Supplemental Material

Blood pressure-lowering and risk of cancer: individual participant-level data meta-analysis and Mendelian randomization studies

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Supplementary Method 1. Details of the design of the individual participant data meta-analysis.

Individual participant data meta-analysis designs

There are two main types of individual participant data (IPD) meta-analysis designs: one-stage and two-stage. The "two-stage" IPD meta-analysis is similar to the conventional meta-analysis of summary statistics, but instead of extracting summary statistics from published papers, researchers acquire individual-level data and then estimate treatment effects (e.g., hazard ratios, mean differences, etc) for each trial separately, based on a "unified statistical analysis plan" across all trials. All other details are identical to classic meta-analysis methods. On the other hand, the "one-stage" IPD meta-analysis is an approach that combines data from all "individual participants" across trials into a single comprehensive statistical model. Unlike the two-stage approach, where trials are analyzed independently, the one-stage method analyzes all data simultaneously while accounting for the clustering of participants within trials. This approach uses advanced statistical techniques, such as mixed-effects or stratified models, to allow each trial to have its own baseline hazard function or intercept while estimating a common treatment effect across all trials. The one-stage method offers greater precision and statistical power by leveraging the full variability of individual-level data. It is particularly advantageous for investigating treatment-covariate interactions, effect modification and subgroup analysis, as it can incorporate both individual- and trial-level covariates into the same model. In the context of the current study that focuses on cancer, it should be noted that the one-stage approach has the added advantage of enabling time-stratified analyses (**Figure 2**) and assessing heterogeneity of effects by baseline variables (**Figure 3**). Such subgroup analyses are not straightforward with the two-stage IPD method. The table below compares one-stage, two-stage, and conventional meta-analysis methods.

Comparison of one-stage, two-stage, and conventional meta-analysis methods			
Aspect	**One-Stage Meta-Analysis**	**Two-Stage Meta-Analysis**	**Conventional Meta-Analysis**
Definition	Combines individual-level data from all trials into a single statistical model.	Analyses each trial separately to calculate trial-specific estimates, which are then pooled using an aggregate data meta-analysis method.	Combines summary-level data (e.g., effect sizes, confidence intervals) reported in published trials.
Data Requirement	Requires individual-level participant data from all trials.	Requires individual-level participant data from all trials.	Requires only published or aggregate summary data from trials.
Analysis unit	Each participant	Trial	Trial
Statistical Power	Greater statistical power as all data is used simultaneously, leveraging individual-level variability.	Relatively lower power due to independent analyses of trials before pooling.	Relatively lower power due to reliance on summary data.
Precision of Estimates	Provides more precise estimates by using the full individual information	May yield less precise pooled estimates, particularly with small sample sizes or few trials.	Limited precision as it depends on the quality and consistency of published summary data.
Handling of Covariates	Facilitates exploration of complex covariate interactions and effect modification at both trial and individual levels.	Limited ability to model covariate interactions or effect modification across studies.	Does not allow for covariate-level exploration or individual-level adjustments.
Flexibility	Can incorporate complex models (e.g., effect modification, stratification, subgroup analysis, time-dependent covariates).	Simpler and more intuitive but less flexible for complex analyses.	Very limited flexibility; focuses on overall effect estimates.
Heterogeneity	Allows direct modelling heterogeneity within the framework of the model.	Provides measures of aggregate level heterogeneity (e.g., I^2, τ^2) and may overlook nuanced patterns.	Assesses heterogeneity using summary statistics but lacks granularity.
Ease of Implementation	Requires advanced statistical expertise and computational resources.	Simpler to implement using established meta-analysis software.	Easiest to implement using standard tools (e.g., RevMan, Excel).

