**Appendix 4: Supplementary figures and tables** [posted as supplied by author]

**Figure A. CONSORT diagram**

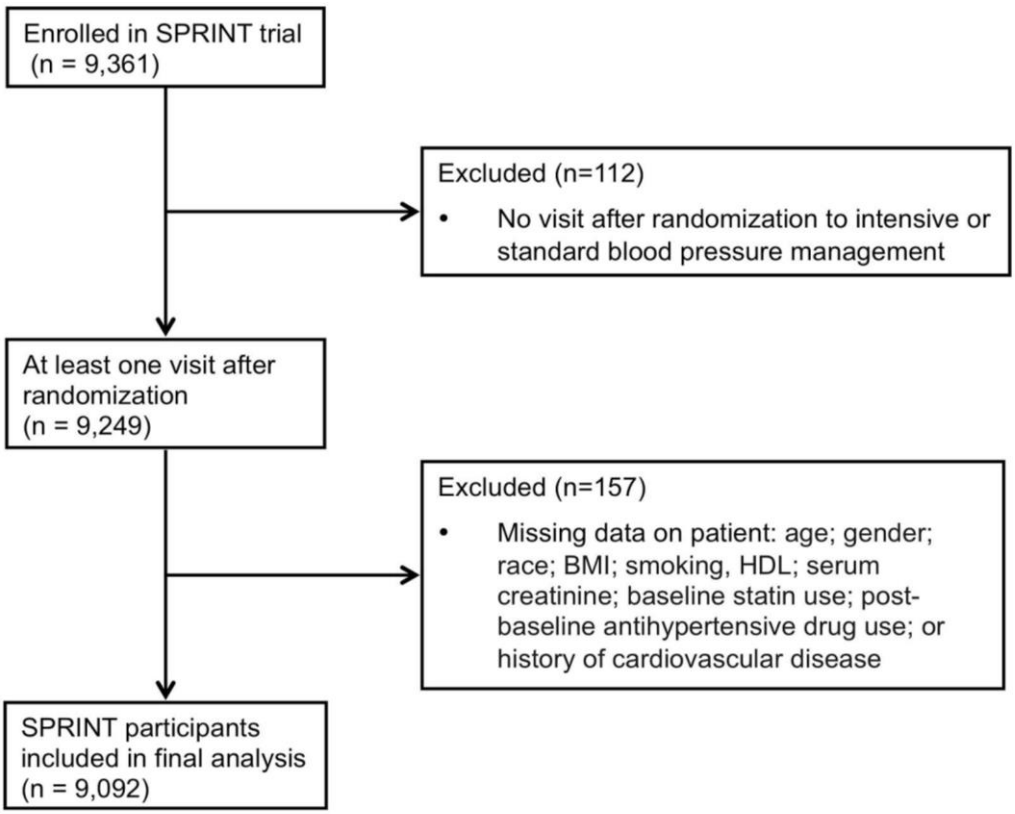
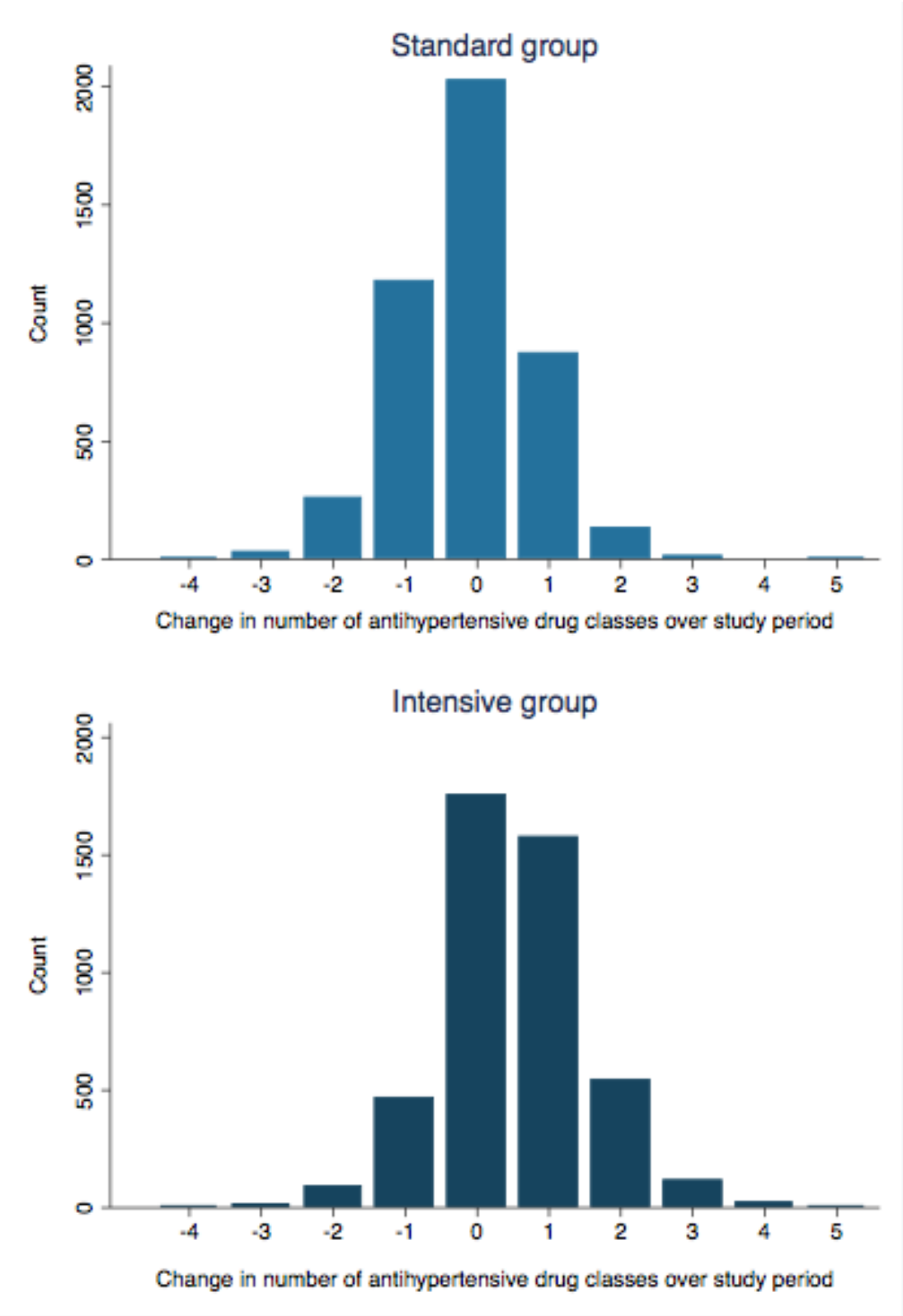
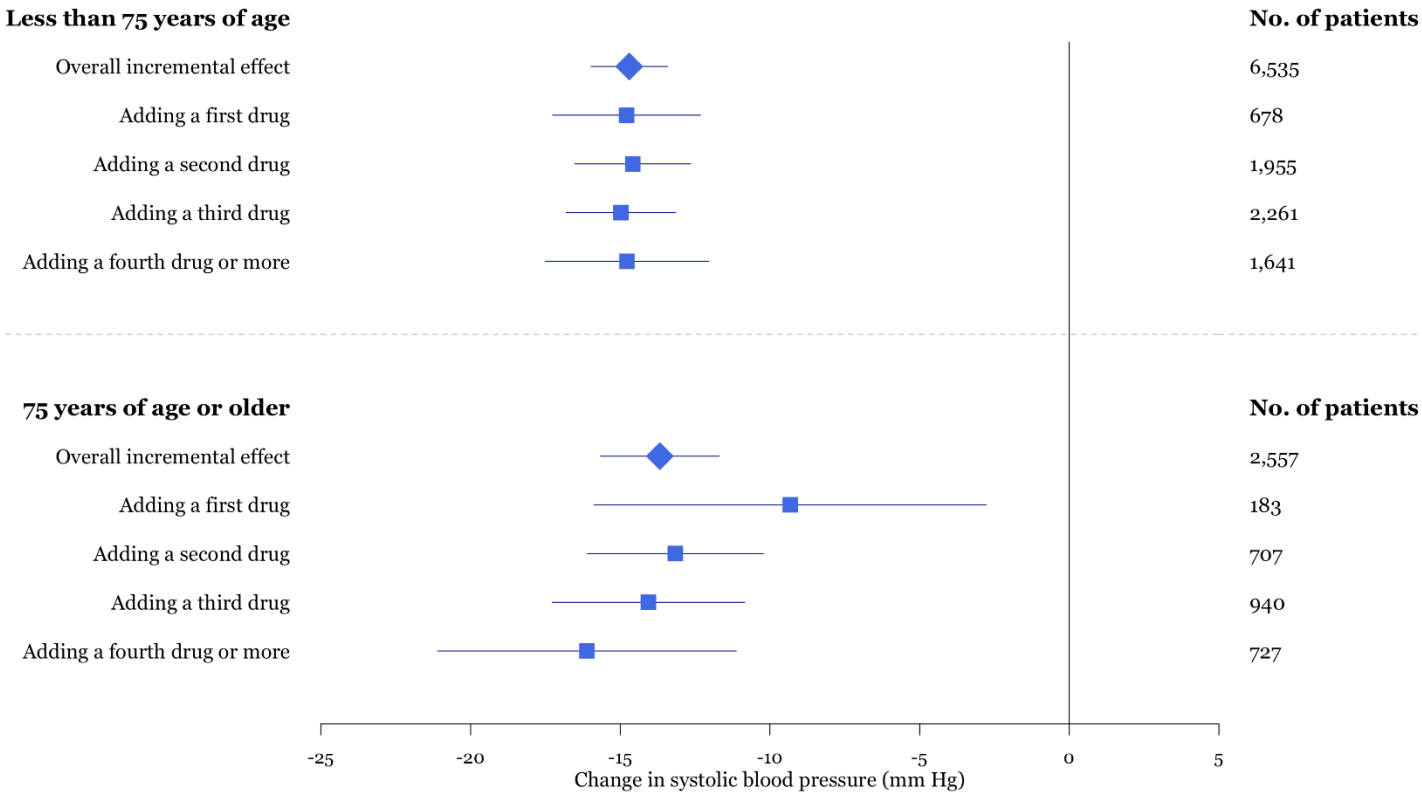


**Figure B. Change in number of antihypertensive drug classes over study**



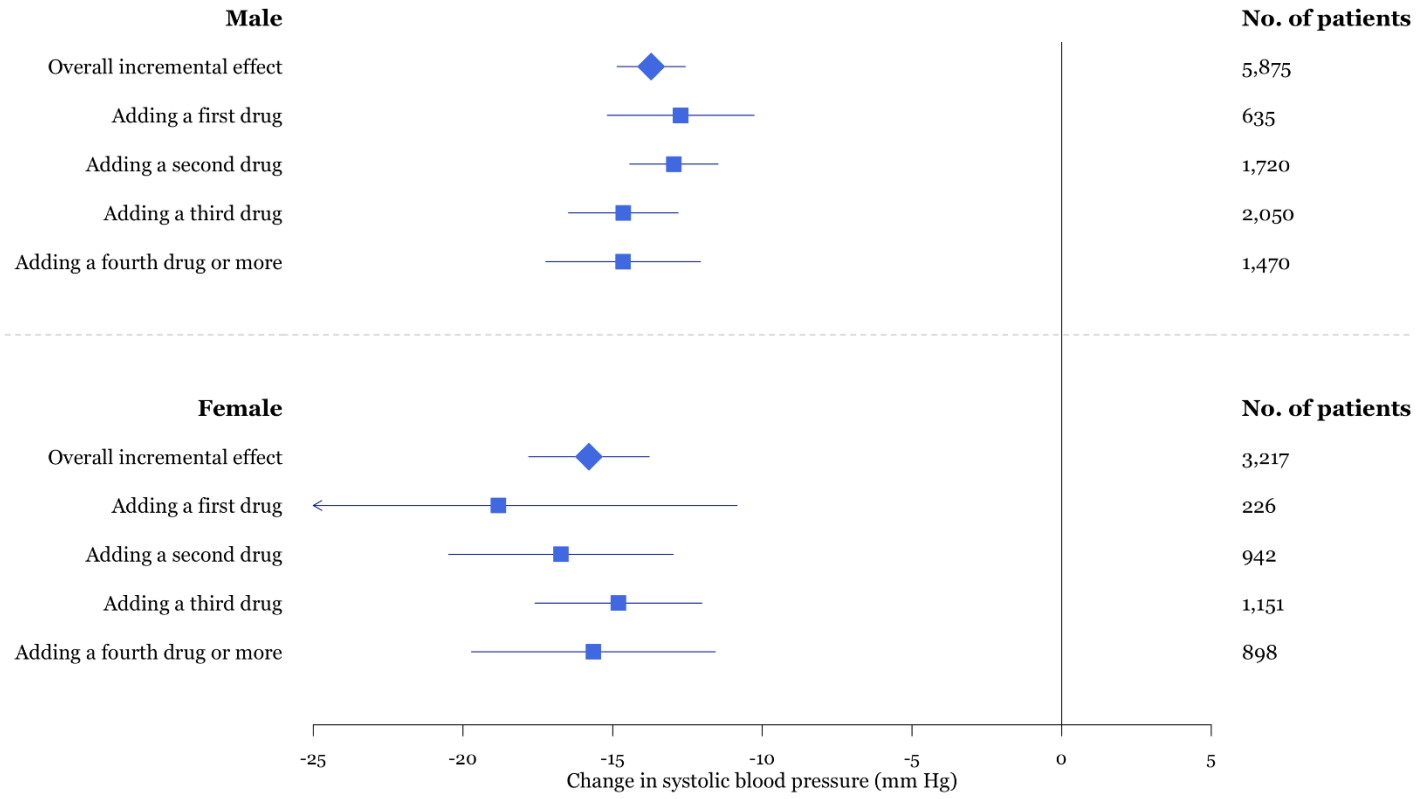
## Figure C. Incremental effects across clinical and demographic subgroups

