Sex Differences in Pulse Pressure Trends With Age Are Cross-Cultural

Joan H. Skurnick, Mordechay Aladjem, Abraham Aviv

Abstract—Sex differences in systolic and diastolic blood pressure levels and trends with age have been consistently observed in both industrialized and unindustrialized populations. However, the impact of sex on pulse pressure, an index of vascular aging, in unindustrialized populations has not been addressed. The objective of this report was to characterize sex differences in aging trends of pulse pressure within unindustrialized populations. Using PubMed and Medline, we identified 60 articles with blood pressure data from unacculturated or partially acculturated populations. Data on 27 populations from 22 articles were included for analysis, on the basis of adequate description of study design and blood pressure measurement. Blood pressure means of adult age groups were modeled by linear and polynomial regression. The pulse pressure levels of women were lower than those of men in early adulthood and higher in older ages. Women had a steeper, steady increase in pulse pressure with age than men (P<0.001), whereas men had a stronger curvilinear upswing in pulse pressure with age (P=0.006). Partially acculturated populations had higher pulse pressures than unacculturated populations. Sex had a stronger effect on pulse pressure than acculturation. Pulse pressure trajectories of unindustrialized populations were slightly attenuated compared with those seen in National Health and Nutritional Examination Surveys III and IV of the US population. A sex effect on pulse pressure trends with age prevails across unacculturated and acculturated populations. Accordingly, the biological principles of arterial aging, as expressed in pulse pressure, are the same in all humans, regardless of demography. (Hypertension. 2010;55:00-00.)

Key Words: blood pressure ■ aging ■ sex factors ■ hypertension ■ humans

Sex differences in age-dependent systolic blood pressure (SBP) and diastolic blood pressure (DBP) trends have been consistently observed in modern industrialized populations. That men and women in less industrialized populations also have different age trends in SBP and DBP has been reported in numerous studies. Despite this wealth of literature, aging trends of pulse pressure (PP) in less industrialized populations have not been addressed.

In this study, we explicitly investigated the sex differences in PP trajectories in less industrialized populations. The focus on PP stems from its recently recognized importance as a risk factor for cardiovascular diseases. In the Framingham Heart Study, neither SBP nor DBP added to the predictive value of PP for coronary heart disease. A study of French men demonstrated that PP predicted cardiovascular mortality independently of mean arterial pressure, although a meta-analysis of Japanese studies found PP to be less predictive of stroke and myocardial infarction than SBP and mean blood pressure. PP is a surrogate of arterial stiffness and, hence, an indicator of arterial aging in modern societies. Should less industrialized populations also exhibit sex differences in PP trends with age, as seen in industrialized societies, this would suggest physiological sex differences in arterial aging that are relatively impervious to changes in environment or lifestyle, with implications for sex-specific differences in cardiovascular risk.

Methods

Study Selection

Using PubMed and Medline, followed by cross-references, we identified 60 articles in which blood pressure data were available for populations that were judged as unacculturated or partially acculturated. Unacculturated societies were defined as remote, with minimal or no contact with industrialized or Westernized (“acculturated”) societies. Partially unacculturated societies were defined as maintaining some contact with acculturated societies. For instance, their locations were within walking distances from major roads, towns, hospitals, or missions.

We selected by consensus of the authors 22 articles with data on 27 populations for inclusion in our analysis. Articles were required to specify how the study population was selected, methods for determination of a participant’s age, and a description of procedures for obtaining blood pressure measurements. To be included in the analysis, data were required to specify SBP and DBP means by sex, with sample size, for ≥3 adult age ranges (≥18 years of age), and which included individuals ≥50 years. Table 1 presents the articles and populations selected for analysis. The data were obtained from field studies between the years 1937 and 1983. The remaining articles and the reasons for their exclusion are presented in Table S1 (available in the online Data Supplement, at http://hyper.ahajournals.org).
Table 1. Twenty-Seven Unacculturated Societies With SBP and DBP by Age Groups

