Annex to:

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Annex B - Analysis of evidence from published scientific literature as preparatory work for the setting of Dietary Reference Values for Sodium

European Food Safety Authority (EFSA)

Summary

The specific objective of the quantitative analysis was to characterise the dose-response relationship between sodium intake and selected health outcomes in the healthy population based on evidence from the published literature; the current report includes a description of the analyses and results addressing the association between sodium urinary excretion and blood pressure, as the evidence identified to answer the other sub-questions as outlined in the protocol was not sufficient to carry out quantitative analyses.

Methods - The expected high heterogeneity across the studies identified to characterise the association between sodium intake and blood pressure was taken into account in meta-analyses and meta-regressions applying a random-effects model. Analyses were conducted at two meta-analytic levels: at study level mean BP differences were meta-analysed with the objective to have a term of comparison with respect to other relevant systematic reviews conducted on similar sets of RCTs that investigated how a reduction in sodium intake is associated with a reduction in blood; at arm level mean BP absolute values were meta-analysed and modelled in dose-response meta-regressions to investigate their association with 24-h mean absolute values of urinary Na excretion. Specific formulae (Higgins 2011) were applied to derive summary data where not directly extracted/available in the necessary format. Statistical heterogeneity was tested using the χ^2 test (Cochran's Q test) and was quantified by calculating the I^2 statistic. Since the expected high level of heterogeneity was confirmed both across studies and arms, possible sources were explored by subgroup analysis, meta-regression and/or sensitivity analysis. Random-effects meta-analyses of summary response measures were carried out using the DerSimonian and Laird approach (DerSimonian et al.1986), which encompasses both sampling variability and variability due to heterogeneity, applying the inverse-variance method. Wald-type 95% confidence intervals were estimated for all summary measures, while in meta-analyses at arm level 95% prediction intervals were approximated by using a *t* distribution with *k*-2 degrees of freedom.

All statistical analyses were performed with STATA version 13.1; all estimates were presented with 95% confidence intervals and all analyses carried out at the level of statistical significance of 0.05.

Included studies - Individual trials were included in the analysis as far as they met the following inclusion criteria: trial design was either randomised controlled parallel, cross-over or cluster-randomised; intervention consisted in a change in sodium intake compared to usual diet, no intervention or placebo; subjects involved were adults (≥ 18 years) and children (6 months to < 18 years) from the general population; and sodium intake was assessed based on urinary sodium excretion calculated from single or multiple 24-h urine collection(s). A total of 32 RCTs on adults, providing 35 comparisons, met the eligibility criteria. All arms (68) from the eligible RCTs comparisons were included; there were seven parallel RCTs, including one cluster-randomised trial, and 25 were cross-over RCTs. The between-group differences in mean 24-hour sodium excretion ranged from 13.3 to 285 mmol/day, with a median mean value of 72 mmol/day. The study size ranged from 11 to 1,159 participants and the duration of the intervention lasted from 4 weeks to 36 months. A total of 17 studies involved hypertensive individuals, eight studies involved normotensive individuals and seven studies involved mixed populations. Information about relevant study-level characteristics was not complete; the following were affected by a high proportion of missing data: mean body mass index (BMI) (63%), ethnicity (54%), mean potassium intake at baseline (37%), mean urinary sodium excretion at baseline (31%).

Study-level pooled estimates - The random-effect meta-analysis of the 32 eligible RCTs showed overall significant effects of sodium reduction on differences in means of SBP (–3.9 (95% CI: –5.1, –2.8) mm Hg; I^2 61.9%, $p < 0.001$; Figure 1:) and DBP (–2.0 (95% CI: –2.8, –1.2) mm Hg; I^2 60.6%, $p < 0.001$; Figure 2:).

Arm-level pooled estimates – The pooled mean estimate across the 68 arms was 137.1 (95% CI: 134.2, 140.1; Figure 3:) mm Hg for SBP and 84.0 (95% CI: 82.03, 85.9; Figure 4:) mm Hg for DBP. Heterogeneity was higher than in the study-level instances with an I^2 of 99% ($p < 0.001$) for both SBP and DBP.

Moderators – Several factors potentially influencing the dose-response relationships were identified *a priori* both from the literature and by the Panel. Methodological sources of heterogeneity included: study design; specific trial design; trial duration; type of intervention; subject position while measuring BP; number of 24-h urinary collections; risk of bias (overall tier and specific domain); publication year; and funding source. Contextual sources of heterogeneity included: mean age; sex; blood pressure status; BMI; ethnicity; potassium intake at baseline; mean SBP and DBP at baseline; and mean urinary sodium excretion at baseline. A larger effect was found in hypertensive than normotensive individuals, for both SBP (hypertensive: –5.6 (95% CI: –8.1, –3.1) mm Hg vs. normotensive: –2.0 (95% CI: –3.3, –0.7) mm Hg) and DBP (hypertensive: –2.9 (95% CI: –4.2, –1.6) mm Hg vs. normotensive: –0.9 (95% CI: –1.6, –0.2) mm Hg). The effect of sodium reduction was higher among subjects aged 50 years or more (SBP –6.1 (95% CI: –8.2, –4.1) mm Hg; DBP –2.9 (95% CI: –4.0, –1.9) mm Hg) than among subjects younger than 50 years (SBP –2.2 (95% CI: –3.3, –1.1) mm Hg; DBP –1.0 (95% CI: –2.0, –0.0).

Dose-response modelling - A one-stage (or 'pool-first') approach was taken, where study-specific data are combined first and then one summary dose–response model is fitted. Mixed-effects meta-regression models were fitted to account for the multilevel structure in the data, with arms nested within studies; two random effects (intercepts) on arm and study and five fixed effects were specified. The independent variable was centered at 49 mmol/day (minimum mean UNa observed in the data set); for each mixed-effects meta-regression model the statistics τ^2, residual I^2 and adjusted R^2 were calculated. Different functional forms were explored for the shape of the dose-response relationship; non-linearities were tested by fitting both restricted cubic splines and linear splines (knot at 130 mmol/day); both splines were no longer statistically significant once both random effects (arms and studies) were specified in the models. Incorporation of the variability around the study intercept into the models helped overcome the 'artefact' deriving from the constraint between the control and intervention groups belonging to the same study.

Dose-response results - A total of 60 points (arms as unit of analysis) from 28 RCTs were included in the final dose-response models; fourteen 14 arms were from parallel RCTs, 46 were from cross-over RCTs and none from cluster-randomised trials. The final set of covariates included in both SBP and DBP models was: mean age at baseline (<40 yrs old (ref.), 40-49, 50-59, >=60 yrs old); blood pressure status at baseline (normotensive (ref.) hypertensive); mean urinary sodium excretion at baseline (<100 mmol/day (ref.), 100-149, >=150 mmol/day); blood pressure measurement method (supine (ref.), sitting); and specific trial design (no run-in (ref.), run-in normal diet, run-in low sodium diet. For each 100 mmol/day increase in mean urinary sodium excretion, holding all other covariates constant, mean systolic blood pressure increased linearly by 5.3 mm Hg (95%CI: 3.6-6.9 mm Hg) and mean diastolic blood pressure increased linearly by 2.6 mm Hg (95%CI: 1.6-3.7 mm Hg). Mean sodium excretion explained only 4% of the heterogeneity across trials arms in the SBP model and 3% in the DBP model; however, in both models the set of moderators explained more than 85% of the between-study heterogeneity. In stratified analyses a larger association was found in hypertensive than normotensive individuals, for both SBP (hypertensive: 6.4 (95% CI: 4.3, 8.6) mm Hg vs normotensive: 4.4 (95% CI: 2.1, 6.6) mm Hg) and DBP (hypertensive: 3.7 (95% CI: 2.5, 5.0) mm Hg vs normotensive: 1.7 (95% CI: 0.1, 3.3) mm Hg). The effect of sodium was higher among subjects aged 50 years or more (SBP 7.1 (95% CI: 5.0, 9.2) mm Hg; DBP 3.8 (95% CI: 2.6, 5.0) mm Hg) than among subjects younger than 50 years (SBP 3.5 (95% CI: 1.5, 7.4) mm Hg; DBP 1.2 (95% CI: –0.4, 2.9). The potential moderating effect of K, BMI, and ethnicity could not be explored due to lack of information; sex showed some variability across subgroups in meta-analyses on trials, but the effect was not replicated in models on arms.

