Age-Associated Changes in Blood Pressure in a Longitudinal Study of Healthy Men and Women

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Background. Current knowledge of age-associated increases in blood pressure is based primarily on unscreened population studies that may not be representative of healthy men and women. We examined longitudinal patterns of change in blood pressure in healthy male and female volunteers from the Baltimore Longitudinal Study of Aging (BLSA).

Methods. Longitudinal mixed-effects regression models are used to estimate the age-associated changes in blood pressure in 1307 men (age 17–97) and 333 women (age 18–93) who have been followed for up to 32 years (mean: 8.4 years for men and 3.4 years for women) and who have been screened for health problems or medications that affect blood pressure.

Results. On average, systolic pressure is relatively stable in men and women until approximately age 45, increases at 5–8 mm Hg per decade in middle age, then accelerates in men and stabilizes in women. Diastolic pressure increases at 1 mm Hg per decade at all ages in men, whereas in women the rate of change in diastolic pressure increases in middle age and then plateaus and may decline after age 70. Additional findings include: (a) BLSA cross-sectional and longitudinal findings are more similar than has been observed in studies of unscreened samples; (b) there is no evidence of a gender cross-over in this group of healthy men and women; and (c) compared to previous studies of unscreened samples, healthy BLSA men and women show a weaker association between baseline blood pressure and subsequent rate of blood pressure change.

Conclusions. These findings suggest that several previously described age-associated patterns of blood pressure change partially reflect the effects of hypertension and its treatment, rather than intrinsic age changes in the blood pressure of healthy individuals.

It is generally believed that systolic blood pressure increases sharply with age in most industrialized societies and that diastolic pressure rises modestly and plateaus or declines after middle age (1–4). A number of studies also indicate that average systolic and diastolic pressures are higher in women than men after age 45–55 (1–4). To a great extent, this view of age-associated differences in blood pressure has been derived from cross-sectional studies of populations which included individuals with known hypertension and other cardiovascular diseases. In contrast to cross-sectional studies, longitudinal data have produced inconsistent results regarding gender- and age-associated changes in blood pressure (3,5–14). However, the longitudinal studies have varied widely in inclusion criteria and in control for historical variations in the treatment of hypertension. The fact that the increase in blood pressure with age does not occur uniformly or universally (15–19) indicates that an increase in blood pressure with advancing age is not inevitable. Thus, the age-associated increase in blood pressure observed in unscreened population studies may not be representative of blood pressure changes in healthy men and women. Therefore, we have examined age-associated cross-sectional and longitudinal trends in blood pressure of 17- to 97-year-old male and female volunteers from the Baltimore Longitudinal Study of Aging (BLSA), who have been rigorously screened to exclude health problems or medication usage that might affect blood pressure.

METHODS

Study population. — Participants are male and female volunteers in the BLSA, an open-panel multidisciplinary study of normal human aging that is conducted by the National Institute on Aging (20). Participants are predominantly White (95%) and well educated (over 75% have a bachelor’s degree or higher). The participants are scheduled to visit the Gerontology Research Center at approximately 2-year intervals where they stay for 2.5 days of evaluation and testing including a physical examination by a health care provider (i.e., physician, physician’s assistant, or nurse practitioner), inventory of medications used, and an intensive set of medical, physiological, and psychological evaluations.

Between 1958 and 1991, 1,478 men and 645 women had blood pressure measurements taken during one or more of their BLSA visits. Because blood pressure can be affected by various diseases or medications, we censored the data of 231 men and 97 women for visits following the diagnosis of any of the following conditions: probable or definite myocardial infarction, angina pectoris, or Q-wave abnormalities on resting ECG (Minnesota Code 1:1 or 1:2); stroke; aortic valvular disease; untreated thyroid disease; renal disease; diabetes; or congestive heart failure. Blood pressure measurements were also excluded at visits where the participants were taking the following medications: diuretics, antihyper-
tensive or cardiovascular medications, bronchodilators, in-
sulin, oral hypoglycemic agents, nonsteroidal antiinflamma-
tory drugs, central nervous system stimulants (2005 visits in
688 men; 976 visits in 420 women), or had other conditions
that might affect blood pressure (hemoglobin $\geq 17.0$ g or
serum creatinine $\geq 1.5$ mg/dL; 206 visits in 154 men, no
visits in women). In addition, any blood pressure measure-
ments taken within 2 years of death (49 visits in 44 men and
5 visits in 5 women) were excluded to avoid any bias due to
occult diseases that might have affected blood pressure. The
censoring and visit exclusions resulted in the exclusion of all
data for 44 men and 312 women. Thus, the final screened
male study group consists of a total of 4,422 observations on
1,037 men (70% of all BLSA men) whose beginning age in
the study was between 17.2 and 96.7 years, and the screened
female study group consists of a total of 749 observations on
333 women (52% of all BLSA women) whose beginning age
in the study was between 18.6 and 92.7 years (Table 1).