<table>
<thead>
<tr>
<th>Source</th>
<th>Publication Year</th>
<th>Population</th>
<th>Sex</th>
<th>Degree of Acculturation*</th>
<th>N†</th>
<th>Oldest Age Group‡</th>
<th>No. of Age Groups</th>
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<td>1955</td>
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<td>Not</td>
<td>108</td>
<td>65</td>
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<td>96</td>
<td>65</td>
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<tr>
<td>Whyte(^29)</td>
<td>1958</td>
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<td>69</td>
<td>50</td>
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<td>Padmavati and Gupta(^28)</td>
<td>1959</td>
<td>Rural Delhi State, India Female</td>
<td>Partly</td>
<td>349</td>
<td>60</td>
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<tr>
<td>Kaminer and Lutz(^24)</td>
<td>1960</td>
<td>Bushmen, Kalahari Desert, Botswana Male</td>
<td>Partly</td>
<td>38</td>
<td>60</td>
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<tr>
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<td>1961</td>
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<td>Fulmer and Roberts(^26)</td>
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<td>166</td>
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(Continued)
Table 1. Continued

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<th>Degree of Acculturation*</th>
<th>N†</th>
<th>Oldest Age Group‡</th>
<th>No. of Age Groups</th>
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<td>333</td>
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<td>Poulter et al9</td>
<td>1984</td>
<td>Luo, Kenya</td>
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<td>Partly</td>
<td>597</td>
<td>65</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Partly</td>
<td>264</td>
<td>65</td>
<td>6</td>
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<tr>
<td>Zein and Assefa21</td>
<td>1986</td>
<td>Rural northwestern Ethiopian community</td>
<td>Female</td>
<td>Partly</td>
<td>182</td>
<td>50</td>
<td>4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Partly</td>
<td>202</td>
<td>50</td>
<td>4</td>
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</table>

*Not indicates unacculturated; partly, partially acculturated.
†Data show the sample size.
‡Data show the bottom of the age range.

Statistical Analysis

PP means were presented by age group for 4 populations. For the remainder, mean PP was computed as the mean SBP minus the mean DBP, indicating that the same individuals provided both SBP and DBP.

Linear Regressions Within Populations

Linear regression analyses were performed within each population, stratified by sex. SBP, DBP, and PP age group means were regressed on the midpoint of the age interval, weighted by the age-group sample size. Where the oldest age group was unbounded, a midpoint was imputed on the basis of the intervals between lower bounds. BP at age 20 years, a nominal onset of adulthood, was used as the intercept. The null hypotheses were as follows: (1) no differences in PP (or SBP or DBP) slopes between men and women within unacculturated and partially acculturated societies; (2) no difference in PP slopes between unacculturated and partially acculturated societies; and (3) no acculturation effect on sex differences in the change in PP with age. Within-population differences between parameters for men and women were used to test for sex effects, given the paired structure of the data. Univariate comparisons of sex- and population-specific intercepts and slopes to model population variability in BP patterns. Polynomial regression analyses also included a 2nd-degree age term (age squared) for curvature and were centered at age 40 years, the approximate overall mean age.

For comparison with PP trends in modern society, regression analyses were performed on National Health and Nutritional Examination Surveys (NHANES) III (1988–1994) and IV (1999–2002) BP measurements for men and women aged ≥20 years, applying the NHANES sample weights to achieve representation of the US population. Means are presented with 95% confidence limits. A P value <0.05 is considered significant. SAS 9.1 software (SAS Institute) was used for computations.

