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Sex-differences in blood pressure and potential implications for cardiovascular risk management

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Abstract

Background: Accurate blood pressure (BP) measurement is critical for optimal cardiovascular risk management. Age-related trajectories for cuff-measured BP accelerate faster in women compared to men, but whether cuff BP represents the intra-arterial (invasive) aortic BP is unknown. This study aimed to determine the sex-differences between cuff BP, invasive aortic BP and the difference between the two measurements.

Methods: Upper-arm cuff BP and invasive aortic BP were measured during coronary angiography in 1615 subjects from the INvaSive blood PressurE ConsorTium database. This analysis comprised 22 different cuff BP devices from 28 studies.

Results: Subjects were 64±11 years (range 40-89) and 32% women. For the same cuff systolic BP (SBP), invasive aortic SBP was 4.4 mmHg higher in women compared with men. Cuff and invasive aortic SBP were higher in women compared with men, but the sex-difference was more pronounced from invasive aortic SBP, was lowest in younger ages and highest in older ages. Cuff diastolic BP (DBP) overestimated invasive DBP in both sexes. For cuff and invasive DBP separately, there were sex*age interactions in which DBP was higher in younger men and lower in older men, compared with women. Cuff pulse pressure underestimated invasive aortic pulse pressure in excess of 10 mmHg for both sexes in older age.

Conclusions: For the same cuff SBP, invasive aortic SBP was higher in women compared with men. How this translates to cardiovascular risk prediction needs to be determined, but women may be at higher BP-related risk than estimated by cuff measurements.

Keywords: diagnostic equipment, pulse wave analysis, physiology, sex factors, hypertension

Non-standard abbreviations

CVD, cardiovascular disease

SBP, systolic blood pressure

PP, pulse pressure

INSPECT, INvaSivE blood PressurE ConsorTium

DBP, diastolic blood pressure

ACC/AHA, American College of Cardiology/American Heart Association

Background

Cardiovascular disease (CVD) is the number one cause of death in both women and men.[1] However, the risk factors, clinical manifestation, underlying pathophysiology and outcomes of CVD differ markedly between sexes.[2, 3] For instance, in the United States, women have a higher prevalence of stroke whereas men have a higher prevalence of coronary heart disease.[4] Mortality due to stroke and heart failure is also higher in women compared with men.[4] The mechanisms that explain sex-differences in CVD risk, including why risk is higher for women compared with men for the same level of blood pressure (BP) are not fully understood.[5, 6] An explanatory factor could be related to sex-differences in high BP, as the leading risk factor for CVD.

A recent large study of four US cohorts found notable sex-differences in the life-course trajectories for cuff-measured BP, whereby women had an accelerated rise in cuff systolic BP (SBP) and pulse pressure (PP) from around the third decade of life.[7] The reasons for these sex-differences in BP trajectories are not known, but may not be entirely from physiological influences.[8, 9] Alternatively, the accuracy of cuff-measured BP itself could be influenced by sex-differences in vascular aging and hemodynamics. Notional support for this hypothesis comes from evidence that increased age[10], and accelerated vascular ageing[11, 12], are associated with systematic bias in the accuracy of cuff BP. The aim of this study was to determine if there were sex-differences in cuff BP by comparison to an invasive BP reference standard.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Overview. The data in this study is from the INvaSivE blood PressurE ConsorTium (INSPECT) database which is an international collaboration including individual level data from 59 studies with upper-arm (brachial) cuff-measured BP and invasive BP (n=3292 subjects). Upper arm cuff BP was measured using automated devices, and invasive BP was measured using fluid-filled or solid-state micromanometer catheters. There was insufficient data to use manual auscultatory cuff BP in the analysis and to perform separate analyses for automated versus auscultatory BP (total n=20 from 2 studies), thus this data was excluded. 1615 subjects aged between 40 to 89 years with complete data on sex, upper-arm cuff BP and invasive aortic BP from 28 individual studies were included in the analysis (a flow chart of study subjects is provided in Figure S1). Invasive brachial and invasive radial BP were not included. The rationale for examining invasive (central) aortic BP is that the heart and brain are exposed to central, not peripheral, BP and there can be large differences in SBP between these arterial measurement sites (i.e. >30 mmHg). Also, the original purpose of non-invasive cuff BP was to estimate the pressure load on the vital organs[13] at "a point fairly close to or… in the aorta itself,"[14] thus altogether it is more clinically relevant to perform the analysis in this study by comparison of cuff BP with invasive aortic BP. Differences in BP were calculated as cuff BP minus invasive BP. PP was calculated as SBP minus diastolic BP (DBP).