Procedures. — On the first day of each biennial visit,
BLSA volunteers undergo an extensive medical history and
physical examination. A seated blood pressure is taken in
both arms with a manual sphygmomanometer appropriately
sized to the arm of the participant. Systolic and diastolic
blood pressures are collected from anthropometric measure-
ments taken at each visit. Individuals are classified as current
cigarette smokers if they report smoking any cigarettes on a
regular basis at that visit.

<p>| Table 1. Characteristics of Longitudinal Follow-up in the Screened BLSA Group |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Age at First Visit</th>
<th>&lt; 30</th>
<th>30-39.9</th>
<th>40-49.9</th>
<th>50-59.9</th>
<th>60-69.9</th>
<th>70-79.9</th>
<th>80+</th>
<th>Total</th>
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<tr>
<td>Total Group</td>
<td>166</td>
<td>234</td>
<td>204</td>
<td>166</td>
<td>128</td>
<td>115</td>
<td>24</td>
<td>1037</td>
</tr>
<tr>
<td>Length of follow-up (yr)</td>
<td>(0.25,5)</td>
<td>(0.32,5)</td>
<td>(0.32,4)</td>
<td>(0.30,7)</td>
<td>(0.21,9)</td>
<td>(0.19,0)</td>
<td>(0.13,4)</td>
<td>(0.32,5)</td>
</tr>
<tr>
<td>Number of visits</td>
<td>3.6</td>
<td>4.5</td>
<td>5.5</td>
<td>4.4</td>
<td>3.7</td>
<td>3.2</td>
<td>2.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Interval between visits (yr)</td>
<td>(1,16)</td>
<td>(1,18)</td>
<td>(1,20)</td>
<td>(1,17)</td>
<td>(1,14)</td>
<td>(1,11)</td>
<td>(1,10)</td>
<td>(1,20)</td>
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<tr>
<td>Men</td>
<td>166</td>
<td>234</td>
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<td>166</td>
<td>128</td>
<td>115</td>
<td>24</td>
<td>1037</td>
</tr>
<tr>
<td>Women</td>
<td>48</td>
<td>68</td>
<td>39</td>
<td>61</td>
<td>55</td>
<td>44</td>
<td>18</td>
<td>333</td>
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</tbody>
</table>

Statistical methods. — The mean blood pressure at base-
line visit (± 95% confidence intervals) is reported for each
5-year age group in all BLSA participants and in the
screened group to determine the baseline comparability of
the two groups.

Linear mixed-effects regression models are used to ana-
lyze the longitudinal data (21,22). Mixed-effects models
allow estimation of the group-average blood pressure curve
and also allow each subject’s estimated longitudinal change
to deviate from the group average. Details of the linear
mixed-effects model are provided in the Appendix.

To determine whether the longitudinal 10-year rate of
change in blood pressure differs depending on baseline
blood pressure level, we use mixed-effects models to predict
the change in blood pressure levels. Linear regression
models are then used to examine the association between
estimated 10-year rate of change in blood pressure and
baseline estimated blood pressure level in individuals with
at least 6 years of follow-up ($n = 462$ men and 88 women).
A two-tailed $p$-value of less than .05 was required for statistical
significance in all analyses.