Uncertainties - Sources of uncertainty specific to the statistical analysis and their potential impact on the final estimates, where possible, were identified and described to inform the overall assessment of the uncertainty in the body of evidence. Among them: the strong 'methodological' component (covariates that were linked to the experimental setting) that explained a large part of the heterogeneity between studies (random effects) introduced specific challenges to model interpretation; the use of data generated in controlled settings to characterise the sodium-blood pressure relationship was not optimal as the experimental setting was broken to conduct an « observational » type of analysis (with paired points); important moderators were not explored (e.g. BMI, ethnicity, potassium intake and energy intake) due to missing information; the models did not take into account the high

inter-individual and intra-individual variability of sodium excretion and BP measurements; meta-regressions modelled the relationship between mean Na and mean BP at 'group' level, being observational in nature and possibly different when explored on individual data (aggregation bias). Publication bias was assessed by visual inspection of the contour funnel plot and by performing the Egger's test for funnel plot asymmetry on mean differences in SBP from the 32 RCTs included in the meta-analyses; the test was statistically significant ($p = 0.001$), but publication bias was not considered a likely explanation for the asymmetry since the studies effects spread across all areas of significance.

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Background

The scientific opinion that addresses the Dietary Reference Values (DRVs) for sodium was conducted in accordance with the NDA Panel's Scientific Opinion on principles for deriving and applying DRVs; some parts of the assessment were undertaken by applying the 4-step approach for evidence use (i.e. plan/carry out/verify/report) described in the EFSA report on principles and process for dealing with data and evidence (the "Prometheus approach") (EFSA, 2015).

The current report was drafted based on: section 3 of the protocol (and related amendments) for sections 5.5 and 6 of the scientific opinion on DRVs for sodium by the NDA WG on Dietary Reference Values for Vitamins (thereafter referred to as "the Prometheus protocol"); the SAP (Statistical Analysis Plan) drafted as an internal document; and the actual analysis carried out consistently with the plan.

The specific objective of the quantitative analysis was to characterise the dose-response relationship between sodium intake and selected health outcomes in the healthy population based on evidence from the published literature. Its results informed section 5.5 of the scientific opinion, which also describes the systematic review steps preliminary to the meta-analyses and meta-regressions, as planned in the Prometheus protocol (literature searches, screening for relevance, risk of bias assessment).

Synthesis of the evidence

Three categories of health outcomes were selected as the most suitable to inform the setting of DRVs: blood pressure, cardiovascular disease related endpoints and bone health (section 2 of the Prometheus protocol). Systematic reviews of the scientific literature were conducted to characterise the relationship between sodium intake and these outcomes.

The characteristics of eligible studies and the outcome of the risk of bias (RoB) assessment are summarized in evidence tables in the Appendices H to L of the scientific opinion. According to the eligibility criteria, 24-h urinary excretion of sodium was used as a marker of sodium intake.

1. Criteria under which study data were quantitatively synthesised

The current report includes a description of the analyses and results addressing the **association between sodium urinary excretion and blood pressure (sub-question 1, part 1)**, as the evidence identified to answer the other sub-questions was not sufficient to carry out quantitative analyses (see sections 5.5.1 to 5.5.3 in the scientific opinion). For the latter, results from the available individual studies (including original dose-response analyses) were either discussed narratively or displayed in forest plots, but neither pooling nor modelling were possible/deemed appropriate (small and heterogeneous bodies of evidence).

The expected high heterogeneity across the studies identified to characterise the association between sodium intake and blood pressure was taken into account in meta-analyses and meta-regressions applying a random-effects model; such a model assumes that the true effects are normally distributed around a pooled weighted mean (or around the linear predictor for models) and allows for residual heterogeneity among responses not otherwise characterised by subgroups analyses (or not modelled by the explanatory variables included in the multivariable models).

Analyses were conducted at two meta-analytic levels, study and arm (i.e. intervention group from trial): at study level mean BP differences were meta-analysed with the objective to have a term of comparison with respect to other relevant systematic reviews conducted on similar sets of RCTs that investigated how a reduction in sodium intake is associated with a reduction in blood pressure (e.g. He et al. 2013, WHO 2012, Graudal 2017, AHRQ 2018); at arm level mean BP absolute values were meta-analysed and modelled in dose-response meta-regressions to investigate their association with 24-h mean absolute values of Na urinary excretion.

All statistical analyses were performed with STATA version 13.1. All estimates were presented with 95% confidence intervals and all analyses carried out at the level of statistical significance of 0.05.

2. Summary measures

In study-level meta-analyses, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were analysed as differences in means between trial arms. Mean differences with related standard errors were calculated based on summary data extracted from the original individual studies: the number of participants included (and assessed) in each arm of each RCT; and means and standard deviations of the baseline and end of trial values in intervention and control arms (at each time point and for each sodium intake level).

In arm-level meta-analyses, SBP and DBP were analysed as mean absolute values for each arm (end of trial); their related standard errors were calculated from the available summary data.

Summary mean differences and summary mean absolute values (with 95% CI) were estimated by pooling the study- or arm- specific means, assuming a random-effects model and applying the inverse-variance method.

Only measurements at the last available time point from each study were analysed; the planned sensitivity analyses on the sub-set of measures taken at 4 weeks were not carried out because of lack of time.

3. Unit of analysis issues

All included trials were assessed in order to check whether the unit of randomization was consistent with the unit of analysis.

The only cluster-randomised trial results (Alli 1992) were included as such in the study- and arm- level meta-analyses and were not retained in the dose-response analysis, because of consistency and reliability issues in the study design and analysis (see Appendix B – Arms data and Appendix C - RoB table).

Cross-over trials were analysed with consideration of the potential related design issues. Since arm estimates were used as points in subsequent arm-level analyses, study estimates were calculated from summary data as reported in the original papers and used in the study-level meta-analyses with no attempt to reproduce paired analyses (Higgins 2011). This might have possibly caused some under-weighing of the effects from cross-over trials; however, estimates from cross-over studies were systematically larger than parallel ones (see related subgroup analyses in Appendix H).