Quality control of data for the INSPECT database included several criteria related to the individual study data collection methods, which have been previously described.[10, 15, 16] Measurements were taken under resting conditions with subjects supine. Only studies that measured cuff and invasive BP either simultaneously, or within an immediate period of each other, to allow for direct comparison, were included. Further, only studies that measured invasive aortic BP at, or proximal to, the aortic arch were included due to potential effects of SBP amplification on the analyses. The Tasmanian Health and Medical Human Research Ethics Committee approved the study (reference: H0015048).

Statistical analyses. Subject characteristics were presented as mean ± standard deviation. The primary analyses were unadjusted and secondary analyses were adjusted for potential mediators including height, weight, heart rate, invasive mean arterial pressure and the presence or absence of coronary artery disease. Analysis of associations between the BP measurements, sex and age (including interaction tests) was performed using linear mixed effect models with age as a continuous variable (fixed effect) and the data source as a random effect. Estimated marginal BP means [95% confidence intervals] for different ages and sex were calculated from the mixed effect models for cuff BP, invasive aortic BP and the difference between cuff and invasive aortic BP. An interaction term for sex*age was used for the models of cuff SBP and DBP and invasive SBP and DBP, based on previous findings from Ji et al.[7] In all other models, sex and age were treated as independent. The analysis was also conducted according to ACC/AHA 2017 Hypertension Guidelines categories from cuff BP measurements.[17] Statistical analysis was conducted using R version 3.6.3 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). The lme4 and ggeffects packages were used for the linear mixed models and mean marginal effects.

Results

Subject characteristics. Subject characteristics were overall representative of patients scheduled for coronary angiography: the average age was 64±11 years, predominately male and with body mass index in the overweight range (Table 1).

Sex-differences in BP. For the same level of cuff SBP, women, compared with men, had 4.4 mmHg higher invasive aortic SBP (Figure S2). Individually, cuff and invasive SBP were on average higher in women compared with men (Table 1). The sex-difference for SBP was lowest at younger ages and highest at older ages and more pronounced from the invasive SBP measurements (Figure 2). There was distinct separation of the invasive SBP mean and 95% CIs for women and men from 50 years of age (higher SBP in women). Cuff SBP was ≥10 mmHg different to invasive aortic SBP (either under- or over-estimation) in 256 (49%) women compared with 472 (42%) men.

For the same level of cuff DBP, invasive aortic DBP was around 2 mmHg higher in men compared with women (Figure S2). Cuff DBP overestimated invasive DBP by approximately 7 mmHg, (Figure 1). When the mean value of DBP was considered, cuff DBP and invasive DBP were similar between women and men (Table 1). However, there was an interaction between sex*age in which DBP was higher in younger men and lower in older men, when compared with women (Figure 1). The downward slope of cuff and invasive DBP with increasing age was less steep in women compared with men.

For the same level of cuff PP, invasive aortic PP was around 2.5 mmHg higher in women compared with men (Figure S2). On average, cuff PP underestimated invasive PP by approximately 9 mmHg, but the underestimation was in excess of 10 mmHg for both sexes in older age (Figure 1). The sex-difference in PP was consistent across different ages. Cuff PP and invasive PP were on average higher in women compared with men. As shown in Figure 2, there was a distinct difference between women and men across the age range for both cuff and invasive PP and the difference was more pronounced for invasive PP.

Sex differences and BP categories. In the optimal and stage 2 hypertension categories, there were significant sex differences in the difference between cuff and invasive SBP (Figure 3). However, in the elevated and stage 1 hypertension categories, the sex difference for the difference between cuff and invasive SBP was attenuated to approximately 2.7 mmHg and was borderline significant for both categories.

Sensitivity analyses.

