Body Mass Index and Risk of Incident Hypertension Over the Life Course
The Johns Hopkins Precursors Study

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Background—The obesity-hypertension link over the life course has not been well characterized, although the prevalence of obesity and hypertension is increasing in the United States.

Methods and Results—We studied the association of body mass index (BMI) in young adulthood, into middle age, and through late life with risk of developing hypertension in 1132 white men of The Johns Hopkins Precursors Study, a prospective cohort study.

Over a median follow-up period of 46 years, 508 men developed hypertension. Obesity (BMI ≥30 kg/m²) in young adulthood was strongly associated with incident hypertension (hazard ratio, 4.17; 95% confidence interval, 2.34–7.42). Overweight (BMI 25 to <30 kg/m²) also signaled increased risk (hazard ratio, 1.58; 95% confidence interval, 1.28–1.96). Men of normal weight at age 25 years who became overweight or obese at age 45 years were at increased risk compared with men of normal weight at both times (hazard ratio, 1.57; 95% confidence interval, 1.20–2.07), but not men who were overweight or obese at age 25 years who returned to normal weight at age 45 years (hazard ratio, 0.91; 95% confidence interval, 0.43–1.92). After adjustment for time-dependent number of cigarettes smoked, cups of coffee taken, alcohol intake, physical activity, parental premature hypertension, and baseline BMI, the rate of change in BMI over the life course increased the risk of incident hypertension in a dose-response fashion, with the highest risk among men with the greatest increase in BMI (hazard ratio, 2.52; 95% confidence interval, 1.82–3.49).

Conclusions—Our findings underscore the importance of higher weight and weight gain in increasing the risk of hypertension from young adulthood through middle age and into late life. (Circulation. 2012;126:2983–2989.)

Key Words: body mass index ■ hypertension ■ follow-up studies ■ longitudinal studies ■ cohort studies ■ men

Epidemiological evidence suggests that the prevalence of hypertension is increasing,1,2 and obesity is a major public health concern.3 Previous investigations of the association between obesity and hypertension have been based on cross-sectional comparisons,4–11 short follow-up intervals,11–19 few assessments of blood pressure and weight,11,13,15–17,20–23 follow-up only through middle age,17,19,22,24 and adjustment only for baseline characteristics that are known to change with age.12,22 Uncertainty remains about the magnitude of the risk of hypertension with obesity and overweight over the life course, and specifically, how changes in weight might modify the risk of hypertension against a background of secular and individual changing lifestyles.

Clinical Perspective on p 2989
The life course perspective contends that lifestyle and behavior in youth and middle age exert their influence on health later in life through established patterns and accumulation of effects that may take years to develop.25 We sought to estimate the association of weight and weight change from young adulthood into middle age and through late life with risk of developing hypertension in The Johns Hopkins Precursors Study. This longitudinal cohort of former medical students consists of >5 decades of follow-up with repeated, validated measures of body weight, blood pressure, and other lifestyle factors known to be associated with blood pressure. In contrast to studies that rely on retrospective reports of body
weight or lifestyle factors, the present study design provides considerable advantages, because we have many assessments of the purported risk factor and factors that might distort estimates of risk (such as smoking, alcohol consumption, and levels of physical activity). Our primary hypothesis was that overweight and obesity would confer risk even when arising in middle age and late life, consistent with a model of accumulating risk throughout the life course.

Methods

Study Sample

The Johns Hopkins Precursors Study, initiated in 1947 by Caroline Bedell Thomas to identify precursors of cardiovascular disease and premature death, represents 57 years of a longitudinal cohort consisting of 1337 students who matriculated into the graduating classes of 1948 to 1964 of The Johns Hopkins University School of Medicine. Study procedures were approved by the School of Medicine Institutional Review Board.

