

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Flint AC, Conell C, Ren X, et al. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. N Engl J Med 2019;381:243-51. DOI: 10.1056/NEJMoa1803180

HYPER Study – Supplementary Appendix

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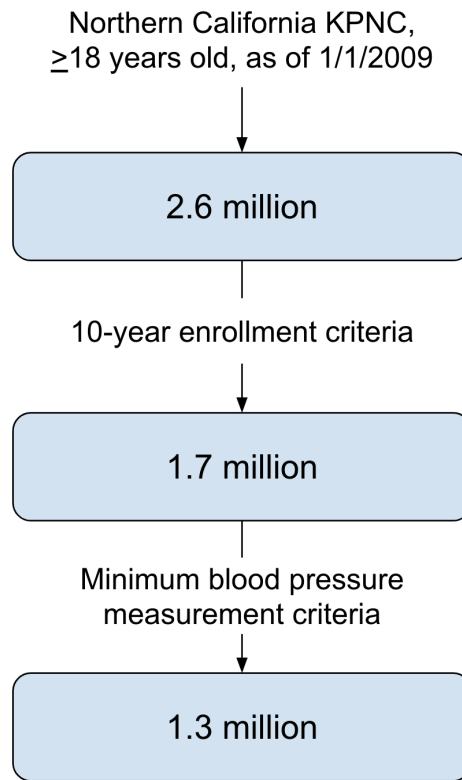
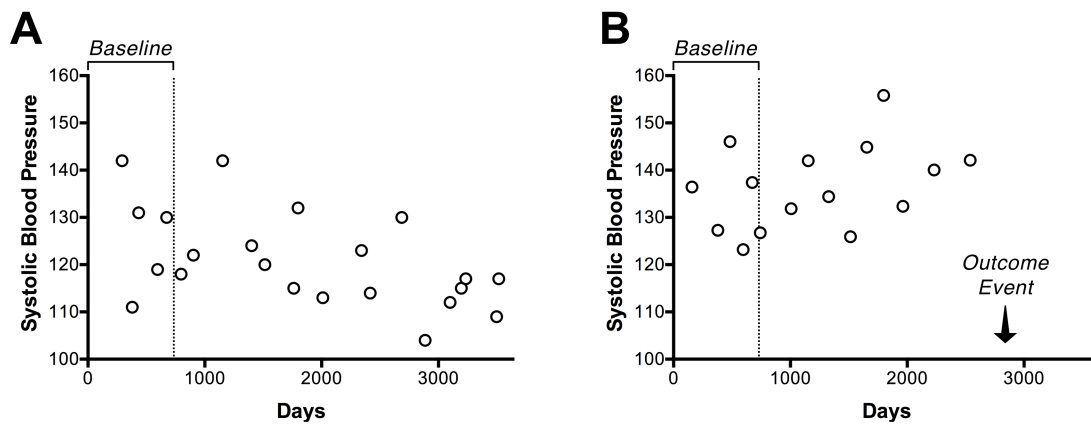
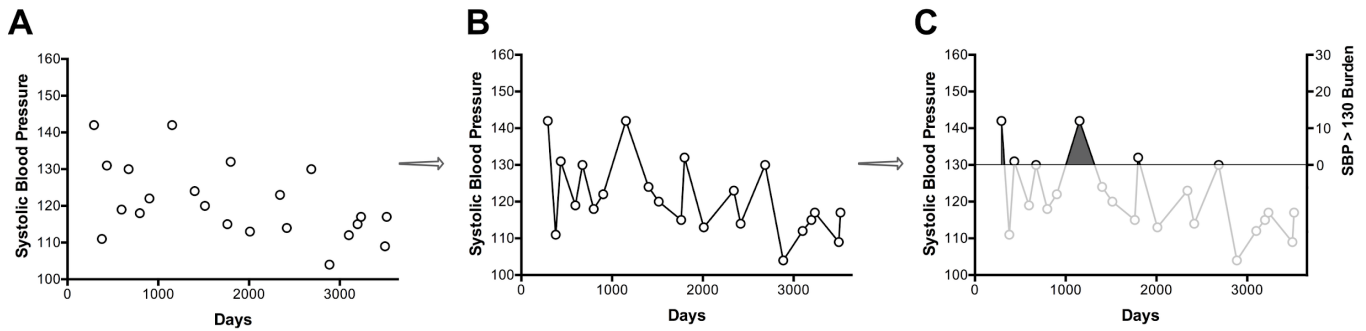
Figure S1: Study Cohort Flow Diagram**Figure S2: Study Design - Baseline and Observation Periods**

