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SYSTEMATIC REVIEW AND META-ANALYSIS

Potassium Intake and Blood Pressure: A Dose-Response Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Epidemiologic studies, including trials, suggest an association between potassium intake and blood pressure (BP). However, the strength and shape of this relationship is uncertain.

METHODS AND RESULTS: We performed a meta-analysis to explore the dose-response relationship between potassium supplementation and BP in randomized-controlled trials with a duration ≥4 weeks using the recently developed 1-stage cubic spline regression model. This model allows use of trials with at least 2 exposure categories. We identified 32 eligible trials. Most were conducted in adults with hypertension using a crossover design and potassium supplementation doses that ranged from 30 to 140 mmol/d. We observed a U-shaped relationship between 24-hour active and control arm differences in potassium excretion and BP levels, with weakening of the BP reduction effect above differences of 30 mmol/d and a BP increase above differences ≈80 mmol/d. Achieved potassium excretion analysis also identified a U-shaped relationship. The BP-lowering effects of potassium supplementation were stronger in participants with hypertension and at higher levels of sodium intake. The BP increase with high potassium excretion was noted in participants with antihypertensive drug-treated hypertension but not in their untreated counterparts.

CONCLUSIONS: We identified a nonlinear relationship between potassium intake and both systolic and diastolic BP, although estimates for BP effects of high potassium intakes should be interpreted with caution because of limited availability of trials. Our findings indicate an adequate intake of potassium is desirable to achieve a lower BP level but suggest excessive potassium supplementation should be avoided, particularly in specific subgroups.

Key Words: blood pressure ■ dietary supplement ■ dose-response meta-analysis ■ potassium

Modification of dietary factors may affect the risk of cardiovascular diseases (CVDs).[1–3] A primary mechanism of action is through lowering blood pressure (BP), the most important major modifiable risk factor for CVD.[4–6] Both a lower sodium and a higher potassium intake have been associated with lowering of BP and a reduction in CVD.[7–10] The role of these elements in BP control has been studied extensively in laboratory and epidemiological studies.[5,11–13] In particular, experimental human studies (ie, randomized controlled trials [RCTs]) suggest that potassium supplementation may decrease BP,[14–17] particularly in adults with hypertension.[12] However, an accurate assessment of the potassium-BP dose-response relationship has not been possible because of a lack of biostatistical models to conduct flexible, curvilinear modeling of RCTs with only 2 levels of exposure (placebo and potassium supplementation).[12,18,19] This has also hampered the use of evidence on the BP effects of potassium in recent risk assessments of adequate potassium intake performed

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CLINICAL PERSPECTIVE

What Is New?

- Use of the new “1-stage” natural cubic spline model allowed, for the first time, pooling of experience in 2-arm randomized controlled trials to characterize the dose-response relationship between potassium supplementation and blood pressure (BP).
- Results of this dose-response meta-analysis suggested a nonlinear relationship that included BP reduction but also indicated that both low and high potassium intake may result in an increased level of BP, particularly but not exclusively in participants with hypertension.

What Are the Clinical Implications?

- There seems to be a U-shaped relationship between potassium intake and BP, which might explain reports of deleterious cardiovascular disease outcomes at low and high intakes of potassium, and suggests an optimal BP-lowering range for potassium intake.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CVD	cardiovascular disease
DBP	diastolic blood pressure
RCT	randomized controlled trial
RoB	risk of bias
SBP	systolic blood pressure

by the European Food Safety Authority and the US National Academy of Medicine.[13,19,20] These assessments have therefore focused on outcomes, such as stroke[21] and other CVD events,[14,19] although this evidence is limited by availability of only a relatively small number of studies that have used an observational design. In contrast, many RCTs have been conducted for estimation of the effect of potassium on BP. Some evidence has accrued from observational studies suggesting that a high potassium intake may increase the risk of hypertension,[22] stroke,[21] and CVD mortality.[23,24] This has resulted in some concern about the potential for long-term adverse effects of a high potassium intake in the general population.[23–29]

In this review, we aimed to assess the dose-response relationship between potassium intake and BP on the basis of use of a new biostatistical method,[30] which allowed us to use experimental studies based on comparisons of 2 levels of potassium exposure, as is typical in most RCTs. In addition, we sought to compare the results of our dose-response meta-analysis with corresponding assessments generated using conventional meta-analysis analytic techniques based on the assumption of a linear association between potassium intake and BP.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Literature Search

We conducted a literature search for articles published on or before March 14, 2020, using the PubMed database, with no language restriction. The research question was configured according to the Population, Exposure, Comparator(s), Outcomes, and Study Design statement and used the search terms “potassium” and “blood pressure.”[31] Details of the search strategy are provided in Table S1. Reference lists were screened to identify additional publications.

A study was considered eligible if: (1) it was performed in participants with hypertension (apart from secondary hypertension) or without hypertension; (2) exposure to potassium was assessed through use of either dietary questionnaires or urinary measurements; (3) the outcome of interest was systolic BP (SBP), diastolic BP (DBP), or both; (4) an experimental design and a minimum intervention duration of 4 weeks had been used, to ensure biological effect of the intervention, increase comparability with long-term habitual potassium intake, and provide consistently with recent systematic reviews[14,18,19]; (5) the intervention was performed using potassium-containing supplements, and not through dietary modification only or by administration of mixed interventions with other active components; and (6) measurements of urinary sodium and potassium excretion obtained before and after potassium supplementation were available. The trial results were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; http://www.covidence.org) for further assessment and data extraction. At least 2 authors reviewed all titles and abstracts independently. If they disagreed, the final decision was reached by a majority decision with the help of a third author.

Risk of Bias Assessment

We conducted an independent assessment of study quality using the risk of bias (RoB) assessment tool (2.0). The following 6 RoB domains were considered: (1) randomization process errors; (2) deviations from the intended interventions; (3) missing outcome data; (4) systematic errors in measurement of the outcome;

(5) bias in selection of the reported result. In addition, we included an evaluation of the (6) RoB related to use of a crossover study design, assessing the use of a washout period and whether the trial duration was at least 4 weeks. Each domain could be characterized as having a low RoB, some concerns, or a high RoB. A study was assigned an overall higher RoB if it was judged to be at higher risk for at least 1 domain, and an intermediate RoB when some concern existed for at least 1 of domains 1, 2, and 6, or for ≥2 domains 3 to 5.

Data Extraction

For each eligible study, the following data were extracted independently by 2 of the authors (M.I.K., T.F.) and confirmed by a third author (D.T.): first author name, publication year, country, duration of potassium intervention phase, number of participants and their characteristics (sex, age, hypertensive status, use of antihypertensive medication), study design, presence and duration of a washout period, modality of BP measurement, type and quantity of the potassium supplements, baseline and achieved potassium excretion level, sodium excretion at baseline and after the intervention, modification of sodium intake, and summary statistics of SBP and DBP levels (mean level in each group, active and control, for crossover studies or mean difference for parallel studies along with SD/SE).

Statistical Analysis

We performed a meta-analysis of SBP and DBP weighted mean differences before and after potassium supplementation for each study and for the relevant subgroups using a "1-stage" natural cubic spline regression model on the basis of a random effects model,[32] assessing heterogeneity with the I^2 statistic.[33] The 1-stage method, consisting of a weighted mixed effects model, was recently developed[30] and used in dose-response meta-analysis,[34,35] and it allowed us to make inferences about the average dose-response relationship between changes in potassium excretion attributable to supplementation or overall potassium excretion at the end of the trial and changes in SBP and DBP levels. The 1-stage approach allowed us to include trials based on 2 levels of exposure, as was the case for most of the trials included in our study. Having no specific parametric assumptions about the shape of the association, we used restricted cubic splines of potassium with 3 knots at fixed percentiles (10%, 50%, and 90%).[36] For comparison, we also used a linear function to model potassium intake in relationship to level of BP. Estimates of the parameters were obtained using restricted maximum likelihood.[30,36]

We defined the mean difference in potassium excretion between the arms of each RCT as the difference between the values of potassium excretion at the end of the trial and the ones at baseline in each arm. Likewise, we defined the mean difference in BP following the intervention as the difference for SBP and DBP at the end of the trial minus the corresponding baseline value.

In addition to the main analysis, we conducted stratified analyses based on study design (parallel versus crossover), hypertension status, use of antihypertensive medication (excluding normotensives), baseline potassium excretion (<75 and ≥75 mmol/d), position during BP measurement (supine, seated, standing, or other), type of BP measurement device (automatic or manual), baseline sodium excretion (<3, 3–4, or ≥4 g/d), and length of follow-up (≥12 weeks). In sensitivity analyses, we excluded trials at high risk for bias. We also reran the main analysis repeatedly, each time without one of the studies, to assess the missing study's influence on overall mean BP change, and we assessed the study-specific dose-response trends in comparison with the corresponding dose-response meta-analysis for all trials.

Publication bias was examined using funnel plots. We used Stata statistical software (Stata Corp, College Station, TX, 2019) for our data analysis, including the 1-stage approach based on the *drmeta* command.[37]

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search flowchart is presented in Figure 1. We retrieved 236 unique study articles, 144 of which were excluded on the basis of the article's title or abstract. Main reasons for exclusion were: nonexperimental design (including case reports), experimental studies where the intervention did not include potassium supplementation or where potassium was included in a mixed intervention with other active components, secondary hypertension, and animal and in vitro studies. Following full-text review, we excluded 60 of the remaining 92 articles because they were review articles, were reports based on a potassium supplementation phase <4 weeks, did not report on urinary excretion of potassium or sodium, did not provide BP levels, were not based on a potassium supplementation trial, and were duplicate reports or detailed studies confined to children.

The Table presents main characteristics of the 32 eligible trials in our meta-analysis.[38–70] The trials were published between 1982 and 2016. They included 1764 participants from Europe (N=17), America (N=7), Asia (N=4), Oceania (N=3), and Africa (N=1). All had been conducted in both sexes, with the exception of 2 that

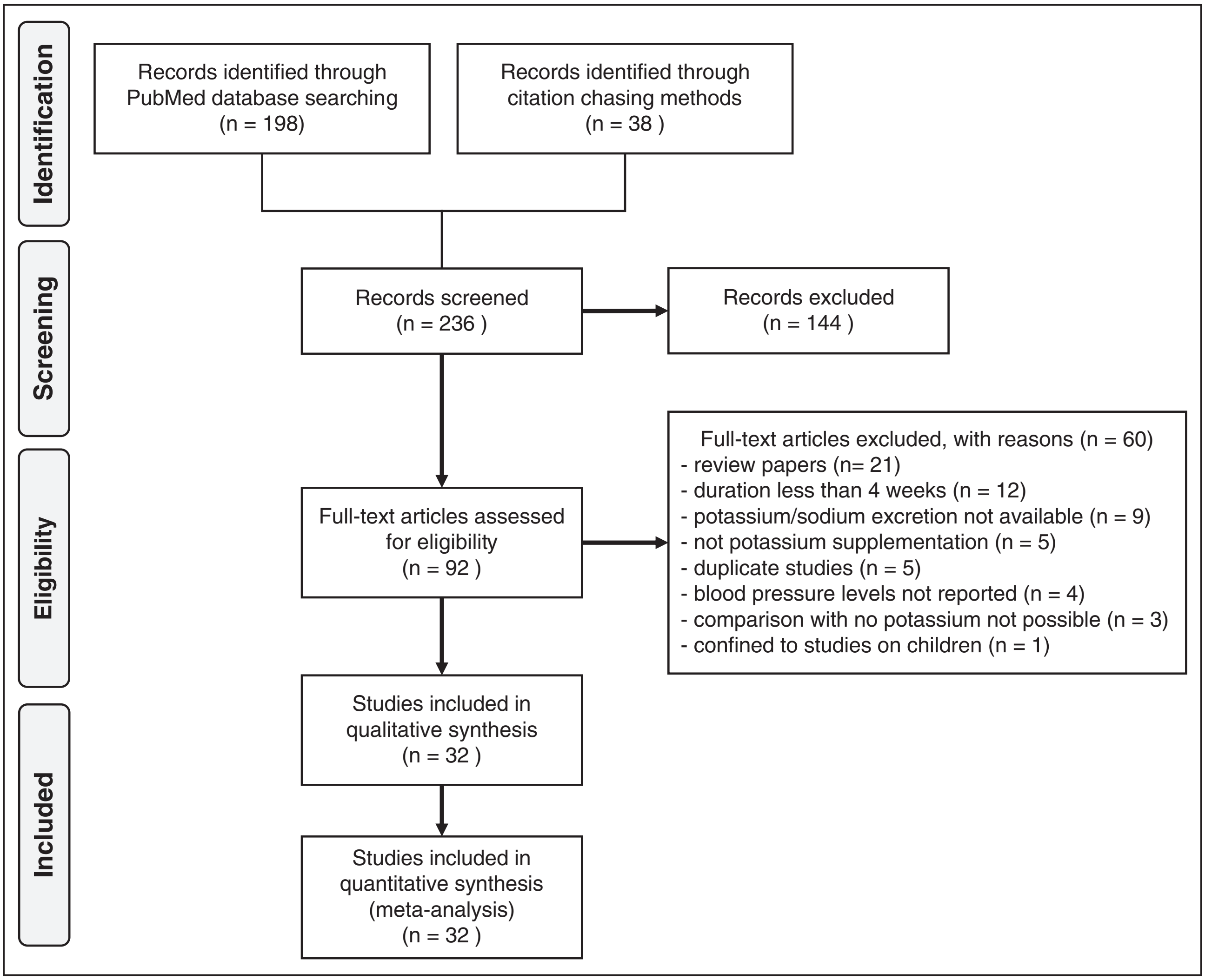

Figure 1. Flowchart of systematic literature search for trials published through March 14, 2020, that met the study inclusion and exclusion criteria.

were restricted to women and 1 to men. Participant age ranged from 18 to 79 years, with mean values between 24 and 75 years. Nine trials used a parallel design, whereas 23 were crossover studies, with 5 of the latter including a washout period of 1 to 5 weeks. Most (N=27) were conducted in participants with hypertension, in 6 of which prior treatment with antihypertensive medication (mainly β blockers, thiazide, or calcium channel blockers) was continued during the trial, whereas 4 trials were restricted to participants without hypertension. BP was measured using an automatic device (n=15), a manual device (N=13), or both (N=4). Potassium was administered in the form of potassium chloride (N=28), citrate (N=6), carbonate (N=2), aspartate (N=1), and/or glucoronate (N=1) at potassium doses that generally ranged from 30 to 120 mmol/d. All the trials had estimates of 24-hour potassium excretion in each study arm, both at baseline and at the end of the intervention. The achieved difference in potassium excretion at the end of the trial ranged from 17 to 131 mmol/d.

RoB assessment results are presented in Table S2, with reference to both single-item evaluation and overall RoB. Overall, we judged only 2 of the trials as having a high RoB.[43,56]

In the dose-response meta-analysis assessing effects of changes in potassium excretion between the control and supplemented groups on BP changes within each trial (Figure 2), we found that mean SBP and DBP levels decreased in the supplemented group with increasing differences in potassium excretion, up to a value of ≈30 mmol/d. At higher levels of supplementation, the decrease in BP was reduced, up to approximately a net difference in urinary potassium of 80 mmol/d. More substantial net differences in urinary potassium between the supplemented and unsupplemented participants resulted in an increase in both SBP and DBP. Increases of 30, 60, 90, and 120 mmol/d in

Table. Characteristics of the 32 Trials Studied

Reference	Year	Country	Duration of suppl. Phase	No. of Participants	Sex	Age, y (Mean)	Age, y (Range)	Design	Wash-out	Hyper-tension	Use of Anti-hyp. medi-cation	BP measure Device	BP Modality of Measure-ment	K Supple-ment	K Quantity	Modifi-cation of Na intake	Baseline uK	uK Suppl./uK Placebo	Achieved uK Difference
Barden 1986[40] (Gr1) (Gr2)	1986	Australia	4 wk	22 22	Women	32	18–55	Crossover	No	No	···	Automatic	Supine and standing	KCl	80	No	49 58	107/52 132/50	55 82
Berry 2010[39]	2010	United Kingdom	6 wk	48	Both	45	22–65	Crossover	≥5 wk	Yes	No	Automatic	Supine and ambulatory (24 h, awake and asleep)	K-cit	40	No	60	87/60	27
Braschi 2008[38]	2008	United Kingdom	6 wk	90 56 (26+30) t 34c	Both	35	22–65	Parallel	···	No	···	Automatic	Seated	KCl K-cit	30	No	72t 78t 72c	90/72 98/72	18 26
Bulpitt 1985[41]	1985	United Kingdom	12 wk	33 14t 19c	Both	55	···	Parallel	···	Yes	Yes	Manual and automatic	Mean of supine and standing	KCl	64	No	72t 61c	95/55	40
Chalmers 1986[42]	1986	Australia	4 wk	24 13t 11c	Both	52	···	Parallel	···	Yes	No	Automatic	Seated	KCl	64	No	71	110/76	34
Forrester 1988[43]	1988	Jamaica	4 wk	23	Both	···	>18	Crossover	No	Yes	Yes	Manual	Supine and standing	KCl	48	No	43	67/43	24
Fotherby 1992[44]	1992	United Kingdom	4 wk	18	Both	75	66–79	Crossover	No	Yes	No	Manual and automatic	Supine, standing and ambulatory (24 h, day-time and night-time)	KCl	60	No	63	99/60	39
Franzoni 2005[45]	2005	Italy	4 wk	104 52t 52c	Both	52	···	Parallel	···	Yes	No	Manual and automatic	Seated and ambulatory (24 h, daytime and nighttime)	K-asp	30	No	58t 55c	82/58	24
Gijsbers 2015[46]	2015	The Netherlands	4 wk	36	Both	66	···	Crossover	No	Yes	No	Automatic	Seated and ambulatory (24 h, daytime and nighttime)	KCl	38	Yes ↑	49	118/55	63
Graham 2014[47]	2014	United Kingdom	6 wk	40	Both	55	40–70	Crossover	2–4 wk	Yes	No	Automatic	Supine	KCl	64	No	79	104/87	17
Grimm 1988[48]	1988	Minnesota, United States	12 wk	198 148t 150c	Men	58	45–68	Parallel	…	Yes	Yes	Manual	Seated	KCl	96	No	82t 76c	150/76	74
Grobbee 1987[49]	1987	The Netherlands	6 wk	40	Both	24	18–28	Crossover	No	Yes	No	Manual	Supine	KCl	72	No	71	131/74	57
Gu 2001[50]	2001	China	12 wk	150 75t 75c	Both	56	···	Parallel	···	Yes	No	Manual	Seated	KCl	60	No	36t 36c	57/34	23
He 2010[70] KCl $KHCO_3$	2010	United Kingdom	4 wk	42	Both	51	18–75	Crossover	No	Yes	No	Automatic	Seated and ambulatory (24 h, daytime and nighttime)	KCl $KHCO_3$	64 64	No	80	122/77 125/77	45 48
Kaplan 1985[51]	1985	Texas, United States	6 wk	16	Both	49	35–66	Crossover	No	Yes	Yes	Manual	Supine	KCl	60	No	46	82/36	46

