Blood Pressure Change and Risk of Hypertension Associated With Parental Hypertension

The Johns Hopkins Precursors Study

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Background: Parental hypertension is used to classify hypertension risk in young adults, but the long-term association of parental hypertension with blood pressure (BP) change and risk of hypertension over the adult life span has not been well studied.

Methods: We examined the association of parental hypertension with BP change and hypertension risk from young adulthood through the ninth decade of life in a longitudinal cohort of 1160 male former medical students with 54 years of follow-up.

Results: In mixed-effects models using 29,867 BP measurements, mean systolic and diastolic BP readings were significantly higher at baseline among participants with parental hypertension. The rate of annual increase was slightly higher for systolic (0.03 mm Hg, \( P = .04 \)), but not diastolic, BP in those with parental hypertension. After adjustment for baseline systolic and diastolic BP and time-dependent covariates—body mass index, alcohol consumption, coffee drinking, physical activity, and cigarette smoking—the hazard ratio (95% confidence interval [CI]) of hypertension development was 1.5 (1.2-2.0) for men with maternal hypertension only, 1.8 (1.4-2.4) for men with paternal hypertension only, and 2.4 (1.8-3.2) for men with hypertension in both parents compared with men whose parents never developed hypertension. Early-onset (at age \( \leq 55 \) years) hypertension in both parents imparted a 6.2-fold higher adjusted risk (95% CI, 3.6-10.7) for the development of hypertension throughout adult life and a 20.0-fold higher adjusted risk (95% CI, 8.4-47.9) at the age of 35 years.

Conclusion: Hypertension in both mothers and fathers has a strong independent association with elevated BP levels and incident hypertension over the course of adult life.

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The National High Blood Pressure Education Program emphasizes primary prevention of hypertension in “individuals at high risk for hypertension,” including those with a family history of hypertension. Hypertension has long been recognized to cluster within families in cross-sectional studies in which hypertension and family history were assessed at the same point in time. Prospective studies of this issue mostly have relied on recall of family history, have had relatively short follow-up periods, and have not distinguished the effect of paternal hypertension vs maternal hypertension or age at onset of hypertension in the parents. Whether hypertension risk associated with parental hypertension is constant through adult life or greater at younger ages is not clear. Furthermore, the few longitudinal studies of parental history and blood pressure (BP) change have primarily enrolled children who were followed up to young adulthood. We examined the effect of parental hypertension on change in BP and the risk of hypertension from young adulthood through the ninth decade of life in a longitudinal cohort study of 1160 former medical students over 54 years of follow-up. The availability of incident hypertension data on both parents, as well as validated self-reports of BP and hypertension in the cohort members, offers a unique opportunity to address this important issue.

Methods

STUDY POPULATION AND MEASUREMENTS

The Johns Hopkins Precursors Study was designed and initiated in 1947. The 1216 male and 121 female students in the classes of 1948 through 1964 of The Johns Hopkins University School of Medicine, Baltimore, Maryland, were eligible for the study. Men of Asian ethnicity and women were excluded from this analysis because of their small numbers. White men who...
had hypertension before graduation (n = 23) or did not have follow-up (n = 14) were also excluded. The remaining 1160 white men made up the study population for the present analysis.

In medical school, participants completed questionnaires about their medical history, health habits, and dietary habits, including physical activities, alcohol consumption, coffee intake, and cigarette smoking. They also underwent a standardized medical examination that included measurement of weight, height, and BP, which was assessed on multiple occasions (median, 9 times) in medical school using a standardized protocol. The mean level of all measurements was used to estimate BP at baseline in this analysis.

**ASSESSMENT OF PARENTAL HYPERTENSION**

Participants were asked in medical school whether their parents had hypertension. Incidence of hypertension in parents was assessed prospectively after graduation through annual questionnaires to the participants. Parental age at diagnosis was recorded using the same protocol as for study participants (see below).