Results

Regression Slopes by Population

Table 2 presents the estimated BP at age 20 years and the slopes, summarized by sex and degree of acculturation. SBP at age 20 years among women was lower than among men,
whereas SBP slopes among women were consistently higher than those among men. There was considerable heterogeneity in slopes, within sex and acculturation category. The within-population differences of women’s minus men’s SBP at age 20 years (mean difference: −6.0 mm Hg [95% CI: −8.0 to −4.0 mm Hg]) and the differences in the slopes of women’s minus men’s (mean difference: 0.28 mm Hg/y [95% CI: 0.16 to 0.40 mm Hg/y]) were significantly different across populations (P<0.001 and P<0.001) and also when stratified by acculturation (all Ps <0.01).

Women’s mean DBP at age 20 years was −3.3 mm Hg lower than the mean for men (95% CI: −4.6 to −1.9 mm Hg; P<0.001). The median and mean slopes of DBP among men showed little or no increase with age. The mean DBP slopes (change per year of age) of women were higher than those of men (mean difference: 0.10 mm Hg/y [95% CI: 0.05 to 0.14 mm Hg/y]; P<0.001) but also showed little DBP increase with age. Higher DBP slopes and lower mean DBP at age 20 years among women than among men were also seen among the subgroup of 16 unacculturated populations (both P values <0.001). Among the 11 partially acculturated populations, women’s DBP slopes were higher but not significantly (P=0.12), and women’s mean DBPs at age 20 years were lower (P=0.030).

The regression lines for PP are a composite reflection of the joint trends in SBP and DBP. Mean PP at age 20 years was lower among women than among men (mean difference: −2.6 mm Hg [95% CI: −4.6 to −0.6 mm Hg]; P=0.014). PP slopes of women were significantly higher than those of men (mean difference: 0.18 mm Hg/y [95% CI: 0.07 to 0.29 mm Hg/y]; P=0.002). Within acculturation strata, women had higher PP slopes and lower mean PPs at age 20 years, although the age 20 difference among unacculturated women was not significant (unacculturated: difference at age 20, P=0.20 and slope, P=0.030; partially acculturated: difference at age 20, P=0.022 and slope, P=0.042).

Unacculturated and partially acculturated populations did not differ in SBP, DBP, or PP levels at age 20 years when tested within sexes. Partially acculturated populations showed higher SBP, DBP, and PP slopes than unacculturated populations within both sexes, but the differences were not significant.

**Linear Regressions Pooled Across Populations**

To examine further the differences in slopes and BP at age 20 years, linear regressions were performed on BP levels pooled across all of the populations. Table 3 again displays that women had lower SBP, DBP, and PP at age 20 years and greater increases with age within each acculturation group of populations. Sex, degree of acculturation, and their interaction were tested jointly as factors affecting age trends in all of the populations, pooled across sexes. SBP and DBP at age 20 years were both lower among women than men (P=0.001; P<0.001) by 2 to 5 mm Hg. Women had significantly higher slopes of increase in SBP and DBP with age (P<0.001 and P=0.006, respectively), although the slopes for DBP were close to 0. The difference in men’s and women’s PP at age 20 years was not significant. However, women’s greater increase

<table>
<thead>
<tr>
<th>Variable</th>
<th>Degree of Acculturation</th>
<th>Sex</th>
<th>Blood Pressure at Age 20 y, mm Hg</th>
<th>Slope: Annual Change in Blood Pressure, mm Hg/y</th>
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<tbody>
<tr>
<td>Systolic</td>
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<td>0.244‡</td>
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<td></td>
<td>Male</td>
<td>114.7</td>
<td>0.066</td>
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<td>0.330</td>
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<td>Diastolic</td>
<td>Not Female</td>
<td>72.8§</td>
<td>0.025¶</td>
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<td></td>
<td>Male</td>
<td>75.6</td>
<td>−0.074</td>
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<td></td>
<td>Partly Female</td>
<td>72.5</td>
<td>0.049</td>
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<td>Male</td>
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<td>0.227¶</td>
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Model includes sex, acculturation, and sex-acculturation interaction as fixed effects on blood pressure at age 20 years and on slope, and population and population-age interaction as random effects.