Analysis was based on a median follow-up of 46 years. Yearly response rates average ~75%, with 90% of the cohort responding at least once every 5 years. We excluded the small number of women (n = 121). Men of Asian ancestry (n = 19), who had hypertension before graduation (n = 19), who had no body mass index (BMI) measurement at baseline (n = 23), who were not available for follow-up (n = 12), or who had no blood pressure measurements over follow-up (n = 10) were excluded. One man whose age at baseline was more than twice the median age of the cohort (23 years) at baseline was excluded. The remaining 1132 white men constitute the sample.

Measurement Strategy

Body Mass Index

BMI, calculated as weight in kilograms divided by the square of height in meters, is an indicator of adiposity used for clinical and public health purposes. In medical school, participants underwent a standardized medical history and physical examination that included measurement of height, weight, and blood pressure. Follow-up consisted of annual mailed questionnaires. From 1954 to 1985, questions about body weight were asked every 3 to 5 years. After 1985, questions on body weight were asked annually except in 1986, 1987, 1990, 1991, 1995, and 1996. Body weight and height have been validated in this cohort, with self-reported height and weight highly correlated with measured weight (r = 0.98) and height (r = 0.95). Height at baseline was used to calculate BMI during follow-up when weight was reported. Keeping the height the same throughout follow-up ensured that any changes in BMI were reflective of changes in weight. The prevalence of missing weights ranged from 5% to 10%, depending on the age. For each of the age decades, the percentage of participants for whom we had the actual BMI values were as follows: For ages between 20 and 29 years, 96.3%; for 30 to 39 years, 91.8%; for 40 to 49 years, 94.3%; for 50 to 59 years, 90.0%; and for 60 to 69 years, 89.7%. We estimated missing weights using a random effects model that combined individual weights from the years available over follow-up with cohort-wide data on linear trends in weight change over the entire follow-up period.

Blood Pressure

Blood pressure was assessed on multiple occasions (a median of 9 times) while the participants were in medical school by use of a standardized protocol. The mean level of measurements in medical school was used to estimate the baseline blood pressure for the present analysis. During follow-up, using annual questionnaires, participants were asked to measure their blood pressure in the right arm in a seated position after 5 minutes of rest. In this sample, self-reported blood pressure was highly correlated with measured systolic (r = 0.72) and diastolic (r = 0.56) blood pressure, comparable to the published correlation between ambulatory and clinic blood pressure measurements.

Questionnaires included an inquiry about a diagnosis of and treatment for hypertension. Hypertension was defined as a blood pressure of 160/95 mm Hg reported on 1 annual questionnaire, 140/90 mm Hg on 2 or more occasions, or hypertension that required drug treatment. The mean of all reported blood pressure values was used when participants reported >1 blood pressure reading on a questionnaire. These criteria for hypertension are consistent with our prior work and are conservative compared with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. A total of 35 268 blood pressure measurements yielded 16 821 annual blood pressure estimates. For participants who met criteria for hypertension, onset was defined as the first reported elevated reading. An end-point committee that consisted of 5 physicians reviewed annual questionnaires, blood pressure reports, and medical records to reach consensus on the diagnosis of hypertension.

Covariates

Assessment of cigarette smoking, alcohol intake, physical activity, and coffee drinking was performed with standard questions at baseline and follow-up. Cigarette smoking and coffee drinking were defined by time-dependent dichotomous variables that reflected changes in smoking behavior and coffee drinking during the entire follow-up. Methods of assessment of physical activity and alcohol intake varied over the follow-up. Physical activity was assessed in medical school and over follow-up with the question, “How much physical training have you had in the past month?” with response categories “none,” “little,” “moderate,” or “much.” In 1978, 1986, 1989, 1993, 1997, 2000, and 2003, participants were asked the number of times per week they engaged in physical activity vigorous enough to work up a sweat. Alcohol intake was assessed in medical school and every 5 years after graduation until 1984 by asking, “How much do you drink?” Possible responses were “never,” “occasional,” “varies,” and “regular.” In 1978, 1986, and later, a quantity-frequency measure of alcohol consumption was administered. On the basis of data from 1978, when both questions were asked, alcohol intake data from all questionnaires were converted to a quantity-frequency scale. Responses to both questions have been strongly related to the incidence of hypertension in this cohort. Parental history of hypertension was defined as a participant’s report of hypertension in a parent at baseline or at any point during follow-up, or a diagnosis of hypertension as either an underlying or other condition reported on the death certificate of a participant’s parent. Parental premature hypertension was defined as the development of hypertension before age 55 years in a participant’s father or before age 65 years in his mother. Hypertension in both parents had a strong independent association with incident hypertension in this study cohort.