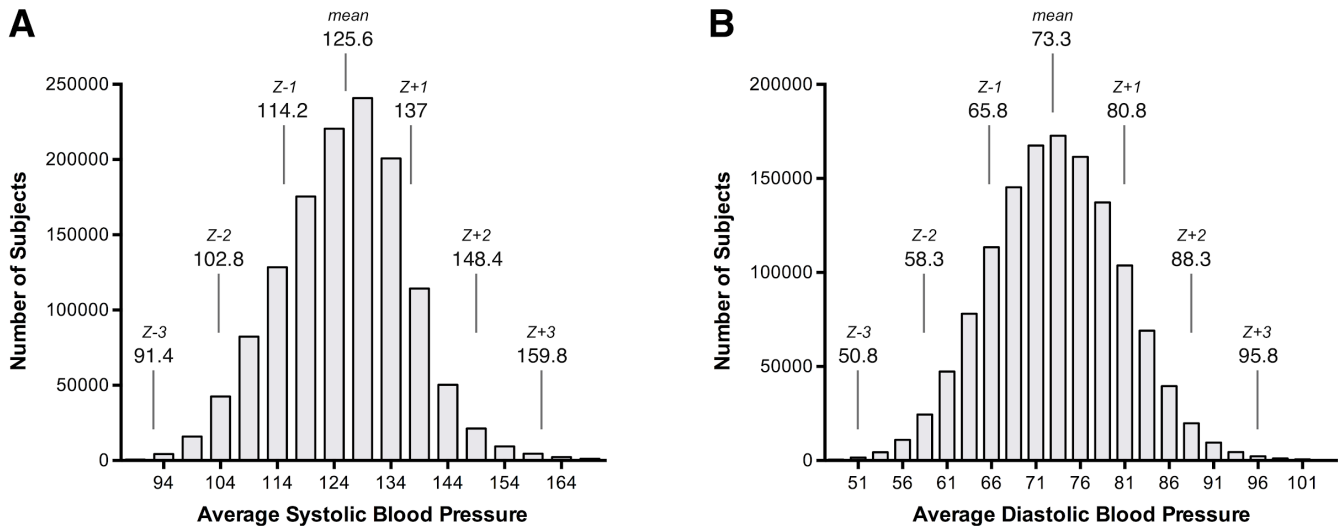
Illustration of the two study periods (baseline and observation). In the baseline period, blood pressure measures are recorded but outcome measures are not (patients with events in the baseline period were excluded). Baseline patient characteristics were recoded at the start of the baseline period. In the observation period, blood pressures continue to be recorded and surveillance occurs for any outcome event (myocardial infarction, ischemic stroke, or hemorrhagic stroke). In (A), an example of 22 anonymized systolic blood pressure values are shown for a patient across the full 10 year (2 year baseline + 8 year outcome observation) study period. In this example, no censoring by outcome event or death occurred, so blood pressures continue to be recorded across the full observation period. In (B), another patient is shown that has an outcome event about two thirds of the way through the observation period. Here, 15 anonymized blood pressures are shown prior to the outcome event—no further blood pressures are recorded after the outcome event.

Figure S3: Determination of time-weighted average blood pressure and hypertension burden



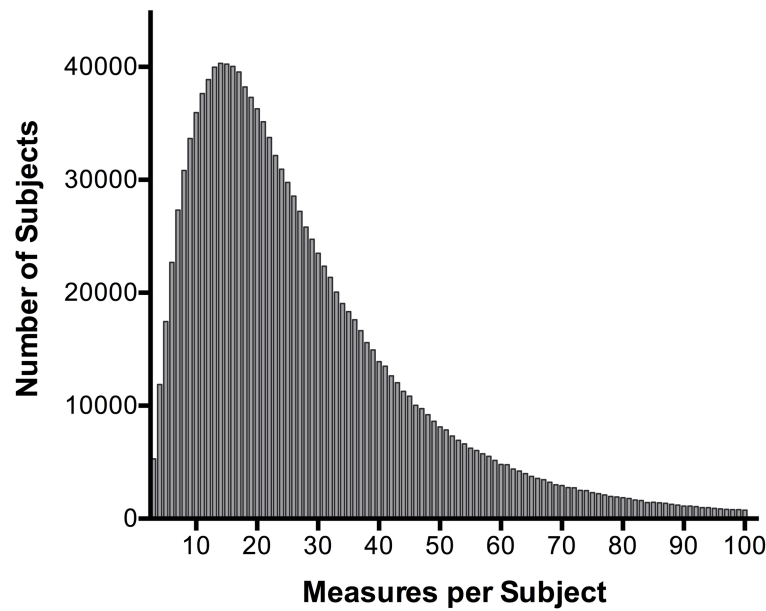
Stepwise process for determining time-weighted average of blood pressure and hypertension burden using a threshold. In (A), an example of 22 anonymized systolic blood pressure values from a patient are shown across the 10 year study period. In (B), linear interpolation is performed to connect the measured values in time. The arithmetic mean is calculated for all of the measured and interpolated values over the period, yielding the time-weighted average blood pressure. In (C), the systolic hypertension burden of systolic blood pressure above a threshold is determined by re-zeroing the interpolated pressure values at the threshold (in this example, 130 mm Hg, as shown on the right Y-axis), such that values above the zero point have positive values but values below the zero point are set to zero (as these 'normal' pressures do not contribute to the burden of hypertensive pressures). The burden of systolic pressure > 130 mm Hg is then calculated as the arithmetic mean of all of the measured and interpolated values over the period after this zeroing procedure.