Responses from the sodium intake arms available from a study were included as long as the arms fell into different intake range subgroups. Two trials (MacGregor 1989 and Sacks 2001) had three intervention groups; the size of the control group, which was common to the two comparisons per study, was divided by two in order to have reasonably independent comparisons. In arm-level meta-analyses and meta-regressions the standard errors were calculated based on the original group size, as each arm contributed as an independent point; however, correlations across arms from the same study were taken into account in the meta-regression models.

4. Dealing with missing data

Specific formulae (Higgins 2011) were applied to derive summary data where not directly extracted/available in the format of the statistics mentioned in section 1.2 (e.g. standard deviations were calculated either from standard errors and group size or from confidence intervals). If no calculation/estimation was possible, the missing data were imputed based on information in the same trial; if available, standard deviations were imputed from other time points values, otherwise from other groups from the same study (Furukawa 2006).

Information about relevant study-level characteristics was moderately complete. The following were affected by a high proportion of missing data: mean body mass index (BMI) (63%), ethnicity (54%), mean potassium intake at baseline (37%), mean urinary sodium excretion at baseline (31%) (Appendix D, Table 3 and Table 4).

Energy intake was extracted as a potential moderator of interest (Na density may reflect the relationship with blood pressure better than absolute Na intake) but information was almost always missing in the original reports.

Blood pressure measurement position was not reported in two trials (Schorr 1996; van Berge-Landry 2004), where it was assumed to be 'sitting' for the subsequent analyses. For Puska 1983, a 50% proportion of female subjects was assumed.

Blood pressure at baseline was missing in 7 trials; an attempt was made to maximise information by categorising it according to mean values, where available, and individual study eligibility criteria (hypertensive; normotensive). The same exercise was not extended to baseline DBP as deemed not useful, so both moderators were subsequently included in models as continuous variables.

Availability of mean BMI information in the final dataset was maximised by using supporting information from the original papers; a categorical variable was created based on the mean values, where available, and individual study eligibility criteria (normal weight, overweight, obese); the missing data proportion in the new variable dropped to 54% and since it was considered inconsistent it was not further analysed as such. While developing the final model BMI missing data were included in a specific category as 'not reported', to be able to compare models with and without BMI as a covariate (i.e. assuring same number of arms in all models).

Baseline potassium intake, ethnicity and UNa at baseline were analysed likewise, although the high proportion of missing values for ethnicity and potassium prevented them from being included in the final models.

Limited attempts to contact the original authors of the individual studies were made to obtain relevant missing data. Mean age at baseline in completed years was retrieved for 4 trials (Dickinson 2014; Santos 2010; van Berge-Landry 1996; ANHMRCDS 1989) out of the original 6 missing it. The 2 trials without were excluded from the final set of the dose-response analyses but were retained in the other analyses as information on mean age was at least available as either younger or older than 50 years old.

5. Assessment of heterogeneity

Statistical heterogeneity was tested using the χ^2 test (Cochran's Q test) and was quantified by calculating the I^2 statistic. I^2 provides an estimate of the proportion of between-study variability that is attributed to heterogeneity rather than chance (Higgins 2002).
I^2 ranged between 0% and 85% in SBP study-level meta-analyses and 0% and 83% in DBP study-level meta-analyses; in arm-level metanalyses it ranged between 0% and 99% for both SBP and DBP.

Since the expected high level of heterogeneity was confirmed both across studies and arms, possible sources were explored by subgroup analysis, meta-regression and/or sensitivity analysis.

6. Data checking

For each variable, the proportion of missing observations was calculated, and range checks carried out to ensure that all values were plausible. The distributions of continuous variables were explored graphically, and the frequency distributions of categorical variables tabulated. Key variables were cross-tabulated or scattered against each other to check for consistency. Summary data were double checked against original publications whenever deemed necessary, and unit conversions of all included urinary sodium excretion values carried out where requested (mg/day converted to mmol/day by dividing by 23).

7. Meta-analyses

Random-effects meta-analyses of summary response measures were carried out using the DerSimonian and Laird approach (DerSimonian 1986), which encompasses both variability due to chance (i.e. the within-study variance component in the denominator of the individual study weight) and variability due to heterogeneity (i.e. the between-study variance component added in the denominator of the individual study weight – tau-squared statistic).

Tau-squared (τ^2) was estimated using the DerSimonian-Laird method (DerSimonian 1986); Wald-type 95% confidence intervals were estimated for all summary measures.

In meta-analyses at arm level 95% confidence intervals of the approximate predictive distribution of a future trial, based on the extent of heterogeneity (95% prediction intervals), were estimated. Prediction intervals incorporate uncertainty in the location and spread of the random effects distribution and were approximated by using the formula mean ± t_{df} x sqrt ($se^2 + \tau^2$), where t is the appropriate centile point (95%) of the t distribution with k-2 degrees of freedom, se^2 is the squared standard error and τ^2 the heterogeneity statistic.
When studies in the specific subgroups were less than 3 the distribution was inestimable and effectively infinite, thus displayed with dotted lines; also, where heterogeneity was zero the prediction intervals were still slightly wider than the confidence intervals as the t-statistic is always greater than the corresponding normal deviate (Higgins and Thompson 2001).

7.1. Studies and arms included in the meta-analyses

The mean SBP and DBP responses measured as differences in means between same trial arms (study-level meta-analyses) and as achieved absolute means in both placebo/control and intervention groups

(arm-level meta-analyses) were included in the analyses as long as the related individual trials met the following inclusion criteria:

- trial design was either randomised controlled parallel, cross-over or cluster-randomised (with a wash-out period of any duration)
- the intervention consisted in a change in sodium intake compared to usual diet, no intervention or placebo; trials with concomitant interventions deemed to affect the outcome of interest were excluded
- subjects involved were adults (≥ 18 years) and children (6 months to < 18 years) from the general population; trials including diseased individuals, individuals on a therapeutic diet (including weight loss diet), hypertensive subjects on blood pressure-lowering medications, trials in pregnant women and trials with specialised exercise (e.g. athletes, militaries) and extreme environmental conditions (e.g. prolonged exposure to unusually high temperature) were excluded.
- sodium intake was assessed based on urinary sodium excretion calculated from single or multiple 24-h urine collection(s). Other types of sodium intake measurements were excluded.

As only two studies in children met the eligibility criteria, they were evaluated individually (see scientific opinion) so that all trials included in the meta-analyses were on adults (18+ yrs old).

A total of 32 RCTs, providing 35 comparisons, met the eligibility criteria (Appendix A). All arms (68) from the eligible RCTs comparisons were included (Appendix B); McGregor 1989 and Sacks 2001 provided two comparisons (three levels of sodium intakes), so 3 arms each were retained in the pool, while all 4 arms were included from Watt 1985 as the two specific populations were considered as independent.

There were seven parallel RCTs, including one cluster-randomised trial, and 25 were cross-over RCTs.

A total of 25 trials modified sodium intake by providing subject with NaCl or placebo tablets or controlled diet with various amounts of Na ('feeding trials'), while seven trials used sodium reduction counselling ('counselling trials').

The between-group differences in mean 24-hour sodium excretion ranged from 13.3 to 285 mmol/day, with a median mean value of 72 mmol/day.

The study size ranged from 11 to 1,159 participants and the duration of the intervention lasted from 4 weeks to 36 months. A total of 17 studies involved hypertensive individuals, eight studies involved normotensive individuals and seven studies involved mixed populations.

Complete evidence tables on the included RCTs are available as an Appendix to the scientific opinion (Appendix I – table I.1, Experimental studies).