Statistical Analysis

We estimated cumulative incidence of hypertension associated with BMI at baseline for 3 categories of BMI (normal [<25.0 kg/m²], overweight [25.0 to <30.0 kg/m²], or obese [≥30.0 kg/m²]) and BMI change using the Cox proportional hazards model. We estimated BMI with hypertension incidence was also assessed with BMI as a time-dependent continuous variable and with BMI at ages 25, 45, and 65 years. We used a standard time-dependent approach, following each participant until development of hypertension or censoring, and updated the BMI for every participant during the follow-up interval. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) relating BMI to risk of hypertension were constructed with the Cox proportional hazards model. Proportionality assumptions were assessed for Cox proportional hazards models with log-log plots for baseline BMI analyses and Schoenfeld tests for time-dependent analyses. In survival models, age was the time variable, and persons who died were considered as censored.
To examine the hypothesis that risk of hypertension varied by the trajectory of BMI over the life course, we derived slopes of rate of BMI change, up to the age of diagnosis of hypertension, using random effects models. Participants without hypertension were kept in the analysis until the end of follow-up. The HR of hypertension associated with rate of BMI change over follow-up was calculated with quartiles of rate of BMI change modeled as a categorical variable in Cox proportional hazards analysis. Multivariate models were developed to adjust for possible confounding variables, including parental premature hypertension and time-dependent data during follow-up on number of cigarettes smoked, cups of coffee taken, alcohol intake, and physical activity. To estimate the effect of change in BMI category over 20 years (from early adulthood to middle age) on the risk of incident hypertension, we modeled change in BMI from age 25 to age 45 years as a time-dependent variable in Cox proportional hazards analysis. Tests of significance were 2-tailed with $\alpha=0.05$.

### Results

#### Sample Characteristics

Table 1 summarizes the characteristics of the 1132 men in medical school. The median BMI at baseline was 23.1 kg/m$^2$. The mean age of men in all 3 BMI categories was similar (23 years), and they all had a normal mean diastolic blood pressure. Obese men had the highest mean systolic blood pressure of 127 mm Hg and were more likely to smoke cigarettes (82%) than others. BMI in medical school was not related to coffee intake, alcohol drinking, physical activity, or a history of parental premature hypertension.

#### Incident Hypertension

During a median follow-up of 46 years, 508 men developed hypertension. The unadjusted cumulative incidence of hypertension was 0.3% at age 25 years, 6.5% at age 45 years, and 37% at age 65 years. A progressive increase in hypertension incidence was statistically significantly associated with higher BMI throughout follow-up (Figure).

### Association of BMI With Incident Hypertension

Compared with men with normal BMI at baseline, overweight men were at 1.5 times increased risk of developing hypertension (unadjusted HR, 1.58; 95% CI, 1.28–1.96; Table 2). Men who were obese at baseline had a $>4$-fold increased risk of developing hypertension (unadjusted HR, 4.17; 95% CI, 2.34–7.42). After adjustment for parental premature hypertension, alcohol drinking, physical activity, coffee drinking, and cigarette smoking at baseline, the risk of developing hypertension compared with men with normal BMI at baseline was essentially unchanged. Proportionality assumptions were met for all models. Results were similar in models that adjusted for time-dependent covariates. Cumulative incidence rates at age 65 years according to baseline BMI are provided in Table 2.

