

## Supplemental Material

### Blood pressure and cause-specific mortality in Mexico City: a Mendelian randomization study

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## Expanded Materials and Methods

### *Study design, participants and data collection*

Between 1998 and 2004, 159 755 adults aged  $\geq 35$  years from the Coyoacán and Iztapalapa districts of Mexico City were recruited into the Mexico City Prospective Study.<sup>1</sup> Baseline data collection included demographic, lifestyle, and participant-reported medical history and medication use. Seated SBP and diastolic blood pressure (DBP) were measured 3 times (at 1-minute intervals) to the nearest 1mmHg using a standard mercury sphygmomanometer. Weight, height, waist and hip circumference were measured, and a 10 mL non-fasting venous blood sample was collected. Body mass index (BMI) was calculated as the weight in kg divided by the square of height in meters. Hemoglobin A1c (HbA<sub>1c</sub>) was measured from the buffy coat sample using validated high-performance liquid chromatography methods<sup>2</sup> on HA-8180 analyzers (Arkray Inc) with calibrators traceable to International Federation of Clinical Chemistry and Laboratory Medicine standards.<sup>3</sup> Between 2015 and 2019, 10 144 surviving participants were revisited in their homes and agreed to take part in a resurvey, which involved similar procedures as the baseline assessment. Ethics approval was granted by the National Council of Science and Technology in Mexico, the Mexican Ministry of Health, the Ethics and Research commission from the Medicine Faculty at the National Autonomous University of Mexico, and the University of Oxford.

### *Genetic instruments for blood pressure*

Participants were genotyped using the Global Screening Array v2 chip from Illumina, as described previously.<sup>4</sup> Imputation was conducted using the Trans-Omics Precision Medicine (TOPMed) version R2 in the GRCh38 imputation server<sup>5</sup> and variants with imputation  $r^2 > 0.4$  were considered valid for these analyses. Genetic risk scores for SBP (SBP-GRS) and DBP (DBP-GRS) were constructed using the 2103 independent (LD  $r^2 < 0.1$ , per Keaton *et al.*<sup>6</sup>) variants association with blood pressure traits recently reported by the International Consortium of Blood Pressure genome-wide association study (GWAS).<sup>6</sup> These variants were identified primarily in studies restricted to European-ancestry participants, but their weights were taken from the trans-ancestry meta-analysis GWAS results from the Million Veteran Program (MVP)<sup>7</sup>. Of these 2103 variants, 52 were not present in either MVP or MCPS and 98 were ambiguous (defined as an A/T or C/G variant with minor allele frequency  $\geq 0.42$ ), leaving 1953 for SBP-GRS and DBP-GRS construction. Alleles were aligned to be trait-increasing in MVP and each weighted GRS was constructed by multiplying individual allele counts with the relevant weight (**Supplemental Data Item 1**).

### *Follow-up for mortality*

Death registration in Mexico City is reliable and complete, with almost all deaths medically certified.<sup>8</sup> Participants are followed for cause-specific mortality through probabilistic linkage based on name (including phonetic coding of names), age and sex to the Mexican System for Epidemiologic Death Statistics (*Sistema Epidemiológico y Estadístico de Defunciones* [SEED]), an electronic death registry in Mexico City administered by the Ministry of Health. Field validation of more than 7000 deaths matched in this way confirmed the reliability of the algorithm in more than 95% of cases. Diseases recorded on death certificates were coded using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), with subsequent review by study clinicians to recode, where necessary, the underlying cause of death.<sup>9</sup> Participant deaths were tracked until 1<sup>st</sup> October 2022. **Table S1** shows the categories of deaths considered in the current report.

### *Statistical methods*

All analyses excluded participants aged  $\geq 75$  years at recruitment, those with missing or implausible data on blood pressure (SBP  $> 250$  or  $< 80$ mmHg, DBP  $> 150$  or  $< 40$ mmHg, or pulse pressure  $< 15$ mmHg) or any covariate (see below), or with uncertain mortality linkage (defined as a  $\geq 1$  year discrepancy in a participant's date of birth as recorded at the baseline

survey compared with the matched death certificate). For the observational analyses, those with any chronic medical condition (other than diabetes) were also excluded to reduce the risk of reverse causality bias, which can happen when pre-existing diseases change baseline blood pressure and thereby distort the true prospective relationship between blood pressure and mortality risk. For the MR analyses, those without genotype array data passing QC<sup>4</sup> were excluded.

The associations between measured SBP and DBP at recruitment and cause-specific mortality were assessed in Cox proportional hazard models stratified by age-at-risk (in five year groups), and adjusted for sex, anthropometry (height, weight, and waist and hip circumference, each split into four equally sized groups), education (university/college/high school, middle school, elementary school, or other), district of residence (two districts), smoking status (never, former, occasional, <10 cigarettes per day, ≥10 cigarettes per day), alcohol consumption (none, former use, current use), leisure-time physical activity (none, up to twice weekly, at least three times weekly), and diabetes status (divided into five groups: no diabetes; undiagnosed diabetes [ie, no previous diagnosis but HbA<sub>1c</sub> ≥6.5%]; previously diagnosed diabetes with HbA<sub>1c</sub> <9%; previously diagnosed diabetes with HbA<sub>1c</sub> ≥9% to <11%; and previously diagnosed diabetes with HbA<sub>1c</sub> ≥11%). The hazard ratios from these observational analyses relating baseline blood pressure to risk were subsequently corrected for regression dilution bias,<sup>10</sup> by dividing both the log hazard ratio and its standard error by an estimate of the regression dilution ratio at around midpoint of the period between recruitment and the 15-year resurvey.<sup>11</sup> This correction is likely to be somewhat conservative, however, as previous studies have found that most of the long-term regression to the mean in blood pressure occurs shortly after an initial baseline assessment.<sup>10</sup>

The MR analyses are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines.<sup>12</sup> As done previously,<sup>13</sup> an additive genetic model of inheritance was assumed throughout. The three core MR assumptions are that the genetic score: (1) predicts the exposure of interest (relevance); (2) is not associated with genetic confounding factors (independence); and (3) is only associated with the outcome via the exposure of interest (exclusion restriction). To account for the blood pressure lowering effects of antihypertensive medications, those reportedly on such a medication at recruitment had their measured SBP increased by 6mmHg and their DBP increased by 3mmHg (based on recent estimates of the long-term effect of antihypertensive medications).<sup>14</sup> The proportion of SBP and DBP variance explained by the SBP-GRS and DBP-GRS ( $r^2$ ) was estimated from the increase in  $r^2$  observed when each instrument was incorporated into a linear model adjusted for age, age-squared, sex, BMI, district of residence and the first seven genetic principal components (PCs) to capture population stratification.<sup>15</sup> The F-statistic was calculated from the square of the t-value from the linear regression model.<sup>16</sup> The primary MR analyses employed the one-sample Wald ratio method,<sup>17</sup> in which the association of the SBP-GRS with SBP (or the DBP-GRS with DBP) was estimated using linear regression after adjustment for age, age-squared, sex, BMI (for consistency with most previous reports<sup>13,18</sup>), district of residence and genetic PCs, and the association between the SBP-GRS (or the DBP-GRS) and cause-specific mortality was estimated using Cox proportional hazards models, stratified by age-at-risk (in five-year groups), and adjusted for sex, BMI, district of residence, and genetic PCs.

In both the observational and the MR analyses, participants who did not die from the cause of interest were censored at the earliest of death from any other cause, the end of the age-at-risk period of interest, or 1 October 2022. The main analyses are of deaths at ages 35-74 years (which are referred to as 'premature' deaths).

Sensitivity analyses included: analyses of mortality by age, sex, district of residence, previously-diagnosed diabetes and thirds of Indigenous American (IAM) ancestry<sup>4</sup>; use of

Steiger filtering<sup>19</sup> to exclude from the GRS any variants for which (in the MVP GWAS)<sup>7</sup> the proportion of variance explained for estimated glomerular filtration rate (eGFR) was statistically significantly greater than that for blood pressure (to mitigate the influence of effects of variants on blood pressure being mediated by kidney function); restriction to participants unrelated to the 3<sup>rd</sup> family degree; use of alternative GRSs constructed with weights solely from MVP individuals of admixed AMR ancestry<sup>7</sup>; and use of a 15/10mmHg adjustment (rather than a 6/3mmHg) adjustment for those on antihypertensive medications at recruitment.

To examine the possibility of horizontal pleiotropy in the MR analyses we performed additional 'two-sample' MR approaches. The weighted-median method<sup>20</sup> is robust to horizontal pleiotropy assuming the majority of variants are valid instruments. Inverse variance-weighted (IVW) MR was also performed because the weighted median method requires a comparator and IVW is the standard two-sample method. MR Egger<sup>21</sup> detects and assesses the significance of horizontal pleiotropy by relaxing the assumption from the IVW method that only the risk factor of interest is mediating the effects on the outcome. MR-PRESSO<sup>22</sup> detects and removes outlier variants. For two-sample methods, associations between individual variants and SBP or DBP were taken from the Million Veteran Program results as for the weights in the primary analysis GRSs. Associations between individual variants and mortality outcomes were assessed using the --coxph option in SUGEN<sup>23</sup> adjusting for age, age-squared, biological sex, BMI, district of residence and genetic PCs.

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**Table S1. Number of deaths at ages 35-74 years by underlying cause (ICD-10 code) among 125 895 participants in the genetic analysis population**

Underlying cause of death	ICD-10 codes (and number of deaths)*
<b>Vascular</b>	
Ischaemic heart disease (n=2005)	I200 (3), I209 (3), I210 (20), I211 (12), I213 (1), I219 (1775), I220 (2), I221 (1), I229 (1), I249 (32), I251 (48), I252 (1), I258 (10), I259 (96)
Cerebrovascular (n=746)	F019 (2), I600 (2), I602 (1), I608 (1), I609 (79), I61 (1), I610 (1), I612 (1), I613 (1), I614 (1), I615 (2), I618 (1), I619 (219), I620 (6), I629 (5), I633 (4), I634 (17), I635 (3), I638 (1), I639 (53), I64X (94), I669 (6), I671 (5), I672 (2), I673 (1), I674 (3), I678 (82), I679 (107), I690 (1), I691 (1), I693 (8), I694 (6), I698 (29)
Other vascular (n=727)	E115 (35), E145 (28), I011 (1), I018 (1), I050 (2), I051 (1), I059 (18), I069 (2), I070 (1), I071 (1), I079 (2), I080 (3), I081 (1), I091 (1), I099 (16), I110 (98), I119 (11), I260 (2), I269 (78), I270 (4), I272 (3), I279 (7), I319 (1), I330 (7), I340 (3), I350 (10), I351 (1), I358 (2), I38X (8), I420 (11), I421 (1), I426 (1), I429 (1), I442 (9), I443 (2), I460 (1), I469 (7), I471 (2), I472 (3), I489 (3), I48X (8), I490 (6), I499 (6), I500 (54), I501 (12), I509 (70), I515 (2), I517 (1), I518 (3), I519 (9), I710 (4), I712 (1), I713 (4), I718 (3), I719 (1), I729 (2), I731 (1), I739 (3), I740 (1), I741 (1), I743 (1), I771 (15), I776 (1), I779 (1), I802 (5), I803 (1), I822 (1), I828 (1), I829 (2), I830 (1), I839 (1), I872 (5), I879 (1), I890 (1), I99X (4), K550 (59), K551 (1), K552 (1), K559 (5), K761 (1), Q210 (1), Q213 (1), Q238 (1), Q248 (1), R570 (34)
<b>Kidney disease</b>	
Chronic kidney disease (n=1740)	E102 (10), E112 (862), E142 (336), I120 (108), I129 (1), I130 (3), I131 (2), I132 (27), N039 (25), N049 (2), N059 (11), N12X (12), N142 (1), N180 (11), N185 (32), N189 (225), N19X (65), N281 (1), N289 (5), Y841 (1)
Other kidney disease (n=313)	N002 (1), N009 (8), N10X (2), N151 (13), N179 (74), N200 (6), N201 (1), N300 (1), N309 (1), N390 (206)
<b>Other disease</b>	
Acute diabetic crisis (n=551)	E100 (3), E101 (2), E110 (164), E111 (182), E140 (105), E141 (88), E162 (7)
Infective <sup>†</sup> (n=816)	A047 (3), A060 (1), A090 (19), A099 (33), A09X (11), A170 (1), A181 (2), A182 (1), A183 (1), A199 (3), A415 (1), A419 (192), A480 (1), A483 (1), A498 (1), A810 (2), A86X (2), B200 (1), B201 (1), B207 (4), B208 (7), B210 (2), B212 (1), B218 (1), B227 (2), B238 (4), B24X (4), B259 (1), B373 (1), B451 (1), B462 (1), B465 (2), B690 (2), B948 (2), B99X (1), G009 (3), G039 (4), G042 (1), G049 (7), G060 (1), H440 (1), H664 (1), H669 (1), K052 (1), K223 (2), K228 (1), K251 (3), K254 (10), K255 (11), K256 (5), K259 (6), K264 (5), K265 (3), K269 (2), K274 (3), K275 (1), K290 (6), K291 (1), K292 (1), K295 (5), K297 (1), K318 (4), K352 (4), K353 (4), K358 (5), K359 (2), K37X (1), K572 (2), K578 (5), K579 (13), K610 (3), K611 (1), K612 (1), K650 (28), K658 (2), K659 (55), K920 (28), K921 (4), K922 (112), L021 (4), L022 (4), L023 (2), L024 (2), L031 (5), L038 (1), L039 (3), L089 (40), L899 (7), L89X (3), L984 (7), M009 (1), M600 (2), M725 (1), M726 (19), M798 (23), M869 (3), N410 (1), N419 (1), N498 (7), N719 (1), N739 (1), R572 (5)
Hepatobiliary (n=1070)	B169 (3), B171 (28), B182 (11), B189 (1), B190 (2), B199 (2), D136 (1), I850 (16), I859 (6), K701 (14), K702 (1), K703 (160), K704 (24), K709 (16), K711 (2), K716 (1), K720 (9), K721 (58), K729 (205), K739 (2), K742 (1), K743 (2), K745 (2), K746 (290), K750 (14), K754 (4), K759 (2), K764 (1), K766 (13), K767 (14), K768 (1), K769 (17), K800 (4), K801 (9), K802 (4), K803 (3), K804 (1), K805 (2), K810 (12), K811 (3), K819 (5), K822 (2), K829 (5), K830 (17), K831 (3), K839 (1), K851 (1), K852 (4), K858 (7), K859 (34), K85X (24), K861 (3), K868 (2), Q447 (1)
Neoplastic (n=2116)	C029 (12), C07X (2), C089 (1), C109 (3), C119 (1), C139 (1), C140 (5), C142 (1), C159 (16), C160 (2), C169 (201), C170 (10), C179 (1), C182 (3), C184 (1), C187 (2), C189 (112), C19X (4), C20X (21), C211 (1), C220 (51), C221 (23), C229 (105), C23X (25), C240 (12), C241 (9), C248 (3), C249 (14), C250 (22), C252 (1), C259 (89), C260 (3), C269 (2), C319 (1), C329 (12), C33X (1), C349 (141), C37X (1), C382 (1), C383 (1), C384 (1), C412 (2), C419 (7), C435 (1), C437 (1), C438 (1), C439 (10), C444 (1), C445 (1), C447 (1), C449 (7), C451 (2), C457 (1), C459 (4), C469 (1), C479 (1), C480 (8), C482 (4), C492 (4), C495 (1), C499 (14), C509 (231), C519 (3), C52X (1), C530 (1), C539 (118), C541 (24), C549 (2), C55X (11), C56X (102), C609 (2), C61X (75), C629 (1), C64X (84), C679 (23), C680 (2), C689 (1), C694 (1), C709 (2), C710 (13), C711 (1), C718 (2), C719 (42), C720 (1), C729 (1), C73X (27), C741 (1), C749 (1), C760 (6), C761 (1), C762 (3), C763 (2), C764 (1), C765 (2), C780 (7), C786 (5), C787 (7), C788 (2), C793 (3), C794 (3), C795 (1), C796 (1), C798 (3), C800 (27), C809 (19), C80X (2), C817 (1), C819 (9), C822 (1), C829 (1), C830 (1), C833 (13), C838 (1), C839 (3), C844 (1), C845 (3), C851 (1), C857 (2), C859 (44), C900 (42), C901 (1), C902 (1), C910 (20), C911 (2), C920 (26), C921 (7), C927 (2), C929 (3), C950 (2), C959 (2), C97X (1), D371 (6), D372 (1), D374 (6), D376 (6), D377 (2), D380 (2), D381 (6), D383 (2), D391 (4), D397 (1), D410 (3), D429 (1), D430 (13), D432 (1), D449 (1), D486 (1), D487 (9), D489 (3)
Respiratory <sup>‡</sup> (n=2072)	A162 (7), A165 (1), A169 (2), B206 (2), B440 (1), B441 (1), B909 (1), E848 (1), J069 (1), J09 (3), J09X (1), J100 (2), J110 (1), J111 (1), J129 (4), J151 (3), J157 (2), J159 (36), J180 (53), J181 (26), J182 (2), J189 (594), J209 (4), J22X (18), J348 (1), J391 (1), J42X (15), J439 (30), J440 (95), J441 (2), J448 (6), J449 (164), J459 (9), J46X (2), J47X (2), J60X (1), J64X (4), J677 (1), J679 (2), J680 (1), J690 (3), J80X (4), J81X (2), J841 (74),