After adjustment for height, weight, heart rate, invasive mean arterial pressure and presence of coronary artery disease, the difference between cuff SBP and invasive aortic SBP in women versus men remained significant but was attenuated to 2.8 mmHg. The sex differences between cuff DBP and PP and invasive aortic DBP and PP were attenuated after adjustment (Figures S3-S4 and Tables S1-S6). The primary results were not significantly different when the analysis was restricted to those cuff BP devices that were confirmed to be validated (Table S7).

Discussion

The principal findings were that for the same level of cuff SBP, women compared with men, had 4.4 mmHg higher invasive aortic SBP. Cuff DBP substantially overestimated invasive DBP in both sexes, but to a slightly greater extent in men. The observations for PP were similar to SBP, but cuff PP underestimated invasive PP to a much greater extent than for SBP or DBP, particularly in older age. The implication of these findings is that high BP may be playing a more significant role in the heightened risk of CVD events among women, but this BP-related risk is underestimated by cuff-measured BP. To our knowledge this is the first study to present data of this nature.

A recent analysis from four longitudinal community cohorts, consisting of 17219 women and 14839 men, investigated sex-differences in cuff BP trajectories.[7] An accelerated rise in cuff SBP and PP was found in women compared with men, and this began in the third decade of life. Other studies have found cuff SBP increased faster in women through midlife [18] but also followed a different age-related pattern of change compared with men.[8] The age-related BP patterns in our cross-sectional analysis showed higher SBP in women in older age, consistent with the previously described longitudinal data. However, although women and men had similar cuff SBP in the fourth and fifth decades, invasive SBP was approximately 6-7 mmHg higher in those decades. Therefore, it is possible that the cross-over to higher SBP values in women may occur at a younger age than previously suggested. When stratified according to cuff BP category, the SBP difference between sexes was most pronounced in the normal and stage 2 hypertension categories. After adjustment for clinical and physiologic variables, including underlying mean arterial pressure, the SBP difference between women and men was attenuated, but remained significant. Altogether, the findings indicate there is a greater SBP and PP load on the cardiovascular system in women compared with men which is under-estimated by cuff BP.

There are substantial differences in cardiovascular physiology between women and men which could theoretically contribute to BP measurement discrepancies between sexes. Although men tend to have greater aortic stiffness, the rate of acceleration in pulse wave velocity (or declining aortic distensibility) with advancing age is greater in women.[8, 19] However, the longitudinal study of Scuteri et al[8] found a general dissociation between the changes in aortic stiffness and BP, albeit based on cuff-measurements of BP, over time. BP waveform features also differ between sexes, with women having more augmented waveform profiles.[20-22] Women, compared with men, have a higher augmentation index from the fourth decade of life,[20] which is associated with worse cardiovascular outcomes independent of cuff BP.[23] Women also tend to have lower SBP amplification.[24] Cuff SBP underestimation of invasive aortic SBP in this study does not imply non-physiological negative SBP amplification but instead that cuff SBP probably underestimated invasive brachial SBP substantially.[15]

Automated cuff BP devices are routinely used in clinical practice as they are non-invasive, cost effective and easy to operate.[25] The process involves the cuff detection of pressure waveforms, which are then processed to create an oscillometric waveform envelope,[26] and device specific algorithms are applied to estimate SBP and DBP. [27] As far as we are aware, these algorithms do not adjust for sex or age. But if sex and age-related differences in cardiovascular physiology and hemodynamics somehow interfere with detection of pressure waveforms or the assumptions of these algorithms, this could explain the sex-differences observed in cuff SBP and PP accuracy. The findings of this study support the idea that sex-specific algorithms may be needed to derive more accurate BP readings from automated BP devices, as suggested previously.[28] This is also relevant to the emerging field of cuffless BP measurement, where balanced representation according to participant sex and age will be an important consideration in designing validation protocols to test the accuracy of this technology.[29] However, determining whether the individual devices in this study may have varying sex-specific BP measurement accuracy was not possible because the study was underpowered to analyse this endpoint. Additional work is also needed with greater phenotyping of subjects to advance this concept.

Automated cuff devices are validated for accuracy by comparison to a non-invasive reference standard, typically mercury auscultation. In this study, the primary results were unchanged when the analysis was restricted to only include those devices that had been validated. This present study used invasive aortic BP as the reference standard, and as such the findings cannot be compared with those of non-invasive validation studies because of the different reference standards used. However, it is important to note that numerous studies comparing automatic devices and mercury auscultation demonstrate that validated devices are more likely to be accurate and have lower variability in BP measurement compared to non-validated devices.[30-32] In clinical practice, only validated devices should be used for measurement of BP.