*Not indicates unacculturated; partly, partially acculturated.
†Data show significant effects on SBP at age 20: sex (P=0.001).
‡Data show significant effects on SBP slope: sex (P<0.001).
§Data show significant effects on DBP at age 20: sex (P<0.001).
¶Data show significant effects on DBP slope: sex (P<0.001).
‖Data show significant effects on PP slope: sex (P=0.005).

Polynomial Regression Parameters Pooled Across Populations

Figure 1 presents plots of PP age-group means from all of the unacculturated and partially acculturated populations. Each panel distinguishes men and women separately for unacculturated and partially acculturated populations. These PP plots reveal upswinging patterns not fully represented by straight-line regression, as also observed in modern populations, for example, the Framingham Heart Study. Polynomial regressions were performed on all of the data, pooled across populations, anchored at age 40 years, the approximate mean age of the populations. Table 4 presents the resulting estimates of BP at age 40 years, change per year (slope), and change per year² (curvature) for each sex and acculturation category.

The polynomial regressions of SBP, DBP, and PP pooled across sex and acculturation all indicated that, in the presence of significant curvature with age, effects of sex and acculturation on BP levels were significant and in some cases...
interactive. SBP levels at age 40 years were higher among unacculturated women than men, but SBP was higher among men than women in partially acculturated populations (interaction $P=0.002$). Women had a significantly greater slope of SBP with age than men ($P<0.001$), whereas men had a greater curvilinear upswing in SBP with age ($P=0.013$). Women had lower DBP at age 40 years ($P<0.001$) and a significantly more positive linear increase in DBP ($P<0.001$).

The consequent age patterns of PP resulted in significant curvilinear upswings in PP with age. The curves in Figure 1 illustrate that mean PP levels for women were lower than men’s in early adulthood and then surpassed those of men through older ages. The PP of women at age 40 years was significantly lower than that of men ($P=0.001$), somewhat less so among partially acculturated populations (interaction $P=0.007$). Women had a significantly steeper steady increase in PP with age than men ($P<0.001$), with little curvilinear upswing. In contrast, men had a stronger upswing in PP with age ($P=0.006$). The upswing was somewhat greater among partially acculturated populations (interaction: $P=0.046$). As can be discerned from Table 4, sex was a more influential factor in age-related trends in SBP, DBP, and PP than acculturation.

**Comparison With a US Population Survey**

For comparison with a modern population, analogous polynomial regressions were performed on NHANES III and IV data. Table 4 includes the parameter estimates for the NHANES population. Figure 2 presents the fitted NHANES PP polynomial regression and the PP polynomial regression obtained by pooling the unacculturated and partially acculturated populations. The NHANES parameters define PP trajectories that, at younger ages, are similar to those of the less acculturated populations. However, PP in NHANES swings upward more rapidly from age 40 years for both sexes. Above approximately age 50 years, the mean PP of US men and women surpassed the means of the less acculturated populations. The PP levels of US women overtook those of US men at approximately age 45 years and widened gradually to $\approx 7$ mm Hg at age 80 years. In comparison, in less acculturated populations, women had higher PP levels by age 40 years, with differences of $\approx 4$ mm Hg from age 50 years and above.

**Discussion**

Our findings underscore the similarity of age-dependent PP trajectories in all societies, suggesting that, regardless of culture or demography, the biological principles of arterial aging are the same in all humans. Moreover, the sex effect on these PP trajectories points to different patterns of arterial aging in women and men.

