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Blood Pressure in Early Adulthood, Hypertension in Middle Age, and Future Cardiovascular Disease Mortality

HAHS (Harvard Alumni Health Study)

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Objectives We sought to examine the association of early adulthood blood pressure with cardiovascular disease (CVD) mortality, while accounting for middle-age hypertension.

Background Elevated blood pressure in middle age is an established CVD risk factor, but evidence for association with measurements earlier in life is sparse.

Methods The HAHS (Harvard Alumni Health Study) is a cohort study of 18,881 male university students who had their blood pressure measured at university entry (1914 to 1952; mean age 18.3 years) and who responded to a questionnaire mailed in either 1962 or 1966 (mean age 45.8 years) in which physician-diagnosed hypertension status was reported. Study members were subsequently followed for mortality until the end of 1998.

Results Following adjustment for age, body mass index, smoking, and physical activity at college entry, compared with men who were normotensive according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria ($<$120/$<$80 mm Hg), there was an elevated risk of coronary heart disease (CHD) mortality (1,917 deaths) in those who were pre-hypertensive (120 to 139/80 to 89 mm Hg) (hazard ratio [HR]: 1.21; 95% confidence interval [CI]: 1.07 to 1.36), stage 1 (140 to 159/90 to 99 mm Hg) (HR: 1.46; 95% CI: 1.25 to 1.70), and stage 2 hypertensive ($\geq$160/$\geq$100 mm Hg) (HR: 1.89; 95% CI: 1.46 to 2.45), incremental across categories ($p_{trend} < 0.001$). After additionally accounting for middle-age hypertension, estimates were somewhat attenuated, but the pattern remained. Similar associations were apparent for total and CVD mortality, but not stroke mortality.

Conclusions Higher blood pressure in early adulthood was associated with elevated risk of all-cause mortality, CVD, and CHD, but not stroke, several decades later. Effects largely persisted after taking into account mediation by middle-age hypertension. Thus, the long-term benefits of blood pressure lowering in early adulthood are promising, but supporting trial data are required. (J Am Coll Cardiol 2011;58:2396–403) © 2011 by the American College of Cardiology Foundation

In addition to cigarette smoking, raised blood cholesterol, and diabetes, elevated blood pressure is a well-established risk factor for developing CHD and stroke (1–4). Associations appear to be strong, independent of other risk factors, and incremental across the full blood pressure range (3,4). However, to date, findings have largely been confined to middle-aged and older populations (5), limiting the understanding of the relationship, if any, with blood pressure measured earlier in life. Like other physiological risk factors, blood pressure measured in early adulthood "tracks" into middle age, such that individuals who initially have higher blood pressure also tend to have higher values in later life (6). It is unknown whether any increased risk of chronic disease apparently conferred by blood pressure in early

See page 2404

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life is merely a function of such correlation, or whether the effects are genuine. Disentangling this issue has potentially important policy implications: if early adulthood blood pressure directly influences disease development, then this may point to the need to implement blood pressure–lowering interventions at an earlier stage in life than is currently the case (7).

To date, a limited number of studies have examined associations between early adulthood blood pressure and long-term CHD or stroke (8–12). In a male student cohort, blood pressure measured around age 20 years was associated with risk of coronary heart disease (CHD) mortality up to 50 years later (9,12). Similar results have been reported in a large study of Swedish men followed into middle age (10). To our knowledge, the role of later blood pressure or hypertension in explaining the early blood pressure–later CHD relationship has yet to be examined.

In the HAHS (Harvard Alumni Health Study), blood pressure and other risk factors were measured directly at university entry, and study members reported physician-diagnosed hypertension during middle-age. Extended mortality surveillance of this cohort, therefore, provides an opportunity to examine the direct impact of blood pressure in early adulthood on the long-term risk of CHD and stroke mortality.