The potential implications of this study are wide-ranging. First, the results indicate the CVD risk related to SBP and PP may not be identified by cuff BP as effectively in women compared with men, and this could lead to underdiagnosis and missed therapeutic potential to prevent avoidable CVD events. Speculatively, this may provide a mechanistic explainer as to why CVD risk is higher for women compared with men for the same level of BP.[5, 6] Indeed, although the sex-differences for the difference between cuff and invasive aortic SBP may appear relatively small based on the mean difference (Table 1), there was a greater proportion of women with ≥10 mmHg under- or over-estimation of invasive aortic SBP (49% vs 42%). There was also substantial overestimation of DBP in women and men, which may contribute to potential overtreatment and is a major contributor to underestimation of PP. Each of these findings could have potentially large ramifications for individuals as well as at the population level. Second, epidemiological data pertaining to fundamental understanding of life-course sex-differences in BP may need to be re-considered due to systematic measurement bias of automated cuff BP between women and men. The sex-related measurement bias raised in this paper is in alignment with other observations of bias from automated cuff-based BP measurements.[11, 12] We do not know whether these issues are applicable to carefully measured mercury sphygmomanometry or only relevant to automated BP devices. However, as automated BP devices are used globally in clinical practice, our findings emphasise the critical need to improve automated cuff BP accuracy.

There are study limitations. All subjects were scheduled for clinically indicated coronary angiography and therefore the results may not be generalisable to healthy people with low CVD risk factor burden, or other disease populations. Further, the study was cross-sectional and the findings are not as robust as longitudinal analyses such as that performed by Ji et al[7] using cuff BP. Nonetheless, our cuff BP findings are similar to the BP sex-difference trends observed by those investigators.[7] Detailed data on variables that may influence cuff BP measurements, such as arm circumference, cuff size, co-morbidities and validation status of some devices were not available. Moreover, data on anti-hypertensive therapy was unavailable in most participants, but may be of relevance to future analyses because of differential effects of certain treatments on aortic, compared with brachial BP.[33] We excluded those younger than 40 because of limited data but it is interesting to note that at younger ages, cuff SBP and DBP overestimated invasive SBP and DBP, with minimal difference in PP. These differences were more pronounced in men as opposed to women. In children, cuff SBP overestimates invasive SBP,[34, 35] but there is a need for further studies on the accuracy of cuff BP in younger people. There was insufficient data for manual auscultatory cuff BP, and whether the study observations would be the same with this method of cuff BP measurement should be examined in future studies. Finally, whether invasive BP, compared with cuff BP, is a superior predictor for clinical outcomes needs to be determined. Overall, additional studies with greater sample sizes and follow-up to clinical outcomes would be beneficial to confirm the observations from the present study.

In conclusion, for the same level of cuff SBP invasive aortic SBP was higher in women compared with men. How this translates to cardiovascular risk prediction is still to be determined, but women may be at higher BP-related CVD risk than estimated by cuff measurements.

Perspectives

CVD is the leading cause of mortality for women. A crucial priority of The Lancet Women and Cardiovascular Disease Commission was to advocate for a global approach to education, screening and treatment of high BP.[35] A recent study which pooled data from 27 542 participants from four large community cohort studies showed that for the same level of SBP, risk of myocardial infarction and stroke was greater in women compared with men.[5] The current study has identified that women compared with men, may be predisposed to more inaccurate measurement of SBP by standard upper arm cuff BP measuring devices that are used in daily clinical practice. More work to urgently understand and address this deficiency in BP measurement for women is warranted. A starting point for future investigations may be to examine whether the well-known sex-differences in arterial waveform shapes may be a contributory factor towards poorer BP measurement accuracy.

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Novelty and Relevance

What Is New?

- This study examined sex-differences in cuff BP compared with invasive aortic BP among men and women undergoing coronary angiography.

What Is Relevant?

- For a given cuff SBP, women had an invasive aortic SBP that was 4.4 mmHg higher than men.
- Cuff DBP overestimated invasive aortic DBP in women and men.