7.2. Overall summary effects

Study-level pooled estimates - The random-effect meta-analysis of the 32 eligible RCTs showed overall significant effects of sodium reduction on differences in means of SBP (–3.9 (95% CI: –5.1, –2.8) mm Hg; I^2 61.9%, $p < 0.001$; Figure 1:) and DBP (–2.0 (95% CI: –2.8, –1.2) mm Hg; I^2 60.6%, $p < 0.001$; Figure 2:).

Arm-level pooled estimates - The pooled mean estimate across the 68 arms was 137.1 (95% CI: 134.2, 140.1; Figure 3:) mm Hg for SBP and 84.0 (95% CI: 82.03, 85.9; Figure 4:) mm Hg for DBP. Heterogeneity was higher than in the study-level instances with an I^2 of 99% ($p < 0.001$) for both SBP and DBP.

Figure 1: Forest plot of the effect of salt reduction on SBP difference in means (study level). Individual study effect estimates are sorted by mean 24-hour urinary Na excretion change between groups.

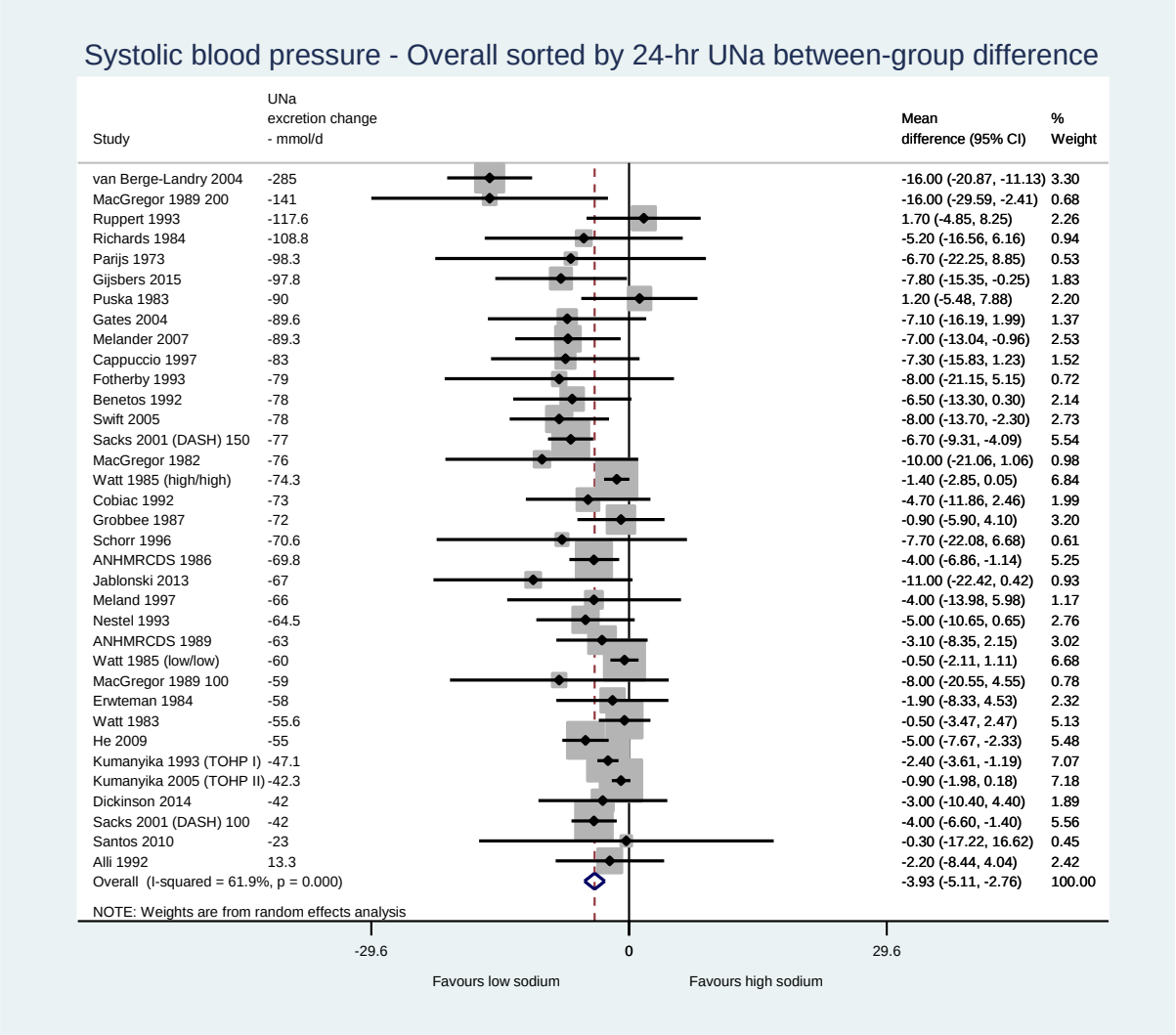


Figure 2: Forest plot of the effect of salt reduction on DBP difference in means (study level). Individual study effect estimates are sorted by mean 24-hour urinary Na excretion change between groups.