### Change in BMI and Incident Hypertension

Compared with the risk for men with normal BMI at age 25 years who remained so at age 45 years (Table 3), men who had normal BMI at age 25 years but were overweight or obese at age 45 years had a higher risk of developing hypertension (HR, 1.57; 95% CI, 1.20–2.07). Men who were overweight or obese at age 25 years who remained overweight or obese at age 45 years were at almost double the risk of developing hypertension (HR, 1.91; 95% CI, 1.46–2.49) compared with men who were of normal BMI at both age 25 and 45 years. The small number of men who were overweight or obese at age 25 years but who lost weight by age 45 years had an HR of 0.91 (95% CI, 0.43–1.92). Small numbers in change categories precluded the use of multivariate analyses. Cumulative incidence rates at age 65 years according to change in BMI category are provided in Table 3.

When BMI was treated as a time-dependent variable, for each 1-kg/m$^2$ higher BMI, the risk of developing hyperten-
sion was increased (HR, 1.06; 95% CI, 1.04–1.08). When BMI was examined at specific ages, a 1-kg/m² higher BMI was associated with higher risk of hypertension at age 25 years (HR, 1.12; 95% CI, 1.08–1.17), at age 45 years (HR, 1.12; 95% CI, 1.08–1.15), and at age 65 years (HR, 1.08; 95% CI, 1.02–1.14). When we considered the rate of change in BMI grouped according to quartiles, the risk of hypertension was higher in a dose-response fashion (Table 4). Point estimates associated with analysis of change in BMI were similar after multivariate adjustment.

**Discussion**

In this long-term prospective study, men who were overweight or obese in early adulthood or middle age were at higher risk of hypertension later in life. Overweight or obese men were consistently at higher risk of hypertension across the entire period of follow-up. Obesity in young adulthood conferred a 3-fold risk of hypertension, even after we accounted for change in lifestyle factors over the life course. Men who were of normal weight in early adulthood but who became overweight or obese in middle life were twice as likely to develop hypertension as men who maintained a normal weight. The corollary is that men who maintained normal weight were at the lowest risk of hypertension after 46 years of follow-up.

Previous investigations had short follow-up times, ascertainment of blood pressure subject to recall bias, assessment on only 2 occasions, or no adjustment for possible confounders during follow-up, or they were limited to a narrow age window that did not extend beyond middle age. The present study examined young adults and tracked their body weight and blood pressure through middle age and draws strength from very high response rates, adjudication of incident hypertension diagnosis, and repeated measures of blood pressure and lifestyle factors over 46 years. Unlike other studies, we estimated individual trajectories of weight over the life course using random effects models that allowed each person to have their own intercept and slope rather than being assigned a population average.

To gauge the extent to which BMI was related to hypertension risk in a dose-response fashion, we sorted respondents into quartiles based on rate of BMI change. Men in quartiles representing increasingly higher levels of BMI change were at increasingly higher risk, even after we accounted for baseline characteristics and lifestyle factors over follow-up.

**Table 2. HRs and Cumulative Incidence of Hypertension Associated With Baseline BMI Among 1132 Men in The Johns Hopkins Precursors Study**

<table>
<thead>
<tr>
<th>Baseline BMI</th>
<th>No. of Hypertension Cases</th>
<th>Cumulative Incidence of Hypertension at Age 65 y (Events/100)</th>
<th>Unadjusted HR</th>
<th>HR Adjusted for Baseline Characteristics*</th>
<th>HR Adjusted for Time-Dependent Characteristics†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (BMI &lt;25 kg/m²)</td>
<td>923</td>
<td>389</td>
<td>34 (31–37)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (BMI 25–&lt;30 kg/m²)</td>
<td>192</td>
<td>107</td>
<td>49 (42–57)</td>
<td>1.58 (1.28–1.96)</td>
<td>1.65 (1.29–2.09)</td>
</tr>
<tr>
<td>Obese (BMI ≥30 kg/m²)</td>
<td>17</td>
<td>12</td>
<td>78 (54–95)</td>
<td>4.17 (2.34–7.42)</td>
<td>4.83 (2.47–9.44)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals.

