] The mean BP and the BP slope was calculated from the four baseline examinations (exams 3, 7, 9, and 11 for earlier time period; and exams 1, 2, 3, and 4 for later time period). The last baseline exam BP were defined as BP at exam 11 for earlier time period and exam 4 for later time period. Abbreviations: CVD, cardiovascular disease; BP, blood pressure.

Table 2

Correlations* among the Blood Pressure Measures in the Two Study Samples

Earlier Time Period (N=1644)							
	Systolic BP slope	Diastolic BP slope	Mean systolic BP	Mean diastolic BP	Last baseline systolic BP	Last baseline diastolic BP	
Systolic BP slope		0.56	0.55	0.35	0.80	0.50	
Diastolic BP slope			0.15	0.29	0.36	0.70	
Mean systolic BP				0.67	0.84	0.48	
Mean diastolic BP					0.57	0.76	
Last baseline systolic BP						0.61	
Last baseline diastolic BP							

Later Time Period (N=1040)							
	Systolic BP slope	Diastolic BP slope	Mean systolic BP	Mean diastolic BP	Last baseline systolic BP	Last baseline diastolic BP	
Systolic BP slope		0.60	0.51	0.29	0.77	0.48	
Diastolic BP slope			0.17	0.28	0.37	0.64	
Mean systolic BP				0.70	0.85	0.57	
Mean diastolic BP					0.58	0.81	
Last baseline systolic BP						0.66	
Last baseline diastolic BP							

* Values are Pearson correlation coefficients for pairwise correlations of blood pressure measures. For definitions of blood pressure measures, see Table 1. All correlations were significant, $p < 0.001$.

Abbreviations: BP, blood pressure.

Table 3

Incidence of Cardiovascular Disease Associated with Blood Pressure Characteristics* in the Earlier and Later Time Periods

	Earlier Time Period (No. of Events, 308; No. at Risk 1644) [†]		Later Time Period (No. of Events, 105; No. at Risk 1040) [†]	
	HR (95 % CI)	LR Chi-square statistic for model [‡]	HR (95 % CI)	LR Chi-square statistic for model [‡]
Models A. BP variables considered individually				
Systolic BP slope	1.32 (1.18–1.47)	235.0	1.30 (1.08–1.56)	116.4
Diastolic BP slope	1.09 (0.97–1.22)	213.9	1.19 (0.97–1.45)	111.4
Mean systolic BP	1.51 (1.35–1.69)	263.7	1.38 (1.14–1.67)	119.5
Mean diastolic BP	1.34 (1.20–1.49)	239.0	1.33 (1.07–1.64)	115.6
Last baseline systolic BP	1.40 (1.26–1.55)	247.6	1.34 (1.12–1.60)	118.9
Last baseline diastolic BP	1.22 (1.09–1.36)	223.4	1.24 (1.02–1.51)	113.3
Models B. Systolic and diastolic BP considered jointly				
Systolic BP slope	1.42 (1.24–1.63)	238.2	1.32 (1.04–1.69)	116.5
Diastolic BP slope	0.88 (0.77–1.01)		0.97 (0.74–1.27)	
Mean systolic BP	1.47 (1.27–1.71)	264.0	1.31 (1.02–1.68)	119.9
Mean diastolic BP	1.04 (0.90–1.20)		1.10 (0.83–1.44)	
Last baseline systolic BP	1.42 (1.24–1.62)	247.8	1.35 (1.06–1.73)	118.9
Last baseline diastolic BP	0.97 (0.85–1.12)		0.98 (0.75–1.29)	

* For definitions of blood pressure characteristics, see Table 1.

[†] Hazard ratios are per 1-standard deviation increase of the blood pressure variable, adjusting for age, sex, total cholesterol, body mass index, smoking, prevalent diabetes, and prior non-major CVD or atrial fibrillation at baseline; all defined as in Table 1.

[‡] Chi-square statistic for the whole Cox regression model, estimating overall model fit.

[§] Event defined as first major cardiovascular disease including fatal or nonfatal recognized acute myocardial infarction, fatal or nonfatal stroke, congestive heart failure, or cardiovascular death. Abbreviations: HR, hazard ratio; CI, confidence interval; BP, blood pressure; LR, likelihood ratio.

Table 4

All-Cause Mortality Associated with Blood Pressure Characteristics* in the Earlier and Later Time Periods

	Earlier Time Period (No. of Deaths, 414; No. at Risk 1644) [†]		Later Time Period (No. of Deaths, 138; No. at Risk 1040) [†]	
	HR (95 % CI)	LR Chi-square statistic for model [‡]	HR (95 % CI)	LR Chi-square statistic for model [‡]
Models A. BP variables considered individually				
Systolic BP slope	1.17 (1.06–1.29)	351.4	1.03 (0.87–1.20)	64.4
Diastolic BP slope	1.12 (1.02–1.23)	347.0	0.98 (0.83–1.15)	64.4
Mean systolic BP	1.29 (1.17–1.42)	368.5	1.17 (0.98–1.38)	67.3
Mean diastolic BP	1.23 (1.12–1.36)	360.0	1.09 (0.91–1.31)	65.2
Last baseline systolic BP	1.25 (1.14–1.37)	362.5	1.02 (0.88–1.20)	64.4
Last baseline diastolic BP	1.23 (1.11–1.35)	358.8	1.00 (0.86–1.18)	64.3
Models B. Systolic and diastolic BP considered jointly				
Systolic BP slope	1.14 (1.02–1.29)	351.7	1.08 (0.86–1.36)	64.8
Diastolic BP slope	1.03 (0.92–1.17)		0.93 (0.74–1.16)	
Mean systolic BP	1.23 (1.08–1.40)	369.8	1.21 (0.95–1.55)	67.5
Mean diastolic BP	1.08 (0.95–1.22)		0.94 (0.72–1.22)	
Last baseline systolic BP	1.17 (1.04–1.32)	365.5	1.05 (0.83–1.33)	64.5
Last baseline diastolic BP	1.11 (0.99–1.25)		0.97 (0.76–1.24)	

* For definitions of blood pressure characteristics, see Table 1.

[†] Hazard ratios are per 1-standard deviation increase of the blood pressure variable, adjusting for age, sex, total cholesterol, body mass index, smoking, prevalent diabetes, and prior non-major CVD or atrial fibrillation at baseline; all defined as in Table 1.

[‡] Chi-square statistic for the whole Cox regression model, estimating overall model fit.

Abbreviations: HR, hazard ratio; CI, confidence interval; BP, blood pressure; LR, likelihood ratio.