Stratified Cox proportional hazard model

In the one-stage IPD approach, individual-level data from different trials, which include participants with varying baseline risks and characteristics, are pooled together and treated as a single dataset for modelling purposes (similar to a large multicentre trial). This requires careful consideration to ensure appropriate statistical analysis. Consequently, accounting for the clustering of participants across trials is an important methodological consideration.[1-3] We used stratified Cox proportional hazards models to pool hazard ratios (HRs) across trials, treating each trial as a stratum in the model to account for trial-specific baseline hazard variations. This approach ensures that between-trial heterogeneity does not affect effect estimation. A stratified Cox model is a variation of the Cox proportional hazards regression model that accounts for stratification factors by allowing the baseline hazard function to vary across levels of a stratifying variable while keeping the regression coefficients constant across those strata. This approach is particularly useful when

there are clusters within the data (e.g., trials, centres, or specific cohorts) that have different baseline hazard functions. [4-8]

Furthermore, in blood pressure -lowering trials, the primary source of heterogeneity is the variability in the blood pressure reduction achieved in each trial, which is mainly influenced by study design and trial intervention type. Therefore, it is reasonable to assume that the only source of heterogeneity is the magnitude of blood pressure reduction across trials. As such, we used a fixed-effects Cox model, adjusted for blood pressure reduction across trials, to address this known source of heterogeneity.[4-10]

Standardization of the effect sizes

Standardization of effect sizes is appropriate when the objective is to pool the effects of blood pressure (BP)-lowering treatments and express the effect for a fixed level of BP reduction. This approach is essential for such analyses because the magnitude of BP reduction varies across trials. Standardization facilitates adjustment for this heterogeneity by assigning greater weight to trials with larger BP reductions, particularly when the hypothesis focuses on assessing the BP-mediated effect. In practical terms, this implies that all else being equal, trials with minimal BP reductions between treatment arms are assigned proportionately lower weights than they would be in the absence of standardization.[9]

Another additional advantage of standardization is that it permits the inclusion of a wide range of BP-lowering trials without necessitating an arbitrary threshold for trial-level achieved BP reduction. For instance, in head-to-head trials comparing one drug with another, the achieved reduction is often modest. Rather than excluding these trials (e.g., with 1 or 2 mmHg BP reduction), standardization enables their inclusion in the analysis, thereby enhancing statistical power while assigning lower weights to account for the smaller achieved BP reduction. To estimate the effect size of treatment per a fixed amount of BP reduction, it is therefore essential to standardize effect sizes to a predefined and clinically meaningful BP level. Without this standardization, the estimated effect size (e.g., hazard ratio) would lack scale, and the interpretation of relative risk reduction would have unclear clinical implications.

For standardization, first, for each trial, the average achieved BP reduction was estimated using a linear mixed-effects model, with further methodological details reported elsewhere.[15] This value (i.e., achieved BP reduction) was subsequently treated as the trial-level BP reduction for each trial participant and incorporated into the dataset as a new variable for analysis. A stratified Cox model was then fitted to estimate the hazard ratio for the treatment effect, adjusted for this trial-level BP reduction. Finally, the relative effect size was rescaled to correspond to a 5 mmHg reduction in systolic BP and a 3 mmHg reduction in diastolic BP, respectively.[7,8]

Supplementary Method 2. Summary of Genome-Wide Association Studies used for SNP-outcome association.

Breast cancer:

The breast cancer genome-wide association study (GWAS) involved participation from seventy-eight studies as part of the OncoArray consortium. Sixty-seven of these studies contributed data on European ancestry, while twelve provided data on Asian ancestry, excluding one Norwegian study due to the absence of controls. The research predominantly consisted of population-based case-control studies or case-control studies nested within population-based cohorts, with some studies specifically targeting cases with a familial history of breast cancer. All participating studies submitted essential information on disease status, age at diagnosis or observation, with many also providing detailed clinico-pathological and lifestyle data. This wealth of information has been carefully curated into the Breast Cancer Association Consortium database. The quality control (QC) stage for the GWAS involved detailed protocols to ensure data integrity. This process included genotype calling, handling of potential errors, and consistency checks across datasets. The GWAS included 122,977 cases and 105,974 controls of European ancestry, and 14,068 cases and 13,104 controls of East Asian ancestry.[11]