(Continued)

Table. Continued

Reference	Year	Country	Duration of suppl. Phase	No. of Participants	Sex	Age, y (Mean)	Age, y (Range)	Design	Wash-out	Hyper-tension	Use of Anti-hyp. medi-cation	BP measure Device	BP Modality of Measure-ment	K Supple-ment	K Quantity	Modifi-cation of Na intake	Baseline uK	uK Suppl./uK Placebo	Achieved uK Difference
Kawano 1998[52]	1998	Japan	4 wk	55	Both	···	36–77	Crossover	No	Yes	Yes	Manual and automatic	Supine and ambulatory (24 h, daytime and nighttime)	KCl	64	No	42	96/54	42
MacGregor 1982[53]	1982	England, United Kingdom	4 wk	23	Both	45	26–66	Crossover	No	Yes	No	Automatic	Supine and standing	KCl	60	No	56	118/62	56
Matlou 1986[54]	1986	South Africa	6 wk	32	Women	51	34–62	Crossover	No	Yes	No	Automatic	Seated	KCl	65	No	62	114/52	62
Matthensen 2012[55]	2012	Denmark	4 wk	21	Both	26	18–40	Crossover	No	No	···	Automatic	Ambulatory	KCl	100	No	76	168/76	92
Miller 1987[56]	1987	Indiana, United States	4 wk	64	Both	42	···	Crossover	No	No	···	Manual	Seated	K-cit K-gluc	60	No	59	82/59	23
Overlack 1985[57]	1985	Germany	8 wk	17	Both	29	22–39	Crossover	No	Yes	No	Manual	Supine and standing	KCl	96	No	66	153/71	82
Overlack 1991[58]	1991	Germany	8 wk	12	Both	37	25–59	Crossover	No	Yes	No	Manual	Seated	K-cit and $KHCO_3$	120	No	74	167/62	105
Overlack 1995[59] KCl K-cit	1995	Germany	8 wk	25 25	Both	48	24–70	Crossover	4 wk	Yes	No	Automatic	Seated	KCl K-cit	120	No	94	202/94 225/94	108 131
Patki 1990[60]	1990	India	8 wk	37	Both	50	···	Crossover	2 wk	Yes	No	Manual	Supine and standing	KCl	60	No	62	82/60	22
Richards 1984[61]	1984	New Zealand	4 wk	12	Both	···	19–52	Crossover	No	Yes	No	Automatic	Supine, standing and intra-arterial 24-h measure	KCl	140	Yes ↓	62	185/62	123
Siani 1987[62]	1987	Italy	15 wk	37 18t 19c	Both	45	21–61	Parallel	···	Yes	No	Manual	Supine and standing	KCl	48	No	57t 62c	87/57	30
Skrabal 1984[63] (Gr1) (Gr2)	1984	Austria	4 wk	21 9 12	Both	32 45	21–46 28–69	Crossover	No	Yes	No yes	Manual	Supine, seated and standing	KCl	40	Yes ↓	80 65	117/80 82/65	38 17
Smith 1985[64]	1985	England, United Kingdom	4 wk	20	Both	53	30–66	Crossover	No	Yes	No	Automatic	Supine and standing	KCl	64	Yes ↓	72	117/67	50
Sundar 1985[65]	1985	India	4 wk	50 25t 25c	Both	46	···	Parallel	···	Yes	No	Manual	Supine	KCl	60	No	57t 55c	81/56	25
Valdes 1991[66]	1991	South America (Chile)	4 wk	24	Both	50	···	Crossover	No	Yes	No	Automatic	Supine and standing	KCl	64	No	57	123/55	68
Vongpatanasi 2016[67]	2016	Texas, United States	4 wk	30	Both	54	···	Crossover	1 wk	Yes	No	Automatic	Office, 24-h average, daytime and nighttime	K-cit KCl	40	No	58	84/58 95/58	26 37
Whelton 1995[68,69]	1995	North America	4 wk	353 178t 175c	Both	26	30–54	Parallel	···	No	No	Manual	Seated	KCl	60	No	59	97/55	42

Values of potassium levels are reported in mmol/d (only integers). BP indicates blood pressure; c, control group; Gr1, group 1; Gr2, group 2; K-asp, potassium aspartate; K-cit, potassium citrate; KCl, potassium chloride; K-gluc, potassium gluconate; $KHCO_3$, potassium bicarbonate; and t, treated group.

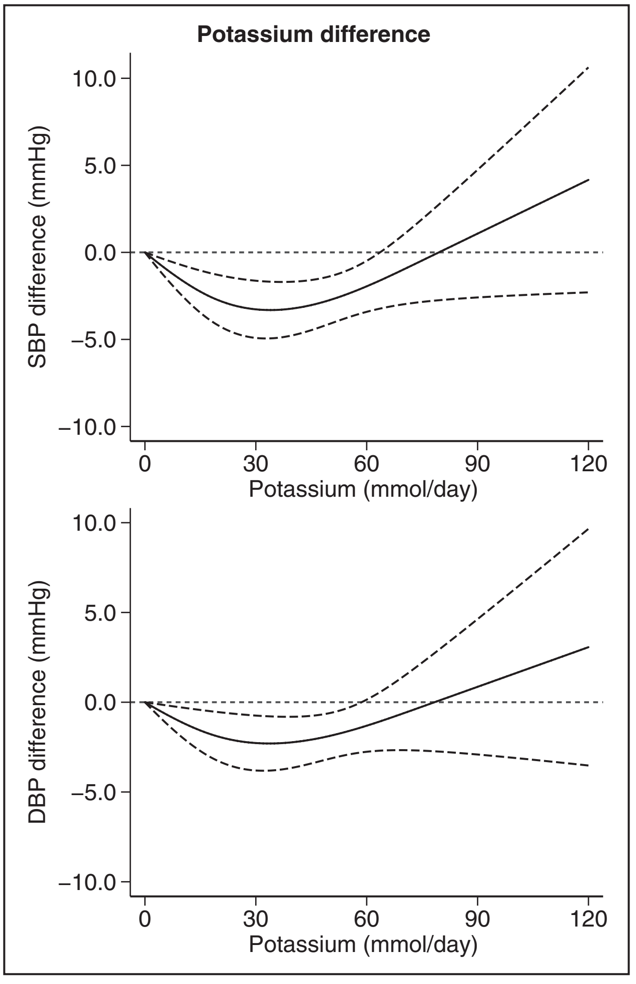

Figure 2. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mm Hg), according to differences in potassium excretion between the treatment arms (potassium supplemented and control group) at the end of the trials.
All studies included (N=32). Spline curve (solid line) with 95% confidence limits (long dashed lines).

net urinary potassium excretion differences between the supplemented and unsupplemented participants resulted in SBP changes of −3.3 (95% CI, −4.9 to −1.6), −2.0 (95% CI, −3.4 to −0.5), 1.1 (95% CI, −2.9 to 4.7), and 4.2 (95% CI, −2.3 to 10.6) mm Hg, respectively. For DBP, the corresponding changes were −2.3 (95% CI, −3.8 to −0.7), −1.3 (95% CI, −2.8 to 0.1), 0.86 (95% CI, −2.9 to 4.6), and 3.1 (95% CI, −3.5 to 9.7) mm Hg, respectively.

When we superimposed the average predicted mean difference in BP estimated according to a linear function into the dose-response graph, it showed an inverse association between potassium supplementation and both SBP and DBP (Figure S1). A forest-plot meta-analysis comparing BP levels in the supplemented and referent groups identified a mean difference of −3.9 (95% CI, −5.2 to −2.6) and −2.4 (95% CI, −3.8 to −1.1) mm Hg for SBP and DBP, respectively (Figure S2).

Figure 3 presents the BP difference in our dose-response meta-analysis on the basis of achieved potassium excretion at the end of the trial, using as a reference point a potassium excretion of 90 mmol/d (3500 mg/d). The SBP and DBP change remained constant in the range of 90 to 150 mmol/d of achieved potassium excretion. Below these ranges of achieved potassium excretion, the intervention effects on BP were unfavorable, and a weak BP increase also appeared to occur at >150 mmol/d. A potassium excretion of 30, 60, 120, 150, and 180 mmol/d resulted in SBP changes of 9.1 (95% CI, 4.6–13.5), 3.9 (95% CI, 2.1–5.8), −0.9 (95% CI, −1.6 to −0.2), −0.2 (95% CI, −2.2 to 1.8), and 0.7 (95% CI, −2.9 to 4.2) mm Hg, respectively, compared with the SBP associated with an excretion of 90 mmol/d. The corresponding DBP changes were 5.3 (95% CI, 0.9–9.7), 2.3 (95% CI, 0.5–4.1), −0.4 (95% CI, −1.5 to 0.7), 0.2 (95% CI, −3.0 to −3.3), and 0.8 (95% CI, −4.6 to 6.2). Again, as for the analysis based on the BP effects of difference in potassium excretion between the 2 exposures, the predicted mean SBP and DBP difference on the basis of a linear regression function shows an inverse association with achieved potassium intake (Figure S1).

When we excluded the studies deemed to have a high RoB, the dose-response analysis yielded similar results of that generated using the entire data set (Figures S3 and S4). We repeated the main analysis after systematically excluding each study in turn from the meta-analysis, and no appreciable variation to the overall mean change in BP was noted (Figures S5 and S6). Similarly, a sensitivity analysis showing variation of the shape across studies identified study-specific trends that were generally similar to the overall dose-response meta-analysis (Figures S7 and S8).

As reported in Figure 4, dose-response analysis according to hypertension status, after removing trials performed in “mixed” samples with normal and high BP, showed a small decrease in mean BP levels associated with an increased potassium excretion up to 20 to 30 mmol/d in both normotensive and hypertensive trials, although in the latter the hypotensive effect of potassium was larger and occurred within a larger range of higher potassium excretion in supplemented participants (up to 90 mmol/d, versus a threshold of 60 mmol/d in those with no hypertension). For the increased BP levels following high amounts of potassium supplementation in participants with hypertension (Figure 5), it was considerably more evident in those receiving pharmacological treatment (starting at ≈60 mmol/d of difference in potassium excretion for the supplemented participants) compared with their counterparts not taking medications, for whom the BP increase started to occur at ≈110 mmol/d of excess

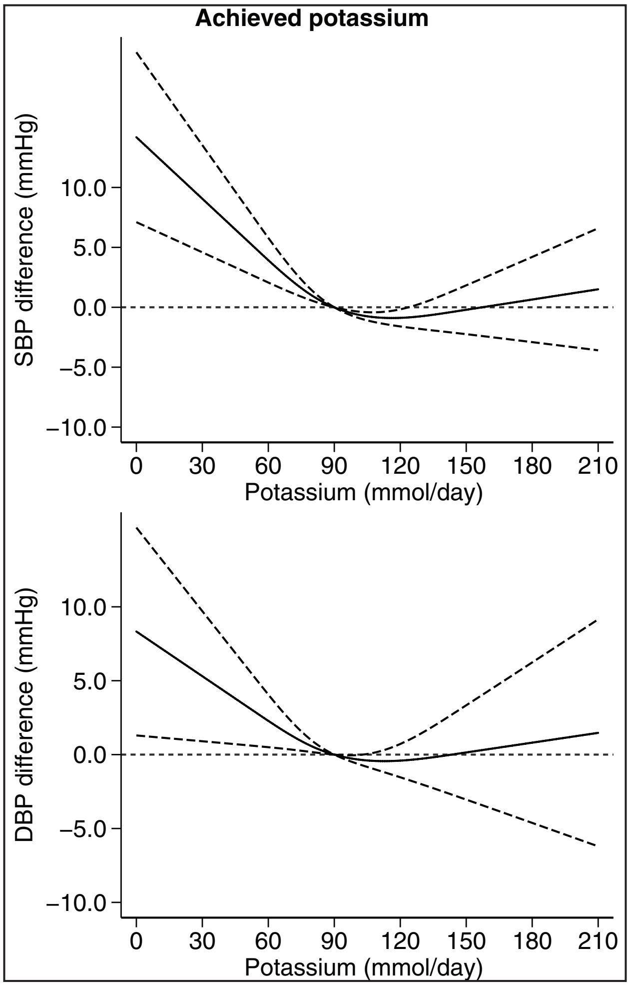

Figure 3. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mm Hg), according to achieved potassium excretion levels between arms (potassium supplemented and control group) at the end of the trials.
All studies included (N=32). Spline curve (solid line) with 95% confidence limits (long dashed lines).

potassium excretion. Further investigations to explore the effect of different antihypertensive treatment could not be performed because the original data did not report such stratified analyses by type of medication.

When we performed a conventional forest plot analysis, it showed a larger BP decrease following potassium supplementation in those with compared with those without hypertension (Figure S9). Among those with hypertension, potassium supplementation was on average more effective in lowering BP in participants not using antihypertensive medication compared with those receiving antihypertensive drug treatment (Figure S10). Considering the effects of achieved potassium excretion according to hypertension status and using 90 mmol/d as the reference value (Figure 6), in those in the normal BP category, we observed increasing BP levels for decreasing potassium exposure below the reference value, whereas >90 mmol/d DBP slightly increased while this did not occur for SBP. In participants with hypertension, the range of 90 to 120 mmol/d was associated with the lowest BP values, whereas above and much more strongly below this range, both SBP and DBP increased. In this subgroup, taking or not antihypertensive drugs did not appear to be associated with major changes in the effect of achieved potassium intake on BP levels (Figure 7).

In an analysis stratified by trial design (crossover versus parallel), the dose-response analysis showed a larger BP decrease in the latter group, but there was a higher increase in BP in those receiving the largest supplementation, starting at approximately a higher excretion of ≈30 mmol/d, in either the overall population or those with hypertension (Figures S11 and S12). The corresponding forest plot analysis showed a larger BP decrease in the crossover studies, in the total sample and analyses restricted to those with hypertension (Figures S13 and S14).

In a dose-response analysis based on pretreatment potassium excretion, a larger effect on mean BP difference was noted in the studies with a urinary potassium <75 mmol/d (Figure S15). Corresponding forest plot analyses showed a consistent pattern of a slightly higher BP-lowering effect (Figure S16).

Dose-response analyses stratified by increasing level of baseline sodium excretion showed that potassium supplementation had different effects on BP values, according to level of sodium excretion (Figure 8), as depicted in the forest plot analysis (Figure S17). Both the lowering and the enhancing effects on BP induced by potassium supplementation were much weaker in the bottom category of sodium intake, <3000 mg/d, particularly for DBP, whereas in the intermediate category of sodium exposure, the threshold from shifting from a BP-lowering effect into a BP-enhancing effect was ≈80 mmol/d of supplemental potassium excretion for SBP and 60 mmol/d for DBP. The highest category of sodium exposure showed the largest decrease of both SBP and DPB, with no evidence of any BP increase, even for the highest amount of potassium supplementation.

The modalities of BP measurement associated with the largest decreases were when BP was measured in the supine and standing positions, and when a manual device was used (Figures S18 through S21).