Methods

The HAHS is an ongoing cohort study of the predictors of chronic disease in males enrolling as undergraduates at Harvard University, Boston, Massachusetts, between 1916 and 1950. In 1962 or 1966 (1962/1966), surviving alumni were sent a health questionnaire on lifestyle and physician-diagnosed diseases, including hypertension. There was a 68% questionnaire response, comprising 21,582 men (13), among whom data from a physical examination at college entry were available in 19,850 (92%). Data on 29 men were discarded on the basis of data errors with recorded dates, leaving 19,821 men. Of these, 18,881 (95%) had complete data for systolic and diastolic blood pressure at college entry and hypertension in 1962/1966, forming our analytical sample.

Assessment of blood pressure and other covariates. University students underwent a standardized medical examination upon college entry when information on smoking (14), blood pressure, height, and weight were measured using standard protocols (15). Examinations were made by 1 of several physicians in the context of a conventional doctor–patient relationship, with the case-taking results itemized on standard forms (14). Physical activity was ascertained from undergraduate athletic records (8). Body mass index (BMI) in kg/m^2 was calculated from measured weight and height.

Questionnaires were mailed to surviving alumni in the 1962/1966 survey when "middle-age" (mean age 45.8 years) hypertension was ascertained from self-reports of physician diagnosis. In an earlier validation study, self-reported hypertension was compared with directly measured blood pressure or treatment for hypertension. Using ≥160 mm Hg systolic and ≥95 mm Hg diastolic blood pressure or a history of treatment for high blood pressure as the criteria for the definition of hypertension at that time, self-reports showed 80% sensitivity and 97% specificity (16).

Abbreviations and Acronyms

BMI = body mass index

CHD = coronary heart disease

CVD = cardiovascular disease

JNC = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Mortality ascertainment. The Harvard Alumni Office maintains listings of deceased alumni and obtains copies of official death certificates. Vital status and cause of death were determined from certificates available until the end of 1998, with >99% completeness (17). Deaths were classified as cardiovascular disease (CVD) for decedents with the International Classification of Diseases (ICD) (Seventh Revision) codes (18) of 330 to 334 and 400 to 446 for the primary or underlying cause of death (19); CHD and stroke deaths were identified by codes 420 and 330 to 334, respectively.

Statistical analyses. In our analyses, we coded blood pressure in 2 ways: 1) *continuously* (standard deviation change in blood pressure); and 2) *categorically* according to the current Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) criteria (see Table 1 for cutoffs) and for a stepwise 10 mm Hg increase in systolic blood pressure (see Table 2 for cutoffs).

Means were derived for continuous measurements stratified by blood pressure categories, and categorical variables were tabulated by these categories. Association between systolic and diastolic blood pressure measurements was assessed by correlation. Having determined that the proportional hazards assumption had not been violated, a series of Cox regression models (20) were fitted for total, CVD, CHD, and stroke mortality across JNC-VI categories. Initially, models were adjusted for age, followed by additional adjustment for BMI, smoking status, and physical activity. We then considered additional adjustment for hypertension in middle age. As this involves the effect of early adulthood blood pressure being estimated conditionally on hypertension in middle age—conceivably on the causal pathway of early adulthood blood pressure and mortality—joint modeling was additionally used to explicitly estimate these inter-relationships (21). We examined the impact of competing risks analyses for cause-specific mortality. Finally, because study entry covered a broad range of years (1914 to 1952), study members recruited earlier would have had reduced access to antihypertensive therapies. We therefore examined to what extent year of measurement modified the association of blood pressure with CVD.

Table 1 HR (95% CI) for the Relation of Blood Pressure in Early and Mid-Adulthood With All-Cause and CVD Mortality (N = 18,881)—HAHS