Colorectal cancer

The colorectal cancer GWAS included data from five primary GWAS alongside a meta-analysis with ten published GWAS, comprising 34,627 cases and 71,379 controls of European ancestry. The analysis utilised rigorous QC measures and imputation based on the 1000 Genomes and UK10K data as reference. After excluding variants with minor allele frequency less than 0.5% and imputation quality score below 0.8, associations between colorectal cancer status and single nucleotide polymorphism (SNP) genotypes were assessed using logistic regression, with risk estimates combined through inverse-variance weighted fixed-effects meta-analysis.[12]

Kidney cancer

The kidney cancer GWAS incorporated data from six genome-wide scans, including two new and four previous studies, totaling 10,784 cases and 20,406 controls of European ancestry. Quality control measures

were rigorously applied to ensure data integrity. The statistical analysis utilized fixed-effects meta-analysis for discovery and targeted replication in an independent set of 3,182 cases and 6,301 controls. This approach confirmed six known renal cell carcinoma (RCC) risk loci and identified seven new loci, enhancing understanding of RCC's genetic basis.[13]

Lung cancer

The study involved a large-scale analysis including 14,803 cases and 12,262 controls of European descent, with subsequent imputation and logistic regression analysis to explore the associations between genetic variants and lung cancer risk. The study successfully identified 18 new susceptibility loci, highlighting the heterogeneity in genetic risk across lung cancer subtypes and emphasizing the complexity of its genetic underpinnings.[14]

Prostate cancer

The prostate cancer GWAS study assembled a new sample series from 52 studies for genotyping with the OncoArray, after rigorous QC, yielding 46,939 prostate cancer cases and 27,910 controls of European ancestry for analysis. Genotypes were imputed to the 1000 Genomes Project reference panel, and a fixed-effects meta-analysis was performed, including 79,194 prostate cancer cases and 61,112 controls. The study identified 63 novel prostate cancer susceptibility variants through logistic regression analysis, adjusted for principal components and study-specific covariates, highlighting significant advancements in understanding prostate cancer genetics.[15]

Skin cancer

The basal cell carcinoma (BCC) study consisted of a two-stage GWAS meta-analysis, totaling 17,187 cases and 287,054 controls. Stage 1 analysis involved 12,945 self-reported BCC cases and 274,252 controls of European ancestry from 23andMe research participants. Stage 2 comprised an independent GWAS cohort of 4,242 BCC cases and 12,802 controls of European ancestry from the Nurses' Health Study and Health Professionals Follow-Up Study. QC measures and genotype imputation were rigorously applied, with meta-analysis combining stages 1 and 2 results to identify 14 novel susceptibility loci for BCC.[16] The cutaneous squamous cell carcinoma (SCC) GWAS study pooled data from six international cohorts, totaling 19,149 SCC cases and 680,049 controls. This comprehensive analysis confirmed 14 previously associated loci and identified eight new susceptibility loci. The study leveraged strict quality control measures and

sophisticated genotyping and imputation strategies to ensure data integrity and accuracy. The statistical approach involved logistic regression adjusted for principal components to account for population stratification, with meta-analysis techniques applied to aggregate findings across cohorts.[17] The cutaneous melanoma GWAS meta-analysis involved 36,760 cases and 375,188 controls, identifying 54 significant loci with 68 independent SNPs. The study highlighted the importance of nevogenesis, pigmentation, and telomere maintenance in melanoma susceptibility, revealing new pathways for research. The analysis also integrated GWAS data of nevus count and hair color, uncovering 31 potential secondary loci, bringing the total to 85 susceptibility loci. This extensive study provides new insights into the genetic architecture of cutaneous melanoma.[18]

Supplementary Method 3. Summary of randomized clinical trials included in individual participant data meta-analysis