HR indicates hazard ratio; BMI, body mass index.

*Models adjusted for parental premature hypertension and number of cigarettes smoked, cups of coffee taken, alcohol intake, and physical activity measured at baseline.

†Models adjusted for parental premature hypertension and time-dependent number of cigarettes smoked, cups of coffee taken, alcohol intake, and physical activity.
The rate of change of BMI at any point during the life course was an independent predictor of risk, regardless of the level of BMI. Each 1-kg/m² higher BMI was associated with increased risk across the life course. For a 5-foot 9-inch-tall man at age 25 years, a 10-lb weight gain over the life course translates to an 18% increased risk of hypertension. For a 65-year-old man of the same height, a 10-lb weight gain translates to a 12% increased risk. Thus, even a small weight gain starting early in life increases the risk for hypertension, whereas small weight gains that do not occur until later in life continue to confer increased risk.

Few studies have examined the life course of BMI and risk of hypertension. Nyamdorj and coworkers¹³ assessed a community sample aged 25 to 74 years on 2 occasions 5 years apart and found that a 1-SD increase in BMI led to a 30% increased risk of hypertension compared with persons whose weight did not change. Chuang and colleagues²¹ used assessments of a young community sample on 2 occasions 10 years apart to find that an increase in BMI increased risk 15%. In the Nurses’ Health Study and the Health Professionals Follow-up Study, each increment in body weight assessed at baseline was associated with higher risk of hypertension after 10 years of follow-up, even within a range of BMI considered normal, but how risk of hypertension was modified by change in BMI was not reported. Consistent with our findings, Juonala and colleagues¹¹ pooled data from 4 prospective studies and found that for persons who were overweight or obese as children but not as adults, the risk of hypertension was comparable to the risk for children who remained at a normal BMI as adults. Adults who were obese were at increased risk, regardless of their weight in childhood, but in contrast to the present study, the mean age of the participants was 11 years at baseline, with a follow-up of 23 years.¹¹ We tested the hypothesis that overweight or obesity would confer risk of development of hypertension beyond young adulthood. None of the studies took a life course perspective or accounted for characteristics that change over time.

A methodological issue common to all longitudinal studies relates to misclassification of exposure (ie, body weight) or outcome (ie, hypertension). In the present sample, self-reports of body weight and blood pressure were highly accurate compared with in-person assessments.³¹ Misclassification because of a tendency to underreport weight or blood pressure at higher levels would be expected to bias our estimates toward the null. Indices of body fat may be most closely associated with incidence of hypertension,⁴⁶ and because body fat shifts from peripheral to central sites with age, BMI may be a less sensitive indicator of adiposity than waist-to-hip ratio.⁴⁷ Nevertheless, in men, BMI may be an adequate measure of percentage body fat.²⁷,⁴⁸ Because measurement of body fat was impractical, weight adjusted for height was used.⁴⁹ The present findings may not be generalizable to women, men of lower socioeconomic status, or ethnic minorities, especially with regard to absolute levels of risk, but our long-term perspective shows how body weight influences risk

### Table 3. HRs and Cumulative Incidence of Hypertension According to Change in BMI (kg/m²) From Early Adulthood to Middle Age Among 871 Men in The Johns Hopkins Precursors Study*

<table>
<thead>
<tr>
<th>BMI at Age 25 y</th>
<th>BMI at Age 45 y</th>
<th>No.</th>
<th>No. of Hypertension Cases</th>
<th>Cumulative Incidence of Hypertension at Age 65 y (Events/100)</th>
<th>Unadjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>584</td>
<td>224</td>
<td>29 (25–33)</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight or obese</td>
<td>Normal</td>
<td>19</td>
<td>7</td>
<td>23 (9–51)</td>
<td>0.91 (0.43–1.92)</td>
</tr>
<tr>
<td>Normal</td>
<td>Overweight or obese</td>
<td>138</td>
<td>68</td>
<td>42 (34–52)</td>
<td>1.57 (1.20–2.07)</td>
</tr>
<tr>
<td>Overweight or obese</td>
<td>Overweight or obese</td>
<td>130</td>
<td>73</td>
<td>51 (42–60)</td>
<td>1.91 (1.46–2.49)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals.