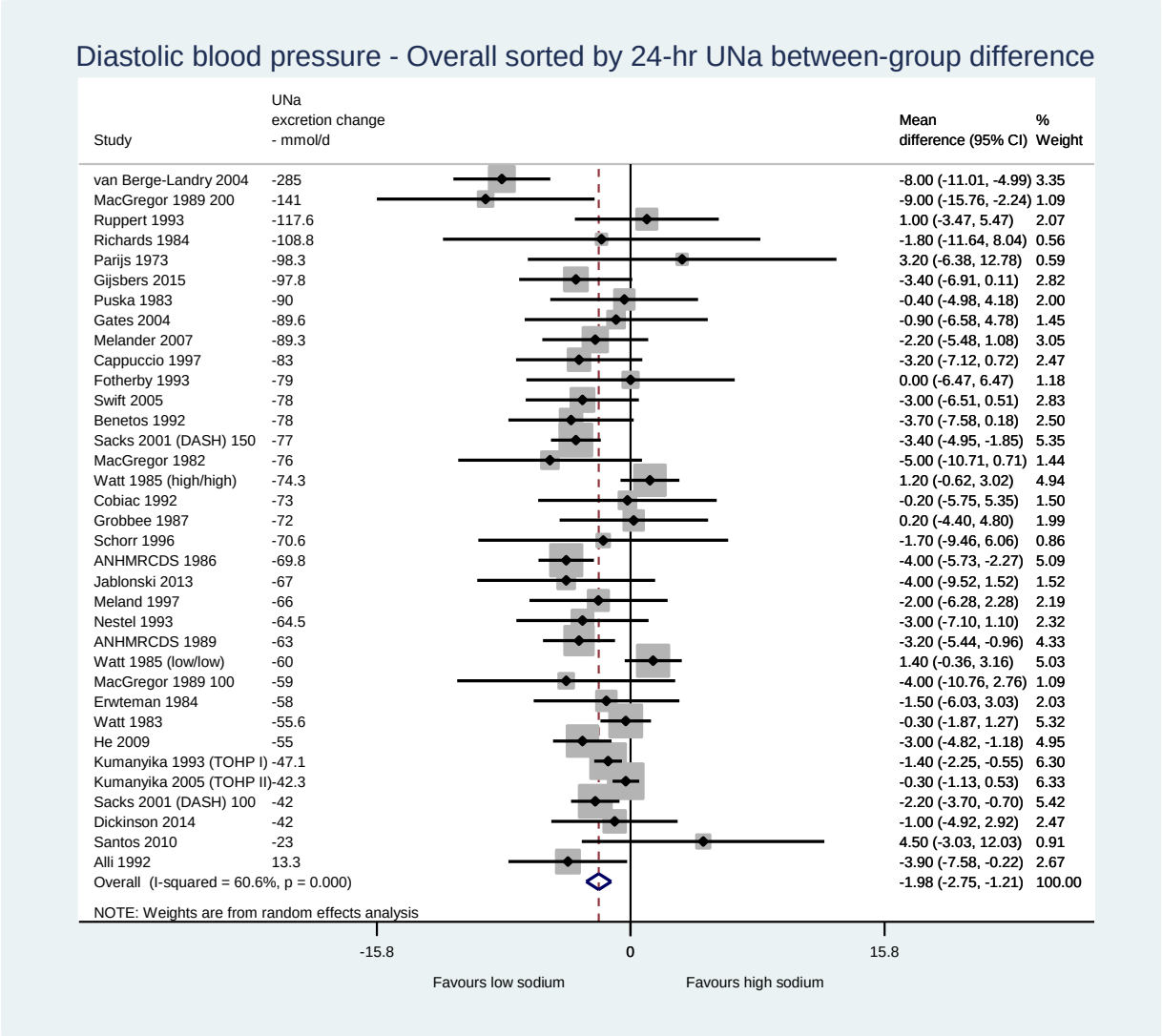


Figure 3: Mean SBP absolute values by trials arms, sorted by mean urinary Na excretion at end of trial. The pooled estimate is reported together with its 95% confidence and prediction intervals.

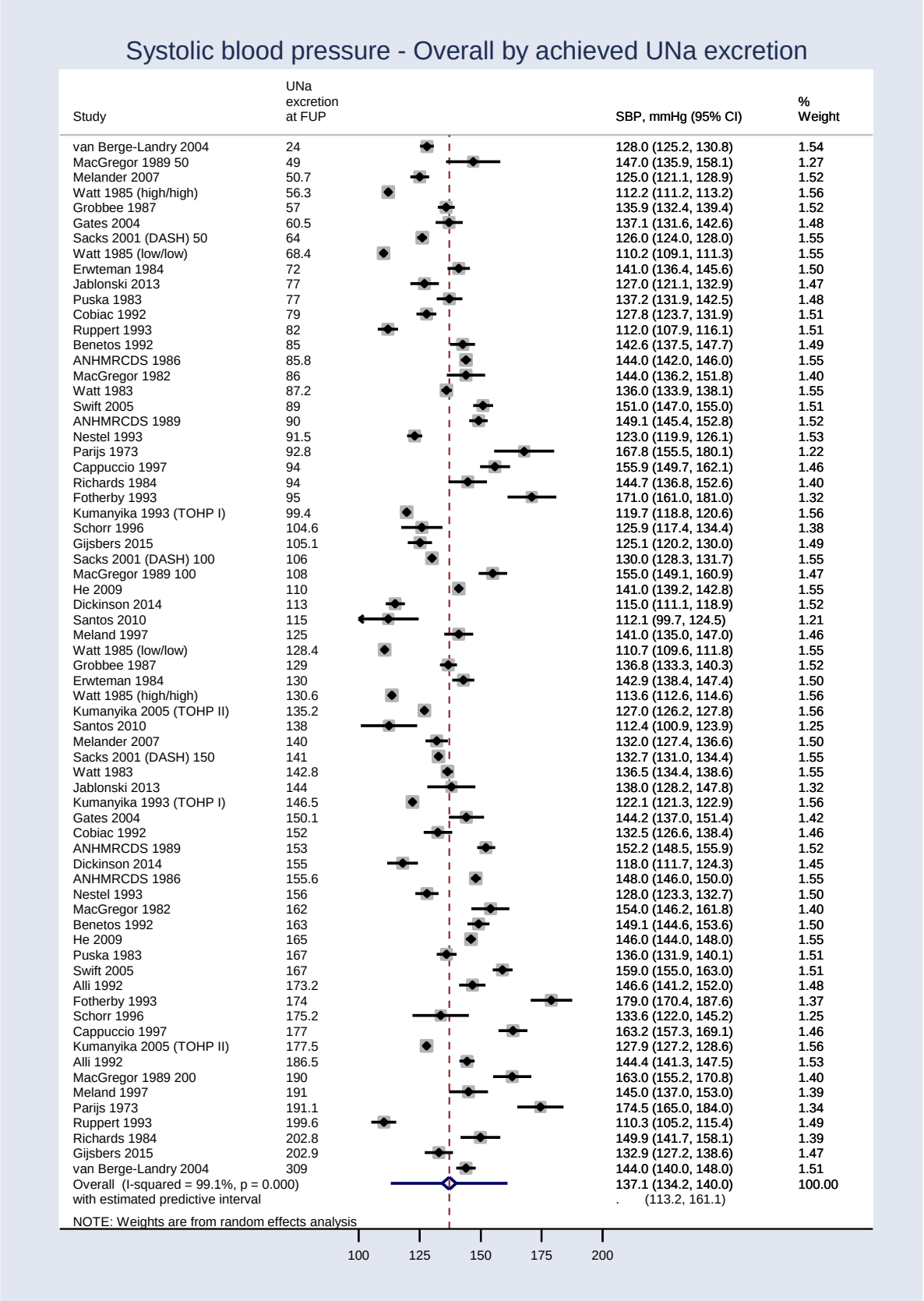
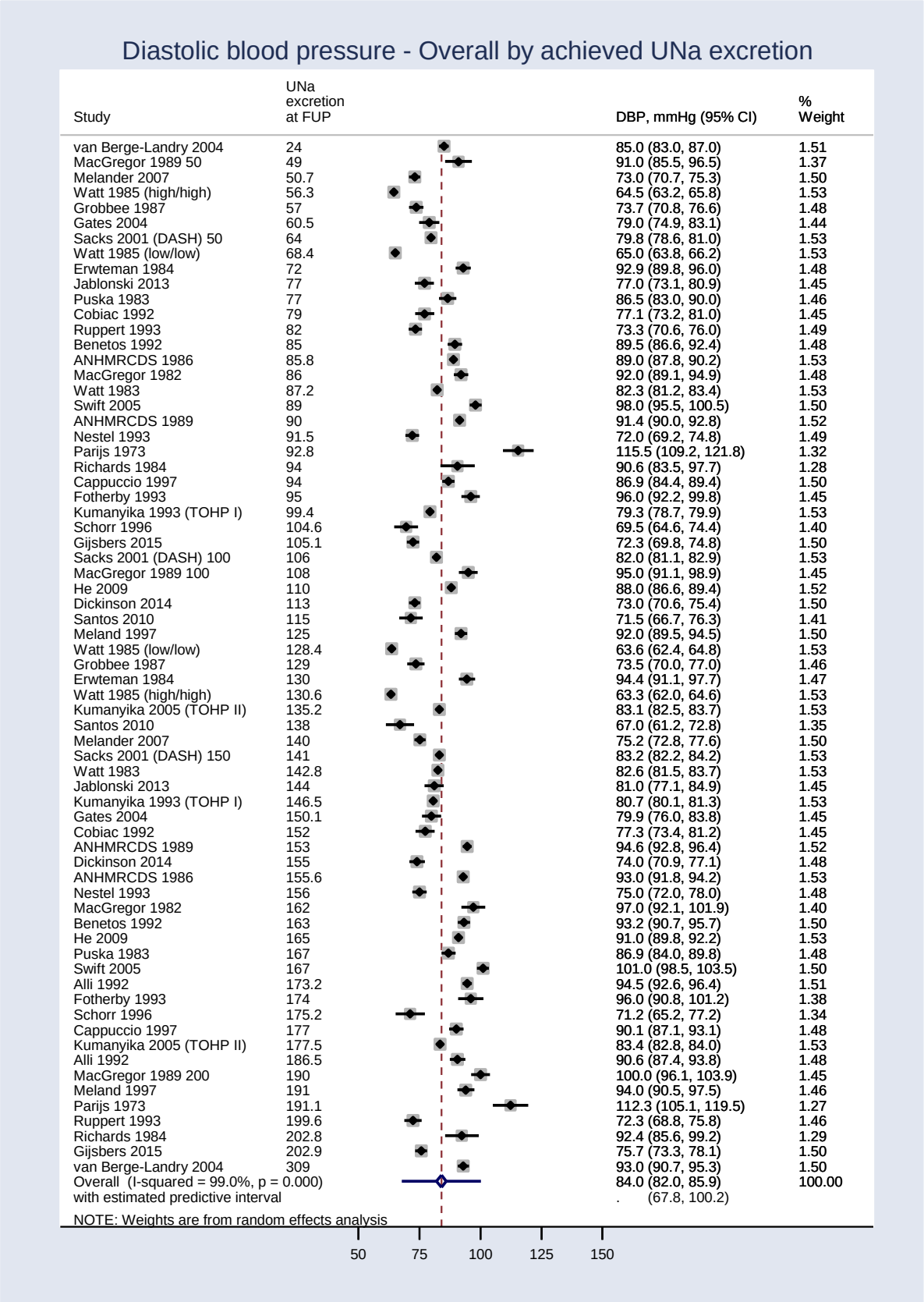