Clinical/Pathophysiological Implications?

- High BP may play a more significant role than previously thought in the heightened risk of CVD events among women due to inaccurate cuff BP measurement.

Figure legends

Figure 1. Sex-stratified cuff blood pressure minus invasive aortic blood pressure across an age range of 40 to 89 years. The solid lines represent women and the dashed lines represent men. The solid and dashed lines are estimated marginal means from linear mixed models and the ribbons are the associated 95% confidence intervals. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Figure 2. Cuff blood pressure and invasive aortic blood pressure stratified by sex across an age range of 40 to 89 years. The solid lines represent women and the dashed lines represent men. The solid and dashed lines are estimated marginal means from linear mixed models and the ribbons are the associated 95% confidence intervals. SBP, systolic blood pressure; DBP, diastolic BP; PP, pulse pressure.

Figure 3. Sex-stratified analysis of the relationship between cuff blood pressure and invasive aortic blood pressure across different ACC/AHA blood pressure categories across an age range of 40 to 89 years. The solid lines represent women and the dashed lines represent men. The solid and dashed lines are estimate marginal means from linear mixed models and the ribbons are the associated 95% confidence intervals. SBP, systolic blood pressure (top row); DBP, diastolic BP (middle row); PP, pulse pressure (bottom row); Normal BP, SBP<120 and DBP<80; Elevated BP, SBP 120-130 and DBP<80; Stage 1 HTN, SBP 130-140 and DBP<90; Stage 2 HTN, SBP≥140 and/or DBP≥90.

Table 1. Clinical characteristics of subjects stratified by sex.

Variable	All data (n=1615)	Women (n=518)	Men (n=1097)

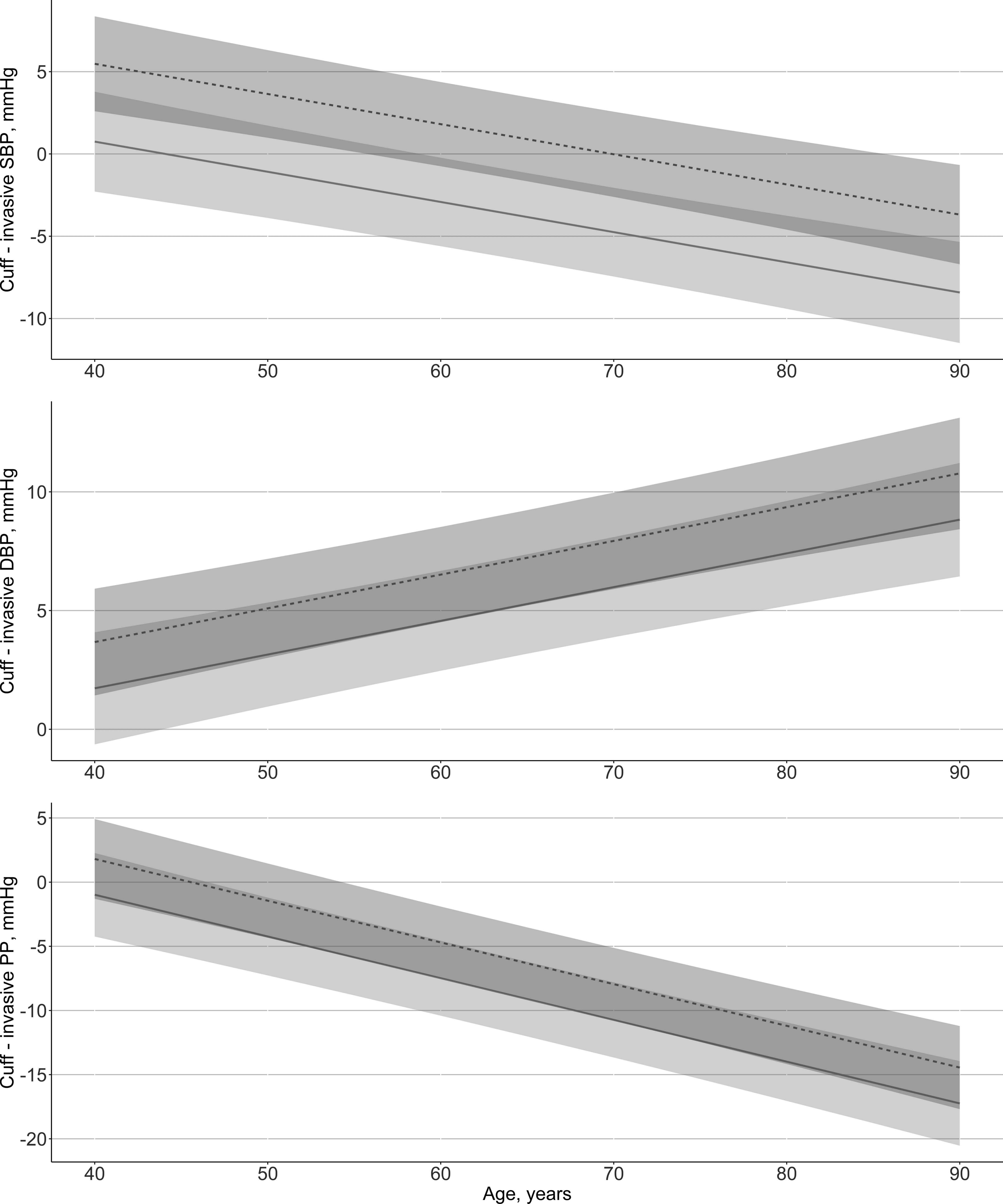
Age (years)	64 ± 11	65 ± 11	64 ± 11
Height (cm)	165 ± 10	157 ± 9	169 ± 9
Weight (kg)	73.6 ± 18	68.7 ± 19	76.0 ± 18
BMI (kg/m^2)	26.8 ± 5	27.6 ± 6	26.4 ± 5
Heart rate (beats/min)	68 ± 12	70 ± 12	67 ± 12
Cuff SBP	136±22	140±24	134±21
Cuff DBP	78±12	76±13	78±12
Cuff PP	58±18	64±19	56±16
Invasive aortic SBP	137±25	144±27	134±24
Invasive aortic DBP	70±13	70±12	70±13
Invasive aortic PP	67±22	74±24	64±21
Cuff – invasive aortic SBP	-1.4±14	-4.4±15	-0.02±13
Cuff – invasive aortic DBP	7.3±11	6.1±12	7.9±10
Cuff – invasive aortic PP	-8.8±15	-10.5±16	-8.0±14