Trial	Country	Type of trial	Randomization groups		Trial sample size (% women)	Age [mean, SD]	Percentage of current smokers (%, n)	Body mass index (kg/m²) [mean, SD]	Median follow-up duration (year)	Explicit exclusion of cancer patients at baseline	Source of cancer outcome	Adjudication	Level of detail of cancer outcomes provided
			Treatment	Comparator									
AASK*[19]	USA	Intensive	More intense BP-lowering	Less intense BP-lowering	1094 (39)	54 (11)	29 (321)	30.6 (6.6)	4.8	No	Routine adverse event	No	Site of cancer diagnosis (lung, colon, breast, prostate, skin, other types)
ABCD*[20]	USA	Intensive	More intense BP-lowering	Less intense BP-lowering	950 (33)	58 (8)	14 (128)	31.7 (5.7)	4.7	Yes (patients with active cancer)	Routine adverse event	No	Cancer diagnosis yes/no (no information on site of cancer)
ACCORD[21]	USA and Canada	Intensive	More intense BP-lowering	Less intense BP-lowering	4733 (48)	63 (7)	13 (626)	32.1 (5.5)	4.7	Yes (cancer within 2 years other than non-melanoma skin)	Pre-specified safety outcome	Yes	Fatal cancer yes/no (no information on site of cancer)
ACTIVE I[22]	Multi-country	Placebo-controlled	ARB	Placebo	9016 (39)	70 (10)	22 (9269)	29.1 (5.8)	4.1	No	Routine adverse event	No	Site of cancer diagnosis (lung, colon, breast, prostate, skin, other)
ADVANCE[23]	Multi-country	Placebo-controlled	ACEi and Diuretic	Placebo	11,140 (43)	66 (6)	14 (1550)	28.3 (5.2)	4.2	No	Routine adverse event	No	ICD-10 codes for site of cancer
ALLHAT[24]	Multi-country	Head-to-head	Diuretic	ACEi CCB Alpha-blocker	42,418 (47)	67 (8)	22 (9269)	29.6 (5.9)	4.8	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, colon, breast, prostate, bladder, other)
ANBP2[25]	Australia	Head-to-head	Diuretic	ACEi	6083 (51)	73 (5)	7 (431)	27.1 (4.2)	4.1	No	Pre-specified safety outcome	Yes	ICD-9 codes for site of cancer
ASCOT-BPLA[26]	Multi-country	Head-to-head	CCB-based	Beta-blocker-based	19,257 (23)	63 (9)	33 (6277)	28.7 (4.6)	5.3	No	Routine adverse event	No	Fatal cancer yes/no (no site of cancer)
BENEDICT[27]	Italy	Placebo-controlled	ACEi CCB ACEi and CCB	Placebo	1204 (47)	62 (8)	12 (146)	29.1 (4.7)	3.1	Yes	Routine adverse event	No	Site of cancer diagnosis (lung, colon, breast, prostate, other)

