Antecedent Blood Pressure, Body Mass Index, and the Risk of Incident Heart Failure in Later Life


Abstract— Higher blood pressure and body mass index (BMI) are risk factors for heart failure. It is unknown whether the presence of these risk factors in midadulthood affect the future development of heart failure. In the community-based Framingham Heart Study, we examined the associations of antecedent blood pressure and BMI with heart failure incidence in later life. We studied 3362 participants (57% women; mean age: 62 years) who attended routine examinations between 1969 and 1994 and examined their systolic and diastolic blood pressure, pulse pressure, and BMI at current (baseline), recent (average of readings obtained 1 to 10 years before baseline), and remote (average of readings obtained 11 to 20 years before baseline) time periods. During 67 240 person-years of follow-up, 518 participants (280 women) developed heart failure. Current, recent, and remote systolic pressure; pulse pressure; and BMI were individually associated with incident heart failure (all \( P < 0.001 \)). Recent systolic pressure (hazards ratio [HR] per 1-SD increment: 1.31; 95% CI: 1.11 to 1.55), pulse pressure (HR per 1-SD increment: 1.33; 95% CI: 1.14 to 1.54), and BMI (HR per unit increase: 1.15; 95% CI: 1.08 to 1.23) were associated with heart failure risk even after adjusting for current measures. Similarly, remote systolic pressure (HR per 1 SD: 1.17; 95% CI: 1.04 to 1.31), pulse pressure (HR per 1 SD: 1.17; 95% CI: 1.06 to 1.31), and BMI (HR per unit: 1.09; 95% CI: 1.05 to 1.14) remained associated with incident heart failure after adjusting for current measurements. Higher blood pressure and BMI in midlife are harbingers of increased risk of heart failure in later life. Early risk factor modification may decrease heart failure burden. (Hypertension. 2007; 50:1-2.)

Key Words: hypertension ■ blood pressure ■ obesity ■ body mass index ■ congestive heart failure ■ cohort studies

The incidence of heart failure increases exponentially in the seventh decade of life and beyond,\(^1\) with an overall lifetime risk of \( \approx 20\% \).\(^2\) Heart failure is often regarded, therefore, as a disease of the elderly. Given the substantial morbidity and adverse outcomes associated with heart failure, disease management guidelines have emphasized the importance of prevention.\(^3\) The development of preventive strategies requires a better understanding of the key risk factors for heart failure and the evolution of these risk factors over the life course. Previous data from the Framingham Heart Study\(^4-6\) and other community-based investigations\(^1,7-10\) have identified several major risk factors for heart failure. These previous studies have focused on risk factors measured on a single occasion and related their levels to heart failure occurrence.

Although previous studies have greatly advanced our understanding of risk factors for heart failure, they did not evaluate the contribution of potential risk factors at an earlier point in the life course, such as in midlife. There is evidence to suggest that lifetime exposure to risk factors enhances the risk of future heart failure development. It is widely accepted that cardiac remodeling, which predisposes to heart failure, evolves over time and in response to risk factor exposures.\(^3\) Blood pressure (BP) and body mass index (BMI) are important modifiable risk factors for heart failure.\(^1,4,5\) Previous observations suggest that higher levels of both BP and BMI averaged over decades are associated with increased left ventricular mass, which is a predictor of heart failure risk.\(^10-12\)

Based on the above data, we hypothesized that higher levels of BP and BMI in midlife would be powerful determinants of heart failure risk in later life and that the hazard conferred by antecedent measurements would remain even after accounting for these risk factors measured in later life.
To test our hypothesis, we prospectively examined the relations of antecedent BP and BMI measures obtained over a period of 2 decades in the midlife period of study participants and the risk of heart failure during longitudinal follow-up.