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. All pressure values are mmHg. Data are presented as mean ± standard deviation.

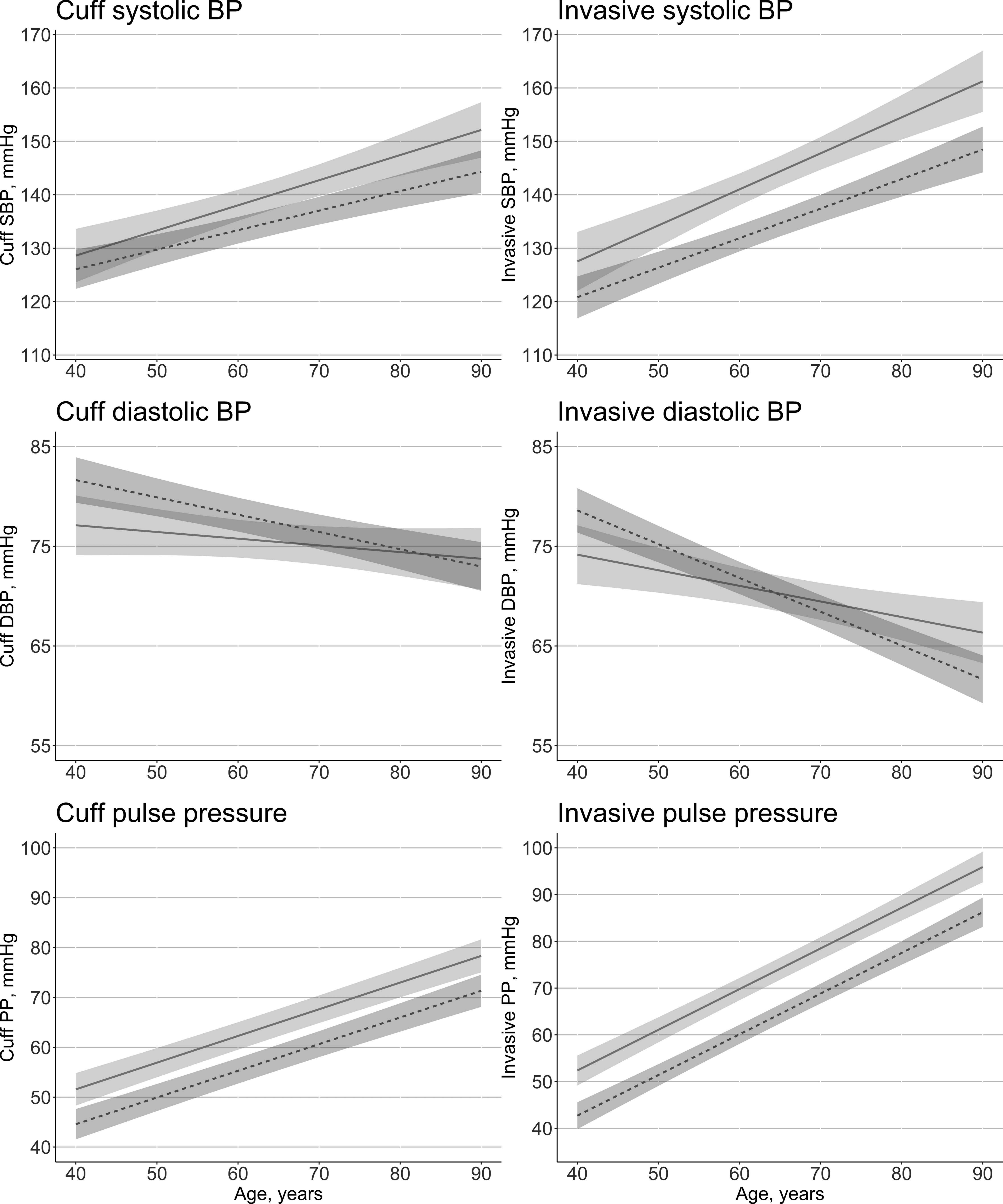
Table 2. Summary of key findings and implications for systolic blood pressure (BP), diastolic BP and pulse pressure.