### Figure C1. Age

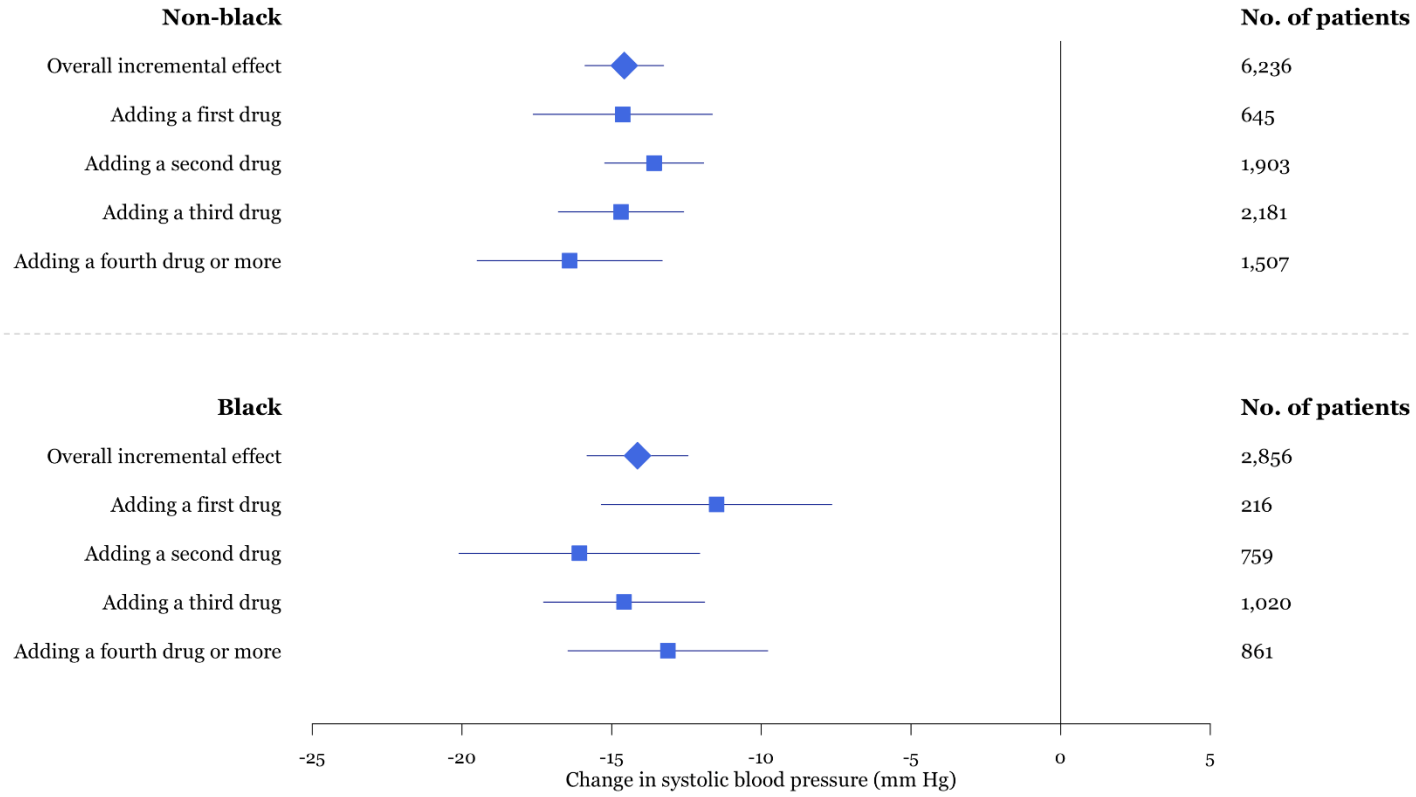



Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Lines represent 95% confidence intervals. Antihypertensive drug classes are measured at baseline and at each patient's final visit. Instrumental variable models were estimated using two-stage ordinary least squares regression.

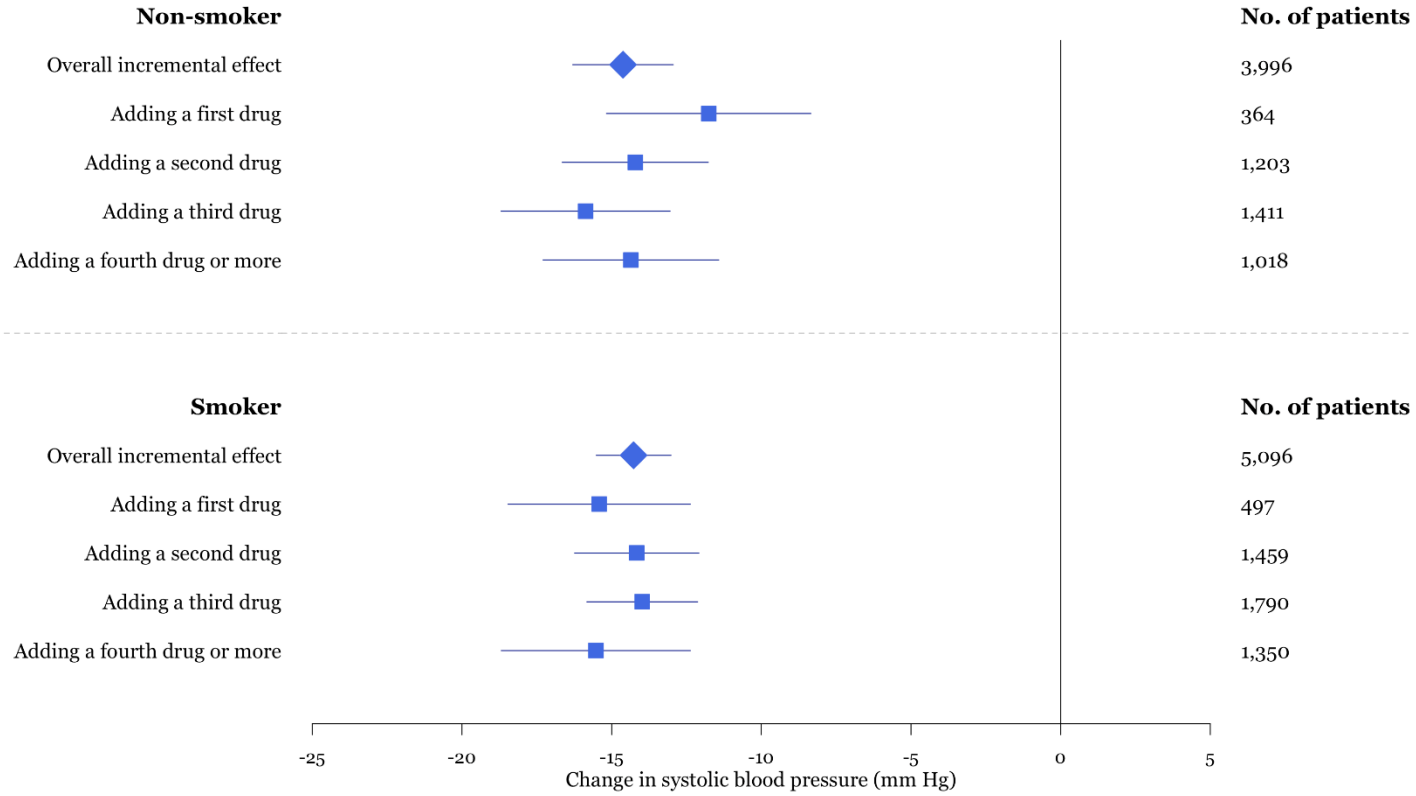
## Figure C2. Sex



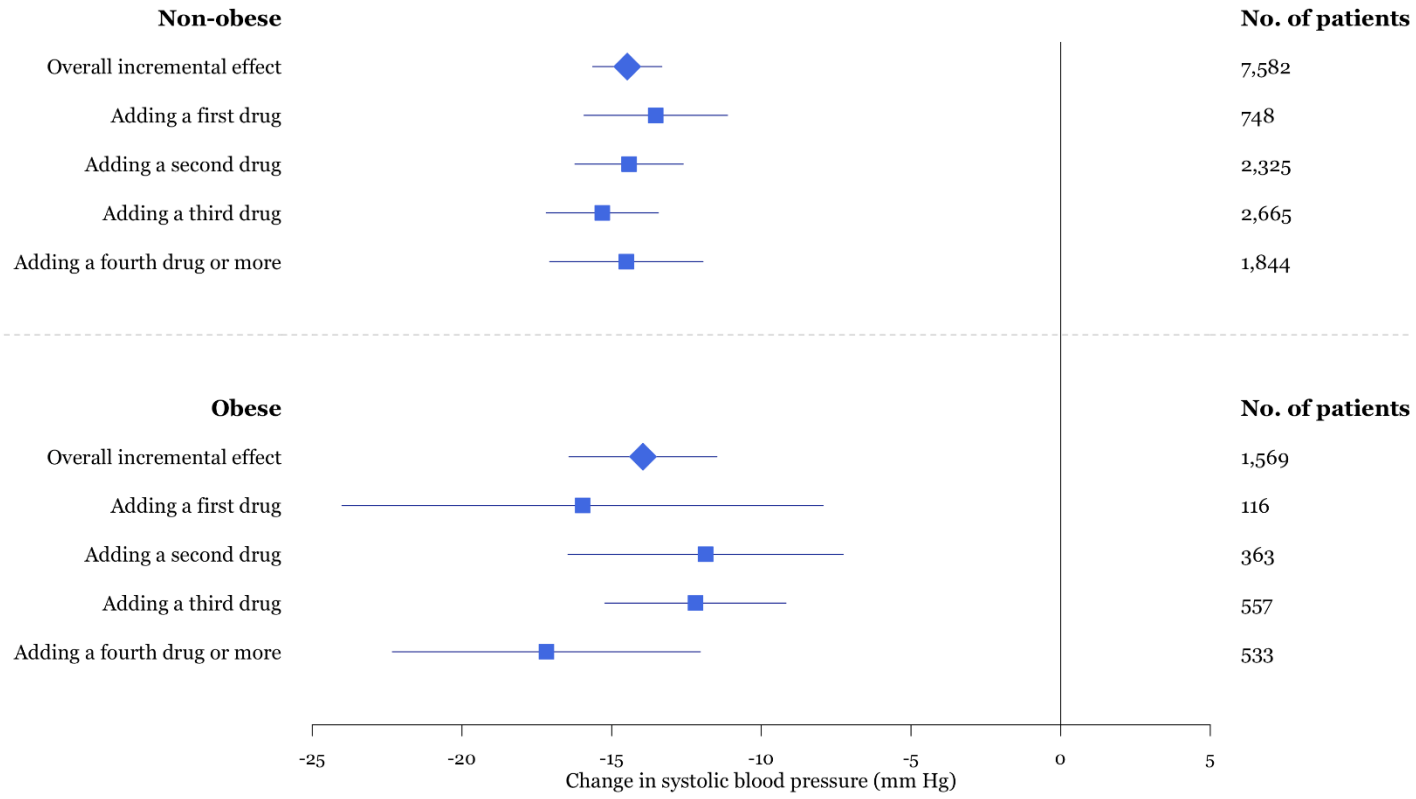
## Figure C3. Black race (race was self reported. Black includes non-Hispanic and Hispnaic black)