		All-Cause				CVD			
	n	Deaths	Age-Adjusted	Age- and University Covariate-Adjusted*	Age-, University Covariate-, and 62/66 Hypertension-Adjusted*	Deaths‡	Age-Adjusted	Age- and University Covariate-Adjusted*	Age-, University Covariate-, and 62/66 Hypertension-Adjusted*
University entry (18.4 yrs)									
Per SD (13.1 mm Hg) increase in systolic blood pressure	18,881	7,972	1.05 (1.03–1.07)	1.05 (1.03–1.08)	1.03 (1.01–1.06)	3,343	1.09 (1.05–1.13)	1.08 (1.04–1.12)	1.04 (1.01–1.09)
Categories of systolic blood pressure, mm Hg									
<105	1,762	728	0.97 (0.89–1.05)	0.99 (0.89–1.09)	0.99 (0.89–1.09)	283	0.95 (0.82–1.09)	0.98 (0.84–1.14)	0.97 (0.83–1.14)
105–114	4,436	1,768	1.00 (ref)	1.00 (ref)	1.00 (ref)	698	1.00 (ref)	1.00 (ref)	1.00 (ref)
115–124	6,491	2,716	1.03 (0.97–1.10)	1.04 (0.97–1.12)	1.03 (0.96–1.10)	1,153	1.11 (1.01–1.22)	1.09 (0.98–1.21)	1.06 (0.96–1.18)
125–134	3,796	1,582	1.01 (0.94–1.08)	1.04 (0.96–1.12)	1.02 (0.94–1.10)	675	1.09 (0.98–1.21)	1.09 (0.97–1.23)	1.05 (0.93–1.18)
135–144	1,707	822	1.17 (1.08–1.27)	1.16 (1.05–1.27)	1.11 (1.01–1.21)	370	1.33 (1.17–1.51)	1.28 (1.11–1.47)	1.18 (1.03–1.36)
145–154	470	242	1.23 (1.07–1.40)	1.24 (1.07–1.43)	1.16 (1.00–1.34)	112	1.43 (1.17–1.75)	1.47 (1.18–1.81)	1.29 (1.04–1.60)
≥155	219	114	1.23 (1.02–1.49)	1.32 (1.08–1.63)	1.18 (0.96–1.45)	52	1.41 (1.07–1.87)	1.43 (1.04–1.95)	1.15 (0.84–1.58)
p Value for trend	18,881	7,972	<0.001	<0.001	0.006	3,343	<0.001	<0.001	0.003
Normal†	6,748	2,531	1.00 (ref)	1.00 (ref)	1.00 (ref)	992	1.00 (ref)	1.00 (ref)	1.00 (ref)
Pre-hypertensive†	9,577	4,013	1.04 (0.99–1.09)	1.05 (0.99–1.11)	1.03 (0.97–1.09)	1,384	1.12 (1.03–1.21)	1.13 (1.04–1.24)	1.09 (1.00–1.20)
Stage 1 hypertension†	2,176	1,176	1.12 (1.05–1.20)	1.14 (1.06–1.24)	1.09 (1.01–1.18)	530	1.27 (1.14–1.41)	1.28 (1.14–1.44)	1.17 (1.04–1.31)
Stage 2 hypertension†	380	252	1.26 (1.11–1.44)	1.28 (1.11–1.48)	1.19 (1.03–1.37)	122	1.53 (1.27–1.85)	1.51 (1.23–1.86)	1.31 (1.06–1.61)
p Value for trend	18,881	7,972	<0.001	<0.001	<0.001	3,028	<0.001	<0.001	0.001
Middle-age (44.4 yrs)									
Nonhypertensive	17,007	6,745	1.00 (ref)			2,704	1.00 (ref)		
Hypertensive	1,874	1,227	1.57 (1.48–1.67)			639	2.02 (1.85–2.20)		

Values are n or hazard ratio (95% confidence interval). Model 1: adjusted by age at college entry; Model 2: adjusted by age, BMI, cigarette smoking status, and physical activity at college entry; Model 3: Adjusted by age, BMI, cigarette smoking status, and physical activity at college entry, and hypertension in 1962/1966; *n = 15,488 due to missing BMI, physical activity, and smoking status data; †Current Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria categories: normotensive (<120/<80 mm Hg), pre-hypertension (120–139/80–89 mm Hg), stage 1 hypertension (140–159/90–99 mm Hg), and stage 2 hypertension (≥160/≥100 mm Hg). ‡The remainder of the CVD deaths (n = 846; 25%) were chiefly myocardial degeneration with atherosclerosis (International Classification of Diseases Seventh Revision [ICD 7] code 422.1; n = 203), other and unspecified diseases of heart (ICD 7 code 434; n = 167), and aortic aneurysm (ICD 7 code 451; n = 105).

BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; HAHS = Harvard Alumni Health Study; HR = hazard ratio; ref = reference.

To account for missing data—affecting at least 1 item for 4,333 (18%) men—we used multiple imputation with 18 imputed datasets (corresponding to the percentage with missing data) (22) among 19,821 men with a physical examination record at university entry and health questionnaire, with valid dates of examination and death, if applicable. Results with these imputed data were very similar to the presented data (results not shown). All analyses were performed in Stata/IC 10.1 (StatCorp, College Station, Texas).

Results

In Table 1, we present the study characteristics according to JNC-VI blood pressure categories at university entry (mean age: 18.3 years). Smoking prevalence decreased with increasing hypertension severity, but otherwise, there was no relation between blood pressure and other variables at university entry (Table 1). Self-reported hypertension in middle age was associated with systolic and diastolic blood pressure at university entry, with 63% and 50% increased risk for standard deviation increases of 12.7 mm Hg (systolic) and 9.9 mm Hg (diastolic), respectively. Systolic and diastolic blood pressure measurements were reasonably correlated ($\rho = 0.40$; $p < 0.001$).

All-cause mortality. In Tables 2 and 3, we present hazard ratios for the relation of blood pressure at university entry with the 4 mortality outcomes (1,063,280 person-years of follow-up; median: 56.3 years). In analyses of all-cause mortality adjusted for age and other covariates at university entry, there was a dose-response relationship across the JNC-VI classification groups ($p < 0.001$) (Table 1). Standard deviation increases in systolic blood pressure were associated with a 5% increase in risk of death from any cause in both age-adjusted and university covariate-adjusted analyses. These increased risks of death were slightly attenuated but persisted even after adjustment for hypertension in middle age. After adjusting for age, hypertension in middle age was associated with an increased risk of total mortality of 57%.

CVD mortality. Compared with all-cause mortality, CVD mortality was more strongly associated with university blood pressure (Table 2, Fig. 1). After adjusting for age- and other university entry variables, dose-response associations were evident across the 4 JNC-VI categories ($p < 0.001$). These gradients were attenuated but remained significant following adjustment for hypertension in middle age. A 1-SD elevation in systolic blood pressure was associated with a significant 8% to 9% increase in risk of CVD death, which was reduced to 4% on further adjustment for hypertension in middle age. Hypertension status in middle age was associated with a 2-fold increased risk of CVD.

CHD mortality. The effect of blood pressure and hypertension status were more pronounced for CHD than CVD mortality (Table 3). Compared with normotensive men, pre-hypertensive men had 20%, stage 1 hypertensive men 43%, and stage 2 hypertensive men 93% elevated risks of CHD mortality after adjustment for all university entry covariates. The results were attenuated after additional control for hypertension status in middle age, but many remained significant. A 1-SD increase in systolic blood pressure was associated with 14% to 15% increased risk, largely persisting on adjustment for hypertension in middle age. A doubling of risk of CHD mortality was experienced by those with a diagnosis of hypertension by middle age.

Stroke mortality. There was no evidence of an association between blood pressure at university entry and stroke

Table 2 Characteristics of Study Participants According to Blood Pressure at University Entry (N = 18,881)—HAHS