On the basis of anthropological studies, it has been proposed that blood pressure may not increase or may increase only slightly with age during adulthood in some isolated societies.18 This phenomenon has been attributed primarily to low salt consumption.19–20 However, questions have been raised about causality, particularly in unacculturated societies.18 In this context, the Intersalt Study was undertaken to focus on the relationship of blood pressure with sodium and potassium urinary excretion, which reflected salt intake, and with lifestyle factors in 52 populations across 32 countries.41 Population differences in the increase of SBP with age were associated with sodium excretion, but the diversity was only partially attributable to salt intake; climate, physical activity, and societal factors were presumed confounders.41 These findings of the Intersalt Study have contributed to the protracted debate about “salt sensitivity.”17,28,29 which centers on the premise that, in humans, the effect of a “high” salt intake is ultimately and almost singularly expressed by blood pressure elevation.

The findings that monogenic forms of human hypertension arise from major mutations in genes encoding sodium transport proteins in the renal tubules42 have only served to bolster the idea that a high salt intake causes hypertension in the general population. However, sodium is vital to diverse networks of biological pathways that are integral components of growth, development, and, therefore, aging. Because aging

Cross-Cultural Sex Differences in Pulse Pressure 5

![Figure 1. Mean PP by age group from 16 unacculturated and 11 partially acculturated populations. Polynomial regression curves are fitted within sex and acculturation group. A. Unacculturated populations: women, $PP=43.8+(age-40)*0.275+(age-40)^2*0.0092$. B. Partially acculturated populations: women, $PP=43.8+(age-40)*0.245+(age-40)^2*0.0083$; men, $PP=43.1+(age-40)*0.041+(age-40)^2*0.0099$.](image)
in industrialized societies is frequently accompanied by a rise in SBP and PP, the question that matters most is whether the influence of sodium on human biology should be defined in terms of blood pressure effects or within the framework of the potential relationship between sodium and biological aging. Another salient matter is how much of the effect of salt can be explained in genetic terms.

The genetic argument in support of the role of salt in human biology is that our genetic makeup has been shaped primarily by natural selection during the preagricultural era,18 when individuals with avid renal sodium absorption capacity enjoyed an evolutionary advantage. The argument goes on to suggest that salt-mediated blood pressure elevation is a modern affliction of a subset of the human population with genetic predilection to retain sodium, because sodium intake of contemporary humans well exceeds the low-sodium/high-potassium diet of their Stone Age ancestors.18 However, Paleolithic diet evolved to meet nutritional needs of humans with an average life span of <30 years.

A central feature of evolution is that natural selection largely operates during the reproductive period. The upper boundary of this period is ~50 years, reflecting the onset of menopause. However, essential hypertension primarily occurs during the postreproductive years, among upper middle aged and elderly persons. Thus, essential hypertension is a modern problem, because humans live much longer than ever before. Moreover, approximately two thirds of patients with essential hypertension manifest systolic hypertension and, hence, a high PP.43–45 The aging factor is, hence, relevant to understanding age-dependent PP trajectories. Accordingly, if salt intake impacted age-dependent blood pressure trajectories, its effect might largely be by accelerating the pace of arterial aging. Indeed, salt might exert a cardiovascular effect independent of that on blood pressure.46,47

Our findings suggest that, in populations not yet industrialized, women and men differ in their patterns of increasing PP with age. Broadly, regardless of acculturation, women tend to have lower SBP in early adulthood and to have a more rapid rise of this variable with age, resulting in a steeper climb of PP in women than in men. We have illustrated that the NHANES III/IV broad survey of the US population exhibits a similar crossover of women’s and men’s PP trends. In the Asklepios survey of healthy middle-aged Belgians, the PP age trend among women also crosses over that of men at age 50 years.48 A sex difference in blood pressure trends with age is seen despite the variety of populations and study