**FOLLOW-UP PROCEDURES**

Information on cigarette smoking, physical activity, alcohol consumption, and coffee intake was obtained at baseline, every 5 years after graduation until 1984, and in 1978, 1986, 1989, 1993, and 1997. Up to 12 such measurements were available for time-dependent analyses. Body weight was obtained at baseline and up to 24 times through 2001. Self-reports of smoking behavior and body weight have been validated in this cohort.

Annual questionnaires were used to assess BP after graduation. Participants were asked to measure their BP in the seated position. The average number of years that participants reported their BP readings was 13, with a range from 1 (n = 37) to 27. Self-reports of BP in this cohort were found to be remarkably accurate in a validation study in which correlation between measured and concurrently reported BP was 0.67 for systolic BP (SBP) and 0.56 for diastolic BP (DBP), values that are comparable to the correlation between ambulatory and clinic BP measurements.

Annual questionnaires asked about diagnosis of and treatment for hypertension. Hypertension was defined as a reported BP measurement greater than or equal to 160/95 mm Hg on 1 annual questionnaire or greater than or equal to 140/90 mm Hg on 2 or more annual questionnaires or as hypertension requiring drug therapy. A diagnosis of hypertension was assigned after review of annual questionnaires, BP reports, and medical records by a committee of 5 internists trained in epidemiology without specific knowledge of the participant’s parental hypertension status. In persons who met the criteria for hypertension, onset was defined as the first report of elevated BP. The present analysis was based on events reported through December 31, 2001, representing a median follow-up of 37 years since graduation. Yearly response rates varied from 68% to 78%, with 87% to 94% of the cohort responding at least once during every 5-year period. Vital status of nonrespondents was ascertained through contacting family members, scanning obituaries, and searching the National Death Index. Vital status was known for more than 94% of the cohort. At the establishment of the institutional review board at The Johns Hopkins Medical Institutions, the study protocol was reviewed and approved.

**STATISTICAL ANALYSIS**

Parental hypertension was categorized into 4 groups: none, mother only, father only, and both parents. Follow-up time was similar for the 4 groups. The association of parental hypertension with change in BP over follow-up was first explored with nonparametric regression using locally weighted smoothing (lowess) and then modeled with linear mixed-effects models that allow participant-specific parameters. The mean of all reported BP values was used when participants reported more than 1 BP reading on an annual questionnaire. The cumulative incidence of hypertension was calculated using Kaplan-Meier analysis. The difference in hypertension incidence between parental hypertension groups was tested using the log-rank test. Age was the time variable used in all survival analyses. Relative risk (hazard ratio [HR]) estimates and corresponding 2-sided 95% confidence intervals (CIs) relating parental hypertension to risk of hypertension were computed using Cox proportional hazards analysis. Multivariate models were developed to adjust for possible confounding variables, including time-dependent data during follow-up on number of cigarettes smoked, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), physical activity, coffee drinking, and alcohol intake. Up to 46 persons with missing data were excluded from the multivariate analysis. Analyses were repeated to assess hypertension risk associated with early onset of parental hypertension, which was defined as onset at age 53 years or younger. Relative risks at different ages associated with early- and late-onset parental hypertension were estimated using interaction terms between age at risk and parental hypertension status in the Cox models. All tests of significance were 2-tailed, with α = .05.

In medical school, 23% (n = 264) of the cohort reported having a parent with hypertension: 127 only in their father, 117 only in their mother, and 20 in both parents. During follow-up, 583 incident cases of parental hypertension occurred. By the end of follow-up, 60% of the cohort (n = 701) had at least 1 parent with hypertension. The characteristics of the men in medical school and their association with parental hypertension status at the end of follow-up are shown in Table 1. Men with positive parental hypertension had higher mean SBP and DBP levels in medical school. Parental hypertension status was not related to BMI, smoking status, alcohol intake, coffee consumption, or frequency of exercise at baseline.