	University Entry JNC-7 Blood Pressure Category§				
	Normal (n = 6,748)	Pre-Hypertensive (n = 9,577)	Stage 1 Hypertension (n = 2,176)	Stage 2 Hypertension (n = 380)	Total (N = 18,881)
University entry (1914–1952)					
Age, yrs	18.3 ± 1.7	18.4 ± 1.8	18.5 ± 2.0	18.4 ± 1.8	18.4 ± 1.8
Systolic blood pressure, mm Hg	108.6 ± 6.7	123.4 ± 7.2	136.5 ± 11.0	147.9 ± 17.1	120.1 ± 12.7
Diastolic blood pressure, mm Hg	66.9 ± 6.8	74.9 ± 7.6	83.1 ± 10.0	94.1 ± 16.3	73.4 ± 9.9
BMI, kg/m^2*	21.4 ± 2.4	21.8 ± 2.5	22.0 ± 2.7	21.9 ± 2.9	21.7 ± 2.5
Physical activity <1 h/week†	2.4 (158)	3.4 (316)	3.5 (73)	5.2 (19)	3.1 (566)
1 to 4 h/week	31.3 (2,021)	30.3 (2,780)	25.9 (547)	27.9 (102)	30.1 (5,450)
≥5 h/week	30.3 (1,958)	31.1 (2,861)	33.1 (697)	27.9 (102)	31.0 (5,618)
Unknown hours	27.4 (1,765)	27.4 (2,516)	30.6 (646)	35.2 (129)	27.9 (5,056)
Varsity athletics	8.5 (551)	7.8 (715)	6.9 (145)	3.8 (14)	7.9 (1,425)
Current smoker‡	37.6 (2,122)	34.0 (2,772)	29.7 (562)	22.5 (76)	34.5 (5,532)
Middle-age (1962 or 1966)					
Age, yrs	44.4 ± 8.4	45.7 ± 9.3	49.5 ± 10.1	52.9 ± 9.5	45.8 ± 9.3
Hypertensive	5.5 (371)	10.1 (968)	19.3 (421)	30.0 (114)	9.9 (1,874)

Values are mean ± SD or n (%). *BMI missing for 168 men. †Physical activity information missing for 766 men. ‡Smoking status unknown for 2,853 men. §Current Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) criteria categories: normotensive (<120/<80 mm Hg), pre-hypertension (120 to 139/80 to 89 mm Hg), stage 1 hypertension (140 to 159/90 to 99 mm Hg), and stage 2 hypertension (≥160/≥100 mm Hg).
Abbreviations as in Table 1.

Table 3 HR (95% CI) for the Relation of Blood Pressure in Early and Mid-Adulthood With CHD and Stroke Mortality (N = 18,881)—HAHS