RESULTS

The number of participants is fairly evenly distributed
across the age range, although the number of participants
over age 80 is limited (Table 1). On average, men have
longer follow-up and more visits than women because
women were not recruited into the BLSA until 1978. Ap-
proximately 50% of the men have 5 or more years of follow-
up and 30% have 10 or more years. Approximately 30% of
the women have 5 or more years of follow-up and 11 % have
10 or more years. The screened groups represent a total of
8,711 person-years of follow-up in the men and 1,132
person-years of follow-up in the women. There is no evi-
dence of selective attrition from the BLSA with respect to
blood pressure. Blood pressures are not significantly differ-
ent in individuals who died or withdrew from the BLSA compared to participants who remained active ($p = .89$ and $p = .91$, respectively, for systolic and diastolic pressure in men; $p = .98$ and $p = .49$, respectively, in women). An analysis to identify birth cohort effects did not identify any consistent effects (data not shown).

Table 2 shows the proportion of participants who were hypertensive at their first examination and the distribution of changes in blood pressure observed over approximately 10 years (mm Hg per decade assessed at the examination nearest to 10 years after first exam). The proportion of hypertensives increases with age in both men and women but is lower in women in each age group. With increasing age, the proportion of men who exhibit increases in systolic blood pressure greater than 5 mm Hg per decade increases from 34% for men aged less than 40, to 48% for men aged 40–59.9, and 54% for men aged 60 and above, whereas 35–40% of women in each age group exhibit such increases (Table 2). For diastolic blood pressure, 35–45% of men and women exhibit increases greater than 5 mm Hg per decade regardless of age. However, men and women age 60 and above both show an increased proportion of individuals with decreases greater than 10 mm Hg per decade compared to younger ages.

Effect of screening. — Figure 1 shows the means ($\pm$ 95% confidence intervals) of the observed blood pressure levels at baseline visit by 5-year age groups for all BLSA participants and for rigorously screened men and women. The confidence intervals in Figure 1 and subsequent figures are wider in women than men because of the smaller number of observations in women. The cross-sectional results from the screened and unscreened data sets are nearly identical for diastolic pressure. However, systolic pressure is approximately 3–5 mm Hg higher in the unscreened men and women after age 60. Systolic pressure increases with cross-sectional age in both the screened and unscreened groups. Cross-sectionally, diastolic pressure appears to plateau between ages 50 and 60 in men and at approximately age 60 in women. Although gender differences in systolic and diastolic pressure narrow with age, there is no evidence of a gender cross-over in either the screened or unscreened data sets.

Cross-sectional vs longitudinal age effects. — Figure 2 and Table 3 show the systolic and diastolic pressure levels and longitudinal changes over 10 years of follow-up as estimated by the linear mixed-effects models. The blood pressure levels shown at the beginning of each 10-year longitudinal curve represent the cross-sectional estimates for different ages at entry into the BLSA. The cross-sectional and longitudinal results for both systolic and diastolic pressure are not significantly different in either sex, except for systolic pressure in men at ages 40 and 70 (Figure 2, Table 3). Forty-year-old men have higher systolic pressures at their initial visit than 30-year-old men who are followed longitudinally to age 40. However, blood pressures in these same men measured in the supine position at first awakening do not reveal a longitudinal decline in systolic pressure in 30-year-olds (data not shown). The lower initial systolic and diastolic pressures in the 70-year-old group of men compared to 60-year-old men who were followed to age 70 probably represent recruiting bias or selective survival. Men who join the BLSA at older ages tend to be healthier than men who joined at younger ages and who reach a similar age while in the study (23). Because of the shorter follow-up in women, this recruiting bias is less evident in female BLSA participants.

Prior to age 45–50, systolic pressure increases with age cross-sectionally but is relatively stable longitudinally in both sexes (Figure 2, Table 3). The longitudinal increase in systolic pressure is approximately 5 mm Hg per decade in both men and women at age 50. After age 50, the longitudinal rate of increase in systolic pressure accelerates to over 8 mm Hg per decade in men, whereas in women the rate of