A total of 29 867 BP measurements were reported over the course of follow-up, and these were averaged to yield 15 723 annual mean BP estimates. As suggested by the exploratory analysis, age was modeled in the mixed-effects analyses as linear with SBP but as quadratic in relation to DBP. Mean SBP and DBP levels over follow-up were higher in participants whose parents had hypertension than in those whose parents did not. These differences in BP readings persisted from young adulthood into the ninth decade of life (Figure 1). Compared with participants without parental hypertension, participants with parental hypertension had a higher rate of SBP increase over time—2.9 mm Hg vs 2.6 mm Hg over 10 years (P = .04)—after time-averaging adjustment for BMI, alcohol consumption, coffee drinking, physical activity, and cigarette smoking. At 35 years of age, the adjusted mean (95% CI) SBP value was 1.9 (0.8-2.9), 1.6 (0.4-2.8), and 3.2 (1.8-4.5) mm Hg higher among participants with maternal hypertension only, paternal hypertension only, and hypertension in both parents, respectively. The corresponding elevations in DBP values were 0.9 (0.2-1.6), 0.6 (−0.2 to 1.4), and 2.4 (1.5-3.2) mm Hg, respectively. The difference in rates of DBP
increase over time between participants with and without parental hypertension was not statistically significant.

Higher BP readings in young adulthood and the higher rate of increase in SBP associated with parental hypertension translated into a statistically significant higher incidence of hypertension in the cohort. By the end of follow-up, 448 men developed hypertension at a median age of 57 years. The unadjusted cumulative incidence of hypertension was 35.8% at age 65 years and 69.2% at age 81 years. Estimates of incidence at the end of follow-up were variable because the staggered enrollment over 17 years resulted in a small number of men with follow-up to age 75 years. Therefore, the cumulative incidence rates were reported at ages 40, 55, and 70 years (Table 2). The cumulative incidence of hypertension by age 40 years was 4 times greater in men whose parents had hypertension (5.3%) than in those whose parents did not (1.3%). A progressive increase in hypertension incidence associated with parental hypertension was seen throughout follow-up; it was lowest in men without parental hypertension and highest in men with hypertension in both parents (Figure 2).

Compared with the risk for men without a hypertensive parent, the HR (95% CI) of developing hypertension was 1.6 (1.3-2.1) for men whose mother had hypertension, 1.8 (1.4-2.4) for men whose father had hypertension, and 2.7 (2.0-3.5) for men with hypertension in both parents after time-dependent adjustment for BMI, alcohol consumption, coffee drinking, physical activity, and cigarette smoking. Early onset of hypertension in the parents carried even greater risk. Men whose mother and father had developed hypertension at age 55 years or younger had a 7.1-fold (95% CI, 4.1-12.2) higher risk of developing hypertension during their adult life compared with those without a hypertensive parent. This excess risk was not affected by adjustment for the variables listed in Table 3 (adjusted model 1) and was not explained by the higher SBP and DBP readings at baseline in men with parental hypertension (adjusted model 2). The calendar year when parental hypertension was first reported was not associated with hypertension risk after adjustment for parents’ age at onset of their hypertension. Participants whose parents had early-onset hypertension experienced an even lower risk (1.6 times greater).