Figure 4: Mean DBP absolute values by trials arms, sorted by mean urinary Na excretion at end of trial. The pooled estimate is reported together with its 95% confidence and prediction intervals.



7.3. Subgroup analyses, investigation of heterogeneity between studies and arms

Several factors potentially influencing the dose-response relationships were identified *a priori* both from the literature and by the Panel.
Subgroup analyses (and corresponding modelling in meta-regressions) were performed to characterise methodological sources of heterogeneity and to evaluate the influence of potential effect modifiers as contextual sources of heterogeneity.

Methodological sources of heterogeneity included:

- Study design: Parallel, Cross-over, Cluster-randomised
- Specific trial design: No run-in, Run-in high sodium diet, Run-in low sodium diet, Run-in normal diet
- Trial duration: 1 month, 2-3 months, ≥ 1 year (based on duration distribution)
- Type of intervention: Feeding, Counselling
- Subject position while measuring BP: Supine, Sitting, Not reported
- Number of 24-h urinary collections: Single 24-h, Multiple 24-h, Not reported
- Risk of bias tier: Tier 1, Tier 2
- Risk of bias, specific domain: Definitively low risk of bias, Probably low risk of bias, High or NR (insufficient information) risk of bias
- Publication year: Before 1995, After 1995 (median year)
- Funding source: Public, Profit, Non-profit, Mixed, Not reported

Contextual sources of heterogeneity included:

- Age: < 50 yrs, old, ≥ 50 yrs old;
- Sex: > 55% men, 45–55% both genders, > 55% women;
- Blood pressure status: Hypertensive, Mixed, Normotensive
- BMI: < 25, 25–29, ≥ 30, NR (not reported)
- Ethnicity: Caucasian, African (including AA – African American), Mixed, NR (not reported)
- Potassium intake at baseline: ≤60 mmol/day, 61-70 mmol/day, 71-80 mmol/day, >80 mmol/day, Not reported
- SBP at baseline: <140 mm Hg, ≥140 mm Hg, Not reported
- DBP at baseline: <90 mm Hg, ≥90 mm Hg, Not reported
- Urinary sodium excretion at baseline: <100 mmol/day, 100-149 mmol/day, ≥150 mmol/day, Not reported

"At baseline" is to be understood as "after run-in" where applicable.

Specific categorisations for urinary sodium excretion at end of trial (main moderator of interest in the dose-response modelling) were used in the study-level subgroup analyses:

- Urinary sodium excretion difference across arms: as categorical in study- and arm-level meta-analyses: ≤50 mmol, 51–75 mmol, 76–100 mmol, > 100 mmol
- Urinary sodium excretion achieved in low sodium arms: ≤1.7 g/day, >1.7 & ≤2 g/day, >2 & ≤2.3 g/day, >2.3 g/day
- Urinary sodium excretion achieved in high sodium arms: ≤3 g/day, >3 & ≤3.6 g/day, >3.6 & ≤4.4 g/day, >4.4 g/day

All subgroup results, both at study level (forest plots - Appendix H) and at arm level (forest plots - Appendix I) were interpreted only qualitatively and summary estimates compared by visual inspection; summaries of the meta-analyses results at study level are reported in Appendix D, Table 3: (SBP) and Table 4: (DBP).

A larger effect was found in hypertensive than normotensive individuals, for both SBP (hypertensive: –5.6 (95% CI: –8.1, –3.1) mm Hg vs. normotensive: –2.0 (95% CI: –3.3, –0.7) mm Hg) and DBP (hypertensive: –2.9 (95% CI: –4.2, –1.6) mm Hg vs. normotensive: –0.9 (95% CI: –1.6, –0.2) mm Hg).

The effect of sodium reduction was higher among subjects aged 50 years or more (SBP –6.1 (95% CI: –8.2, –4.1) mm Hg; DBP –2.9 (95% CI: –4.0, –1.9) mm Hg) than among subjects younger than 50 years (SBP –2.2 (95% CI: –3.3, –1.1) mm Hg; DBP –1.0 (95% CI: –2.0, –0.0).

With respect to sex, a higher effect was found in studies which consisted mostly of men (i.e. > 55% of total sample) than in studies which consisted mostly of women. The exploration of the potential moderating effects of ethnicity, BMI, or potassium intake was limited by the large number of studies for which information on these factors was lacking.

Larger effects were found in cross-over compared to parallel trials and when measuring BP in supine position (SBP -5.6 (95% CI: -7.5, -3.6) mm Hg; DBP -2.7 (95% CI: -3.8, -1.5) mm Hg) compared to sitting position (SBP -2.5 (95% CI: -3.6, -1.5) mm Hg; DBP -1.4 (95% CI: -2.3, -0.5) mm Hg).

After exclusion of the van Berge-Landry study as an outlier, the effect of sodium reduction on SBP was –1.8 (95% CI: –2.9, –0.8) in 'counselling' trials and –4.0 (95% CI: –5.3, –2.7) in 'feeding' trials. The respective values for DBP were –1.7 (95% CI: –2.6, –0.9) and –1.8 (95% CI: –3.2, –0.5). The effect of sodium reduction was smaller in trials of longer duration (≥ 1 year) compared to trials of shorter duration (4 weeks).