Analyses restricted to trials with a duration of ≥12 weeks (N=5) are shown in Figure S22. The analysis based on the amount of supplemental potassium showed a comparable trend to that observed in the entire set of studies, although there was evidence of an increased BP-enhancing effect at a lower level of excess potassium exposure (ie, for <60 mmol/d of potassium difference between intervention and control arms), whereas this occurred at >60 mmol/d in

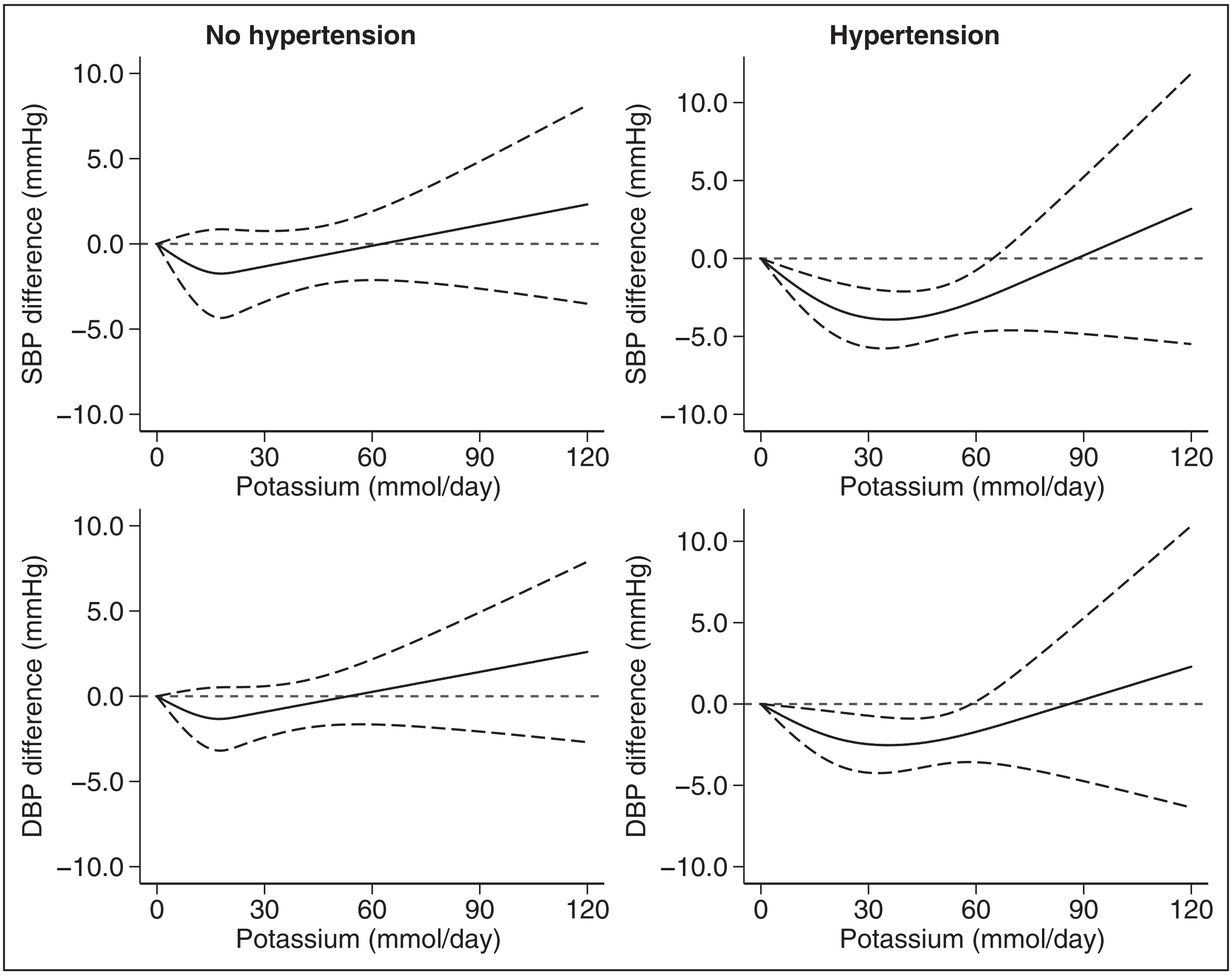

Figure 4. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mm Hg), according to differences in potassium excretion between the treatment arms at the end of the trials in participants with no hypertension (N=5) and with hypertension (N=27).
Spline curve (solid line) with 95% confidence limits (long dashed lines).

the entire data set (Figure 2). For the analysis based on achieved potassium excretion at the end of the trial, the results of this subgroup analysis based on the longest duration studies showed that 90 mmol/d of potassium excretion was the amount associated with the most favorable effects on both SBP and DPB, with slightly lower estimates compared with the entire set of studies (Figure 3). However, in this subset of studies, there was no indication of an effect of high potassium intake in increasing DBP, which was different from what was observed in the entire set of studies. However, the effect estimates yielded by these analyses were statistically imprecise, because of the considerably lower number of studies compared with the overall trials available.

Funnel plots provided slight evidence of an asymmetric distribution for SBP (Figure S23), suggesting the possible occurrence of some publication bias. However, no such evidence emerged for DBP, thus reducing the likelihood of a major publication bias.

DISCUSSION

The end point most investigated in studies assessing the relationship between potassium exposure and human health is BP. This is also the only end point for which a large number of experimental human studies are available, generally in the form of RCTs with either a crossover or a parallel design, this being the study design with the strongest level of evidence with reference to the risk of exposure misclassification and confounding.

Despite apparently strong evidence that potassium supplementation decreases SBP and DBP,[12,14,18,71] the exact dose-response of the association has not been well established.[13] The main reason for this is lack of a valid method for assessing dose-response in the

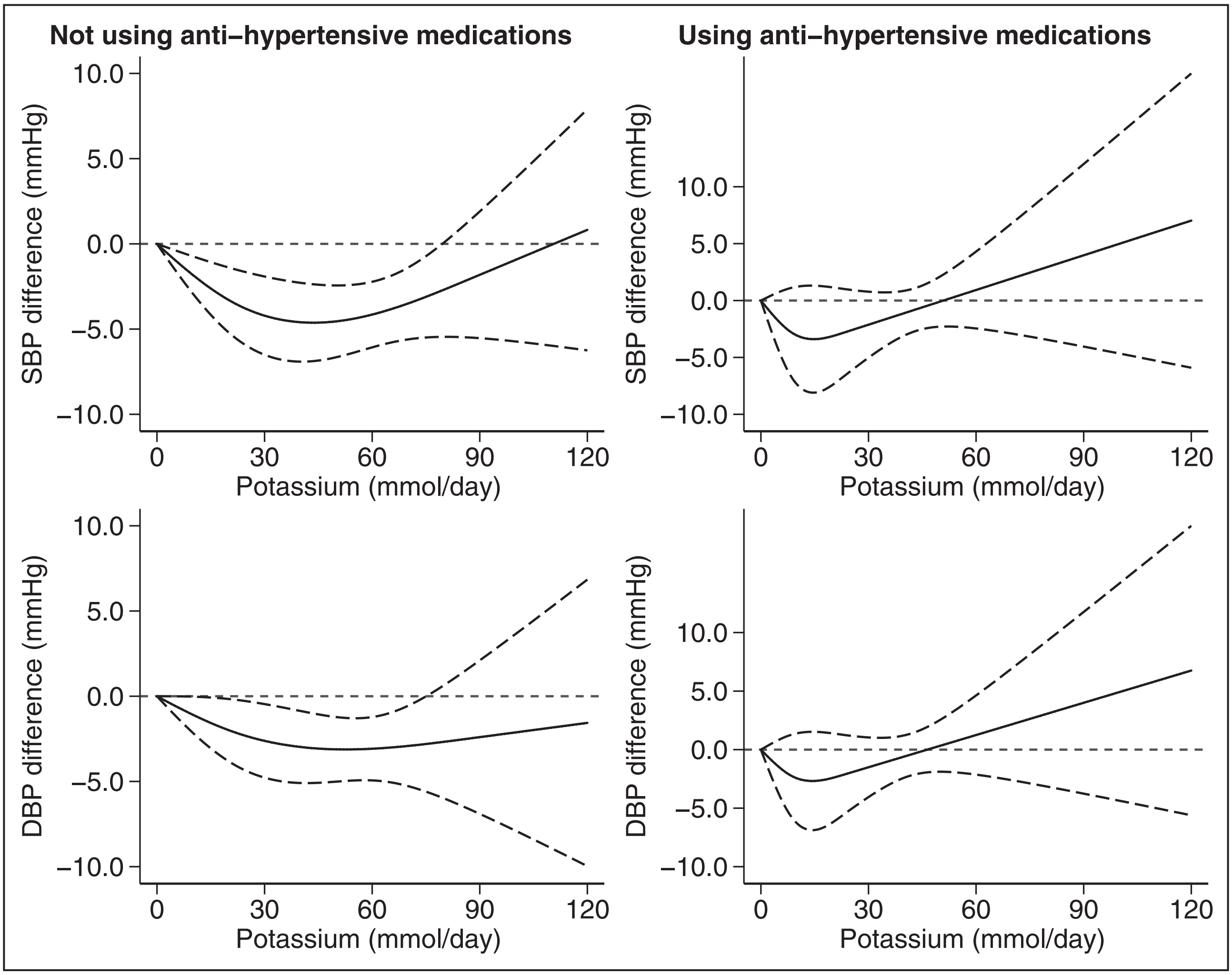

Figure 5. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mm Hg), according to differences in potassium excretion between the treatment arms at the end of the trials in subjects with hypertension not taking antihypertensive medications (N=22) and using antihypertensive medications (N=6). Spline curve (solid line) with 95% confidence limits (long dashed lines).

commonly used 2-arm trial design that compares participants assigned to potassium supplementation or placebo. The biostatistical tools previously available for randomized comparison of dose-response effect required at least 3 levels of exposure within each trial (independent of trial design), to allow calculation of a flexible, nonlinear dose-response relationship between the exposure of interest and the outcome.[19] This limitation has substantially hampered the use of human experimental studies for the accurate risk assessment of potassium supplementation,[13] in both the general population and selected subgroups, such as those with or at high risk for hypertension. Attempts have been made to assess the dose-response relationship between potassium intake and BP with meta-regression models based on the assumption of a “straight-line relationship”[18] or forest plots based on comparison of the highest versus lowest intake levels, which in addition compare heterogeneous exposure categories.[14] Unfortunately, none of these approaches allows detection and assessment of nonlinear dose-response relationships.

By using a new “1-stage” model that allows for inclusion of trials with only 2 levels of exposure, as is the case for most RCTs, we detected a dose-response curve for the BP effects of potassium that was curvilinear across a wide range of treatment differences and absolute values of potassium exposure. This may have major implications in the risk assessment of potassium supplementation. Our finding of a U-shaped relationship between potassium intake and BP was somewhat unexpected on the basis of previous clinical trial meta-analyses and assessments. Although it confirms previous reports that a minimum dose of potassium is necessary for a BP-lowering effect of potassium supplementation, it also suggests that high

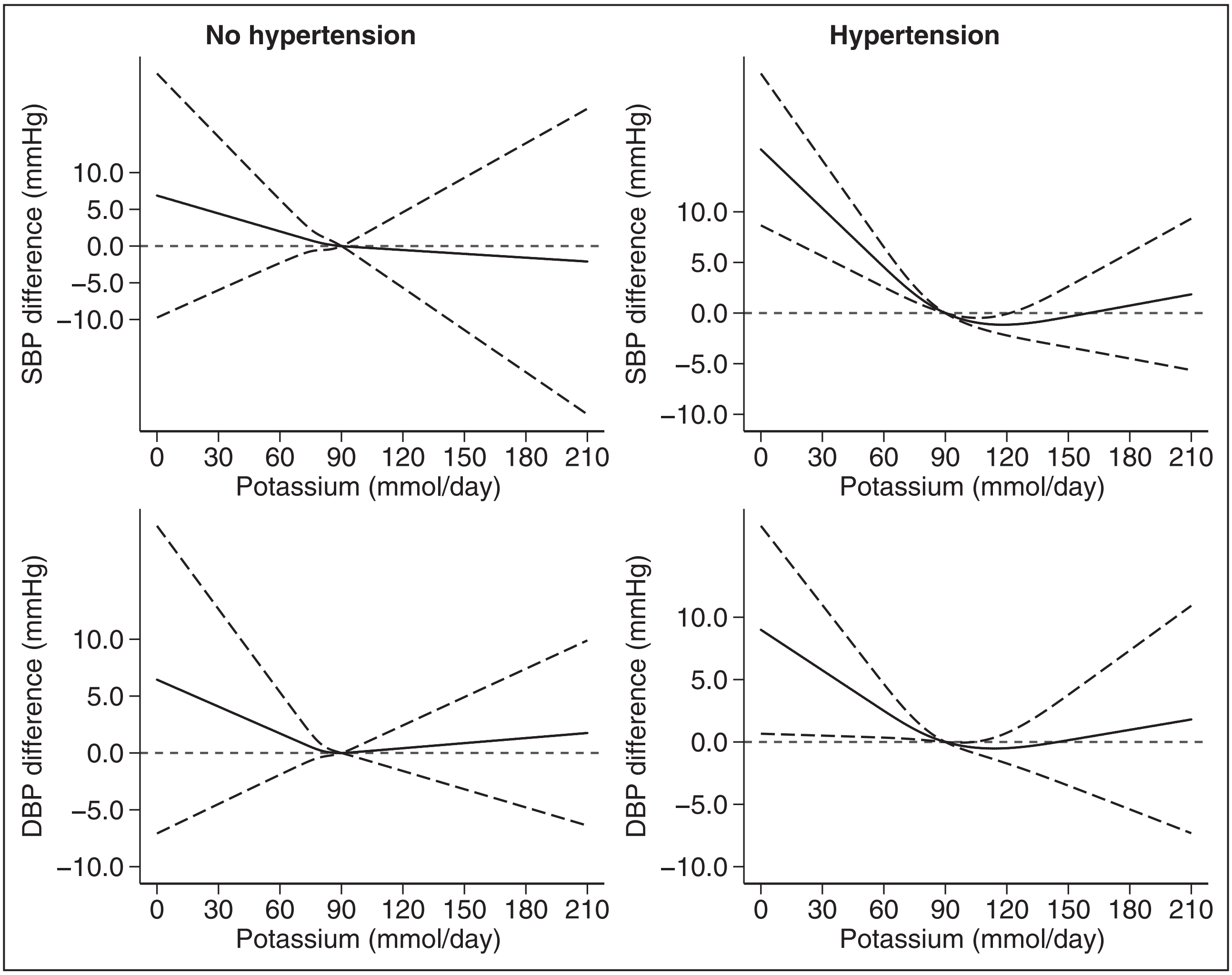

Figure 6. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mm Hg), according to achieved potassium excretion levels between arms at the end of the trials in participants with no hypertension (N=5) and with hypertension (N=27).
Spline curve (solid line) with 95% confidence limits (long dashed lines).

doses of potassium may result in a higher level of BP. The BP-increasing effect of high potassium exposure was observed in both our overall results and the subgroup analyses of participants with hypertension or a normal level of BP, although being stronger in the former group. The optimal levels of "supplemental" (net difference between the 2 arms) and overall (achieved) potassium excretion appeared to be 30 and 90 to 130 mmol/d (1200 and 3500–5100 mg/d), respectively. The corresponding intakes would be higher (ie, by using the generally adopted conversion factor of 1.3,[20,21,72–74] ≈1500 mg/d of supplemental potassium and an overall intake of 4500–6500 mg/d). However, these estimates are based on a heterogeneous population mainly composed by adults with hypertension, and therefore not necessarily representing the general population. In addition, the estimates are based on experience in trials that disproportionally represent short-term interventions. Estimates for those with a normal level of BP are lower than the aforementioned ones (ie, ≈800 mg/d of supplemental potassium and 4500 mg/d of total potassium intake), and these figures are consistent with those yielded by the trials of longer duration.

On the basis of the most recent observational epidemiologic literature, a tendency toward a U-shaped effect of potassium supplementation on BP was not entirely unexpected. In a recent dose-response meta-analysis of nonexperimental epidemiologic studies, potassium intake appeared to have a dual relationship with the risk of stroke, lower at up to an intake of ≈90 mmol (3500 mg)/d, and higher at high levels.[21] This pattern was noted both in BP adjusted and unadjusted analyses. In a Chinese community cohort study, participants with the lowest and highest intake of potassium had an increased risk of hypertension,

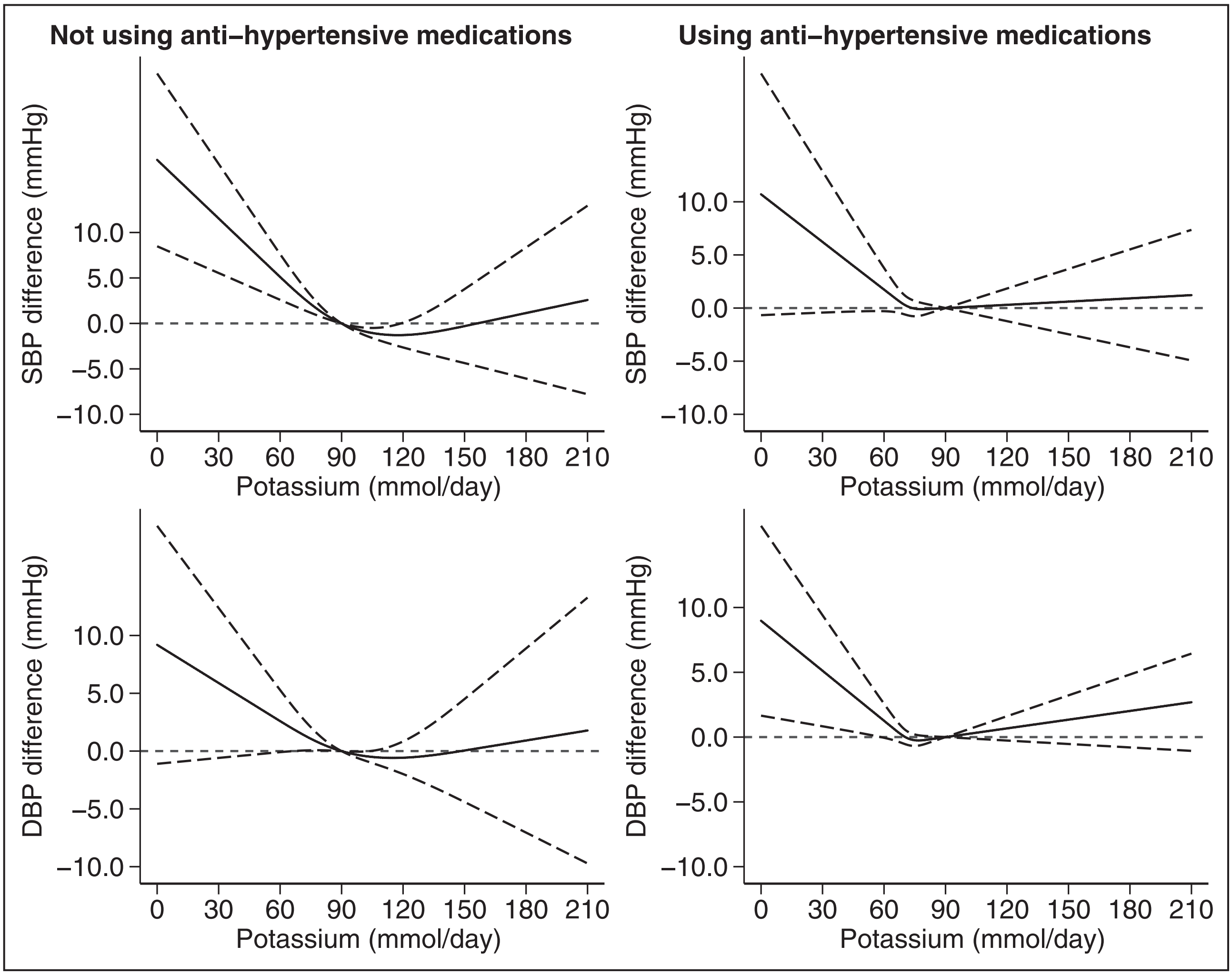

Figure 7. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mm Hg), according to achieved potassium excretion levels between arms at the end of the trials in participants with hypertension not taking antihypertensive medications (N=22) and using antihypertensive medications (N=6).
Spline curve (solid line) with 95% confidence limits (long dashed lines).