Figure S4: Distribution of average systolic and diastolic blood pressures

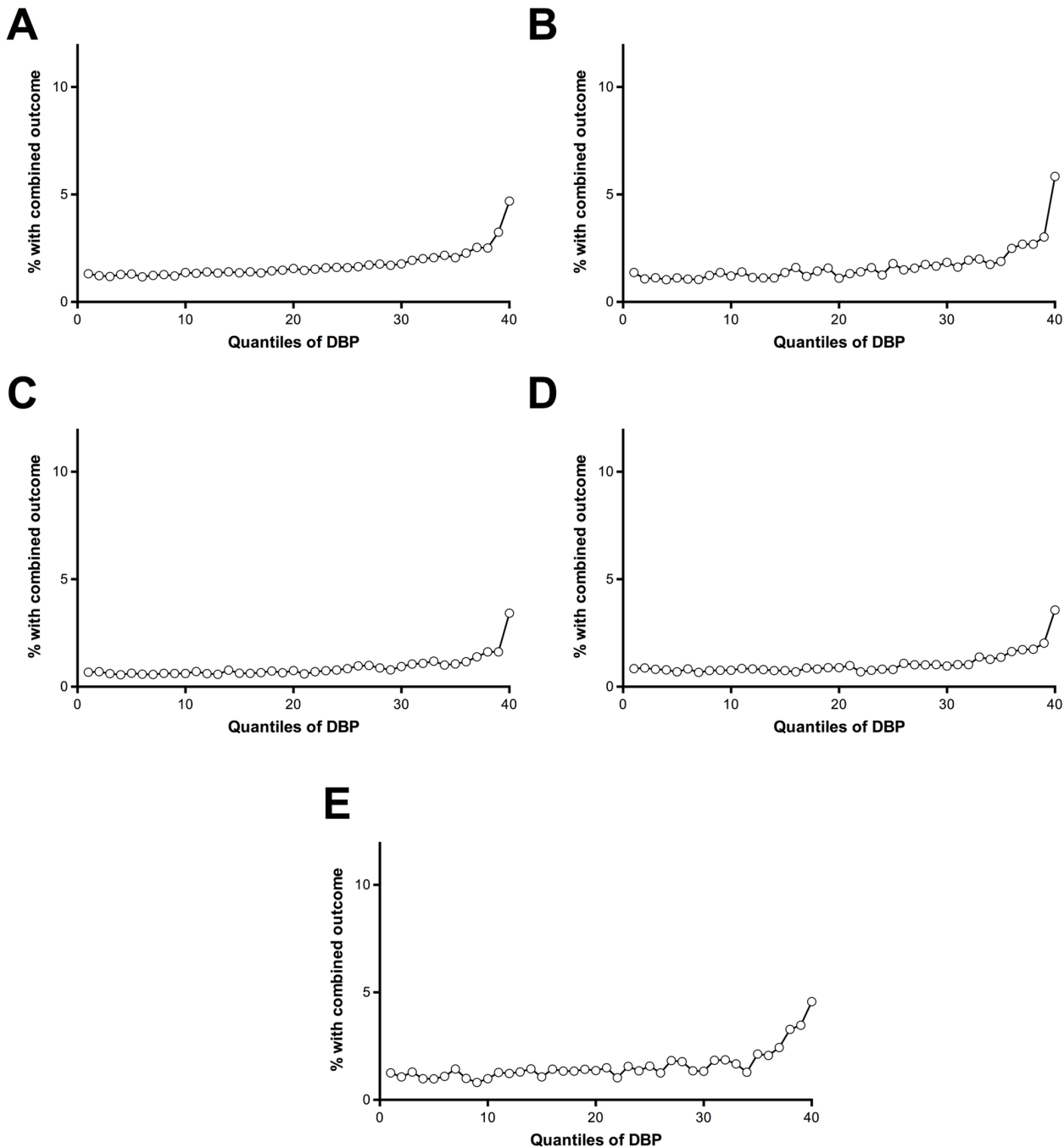


Distribution of time-weighted average blood pressures for each participant, with systolic pressures displayed in (A) and diastolic pressures displayed in (B). Bin width for systolic = 5 mm Hg, and for diastolic = 2.5 mm Hg; x-axis values represent bin centers in mm Hg. The mean and standard deviations above and below the mean (Z-scores) are displayed with the corresponding blood pressure values in mm Hg.