CAMELOT[28]	Multi-country	Placebo-controlled	CCB ACEI	Placebo	1991 (26)	58 (10)	26 (528)	29.8 (5.3)	1.6	No	Routine adverse event	No	Site of cancer diagnosis (text description)
CASE-J[29]	Japan	Head-to-head	CCB	ARB	4703 (45)	64 (11)	22 (1025)	24.5 (3.7)	3.1	Yes (cancer within 5 years of enrolment)	Routine adverse event	No	Site of cancer diagnosis (text description)
COLM[30]	Japan	Head-to-head	Diuretic and ARB	CCB and ARB	5141 (48)	74 (5)	11 (551)	24.3 (3.4)	3.0	Yes (patients with malignant tumours)	Routine adverse event	Yes	MedDRA codes for site of cancer
CONVINCE[31]	Multi-country	Head-to-head	CCB	Beta-blocker Diuretic	16476 (55)	66 (7)	23 (3795)	-	2.8	Yes (untreated malignancy within 5 years of enrolment)	Pre-specified safety outcome	Yes	Cancer diagnosis yes/no (no information on site of cancer)
COPE[32]	Japan	Head-to-head	Beta-blocker and CCB Diuretic and CCB	ARB and CCB	3293 (49)	64 (11)	21 (700)	24.5 (3.4)	3.6	Yes (cancer 5 years prior to study entry)	Routine adverse event	No	MedDRA codes for site of cancer
DIABHYCAR[33]	The Nether-lands	Placebo-controlled	ACEi	Placebo	4912 (30)	65 (8)	15 (756)	29.2 (4.6)	3.9	Yes	Routine adverse event	No	Site of cancer diagnosis (text description)
Dutch-TIA[34]	The Nether-lands	Placebo-controlled	Beta-blocker	Placebo	1473 (36)	64 (10)	47 (693)	-	2.3	No	Routine adverse event	No	Fatal cancer yes/no (no information on site of cancer)
ELSA[35]	Multi-country	Head-to-head	CCB	Beta-blocker	2334 (45)	57 (7)	20 (478)	27.2 (3.8)	3.4	No	Routine adverse event	No	ICD-9 codes for site of fatal cancer
EUROPA[36]	Multi-country (Europe)	Placebo-controlled	ACEi	Placebo	12,218 (15)	61 (9)	15 (1862)	27.4 (3.5)	4.2	No	Routine adverse event	No	Site of cancer diagnosis (text description)
EWPHE[37]	Multi-country	Placebo-controlled	Diuretic	Placebo	840 (70)	71 (8)	17 (143)	26.4 (4.5)	4.6	Yes	Routine adverse event	No	ICD-8 codes for site of cancer
HDFP[38]	USA	Intensive	More intense BP-lowering	Less intense BP-lowering	10,940 (46)	51 (10)	39 (4248)		6.7	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, colon, breast, prostate, bladder, other); ICD-8 codes
HIJ-CREATE[39]	Japan	Head-to-head	ARB	Non-ARB	2049 (20)	65 (9)	25 (509)	24.6 (3)	4.0	Yes (known malignant neoplasm)	Routine adverse event	Yes	Site of cancer diagnosis (text description)

HOMED-BP*[40]	Japan	Intensive	More intense BP-lowering	Less intense BP-lowering	3518 (50)	60 (10)	21 (743)	24.4 (3.5)	4.9	No	Routine adverse event	No	ICD-10 codes for site of fatal cancer
HOPE[41]	Multi-country	Placebo-controlled	ACEi	Placebo	9297 (27)	66 (7)	14 (1319)	27.7 (4.4)	4.5	No	Pre-specified safety outcome	Yes	Cancer diagnosis yes/no (no information on site of cancer)
IDNT[42]	USA	Placebo-controlled	ARB CCB	Placebo	1715 (34)	59 (8)	-	30.8 (5.8)	2.6	No	Routine adverse event	Yes	Site of cancer diagnosis (text description)
INVEST[43]	Multi-country	Head-to-head	CCB	Non-CCB	21,320 (52)	66 (10)	12 (2809)	29.2 (7.1)	2.8	Yes (skin, prostate and other cancer with shortened survival expected)	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, colon, breast, prostate, bladder, other)
JMIC-B[44]	Japan	Head-to-head	CCB	ACEi	1650 (31)	65 (85)	34 (563)	24 (2.9)	2.3	No	Pre-specified safety outcome	Yes	ICD-9 codes for site of fatal cancer
LIFE[45]	Multi-country	Head-to-head	ARB	Beta-blocker	9193 (54)	67 (7)	16 (1499)	28 (4.8)	4.9	No	Pre-specified safety outcome	No	Site of cancer diagnosis (text description)
MOSES[46]	Germany and Austria	Head-to-head	CCB	ARB	1352 (46)	68 (10)	18 (247)	27.5 (4.3)	3.3	No	Routine adverse event	Yes	ICD-10 codes for site of cancer
NICS-EH[47]	Japan	Head-to-head	Diuretic	CCB	414 (67)	70 (7)	9 (38)	23.4 (3.1)	3.2	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, bowel, breast, other)
ONTARGET[48]	Multi-country	Head-to-head	ACEi and ARB	ACEi ARB	25,620 (27)	67 (7)	13 (3225)	28.2 (4.8)	4.8	No	Pre-specified safety outcome	No	Site of cancer diagnosis (lung, colon, breast, prostate, other)
PART-2[49]	New Zealand	Placebo-controlled	ACEi	Placebo	617 (18)	60 (8)	16 (100)	26.8 (3.6)	4.6	No	Routine adverse event	No	Site of cancer diagnosis (lung, colon, breast, other)
PREVEND IT[50]	The Nether-lands	Placebo-controlled	ACEi	Placebo	864 (35)	51 (12)	40 (345)	26.4 (4.4)	3.8	No	Routine adverse event	No	ICD-10 codes for site of fatal cancer
PREVENT[51]	USA and Canada	Placebo-controlled	CCB	Placebo	825 (20)	57 (10)	25 (204)	28 (4.8)	3.0	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (text description)