### Table 1. Characteristics of 1160 White Men Assessed in Medical School by Parental Hypertension Status at the End of Follow-up: The Johns Hopkins Precursors Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Neither Parent</th>
<th>Mother Only</th>
<th>Father Only</th>
<th>Both Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, No. (%)</td>
<td>1160 (100)</td>
<td>459 (40)</td>
<td>327 (28)</td>
<td>208 (18)</td>
<td>166 (14)</td>
</tr>
<tr>
<td>Age at graduation, y</td>
<td>26.4 (2.4)</td>
<td>26.4 (2.6)</td>
<td>26.6 (2.8)</td>
<td>26.2 (1.9)</td>
<td>26.1 (1.8)</td>
</tr>
<tr>
<td>Alcohol, drinks/wk</td>
<td>6.5 (4.0)</td>
<td>6.6 (4.0)</td>
<td>6.7 (4.1)</td>
<td>6.6 (4.2)</td>
<td>6.1 (3.5)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.1 (2.5)</td>
<td>22.9 (2.2)</td>
<td>23.2 (2.6)</td>
<td>23.2 (2.7)</td>
<td>23.1 (2.7)</td>
</tr>
<tr>
<td>Coffee intake, cups/d</td>
<td>2.3 (1.8)</td>
<td>2.3 (1.8)</td>
<td>2.3 (1.9)</td>
<td>2.3 (1.9)</td>
<td>2.0 (1.9)</td>
</tr>
<tr>
<td>Exercise/wk</td>
<td>0.8 (1.0)</td>
<td>0.8 (1.1)</td>
<td>0.8 (1.1)</td>
<td>0.8 (1.0)</td>
<td>0.7 (1.0)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>115.3 (8.7)</td>
<td>114.4 (8.3)</td>
<td>116.1 (8.8)</td>
<td>115.1 (8.6)</td>
<td>116.6 (9.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.5 (6.5)</td>
<td>68.4 (6.3)</td>
<td>69.8 (6.6)</td>
<td>70.3 (6.5)</td>
<td>70.8 (6.2)</td>
</tr>
<tr>
<td>Cigarette smokers, No. (%)</td>
<td>547 (51)</td>
<td>217 (53)</td>
<td>180 (62)</td>
<td>99 (52)</td>
<td>71 (45)</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
<sup>a</sup>Values are expressed as mean (SD) unless otherwise indicated.
<sup>b</sup>The median (interquartile range) age at onset for paternal and maternal hypertension was 61 (53-70) and 63 (54-71) years, respectively.
<sup>c</sup>The distribution of parental hypertension at baseline was as follows: neither parent, 896; father only, 127; mother only, 117; and both parents, 20.
<sup>d</sup>P<.01 (1-way analysis of variance).
<sup>e</sup>P<.001 (1-way analysis of variance).

### Figure 1

Systolic (A) and diastolic (B) blood pressure (BP) and age by parental hypertension status in 1160 white men (nonparametric regression analysis, lowess smoothing fit of 15723 BP measurements).
higher risk of hypertension at younger ages. Participants with both parents with early-onset hypertension were estimated to have a 20-fold higher adjusted risk of developing hypertension at age 35 years, compared with those without parental hypertension (Table 4). Risk estimates associated with early-onset parental hypertension declined progressively with older age.

When parental hypertension status by the participants' age of 35 years was used as the predictor, the adjusted HRs (95% CIs) for the development of hypertension at the age of 35 years were 20.4 (8.9-46.6), 3.0 (1.7-5.2), and 2.9 (1.6-5.0) among men with early-onset hypertension in both parents, men with early-onset hypertension in only 1 parent, and men with parents with only late-onset hypertension, respectively, compared with men who had hypertension-free parents at 35 years of age. The corresponding age-specific adjusted HRs (95% CIs) for the development of hypertension at age 45 years of age were 9.84 (5.5-17.5), 3.7 (1.6-5.0), and 2.4 (1.7-3.5), and 2.2 (1.5-3.2). The reference group in this set of analyses included men whose parents developed hypertension after their sons were older than 35 years.

We also examined the impact of parental hypertension among those at lowest risk of hypertension (n = 625) whose BMI was lower than 25 and who never drank more than 14 drinks of alcohol per week throughout follow-up to age 50 years. The risk estimates associated with parental hypertension were very similar to those based on the entire cohort. Participants with both parents with early-onset hypertension had a 7.40-fold (95% CI, 3.59-15.25) higher adjusted risk of developing hypertension, while participants with one parent with early-onset hypertension and the other parent having late-onset or no hypertension had a 2.89-fold (95% CI, 2.01-4.17) higher adjusted risk.