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 40</td>
<td>40–59.9</td>
<td>Age ≥ 60</td>
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<td>Age ≥ 60</td>
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<tr>
<td>Percent hypertensive at first exam (systolic ≥ 140 or diastolic ≥ 90 mm Hg)</td>
<td>(58/400)</td>
<td>(96/370)</td>
<td>(109/267)</td>
<td>(1/116)</td>
<td>(8/100)</td>
<td>(37/117)</td>
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<td>Percent exhibiting change in blood pressure level (mm Hg/decade)</td>
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<tr>
<td>Systolic</td>
<td>n = 231</td>
<td>n = 215</td>
<td>n = 89</td>
<td>n = 24</td>
<td>n = 42</td>
<td>n = 30</td>
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<tr>
<td>&gt;10 decline</td>
<td>28%</td>
<td>21%</td>
<td>18%</td>
<td>14%</td>
<td>12%</td>
<td>19%</td>
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<td>8</td>
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<td>12</td>
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<td>8</td>
</tr>
<tr>
<td>5 decline to 5 increase</td>
<td>30</td>
<td>23</td>
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</tr>
<tr>
<td>&gt;10 increase</td>
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<td>36</td>
<td>33</td>
<td>33</td>
<td>21</td>
<td>23</td>
</tr>
</tbody>
</table>
increase slows to 4 mm Hg per decade at age 60 and is virtually flat after age 70.

Diastolic pressure increases longitudinally at a constant rate of 1 mm Hg per decade in men aged 30–80 (Table 3). However, in women, diastolic pressure changes minimally before age 40, increases at a rate of 3–4 mm Hg per decade during middle age, then plateaus at age 60, followed by evidence of a decline after age 70.

Gender differences. — Both cross-sectionally and longitudinally, women have significantly lower systolic and diastolic pressures than men at all ages (Figure 2, Table 3). The gender difference in systolic pressure narrows from approximately 12 mm Hg at age 30 to approximately 6 mm Hg at age 70, but there is no gender cross-over. The gender difference in diastolic pressure narrows only slightly from 5.8 mm Hg at age 30 to 4.3 mm Hg at age 70. Use of estrogen-containing medications (i.e., estrogen replacement therapy, contraceptives) does not significantly affect systolic or diastolic pressure in BLSA women overall (p = .59 for systolic and p = .73 for diastolic), or in women younger than 45 years (p = .87 for systolic and p = .58 for diastolic), women aged 45–
Baseline blood pressure and subsequent rate of change.
- In these healthy individuals, baseline blood pressure levels accounted for less than 5% of the variance in 10-year rate of change in blood pressure, except for systolic pressure in men. Figure 3 shows that high baseline systolic pressures tend to be associated with more rapid increases in systolic pressure in men of all ages. Baseline systolic pressure accounts for 14% of the variance in rate of change in systolic pressure. In men, each 10 mm Hg elevation in baseline systolic pressure is associated with approximately a 2 mm Hg per decade increase in the 10-year rate of change in systolic pressure, regardless of age.

DISCUSSION
Previous unscreened population studies have been extremely useful in understanding the medical and public health ramifications of the associations between chronologic age and blood pressure. However, the findings from unscreened samples may not be generalizable to healthy individuals. The present study has the advantages of careful screening to exclude individuals with diseases or medication usage that may affect the age-associated trends in blood pressure and a long-term longitudinal design across a broad age range in both sexes. Thus, these findings provide a clearer description of age-associated changes in blood pressure in these healthy BLSA men and women without the confounding influences of diseases or medications known to affect blood pressure. Additional findings include: (a) BLSA cross-sectional and longitudinal findings are more similar than has been observed in studies of unscreened samples; (b) there is no evidence of a gender cross-over in this group of healthy men and women; and (c) compared to previous studies of unscreened samples, healthy BLSA men and women show a weaker association between baseline blood pressure and subsequent rate of blood pressure change.

Age effects.
- The BLSA cross-sectional and longitudinal findings are generally quite similar. On average, systolic blood pressure is relatively stable in healthy men and women until middle age (approximately age 50 in men and age 40 in women), then increases by 5–8 mm Hg per decade. Women may show some longitudinal evidence of a plateau or decline in systolic blood pressure after age 70, but men do not. Diastolic pressure increases steadily in healthy BLSA men at a rate of 1 mm Hg per decade with no sign of a plateau or decline. Diastolic pressure in women is relatively stable between ages 30 and 40, increases significantly between ages 40 and 60, but then stabilizes and may decline slightly after age 70. Overall, systolic pressure increases about 15 mm Hg in men and 21 mm Hg in women over this interval.