		CHD				Stroke			
	n	Deaths	Age-Adjusted	Age- and University Covariate-Adjusted*	Age-, University Covariate-, and Hypertension-Adjusted*	Deaths	Age-Adjusted	Age- and University Covariate-Adjusted*	Age-, University Covariate-, and Hypertension-Adjusted*
University entry (18.4 yrs)									
Per SD (13.1 mm Hg) increase in systolic blood pressure	18,881	1,917	1.15 (1.10–1.20)	1.14 (1.09–1.20)	1.10 (1.05–1.16)	580	1.01 (0.93–1.09)	1.00 (0.91–1.10)	0.96 (0.88–1.05)
Categories of systolic blood pressure, mm Hg									
<105	1,762	148	0.94 (0.78–1.14)	0.93 (0.75–1.16)	0.93 (0.75–1.15)	56	0.96 (0.70–1.31)	0.95 (0.67–1.34)	0.94 (0.67–1.34)
105–114	4,436	370	1.00 (ref)	1.00 (ref)	1.00 (ref)	134	1.00 (ref)	1.00 (ref)	1.00 (ref)
115–124	6,491	672	1.22 (1.08–1.39)	1.17 (1.01–1.34)	1.14 (0.99–1.31)	194	0.96 (0.77–1.19)	0.93 (0.73–1.18)	0.90 (0.71–1.15)
125–134	3,796	390	1.20 (1.04–1.38)	1.16 (0.99–1.36)	1.12 (0.96–1.32)	111	0.92 (0.71–1.18)	0.82 (0.62–1.09)	0.79 (0.59–1.04)
135–144	1,707	235	1.61 (1.37–1.90)	1.54 (1.29–1.85)	1.43 (1.19–1.71)	59	1.08 (0.80–1.47)	0.98 (0.70–1.38)	0.90 (0.64–1.27)
145–154	470	69	1.68 (1.30–2.18)	1.67 (1.27–2.21)	1.48 (1.12–1.95)	19	1.23 (0.76–1.99)	1.27 (0.77–2.10)	1.11 (0.67–1.83)
≥155	219	33	1.72 (1.20–2.46)	1.68 (1.13–2.50)	1.36 (0.91–2.03)	7	0.99 (0.45–2.05)	1.13 (0.53–2.44)	0.88 (0.41–1.91)
p Value for trend	18,881	1,917	<0.001	<0.001	<0.001	580	0.630	0.898	0.510
Normal†	6,748	542	1.00 (ref)	1.00 (ref)	1.00 (ref)	180	1.00 (ref)	1.00 (ref)	1.00 (ref)
Pre-hypertensive†	9,577	980	1.20 (1.08–1.33)	1.21 (1.07–1.36)	1.17 (1.03–1.32)	278	0.98 (0.81–1.18)	0.99 (0.80–1.22)	0.95 (0.76–1.17)
Stage 1 hypertension†	2,176	315	1.43 (1.25–1.65)	1.46 (1.25–1.70)	1.33 (1.14–1.56)	104	1.27 (1.00–1.62)	1.28 (0.98–1.67)	1.16 (0.88–1.52)
Stage 2 hypertension†	380	80	1.93 (1.53–2.45)	1.89 (1.46–2.45)	1.63 (1.26–2.12)	18	1.12 (0.69–1.83)	1.28 (0.78–2.09)	1.09 (0.66–1.79)
p Value for trend	18,881	1,917	<0.001	<0.001	<0.001	580	0.122	0.082	0.372
Middle-age (44.4 yrs)									
Nonhypertensive	17,007	1,550	1.00 (ref)			459	1.00 (ref)		
Hypertensive	1,874	367	2.06 (1.76–2.27)			121	2.18 (1.65–2.58)		

Values are n or hazard ratio (95% confidence interval). Model 1: adjusted by age at college entry; Model 2: adjusted by age, BMI, cigarette smoking status. and physical activity at college entry; Model 3: adjusted by age, BMI, cigarette smoking status, and physical activity at college entry and hypertension in 1962/1966. *n = 15,488 due to missing BMI, physical activity, and smoking status data. †Current Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria categories: normotensive (<120/<80 mm Hg), pre-hypertension (120–139/80–89 mm Hg), stage 1 hypertension (140–159/90–99 mm Hg), and stage 2 hypertension (≥160/≥100 mm Hg).

CHD = coronary heart disease; other abbreviations as in Table 1.

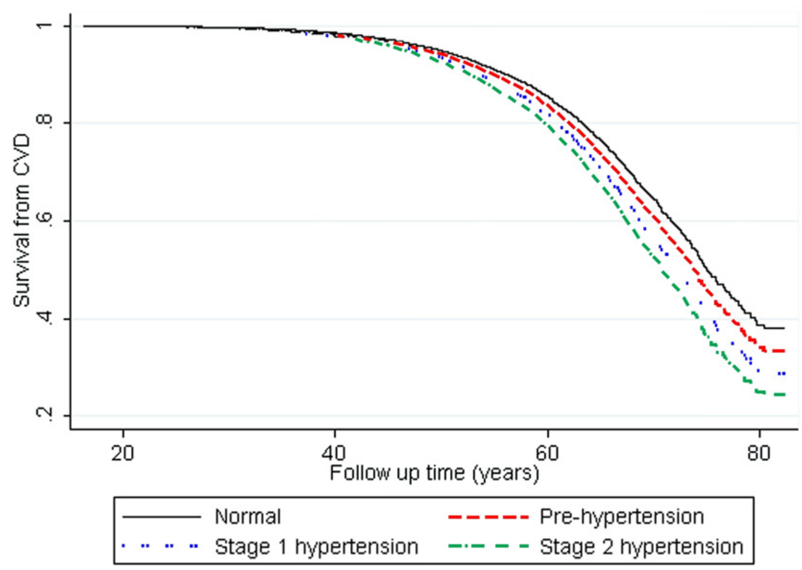

Figure 1 **Survival Curves for CVD Mortality by Blood Pressure Categories at College Entry (Mean Age 18.4 Years)**