### Table 4. Polynomial Regression Parameters for Change in SBP, DBP, and PP With Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Degree of Acculturation</th>
<th>Sex</th>
<th>BP at age 40 y, mm Hg</th>
<th>Slope: Change in BP/y, mm Hg/y</th>
<th>Curvature: Change in BP/y², mm Hg/y²</th>
<th>BP at Age 40 y, mm Hg</th>
<th>Change in BP/y, mm Hg/y</th>
<th>Change in BP/y², mm Hg/y²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>Not</td>
<td>Female</td>
<td>117.0†</td>
<td>0.333‡</td>
<td>−0.00276§</td>
<td>115.1</td>
<td>0.612</td>
<td>0.0055</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>115.2</td>
<td>−0.056</td>
<td>0.0054</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Partly</td>
<td>Female</td>
<td>117.4</td>
<td>0.379</td>
<td>0.00469</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>119.2</td>
<td>0.082</td>
<td>0.00685</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>Female</td>
<td>116.8</td>
<td>0.341</td>
<td>0.00175</td>
<td>115.1</td>
<td>0.612</td>
<td>0.0055</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>116.8</td>
<td>−0.003</td>
<td>0.00684</td>
<td>122.0</td>
<td>0.380</td>
<td>0.0044</td>
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<tr>
<td>Diastolic</td>
<td>Not</td>
<td>Female</td>
<td>73.7</td>
<td>0.069¶</td>
<td>−0.00396</td>
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<tr>
<td></td>
<td></td>
<td>Male</td>
<td>74.7</td>
<td>−0.038</td>
<td>−0.00345</td>
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<td></td>
<td>Partly</td>
<td>Female</td>
<td>73.9</td>
<td>0.142</td>
<td>−0.00358</td>
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<tr>
<td></td>
<td></td>
<td>Male</td>
<td>76.0</td>
<td>0.039</td>
<td>−0.00303</td>
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<tr>
<td></td>
<td>Combined</td>
<td>Female</td>
<td>73.7</td>
<td>0.100</td>
<td>−0.00385</td>
<td>73.2</td>
<td>0.275</td>
<td>−0.0080</td>
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<tr>
<td></td>
<td></td>
<td>Male</td>
<td>75.2</td>
<td>−0.009</td>
<td>−0.00299</td>
<td>78.7</td>
<td>0.252</td>
<td>−0.0103</td>
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<tr>
<td>Pulse pressure</td>
<td>Not</td>
<td>Female</td>
<td>43.4*</td>
<td>0.271**</td>
<td>0.00122††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>40.5</td>
<td>−0.012</td>
<td>0.00896</td>
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<tr>
<td></td>
<td>Partly</td>
<td>Female</td>
<td>43.5</td>
<td>0.238</td>
<td>0.00827</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>43.3</td>
<td>0.044</td>
<td>0.00988</td>
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</tr>
<tr>
<td></td>
<td>Combined</td>
<td>Female</td>
<td>43.1</td>
<td>0.246</td>
<td>0.00557</td>
<td>41.9</td>
<td>0.34</td>
<td>0.0135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>41.6</td>
<td>0.010</td>
<td>0.00982</td>
<td>43.4</td>
<td>0.13</td>
<td>0.0147</td>
</tr>
</tbody>
</table>

Model includes sex, acculturation, and sex-acculturation interaction as fixed effects on blood pressure at age 20 years, slope and curvature, and population and population-age interaction as random effects.

*Not indicates unacculturated; partly, partially acculturated.
†Data show significant effects on SBP at age 40 years: sex-acculturation interaction (P=0.002).
‡Data show significant effects on SBP slope: sex (P<0.001).
¶Data show significant effects on SBP curvature: sex (P<0.01).
**Data show significant effects on SBP slope: sex (P<0.001).
††Data show significant effects on PP at age 40: sex (P=0.001).
#Data show significant effects on PP curvature: sex (P<0.001) and sex-acculturation interaction (P=0.007).
§Data show significant effects on BP at age 40: sex (P=0.001).
Data show significant effects on DBP slope: sex (P<0.01).
Figure 2. Polynomial regression curves fitted to A. Mean PP by age group across 27 unacculturated and partially acculturated populations. Women: PP = 43.1 + (age – 40)*0.246 + (age – 40)^2*0.0056. Men: PP = 41.6 + (age – 40)*0.010 + (age – 40)^2*0.0098. B, NHANES III and IV PP readings among adults. Women: PP = 41.9 + (age – 40)*0.337 + (age – 40)^2*0.0136. Men: PP = 43.4 + (age – 40)*0.128 + (age – 40)^2*0.0147.