although the increase was much higher in the latter group,[22] thus suggesting that both rather low and high intakes of potassium may adversely affect BP levels. In the FHS (Framingham Heart Study), those with a higher level of serum potassium progressed to a higher level of BP or directly to hypertension during a 4-year period of follow-up,[75] with a J-shaped association for women and a U-shaped association for men. However, participants with a potassium level >6.3 mmol were excluded, and the authors dismissed their results as being not "statistically significant." In the BRHS (British Regional Heart Study), baseline potassium levels were positively associated with excess mortality, including increased CVD mortality.[76] Results from the National Health and Nutrition Examination Survey I also showed higher CVD mortality for participants in the highest category of baseline serum potassium compared with the intermediate one, with the lowest exposure category also showing a (slightly) increased risk of death.[77] In addition, the possibility that chronic hyperkalemia, usually defined on the basis of the general population distribution, has a U-shaped association with general mortality is now being acknowledged[24,25] and has been a source of some concern, on the basis of the consistent results of several cohort studies performed in diseased, high-risk or healthy participants.[28,78–82]

The public health implications of our findings of a U-shaped relationship between potassium excretion and BP levels appears to be considerably more important for a potassium intake that is too "low" rather than too "high," also recognizing that the situation is different in clinical practice, where risk associated with hyperkaliemia has a different pattern[11,24] and therapy.[83] In fact, potassium intake even in "acculturated" populations with an adequate diet tends to be lower, and sometimes much lower, than the adequate intake identified and recommended by risk

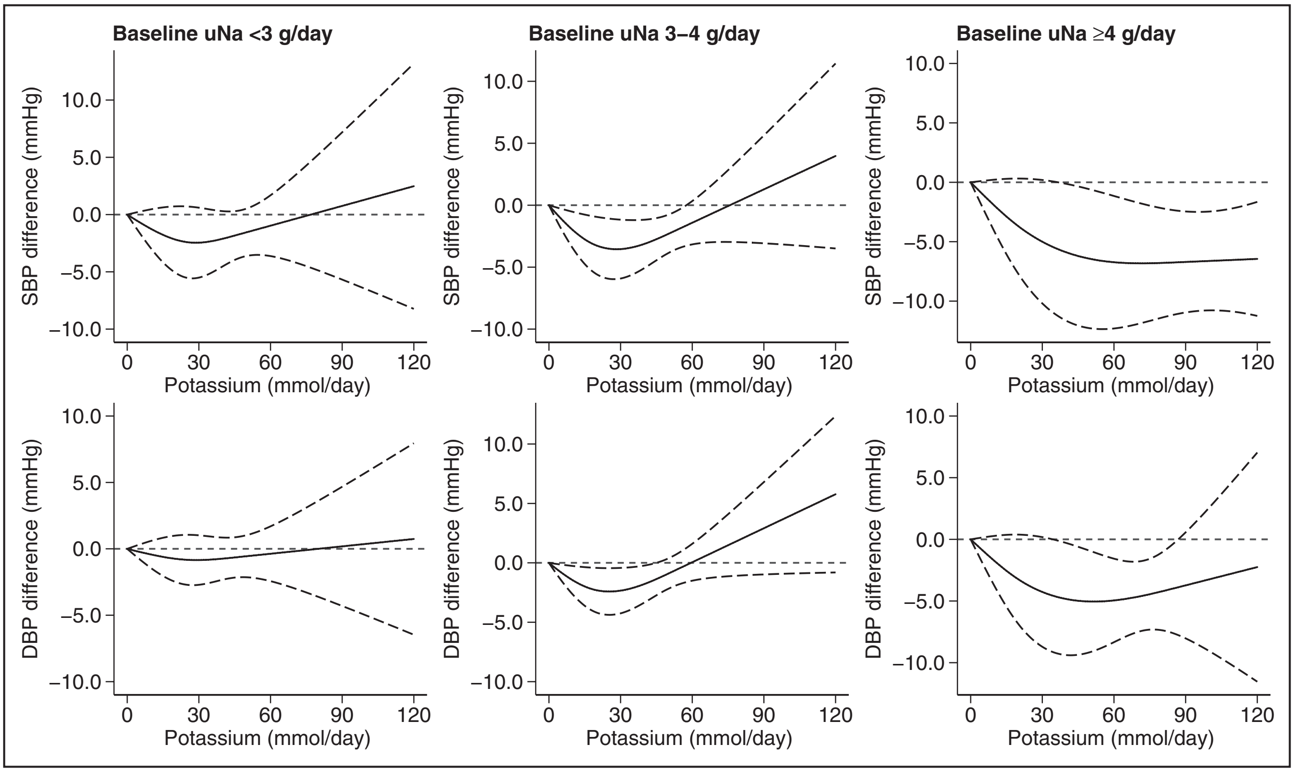

Figure 8. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mm Hg), according to studies with baseline sodium (uNa) <3 g/d (N=8), between 3 and 4 g/d (N=17), and ≥4 g/d (N=9). Spline regression curve (solid line) with 95% confidence limits (long dashed lines).

assessment agencies, public health authorities, and professional societies.[13,20,84] Therefore, dietary advice to increase potassium intake is likely to have beneficial effects and result in decreased BP levels in most populations. On the other hand, some populations and some selected subgroups and particularly some individuals (namely, those with hypertension treated with antihypertensive medication), if having a high baseline potassium intake, should be advised not to exceed the potassium intake levels found to be optimal in this meta-analysis. This may also be true for individuals with low-to-intermediate sodium intake, because our analysis also suggests that those with a high sodium intake, as is typical in Western populations,[85–87] benefit disproportionately from potassium supplementation and may also be more resistant to the BP increase following administration of a high potassium intake, suggesting an interaction between the 2 minerals. In addition, the number of studies was not enough to allow us to perform more detailed stratified subgroup analyses based on presence or absence of hypertension status and category of sodium intake, thus preventing us from verifying the presence of a possible interaction between hypertension status and sodium intake. Our BP estimates for the BP effect of a high potassium intake had wide CIs, making them less certain than BP effects at lower intakes of potassium, because of the small number of studies with relevant information at higher intakes of potassium and the resulting statistical imprecision of the effect estimate. In addition, the results based on achieved potassium excretion yielded little evidence of an increase in BP following a high potassium intake, further calling for caution about the effects of high intake of potassium on BP.

Our results also provide support for the population goals for potassium intake recently set by international authorities, such as the 90 mmol/d (3500 mg/d) adequate intake adopted by the European Food Safety Authority[20] and the 87/66 mmol/d (3400–2600 mg/d) in men/women, recommended by the US National Academy of Medicine,[13] based on the outcome of observational studies on potassium intake and several health end points, such as the risk of stroke for the adequate intake set by the European Food Safety Authority.

There is strong biological plausibility for a decrease in BP with a low intake of potassium, and some evidence to support an increase in BP at high levels of intake. Several experimental studies in laboratory settings and in animals have identified several mechanisms that may explain the BP-lowering effect of potassium supplementation.[88–90] Conversely, a high potassium intake could favor sodium excretion and an increase in renin activity and aldosterone levels, also dependent on preexisting electrolyte balance.[11,91–95]

Limitations of our meta-analysis and of the underlying studies include the fact that most of the trials included were of relatively short duration, including both the period of supplementation and follow-up (median, 4 weeks). Despite exclusion of trials with <4 weeks of potassium supplementation and follow-up, which may not reflect the long-term effects of habitual potassium intake also attributable to the physiological adaptations that occur over time as a general response to dietary habits, extrapolation of our overall results to long-term effects of potassium intake should still be made with caution. However, our analysis, restricted to the studies with the longest duration, yielded similar results and provides some reassurance that our findings may be extrapolated to longer periods of intake and therefore be more readily applicable to the general population. Also, our results, particularly in stratified analyses, were affected by statistical imprecision, particularly for the highest intakes of potassium and the longest duration of follow-up, because of limited availability of studies in these settings.

In conclusion, this is the first meta-analysis to investigate the effects of potassium supplementation on BP levels and with a specific focus on the dose-response relationship. We found evidence for a nonlinear association, and for effect modification in those with hypertension, taking antihypertensive medication, or having a high sodium intake. Our findings for the effects of potassium intake on BP may explain, at least in part, the recently observed U-shaped associations between serum potassium levels and risk of adverse outcomes in observational studies. They also support current European and US dietary recommendations for potassium intake and underscore the need to carefully address and manage potassium intake within comprehensive efforts to prevent CVD in both the general population and high-risk subgroups.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

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SUPPLEMENTAL MATERIAL

Table S1. **PubMed search strategy for potassium supplementation and blood pressure levels in experimental studies.**

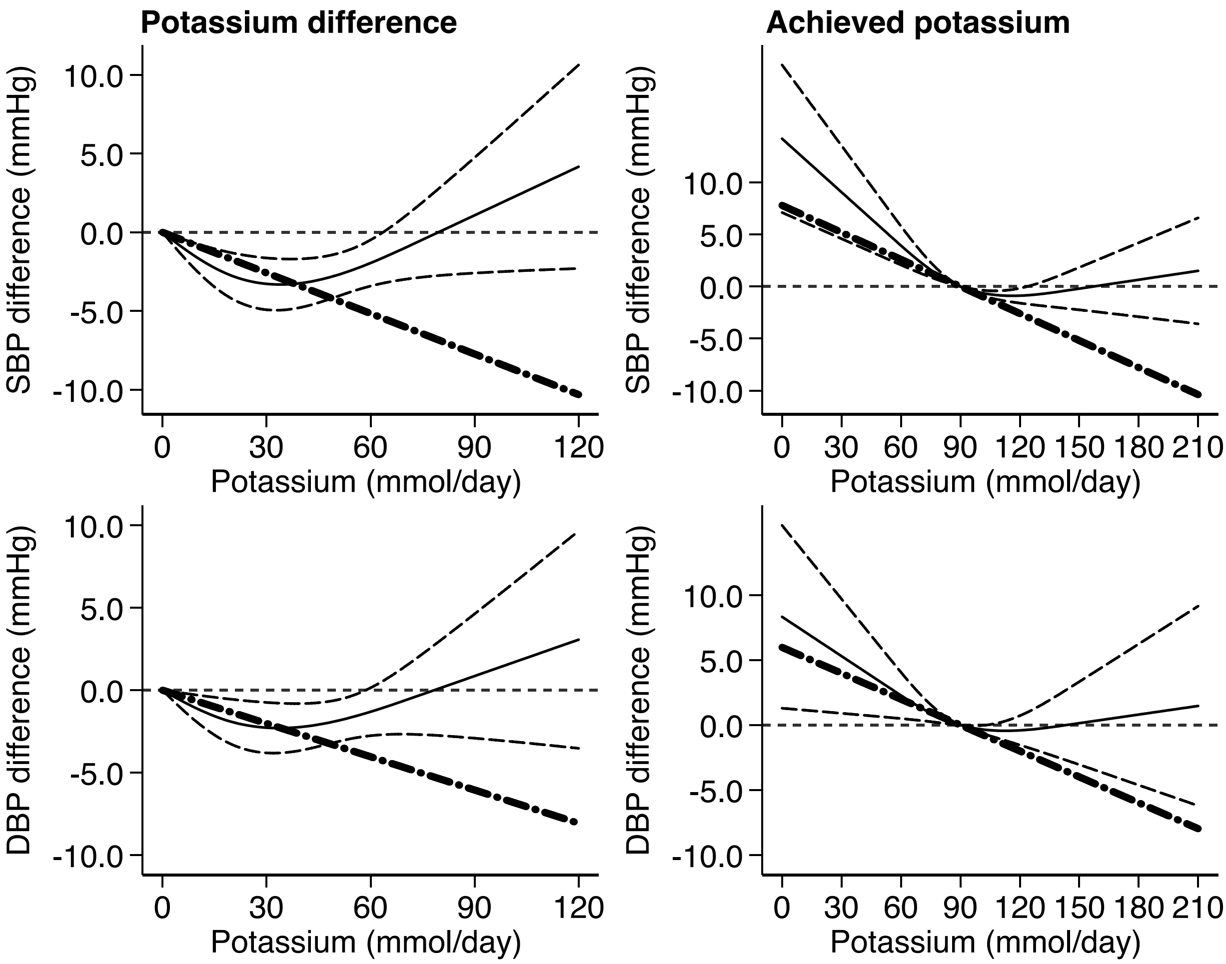
Database	**Search strategy**
PubMed	((“blood pressure”[MeSH Term] OR “blood pressure determination”[MeSH Term] OR “arterial pressure”[MeSH Term]) OR “hypertension”[MeSH Term] OR “blood pressure”[tiab] OR “hypertension”[tiab]) AND (“potassium, dietary”[MeSH Term] OR “potassium”[MeSH Term] OR “potassium chloride”[MeSH Term] OR “potassium”[tiab] OR “potassium chloride”[tiab]) AND (“dietary supplements”[MeSH Term] OR “supplement”[tiab]) NOT (“animals”[MeSH Term] NOT “humans”[MeSH Term])

Table S2. Risk of bias of included studies.

References	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domani 6	Overall RoB
Barden 1986[40]	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Berry 2010[39]	Some Concerns	Low	Low	Low	Some Concerns	Low	Some Concerns
Braschi 2008[38]	Low	Low	Low	Low	Low	Low	Low
Bulpitt 1985[41]	Some Concerns	Low	Low	Low	Some Concerns	Low	Some Concerns
Chalmers 1986[42]	Some Concerns	Low	Low	Low	Low	Low	Some Concerns
Forrester 1988[43]	High	Low	Low	Low	Some Concerns	Some Concerns	High
Fotherby 1992[44]	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Franzoni 2005[45]	Some Concerns	Low	Low	Low	Some Concerns	Low	Some Concerns
Gijsbers 2015[46]	Low	Low	Low	Low	Low	Some Concerns	Some Concerns
Graham 2014[47]	Low	Low	Low	Low	Low	Low	Low
Grimm 1988[48]	Low	Low	Low	Low	Low	Low	Low
Grobbee 1987[49]	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Gu 2001[50]	Low	Low	Low	Low	Some Concerns	Low	Low
He 2010[94]	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Kaplan 1985[51]	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Kawano 1998[52]	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
MacGregor 1982[53]	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Matlou 1986[54]	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Matthensen 2012[55]	Some Concerns	Low	Low	Low	Some Concerns	Low	Some Concerns
Miller 1987[56]	High	Low	Low	Low	Some Concerns	Low	High
Overlack 1985[57]	Some Concerns	Some Concerns	Low	Low	Some Concerns	Some Concerns	Some Concerns
Overlack 1991[58]	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Overlack 1995[59]	Some Concerns	Low	Low	Low	Some Concerns	Low	Some Concerns
Patki 1990[60]	Low	Low	Low	Low	Some Concerns	Low	Low
Richards 1984[61]	Some Concerns	Low	Some Concerns	Low	Some Concerns	Some Concerns	Some Concerns
Siani 1987[62]	Low	Low	Low	Low	Some Concerns	Low	Low
Skrabal 1984[63]	Some Concerns	Low	Low	Some Concerns	Some Concerns	Some Concerns	Some Concerns
Smith 1985[64]	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Sundar 1985[65]	Some Concerns	Low	Low	Low	Some Concerns	Low	Some Concerns
Valdes 1991[66]	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Vongpatanasin 2016[67]	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Whelton 1995[68, 69]	Low	Low	Low	Low	Some Concerns	Low	Low

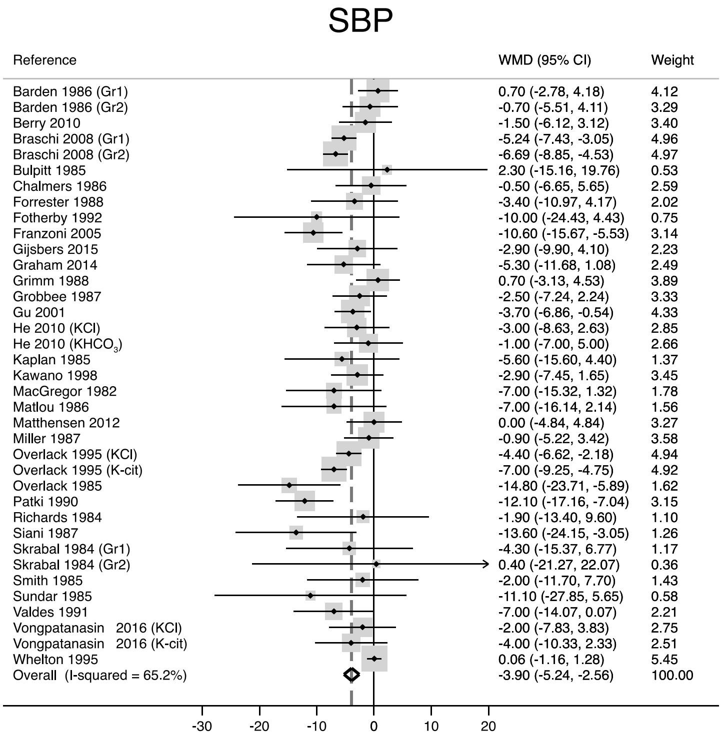
Domains are: 1) randomization process errors; (2) deviations from the intended interventions; (3) missing outcome data; (4) systematic errors in measurement of the outcome; (5) bias in selection of the reported result; (6) use of a wash-out period in cross-over study design.

Figure S1. **Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to differences in potassium excretion between the treatment arms at the end of the trials, and to achieved potassium excretion levels between arms at the end of the trials.**



Spline curve (solid line) with 95% confidence limits (long dashed lines), and background dash-dotted line using a linear function in a dose-response meta-analysis.

Figure S2. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels between potassium treated and non-treated groups considering overall studies.