Methods

Study Sample and Design

The design and selection criteria of the original Framingham Heart Study have been reported elsewhere. The present investigation focused on systolic BP, diastolic BP, pulse pressure, and BMI because these variables: (1) are major risk factors for heart failure, (2) are modifiable with lifestyle or pharmacological interventions, (3) are easily measured, (4) were repeatedly measured at biennial Heart Study visits, and (5) are continuous variables that can be averaged for analyses. We used a sampling strategy for the present investigation that maximized the use of longitudinal biennial observations of this cohort (Figure 1). Participants were eligible: (1) if they attended a biennial examination between the 11th (1969–1971) and 22nd examination cycles (1991–1994) without previous heart failure, referred to as the baseline examination; (2) if they had data on BP and BMI (referred to as current measurements) and other covariates (risk factors for heart failure) at that examination; and (3) if they had ≥3 measurements of BP and BMI during the preceding decade (1 to 10 years; referred to as recent measurements) and ≥3 measurements 11 to 20 years before the baseline examination (referred to as remote measurements).

If participants attended multiple examinations within a decade, the first of those qualifying examinations (based on the above criteria) was considered the baseline examination; thus, a participant who attended examination cycles 11, 12, and 13 would be included in our study at the 11th biennial examination if at that examination he or she met all 3 of the eligibility criteria. This examination cycle was considered the baseline examination; thus, a participant who met all 3 of the eligibility criteria. This examination cycle was considered the baseline examination; thus, a participant who attended examination cycle 11 was eligible again in the next decade after the initial baseline examination; eg, participants attending examination cycle 11 were eligible again in the 1990s if they were free of heart failure and had ≥3 measurements of BP and BMI during the preceding decade (1 to 10 years; referred to as recent measurements) and had ≥3 measurements 11 to 20 years before the baseline examination (referred to as remote measurements).

Measurement of BP and Covariates

At each biennial examination, study participants underwent a physical examination (with medical history), laboratory assessment of cardiovascular disease risk factors, and routine electrocardiography. BP was measured twice by a physician with a mercury column sphygmomanometer, with the participant seated in a chair after a period of rest. The average of 2 such readings was taken as the examination BP. BMI was calculated as weight in kilograms divided by the square of height in meters. Hypertension was defined as BP ≥140/90 mm Hg or if the patient was on antihypertensive treatment. The status of other clinical risk factors was also determined at each examination. Diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dL, a casual value ≥200 mg/dL, or if the participant was receiving oral hypoglycemic agents or insulin for diabetes control. Current smoking was defined as having smoked ≥1 cigarette per day during the year preceding the baseline examination. Previous myocardial infarction was defined by the occurrence of symptoms, elevated circulating concentrations of myocardial necrosis markers, and electrocardiographic changes, which occurred before heart failure onset. Valve disease was defined by clinical criteria of a systolic murmur grade ≥3/6 or any diastolic murmur at a baseline examination.

Outcome

The primary outcome of this study was a validated first episode of heart failure occurring in the follow-up period after the baseline examination. All of the study participants were under routine surveillance for development of cardiovascular disease events, including heart failure. Information about incident cardiovascular events on follow-up was obtained with the aid of medical histories, physical examinations at the heart study, hospitalization records, and communication with personal physicians. All of the suspected new events were reviewed by a panel of 3 experienced investigators, who evaluated all of the available pertinent medical charts. Heart failure events were determined according to the previously published Framingham criteria. Briefly, a history of paroxysmal nocturnal dyspnea or orthopnea, presence of jugular venous distention, hepatojugular reflux, pulmonary rales, radiographic cardiomegaly, chest x-ray evidence of acute pulmonary edema, third heart
sound, central venous pressure >16 cm of water, and weight loss of >4.5 kg during the first 5 days of treatment for suspected heart failure constitute the major criteria. Bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, and heart rate >120 bpm comprise the minor criteria. The presence of 2 major or 1 major and 2 minor criteria was used to define an episode of heart failure. Criteria were attributed to heart failure only in the absence of an alternative explanation for the symptoms and signs by other medical conditions (eg, cirrhosis, renal failure, or chronic pulmonary disease).