J848 (1), J849 (10), J850 (2), J852 (2), J869 (9), J90X (5), J939 (1), J942 (2), J960 (5), J961 (1), J969 (3), J980 (1), J981 (1), J984 (15), J985 (5), J988 (8), J989 (1), Q311 (1), U071 (513), U072 (299), U099 (1)

External/other/ill-defined (n=997) D033 (1), D27X (1), D320 (1), D329 (9), D352 (1), D420 (1), D467 (1), D469 (6), D471 (1), D472 (1), D474 (1), D479 (1), D619 (4), D649 (5), D682 (1), D693 (2), D694 (1), D696 (3), D699 (3), D70X (2), D733 (1), D762 (1), E035 (1), E039 (12), E049 (1), E055 (1), E059 (3), E065 (1), E116 (3), E119 (8), E129 (1), E146 (3), E149 (5), E230 (1), E249 (2), E279 (1), E43X (1), E440 (1), E660 (1), E725 (1), E835 (1), E86X (4), E870 (1), E872 (10), E874 (1), E875 (2), E876 (1), E878 (1), E889 (2), F03X (6), F09X (1), F102 (5), F182 (1), F209 (2), G10X (6), G121 (1), G122 (17), G20X (7), G231 (1), G300 (1), G309 (2), G310 (1), G35X (1), G379 (1), G403 (1), G409 (10), G419 (2), G439 (1), G589 (1), G610 (5), G709 (1), G710 (2), G809 (1), G822 (1), G919 (4), G931 (10), G934 (5), G935 (1), G936 (2), G938 (1), G958 (1), I10X (3), K088 (1), K102 (1), K137 (1), K389 (1), K403 (1), K404 (1), K409 (1), K419 (1), K420 (4), K429 (2), K430 (2), K439 (2), K440 (1), K460 (3), K461 (1), K469 (2), K513 (1), K519 (1), K529 (6), K560 (2), K562 (1), K566 (40), K567 (1), K593 (5), K628 (1), K630 (1), K631 (23), K632 (4), K635 (1), K638 (1), K639 (5), K661 (1), K918 (1), K931 (1), L100 (1), L109 (1), L511 (2), L512 (1), L921 (1), L958 (1), L988 (1), M050 (1), M068 (1), M069 (16), M100 (1), M109 (1), M139 (1), M311 (2), M313 (1), M319 (1), M321 (3), M329 (1), M340 (1), M349 (1), M469 (1), M623 (5), M799 (1), N40X (8), N948 (1), O622 (1), O720 (1), R040 (1), R100 (3), R11X (1), R190 (1), R571 (17), R579 (2), R58X (3), R688 (20), R69X (1), R99X (190), S729 (2), T07X (1), T874 (1), V011 (1), V029 (1), V041 (1), V051 (1), V093 (3), V099 (64), V182 (1), V209 (1), V299 (1), V439 (1), V489 (1), V496 (1), V499 (12), V580 (1), V719 (1), V785 (1), V878 (6), V892 (10), V899 (3), W018 (1), W060 (1), W100 (13), W104 (1), W105 (1), W108 (2), W126 (1), W130 (9), W134 (2), W138 (1), W139 (2), W170 (4), W172 (1), W174 (1), W176 (1), W178 (2), W179 (1), W18 (1), W180 (5), W181 (1), W184 (2), W188 (1), W190 (8), W194 (1), W195 (1), W199 (3), W206 (1), W250 (1), W314 (1), W340 (1), W370 (1), W704 (1), W744 (2), W748 (3), W769 (1), W780 (1), W789 (1), W799 (1), W849 (1), W878 (2), X09 (1), X090 (3), X094 (1), X099 (1), X219 (1), X314 (1), X360 (1), X459 (1), X470 (1), X590 (3), X594 (1), X598 (1), X599 (28), X640 (1), X650 (1), X680 (1), X700 (5), X740 (3), X780 (3), X800 (1), X840 (1), X910 (1), X912 (1), X914 (2), X950 (3), X954 (17), X955 (1), X959 (1), X990 (6), X994 (5), X999 (2), Y044 (1), Y048 (1), Y084 (1), Y099 (1), Y159 (1), Y200 (1), Y240 (1), Y244 (3), Y245 (1), Y248 (1), Y249 (2), Y260 (2), Y280 (1), Y330 (1), Y334 (1), Y338 (1), Y340 (5), Y344 (6), Y346 (1), Y348 (2), Y349 (14), Y405 (1), Y579 (3), Y838 (1), Y839 (4), Y846 (1)

ICD-10: international classification of disease, 10<sup>th</sup> edition. \* Only codes identified as primary causes of death in the study population are presented. † Excludes respiratory infections. ‡ Includes respiratory infections.

**Table S2. Baseline characteristics of 125 895 participants (genetic analysis population) aged 35-74 years at recruitment by fifth of genetic risk score for diastolic blood pressure**

	Genetic risk score for diastolic blood pressure					Difference (mean [SE] or %) between fifth V and fifth I
	I (n=25 179)	II (n=25 179)	III (n=25 179)	IV (n=25 179)	V (n=25 179)	
Age, sex, ancestry and socioeconomic factors						
Age (years)	50 (11)	50 (11)	50 (11)	50 (11)	50 (11)	-0.1 (0.1)
Men	33.1%	32.2%	31.8%	32.0%	32.1%	-1.0%
Indigenous American ancestry	65.4%	66.8%	66.9%	66.7%	65.1%	-0.3%
Resident in Coyoacán	38.7%	38.3%	38.2%	38.7%	39.0%	0.3%
University/high school education	16.6%	16.0%	15.7%	15.8%	16.2%	-0.5%
Physical measurements						
Systolic blood pressure (mmHg)	125.8 (16.3)	126.9 (16.7)	127.5 (17.1)	128.2 (17.1)	129.8 (17.9)	4.0 (0.2)
Diastolic blood pressure (mmHg)	82.0 (10.0)	83.0 (10.2)	83.3 (10.3)	83.9 (10.4)	85.1 (10.9)	3.1 (0.1)
Body mass index (kg/m²)	29.1 (4.9)	29.2 (5.0)	29.2 (4.9)	29.1 (4.9)	29.2 (5.0)	0.1 (0.0)
Waist:hip ratio	0.90 (0.07)	0.90 (0.07)	0.90 (0.07)	0.90 (0.07)	0.90 (0.07)	0.00 (0.0)
Lifestyle						
Current smoker	52.4%	51.7%	51.2%	51.0%	52.1%	-0.3%
Current drinker	67.9%	68.0%	67.4%	67.6%	67.3%	-0.6%
Regular leisure time physical activity	22.4%	22.6%	22.3%	22.2%	22.7%	0.3%
Medical history and medication use						
Previously-diagnosed diabetes	13.6%	13.5%	13.1%	12.4%	12.1%	-1.5%
Previously-diagnosed hypertension	14.6%	17.6%	19.3%	21.1%	25.0%	10.4%
Antihypertensive medication use	10.6%	13.1%	14.0%	15.7%	18.9%	8.3%
Antithrombotic medication use	2.8%	2.6%	2.7%	2.8%	2.9%	0.1%
Lipid-lowering medication use	<1%	<1%	<1%	<1%	<1%	-0.1%

Mean (SD) or % shown. \*for differences in means. SD: standard deviation, SE: standard error.

**Table S3. Baseline characteristics of 133 027 participants (observational analysis population) aged 35-74 years at recruitment by baseline systolic blood pressure**

	Baseline systolic blood pressure					Overall (n=133 027)
	<115 mmHg (n=29 888)	115-124 mmHg (n=38 117)	125-134 mmHg (n=31 863)	135-144 mmHg (n=17 877)	≥145 mmHg (n=15 282)	
Age, sex, ancestry and socioeconomic factors						
Age, years	46 (9)	48 (10)	51 (11)	55 (11)	58 (10)	50 (11)
Male	24.9%	33.4%	36.1%	35.5%	32.7%	32.4%
Indigenous American ancestry	66.6%	66.5%	66.3%	66.0%	65.8%	66.3%
Resident of Coyoacán	35.3%	38.3%	41.0%	42.3%	43.5%	39.4%
University/high school educated	20.5%	18.8%	14.7%	11.7%	8.7%	16.1%
Physical measurements						
Systolic blood pressure, mmHg	107.6 (5.9)	120.4 (2.5)	129.7 (2.6)	139.4 (2.6)	158.0 (12.5)	126.6 (16.1)
Diastolic blood pressure, mmHg	72.5 (6.6)	80.2 (5.1)	85.5 (5.9)	90.0 (6.9)	97.0 (10.2)	83.0 (10.1)
Body mass index, kg/m²	27.5 (4.3)	28.7 (4.5)	29.8 (5.0)	30.3 (5.3)	30.5 (5.5)	29.1 (4.9)
Waist-hip ratio	0.88 (0.07)	0.89 (0.07)	0.91 (0.07)	0.91 (0.07)	0.92 (0.07)	0.90 (0.07)
Lifestyle behaviours						
Current smoker	36.5%	35.1%	32.0%	29.7%	25.1%	32.8%
Current drinker	69.8%	70.2%	68.6%	66.5%	61.1%	68.2%
Any regular leisure-time physical activity	22.5%	23.4%	22.3%	21.2%	20.3%	22.3%
Medical history and medication use						
Previously-diagnosed diabetes	7.3%	9.3%	13.6%	17.4%	24.0%	12.7%
Previously-diagnosed hypertension	5.0%	8.9%	19.5%	31.9%	51.5%	18.6%
Antihypertensive medication use	3.3%	6.0%	13.9%	23.2%	38.9%	13.4%
Anti-thrombotic medication use	1.7%	1.9%	2.4%	2.9%	3.8%	2.3%
Lipid-lowering medication use	<1%	<1%	<1%	<1%	<1%	<1%

Mean (SD) or % shown. Table excludes those with prior chronic disease at recruitment (ischaemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, emphysema), missing or extreme data on blood pressure or any covariate (sex, district of residence, educational level attained, anthropometry, smoking status, alcohol intake, leisure time physical activity, diabetes status). SD: standard deviation.

**Table S4. Baseline characteristics of 133 027 participants (observational analysis population) aged 35-74 years at recruitment by baseline diastolic blood pressure**

	Baseline diastolic blood pressure					Overall (n=133 027)
	≤75 mmHg (n=26 879)	76-80 mmHg (n=28 237)	81-85 mmHg (n=27 017)	86-90 mmHg (n=25 371)	>90 mmHg (n=25 523)	
Age, sex, ancestry and socioeconomic factors						
Age, years	47 (10)	49 (10)	50 (10)	52 (11)	54 (10)	50 (11)
Male	23.8%	31.4%	34.1%	35.6%	37.3%	32.4%
Indigenous American ancestry	66.7%	66.6%	66.2%	66.3%	65.1%	66.3%
Resident of Coyoacán	35.5%	36.0%	39.7%	41.4%	45.2%	39.4%
University/high school educated	18.9%	17.5%	17.0%	14.2%	12.5%	16.1%
Physical measurements						
Systolic blood pressure, mmHg	110.7 (10.2)	120.3 (9.1)	125.0 (9.0)	132.7 (10.2)	146.0 (15.6)	126.6 (16.1)
Diastolic blood pressure, mmHg	69.4 (4.3)	78.7 (1.6)	82.4 (1.3)	88.1 (1.7)	97.5 (7.0)	83.0 (10.1)
Body mass index, kg/m <sup>2</sup>	27.6 (4.4)	28.6 (4.6)	29.2 (4.7)	29.9 (5.1)	30.6 (5.3)	29.1 (4.9)
Waist-hip ratio	0.88 (0.07)	0.89 (0.07)	0.90 (0.07)	0.91 (0.07)	0.92 (0.07)	0.90 (0.07)
Lifestyle behaviours						
Current smoker	35.4%	34.0%	33.3%	31.3%	29.7%	32.8%
Current drinker	68.6%	68.6%	69.2%	67.8%	66.4%	68.2%
Any regular leisure-time physical activity	22.2%	23.3%	22.7%	22%.0	21.1%	22.3%
Medical history and medication use						
Previously-diagnosed diabetes	9.7%	11.0%	11.8%	14.4%	16.8%	12.7%
Previously-diagnosed hypertension	6.8%	10.8%	13.8%	23.5%	39.6%	18.6%
Antihypertensive medication use	4.9%	7.5%	9.6%	17.1%	29.2%	13.4%
Anti-thrombotic medication use	1.9%	1.9%	2.1%	2.6%	3.1%	2.3%
Lipid-lowering medication use	<1%	<1%	<1%	<1%	<1%	<1%

Mean (SD) or % shown. Table excludes those with prior chronic disease at recruitment (ischaemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, emphysema), missing or extreme data on blood pressure or any covariate (sex, district of residence, educational level attained, anthropometry, smoking status, alcohol intake, leisure time physical activity, diabetes status). SD: standard deviation.