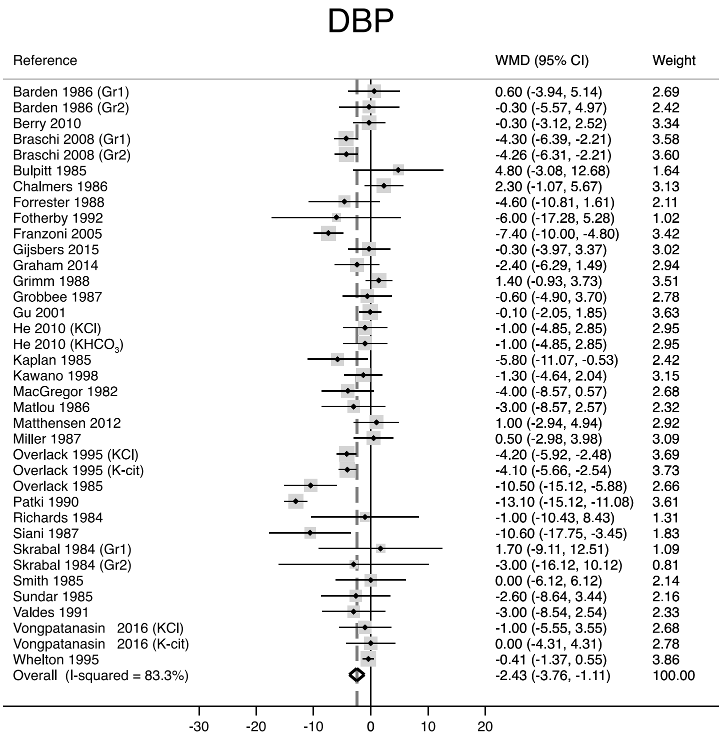
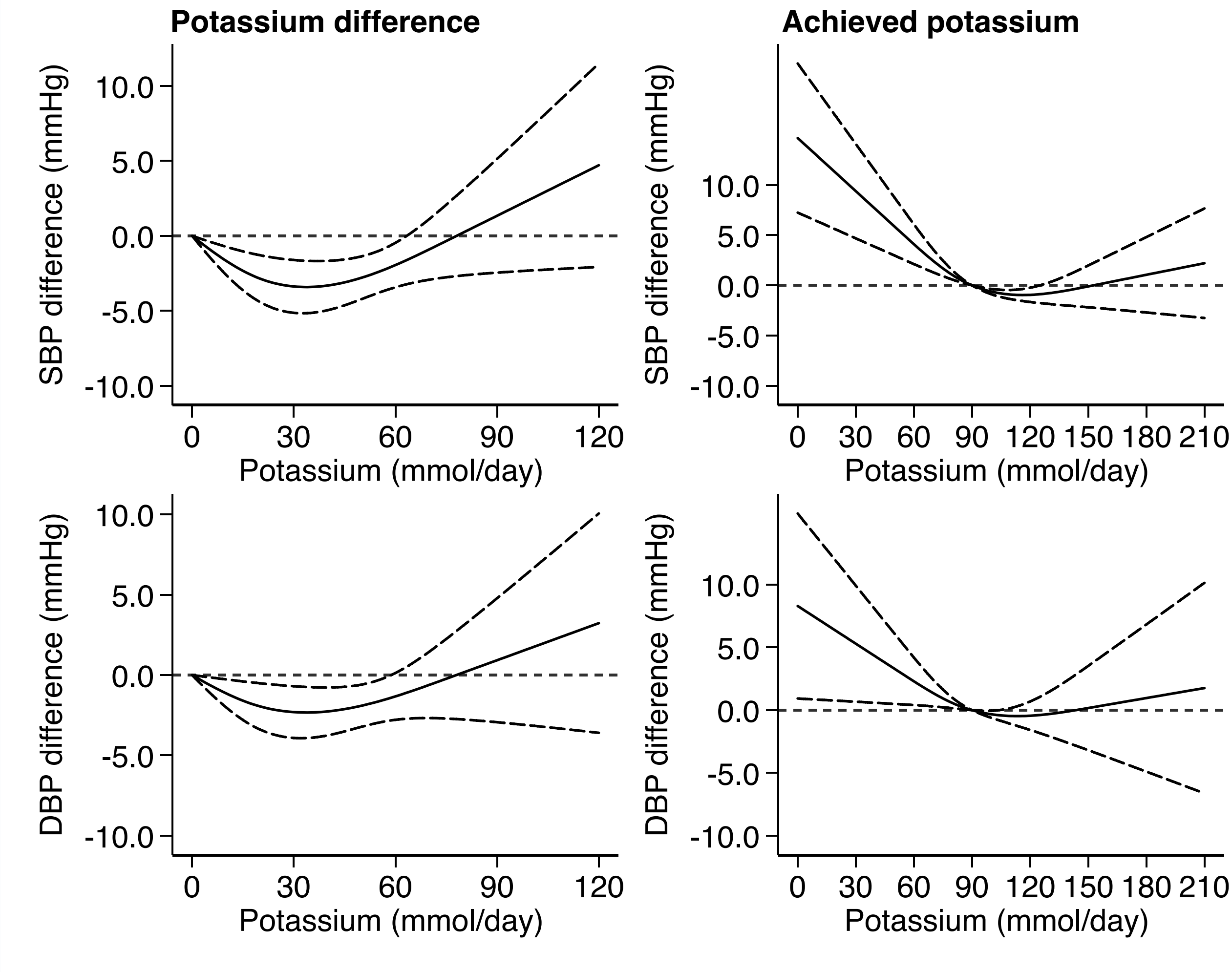


Figure S3. **Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) after excluding the two trials at high risk of bias according to differences in potassium excretion between the treatment arms at the end of the trials, and to achieved potassium excretion levels between arms at the end of the trials (N=30).**



Spline curve (solid line) with 95% confidence limits (long dashed lines).

Figure S4. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups after excluding the two studies at high risk of bias (N=30).

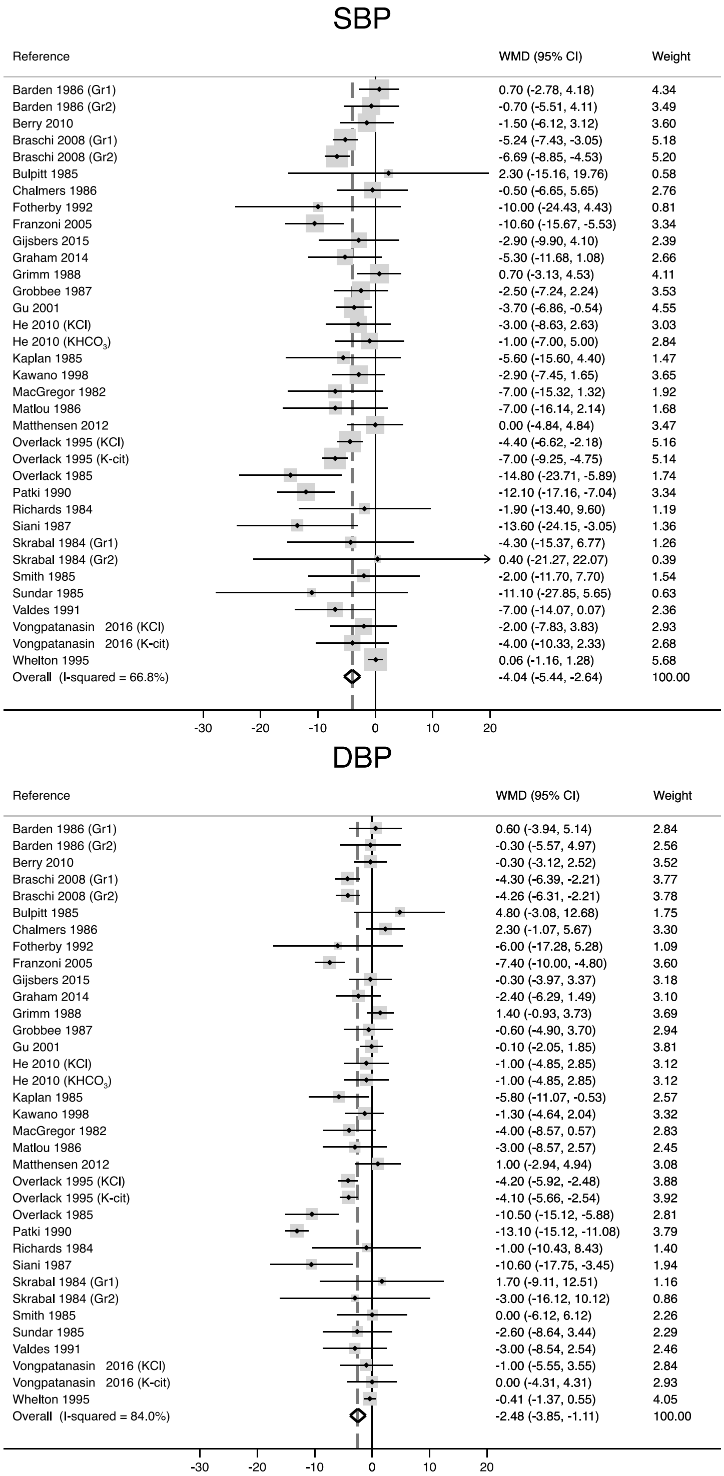
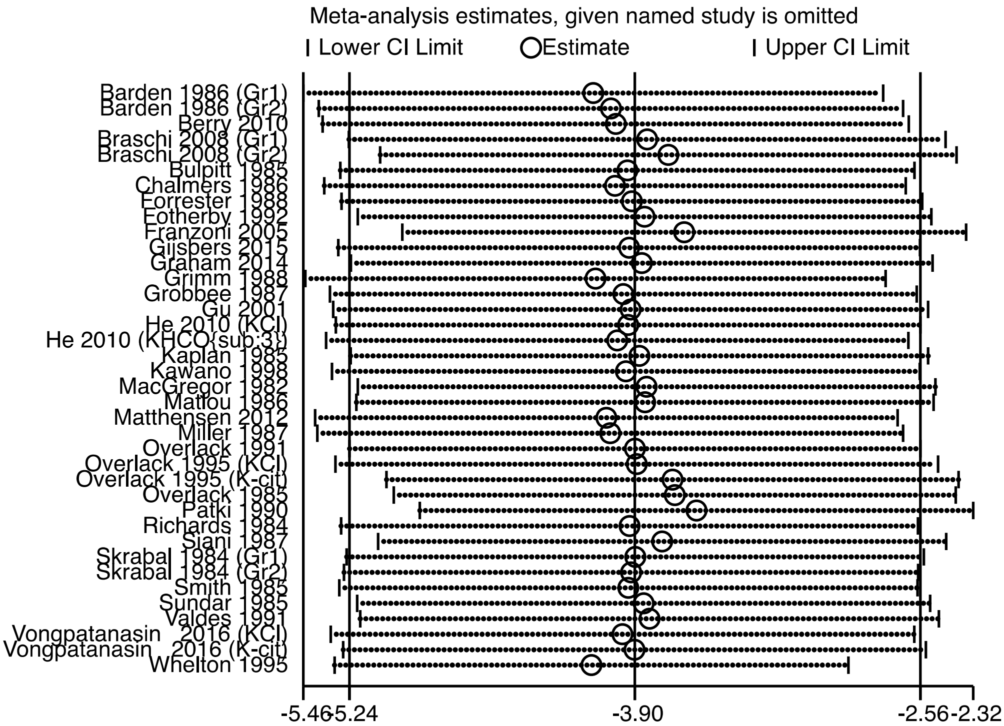
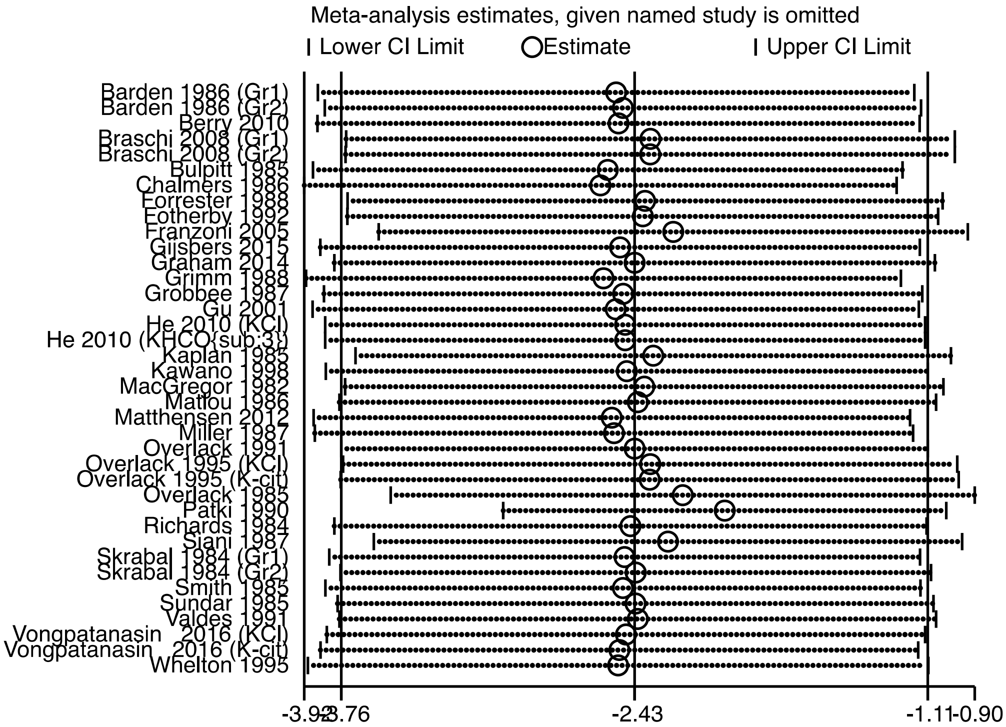


Figure S5. Sensitivity analysis of mean difference for changes in systolic (SBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups after removal of single study result (leave-one-out analysis).



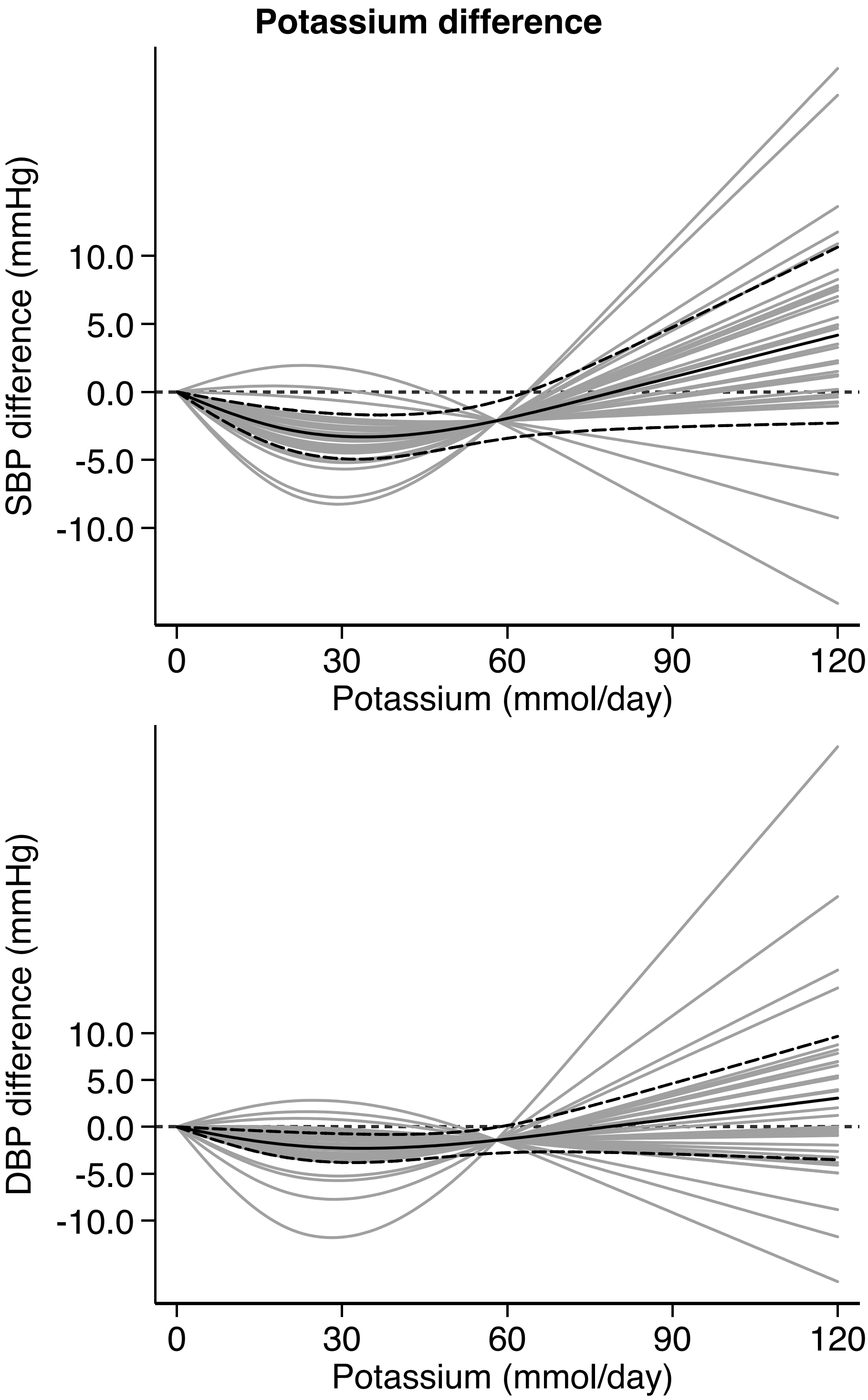
Each given named study is omitted when computing the overall meta-analysis summary estimate.

Figure S6. Sensitivity analysis of mean difference for changes in diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups after removal of single study result (leave-one-out analysis).