Statistical Analyses
For each qualifying baseline examination and separately for each BP component and for BMI, we defined 3 measures for study participants (Figure 1), as follows: (1) current measure, at the baseline examination; (2) recent antecedent measure, the average of all of the available measurements during the decade preceding the baseline examination; and (3) remote antecedent measure, the average of all of the available measurements obtained 11 to 20 years before the baseline examination.

We determined the association of current (or baseline), previous, or remote measures of systolic BP, diastolic BP, pulse pressure, and BMI with the incidence of heart failure on follow-up using age-stratified Cox proportional hazards regression, after confirming that the assumption of proportionality of hazards was met. Age-stratified analysis was performed because of the potential for differing hazards for heart failure incidence across age categories; this analytical approach still yielded a single hazard ratio for all of the participants across all of the age strata. Participants were categorized into 4 strata (50 to 59, 60 to 69, 70 to 79, or ≥80 years), according to their age at the baseline examination. After verifying that there was no interaction of BP measures and BMI by sex, we performed analyses pooling men and women and adjusted for sex as a covariate.

Separate regression models were examined for current, recent, and remote antecedent measurements. Systolic BP, diastolic BP, and pulse pressure were evaluated in separate models. We estimated hazards ratios (HRs) for heart failure events for a 1-SD increment of the individual BP component and per unit increase in BMI.

Models were constructed hierarchically. First, current, recent, and remote BP and BMI measures were entered individually, adjusting for other heart failure risk factors including age, sex, serum cholesterol, hypertension treatment, diabetes mellitus, smoking, valve disease, and previous myocardial infarction (all defined at the baseline examination) and for incidence of an interim myocardial infarction on follow-up (multivariable models A). Participants who developed new-onset heart failure were defined to have had a primary outcome event, with censoring on death. Models for BP variables were adjusted for baseline BMI, and, conversely, models for BMI were adjusted for baseline systolic and diastolic BP (both entered as model covariates).

Second, we examined the association of antecedent (eg, previous or remote) BP and BMI when entered simultaneously with the corresponding baseline measures, adjusting for the clinical covariates noted above (multivariable models B). These analyses were performed to determine whether antecedent BP or BMI measures incrementally predicted heart failure above and beyond baseline (or current) measurements.

Secondary Analyses
We tested for effect modification by age, sex, hypertension status, obesity (<30 versus ≥30 kg/m²), and the calendar period of the baseline examination by modeling corresponding interaction terms (separately for current and antecedent BP and BMI measurements) in multivariable models. In addition, we repeated analyses for select subgroups defined at baseline: individuals without previous myocardial infarction or angina, participants without diabetes mellitus, people without valve disease, and subjects without electrocardiographic left ventricular hypertrophy (voltage criteria plus repolarization abnormalities).

Antecedent BP measures may predict risk of heart failure better than current BP simply because the former averaged several measures within a decade, whereas the latter, as a single determination, was more susceptible to regression dilution bias. Therefore, we also performed supplementary analyses modeling single random measures of current, recent, and remote antecedent BP and BMI.

To gain insights into the impact of changes in BP and BMI over time, we examined the effects of antecedent and current measures of these variables on the development of heart failure by cross-classifying individuals according to their current and remote hypertension or obesity status. Participants were classified as currently hypertensive if their current BP was ≥140/90 mm Hg or if they were on treatment with antihypertensive medications. The remote examinations of participants were also examined, and participants were classified as hypertensive if any BP was measured to be ≥140/90 mm Hg or if they were taking antihypertensive medications during that time. Participants were classified into 4 mutually exclusive groups that were compared for their hazard of heart failure: (1) remote nonhypertensive, current nonhypertensive (served as referent); (2) remote nonhypertensive, current hypertensive; (3) remote hypertensive, current nonhypertensive; and (4) remote hypertensive, current hypertensive. Similarly, the BMI of participants at the current and at the remote examinations was examined for the presence of obesity (BMI ≥30 kg/m²), and individuals were classified into 4 groups: (1) remote BMI <30 kg/m², current BMI <30 kg/m² (referent); (2) remote BMI <30 kg/m², current BMI ≥30 kg/m²; (3) remote BMI ≥30 kg/m², current BMI <30 kg/m²; and (4) remote BMI ≥30 kg/m², current BMI ≥30 kg/m². These groups were compared for their hazard of heart failure on follow-up.