**Table S5. Genetic associations of SBP with cause-specific mortality using robust Mendelian randomization methods based on summary-level data**

Cause of death	Mortality RR (95% CI) per 10mmHg higher genetically-predicted SBP				
	IVW *	Weighted median †	MR-Egger ‡	MR Egger intercept	MR PRESSO §
Ischemic heart disease	1.70 (1.46 - 1.97)	1.60 (1.24 - 2.06)	1.64 (1.29 - 2.10)	0.0050	1.70 (1.46 - 1.97)
Cerebrovascular disease	1.79 (1.40 - 2.28)	2.82 (1.83 - 4.32)	2.32 (1.55 - 3.48)	-0.0415	1.55 (1.13 - 2.11)
Other vascular disease	1.42 (1.11 - 1.82)	1.94 (1.25 - 3.01)	1.37 (0.91 - 2.07)	0.0052	1.42 (1.10 - 1.83)
<b>All vascular disease</b>	<b>1.65 (1.48 - 1.85)</b>	<b>1.54 (1.27 - 1.87)</b>	<b>1.71 (1.42 - 2.06)</b>	<b>-0.0051</b>	<b>1.65 (1.47 - 1.86)</b>
Chronic kidney disease	1.41 (1.20 - 1.65)	1.29 (0.97 - 1.71)	1.28 (0.98 - 1.67)	0.0150	1.41 (1.18 - 1.67)
Other kidney disease	1.27 (0.87 - 1.85)	1.11 (0.58 - 2.12)	1.15 (0.62 - 2.16)	0.0150	1.27 (0.87 - 1.85)
<b>Any kidney disease</b>	<b>1.38 (1.19 - 1.60)</b>	<b>1.26 (0.97 - 1.63)</b>	<b>1.26 (0.98 - 1.61)</b>	<b>0.0150</b>	<b>1.38 (1.18 - 1.62)</b>
Acute diabetic crises	1.10 (0.83 - 1.47)	1.01 (0.62 - 1.64)	0.93 (0.58 - 1.49)	0.0274	1.10 (0.83 - 1.46)
Hepatobiliary disease	0.90 (0.73 - 1.10)	0.84 (0.59 - 1.20)	0.7 (0.5 - 0.98)	0.0393	0.90 (0.73 - 1.10)
Infection	1.03 (0.81 - 1.30)	0.82 (0.54 - 1.23)	1.03 (0.7 - 1.51)	-0.0002	1.03 (0.81 - 1.30)
Cancer	0.96 (0.83 - 1.10)	1.04 (0.81 - 1.32)	0.89 (0.7 - 1.13)	0.0109	0.96 (0.83 - 1.10)
Respiratory disease	1.04 (0.90 - 1.20)	1.11 (0.86 - 1.44)	1.02 (0.8 - 1.3)	0.0036	1.04 (0.90 - 1.20)
External/other/ill-defined	1.31 (1.06 - 1.61)	1.26 (0.88 - 1.82)	1.06 (0.75 - 1.51)	0.0325	1.31 (1.06 - 1.60)
<b>All-cause</b>	<b>1.22 (1.15 - 1.30)</b>	<b>1.19 (1.07 - 1.32)</b>	<b>1.15 (1.04 - 1.26)</b>	<b>0.0103</b>	<b>1.22 (1.15 - 1.30)</b>

All analyses are adjusted for age, age-squared, body mass index, district of residence and seven genetic principal components. For each approach the SNP-SBP effect estimates and their standard errors were taken from the Million Veteran Program trans-ancestry meta-analysis GWAS of mean SBP, with the alleles aligned to be SBP-increasing.

\* An IVW linear regression of the 1953 SNP-mortality effects on the 1953 (aligned) SNP-SBP effects is performed in which the regression line is forced through the origin. It relies on the assumption of no 'horizontal pleiotropy' (ie, it assumes that all of the SNPs affect mortality only through SBP and not through any other mechanism).

† The weighted median approach applies the ratio method to each SNP, orders the results, assigns them normalised inverse-variance weights (to capture the 'information content' of each SNP), then selects the ratio estimate at which the cumulative information content first passes half of the total information content. It relies on the assumption that at least half of the statistical information on the SNP-SBP associations comes from valid instrumental variables. It is more robust to individual genetic variants with strongly outlying causal estimates compared with the IVW and MR-Egger methods

‡ A modifications of the IVW approach in which the regression is not forced through the origin. The intercept provides an estimate of net horizontal pleiotropic effects under the assumption that any such effects are uncorrelated with the SNP-exposure effects (known as the InSIDE assumption). For each RR shown in the above table, the intercept term was non-significant at the 5% level after correction for multiple testing.

§ Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) identifies SNPs with horizontal pleiotropic effects based on their contributions to heterogeneity and removes them from the analyses. A single outlier was found for the chronic kidney disease and two for all-cause mortality, and none for the other analyses. CI: confidence interval, IVW: inverse variance weighted, MR: Mendelian randomization, RR: rate ratio, SBP: systolic blood pressure, SNP: single nucleotide polymorphism.

**Table S6. Genetic associations of DBP with cause-specific mortality using robust Mendelian randomization methods based on summary-level data**

Cause of death	Mortality RR (95% CI) per 5mmHg higher genetically-predicted DBP				
	IVW *	Weighted median †	MR-Egger ‡	MR Egger intercept	MR PRESSO §
Ischemic heart disease	1.22 (1.08 - 1.38)	1.22 (1.00 - 1.50)	1.13 (0.93 - 1.38)	0.0074	1.22 (1.07 - 1.38)
Cerebrovascular disease	1.43 (1.17 - 1.75)	1.34 (0.96 - 1.88)	1.37 (0.99 - 1.90)	0.0040	1.35 (1.04 - 1.75)
Other vascular disease	1.37 (1.11 - 1.68)	1.65 (1.18 - 2.30)	1.53 (1.10 - 2.12)	-0.0107	1.37 (1.11 - 1.69)
<b>All vascular disease</b>	<b>1.29 (1.17 - 1.42)</b>	<b>1.29 (1.10 - 1.51)</b>	<b>1.25 (1.08 - 1.46)</b>	<b>0.0029</b>	<b>1.29 (1.17 - 1.43)</b>
Chronic kidney disease	0.91 (0.79 - 1.04)	1.06 (0.84 - 1.33)	0.87 (0.70 - 1.08)	0.0040	0.90 (0.78 - 1.04)
Other kidney disease	1.03 (0.75 - 1.42)	0.79 (0.47 - 1.32)	0.83 (0.50 - 1.37)	0.0213	1.03 (0.75 - 1.42)
<b>Any kidney disease</b>	<b>0.93 (0.82 - 1.05)</b>	<b>0.98 (0.79 - 1.20)</b>	<b>0.86 (0.71 - 1.05)</b>	<b>0.0063</b>	<b>0.93 (0.81 - 1.06)</b>
Acute diabetic crises	0.78 (0.61 - 0.99)	0.68 (0.46 - 1.01)	0.66 (0.45 - 0.97)	0.0159	0.78 (0.61 - 0.99)
Hepatobiliary disease	1.18 (0.99 - 1.40)	1.38 (1.04 - 1.83)	1.43 (1.09 - 1.89)	-0.0188	1.18 (0.99 - 1.40)
Infection	1.01 (0.83 - 1.23)	0.88 (0.64 - 1.22)	1.05 (0.77 - 1.43)	-0.0035	1.01 (0.83 - 1.23)
Cancer	0.99 (0.88 - 1.12)	1.06 (0.87 - 1.30)	1.03 (0.85 - 1.25)	-0.0044	0.99 (0.88 - 1.11)
Respiratory disease	0.98 (0.86 - 1.10)	0.99 (0.81 - 1.21)	1.03 (0.84 - 1.25)	-0.0050	0.98 (0.86 - 1.10)
External/other/ill-defined	1.19 (1.00 - 1.42)	1.18 (0.89 - 1.58)	1.19 (0.90 - 1.58)	-0.0001	1.19 (1.00 - 1.42)
<b>All-cause</b>	<b>1.07 (1.02 - 1.12)</b>	<b>1.05 (0.97 - 1.14)</b>	<b>1.08 (1.00 - 1.16)</b>	<b>-0.0007</b>	<b>1.08 (1.02 - 1.13)</b>

All analyses are adjusted for age, age-squared, body mass index, district of residence and seven genetic principal components. For each approach the SNP-DBP effect estimates and their standard errors were taken from the Million Veteran Program trans-ancestry meta-analysis GWAS of mean DBP, with the alleles aligned to be DBP-increasing.

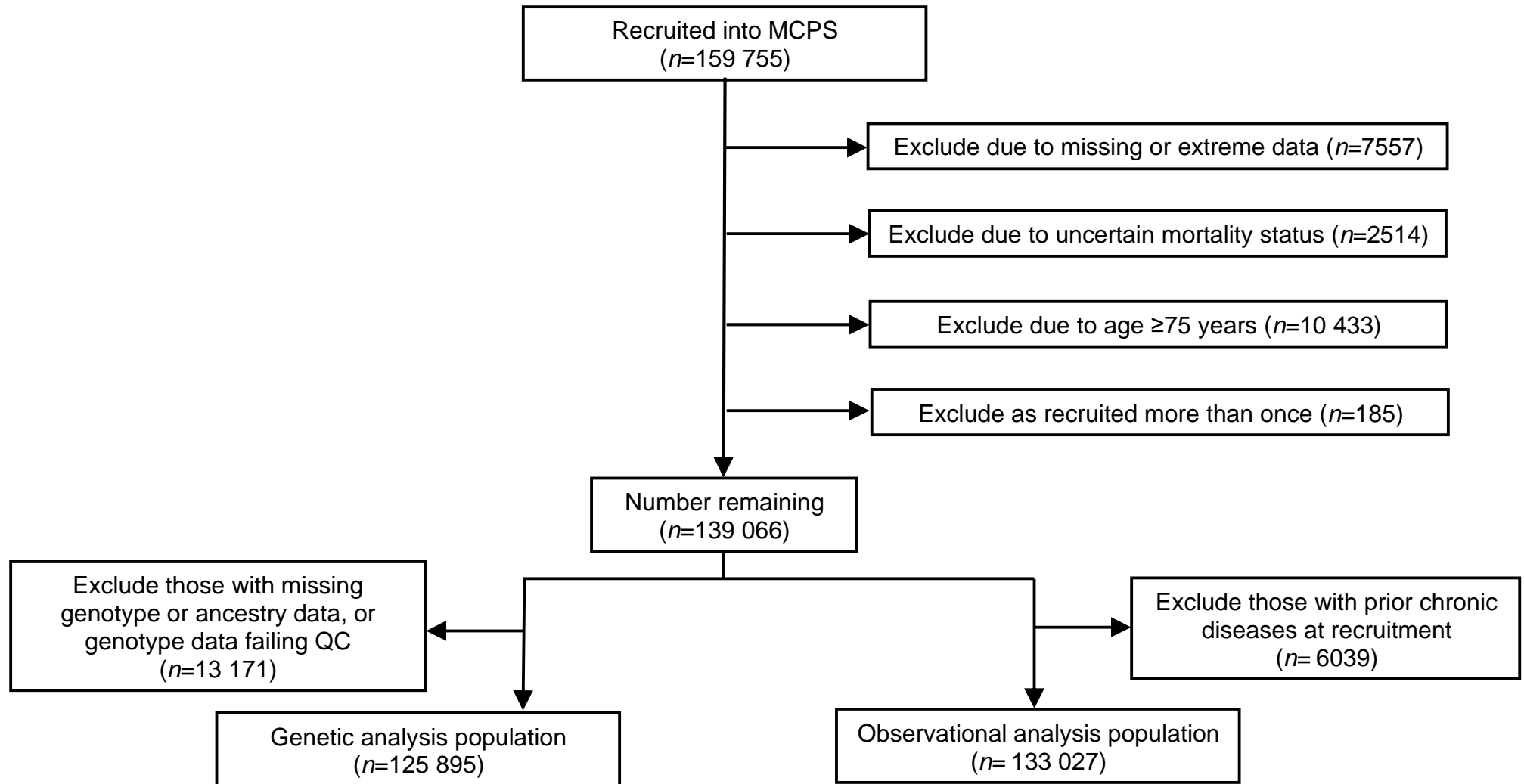
\* An IVW linear regression of the 1953 SNP-mortality effects on the 1953 (aligned) SNP-DBP effects is performed in which the regression line is forced through the origin. It relies on the assumption of no 'horizontal pleiotropy' (ie, it assumed that all of the SNPs affect mortality only through DBP and not through any other mechanism).