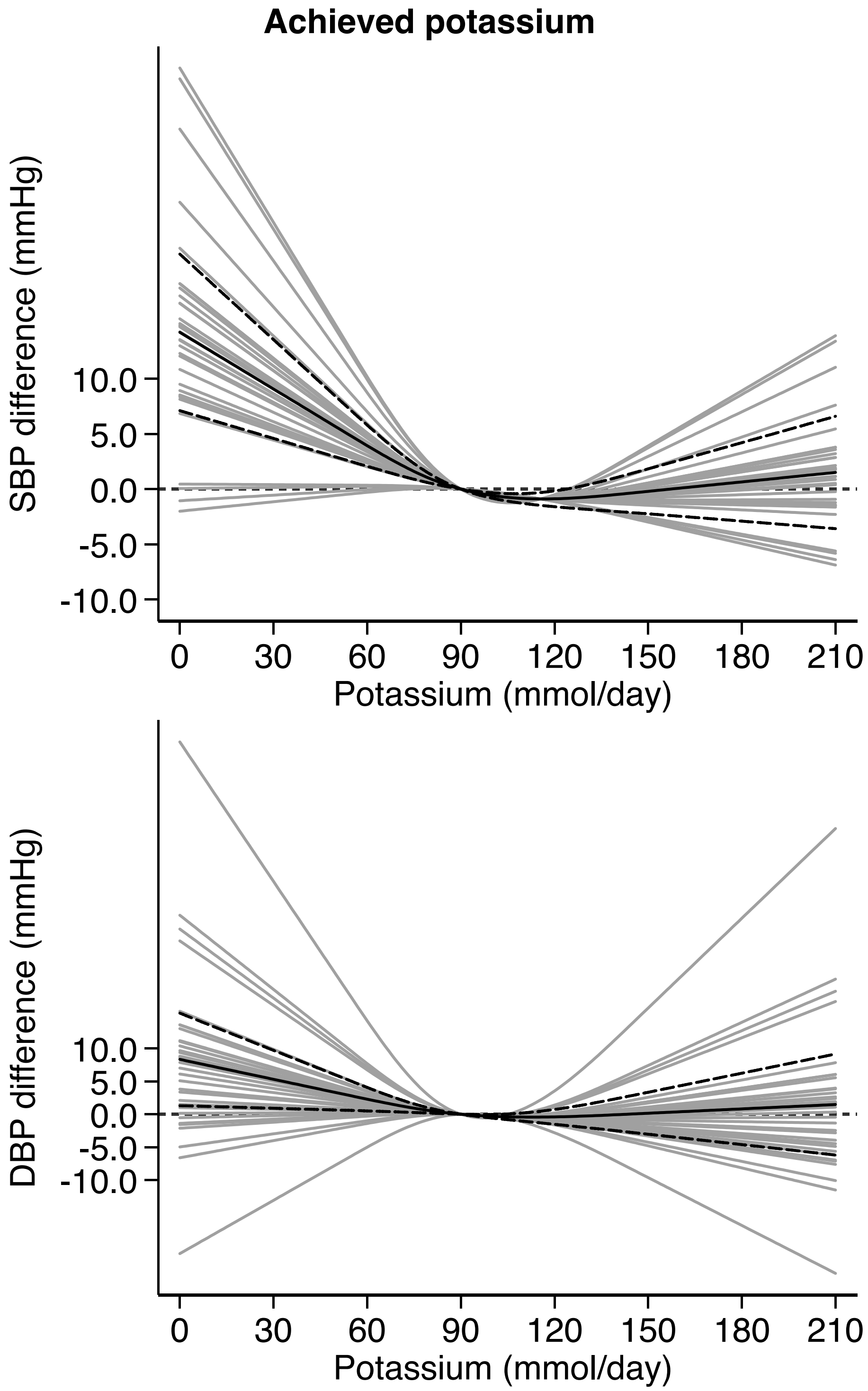
Each given named study is omitted when computing the overall meta-analysis summary estimate.

Figure S7. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to differences in potassium excretion between the treatment arms (potassium supplemented and control group) at the end of the trials.



All studies included (N=32). Sensitivity analysis of overall spline curve (black solid line) with 95% confidence limits (black dashed lines) and the study-specific trends showing the influence of variation across studies (gray solid lines).

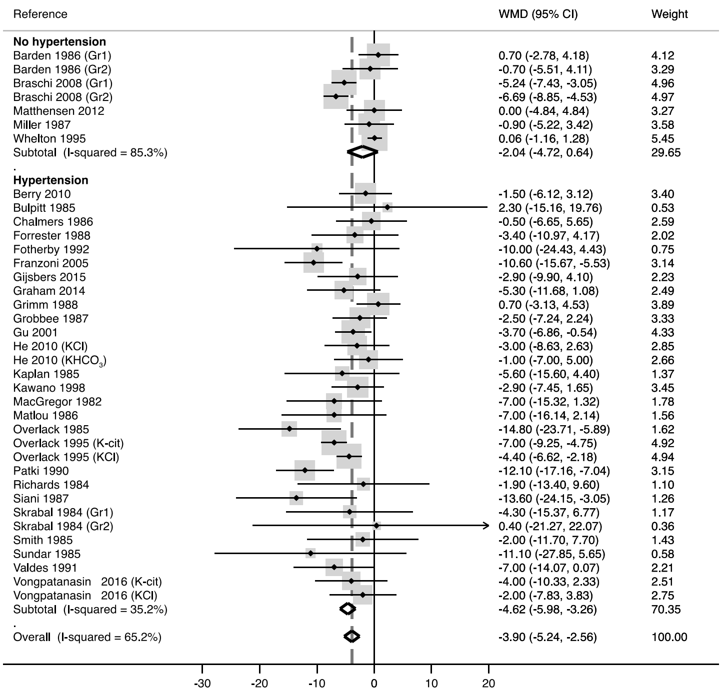
Figure S8. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to achieved potassium excretion levels between arms (potassium supplemented and control group) at the end of the trials.



All studies included (N=32). Sensitivity analysis of overall spline curve (black solid line) with 95% confidence limits (black dashed lines) and the study-specific trends showing the influence of variation across studies (gray solid lines).

Figure S9. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups in participants with hypertension and with no hypertension.

SBP



DBP

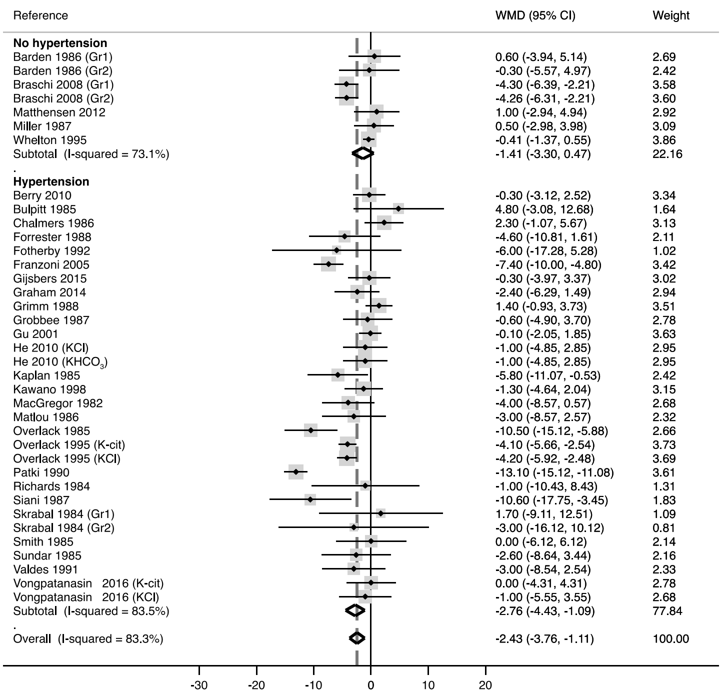
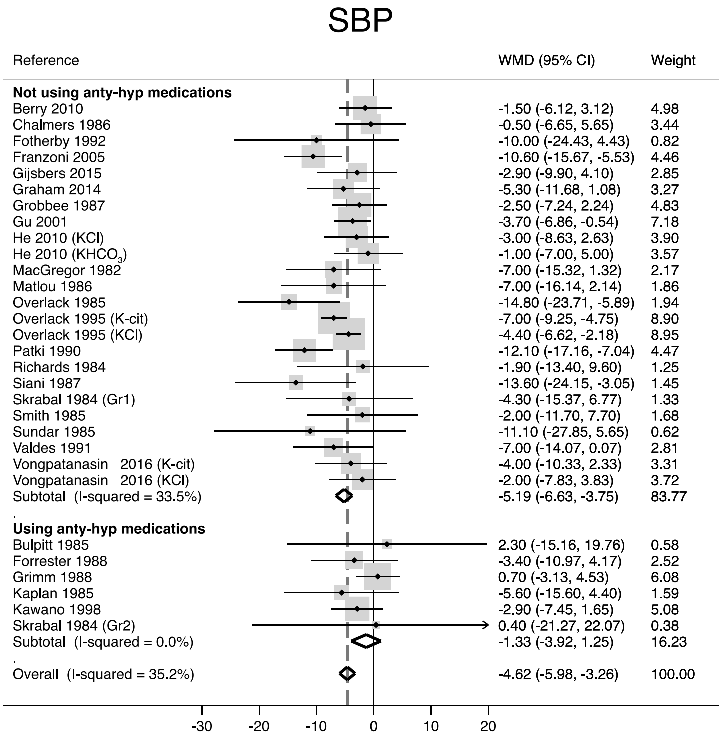


Figure S10. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups in participants with hypertension by use of anti-hypertensive medications.



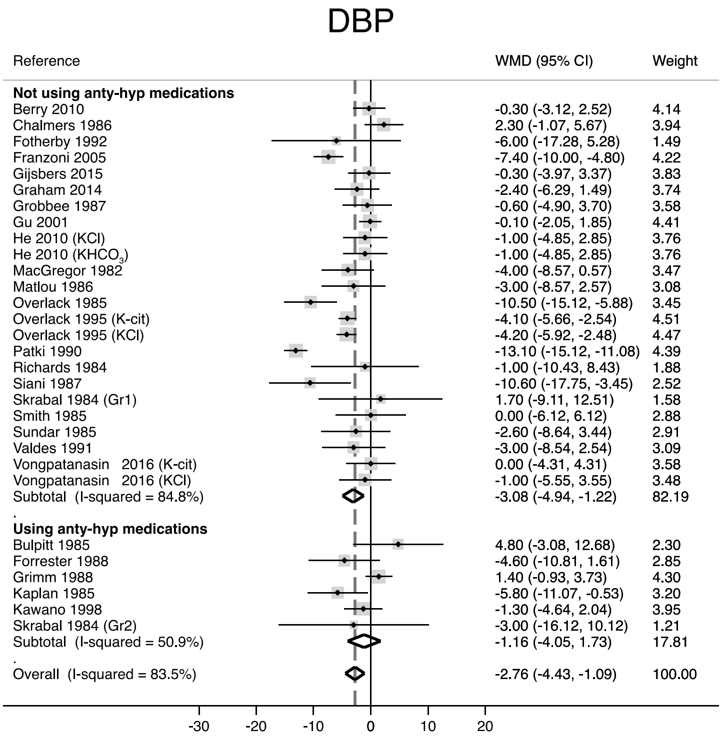
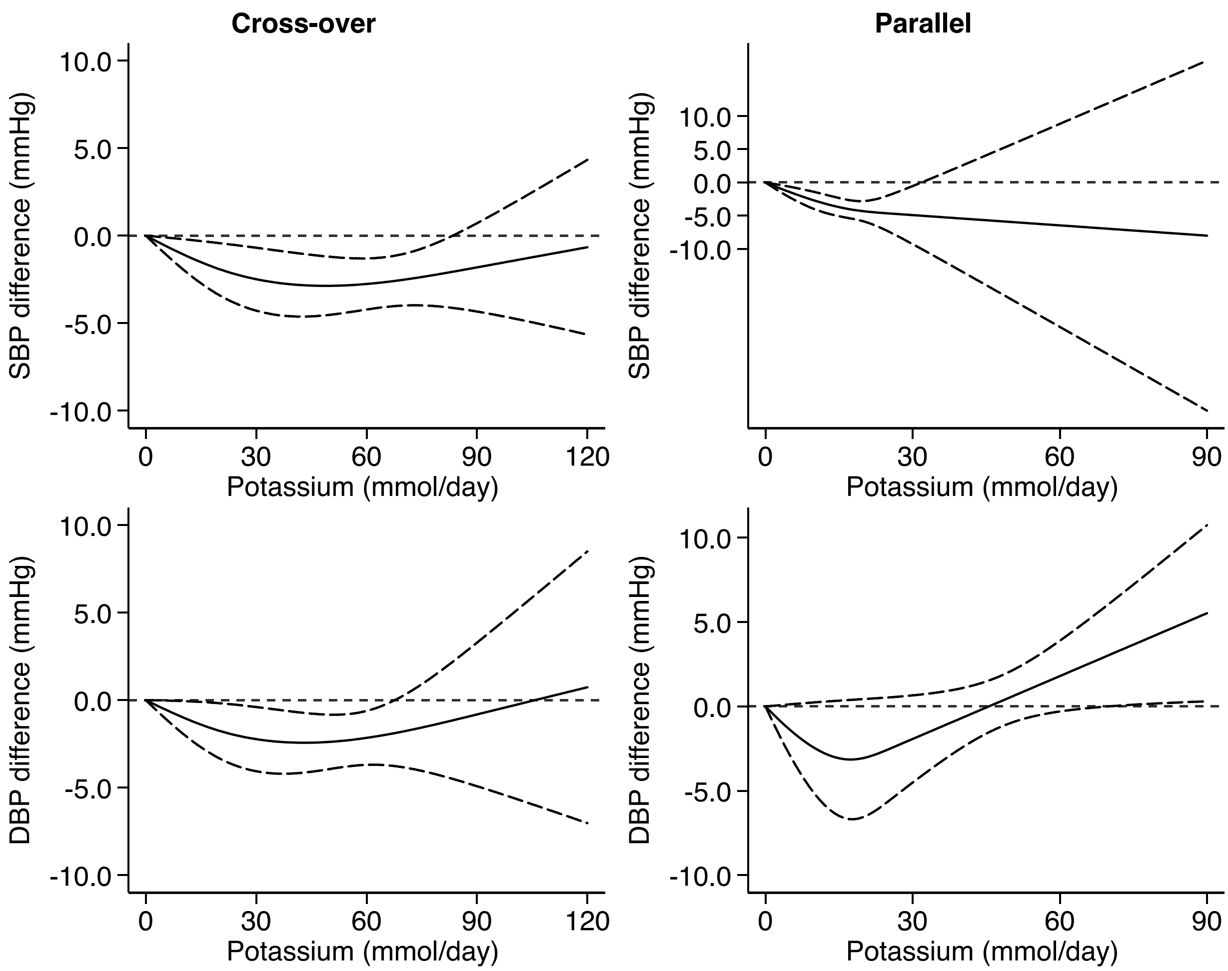
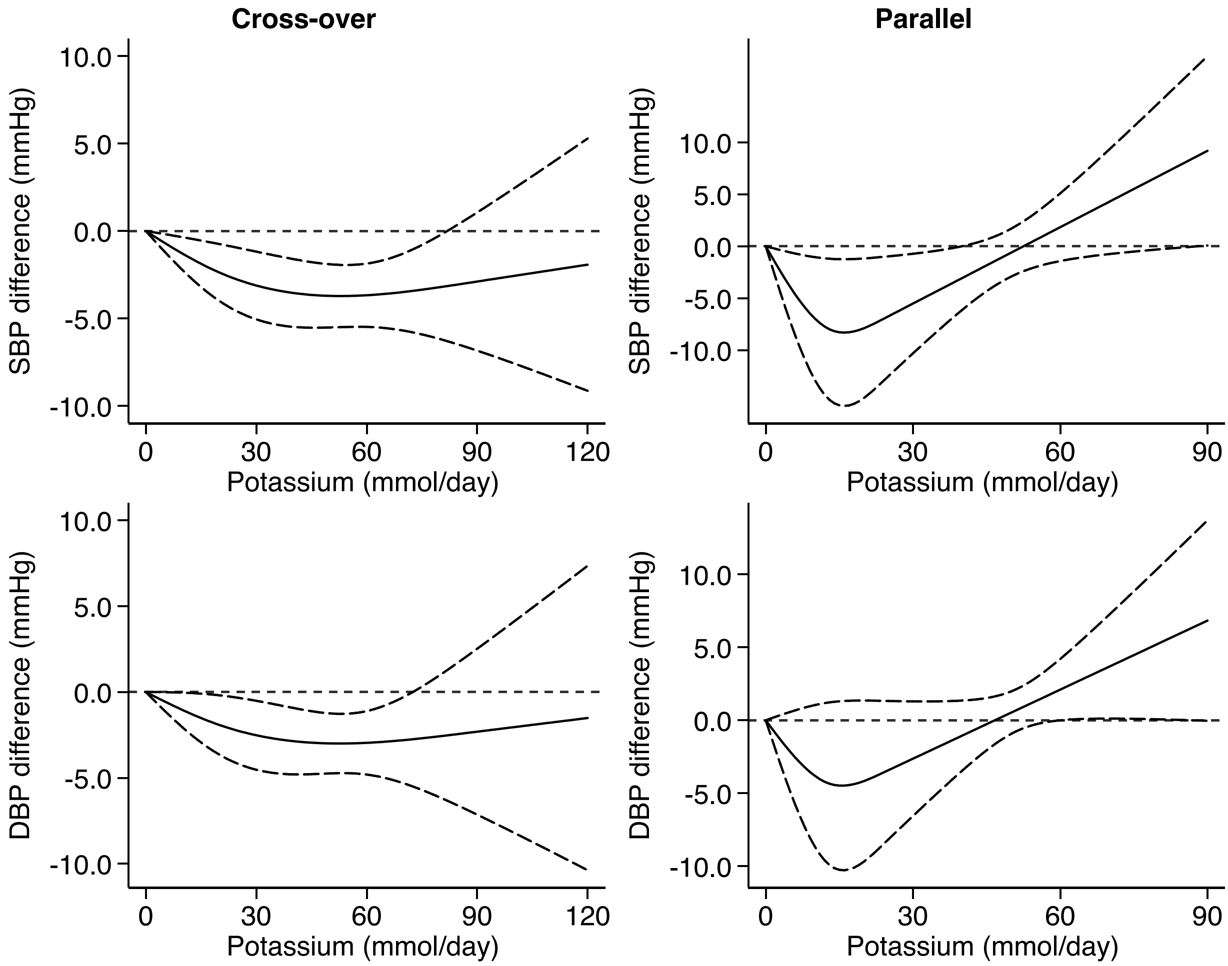


Figure S11. **Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to differences in potassium excretion between the treatment arms at the end of the trials and by study design (cross-over N=23 vs. parallel N=9).**



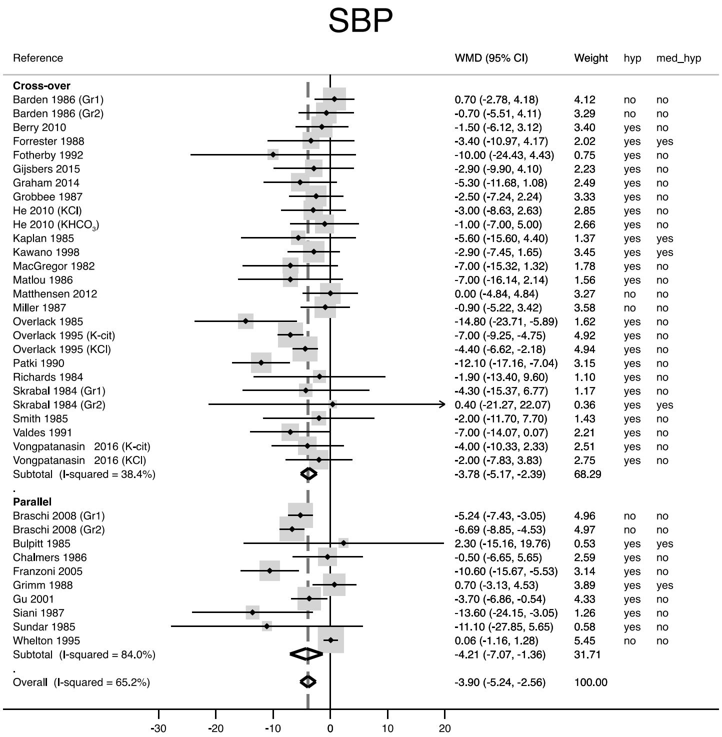
Spline curve (solid line) with 95% confidence limits (long dashed lines).