In this long-term prospective study, paternal hypertension and maternal hypertension were both strongly and independently associated with higher BP readings as well as with the development of hypertension over the adult life course. The higher BP readings at the end of adolescence and the greater increase in BP measurements, mainly SBP, during the adult life in men with parental hypertension placed those men at higher risk for future hypertension. Men with both parents with hypertension or men with 1 parent who was hypertensive before the age of 55 years had a much higher risk of developing hypertension, especially at a younger age.

Hypertension has been long recognized to run in families. The heritable portion of BP is estimated to range between 35% and 65%. This BP concordance within families is likely attributable both to shared environmental exposures and to genetic susceptibility. For example, BP concordance between spouses is greater than that between nonspouses, and it is greater among biological siblings than among adoptive siblings living in the same household. Concordance is also greater among monozygotic twins than among dizygotic twins. The shared genetic susceptibility is likely the result of many genetic variants acting together to increase BP.

While the familial component of BP is well described, the risk of hypertension developing as a result of family history has not been well quantified. In a large cross-sectional study, Stamler et al found that a parental history of hypertension was associated with twice the risk of the development of hypertension. However, cross-sectional studies are subject to recall bias. Persons with hypertension are probably more likely than those without hypertension to know if their parents had hypertension. Prospective studies of young persons have minimized this bias by assessing family history before the participants develop hypertension. In the first reported prospective study, age and follow-up time-adjusted incidence of hypertension was 1.7 times greater among men with a parental history of hypertension than among those
The risks associated with a family history of hypertension ranged from 1.7 for older men to 2.5 for younger men after 13 years of follow-up. The authors postulated greater knowledge of family medical history among women and better detection of hypertension in mothers than fathers as possible explanations of their findings. In our longitudinal study, parental hypertension, as measured in our study, may be more feasible to assess in the clinical setting than the complete family history of hypertension. The strengths of this study include the repeated assessments of incident hypertension in the parents, the very high response rates at baseline and follow-up, and the repeated measures of BP and possible confounders during a median follow-up of 37 years. Cohort members are physicians, and their self-reports have been further validated. Other unique features include the ability to account for, in a time-varying fashion, potential confounding factors assessed throughout the adult life and the ability to examine the effect of parental hypertension not only on risk of hypertension but also on rate of BP change over the adult life. The nonparametric analysis using lowess smoothing allowed exploration of BP trajectories by parental hypertension status without the assumptions mandated by parametric models. Longitudinal analysis using mixed-effects modeling accounted for changes in BP due to age, intra-individual correlation in BP over time, and the influence of other time-dependent confounders. Analyses using calendar year when parental hypertension occurred suggest that changes in the definition of hypertension during the long period of follow-up did not appreciably alter the estimated risk associated with parental hypertension. The results presented herein, however, are strictly generalizable.

### Table 3. Hazard Ratios of Incident Hypertension Associated With Parental Hypertension (Cox Proportional Hazards Analysis of 1160 White Men)

<table>
<thead>
<tr>
<th>Parental Hypertension</th>
<th>No.</th>
<th>Unadjusted</th>
<th>Adjusted Model 1</th>
<th>Adjusted Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>459</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mother only</td>
<td>327</td>
<td>1.7 (1.4-2.2)</td>
<td>1.6 (1.3-2.1)</td>
<td>1.5 (1.2-2.0)</td>
</tr>
<tr>
<td>Father only</td>
<td>208</td>
<td>1.9 (1.5-2.5)</td>
<td>1.8 (1.4-2.4)</td>
<td>1.8 (1.4-2.4)</td>
</tr>
<tr>
<td>Both parents</td>
<td>166</td>
<td>2.6 (2.0-3.5)</td>
<td>2.7 (2.0-3.5)</td>
<td>2.4 (1.8-3.2)</td>
</tr>
<tr>
<td>None</td>
<td>459</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>One parent, late onset</td>
<td>375</td>
<td>1.7 (1.3-2.1)</td>
<td>1.6 (1.2-2.0)</td>
<td>1.5 (1.2-2.0)</td>
</tr>
<tr>
<td>Both parents, late onset</td>
<td>86</td>
<td>1.9 (1.3-2.7)</td>
<td>1.9 (1.3-2.7)</td>
<td>1.7 (1.2-2.5)</td>
</tr>
<tr>
<td>One parent, early onset</td>
<td>160</td>
<td>2.2 (1.7-3.0)</td>
<td>2.0 (1.5-2.7)</td>
<td>1.9 (1.4-2.6)</td>
</tr>
<tr>
<td>One parent, early onset; other parent, late onset</td>
<td>62</td>
<td>3.2 (2.2-4.7)</td>
<td>3.4 (2.3-4.9)</td>
<td>3.1 (2.1-4.6)</td>
</tr>
<tr>
<td>Both parents, early onset</td>
<td>18</td>
<td>6.6 (3.9-11.3)</td>
<td>7.1 (4.1-12.2)</td>
<td>6.2 (3.6-10.7)</td>
</tr>
</tbody>
</table>