Population-attributable risks (PARs) were calculated by determining the proportion of heart failure cases occurring among participants with risk factors (BP or BMI) exceeding the median value (p₂), and the multivariable-adjusted relative risk (RR, equivalent to HR from multivariable models) using the following equation:

\[ \text{PAR} = \frac{p_2 \times (RR - 1)}{RR} \times 100 \]

All of the analyses were performed using SAS version 8.2, and 2-sided P<0.05 was used to define statistical significance.

Results
Participants
The 3362 participants provided a total of 67 240 person-years of follow-up, and 518 individuals developed new-onset heart failure on follow-up, yielding an overall event rate of 0.92 per 100 person-years. The clinical characteristics of participants at the first qualifying baseline examination are shown in Table 1, including mean levels of systolic BP, diastolic BP, pulse pressure, and BMI for the baseline and antecedent time periods. Current levels of systolic BP and pulse pressure and BMI were higher compared with antecedent measurements.

Relations of Antecedent BP or BMI to Current Measurements
To examine the association of antecedent BP or BMI with current measurements of these variables, we examined the partial R² values for recent and remote measures, adjusting for age, sex, smoking status, and diabetes using multivariable linear regression. Models for current BMI were additionally adjusted for current systolic BP, and models for current BP were adjusted for current BMI. Adjusted recent and remote systolic BP only partly explained the variation in current SBP, with partial R² values of 0.571 and 0.251, respectively. Adjusted recent and remote diastolic BP only partly contrib-
Relations of Current or Antecedent BP to Heart Failure Risk

Modeled individually, higher levels of current, recent, and remote values of systolic BP and pulse pressure were associated with increased risk of heart failure (Table 2, Model A). An increment of 1 SD in recent systolic BP was associated with a multivariable-adjusted 36% increase in the risk of heart failure, and a 1-SD increase in pulse pressure conferred a 31% higher risk. Diastolic BP was not a significant predictor of heart failure in these models. In models that adjusted for current levels of corresponding BP measures, previous and remote systolic BP and pulse pressure remained significantly associated with incident heart failure (Table 2, Model B).
The relations of single measurements of antecedent BP and BMI, antecedent systolic BP, pulse pressure, and BMI measures with heart failure risk remained robust in analyses that additionally adjusted for current BP and BMI measurements, respectively. A single measure of current, previous, or remote DBP was not associated with heart failure development (Figure 2B), consistent with results in Table 2.

Cross-Classification of Participants According to Current Versus Remote BP and Obesity Status

Of the study cohort, 2274 individuals were nonhypertensive in both the remote and current time periods; 1787 were nonhypertensive in the remote time period but were currently hypertensive; 196 were hypertensive in the remote period but were nonhypertensive in the current time period; and 2045 were hypertensive in both the remote and current periods. For BMI, there was a graded risk of heart failure, which was highest in those with remote and current hypertension. Table 5 shows results of similar analyses for participants classified according to presence versus absence of obesity in the remote and current time periods. These analyses demonstrated an increase in heart failure risk, especially in those with a BMI \( \geq 30 \text{ kg/m}^2 \) in the remote time period.

### PARs

The PARs for systolic BP that were at or more than the median value in the current (\( \geq 138 \text{ mm Hg} \)), recent (\( \geq 137 \text{ mm Hg} \)), and remote (\( \geq 129 \text{ mm Hg} \)) time periods were 17%, 19%, and 16%, respectively. For pulse pressure, the PARs for a pulse pressure at or more than the median value were 17%, 19%, and 12%, respectively. Finally, the PARs for BMI, which were at or more than the median value in the current (\( \geq 25.8 \text{ kg/m}^2 \)), recent (\( \geq 25.8 \text{ kg/m}^2 \)), and remote (\( \geq 25.4 \text{ kg/m}^2 \)) time periods were 18%, 20%, and 22%, respectively.