Figure S12. **Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to differences in potassium excretion between the treatment arms at the end of the trials and by study design (cross-over N=23 vs. parallel N=9), in subjects with hypertension only.**



Spline curve (solid line) with 95% confidence limits (long dashed lines).

Figure S13. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups in all participants after stratification by study design (cross-over vs. parallel).



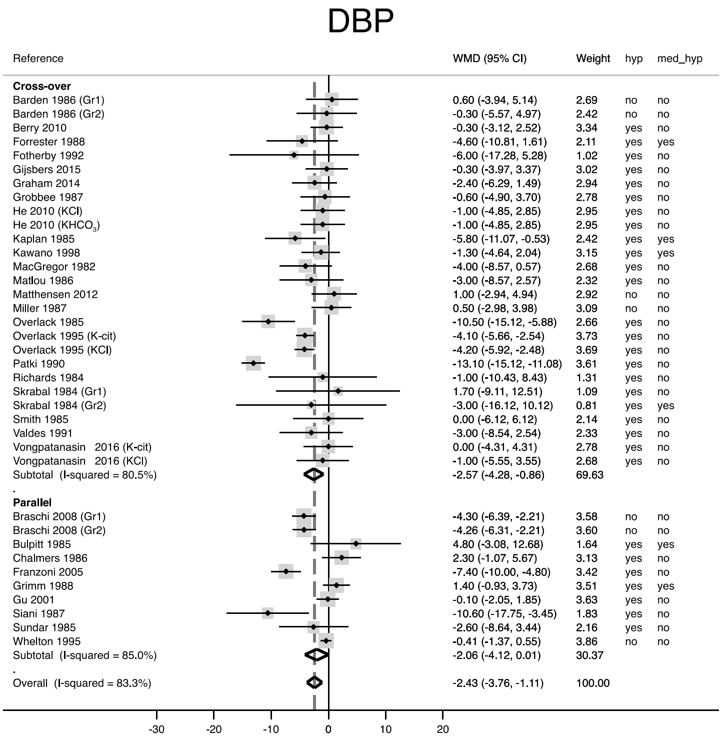


Figure S14. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups after stratification by study design (cross-over vs. parallel) in subjects with hypertension only.

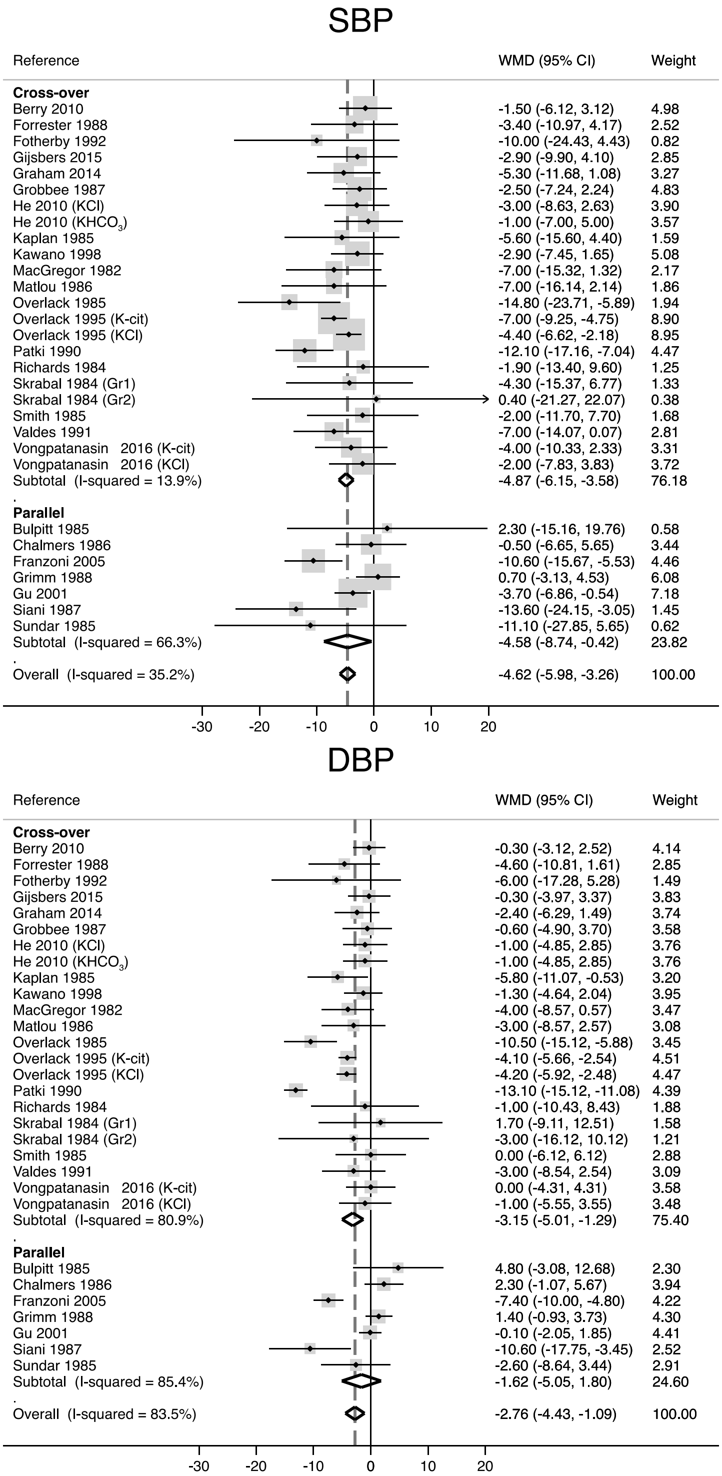
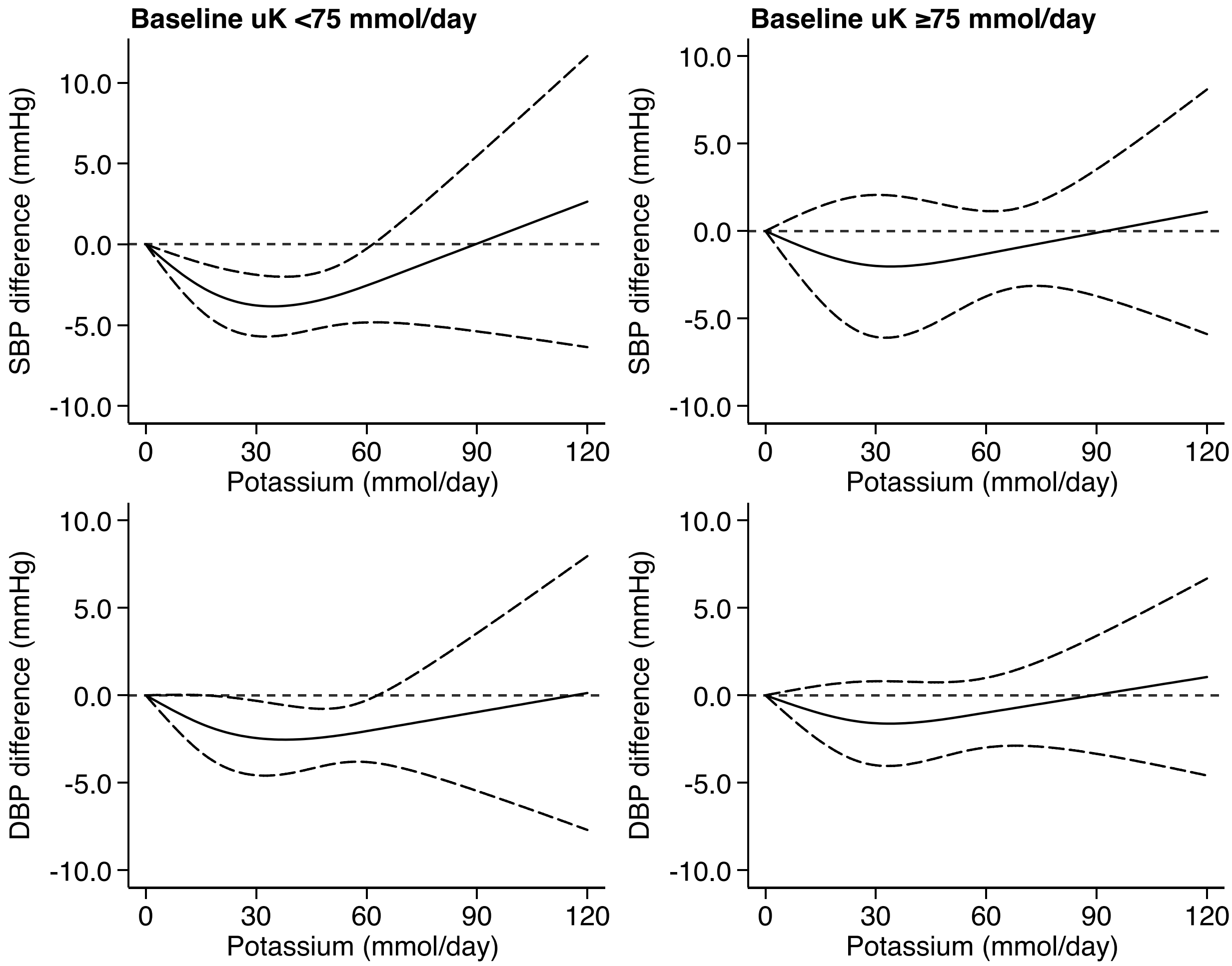
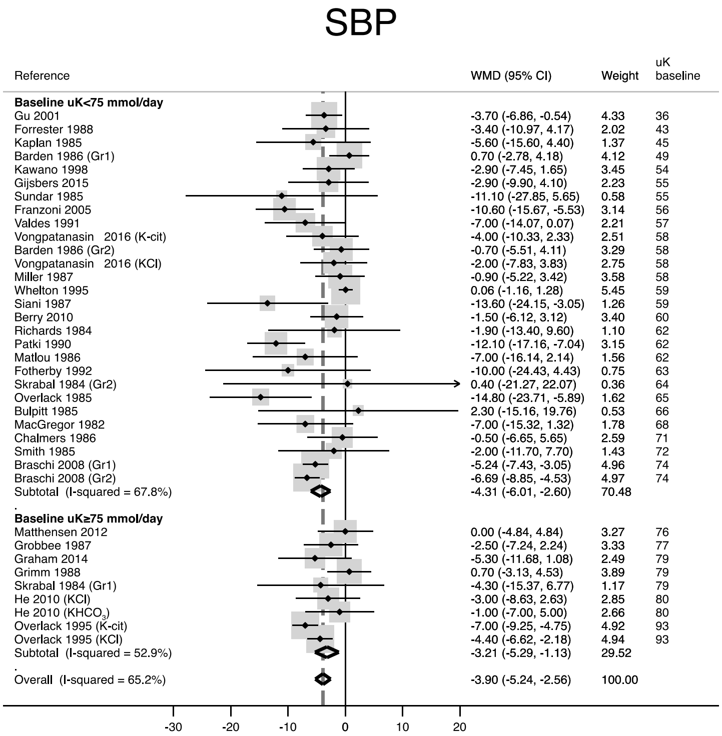


Figure S15. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to differences in potassium excretion between the treatment arms at the end of the trials in studies with baseline potassium excretion (uK) below 75 mmol/day (N=26), and equal or above 75 mmol/day (N=8).



Spline curve (solid line) with 95% confidence limits (long dashed lines).

Figure S16. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups after stratification by baseline potassium (uK <75 mmol/day, and ≥75 mmol/day).



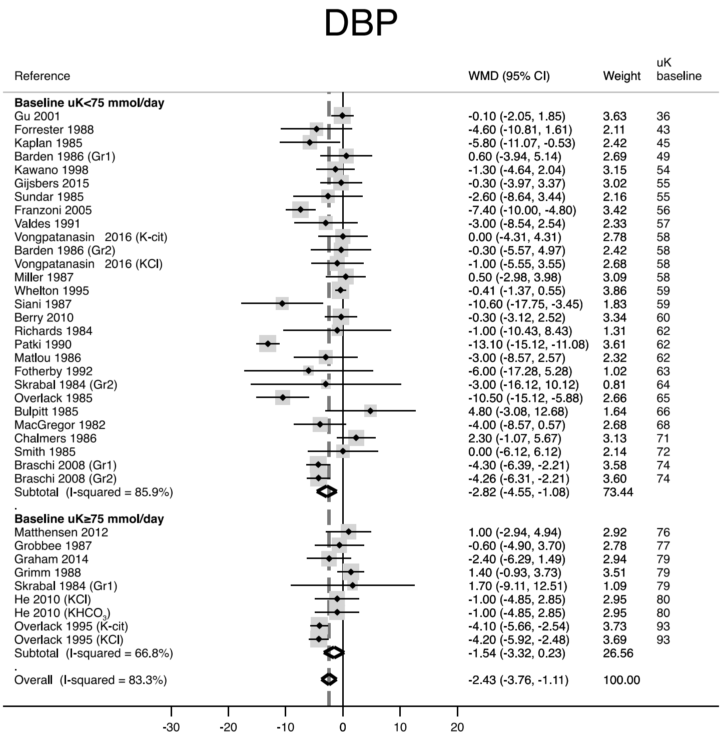
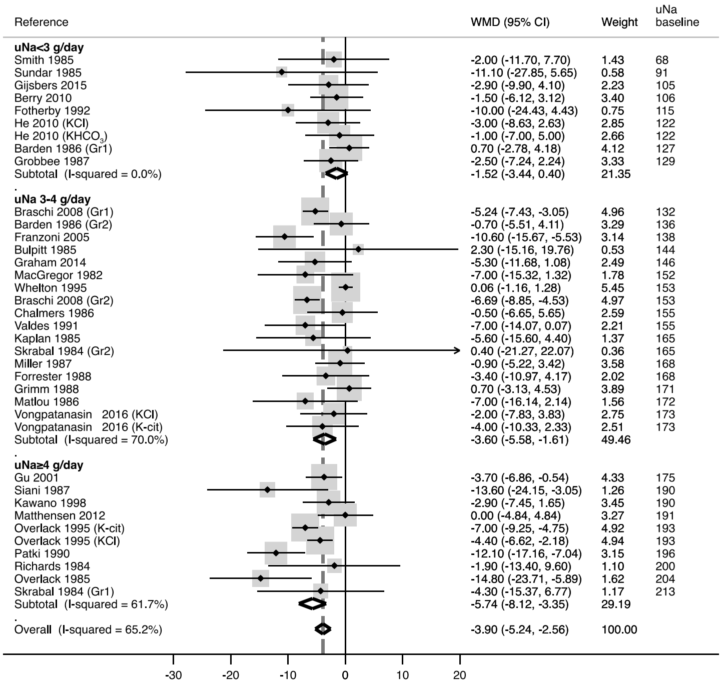


Figure S17. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups after stratification by baseline sodium (uNa <3 g/day, 3-4 g/day, and ≥4 g/day).