† The weighted median approach applies the ratio method to each SNP, orders the results, assigns them normalised inverse-variance weights (to capture the 'information content' of each SNP), then selects the ratio estimate at which the cumulative information content first passes half of the total information content. It relies on the assumption that at least half of the statistical information on the SNP-DBP associations comes from valid instrumental variables. It is more robust to individual genetic variants with strongly outlying causal estimates compared with the IVW and MR-Egger methods

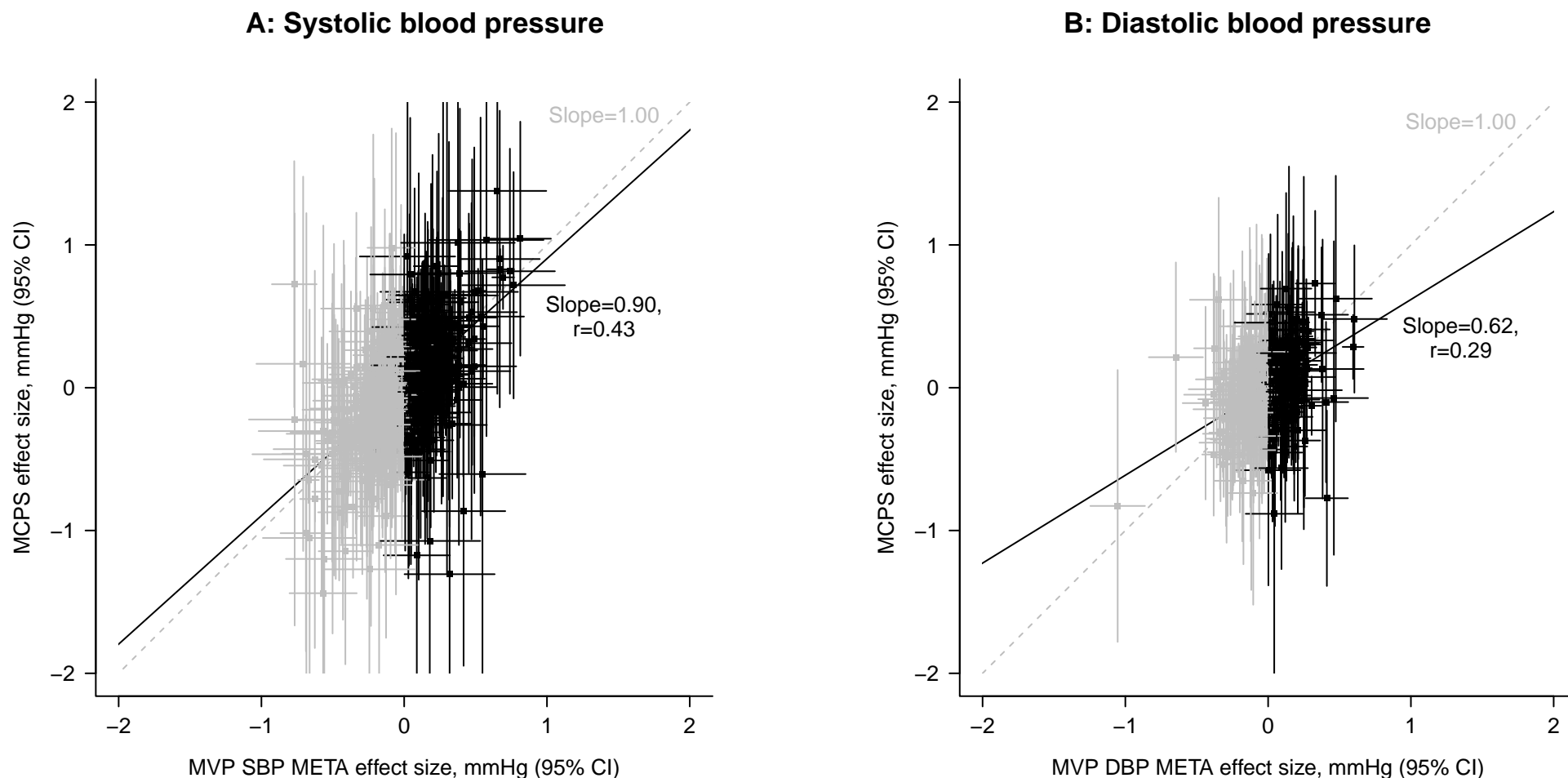
‡ A modifications of the IVW approach in which the regression is not forced through the origin. The intercept provides an estimate of net horizontal pleiotropic effects under the assumption that any such effects are uncorrelated with the SNP-exposure effects (known as the InSIDE assumption). For each RR shown in the above table, the intercept term was non-significant at the 5% level after correction for multiple testing.

§ Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) identifies SNPs with horizontal pleiotropic effects based on their contributions to heterogeneity and removes them from the analyses. A single outlier was found for the chronic kidney disease and two for all-cause mortality, and none for the other analyses. CI: confidence interval, DBP: diastolic blood pressure, IVW: inverse variance weighted, MR: Mendelian randomization, RR: rate ratio, SNP: single nucleotide polymorphism.

**Figure S1: Participant flow diagram**



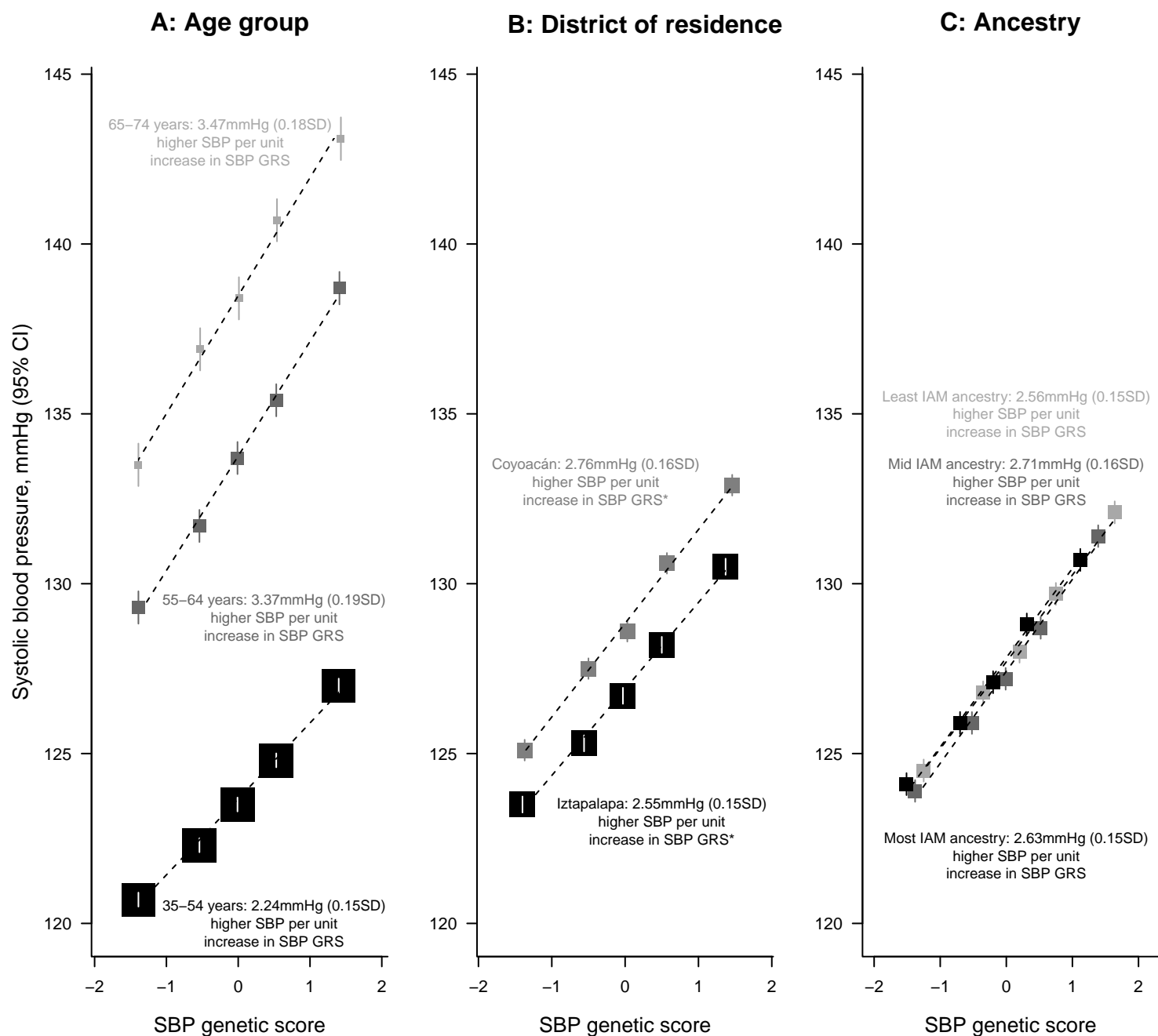
**Figure S2: Comparison of effect sizes for genetic variants in SBP–GRS and DBP–GRS**



Shown are 1953 variants from the SBP (A) and DBP (B) genetic scores with their effect sizes from the MVP and MCPS GWAS. To aid interpretation, effect sizes are displayed as listed in the MVP results. Variants with negative effect estimates in MVP (coloured grey here) are re-orientated so the trait-increasing allele is used when GRS are calculated. CI: confidence interval, DBP: diastolic blood pressure, MCPS: Mexico City Prospective Study, MVP: Million Veteran Program, SBP: systolic blood pressure

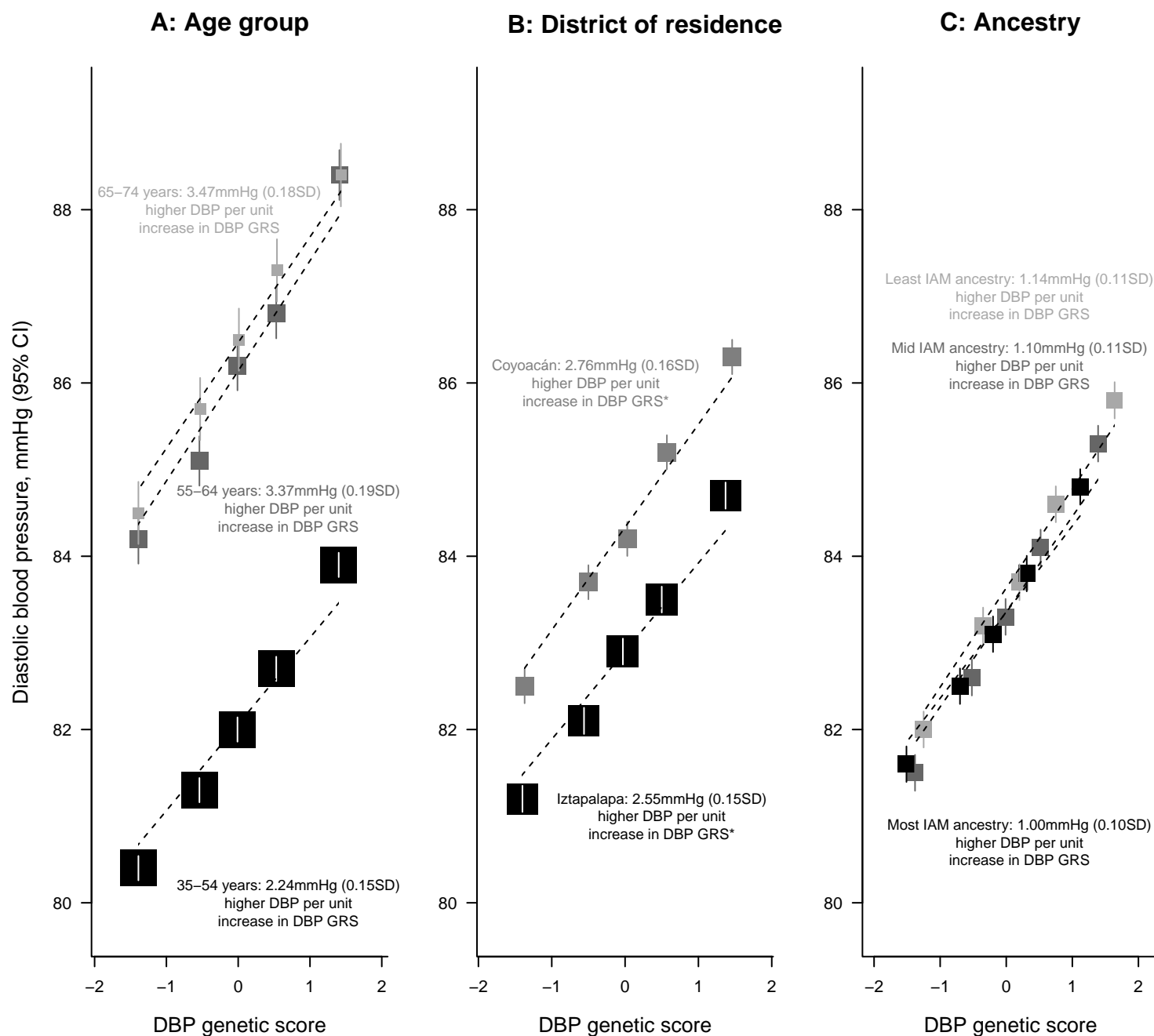


**Figure S3: Association of SBP GRS with SBP at recruitment by age, district and Indigenous American ancestry proportion**



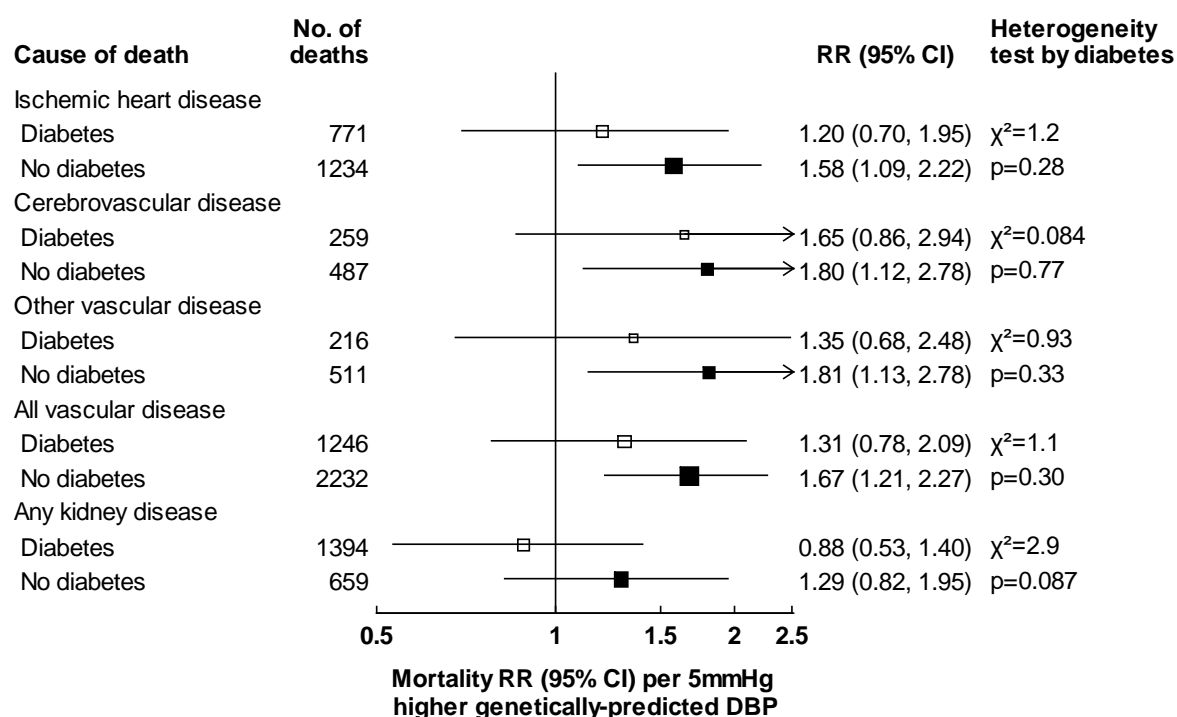
Each panel shows five equally-sized groups for each cohort stratum. \*Adjusted for age, age-squared, sex, BMI and seven genetic PCs. All other estimates are adjusted for age, age-squared, sex, BMI, district of residence and seven genetic PCs. BMI: body mass index, CI: confidence interval, DBP: diastolic blood pressure, GRS: genetic risk score, IAM: Indigenous American ancestry, PC: principal component, RR: rate ratio, SBP: systolic blood pressure, SD: standard deviation