## Figure C4. Smoking status



## Figure C5. Obesity (defined as BMI ≥35)



## Figure C6. History of cardiovascular disease (CVD)

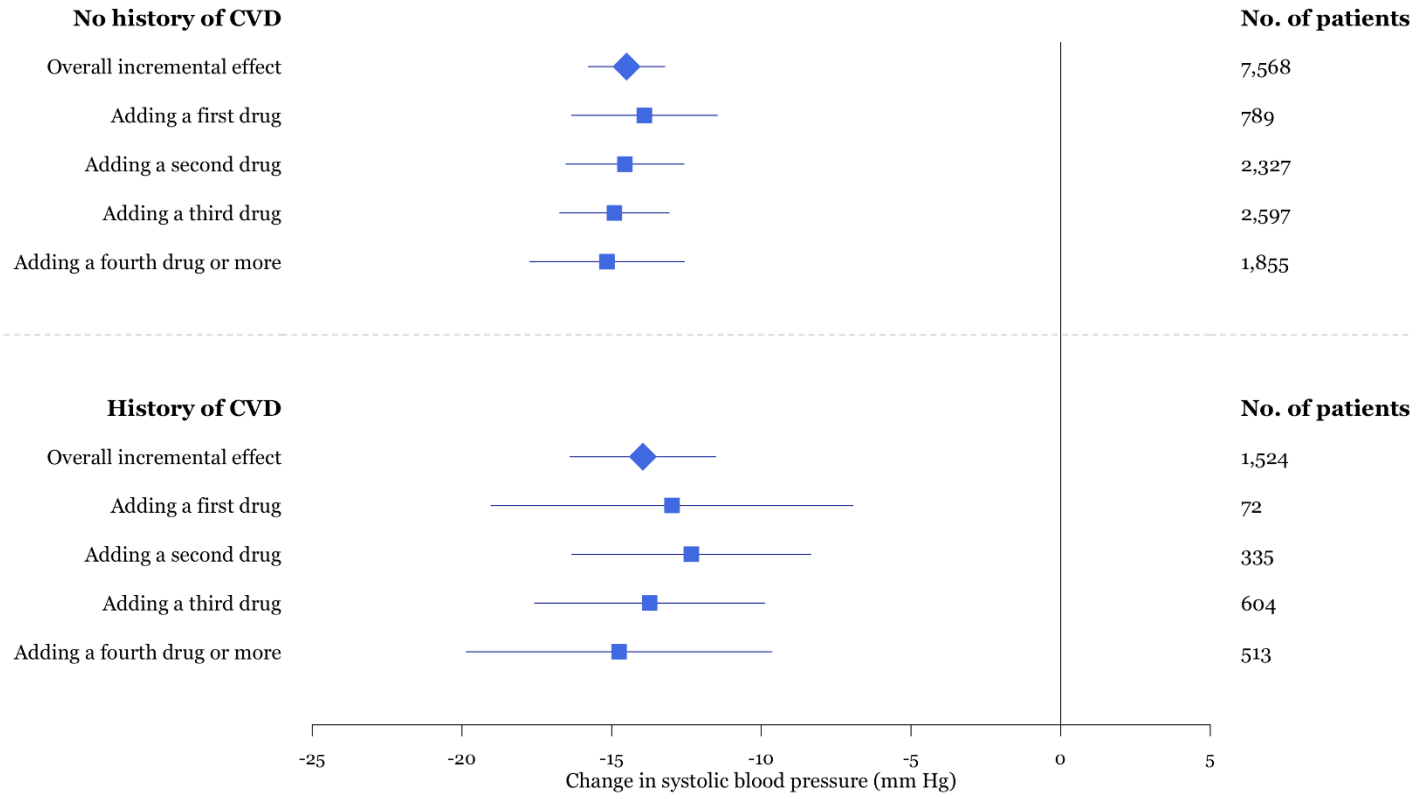


**Figure C7. History of chronic kidney disease (CKD). Category "no history of CKD includes some participants with unknown CKD status at baseline)**

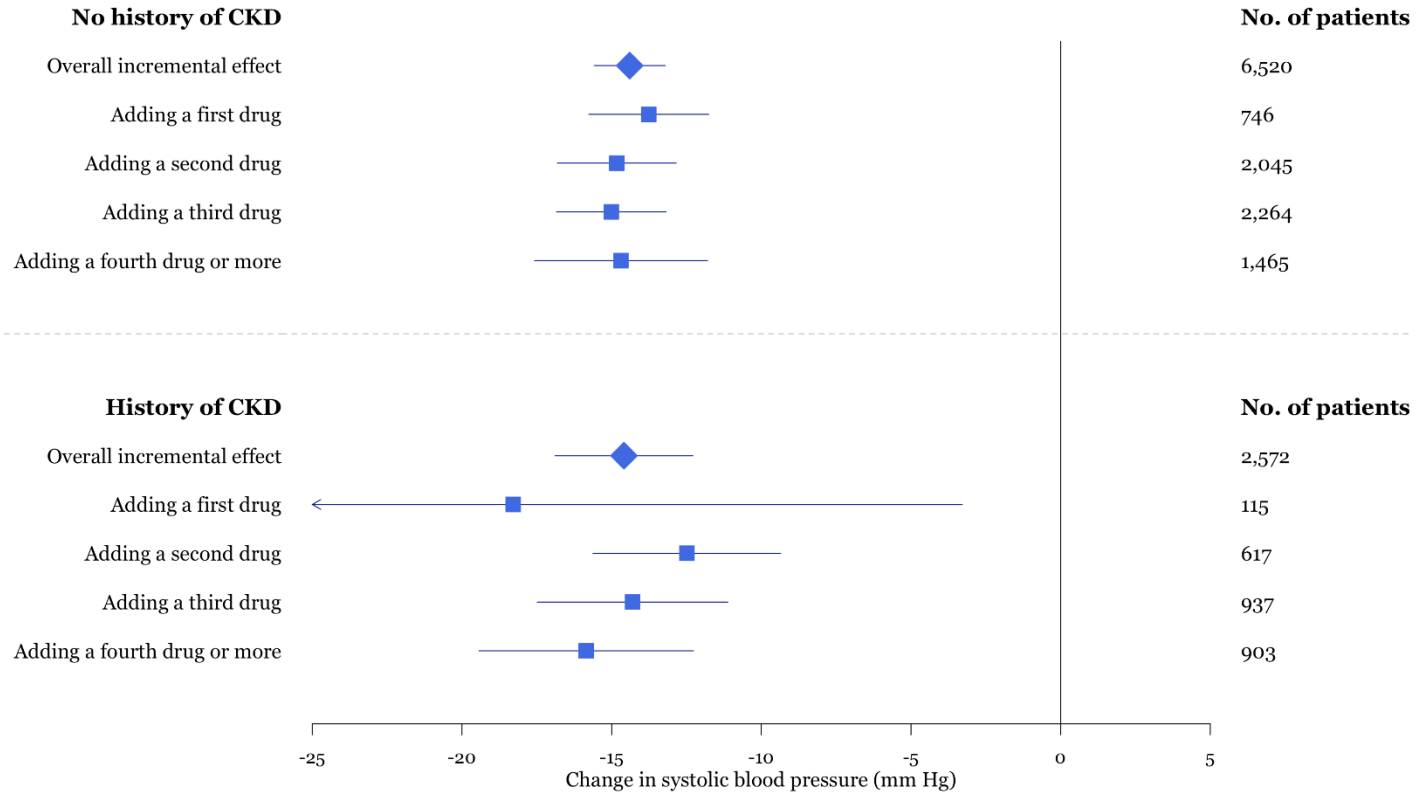
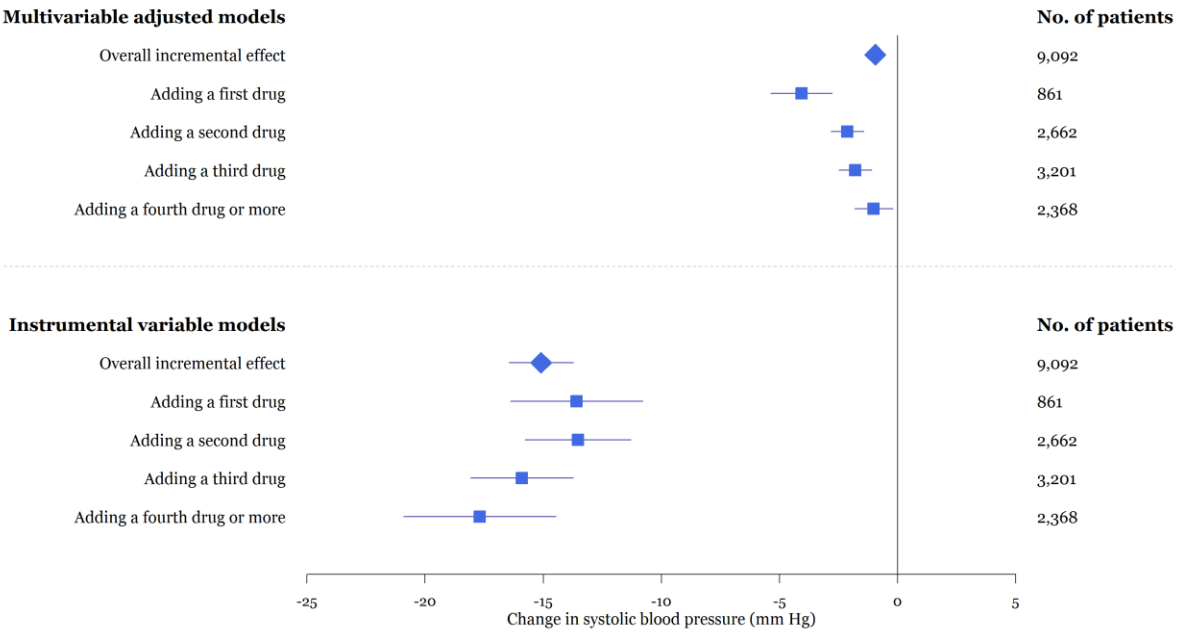
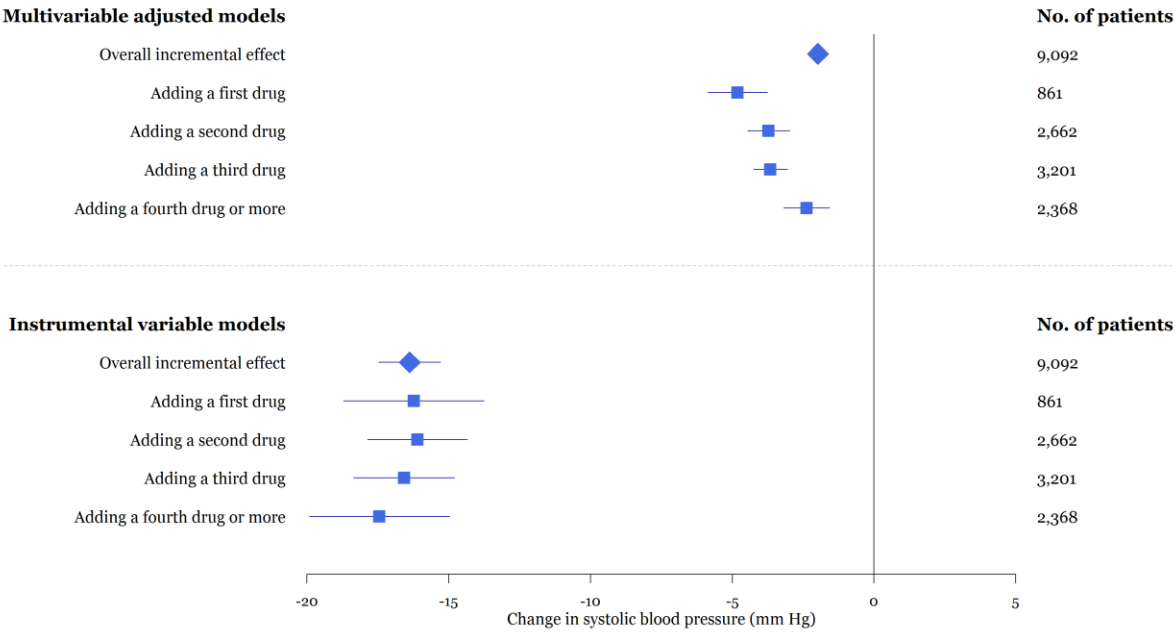