HR indicates hazard ratio; BMI, body mass index.

*Men who developed hypertension before age 45 years were excluded.

### Table 4. HR of Hypertension According to Rate of BMI Change (Slope) Quartiles Over 46 Years in 1132 Men in The Johns Hopkins Precursors Study

<table>
<thead>
<tr>
<th>Rate of BMI Change (Slope in kg/m² per Year)</th>
<th>Unadjusted HR</th>
<th>HR Adjusted for Baseline Time-Dependent Characteristics†</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quartile (−11.1 to −1.79)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Second quartile (−1.80 to −0.11)</td>
<td>1.35 (1.03–1.77)</td>
<td>1.43 (1.09–1.87)</td>
</tr>
<tr>
<td>Third quartile (−0.10 to 1.59)</td>
<td>1.84 (1.42–2.39)</td>
<td>1.94 (1.49–2.52)</td>
</tr>
<tr>
<td>Fourth quartile (1.60 to 15.9)</td>
<td>2.37 (1.84–3.06)</td>
<td>2.58 (1.99–3.33)</td>
</tr>
</tbody>
</table>

Slopes were derived from random effects models with BMI values up to the age of diagnosis of hypertension. Values in parentheses are 95% confidence intervals.

HR indicates hazard ratio; BMI, body mass index.

*Models adjusted for parental premature hypertension and baseline number of cigarettes smoked, cups of coffee taken, alcohol intake, physical activity, and BMI measured at baseline.

†Models adjusted for parental premature hypertension and time-dependent number of cigarettes smoked, cups of coffee taken, alcohol intake, physical activity, and BMI measured at baseline.
even after accounting for changing lifestyle factors. We have no reason to believe that the relationship between obesity and overweight with hypertension in the present sample is any different from other populations, even though the prevalence of risk factors may differ. No information on dietary factors associated with hypertension incidence was available. Multivariate analyses suggest little of the association of hypertension and BMI at baseline and over follow-up was mediated through family history of hypertension or important time-dependent factors associated with blood pressure.

The temporal relationship established by the long follow-up and repeated assessment of both body weight and blood pressure provides strong evidence for the association between trajectories of BMI and incident hypertension. Our findings suggest even a modest gain in weight beginning early in life was associated with a substantially higher risk of hypertension. Obesity and overweight continued to confer higher risk of hypertension even when they occurred late in life.

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**Disclosures**

None.

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None.

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Clinical Perspective

In this long-term prospective cohort study, we studied the association of body mass index with risk of developing hypertension from young adulthood into middle age and through late life. Repeated assessments of body mass index, blood pressure, and risk factors for developing hypertension over the life course enabled us to examine the influence of lifestyle and behavior in young adult life through middle age on health later in life. Obesity in young adulthood conferred a 3-fold risk of hypertension after 46 years of follow-up, even after we accounted for change in lifestyle factors over the life course. Men who were of normal weight in early adulthood but who became overweight or obese in midlife were twice as likely to develop hypertension as men who maintained a normal weight. Loss of weight between young adulthood and middle age conferred no additional risk. Rate of change of body mass index over the life course was an independent predictor of risk of hypertension, independent of the level of body mass index, cigarette smoking, alcohol intake, physical activity, and coffee drinking. Although the data were observational, the temporal relationship established by the long follow-up and repeated assessment of both body weight and blood pressure provided strong evidence for the association between body mass index and hypertension. This study showed that increase of weight at any time in the life course increased the risk of developing hypertension after adjustment for other risk factors.
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