**Figure S4: Association of DBP GRS with DBP at recruitment by age, district and Indigenous American ancestry proportion**



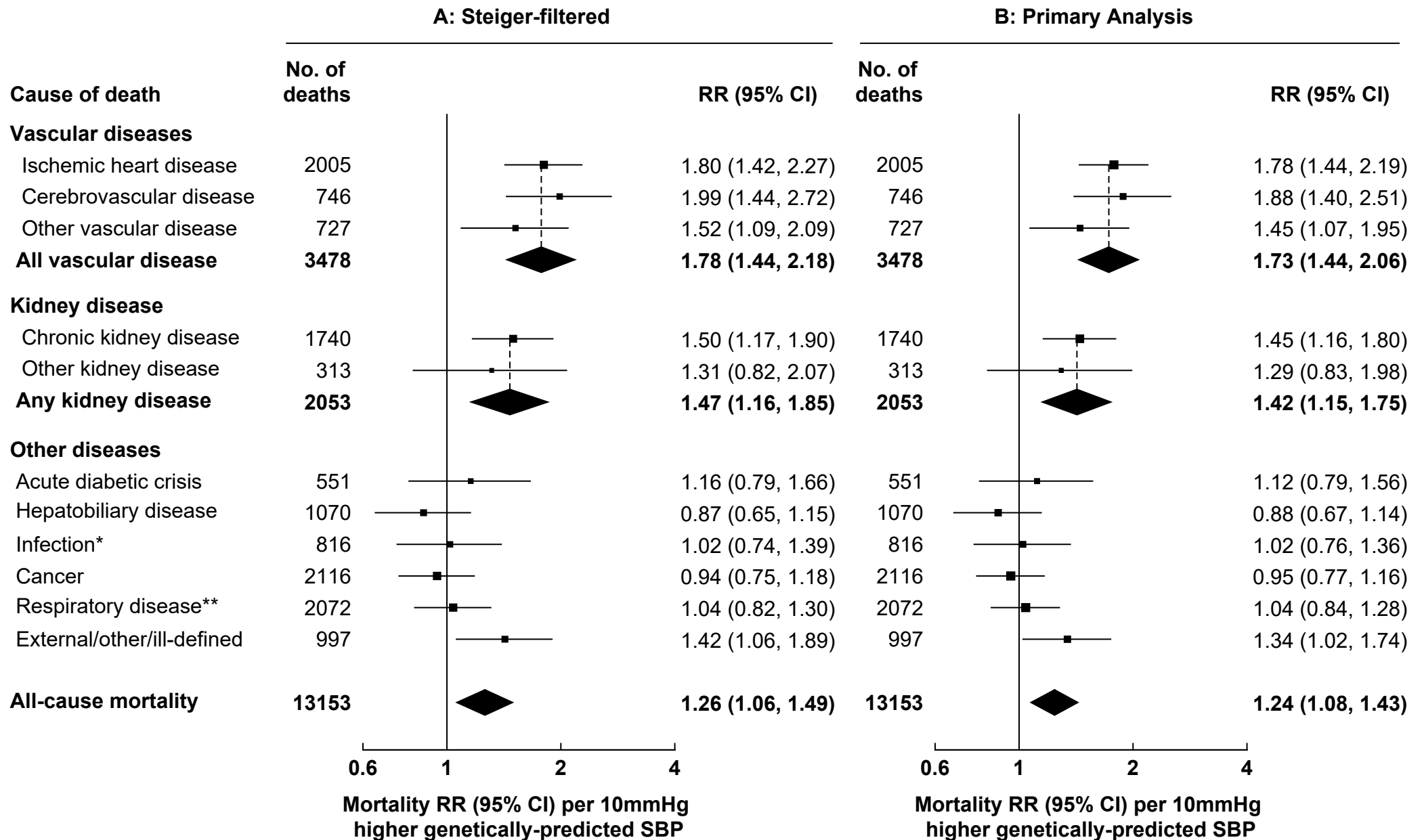
Each panel shows five equally-sized groups for each cohort stratum. \*Adjusted for age, age-squared, sex, BMI and seven genetic PCs. All other estimates are adjusted for age, age-squared, sex, BMI, district of residence and seven genetic PCs. BMI: body mass index, CI: confidence interval, DBP: diastolic blood pressure, GRS: genetic risk score, IAM: Indigenous American ancestry, PC: principal component, RR: rate ratio, SBP: systolic blood pressure, SD: standard deviation

**Figure S5: Associations between genetically-predicted DBP and cardiovascular and kidney mortality by diabetes status**



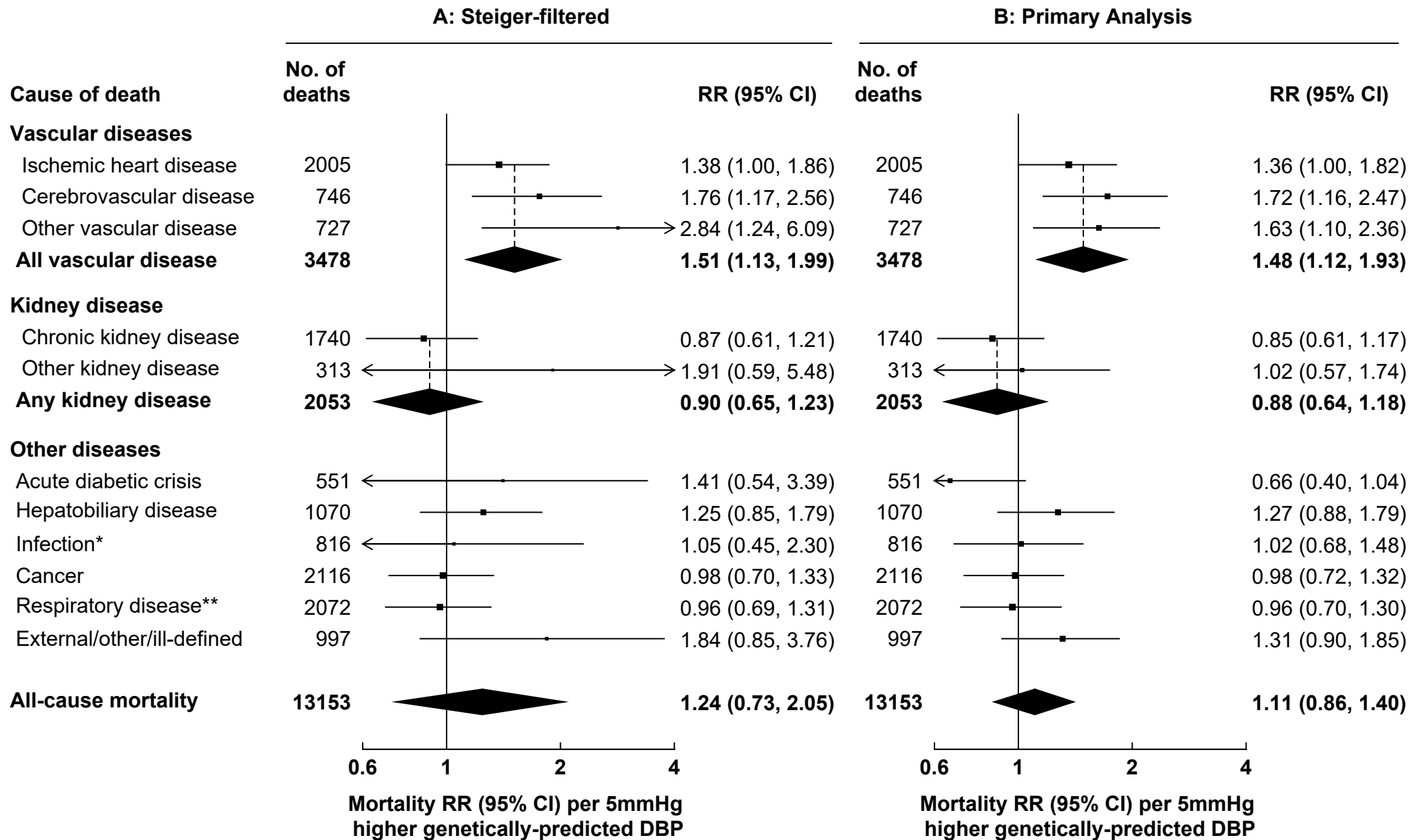
Mortality rate ratios (RRs) are per 5mmHg higher genetically-predicted DBP and are stratified by diabetes status and adjusted for age-at-risk, sex, body mass index and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). DBP = diastolic blood pressure.

# Figure S6: Comparison of Steiger-filtered and primary SBP analyses



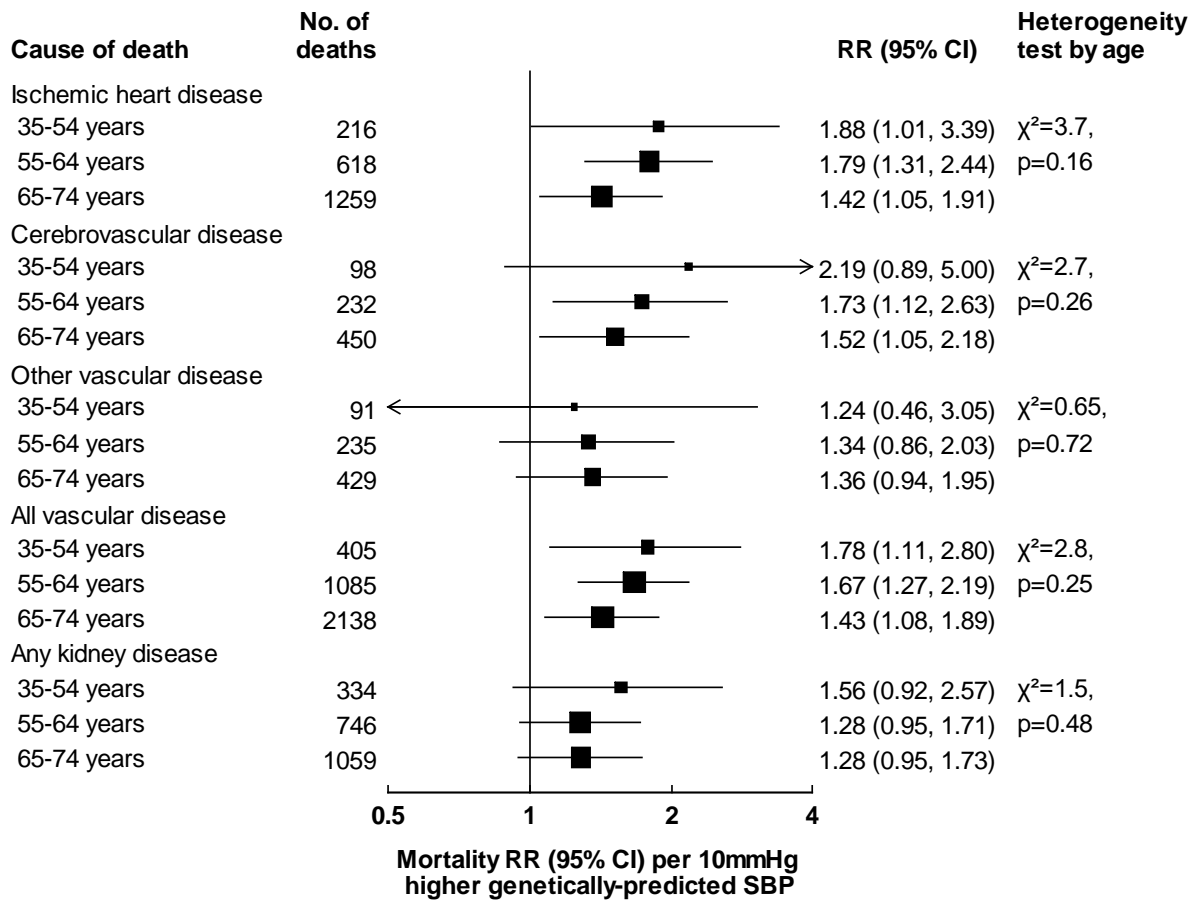
Mortality rate ratios (RRs) are per 10mmHg higher genetically-predicted SBP using a Steiger-filtered genetic score for SBP from which variants with a significantly stronger effect on estimated glomerular filtration rate are removed (A), and the primary analyses (B). Both sets of analyses are adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). SBP: systolic blood pressure.