**Figure D. Incremental effect of antihypertensive drugs on systolic blood pressure at the three-month visit**



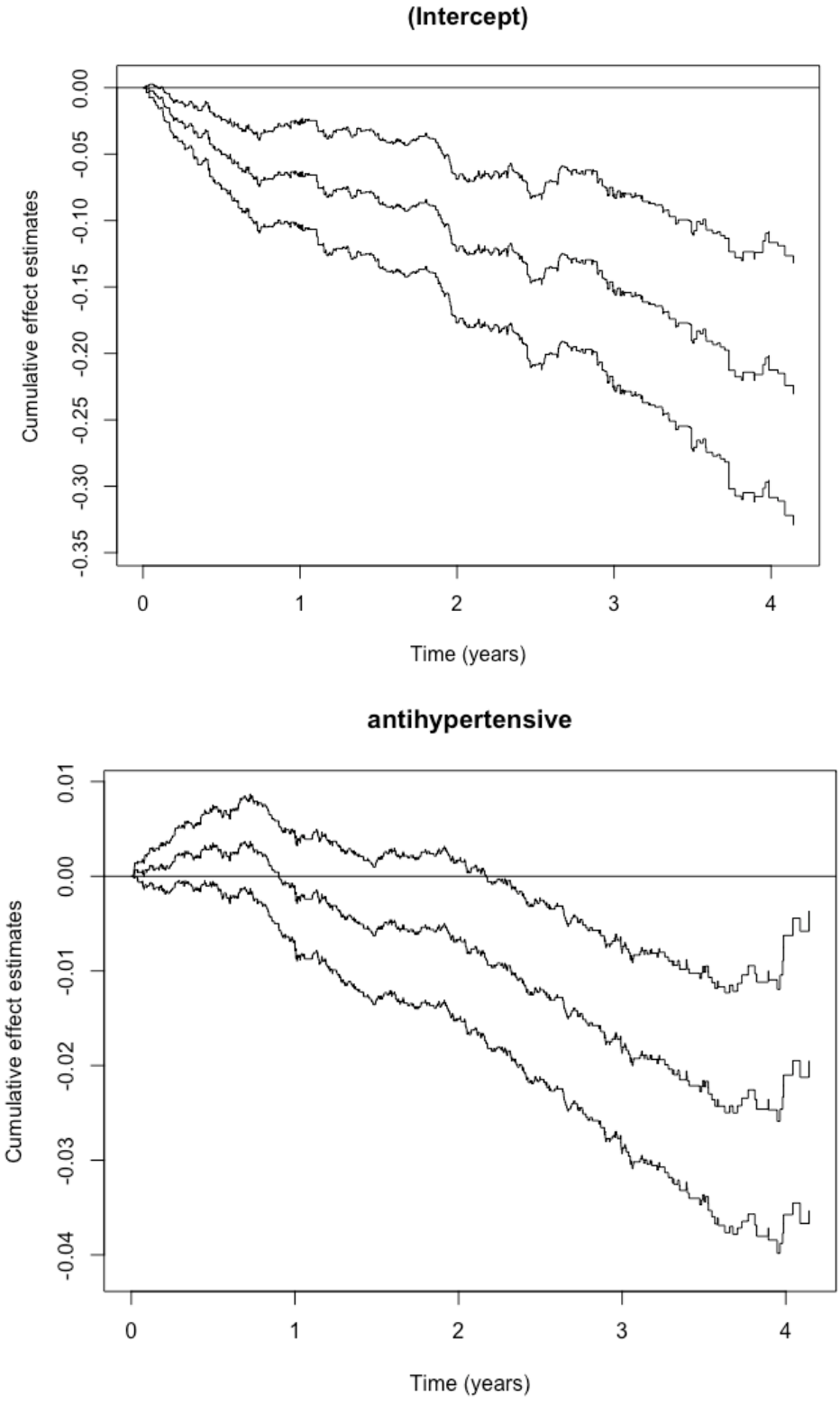

Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Lines represent 95% confidence intervals. Systolic blood pressure is measured at the three-month visit. Antihypertensive drug classes are measured at baseline and at exit of the two-month visit. Multivariable adjusted models were estimated using ordinary least squares regression. Instrumental variable models were estimated using two-stage ordinary least squares regression.

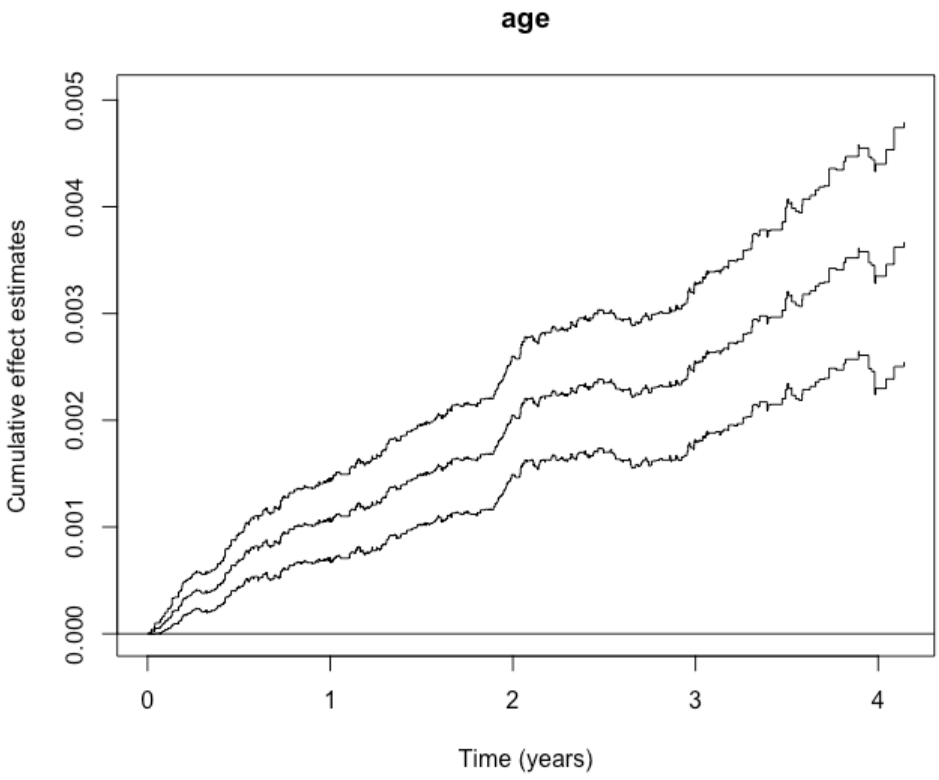
**Figure E. Incremental effect of mean number of antihypertensive drugs on systolic blood pressure**

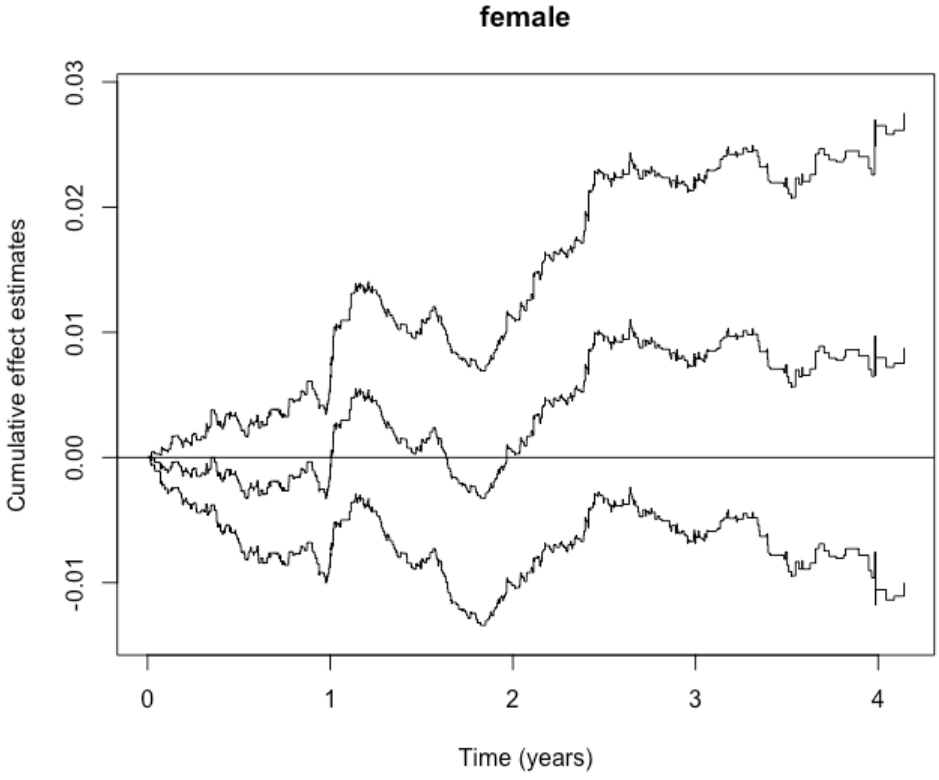


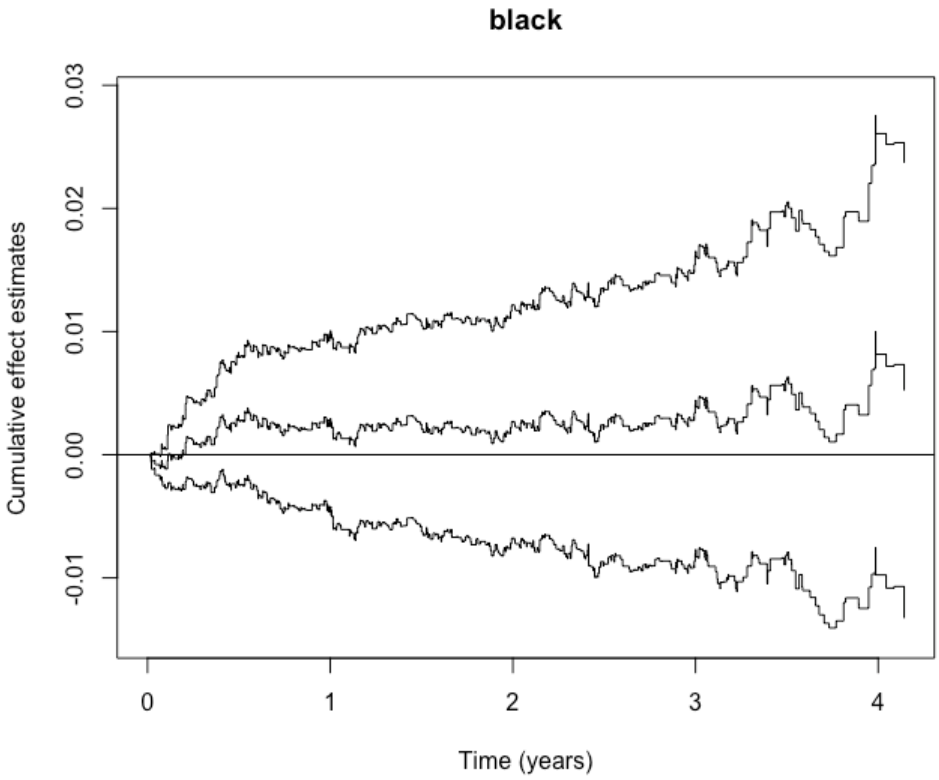

Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Lines represent 95% confidence intervals. Systolic blood pressure is measured at the final visit. We calculated the mean number of antihypertensive drug classes a patient was recorded as being prescribed over the study period. Multivariable adjusted models were estimated using ordinary least squares regression. Instrumental variable models were estimated using two-stage ordinary least squares regression.