Figure S5: Distribution of number of blood pressure measures per participant

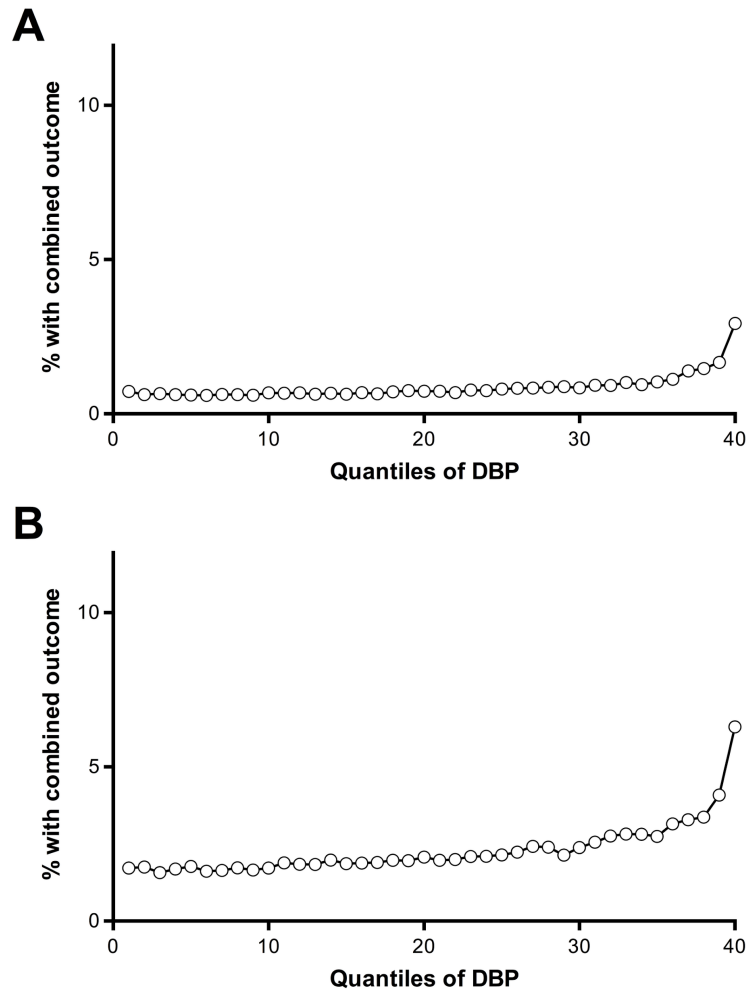


Distribution of number of blood pressure measures per participant, with each count plotted separately (bin width = 1). The median number of blood pressure measures per participant was 22 (interquartile range 13-36), with a mean of 27.9 measures per participant. The plot of the distribution is truncated on the right side of the X-axis at a count of 100 measures—19,712 participants had more than 100 blood pressure measures.