# Figure S7: Comparison of Steiger-filtered and primary DBP analyses



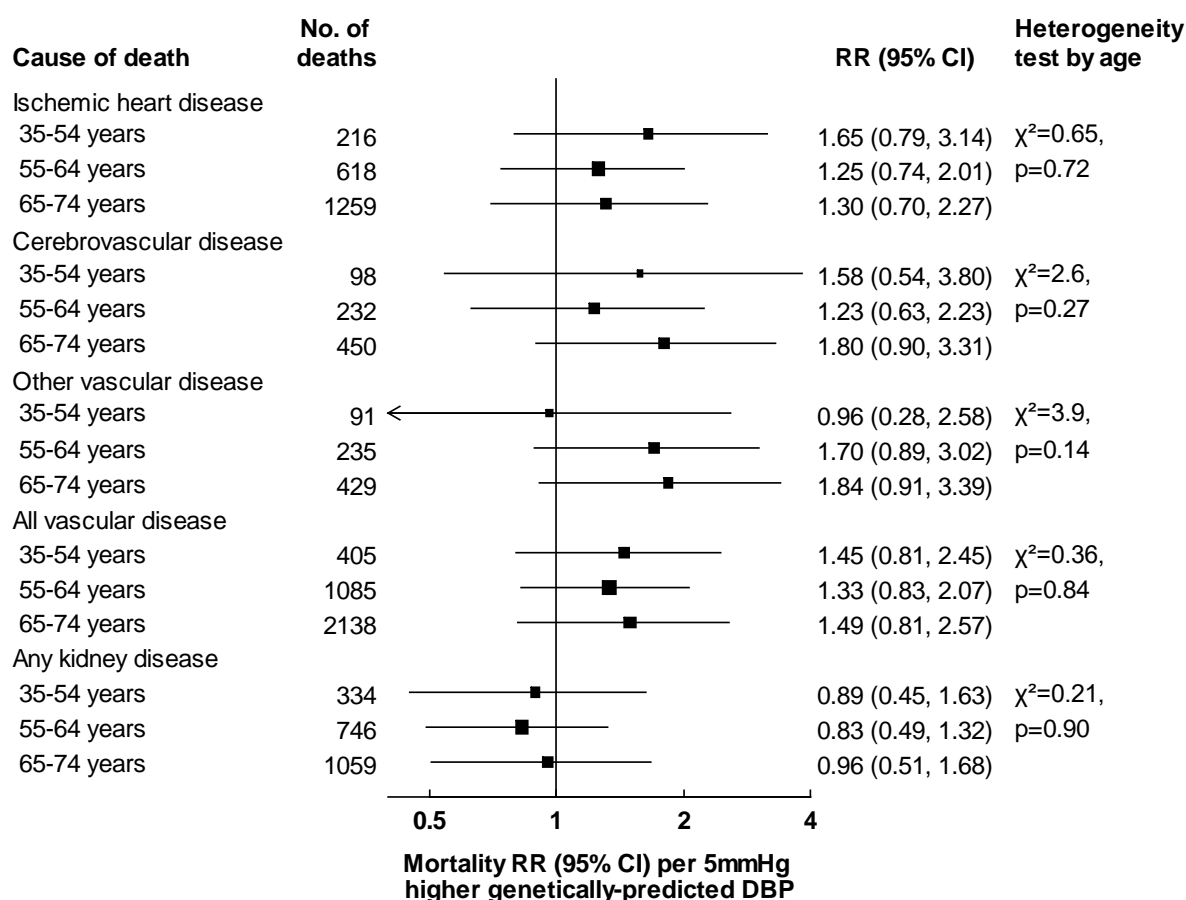
Mortality rate ratios (RRs) are per 5mmHg higher genetically-predicted DBP using a Steiger-filtered genetic score for SBP from which variants with a significantly stronger effect on estimated glomerular filtration rate are removed (A), and the primary analyses (B). Both sets of analyses are adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). DBP: diastolic blood pressure.

**Figure S8: Associations between genetically-predicted SBP and cardiovascular and kidney mortality by age group**



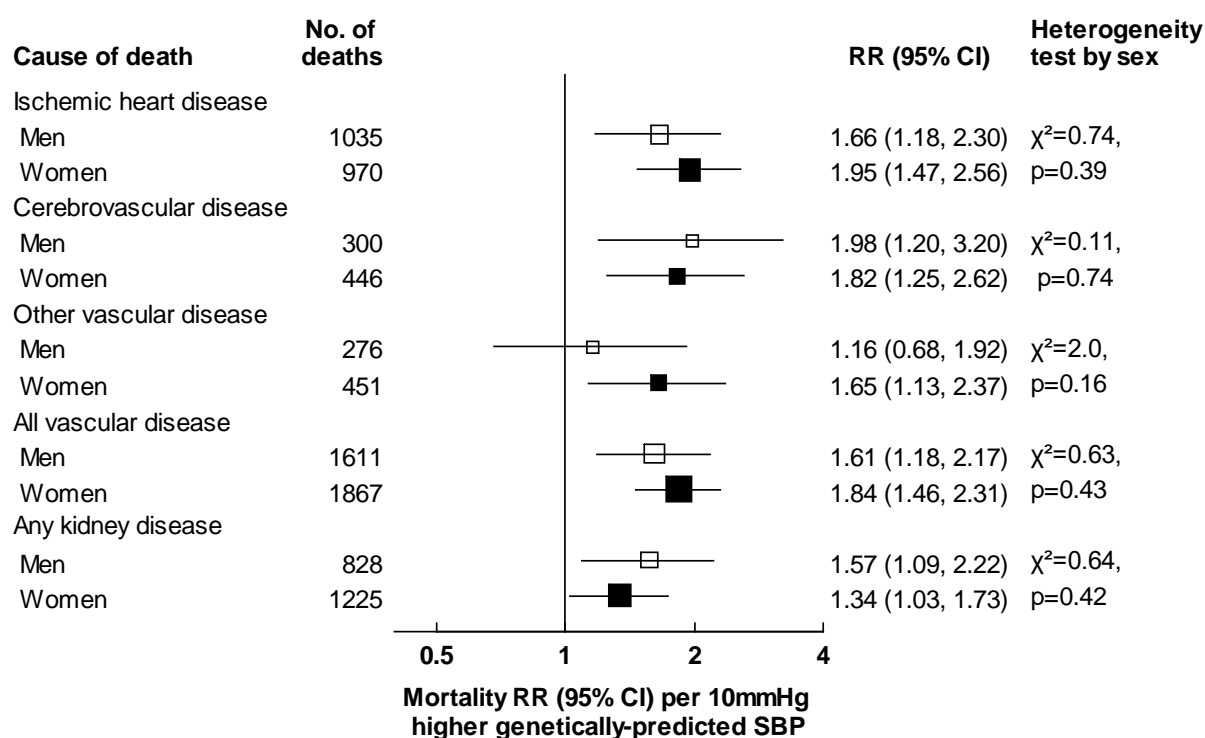
Mortality rate ratios (RRs) are per 10mmHg higher genetically-predicted SBP and are stratified by age-at-risk and adjusted for sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). SBP = systolic blood pressure.

**Figure S9: Associations between genetically-predicted DBP and cardiovascular and kidney mortality by age group**



Mortality rate ratios (RRs) are per 5mmHg higher genetically-predicted DBP and are stratified by age-at-risk and adjusted for sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). DBP = diastolic blood pressure.

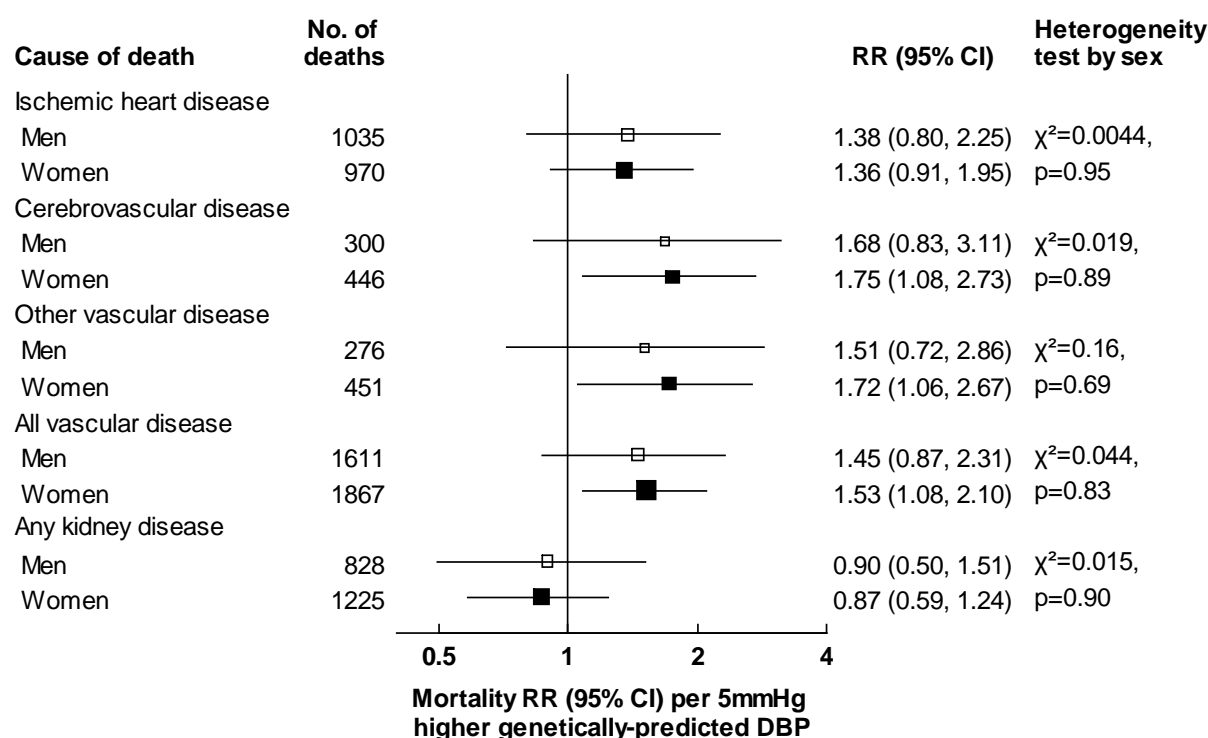
**Figure S10: Associations between genetically-predicted SBP and cardiovascular and kidney mortality by biological sex**



Mortality rate ratios (RRs) are per 10mmHg higher genetically-predicted SBP and are stratified by sex and adjusted for age-at-risk, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). SBP = systolic blood pressure.

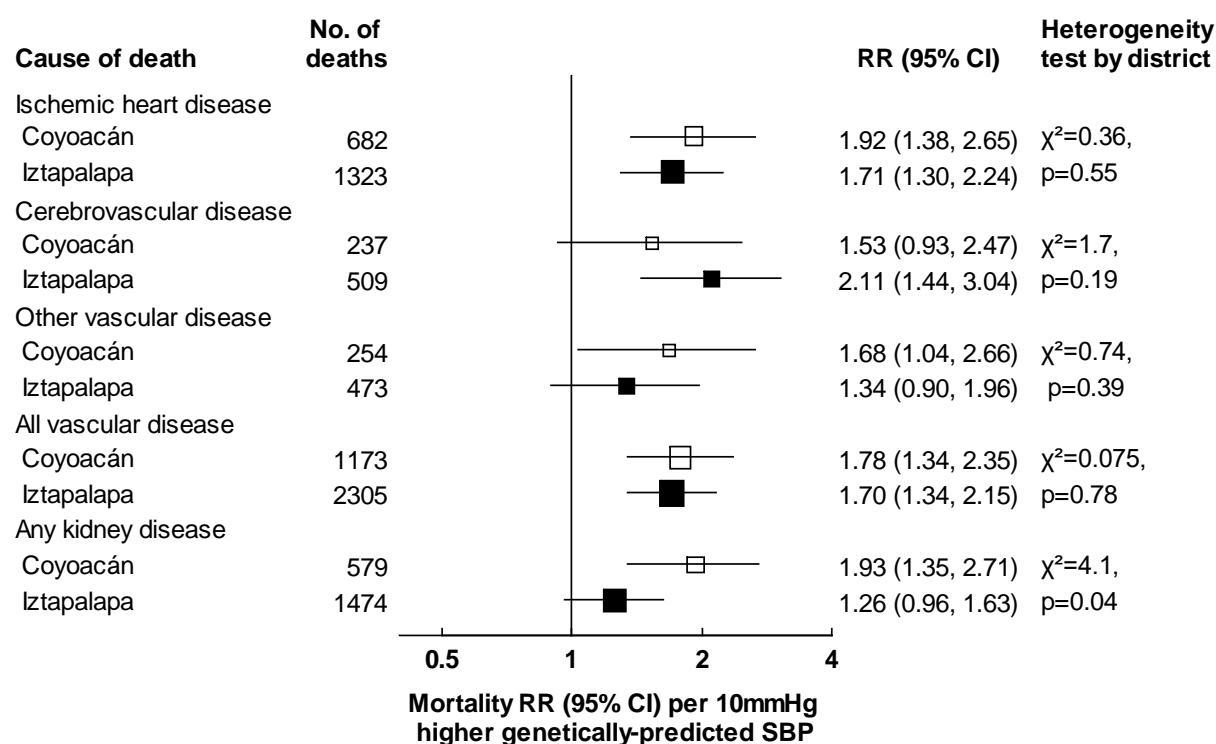


**Figure S11: Associations between genetically-predicted DBP and cardiovascular and kidney mortality by biological sex**



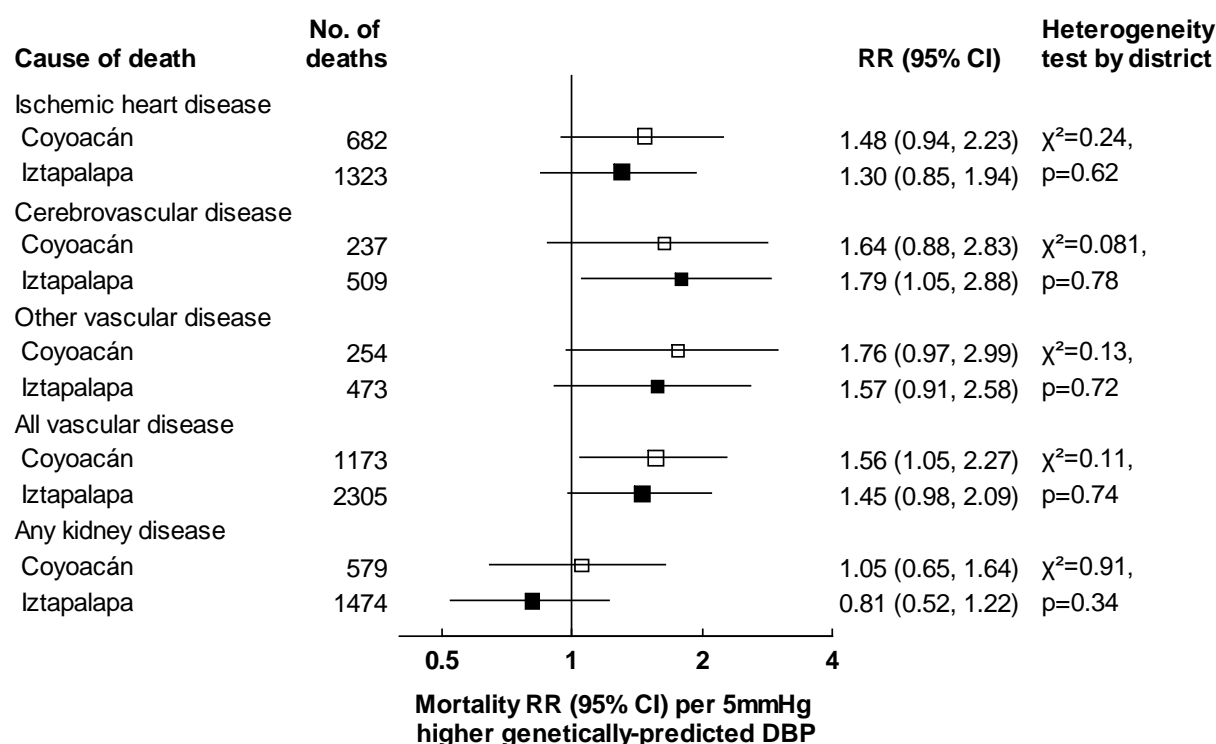
Mortality rate ratios (RRs) are per 5mmHg higher genetically-predicted DBP and are stratified by sex and adjusted for age-at-risk, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). DBP = diastolic blood pressure.