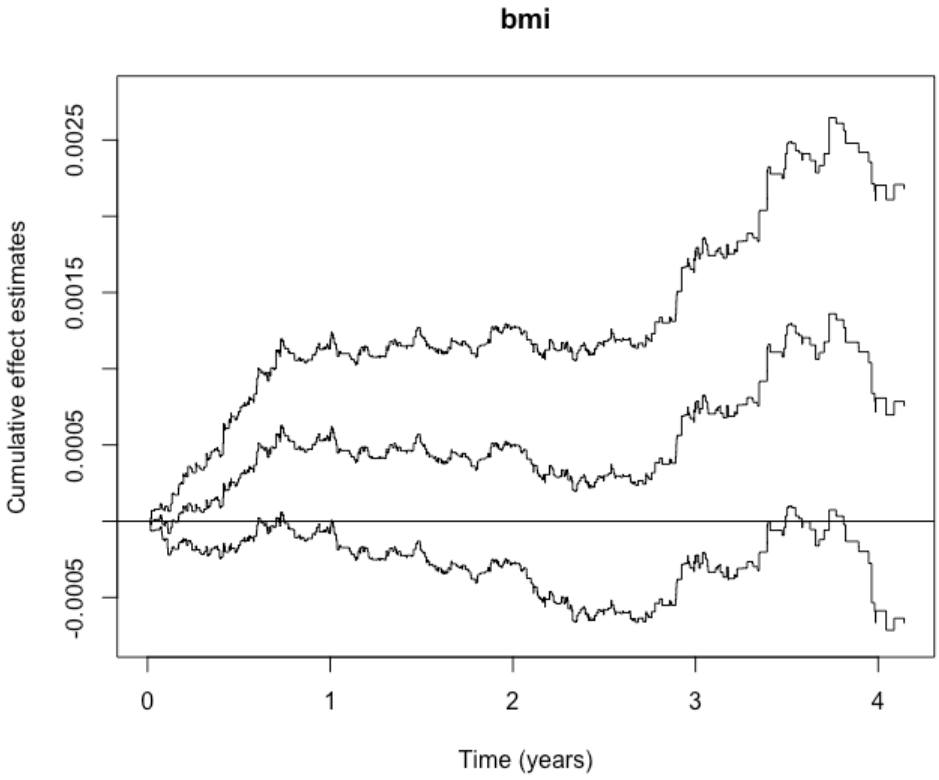
**Figure F. Cumulative coefficient plots of the incremental effects on composite major cardiovascular events**




age
Cumulative effect estimates
0.000
0.001
0.002
0.003
0.004
0.005
0
1
2
3
4
Time (years)


female
Cumulative effect estimates
-0.01
0.00
0.01
0.02
0.03
0
1
2
3
4
Time (years)


black
Cumulative effect estimates
0.03
0.02
0.01
0.00
-0.01
0
1
2
3
4
Time (years)


bmi
Cumulative effect estimates
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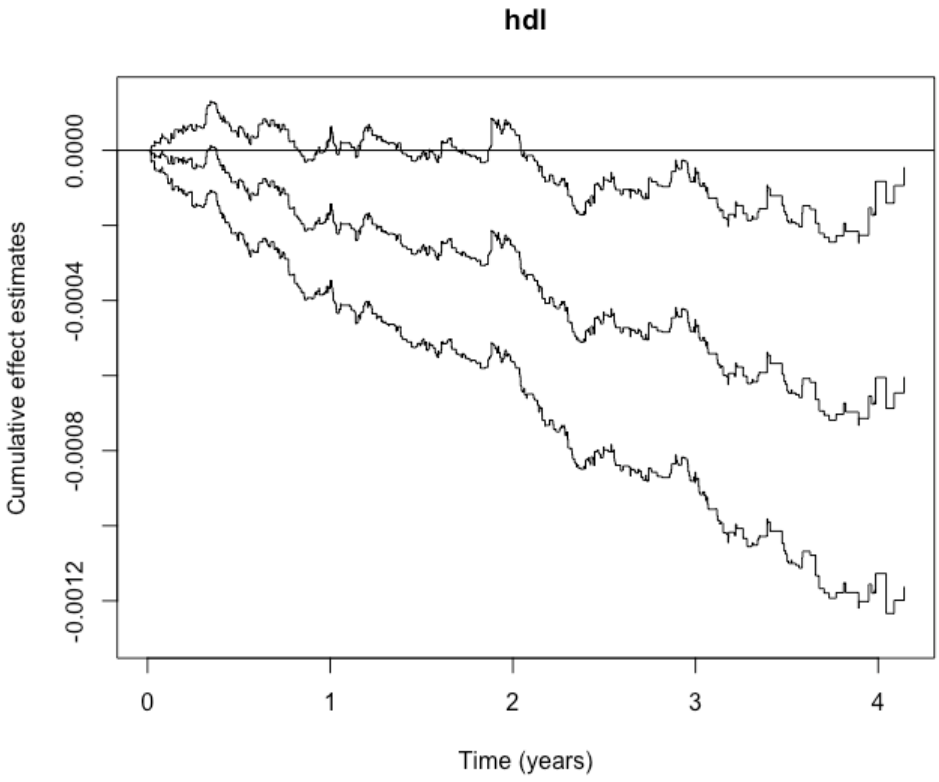
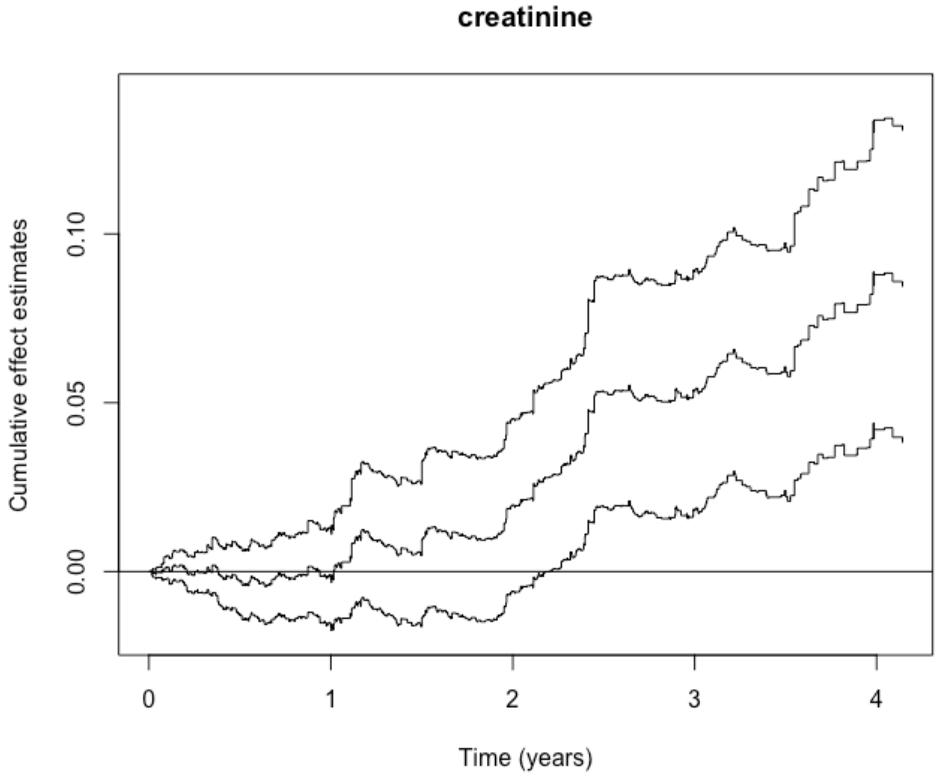
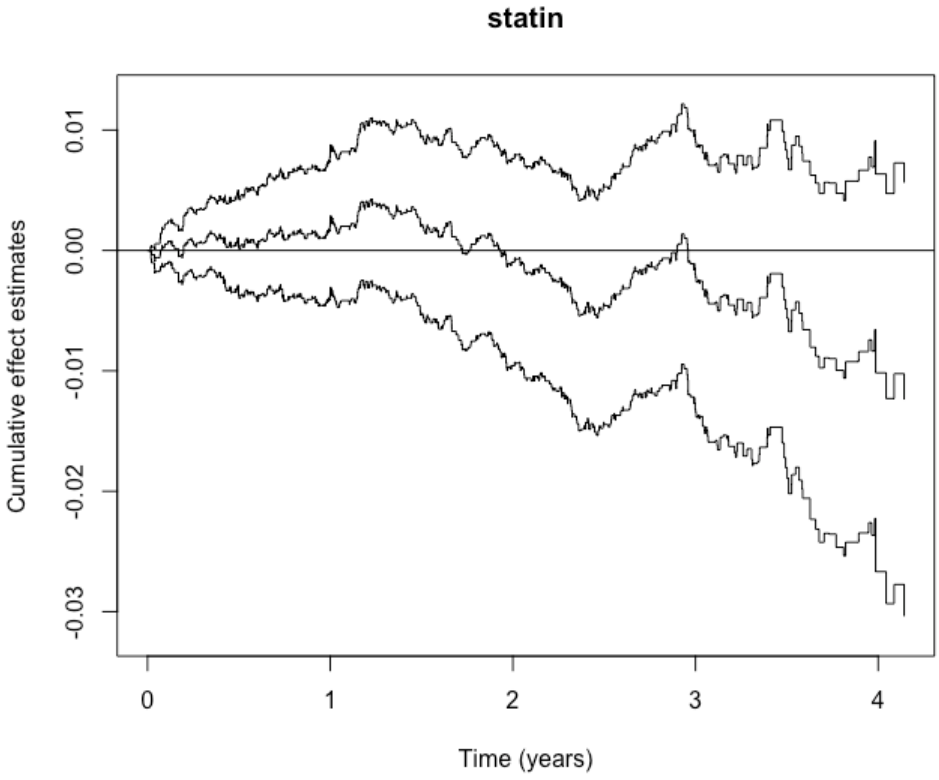
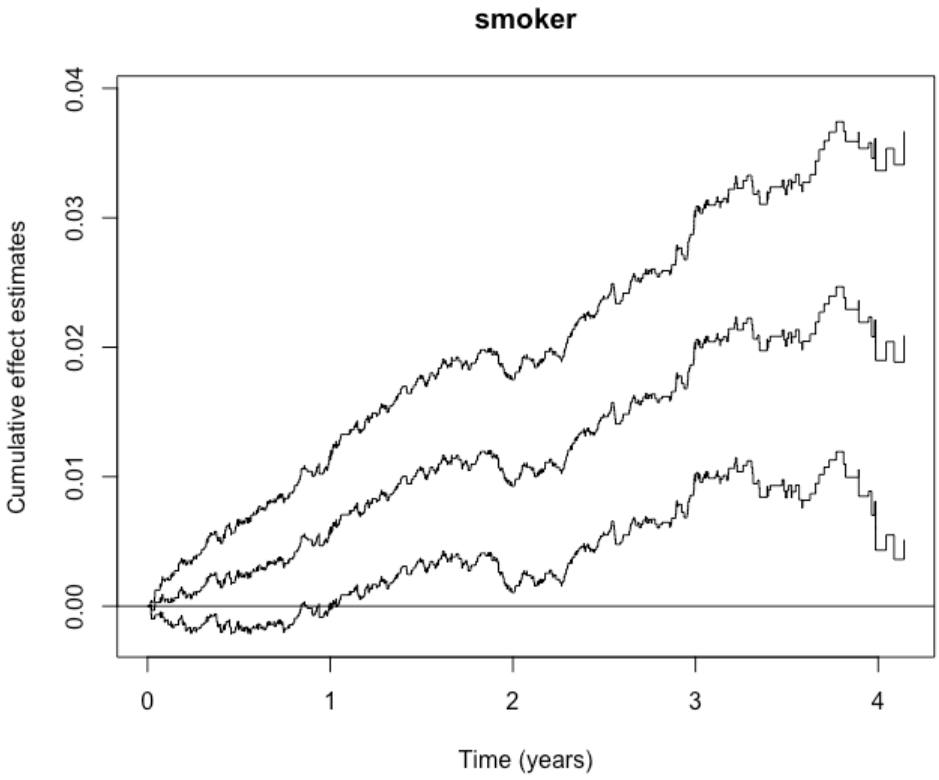
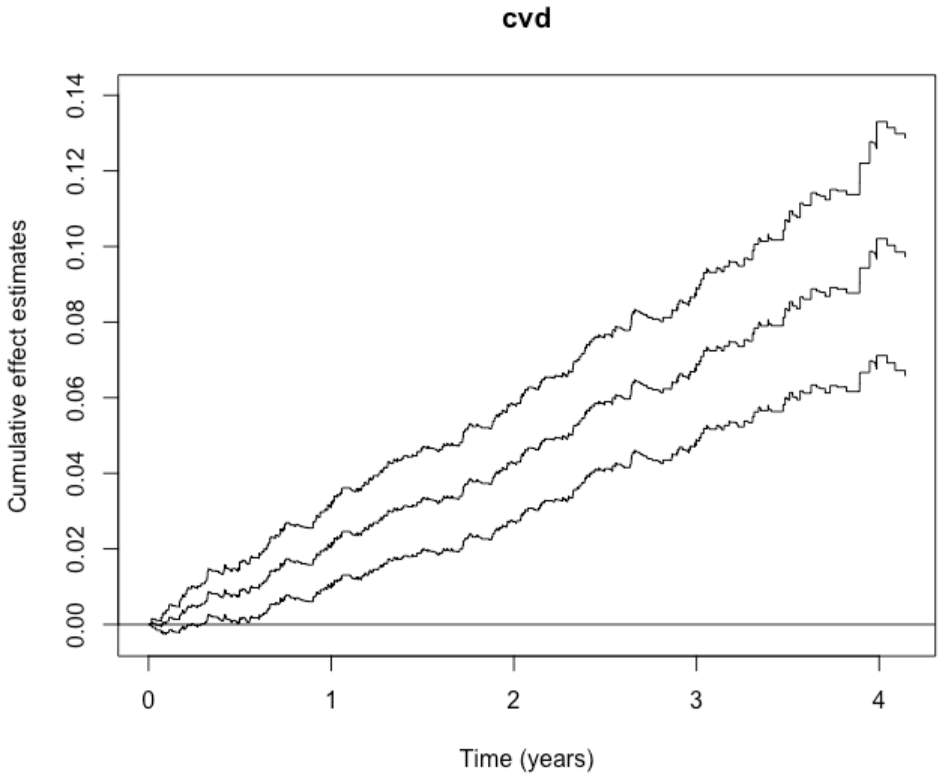
0.0015
0.0005
-0.0005
0
1
2
3
4
Time (years)


hdl
Cumulative effect estimates
0.0000
-0.0004
-0.0008
-0.0012
0
1
2
3
4
Time (years)


creatinine
Cumulative effect estimates
0.10
0.05
0.00
0
1
2
3
4
Time (years)


statin
Cumulative effect estimates
0.01
0.00
-0.01
-0.02
-0.03
0
1
2
3
4
Time (years)


smoker
Cumulative effect estimates
0.04
0.03
0.02
0.01
0.00
0
1
2
3
4
Time (years)


cvd
Cumulative effect estimates
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0
1
2
3
4
Time (years)