### Discussion

In our longitudinal study of a large community-based cohort, we observed that antecedent systolic BP, pulse pressure, and BMI measured from \( \leq 20 \) years before a baseline examination were significant predictors of future heart failure risk. Furthermore, antecedent BP (systolic and pulse pressure) and BMI readings were associated with heart failure incidence even after accounting for current BP and BMI. These data suggest that effective heart failure prevention strategies are best conceived as lifelong initiatives rather than as beginning in the seventh decade, at which point in time the risk of developing the condition begins to escalate.

The lack of association of diastolic BP (current or antecedent) with heart failure risk is not surprising given that diastolic BP decreases in the elderly, paralleled by an increase in systolic BP that reflects the age-associated increase in pulsatile hemodynamic load (and pulse pressure). The effects...
of systolic BP and pulse pressure were similar in their magnitude of effect on heart failure risk. The correlations of systolic BP with pulse pressure may partly explain their similar magnitudes of effect: the age- and sex-adjusted correlation coefficients exceeded 0.85 in the current, recent, and remote time periods.

Comparison With Previous Reports
Several previous studies have related single baseline measurements of risk factors to incident heart failure. In these previous studies, baseline systolic BP, pulse pressure, and BMI in middle-aged-to-elderly cohorts were significant predictors of future heart failure risk. Previous investiga-

Table 5. Risk of Heart Failure According to Cross-Classification of Remote and Current Hypertension and Obesity Status

<table>
<thead>
<tr>
<th>Cross-Classified by Condition</th>
<th>Incidence of Heart Failure Events</th>
<th>Multivariable-Adjusted Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-Years of Follow-up</td>
<td>No. of Events/No. at Risk (%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote non-HTN, current non-HTN</td>
<td>20 793</td>
<td>75/2274 (3.3)</td>
</tr>
<tr>
<td>Remote non-HTN, current HTN</td>
<td>15 559</td>
<td>147/1787 (8.2)</td>
</tr>
<tr>
<td>Remote HTN, current non-HTN</td>
<td>1519</td>
<td>18/196 (9.2)</td>
</tr>
<tr>
<td>Remote HTN, current HTN</td>
<td>16 100</td>
<td>267/2045 (13.1)</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote BMI &lt;30, current BMI</td>
<td>44 967</td>
<td>346/5197 (6.7)</td>
</tr>
<tr>
<td>Remote BMI &lt;30, current BMI</td>
<td>4454</td>
<td>52/508 (10.2)</td>
</tr>
<tr>
<td>Remote BMI ≥30, current BMI</td>
<td>1162</td>
<td>32/163 (19.6)</td>
</tr>
<tr>
<td>Remote BMI ≥30, current BMI</td>
<td>4850</td>
<td>80/592 (13.5)</td>
</tr>
</tbody>
</table>

No. at risk refers to number of person observations.

*Multivariable adjustment for the following covariates: age, sex, BMI, smoking status, previous myocardial infarction, diabetes, valvular heart disease, and serum cholesterol (all defined at the baseline examination) and for incidence of an interim myocardial infarction on follow-up.

†Multivariable adjustment for the following covariates: age, sex, systolic and diastolic BP, smoking status, previous myocardial infarction, diabetes, valvular heart disease, hypertension therapy, and serum cholesterol (all defined at the baseline examination) and for incidence of an interim myocardial infarction on follow-up.
Mechanisms Underlying the Observed Associations

There are several potential reasons why antecedent BP and BMI measures predict heart failure in later life. First, long-term exposure to BP and BMI have been correlated with intermediate left ventricular remodeling phenotypes that are associated with future heart failure risk.\(^\text{11,23}\) Second, risk factors such as BP and BMI are dynamic and vary over the life course of individuals. Although the numerical value of BP or BMI on a single occasion may be similar in 2 individuals, their past exposure may be different and, therefore, contribute differentially to the propensity for heart failure. Third, we averaged antecedent BP and BMI based on \(\geq 3\) measurements. It is conceivable that regression dilution bias\(^\text{16}\) may explain the incremental information provided by using averaged multiple measurements of antecedent BP and BMI relative to single-occasion current measurements. It is noteworthy that this is unlikely to be the sole explanation for our observations, because even a single randomly selected antecedent BP or BMI measurement predicted heart failure incrementally over current BP and BMI.