**Figure S12: Associations between genetically-predicted SBP and cardiovascular and kidney mortality by district of residence**



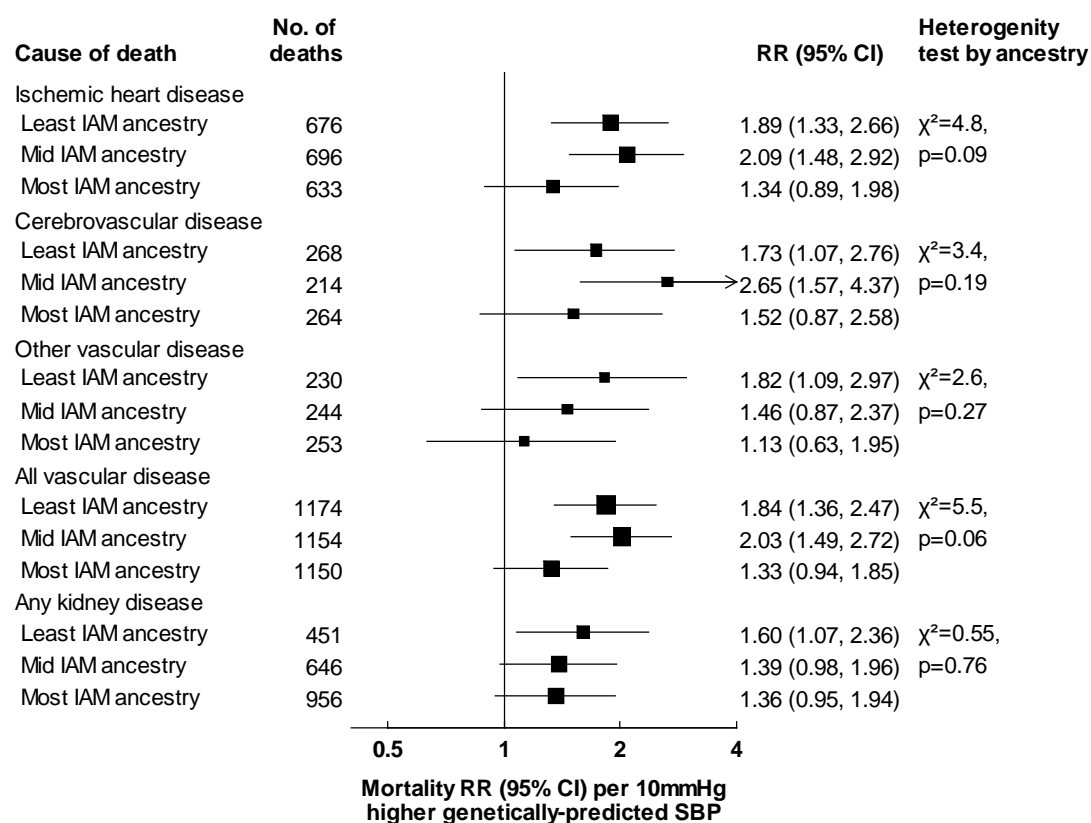
Mortality rate ratios (RRs) are per 10mmHg higher genetically-predicted SBP and are stratified by district of residence and adjusted for age-at-risk, sex, body mass index and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). SBP = systolic blood pressure.

**Figure S13: Associations between genetically-predicted DBP and cardiovascular and kidney mortality by district of residence**



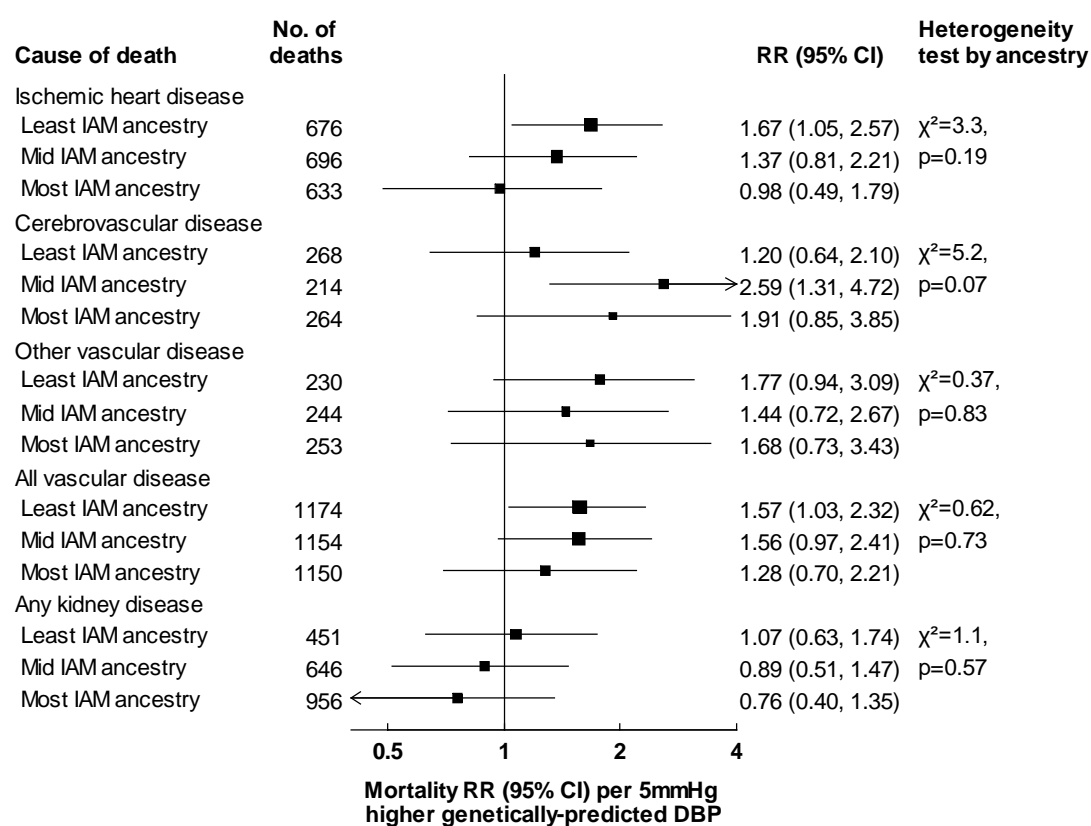
Mortality rate ratios (RRs) are per 5mmHg higher genetically-predicted DBP and are stratified by district of residence and adjusted for age-at-risk, sex, body mass index and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). DBP = diastolic blood pressure.

**Figure S14: Associations between genetically-predicted SBP and cardiovascular and kidney mortality by ancestry group**



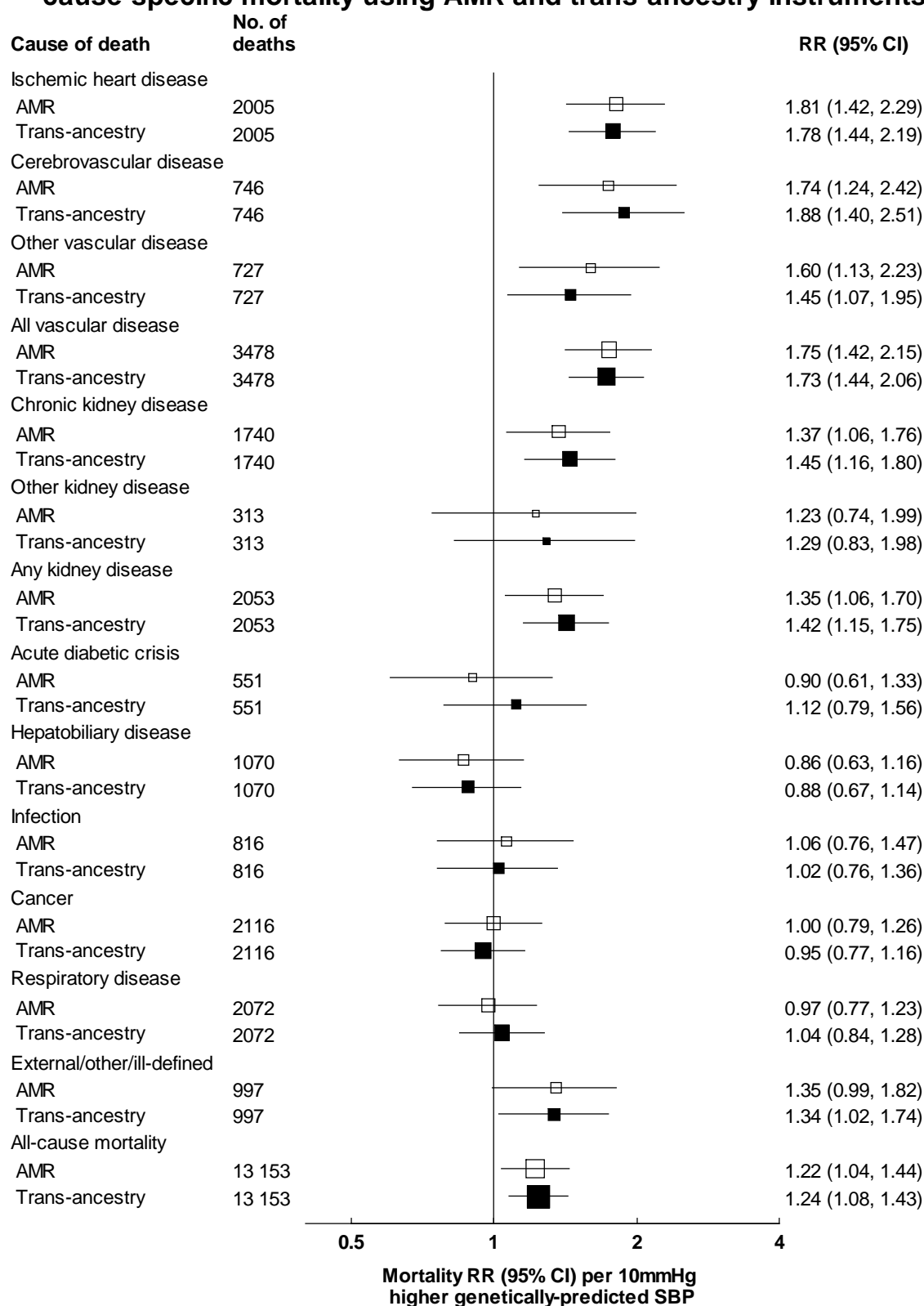
Mortality rate ratios (RRs) are per 10mmHg higher genetically-predicted SBP and are stratified by AMR ancestry and adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). IAM = Indigenous American, SBP = systolic blood pressure.

**Figure S15: Associations between genetically-predicted DBP and cardiovascular and kidney mortality by ancestry group**



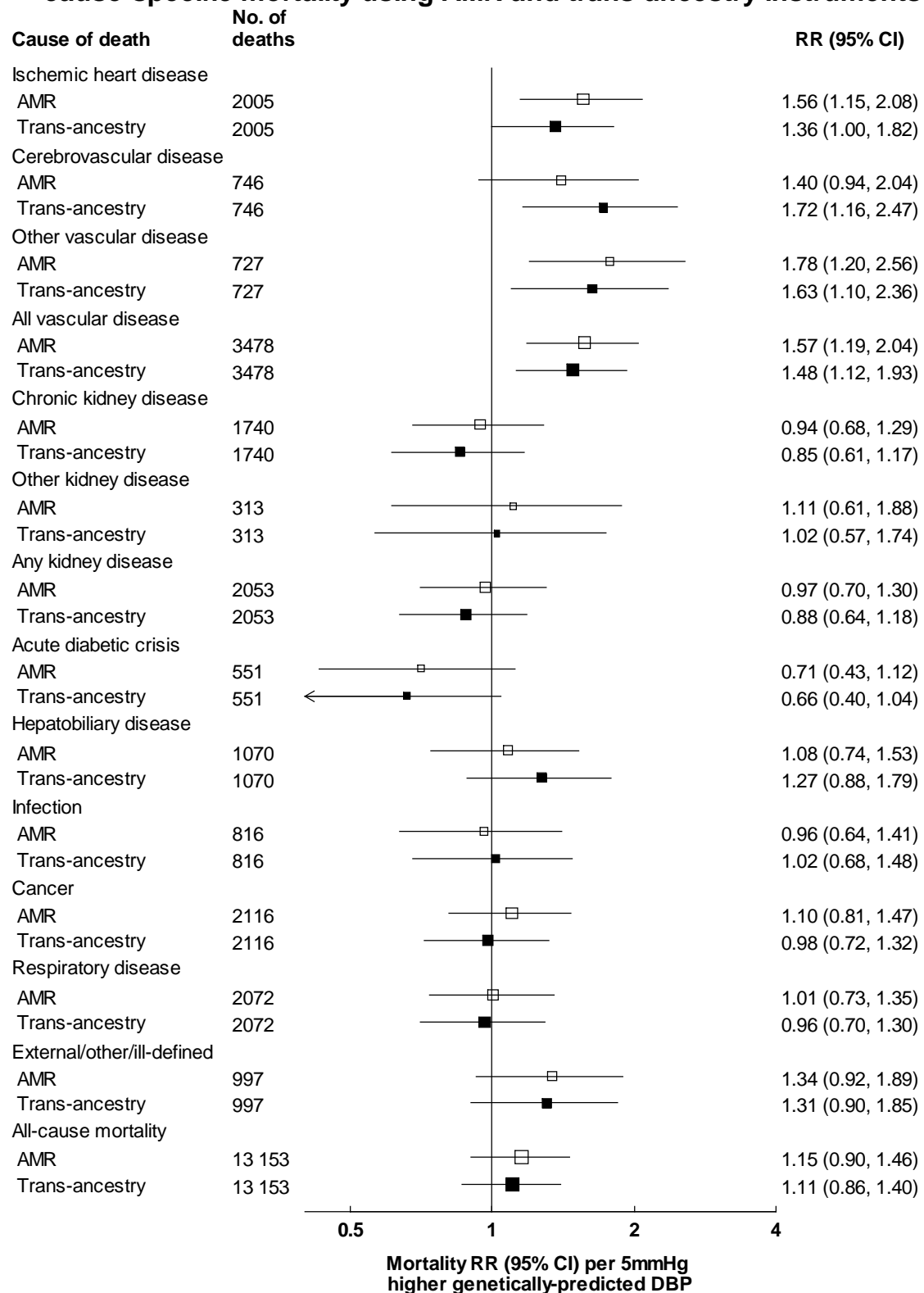
Mortality rate ratios (RRs) are per 5mmHg higher genetically-predicted DBP and are stratified by AMR ancestry and adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). DBP = diastolic blood pressure, IAM = Indigenous American.