PRoFESS[52]	Multi-country	Placebo-controlled	ARB	Placebo	19,798 (36)	66 (8)	21 (4231)	26.8 (5)	2.5	Yes	Pre-specified safety outcome	Yes	Site of cancer diagnosis (text description)
PROGRESS[53]	Multi-country (Asia, Australa-sia and Europe)	Placebo-controlled	ACEi and/or Diuretic	Placebo	6105 (30)	64 (10)	21 (1279)	25.7 (3.8)	3.9	No	Pre-specified safety outcome	No	Site of cancer diagnosis (lung, colon, breast, prostate, other)
SHEP[54]	USA	Placebo-controlled	Diuretic and Beta-blocker	Placebo	4736 (57)	72 (7)	13 (597)	27.1 (4.8)	5.0	Yes	Routine adverse event	Yes	Cancer diagnosis yes/no (no information on site of cancer)
SPRINT[55]	USA and Puerto Rico	Intensive	More intense BP-lowering	Less intense BP-lowering	9361 (36)	68 (9)	13 (1240)	29.9 (5.8)	3.0	Yes (cancer in past 2 years; exceptions for patients able to complete trial)	Routine adverse event	Yes	MedDRA codes for site of cancer
STOP Hyper-tension-2[56]	Sweden	Head-to-head	Beta-blocker and/or Diuretic	ACEi CCB	6614 (67)	76 (4)	9 (594)	26.7 (4)	4.5	No	Routine adverse event	No	Site of cancer diagnosis (text description)
Syst-Eur[57]	Multi-country	Placebo-controlled	CCB	Placebo	4695 (67)	70 (7)	7 (343)	27 (4.1)	2.6	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, colon, breast, prostate, other)
TRANSCEND[58]	Multi-country	Placebo-controlled	ARB	Placebo	5926 (43)	68 (7)	10 (582)	28.2 (4.8)	4.9	No	Pre-specified safety outcome	No	Site of cancer diagnosis (lung, colon, breast, prostate, other)
VALIS [59]	Japan	Intensive	More intense BP-lowering	Less intense BP-lowering	3079 (62)	76 (4)	15 (450)	23.5 (3.4)	2.6	No	Routine adverse event	Yes	MedDRA codes for site of cancer
VALUE[60]	Multi-country	Head-to-head	CCB-based	ARB-based	15,245 (42)	67 (8)	24 (3664)	28.6 (5)	4.2	No	Routine adverse event	No	MedDRA codes for site of cancer

* AASK, ABCD and HOMED-BP also included head-to-head drug class comparisons in their study design.