Numbers at risk: start of follow-up: 18,881; Year 20: 18,868; Year 40: 18,027; Year 60: 6,207; Year 80: 48. CVD = cardiovascular disease.

mortality (Table 3). Those with hypertension in middle age had more than double the subsequent risk of stroke mortality. For the 25% of CVD deaths due to causes other than stroke and CHD, blood pressure associations were nonsignificant (data not shown).

Results for diastolic blood pressure were similar to those for systolic blood pressure throughout. When we repeated analyses using more discrete groupings of blood pressure, the results were essentially unchanged (Tables 2 and 3). Results herein concurred with joint models (data not shown). Additional adjustment for height as a proxy for early-life socioeconomic position did not impact our results. In re-analyses of all models confined to the subset of participants with no missing covariate data (n = 15,488), results were consistent with those presented. Competing risks analyses produced similar results to those presented in Tables 2 and 3, indicating deaths from alternative causes did not materially impact on findings. Finally, there was no interaction ($p = 0.84$) between blood pressure and CVD according to year of study entry.

Discussion

In this large cohort of men with long-term follow-up, higher blood pressure in early adulthood was associated with elevated risks of CVD mortality and CHD mortality several decades later, effects that remained after accounting for hypertension in middle age.

Comparison with other studies. Four decades ago, a report based on a nested case-control study within the present cohort identified systolic blood pressure levels of over 130 mm Hg to be associated with a 40% increased risk of CHD death (8). In an era before statistical computing, it was not possible to examine the role of confounding factors, and the number of events was considerably lower than in the present analyses. Additionally, there were insufficient deaths to facilitate an examination of the extent to which the development of hypertension at middle adulthood affects the association between early adult blood pressure and future CVD.

There are few comparable studies by which to consider our results, especially given our median follow-up of almost 60 years in this cohort. Among men who were students at Glasgow University during 1948 to 1968, a 10-mm Hg increase in systolic blood pressure measured at around age 20 years was associated with a 15% increased risk of CHD mortality (12), which remained following multivariable adjustment (9). More recently, blood pressure in late adolescence was positively associated with early incidence of CHD and stroke in a large cohort of Swedish men (10). Compared with those of McCarron et al. (9,12), the association between blood pressure and all-cause, CVD and CHD mortality were generally weaker but statistically more robust in the present analyses, possibly due to our much larger number of events (Table 4). Our findings were in accord with those of Miura et al. (11), whose analyses were based on an older population at baseline (maximum age of study members was 39 years). None of these studies accounted for the impact of later adulthood blood pressure on the association between early blood pressure and subsequent CVD. However, 1 study did find that pre-hypertension

Table 4 **Comparisons of HR (95% CI) for the Relation of Blood Pressure Patterns in Early Adulthood With CHD Mortality: Our Results in Relation to Previously Published Studies**

	HAHS (Unadjusted)		University of Glasgow Alumni (12) (Unadjusted)		HAHS (Adjusted*)		Chicago Heart Association Study (11) (Adjusted†)	
JNC-6 Classification	No. of Deaths	HR (95% CI)	No. of Deaths	HR (95% CI)	No. of Deaths	HR (95% CI)	No. of Deaths	HR (95% CI)
Optimal	573	1.00 (ref)	11	1.00 (ref)	405	0.84 (0.74–0.96)	11	1.39 (0.67–2.86)
Normal	698	1.19 (1.06–1.33)	44	1.19 (0.62–2.32)	523	1.00 (ref)	22	1.00 (ref)
Borderline	348	1.26 (1.11–1.44)	81	1.65 (0.88–3.12)	263	1.05 (0.91–1.22)	40	1.37 (0.81–2.30)
Stage 1 hypertension	336	1.45 (1.27–1.66)	79	1.66 (0.88–3.13)	272	1.23 (1.06–1.42)	78	1.62 (1.00–2.61)
Stage 2 hypertension	68	1.67 (1.30–2.14)	16	2.73 (1.26–5.92)	57	1.46 (1.11–1.93)	33	2.51 (1.44–4.37)
Stage 3 hypertension	17	4.22 (2.61–6.84)	3	2.91 (0.80–10.55)	11	2.87 (1.58–5.23)	13	3.60 (1.71–7.59)
p Value for trend		<0.001		0.002		<0.001		NA