Three population subgroup meta-analyses were planned: adults vs. children; females vs. males; normotensive vs. hypertensive); results from individual studies on specific sub-populations were not used in separated subgroup meta-analyses as the number of estimates per sub-population was limited. Subgroup analyses by sex and BP status were carried out by classifying the trials according to the proportion of sub-populations and related eligibility criteria.

Subgroup analyses were repeated at the arm level (Appendix I); the same *a priori* categorisations of relevant potential modifiers were applied to identify candidate moderators to be included in the multivariable models.

8. Dose-response models

As the number of intake categories was not sufficient to estimate study-specific trends (i.e. less than 3), a one-stage (or 'pool-first') approach was taken, where study-specific data are combined first and then one summary dose–response model is fitted. In fact, most RCTs had just a "low" sodium intake group and a "high" sodium intake group.

Mixed-effects meta-regression models were fitted to account for the multilevel structure in the data, with arms nested within studies; two random effects (intercepts) on arm and study were specified and fixed effects were included from the list of potential moderators tested in univariate meta-regressions.

Mixed-effects models incorporated the extra variability (between-studies) in the same way as in a random-effects meta-analysis, with larger studies having more influence on the relationship than smaller studies (weighted by the precision of their respective response estimate). The approach allowed for the residual heterogeneity among dose-response estimates that could not be otherwise explained by the explanatory variables identified and tested.

8.1. Trials arms included in the dose-response models

A total of 60 points (arms as unit of analysis) from 28 RCTs were included in the final dose-response models.

Two RCTs were excluded from the meta-analysis pool because of missing information on age, after contacting the authors to possibly retrieve it (Puska et al. 1983, Richards et al. 1984). One (Alli et al. 1992) was excluded after thorough consideration of some inconsistencies in the design and results of the study. Van Berge-Landry was retained only for sensitivity analysis, given that it was the only study with UNa values in the control and intervention arms well beyond the range covered by all other trials (achieved mean urinary excretion: 309 and 24 mmol/day respectively). Two arms were included from all trials except for McGregor et. al 1989 (3), Sacks et. al 2001 (3) and Watt et. al 1985 (4).

In total 14 arms were from parallel RCTs, 46 were from cross-over RCTs and none from cluster-randomised trials. Relevant arm-level summary data are reported in Appendix B, while all study-level characteristics that apply also to arms are reported in Appendix A.

8.2. Models specification

Multilevel mixed-effects generalised linear models were fitted to the two(three)-level hierarchical data, with two observed levels, studies and arms, and a first level – subjects - that contains aggregated data (therefore, three implicit levels). Standard deviations were constrained to be equal to their estimated values at arm level. The mean-variance adaptive Gauss-Hermite quadrature was applied to estimate the integral required to calculate the log likelihood.

The independent variable was centered at 49 mmol/day (minimum mean UNa observed in the data set); by doing so the 0 point for UNa excretion was shifted to 49 mmol/day, as 0 is out of the range of plausible UNa values. Accordingly, the slope (regression coefficient) between UNa and mean BP did not change while the interpretation of the intercept (i.e. the mean of the response when all predictors are equal to their reference) was mean BP at 49 mmol/day (instead of mean BP at 0 mmol/day).

Mean urinary sodium excretion was modelled with restricted cubic splines to ensure more flexibility, as no assumptions on the dose-response curve shape are required; also, non-linear non-monotonic functional relationships (e.g. J-shaped curves) can be accommodated using only two parameters.

Different functional forms were explored for the shape of the dose-response relationship; non-linearities were tested by fitting both restricted cubic splines (three knots at 105, 128 and 145 mmol/day – Harrell's recommended percentiles) and linear splines (knot at 130 mmol/day). When only one random effect was specified in the models (trial arms), a steeper increase was detected at around 130 mmol/day; however, both splines were no longer statistically significant ($p = 0.4464$ and $p = 0.78$, respectively) once both random effects (arms and studies) were specified in the models.

Incorporation of the variability around the study intercept into the models helped overcome the 'artefact' deriving from the constraint between the control and intervention groups belonging to the same study; the distribution of low sodium arms was to some extent determined by both the distribution of the paired high sodium arms (representing « habitual » Na intake groups) and the magnitude of the between groups difference in UNa (Appendix E, Figure 8).

For each mixed-effects meta-regression model the statistics τ^2, *residual* I^2 and adjusted R^2 were calculated.

The change in τ^2 after inclusion of each covariate gives the amount of heterogeneity explained by the fitted model, and this value over the τ^2 from the null model gives the proportion of between-study variance explained (a type of adjusted R^2). τ^2 decreased from 275 to 33 (SBP) and from 129 to 19 (DBP) in the final models, with included factors explaining up to 88% (85% for DBP) of heterogeneity (Appendix E, Table 5).

The *residual* I^2 statistics gives a measure of the percentage of the residual variation (the one not explained by the covariates) that is attributable to between-study heterogeneity. Residual I^2 also decreased after inclusion of the final set of covariates yet remaining very high (90%) (Appendix E, Table 5).

In addition to the evaluation of the relative reduction of τ^2 and of the joint testing (using the F distribution) of covariates as introduced in the model, a backward elimination process was used to check the set of explanatory variables identified by manual fitting in the final model as significant predictors of mean SBP and DBP.

8.3. Model diagnostics

Outliers and influential studies were detected and tests for normality and homoscedasticity carried out to check for model assumptions (e.g. normality of the random effects).
The normal probability plot of the standardised predicted random effects did not show substantial departure from normality; no outliers were identified by evaluation of standardised residual values, as none was smaller than -1 or larger than +1 (Appendix E, Figure 7:) as estimated from the final models.

8.4. Dose-response moderators

A selection of priority study-level characteristics tested in independent subgroup analyses at arm level were incorporated in the meta-regression models one at a time and in the final multivariable models as follows:

- Urinary sodium excretion at end of trial: as continuous (mean values in mmol/day) – main predictor of interest
- Age: as continuous (mean age in completed years) and as categorical (<50 yrs old, ≥50 yrs old; < 40 yrs old, 40-49 yrs old, 50-59 yrs old, ≥ 60 yrs old)
- Sex: > 55% men, 45−55% both genders, > 55% women; > 50% men, > 50% women;
- BMI: < 25, 25−29, ≥ 30, NR (not reported)
- Ethnicity: Caucasian, African (including AA – African American), Mixed, NR (not reported)
- Blood pressure status: Hypertensive, Mixed, Normotensive; Hypertensive, Normotensive
- Potassium intake at baseline: as continuous (mmol/day) and as categorical (≤60 mmol/day, 61-70 mmol/day, 71-80 mmol/day, >80 mmol/day, Not reported)
- SBP at baseline: as continuous (mean values in mm Hg), as categorical: <140 mm Hg, ≥140 mm Hg, Not reported
- DBP at baseline: as continuous (mean values in mm Hg), as categorical: <90 mm Hg, ≥90 mm Hg, Not reported
- Urinary sodium excretion at baseline: as continuous (mmol/day) and as categorical (<100 mmol/day, 100-149 mmol/day, ≥150 mmol/day, Not reported)
- Study design: Parallel, Cross-over, Cluster-randomised
- Specific trial design: No run-in, Run-in high sodium diet, Run-in low sodium diet, Run-in normal diet; No run-in, Run-in normal diet, Run-in low sodium diet (high sodium lumped with normal diet)
- Trial duration: as continuous (in weeks) and as categorical (1 month, 2-3 months, ≥ 1 year),
- Type of intervention: Feeding, Counselling
- Subject's position while measuring BP: Supine, Sitting
- Number of 24-h urinary collections: Single 24h, Multiple 24h, Not reported
- Risk of bias tier: Tier 1, Tier 2
- Risk of bias, specific domain 'Outcome': Definitively low risk of bias, Probably low risk of bias, High or NR (insufficient information) risk of bias

"At baseline" is to be understood as "after run-in" where applicable.