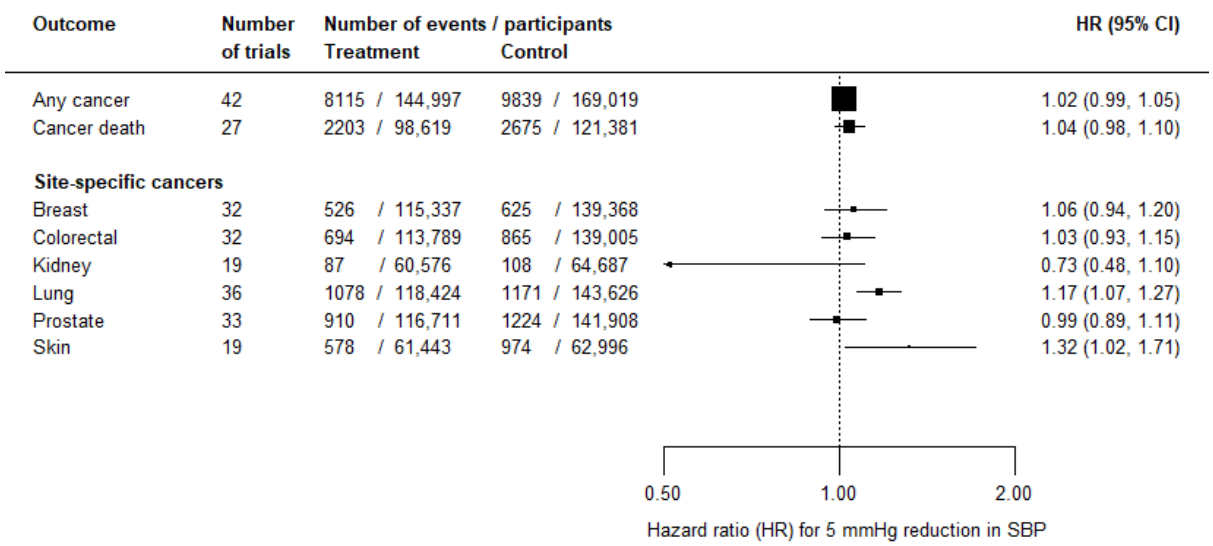
ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin-II receptor blockers; CCB=calcium channel blockers.

SD: standard deviation

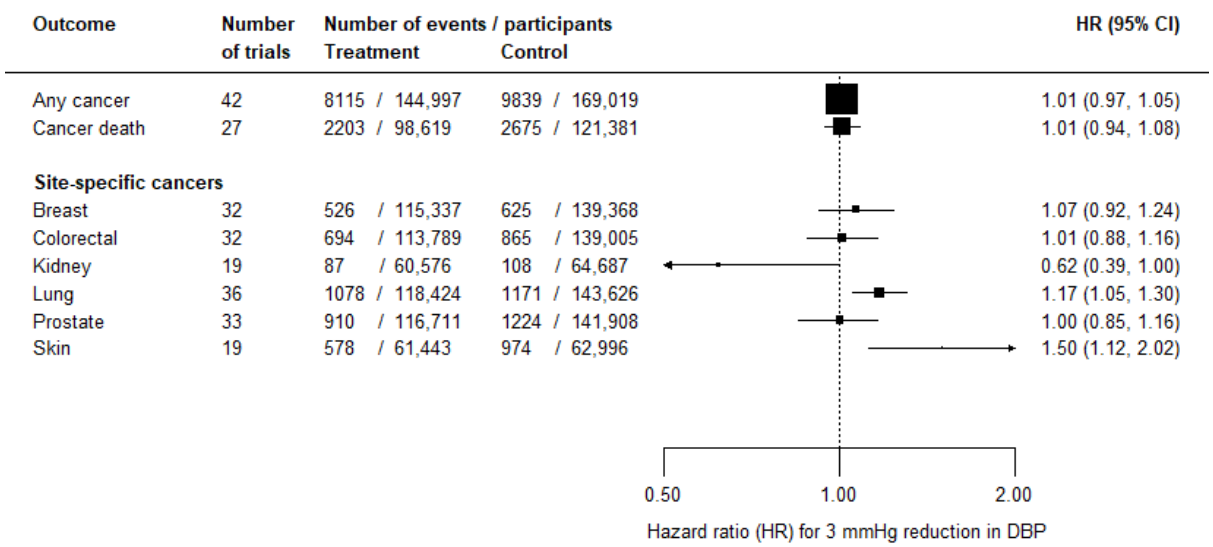
Supplementary Figure 1. Effects of blood pressure-lowering on incident cancer, cancer death and site-specific cancer, accounting for competing risk of non-cancer death.

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: hazard ratio, CI: confidence intervals

Panel A: Systolic blood pressure reduction



Panel B: Diastolic blood pressure reduction



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