*Adjusted by age, BMI, cigarette smoking status, and physical activity at college entry. †Adjusted by age, BMI, BMI2, cigarettes per day, serum cholesterol level, electrocardiographic abnormality, race, and education. ‡Previous Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria categories: optimal (<120/<80 mm Hg), normal (120–129/80–84 mm Hg), borderline (130–139/85–89 mmHg), stage 1 hypertension (140–159/90–99 mm Hg), stage 2 hypertension 160–179/100–109 mm Hg), and stage 3 hypertension (≥180/≥110 mm Hg).
NA = not available; other abbreviations as in Tables 1 and 3.

measured in young adults predicted an alternative measure of CHD—coronary calcification—after adjusting for subsequent hypertension in middle age (23).

The lack of an association between university blood pressure and total stroke mortality is surprising. Compared with those of McCarron et al. (12), associations for JNC-VI groupings were generally of low magnitude but similarly statistically nonsignificant. The weaker association for stroke versus CHD mortality may reflect blood pressure–related atherosclerosis taking place earlier in adulthood compared with the antecedents of stroke. There has been a suggestion of a stronger association of blood pressure with hemorrhagic compared with ischemic stroke (10), but we lacked the resolution to differentiate by stroke subtype.

Study strengths and limitations. This study takes advantage of its large sample size and number of outcomes, and is, to our knowledge, the first to examine the potential mediating role of middle-aged hypertension. This study is not, of course, without shortcomings. First, confined to a population of male university alumni, the representativeness of these data in terms of sex, ethnicity (subjects are primarily white), social class, and lifestyle (this cohort has a relatively low smoking prevalence, which would explain the fewer cardiovascular deaths compared with U.S. mortality statistics [24]) is uncertain. It is possible that the association between blood pressure and mortality may differ by sex, social strata, and ethnicity, but we were unable to explore these potential differences. Second, since these analyses are confined to those responding to the mailed questionnaire in 1962/1966, they may be subject to certain errors such as survivor or participation biases. For instance, respondents at 1962/1966 had lower BMI at time of university entry than the nonrespondents, although the 2 groups did not differ markedly in other hypertension- and CVD-related characteristics (25). Third, information on blood pressure in middle age is restricted to the dichotomous measure of self-reported, physician-diagnosed hypertension (16), and some random misclassification would be expected, potentially producing residual confounding of the relationship between early adulthood blood pressure and mortality in later life. However, although the broader hypertension range in middle age is not being fully captured, at the time of the 1962/1966 questionnaire, a blood pressure measurement of 160/95 mm Hg was the clinical threshold for hypertension. Further, this study population consisted of high socioeconomic status men who would be more likely to exhibit and afford healthcare-seeking behavior (26). Indeed, our data on hypertension have been shown to have high sensitivity and specificity (16), thereby minimizing any potential impact of misclassification. Finally, we lacked a measurement of blood cholesterol level at university entry, and were thus unable to assess potential confounding by this (27) and other coronary risk factors such as parental history of CHD and diet.

Conclusions

In this cohort, higher measured blood pressure in early adulthood was associated with an elevated risk of total, CVD, and CHD mortality several decades later, which appeared to persist even after accounting for self-reported hypertension in middle age. These results lend weight to blood pressure–lowering strategies beginning earlier in the life course than is currently the case. However, there is a lack of clinical trial data to assess the efficacy and potential harm of such intervention.

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