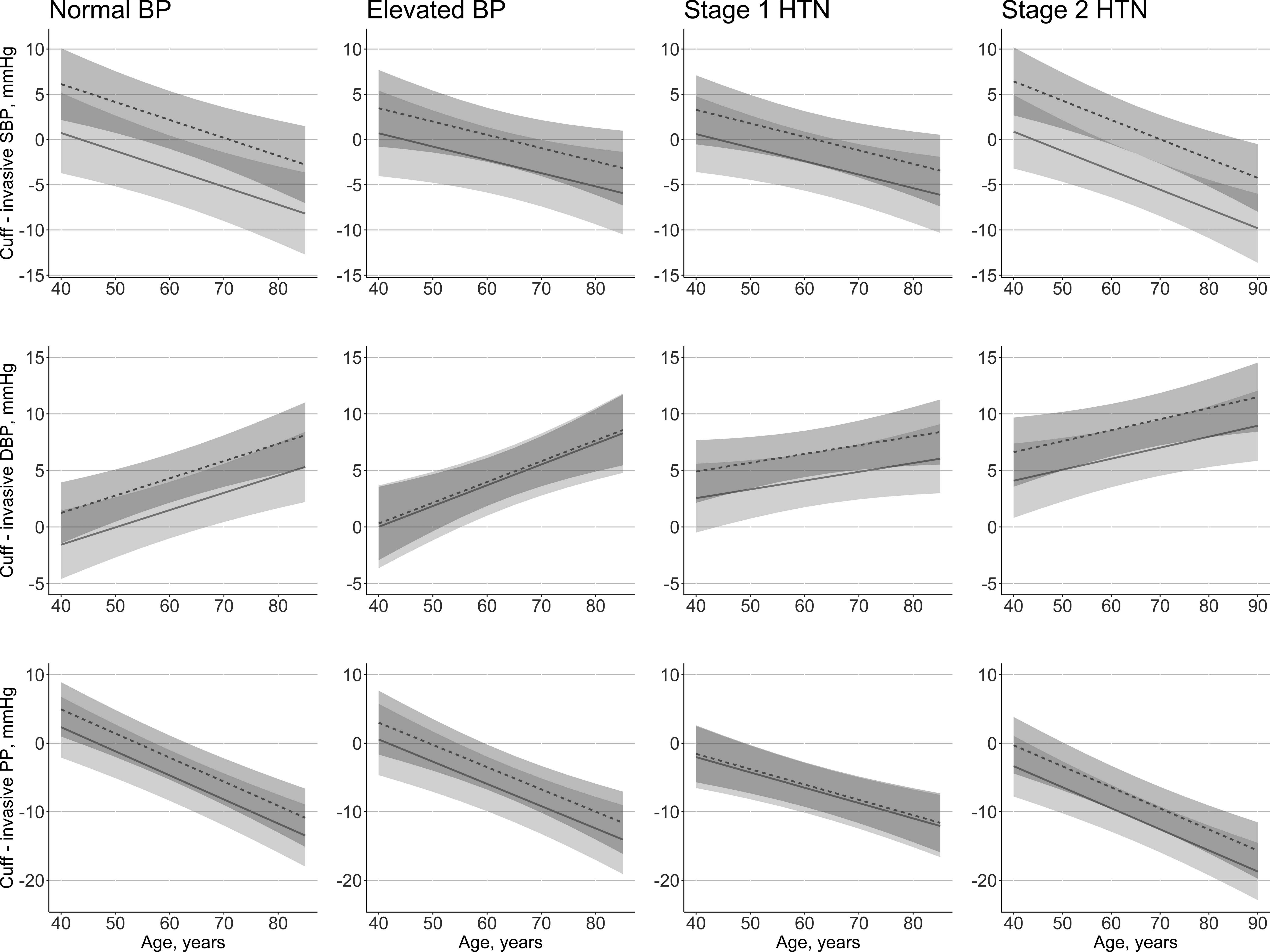
	Cuff	Invasive	Difference between cuff and invasive	Key findings /implications
Systolic BP	Higher in women compared with men.	Higher in women compared with men (more pronounced difference compared to cuff data).	Cuff underestimated invasive values more in women compared with men.	• Risk related to raised systolic BP more likely to be missed in women compared with men. • Increased potential for misdiagnosis (under-diagnosis and therefore missed opportunity to intervene) in women.
Diastolic BP	Higher in younger men, lower in older men compared with women.	Higher in younger men, lower in older men compared with women. Steeper age-related negative slope for men compared to cuff BP.	Cuff overestimated invasive values in women and men.	• Risk related to lower diastolic BP in older age more likely to be missed in men. • Increased potential for excessive therapeutic lowering of diastolic BP due to cuff diastolic BP overestimation of true diastolic BP.
Pulse pressure	Higher in women compared with men, similar slopes with age.	Higher in women compared with men (more pronounced difference compared to cuff data), similar slopes with age.	Large underestimation of PP in older women and men.	• Risk related to pulse pressure missed in both sexes, with higher underestimation in women.

Broad potential implications
Misdiagnosis that could lead to preventable cardiovascular events
Life-course sex-differences in BP generated from cuff BP measurements in large epidemiological studies may need to be reconsidered
Data on hypertension prevalence and control across different ages and sex may need to be reconsidered
Sex-specific treatment targets may need to be considered



Cuff - invasive SBP, mmHg
5
0
-5
-10
40
50
60
70
80
90
Cuff - invasive DBP, mmHg
10
5
0
40
50
60
70
80
90
Cuff - invasive PP, mmHg
5
0
-5
-10
-15
-20
40
50
60
70
80
90
Age, years


Cuff systolic BP
Cuff SBP, mmHg
Invasive systolic BP
Invasive SBP, mmHg
Cuff diastolic BP
Cuff DBP, mmHg
Invasive diastolic BP
Invasive DBP, mmHg
Cuff pulse pressure
Cuff PP, mmHg
Invasive pulse pressure
Invasive PP, mmHg
Age, years
Age, years



Normal BP
Elevated BP
Stage 1 HTN
Stage 2 HTN
Cuff - invasive SBP, mmHg
Cuff - invasive DBP, mmHg
Cuff - invasive PP, mmHg
Age, years