Thus, these healthy BLSA men do not show any sign of a plateau or decline in systolic or diastolic pressure, whereas women exhibit a plateau for both systolic and diastolic pressure. This contrasts with other longitudinal results in unscreened samples in which systolic pressure did not plateau over time in either men or women, whereas diastolic pressure exhibited a plateau followed by a decline in both men and women (3); both systolic and diastolic pressure declined in men and women aged 65–98 years (5), or systolic pressure declined after age 65 in both men and women primarily due to secular trends in treatment of hypertension (24).

The similarity between the BLSA cross-sectional and longitudinal findings probably reflects the health and medi-
cation screening in our study. The screening minimizes the confounding effects of age-associated differences in the incidence and prevalence of hypertension and its treatment. Furthermore, our analyses do not reveal any significant selective attrition with respect to blood pressure in these healthy men and women. In contrast, the Framingham study (3) shows a more marked difference between cross-sectional and longitudinal results, perhaps because their results are based on an unscreened sample in whom selective mortality associated with hypertension would be expected to have a greater impact. Other studies have observed significant cohort differences in systolic and diastolic pressure in men and women over age 65 (5).

**Gender difference.** — BLSA women have lower blood pressures than men across the adult age span and do not exhibit the gender cross-over in systolic pressure which has been observed in most cross-sectional studies. In this study, longitudinal rates of change in blood pressure are similar between sexes. These findings are not affected significantly by use of estrogen-containing medications, although we could not control for dosage or individual medications. Diastolic pressure is approximately 4–6 mm Hg lower in women than in men at all ages, whereas the gender difference in systolic pressure shrinks from approximately 11 mm Hg lower for women at age 40 to only 5.5 mm Hg lower at age 70. This is similar to longitudinal results reported from the Framingham study, where the mean systolic pressures of men and women converge but do not cross over, and the age-associated trends for diastolic pressure are roughly parallel in men and women (3). The gender cross-over observed by others in unscreened samples may be related to a combination of selective mortality in men with elevated blood pressure, more aggressive treatment of hypertension in men, and perhaps age and cohort differences in the treatment of hypertension.

**Baseline blood pressure and subsequent rate of change.** — A number of studies in unscreened samples have reported a significant positive association between baseline blood pressure levels and subsequent rates of blood pressure change (9–12). In healthy BLSA men and women, baseline blood pressure level explains little of the variance in 10-year rate of change in blood pressure, except for a modest relationship for systolic pressure in men. The weaker association in these healthy volunteers suggests that the accelerated rise in blood pressure in men with higher initial pressures may reflect the progression of hypertension rather than an aging effect per se.

**Between-subject variability.** — Although average patterns can be detected, there is a significant degree of between-person variability in both blood pressure level and longitudinal pattern of change that makes it difficult to extrapolate the average trends to individual subjects. At any age, many individuals show little or no longitudinal increase in systolic or diastolic pressure. Thus, age-associated increases in blood pressure are neither universal nor inevitable.

**Study limitations.** — Although longitudinal studies allow a direct estimation of changes in blood pressure, they are still subject to possible confounding due to cohort effects, secular trends, selective attrition, and other factors. However, examination of the BLSA data revealed no evidence of these biases. Although our efforts to screen for medical problems that affect blood pressure might have missed some occult disease, this is unlikely to seriously bias the results because similar findings are obtained in the unscreened data. Since the BLSA study group is predominantly White and middle to upper class, these results may not be generalizable to minority or lower socioeconomic groups. Lastly, BLSA participants are health-conscious volunteers who may be more likely to take an active role in prevention and intervention efforts than the general population.

**Conclusions**

These findings demonstrate that in a group of male and female volunteers screened to exclude diseases and medication use that affect blood pressure, cross-sectional and longitudinal blood pressure patterns are more similar than is usually observed in unscreened population studies. In further contrast to previous studies in unscreened populations, these healthy volunteers have no gender cross-over in blood pressure and have only a weak association between baseline blood pressure and subsequent rate of pressure change. These findings suggest that several of the previously described age-associated patterns of blood pressure change partially reflect the effects of hypertension and its treatment, rather than intrinsic blood pressure changes in healthy individuals as they age.