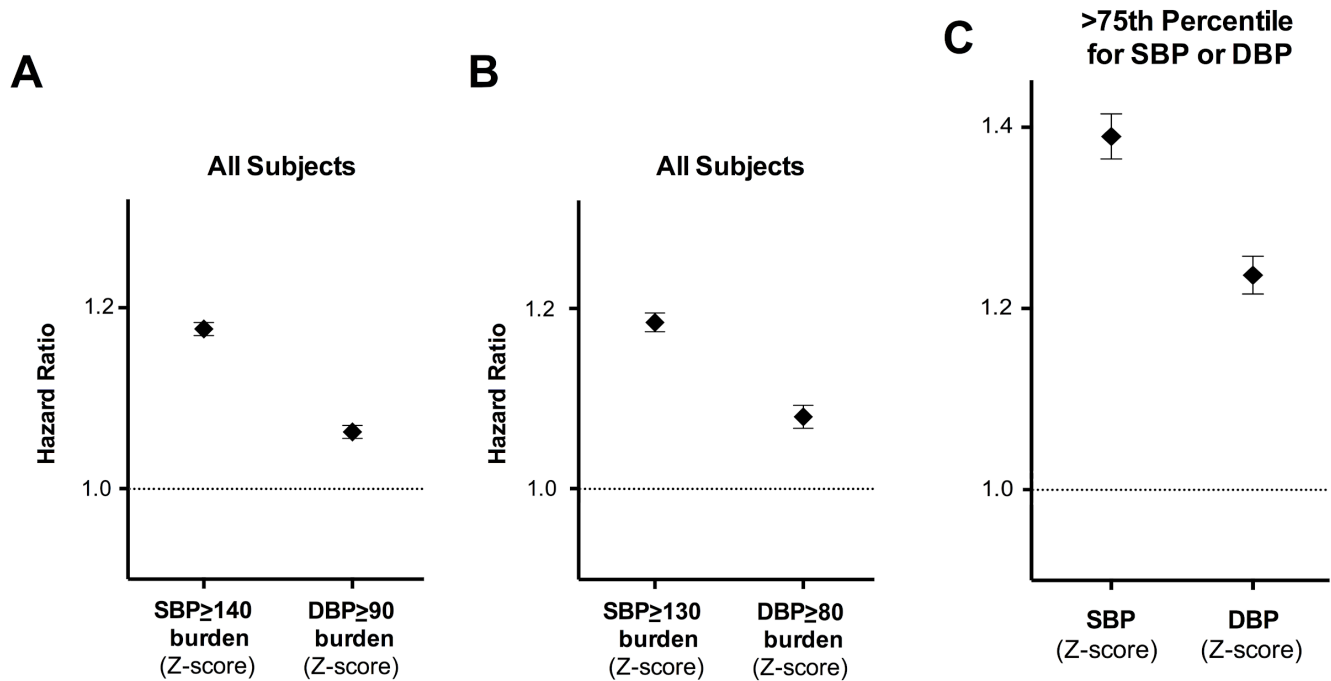
Figure S6: Relation of diastolic blood pressure to outcomes, stratified by race/ethnicity

Each panel shows percentage of participants with the composite outcome according to 40 quantiles of diastolic blood pressure (DBP), controlling for demographics and comorbidities, from margins estimation of multivariable logistic regression with covariates held at means. For each panel, the overall cohort is stratified by race/ethnicity, with race/ethnicity = White shown in (A), race/ethnicity = Black shown in (B), race/ethnicity = Hispanic shown in (C), race/ethnicity = Asian shown in (D), and race/ethnicity = Other/Unknown shown in (E). As seen with the overall cohort (Figure 3), no J-curve relation is seen between diastolic blood pressure and outcomes in adjusted analysis in the different subsets of race/ethnicity. Receiver-Operator Characteristics area under the curve (C-statistic) is 0.809 for the model in (A), 0.812 for (B), 0.851 for (C), 0.832 for (D), and 0.824 for (E). Pseudo R^2 is 0.1449 for the model in (A), 0.153 for (B), 0.188 for (C), 0.164 for (D), and 0.1636 for (E).

Figure S7: Relation of diastolic blood pressure to outcomes, stratified by sex



Each panel shows percentage of participants with the composite outcome according to 40 quantiles of diastolic blood pressure (DBP), controlling for demographics and comorbidities, from margins estimation of multivariable logistic regression with covariates held at means. For each panel, the overall cohort is stratified by sex, with female ($n=752,190$) in (A) and male ($n=563,416$) in (B). As seen with the overall cohort (Figure 3), no J-curve relation is seen between diastolic blood pressure and outcomes in adjusted analysis when men and women are analyzed separately. Receiver-Operator Characteristics area under the curve (C-statistic) is 0.850 for the female stratified model in (A) and 0.782 for the male-stratified model in (B). Pseudo R^2 is 0.1857 for the model in (A) and 0.1235 for the model in (B).