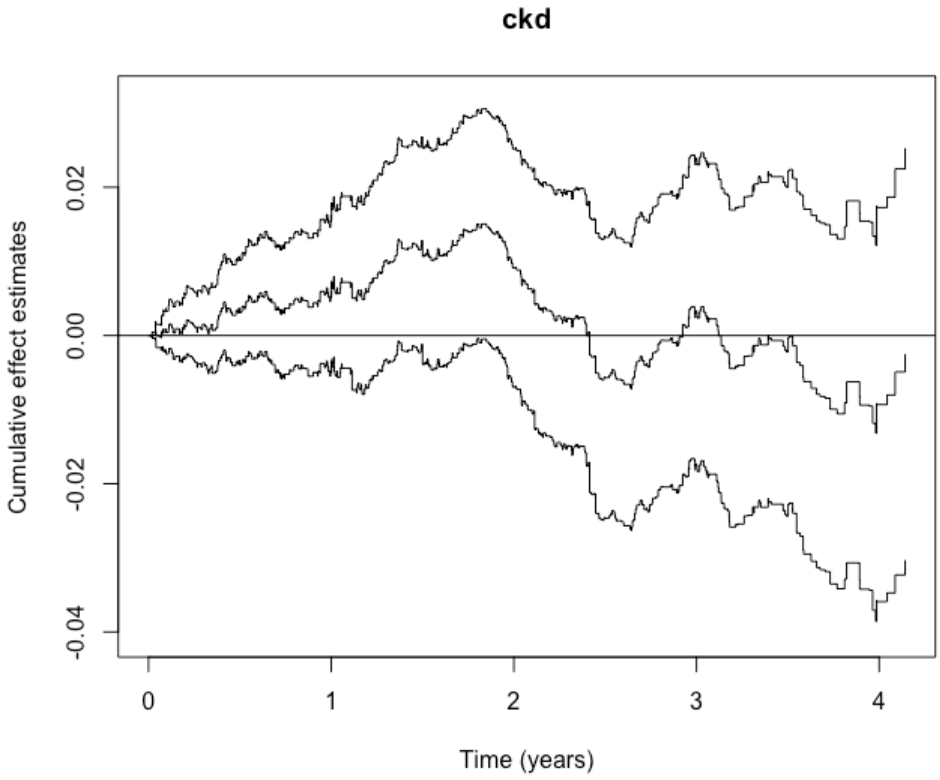
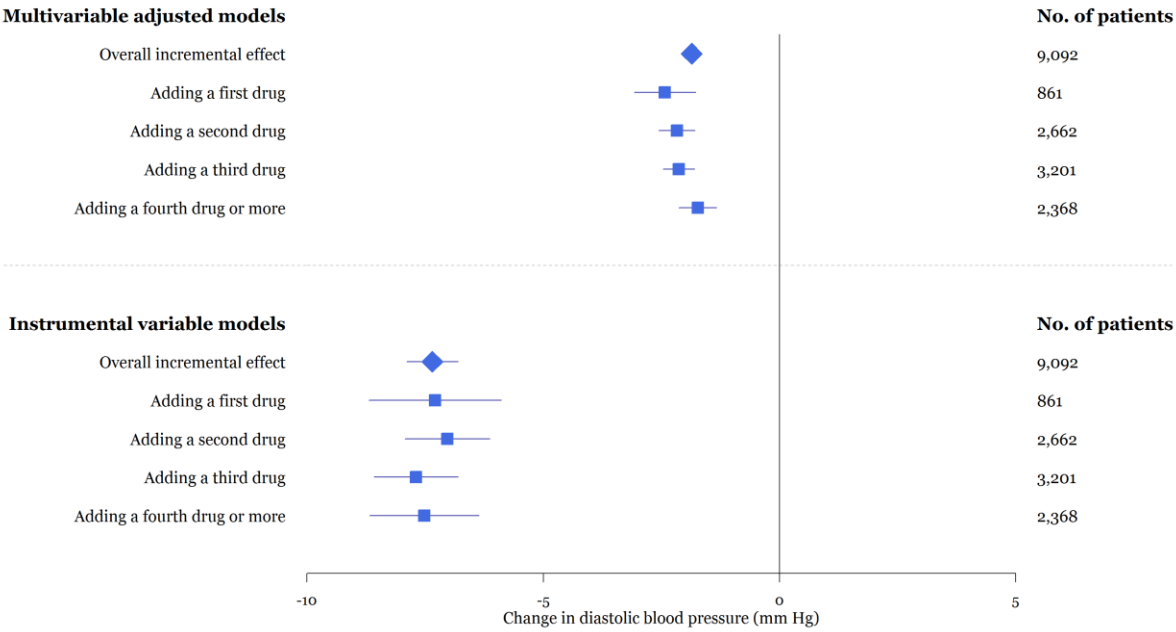
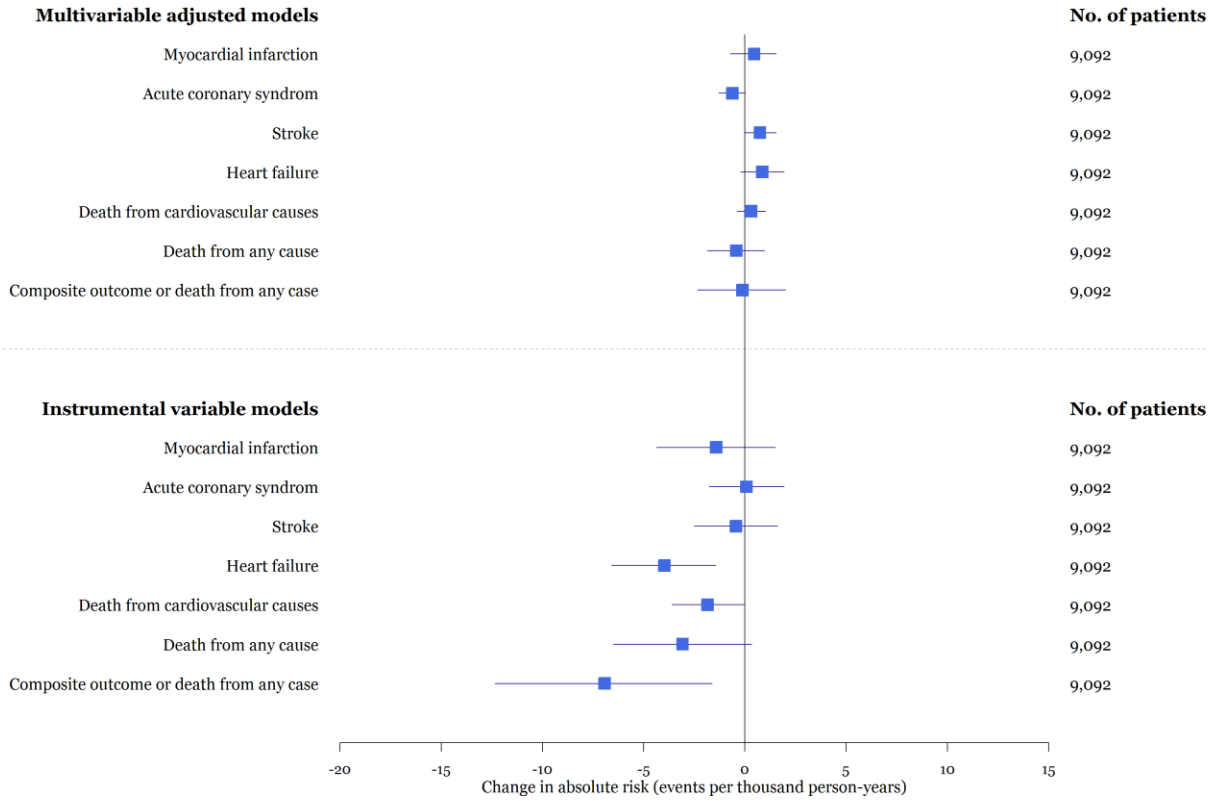

ckd
Cumulative effect estimates
-0.04
-0.02
0.00
0.02
0
1
2
3
4
Time (years)

**Figure G. Incremental effect of antihypertensive drugs on diastolic blood pressure**



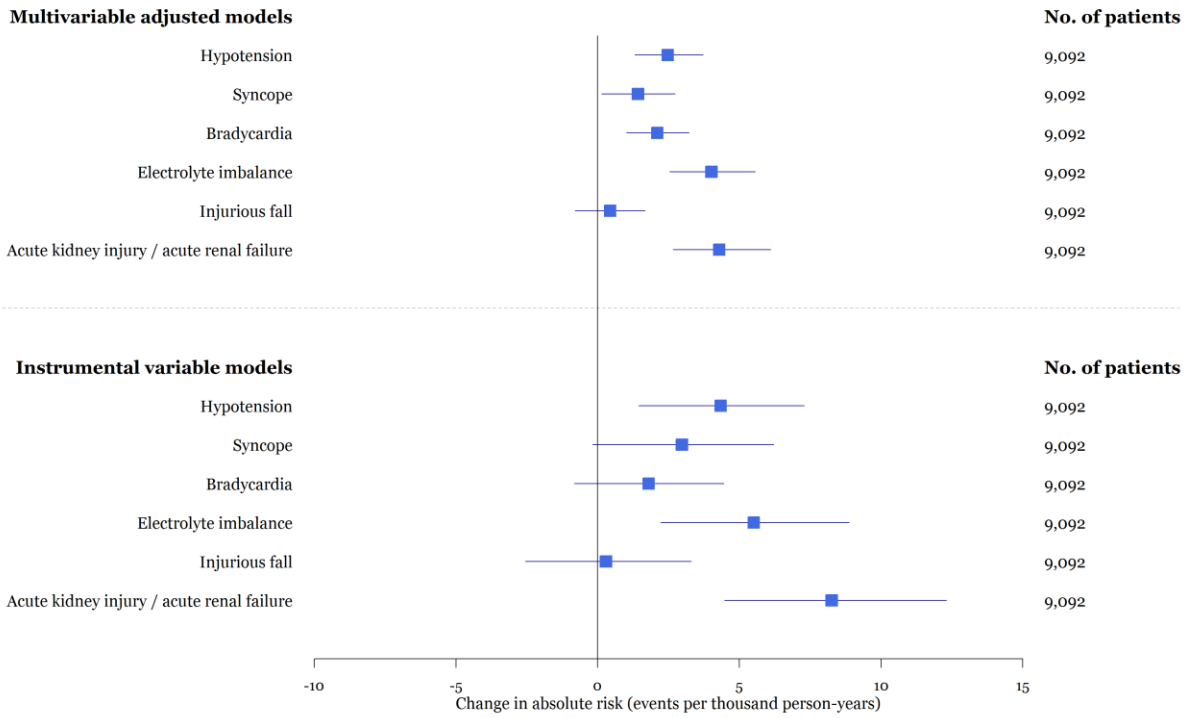

Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Lines represent 95% confidence intervals. Diastolic blood pressure represents each patient's final recorded blood pressure measurement. Antihypertensive drug classes are measured at baseline and at the latest visit at which there is also a recorded blood pressure measurement. Multivariable adjusted models were estimated using ordinary least squares regression. Instrumental variable models were estimated using two-stage ordinary least squares regression.