SBP



DBP

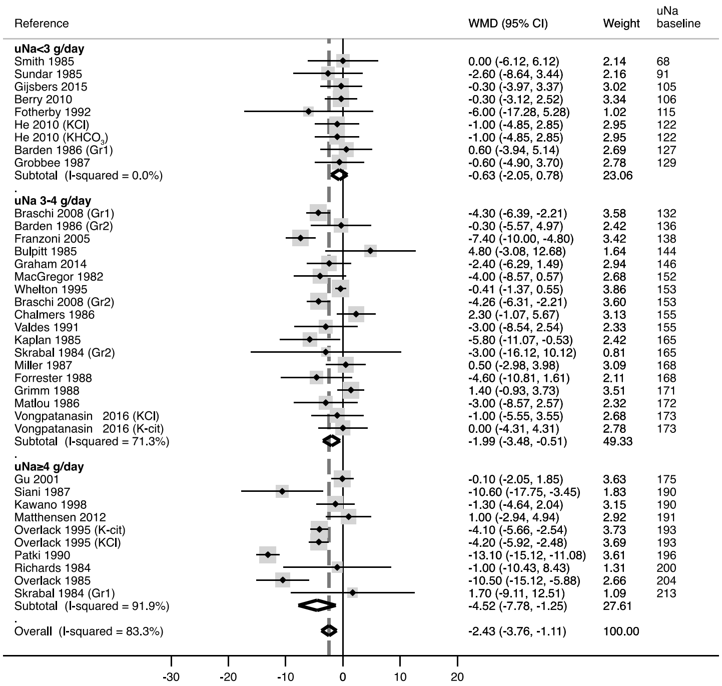
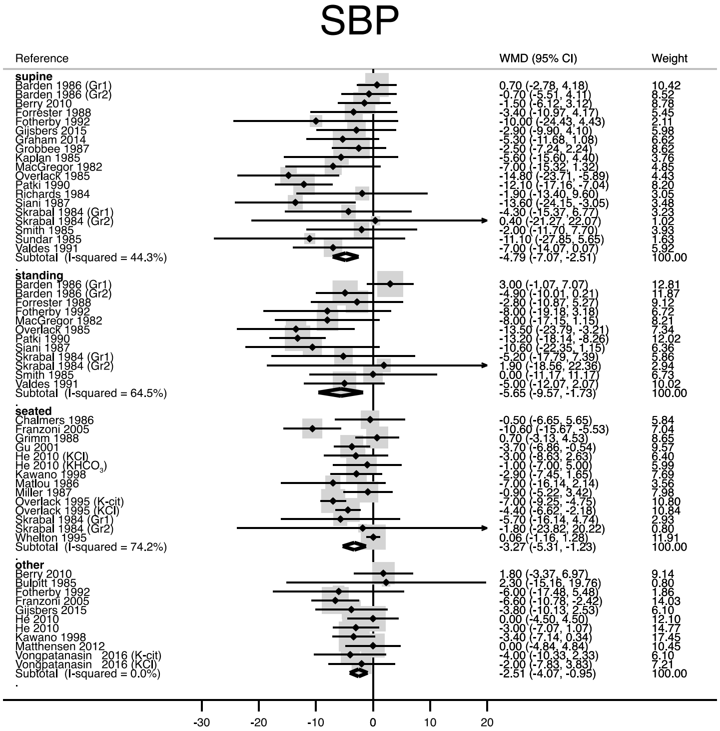


Figure S18. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups by position of BP measurement (supine, standing, seated, or other).



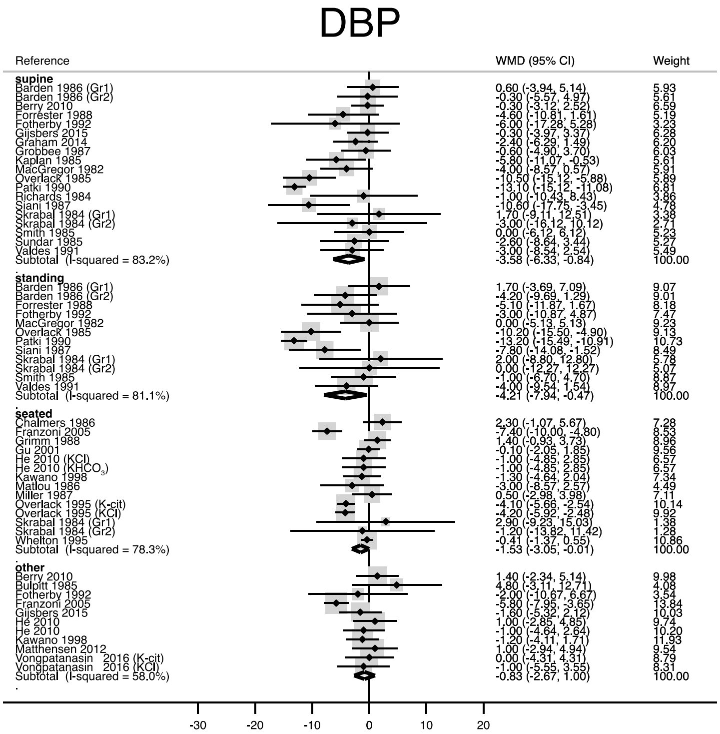


Figure S19. Meta-analysis of mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) between potassium treated and non-treated groups by blood pressure measurement modality (automatic vs. manual).

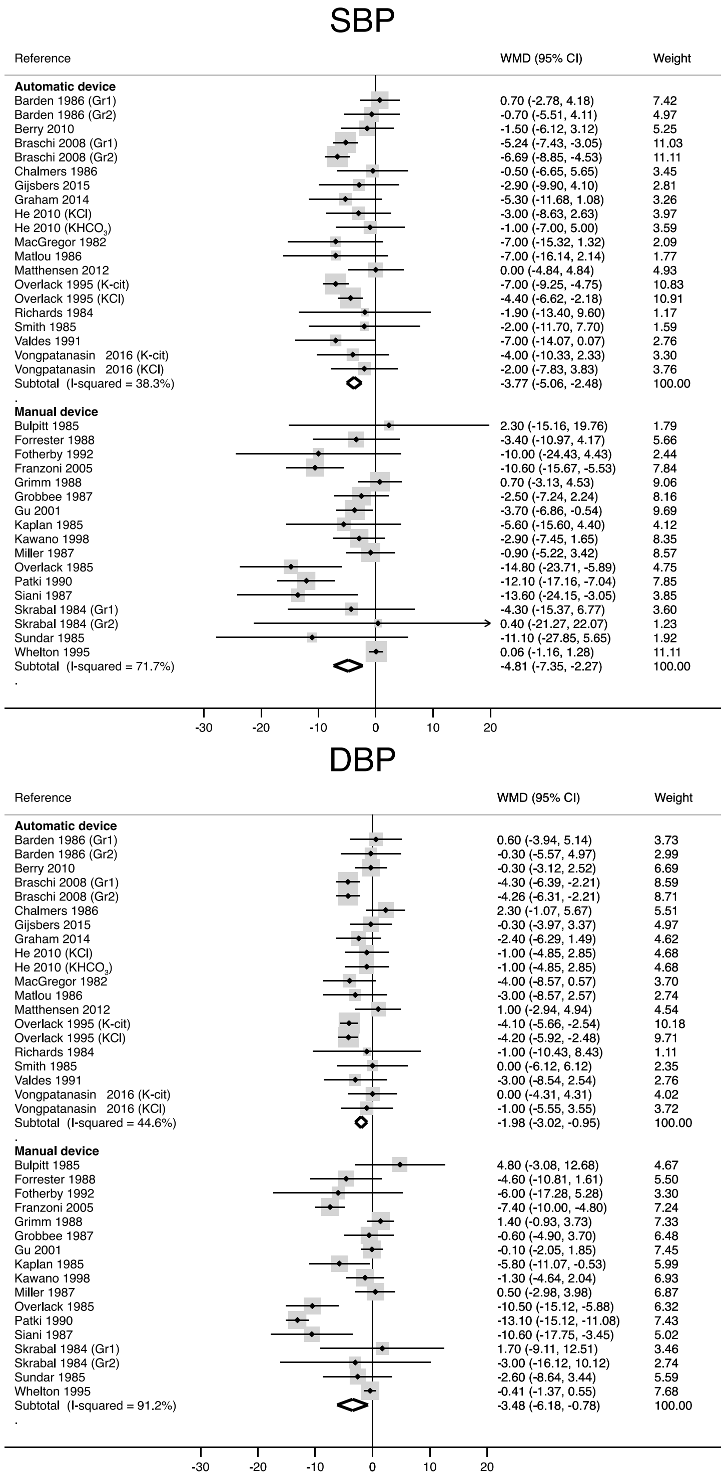
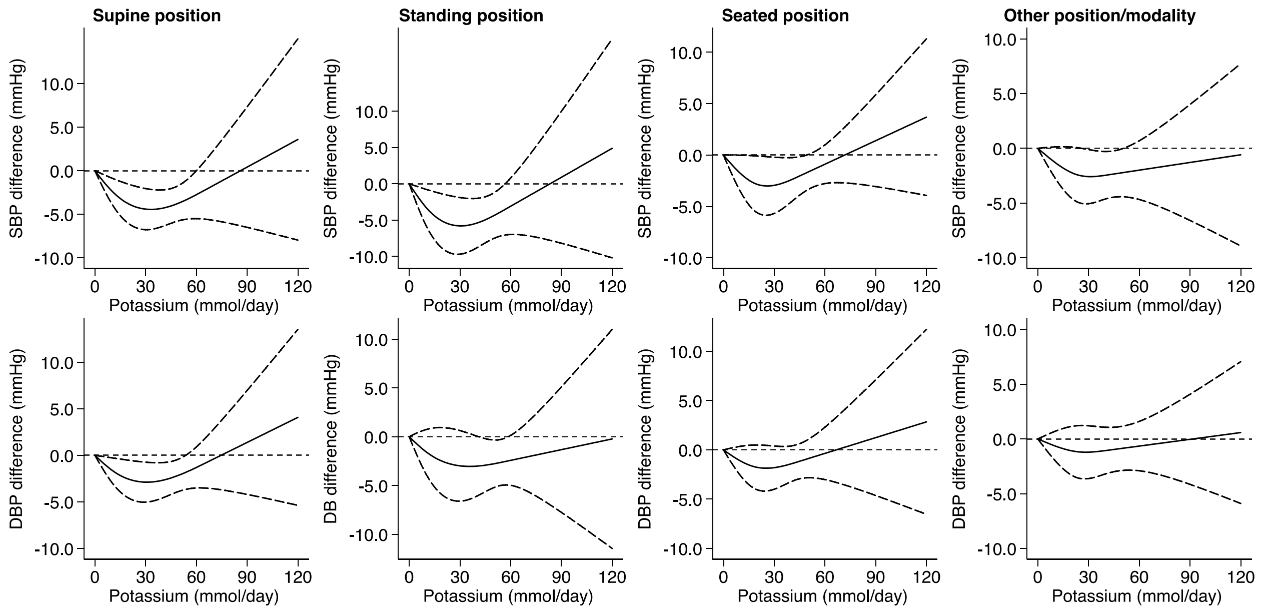
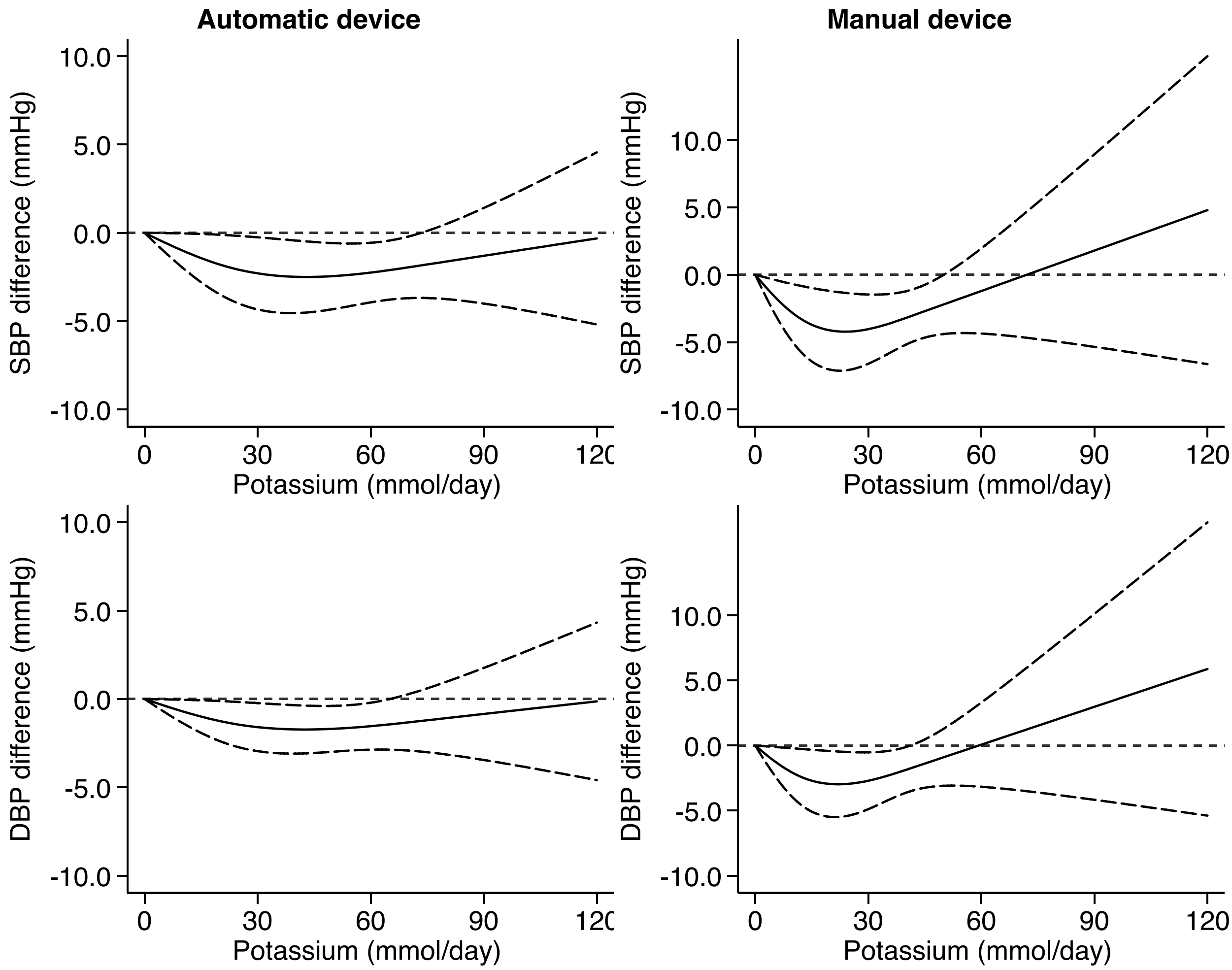


Figure S20. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to differences in potassium excretion between the treatment arms at the end of the trials by position of BP measurement (supine N=19, standing N=11, seated N=11, or other N=9).



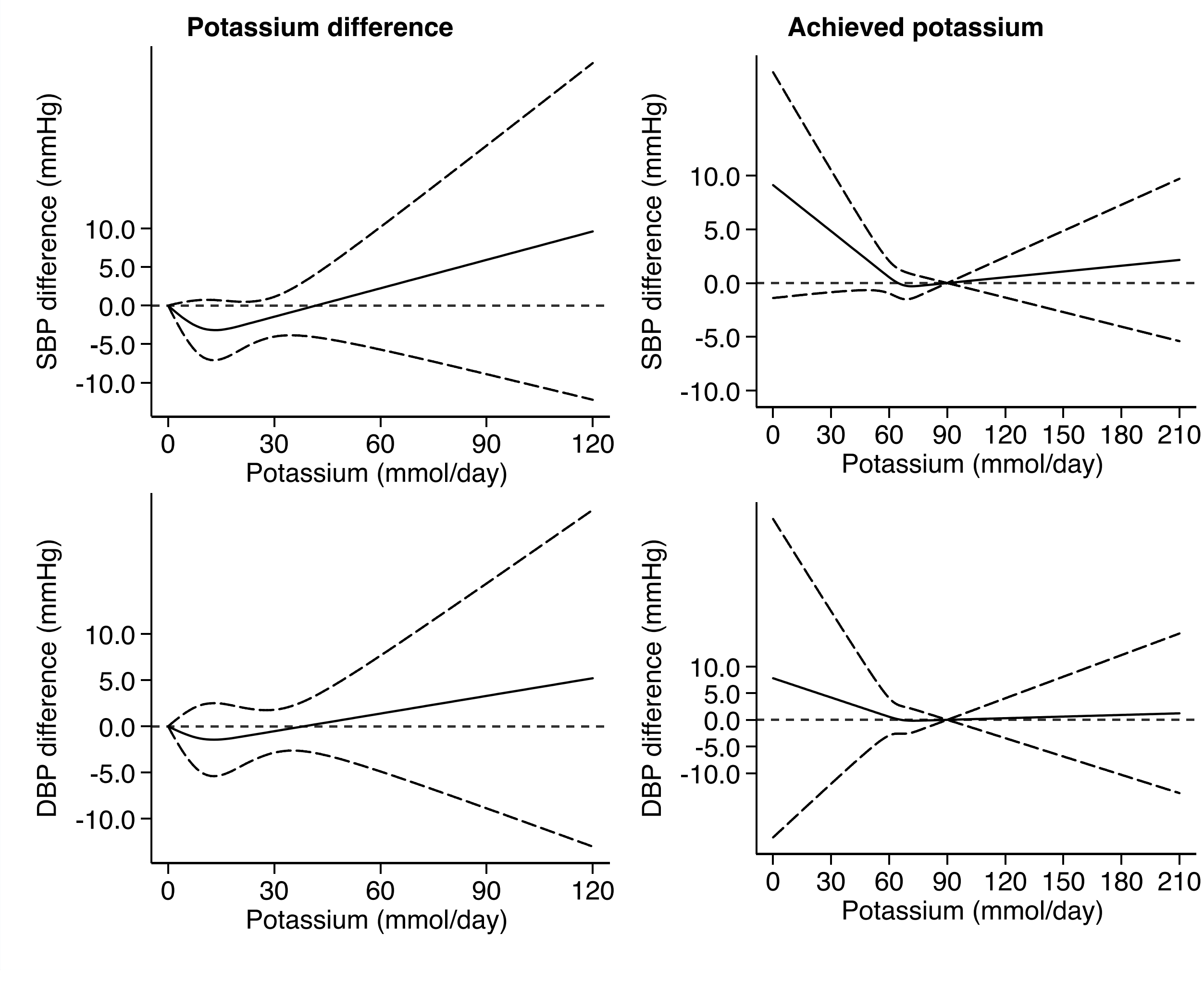
Spline curve (solid line) with 95% confidence limits (long dashed lines).

Figure S21. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to differences in potassium excretion between the treatment arms at the end of the trials by BP measurement modality (automatic N=15 vs. manual device N=17).



Spline curve (solid line) with 95% confidence limits (long dashed lines).

Figure S22. Dose-response meta-analysis of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels (as mmHg) according to differences in potassium excretion between the treatment arms at the end of the trials with duration ≥12 weeks (N=5).



Spline curve (solid line) with 95% confidence limits (long dashed lines).

Figure S23. **Funnel plots for publication bias for mean difference for changes in systolic (SBP) and diastolic (DBP) blood pressure levels (as mmHg) and its standard error (SE).**