**Figure S16: Associations between genetically-predicted SBP and cause-specific mortality using AMR and trans-ancestry instruments**



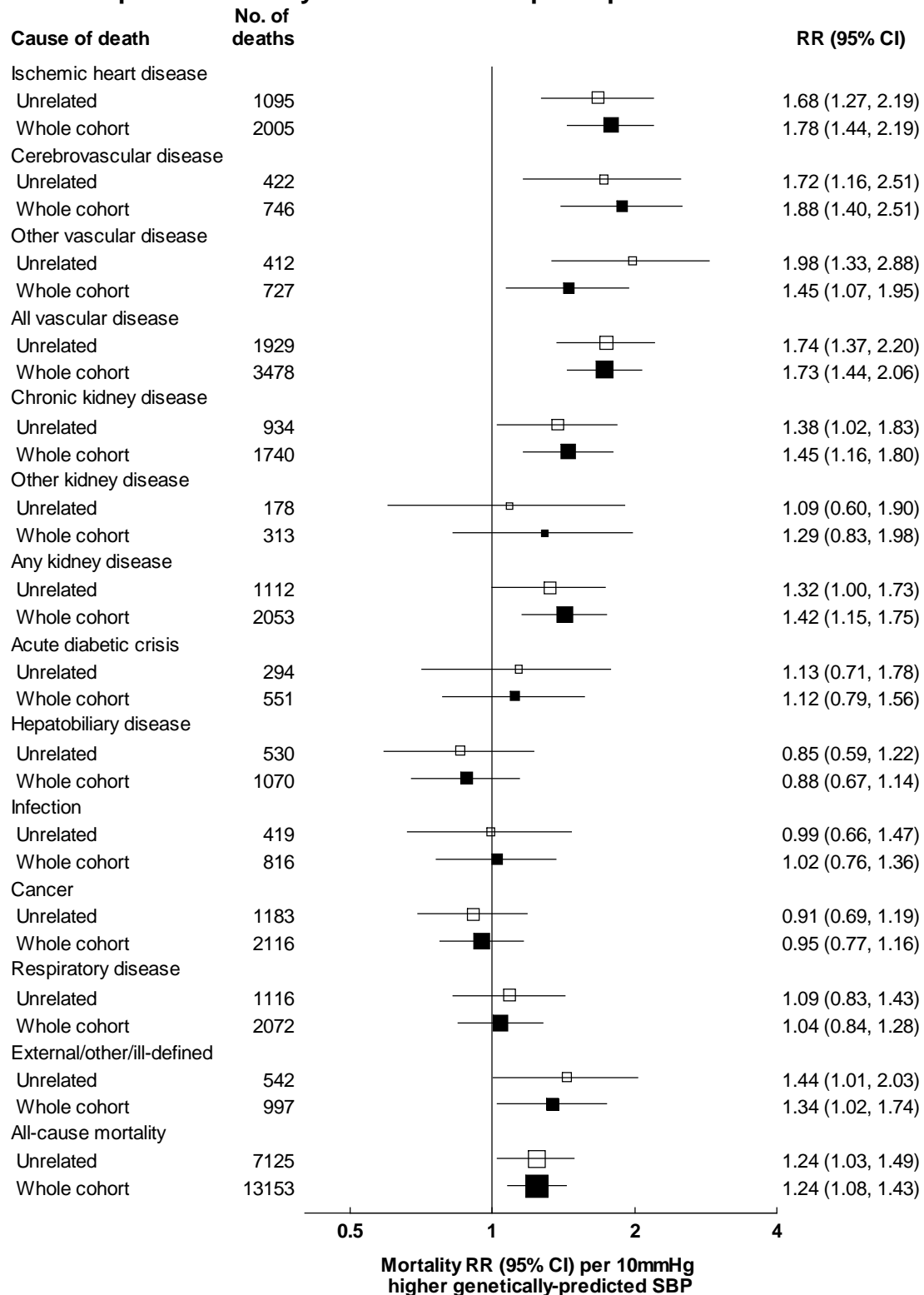
Mortality rate ratios (RRs) are per 10mmHg higher genetically-predicted SBP using genetic scores for SBP constructed with AMR and trans-ancestry weights. Both sets of analyses are adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). AMR: admixed American, SBP: systolic blood pressure.

**Figure S17: Associations between genetically-predicted DBP and cause-specific mortality using AMR and trans-ancestry instruments**



Mortality rate ratios (RRs) are per 5mmHg higher genetically-predicted DBP using genetic scores for SBP constructed with AMR and trans-ancestry weights. Both sets of analyses are adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). AMR: admixed American, DBP: diastolic blood pressure.

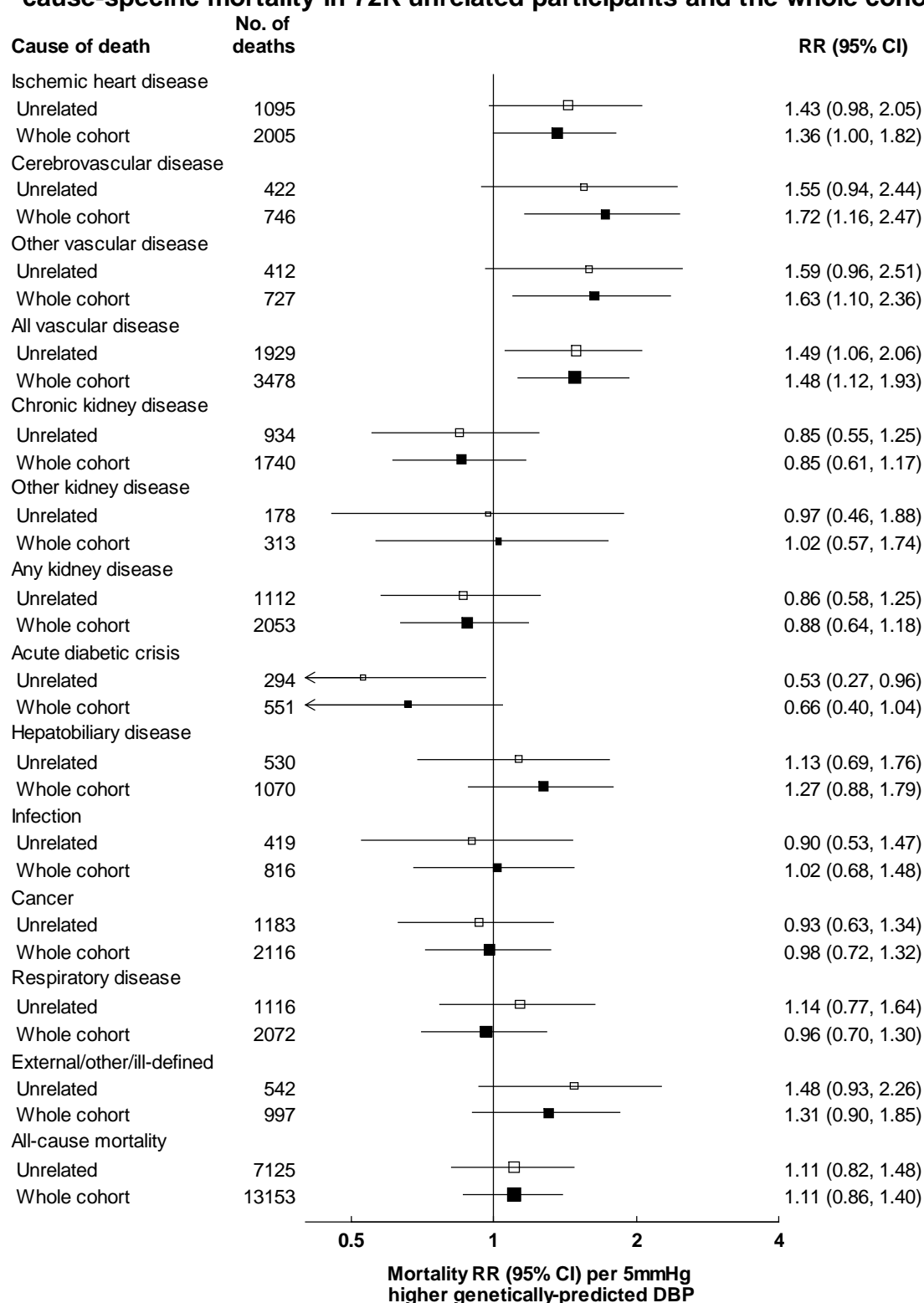
**Figure S18: Associations between genetically-predicted SBP and cause-specific mortality in 72K unrelated participants and the whole cohort**



Mortality rate ratios (RRs) are per 10mmHg higher genetically-predicted SBP in analyses run in a set of 72K participants unrelated at the third degree, and the whole cohort. Both sets of analyses are adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). SBP: systolic blood pressure.



**Figure S19: Associations between genetically-predicted DBP and cause-specific mortality in 72K unrelated participants and the whole cohort**

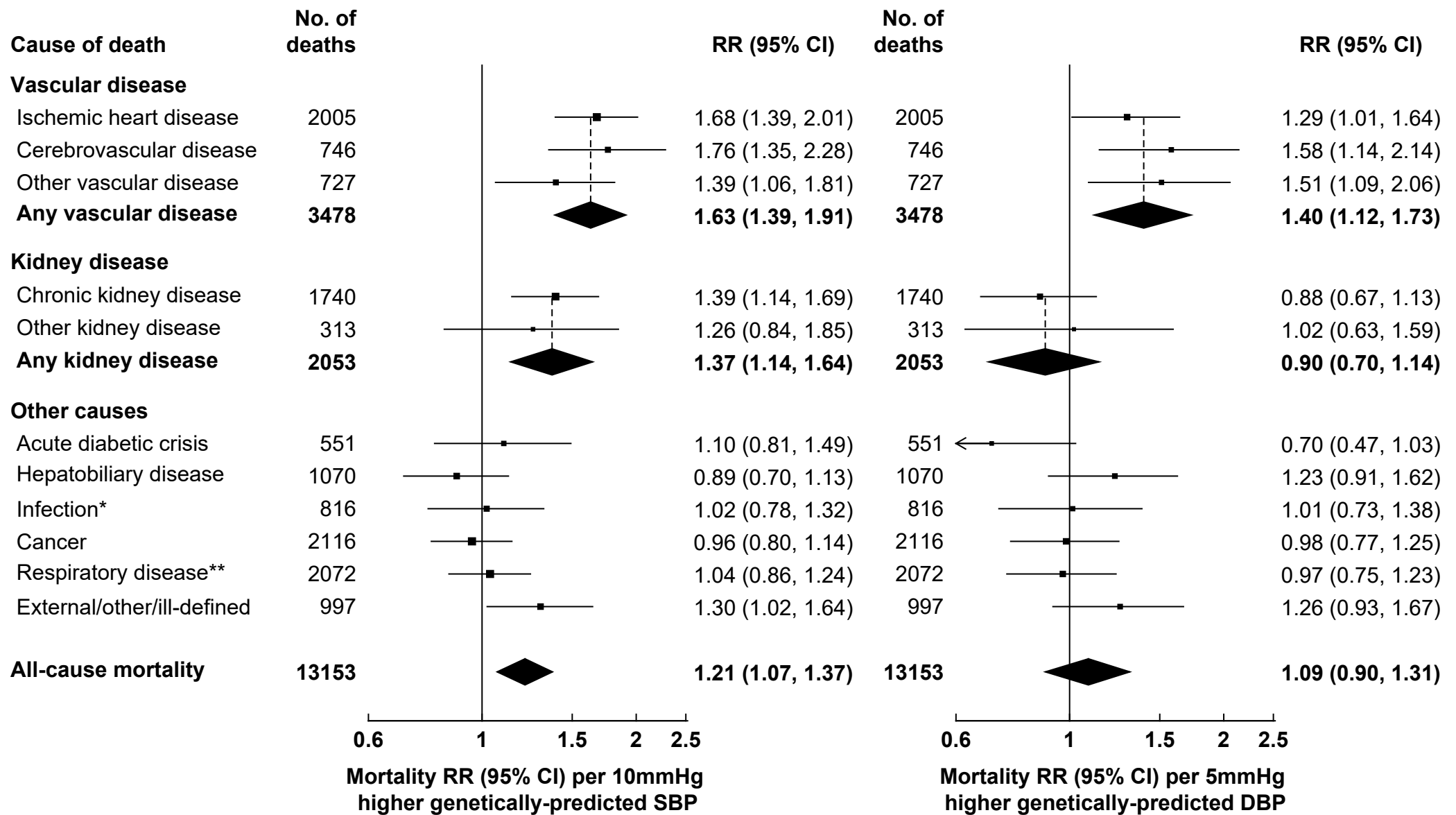


Mortality rate ratios (RRs) are per 5mmHg higher genetically-predicted DBP in analyses run in a set of 72K participants unrelated at the third degree, and the whole cohort. Both sets of analyses are adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). DBP: diastolic blood pressure.

**Figure S20: Genetic associations of SBP and DBP with cause-specific mortality using a 15/10mmHg correction for antihypertensive use**

**A: Genetically-predicted SBP**

**B: Genetically-predicted DBP**



Mortality rate ratios (RRs) are per 10mmHg higher genetically-predicted SBP (A) or 5mmHg higher genetically-predicted DBP (B) when participants taking antihypertensive medications had their SBP increased by 15mmHg and DBP by 10mmHg. Both sets of analyses are adjusted for age-at-risk, sex, body mass index, district of residence and the first 7 genetic principal components. The size of each square is inversely proportional to the variance of the log RR. Horizontal lines represent 95% confidence intervals (CI). \*Excludes respiratory infections. \*\*Includes respiratory infections. DBP: diastolic blood pressure, SBP: systolic blood pressure.