designs, underscoring the robustness of the sex effect. Although not all 27 of the within-population estimates show higher PP in women aged 20 years than in men in PP slope, the within-population sex differences are significant, within and across acculturation classes. Most population subsets contain only a few age levels, with some relatively small sample sizes. We would expect, because of statistical variability alone, that not all of the observed within-population results would track overall trends.

Trajectories on the basis of longitudinal follow-up of individuals in these populations might not have shown the same aging patterns. As noted by Pearson et al., cross-sectional aging trends may reflect selective mortality. The longitudinal Framingham Heart Study reported PP trends for healthy or untreated hypertensive women that were lower at a younger age and then converged or slightly overtook the PP levels of comparable men. The Baltimore Longitudinal Study of Aging of healthy volunteers observed little difference in results from cross-sectional and longitudinal analyses. Women had consistently lower SBP and DBP levels. Although SBP increased with age, the gap narrowed between men’s higher SBP and women’s lower SBP because of steeper SBP increases in women up to age 70 years. With a smaller sex difference in DBP levels and flatter trajectories, the narrowing of the SBP differences would be reflected in PP trends, albeit without crossover.

We underscore limitations of our study. Our regression analyses are “ecological,” in that the observations are age-group means, rather than individual BP measurements. We nevertheless have compared our trend results with those from well-known cross-sectional studies of individuals. Our designation of populations as unacculturated versus partially acculturated is subjective and crude. We note that degree of acculturation may be a surrogate for or confounded by differences in diet, cultural practices, and study procedures, particularly in measurement of blood pressure. We were unable to classify with any confidence the population diets. We cannot rule out the possibility that sex differences in PP trends are consequences of sex differences in a time-varying exposure to a covariate. However, the regression patterns, if indirect, would be attenuated from the underlying covariate trends, which would imply very strong covariate effects on PP. Furthermore, such sex-specific covariate effects and time trends would have to be consistent across our diverse populations to produce such an effect. It is more likely that the sex differences in PP trends seen cross-culturally in less acculturated and modern societies do not depend on external confounders such as lifestyle and diet. Although there is no doubt that PP and vascular stiffness are related to salt intake, a phenomenon that is clearly evident in the elderly, it is unlikely that the age-related PP trajectory and its modification by sex can be solely explained by salt intake. PP may nevertheless be a surrogate for sex-dependent physiological differences, which is salient to our interpretation of the results.

Finally, our study has focused on societies untouched by environmental confounders of modern times, an undertaking no longer feasible, as so few populations remain truly remote. For this reason alone, recognition that a sex effect on PP trajectories, and, by implication, arterial aging, is independent of acculturation is highly relevant to perspectives on essential hypertension and cardiovascular risk.

Perspectives
Among less acculturated populations, an effect of sex on the PP trajectory was observed regardless of interpopulation variations in environmental exposures, including salt intake. Thus, the age-dependent differences in PP trajectories between women and men seen across societies most likely stem from sex-related differences in arterial aging. It follows, then, that if a high salt intake increases the likelihood of cardiovascular disease, its effect is primarily mediated by accelerating arterial aging. To tackle the problem of age-dependent rises in PP, we must confront the underlying biology of the aging process itself.

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Sex Differences in Pulse Pressure Trends with Age Are Cross-Cultural

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Table S1. Articles Excluded from Analyses

Populations deemed acculturated, not rural or isolated


**Blood pressure values not presented as mean, N per age group**


**Data presented graphically**


Data not presented by sex


Data for males only


Exclusion of subjects with hypertension


Data presented in other publications


Review articles with no original data