**Figure H. Incremental effect of antihypertensive drugs on component major cardiovascular events and all-cause mortality**



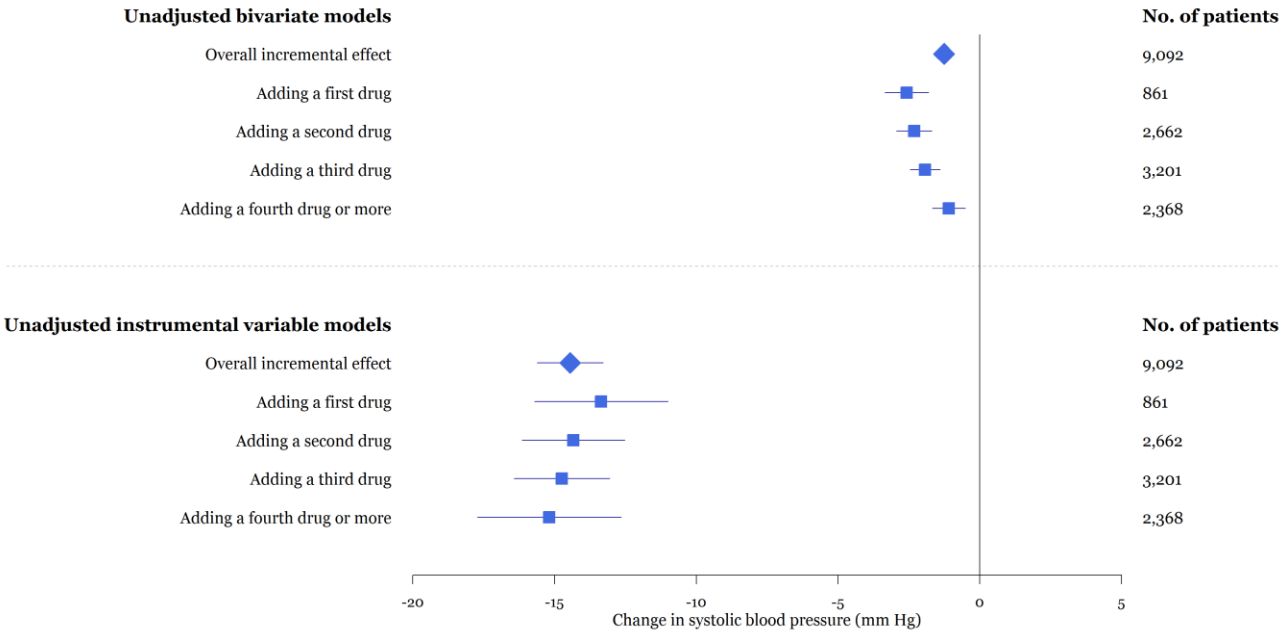

Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Lines represent 95% confidence intervals. Antihypertensive drug classes are measured at baseline and at each patient's final visit. For patients who experienced a major cardiovascular event, we used the last recorded value of drug classes before event incidence. We estimated additive hazards models to account for the right-censored nature of survival outcomes such as risk of major cardiovascular events.[29]

**Figure I. Incremental effect of antihypertensive drugs on component serious adverse events**



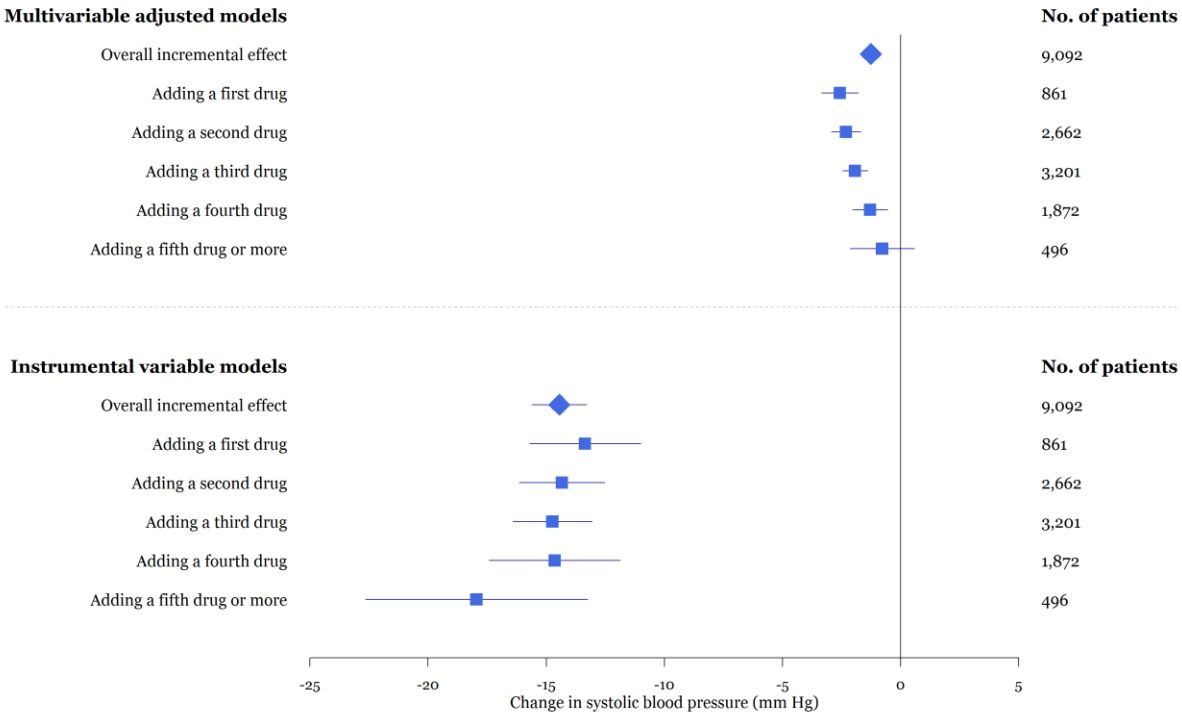

Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Lines represent 95% confidence intervals. Antihypertensive drug classes are measured at baseline and at each patient's final visit. For patients who experienced a serious adverse event, we used the last recorded value of drug classes before event incidence. We estimated additive hazards models to account for the right-censored nature of survival outcomes such as risk of serious adverse events.[29]

**Figure J. Incremental effect of antihypertensive drugs on systolic blood pressure in unadjusted models**




Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Lines represent 95% confidence intervals. Systolic blood pressure represents each patient's final recorded blood pressure measurement. Antihypertensive drug classes are measured at baseline and at the latest visit for which there was also a recorded blood pressure measurement. Unadjusted bivariate models were estimated using ordinary least squares and were not adjusted for any covariates. Unadjusted instrumental variable models were estimated using two-stage ordinary least squares regression and were not adjusted for any covariates.

**Figure K. Incremental effect of adding a fifth or more antihypertensive drug class on systolic blood pressure**




Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Lines represent 95% confidence intervals. Systolic blood pressure represents each patient's final recorded blood pressure measurement. Antihypertensive drug classes are measured at baseline and at the latest visit for which there was also a recorded blood pressure measurement. Multivariable adjusted models were estimated using ordinary least squares regression. Instrumental variable models were estimated using two-stage ordinary least squares regression.

**Table A. Distribution of number of antihypertensive drug classes at each patient's final visit by randomization status**

| Final number of antihypertensive drug classes[a] | Standard (N= 4523) | Intensive (N= 4569) |
|---|---|---|
| 0 | 486 (10.7%) | 80 (1.8%) |
| 1 | 1432 (31.7%) | 464 (10.2%) |
| 2 | 1505 (33.3%) | 1383 (30.3%) |
| 3 | 796 (17.6%) | 1499 (32.8%) |
| 4 | 250 (5.5%) | 855 (18.7%) |
| 5 | 50 (1.1%) | 242 (5.3%) |
| 6 | 3 (0.1%) | 39 (0.9%) |
| 7 | 1 (<1%) | 7 (0.2%) |

[a] Final number of antihypertensive drug classes were measured at the latest visit for which there was also a recorded blood pressure measurement.

**Table B. Change in number of antihypertensive drug classes over study period by number of drug classes at baseline**

| | Change in number of drug classes over study period[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Number of antihypertensive drug classes at baseline** | **-4** | **-3** | **-2** | **-1** | **0** | **+1** | **+2** | **+3** | **+4** | **+5** |
| *Standard group (target < 140 mm Hg)* | | | | | | | | | | |
| 0 drug classes at baseline | 0 | 0 | 5 | 74 | 224 | 111 | 19 | 3 | 0 | 1 |
| 1 drug class at baseline | 0 | 0 | 26 | 287 | 673 | 301 | 43 | 4 | 0 | 0 |
| 2 drug classes at baseline | 0 | 5 | 96 | 424 | 718 | 275 | 47 | 7 | 0 | 0 |
| 3 or more drug classes at baseline | 3 | 27 | 133 | 392 | 414 | 179 | 24 | 2 | 0 | 0 |
| *Intensive group (target < 120 mm Hg)* | | | | | | | | | | |
| 0 drug classes at baseline | 0 | 0 | 4 | 26 | 129 | 169 | 74 | 16 | 3 | 0 |
| 1 drug class at baseline | 0 | 0 | 19 | 100 | 466 | 507 | 180 | 48 | 5 | 0 |
| 2 drug classes at baseline | 0 | 5 | 30 | 168 | 652 | 537 | 191 | 36 | 5 | 1 |
| 3 or more drug classes at baseline | 4 | 9 | 39 | 170 | 504 | 358 | 93 | 13 | 3 | 1 |

[a]Represents change between number of drug classes at the baseline visit and the final visit of the study at which there was also a blood pressure measurement. Numbers represent counts of patients in each cell.

## Table C. Instrument strength stratified by number of drug classes at baseline

| Stratified instrumental variable analyses | *F* statistic | Partial $R^2$ |
|---|---|---|
| 0 drug classes at baseline | 230 | 0.26 |
| 1 drug class at baseline | 515 | 0.23 |
| 2 drug classes at baseline | 463 | 0.19 |
| 3 or more drug classes at baseline | 298 | 0.15 |

## Table D. Baseline characteristics of the SPRINT study participants by SPRINT randomization status

| Characteristics | Standard (N= 4,523) | Intensive (N= 4,569) | *P* value |
|---|---|---|---|
| Age - years (SD) | 67.8 (9.4) | 67.9 (9.4) | 0.8 |
| Female - no. (%) | 1583 (35.0%) | 1634 (35.8%) | 0.5 |
| Black - no. (%)[a] | 1442 (31.9%) | 1414 (30.9%) | 0.3 |
| BMI - $kg/m^2$ (SD)[b] | 29.8 (5.7) | 29.9 (5.8) | 0.4 |
| Fasting HDL - mg/dl (SD) | 52.7 (14.6) | 52.9 (14.4) | 0.6 |
| Serum creatinine - mg/dl (SD) | 1.1 (0.3) | 1.1 (0.3) | 0.9 |
| Statin use - no. (%) | 2018 (44.6%) | 1952 (42.7%) | 0.07 |
| Ever smoker - no. (%) | 2530 (55.9%) | 2566 (56.2%) | 0.8 |
| History of cardiovascular disease - no. (%) | 760 (16.8%) | 764 (16.7%) | 0.9 |
| History of chronic kidney disease - no. (%)[c] | 1267 (28.0%) | 1305 (28.6%) | 0.6 |
| Blood pressure - mm Hg (SD) | | | |
| Systolic | 139.7 (15.4) | 139.7 (15.8) | 0.9 |
| Diastolic | 78.1 (12.0) | 78.2 (11.9) | 0.6 |

SI conversions factor: To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for glucose to millimoles per liter, multiply by 0.05551. HDL denotes high-density lipoprotein.

[a]Race was self-report. Black race includes Hispanic black and black.

[b]The body-mass index is the weight in kilograms divided by the square of the height in meters.

[c]No history of chronic kidney disease includes some participants with unknown chronic kidney disease status at baseline.