**Acknowledgments**

We wish to acknowledge the contributions of Dr. James L. Fozard, associate scientific director for the BLSA; Dr. E. Jeffrey Metter, medical officer for the BLSA; and all the BLSA clinical staff who collected the data used in this study.

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**References**

AGE-ASSOCIATED CHANGES IN BLOOD PRESSURE

Appendix

Linear mixed-effects regression models are used to analyze these longitudinal data (21,22). Mixed-effects models allow estimation of the group-average blood pressure curve and also allow each subject’s estimated longitudinal change to deviate from the group average.

In the mixed-effects model, the fixed-effects estimate the average intercept and rates of change for the independent variables, while the random effects represent the deviation for each individual from the average intercept and slope terms. Thus, the random effects account for natural heterogeneity in initial level and patterns of change among the individuals in the study. Mixed-effects models account for correlation among repeated measurements within individuals and allow for the analysis of unbalanced data where individuals have differing numbers of observations taken at varying intervals between the observations. In fact, individuals with even a single observation can be included, although they contribute only to the cross-sectional estimates and not the longitudinal estimates.

Arranging the terms in the mixed-effects model to see how the longitudinal change depends upon first age, the full model for systolic and diastolic pressures on the $n$ subject at time $j$ is:

\[ y_{ij} = (\beta_0 + b_{0j}) + (\beta_1 + b_{1j}) \text{time}_{ij} + (\beta_2 + b_{2j}) \text{time}^2_{ij} + b_{3j} \text{fage}_j + b_{4j} \text{fage}^2_j, \]

where longitudinal change is represented by follow-up time ($\text{time}$ and $\text{time}^2$), and cross-sectional differences are represented by polynomial terms in age at first visit ($\text{fage}$, $\text{fage}^2$, and $\text{fage}^3$). Interaction terms are included to allow the longitudinal patterns of change to differ with age at entry (interactions between powers of $\text{fage}$ and $\text{times}$). Several variables are included to adjust statistically for the effects of body mass index, cigarette smoking, and the use of estrogen-containing sex hormones. BMI represents lean people ($\text{BMI} < 20 \text{ kg/m}^2$), BMI2 are overweight people ($20 \leq \text{BMI} < 30 \text{ kg/m}^2$) and BMI3 is overweight people ($30 \leq \text{BMI} < 30 \text{ kg/m}^2$). Fcig is a variable for cigarette smoking at the first visit whereas Cigct indicates whether or not they are currently smoking at each visit. Status shows whether the person had withdrawn from the study which tests for selective attrition. Sexhorm indicates whether the woman was taking sex hormones. The full model for men excludes the Sexhorm term.

Three random effects $(b_{0j}, b_{1j}, b_{2j})$ are included in the full model to account for natural heterogeneity among individuals with respect to blood pressure level (intercept), and longitudinal change ($\text{time}$ and $\text{time}^2$). Thus, each person’s longitudinal systolic and diastolic blood pressure patterns have level and shape that deviate from the overall average.

In order to reduce the multicollinearity among the polynomial and interaction terms, the follow-up time and first age variables are centered on the mean follow-up time and age at first visit by subtracting 4 and 52 years respectively from $\text{time}$ and $\text{fage}$ for men and 1.5 and 55 years respectively for women (25). The most parsimonious well-formed models (26) are obtained by backward elimination of the highest-order nonsignificant polynomial and cross-product terms. Terms are retained in the model if they reach a significance level of 0.05. We use FORTRAN software developed by Mary Lindstrom which uses a Newton-Raphson algorithm to obtain restricted maximum likelihood estimators for the mixed-effects models and assumed an unstructured variance-covariance matrix for the random effects (22).

The final models for men included fixed-effects terms 0–4, 14–16 and random-effects terms 0–2 for diastolic pressure and fixed-effects terms 0–11, 14–16 and random-effects terms 0–2 for systolic pressure. The final models for women included fixed-effects terms 0–11, 15–16 and random-effects terms 0–2 for diastolic pressure and fixed-effects terms 0–10, 12, 15–16, 19 and random-effects terms 0–1 for systolic pressure. Parameter estimates and the estimated standard errors for the final models are available from the authors upon request.