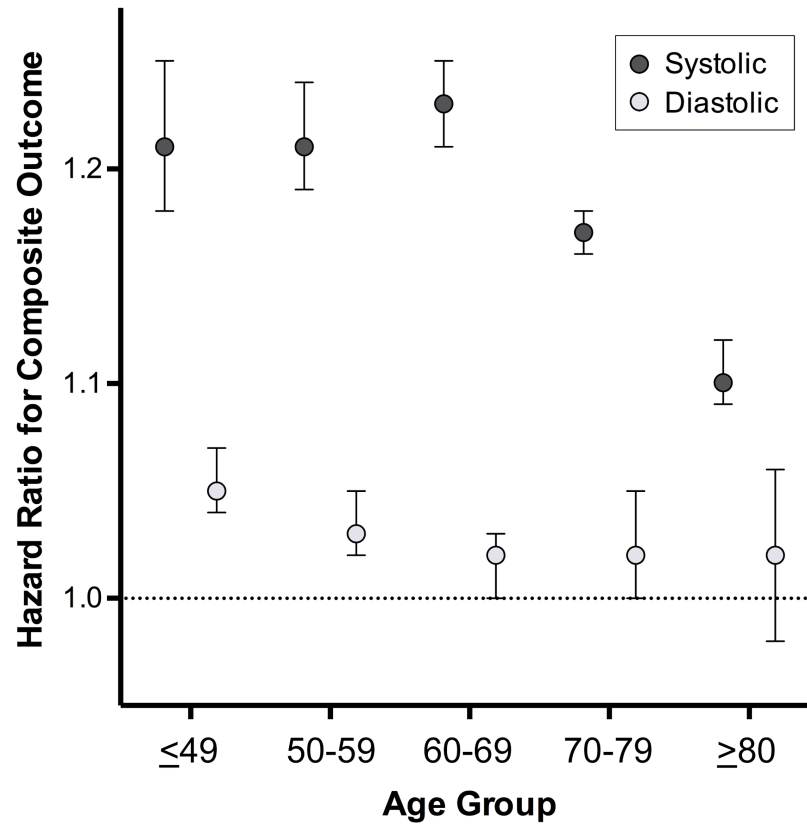
Figure S8: Multivariable modeling of adverse cardiovascular outcomes

A. Multivariable Cox regression model of survival free of the composite outcome (myocardial infarction, ischemic stroke, or hemorrhagic stroke) for all participants, with burden of systolic and diastolic hypertension defined using thresholds of SBP \geq 140 mm Hg and DBP \geq 90 mm Hg. Single model including both systolic and diastolic Z-score normalized hypertension burden with control for demographics and comorbidities. Markers indicate the hazard ratio and error bars indicate the 95% confidence interval for the hazard ratio. Hazard ratios are per Z-score of predictor.

B. Multivariable Cox regression model of survival free of the composite outcome for all participants, with burden of systolic and diastolic hypertension defined using thresholds of SBP \geq 130 mm Hg and DBP \geq 80 mm Hg. Single model including both systolic and diastolic Z-score normalized hypertension burden with control for demographics and comorbidities.

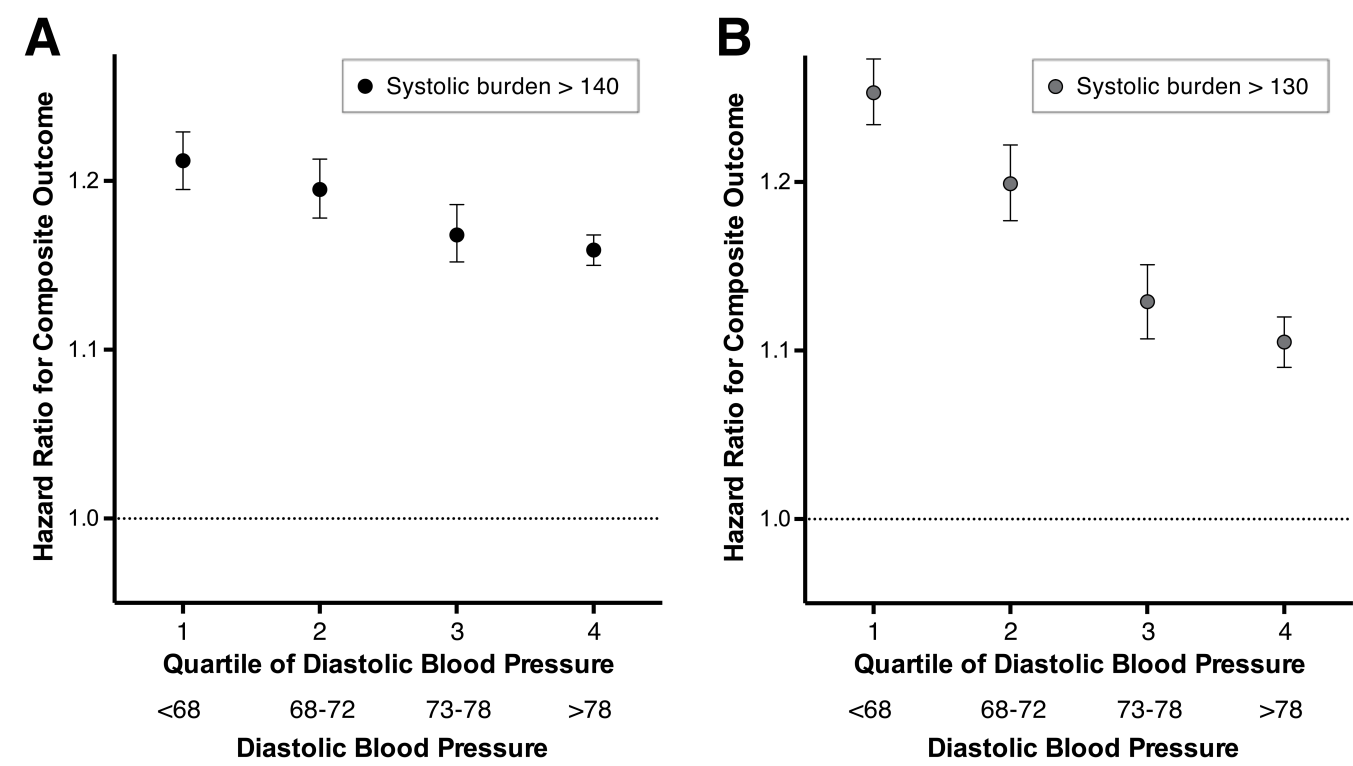
C. Multivariable Cox regression model using continuous systolic and diastolic blood pressure burden for participants above the 75th percentile for systolic (>133 mm Hg) or diastolic (>78 mm Hg) blood pressure, to capture a range of blood pressures from normal to elevated. Single model including both systolic and diastolic Z-score normalized hypertension burden with control for demographics and comorbidities.