Strengths and Limitations

The strengths of our investigation include the longitudinal design with routinely ascertained BP and BMI spanning over 4 decades, the standardized measurements of BP and BMI, and the use of the same criteria for a diagnosis of heart failure. We must acknowledge several limitations of our study, however. We did not examine the contributions of antecedent BP and BMI to the risk of systolic versus diastolic heart failure, largely because echocardiographic evaluation was not available in the initial 3 decades after the initiation of the Heart Study. In addition, our sample is predominantly white, and the generalizability of our findings to other ethnicities is unknown. Also, we focused on antecedent BP and BMI in our analyses because they are quantitative traits that can be averaged easily. We did not investigate the importance of antecedent levels of other categorical heart failure risk factors. Last, we did not examine the impact of change in BP or BMI levels over time on the risk of heart failure in the present investigation.

Perspectives

Although hypertension and high BMI detected in later life are associated with heart failure risk, the effects of these conditions likely begin far earlier. High BP and elevated BMI in midlife or earlier life may contribute to progressive remodeling of the heart and vasculature, which may predispose to heart failure decades later. Therefore, the prevention of heart failure should begin early in the life course and should include screening for elevated BP and BMI. Guidelines for primary prevention recommend regular, periodic BP checks beginning in early adulthood.\(^\text{24,25}\) Guidelines also recommend screening for obesity beginning in early adulthood and behavioral modification to reduce elevated BMI.\(^\text{24,26}\) However, elevated BP and obesity are often controlled suboptimally. In the case of hypertension, treatments in younger adults may not be initiated or may be delayed until sequelae develop.\(^\text{27–29}\) Failure to identify or treat such modifiable risk factors early may result in the loss of opportunities to reduce the incidence of heart failure in later life.

Conclusions

Our findings suggest that higher BP and excess BMI exert adverse effects over time, and the presence of these risk factors increases the risk of incident heart failure in later life. These data, although observational, are consistent with the notion that effective prevention of heart failure is best achieved by adequate control of BP and BMI throughout the life course of individuals.

Appendix

Sampling Strategy

In our analyses, we included participants who had \(\geq 1\) examination between exams 11 and 22 (inclusive). The first examination in this period is considered the initial baseline examination; a participant could have \(\leq 3\) baseline exams, with a new baseline starting every 10 years. There were 3703 such participants eligible. We excluded 90 participants with prevalent heart failure (before the initial baseline examination) to yield 3613 participants. We further excluded 205 participants who did not have \(\geq 3\) values of BP or BMI measurements in the previous decade for any of their 3 baseline exams. If a participant’s initial baseline examination did not have \(\geq 3\) BP/BMI measurements in the previous decade, but a subsequent baseline examination had \(\geq 3\) BP/BMI measurements in the previous decade, then the subsequent baseline examination was considered the initial baseline examination (even with this algorithm, all of the subjects had their initial baseline examination between examinations 11 and 22, inclusive). This yielded 3408 eligible participants. We excluded 46 additional participants who did not have a complete risk factor profile for any of their 3 baseline examinations. If a participant’s initial baseline examination did not have a complete risk factor profile, but a subsequent baseline examination did, then this subsequent baseline examination was considered the initial baseline examination. Again, with this algorithm, all of the subjects had an initial baseline examination between examinations 11 and 22, inclusive, with 84% having the initial baseline examination at the 11th examination cycle and 13% having the initial baseline examination at the 12th examination cycle. This yields 3362 participants for analysis.

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