**Table E. Incremental effects of antihypertensive drugs on systolic blood pressure, major cardiovascular events, and serious adverse events at three-month visit and over the study period**

| | Systolic blood pressure, (mm Hg) | Major cardiovascular events (per thousand person-years) | Serious adverse events (per thousand person-years) |
|---|---|---|---|
| | Incremental effects on blood pressure (95% CI) | | |
| **Models not adjusted for confounding** | | | |
| Number of drug classes at three-month visit[a] | -0.9 (-1.3, -0.6) | 2.7 (0.4, 5.2) | 17.4 (9, 26.1) |
| Mean number of drug classes over study period[b] | -2.0 (-2.3, -1.6) | 2.3 (0, 4.5) | 13.7 (5.7, 22) |
| **Instrumental variable models** | | | |
| Number of drug classes at three-month visit[a] | -15.1 (-16.5, -13.7) | -9.1 (-16.2, -2.3) | 18.3 (-6, 43.6) |
| Mean number of drug classes over study period[b] | -16.4 (-17.5, -15.3) | -7.1 (-12.8, -1.7) | 14.2 (-5.4, 33.4) |

[a]Systolic blood pressure is measured at the three-month visit. Antihypertensive drug classes are measured at baseline and at the exit of the two-month visit.
[b]Systolic blood pressure is measured at the final visit. We calculated the mean number of antihypertensive drug classes a patient was recorded as being prescribed over the study period.
CI is confidence interval.

**Table F. Incremental effects of antihypertensive drugs on total number of blood pressure measurements**

| | Incremental effect on no. of measurements (95% confidence interval) |
|---|---|
| **Multivariable adjusted models** | |
| Final number of drug classes | 0.15 (0.07, 0.23) |
| Mean number of drug classes over study period | 0.17 (0.08, 0.26) |
| **Instrumental variable models** | |
| Final number of drug classes | 0.07 (-0.09, 0.22) |
| Mean number of drug classes over study period | 0.08 (-0.10, 0.25) |

**Table G. Nonparametric tests of constant additive effects on composite major cardiovascular events and serious adverse events**

| | *P* value[a] | |
|---|---|---|
| **Variable** | **Major cardiovascular events** | **Serious adverse events** |
| Antihypertensive drug | 0.3 | 0.4 |
| Age | 0.7 | 0.1 |
| History of cardiovascular disease | 0.9 | 0.6 |
| History of chronic kidney disease[b] | 0.1 | 0.3 |
| Creatinine | 0.1 | 0.4 |
| Female | 0.6 | 0.4 |
| Black[c] | 0.9 | 0.4 |
| BMI | 0.4 | 0.4 |
| HDL | 0.7 | 0.3 |
| Smoker | 0.6 | 0.1 |
| Statin | 0.2 | 0.7 |
| Intercept | 0.8 | 0.1 |

[a]Kolmogorov-Smirnov test: null hypothesis is constant (time-invariant) additive effect.
[b]No history of chronic kidney disease includes some participants with unknown chronic kidney disease status at baseline.
[c]Race was self-report. Black race includes non-Hispanic and Hispanic black participants.

**Comparison with semi-parametric additive hazards models.** We estimated semi-parametric additive hazards models and confirmed that time-invariant parameters did not differ significantly from coefficients derived from weighted averages of time-variant, non-parametric models. In semi-parametric models, the incremental effect of antihypertensive drug classes was -7.7 events per 1,000 patient years for composite major cardiovascular events (95% CI, -16.2 to 0.8) and 10.2 events per 1,000 patient years for composite serious adverse events (95% CI, 0.8 to 20.0).

**Table H. Differences in incremental effects on blood pressure when adding first, second, third, or fourth or more antihypertensive drug class**

| | Difference in incremental effects on blood pressure across baseline number of drug classes | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2nd vs. 1st added class | | 3rd vs. 2nd added class | | 4th vs. 3rd added class | | 4th vs. 1st added class | | Interaction model[a] | |
| | Difference (95% CI) | *P* value | Difference (95% CI) | *P* value | Difference (95% CI) | *P* value | Difference (95% CI) | *P* value | Interaction term | *P* value for interaction |
| **Standard adjusted models** | | | | | | | | | | |
| Systolic | 0.5 (-0.5, 1.4) | 0.3 | 0.3 (-0.4, 1.0) | 0.5 | 0.9 (0.1, 1.6) | 0.03 | 1.6 (0.6, 2.6) | 0.002 | 0.6 | <0.001 |
| Diastolic | 0.3 (-0.5, 1.0) | 0.5 | 0.0 (-0.4, 0.5) | 0.9 | 0.4 (-0.1, 0.9) | 0.1 | 0.7 (-0.1, 1.4) | 0.07 | 0.2 | 0.03 |
| **Instrumental variable models** | | | | | | | | | | |
| Systolic | -0.3 (-2.2, 1.5) | 0.7 | -0.5 (-1.9, 0.9) | 0.5 | -0.4 (-2.0, 1.3) | 0.7 | -1.2 (-3.3, 0.8) | 0.2 | --[b] | --[b] |
| Diastolic | 0.3 (-1.2, 1.7) | 0.7 | -0.7 (-1.7, 0.4) | 0.2 | 0.2 (-1.0, 1.4) | 0.8 | -0.2 (-1.8, 1.3) | 0.8 | --[b] | --[b] |

[a]We interacted the final number of antihypertensive drug classes with the number of drug classes at baseline to formally test whether the incremental effects of antihypertensive drugs varied systematically across baseline number of drug classes.
[b]We did not estimate interaction instrumental variable models because interacting the instrument (randomization status) with a potential confounder (the number of drug classes at baseline) would render the instrumental variable analysis invalid.
CI is confidence interval.

## Table I. Incremental effects on systolic blood pressure across clinical and demographic subgroups

| | Adding 1st drug class | | Adding 2nd drug class | | Adding 3rd drug class | | Adding 4th or more drug class | |
|---|---|---|---|---|---|---|---|---|
| **Subgroup** | **Incremental effect (95% CI)** | ***P* value** | **Incremental effect (95% CI)** | ***P* value** | **Incremental effect (95% CI)** | ***P* value** | **Incremental effect (95% CI)** | ***P* value** |
| **Age** | | | | | | | | |
| < 75 years | -14.8 (-17.3, -12.4) | <0.001 | -14.6 (-16.6, -12.7) | <0.001 | -15.1 (-16.9, -13.2) | <0.001 | -14.8 (-17.5, -12.1) | <0.001 |
| ≥ 75 years | -9.3 (-15.8, -2.8) | 0.005 | -13.1 (-16.1, -10.2) | <0.001 | -14.1 (-17.3, -10.9) | <0.001 | -16.1 (-21.0, -11.1) | <0.001 |
| Difference | 5.5 (0.7, 10.3) | 0.02 | 1.5 (-1.0, 4.1) | 0.2 | 1.0 (-1.5, 3.5) | 0.4 | -1.3 (-4.6, 1.9) | 0.4 |
| **Sex** | | | | | | | | |
| Male | -12.7 (-15.2, -10.3) | <0.001 | -13.0 (-14.4, -11.5) | <0.001 | -14.6 (-16.5, -12.8) | <0.001 | -14.6 (-17.2, -12.1) | <0.001 |
| Female | -18.8 (-26.8, -10.8) | <0.001 | -16.7 (-20.5, -13.0) | <0.001 | -14.8 (-17.6, -12.0) | <0.001 | -15.6 (-19.7, -11.6) | <0.001 |
| Difference | -6.1 (-10.9, -1.3) | 0.01 | -3.8 (-6.0, -1.5) | 0.001 | -0.2 (-2.4, 2.1) | 0.9 | -1.0 (-4.0, 2.0) | 0.5 |
| **Race**[a] | | | | | | | | |
| Non-black | -14.6 (-17.6, -11.6) | <0.001 | -13.6 (-15.2, -11.9) | <0.001 | -14.7 (-16.8, -12.6) | <0.001 | -16.4 (-19.5, -13.3) | <0.001 |
| Black | -11.5 (-15.3, -7.6) | <0.001 | -16.1 (-20.1, -12.1) | <0.001 | -14.6 (-17.3, -11.9) | <0.001 | -13.1 (-16.5, -9.8) | <0.001 |
| Difference | 3.1 (-0.2, 6.5) | 0.06 | -2.5 (-4.8, -0.2) | 0.04 | 0.1 (-2.1, 2.3) | 0.9 | 3.3 (0.6, 6.0) | 0.02 |
| **Obesity**[b] | | | | | | | | |
| Non-obese | -13.5 (-16.0, -11.1) | <0.001 | -14.4 (-16.2, -12.6) | <0.001 | -15.3 (-17.2, -13.4) | <0.001 | -14.5 (-17.1, -11.9) | <0.001 |
| Obese | -16.0 (-24.1, -7.8) | <0.001 | -11.8 (-16.4, -7.3) | <0.001 | -12.2 (-15.2, -9.2) | <0.001 | -17.2 (-22.4, -12.1) | <0.001 |
| Difference | -2.4 (-6.7, 1.9) | 0.3 | 2.6 (-0.5, 5.6) | 0.1 | 3.1 (0.5, 5.7) | 0.02 | -2.7 (-5.9, 0.5) | 0.1 |
| **Smoking** | | | | | | | | |
| Never-smoker | -11.8 (-15.2, -8.3) | <0.001 | -14.2 (-16.7, -11.8) | <0.001 | -15.9 (-18.7, -13.0) | <0.001 | -14.4 (-17.3, -11.4) | <0.001 |
| Ever-smoker | -15.4 (-18.5, -12.4) | <0.001 | -14.2 (-16.2, -12.1) | <0.001 | -14.0 (-15.8, -12.1) | <0.001 | -15.5 (-18.7, -12.4) | <0.001 |
| Difference | -3.7 (-6.8, -0.5) | 0.02 | 0.0 (-1.9, 2.0) | 0.96 | 1.9 (-0.2, 4.0) | 0.08 | -1.2 (-3.8, 1.5) | 0.4 |
| **History of cardiovascular disease** | | | | | | | | |
| No | -13.9 (-16.3, -11.5) | <0.001 | -14.6 (-16.5, -12.6) | <0.001 | -14.9 (-16.7, -13.1) | <0.001 | -15.2 (-17.7, -12.6) | <0.001 |
| Yes | -13.0 (-19.0, -6.9) | <0.001 | -12.3 (-16.3, -8.3) | <0.001 | -13.7 (-17.6, -9.9) | <0.001 | -14.8 (-19.9, -9.6) | <0.001 |
| Difference | 0.9 (-3.5, 5.4) | 0.7 | 2.2 (-0.7, 5.1) | 0.1 | 1.2 (-1.4, 3.7) | 0.4 | 0.4 (-3.4, 4.2) | 0.8 |
| **History of chronic kidney disease**[c] | | | | | | | | |
| No | -13.8 (-15.8, -11.8) | <0.001 | -14.8 (-16.8, -12.8) | <0.001 | -15.0 (-16.8, -13.2) | <0.001 | -14.7 (-17.6, -11.8) | <0.001 |
| Yes | -18.3 (-33.3, -3.3) | 0.02 | -12.5 (-15.6, -9.4) | <0.001 | -14.3 (-17.5, -11.1) | <0.001 | -15.9 (-19.4, -12.3) | <0.001 |
| Difference | -4.5 (-13.1, 4.1) | 0.3 | 2.3 (-0.1, 4.8) | 0.06 | 0.7 (-1.6, 3.1) | 0.6 | -1.2 (-4.2, 1.8) | 0.4 |

[a]Race was self-report. Black race includes non-Hispanic and Hispanic black participants.
[b]Obesity is defined as a body-mass index greater than or equal to 35.
[c]No history of chronic kidney disease includes some participants with unknown chronic kidney disease status at baseline.
CI is confidence interval.

**Table J. Reduced-form analyses of the effect of randomization status on changes in prescribed number of drug classes and systolic blood pressure**

| | Change in number of antihypertensive drug classes | Change in systolic blood pressure (mm Hg) |
|---|---|---|
| **Overall effect of randomization status** | 1.0 (0.9, 1.0) | -14.1 (-14.8, -13.4) |
| **Effect by number of antihypertensive drug classes at baseline** | | |
| 0 drug classes at baseline | 1.1 (1.0, 1.2) | -15.3 (-17.1, -13.6) |
| 1 drug class at baseline | 1.0 (0.9, 1.1) | -14.3 (-15.4, -13.2) |
| 2 drug classes at baseline | 0.9 (0.9, 1.0) | -14.0 (-15.1, -12.9) |
| 3 or more drug classes at baseline | 0.9 (0.8, 1.0) | -13.6 (-14.9, -12.3) |

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