*Adjusted for time-dependent covariates: body mass index, number of cigarette smoked per day, drinks of alcohol consumed per week, cups of coffee consumed per day, and frequency of exercise per week.

Table 4. Hazard Ratios of Hypertension Developing at Specific Ages Associated With Early- and Late-Onset Parental Hypertension Compared With No Parental Hypertension (Cox Proportional Hazards Analysis of 1160 White Men)

<table>
<thead>
<tr>
<th>Age at Risk, y</th>
<th>Hazard Ratio a (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1.9 (1.1-3.3) 3.1 (1.7-5.6) 20.0 (8.4-47.9)</td>
</tr>
<tr>
<td>35</td>
<td>1.7 (1.2-2.5) 2.6 (1.7-3.9) 10.3 (5.6-18.9)</td>
</tr>
<tr>
<td>45</td>
<td>1.6 (1.2-2.1) 2.2 (1.7-2.9) 5.3 (2.6-10.6)</td>
</tr>
<tr>
<td>55</td>
<td>1.5 (1.1-2.0) 1.9 (1.3-2.7) 2.7 (0.9-7.8)</td>
</tr>
<tr>
<td>65</td>
<td>1.4 (0.9-2.2) 1.6 (0.9-2.7) 1.4 (0.3-6.3)</td>
</tr>
</tbody>
</table>

a Adjusted for baseline systolic and diastolic blood pressure readings and time-dependent covariates: body mass index, number of cigarette smoked per day, drinks of alcohol consumed per week, cups of coffee consumed per day, and frequency of exercise per week.

b Including 1 late only and both late.
cc Including 1 early only and 1 early, 1 late.
only to white men with high socioeconomic status. Information on other dietary factors associated with hypertension incidence, such as dietary intake of sodium, potassium, and fiber, was not available. Therefore, our results do not allow us to estimate what portion of the risk associated with parental history is attributable to these lifestyle variables. Although residual confounding cannot be completely ruled out, multivariate analyses (Table 3) and analyses using the low-risk subgroup suggest that little of the effect of parental history of hypertension was mediated through inherited patterns in adiposity, cigarette smoking, alcohol use, coffee drinking, and physical activity.

Men with a parental history of hypertension are at high risk of developing hypertension. In a recent editorial, Guttman et al13 called the "failure to realize the value of family history in dealing with more common, multifactorial disorders," such as hypertension, a disservice to patients and cited "common underestimation by clinicians of the value of family history" as a top obstacle to a more consistent and more effective use of such information in providing care to patients. Our findings emphasize the importance of asking patients about parental hypertension to identify those who are at high risk of developing hypertension, especially at a young age, for both population-based and individual-level interventions.14-16 They also underscore the importance of primary prevention and BP monitoring early in life for both white men and for those with at least one parent with early-onset hypertension.

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Additional Contributions: The dedicated participation of the members of the Johns Hopkins Precursors Study cohort over 54 years made this work possible.

REFERENCES


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