Figure S9: Impact of systolic and diastolic hypertension on outcome, according to age



Relation of systolic and diastolic hypertension burden (>140/90 mm Hg) on combined cardiovascular outcome, stratified according to age groups. Dark gray circles indicate hazard ratio for systolic hypertension burden (>140 mm Hg) and light gray circles indicate hazard ratio for diastolic hypertension burden (>90 mm Hg), with error bars indicating 95% confidence intervals for the hazard ratio estimates. Hazard ratios are from multivariable survival models controlling for demographics and comorbidities. Hazard ratios are per Z-score of predictor. Number of participants in each age group: ≤49: n=570,745; 50-59: n=286,123; 60-69: n=232,893; 70-79: n=146,865; ≥80: n=79,737.

Figure S10: Impact of systolic hypertension according to quartile of diastolic blood pressure



Relation of systolic hypertension burden to combined cardiovascular outcome, stratified according to 4 quartiles of weighted average diastolic blood pressure.

A. Black circles indicate hazard ratio for systolic hypertension burden (>140 mm Hg), with error bars indicating 95% confidence intervals for the hazard ratio estimates.

B. Gray circles indicate hazard ratio for systolic hypertension burden (>130 mm Hg), with error bars indicating 95% confidence intervals for the hazard ratio estimates.

Hazard ratios are from multivariable survival models controlling for demographics and comorbidities. Corresponding diastolic blood pressure ranges are given below each quartile. Number of participants in each quartile: (1) <68: n=375,930; (2) 68-72: n=334,609; (3) 73-78: n=313,410; (4) >78: n=292,414.

Table S1: Multivariable survival models according to race / ethnicity

Models control for demographics and comorbidities. Hazard ratios are per Z-score of predictor.

140/90 mm Hg hypertension burden among race/ethnicity = **White:**

n = 721,981	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.16	1.15 - 1.17	<0.001
DBP>90 mm Hg Burden	1.06	1.04 - 1.07	<0.001

140/90 mm Hg hypertension burden among race/ethnicity = **Black:**

n = 98,727	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.16	1.14 - 1.18	<0.001
DBP>90 mm Hg Burden	1.06	1.05 - 1.08	<0.001

140/90 mm Hg hypertension burden among race/ethnicity = **Hispanic:**

n = 205,393	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.21	1.19 - 1.23	<0.001
DBP>90 mm Hg Burden	1.07	1.05 - 1.09	<0.001

140/90 mm Hg hypertension burden among race/ethnicity = **Asian:**

n = 205,072	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.22	1.20 - 1.24	<0.001
DBP>90 mm Hg Burden	1.06	1.04 - 1.08	<0.001

140/90 mm Hg hypertension burden among race/ethnicity = **Other / Unknown:**

n = 84,433	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.22	1.19 - 1.24	<0.001
DBP>90 mm Hg Burden	1.04	1.01 - 1.07	0.009

Table S2: Multivariable survival models according to sex

Models control for demographics and comorbidities. Hazard ratios are per Z-score of predictor.

140/90 mm Hg hypertension burden among **women**:

n = 752,190	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.16	1.15 - 1.17	<0.001
DBP>90 mm Hg Burden	1.06	1.05 - 1.08	<0.001

140/90 mm Hg hypertension burden among **men**:

n = 563,416	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.18	1.16 - 1.19	<0.001
DBP>90 mm Hg Burden	1.06	1.05 - 1.07	<0.001

Table S3: Multivariable survival models using blood pressure predictors restricted to the baseline period

Models control for demographics and comorbidities. Blood pressure predictors use blood pressure measures obtained from the 2-year baseline period for all participants, with surveillance for combined outcome events in the 8-year surveillance period, calculated in the same fashion as for our primary predictors. Hazard ratios are per Z-score of predictor.

140/90 mm Hg hypertension burden using **baseline blood pressures** only:

n = 1,315,606	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.14	1.14 - 1.15	<0.001
DBP>90 mm Hg Burden	1.04	1.03 - 1.05	<0.001

130/80 mm Hg hypertension burden using **baseline blood pressures** only:

n = 1,315,606	Hazard Ratio	95% CI	P value
SBP>130 mm Hg Burden	1.18	1.17 - 1.19	<0.001
DBP>80 mm Hg Burden	1.07	1.06 - 1.08	<0.001

Table S4: Multivariable survival models according to baseline cardiovascular disease

Models control for demographics and comorbidities. Baseline cardiovascular disease defined as any presence of coronary artery disease, congestive heart failure, history of myocardial infarction, or history of stroke in baseline period. Hazard ratios are per Z-score of predictor.

140/90 mm Hg hypertension burden among participants **without baseline cardiovascular disease**:

n = 1,179,647	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.18	1.17 - 1.19	<0.001
DBP>90 mm Hg Burden	1.06	1.05 - 1.07	<0.001

140/90 mm Hg hypertension burden among participants **with baseline cardiovascular disease**:

n = 135,959	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.16	1.14 - 1.17	<0.001
DBP>90 mm Hg Burden	1.07	1.05 - 1.09	<0.001

Table S5: Multivariable survival models according to baseline ACC risk estimation

Models control for demographics and comorbidities. Baseline ACC pooled cohort risk calculated according to published equations (Goff-DC, Circulation 2014, 129[25 Suppl 2]: S49-73).

140/90 mm Hg hypertension burden among participants **with baseline ACC risk <10%**:

n = 523,788	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.24	1.22 - 1.17	<0.001
DBP>90 mm Hg Burden	1.06	1.04 - 1.07	<0.001

140/90 mm Hg hypertension burden among participants **with baseline ACC risk \geq 10%**:

n = 308,714	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.17	1.16 - 1.17	<0.001
DBP>90 mm Hg Burden	1.05	1.04 - 1.06	<0.001

Table S6: Multivariable survival models according to antihypertensive medication use

Models control for demographics and comorbidities. Antihypertensive use for these analyses was defined as medications prescribed with a diagnosis of hypertension provided as the indication for prescription. Both models were restricted to participants with at least one hypertensive (>140/90 mm Hg) measure in the study period. Hazard ratios are per Z-score of predictor.

In the first model, criteria for antihypertensive use were active outpatient antihypertensive prescription^{*} beginning prior to the observation period with evidence of continued prescription in the observation period, with more than one order for antihypertensive medication during the observation period and the last prescription for an antihypertensive occurring in the last year of observation.

In the second model, non-use of antihypertensives was defined as a lack of antihypertensive prescription throughout the study period.

140/90 mm Hg hypertension burden among participants **on antihypertensive medications:**

n = 126,181	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.17	1.16 - 1.18	<0.001
DBP>90 mm Hg Burden	1.05	1.04 - 1.07	<0.001

140/90 mm Hg hypertension burden among participants **not on antihypertensive medications:**

n = 390,619	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.13	1.10 - 1.17	<0.001
DBP>90 mm Hg Burden	1.08	1.05 - 1.11	<0.001

^{*} All prescriptions in KPNC are electronic and require diagnosis indication, allowing us to electronically capture all antihypertensive prescriptions using the criteria listed.

Table S7: Multivariable survival models with and without control for number of BP measures

Models control for demographics and comorbidities. Antihypertensive use for these analyses was defined as medications prescribed with a diagnosis of hypertension provided as the indication for prescription. Both models were restricted to participants with at least one hypertensive (>140/90 mm Hg) measure in the study period. Hazard ratios are per Z-score of predictor.

140/90 mm Hg hypertension burden among all participants:

n = 1,315,606	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.18	1.17 - 1.18	<0.001
DBP>90 mm Hg Burden	1.06	1.05 - 1.07	<0.001

140/90 mm Hg hypertension burden all among participants **including control for number of BP measures**:

n = 1,315,606	Hazard Ratio	95% CI	P value
SBP>140 mm Hg Burden	1.18	1.17 - 1.19	<0.001
DBP>90 mm Hg Burden	1.06	1.06 - 1.17	<0.001