8.5. Dose-response models results

The final set of covariates included in both SBP and DBP models was: mean age at baseline (<40 yrs old (ref.), 40-49, 50-59, >=60 yrs old); blood pressure status at baseline (normotensive (ref.) hypertensive); mean urinary sodium excretion at baseline (<100 mmol/day (ref.), 100-149, >=150 mmol/day); blood pressure measurement method (supine (ref.), sitting); and specific trial design (no run-in (ref.), run-in normal diet, run-in low sodium diet) Table 1: and Table 2:).

For each 100 mmol/day increase in mean urinary sodium excretion, holding all other covariates constant, mean systolic blood pressure increased linearly by 5.3 mm Hg (95%CI: 3.6-6.9 mm Hg) and mean diastolic blood pressure increased linearly by 2.6 mm Hg (95%CI: 1.6-3.7 mm Hg). Similar effects were estimated in crude models (with no other moderators than sodium excretion).

Mean sodium excretion explained only 4% of the heterogeneity across trials arms in the SBP model and 3% in the DBP model (3% and 2% respectively when study was introduced as a random intercept). However, in both models the set of moderators explained more than 85% of the between-study heterogeneity.

In stratified analyses a larger association was found in hypertensive than normotensive individuals, for both SBP (hypertensive: 6.4 (95% CI: 4.3, 8.6) mm Hg vs normotensive: 4.4 (95% CI: 2.1, 6.6) mm Hg) and DBP (hypertensive: 3.7 (95% CI: 2.5, 5.0) mm Hg vs normotensive: 1.7 (95% CI: 0.1, 3.3) mm Hg). The effect of sodium was higher among subjects aged 50 years or more (SBP 7.1 (95% CI:

5.0, 9.2) mm Hg; DBP 3.8 (95% CI: 2.6, 5.0) mm Hg) than among subjects younger than 50 years (SBP 3.5 (95% CI: 1.5, 7.4) mm Hg; DBP 1.2 (95% CI: –0.4, 2.9).

Potential moderating effects of K, BMI, and ethnicity could not be explored due to lack of information; sex showed some variability across subgroups in meta-analyses on trials, but the effect was not replicated in models on arms (proportion of males: <=50%, >50%) as it did not explain the between-study heterogeneity, neither in the univariate analyses nor in the multivariable models.

Mean baseline blood pressure was the factor explaining the highest proportion of between-study variability (86% and 80% in univariate meta-regression models for SBP and DBP respectively).
It is expected that baseline values can serve as a surrogate for many influencing factors, potentially including some of those that could not be measured in the analysed trials (or for which there was incomplete information) (Section 1.4). Given the presence of missing data (17%) and the limited informativeness of models with baseline SBP and baseline DBP as major predictors, the final adjusted models did not include them among the moderators.

A linear dose-response relationship was estimated between mean sodium urinary excretion and mean SBP and DBP at arm level (Figure 5: and Figure 6:) in the range of mean UNa between 49 and 209 mmol/day. A sensitivity analysis carried out to assess the impact of the inclusion of van Berge-Landry arms showed practically no change in the regression coefficient for sodium (SBP 5.4 (95% CI: 4.1, 6.7) mm Hg; DBP 2.7 (95% CI: 1.9, 3.5) mm Hg) in fully adjusted models (Appendix F, Figure 10: ; figure on DBP not shown).

Table 1: Multivariable mixed-effects meta-regression model on **systolic blood pressure**, only fixed effects reported. Centered at 49 mmol/d sodium excretion (minimum mean UNa observed in the data set); total heterogeneity (random effect on trial) estimated from null model = 275.2 (95% CI: 161.4 - 468.9), residual heterogeneity from full model = 33.4 (95% CI: 13.3 to 53.5).

Covariate	β coefficient	Std. Error	P>|z|	95% Confidence Interval
Mean UNa excretion – 100 mmol/d per unit	**5.3**	**0.8**	**<0.001**	**(3.6 to 6.9)**
Age at baseline				
Age < 40 yrs old*	0			
Age 40-49 yrs old	18.2	4.4	<0.001	(9.6 to 26.9)
Age 50-59 yrs old	11.6	4.7	0.013	(2.4 to 20.7)
Age >= 60 yrs old	12.4	4.2	0.003	(4.3 to 20.6)
Blood pressure status				
Normotensive*	0			
Hypertensive	11.4	4.5	0.011	(2.6 to 20.1)
UNa excretion at baseline				
<100 mmol/d*	0			
100-149 mmol/d	25.2	6.3	<0.001	(12.7 to 37.6)
>=150 mmol/d	18.7	6.4	0.004	(6.0 to 31.3)
Not reported	13.4	5.3	0.012	(3.0 to 23.8)
BP measurement method				
Point office, supine*	0			
Point office, sitting	-13.2	3.2	<0.001	(-19.6 to -6.9)
Specific trial design				
No Run-in*		0		
Run-in, Normal Diet	11.9	3.4	<0.001	(5.3 to 18.5)
Run-in, Low Na Diet	19.7	5.1	<0.001	(9.7 to 29.8)
Constant	95.5	6.8	<0.001	(82.2 to 108.8)

* reference category

Table 2: Multivariable mixed-effects meta-regression model on **diastolic blood pressure**, only fixed effects reported. Centred at 49 mmol/d sodium excretion (minimum mean UNa observed in the data set); total heterogeneity (random effect on trial) estimated from null model = 129.1 (95% CI: 76.1 - 218.8), residual heterogeneity from full model = 18.8 (95% CI: 8.1 to 29.4).

Covariate	β coefficient	Std. Error	P>|z|	95% Confidence Interval
Mean UNa excretion – 100 mmol/d per unit	**2.6**	**0.5**	**<0.001**	**(1.6 to 3.7)**
Age at baseline				
Age < 40 yrs old*	0			
Age 40-49 yrs old	18.2	3.2	<0.001	(11.9 to 24.6)
Age 50-59 yrs old	11.8	3.5	0.001	(5.1 to 18.6)
Age >= 60 yrs old	7.8	3.1	0.011	(1.8 to 13.8)
Blood pressure status				
Normotensive*	0			
Hypertensive	8.7	3.3	0.008	(2.3 to 15.1)
UNa excretion at baseline				
<100 mmol/d*	0			
100-149 mmol/d	10.4	4.5	0.022	(1.5 to 19.3)
>=150 mmol/d	10.2	4.7	0.028	(1.1 to 19.4)
Not reported	10.4	3.8	0.007	(2.9 to 17.9)
BP measurement method				
Point office, supine*	0			
Point office, sitting	-6.6	2.4	0.005	(-11.3 to -2.0)
Specific trial design				
No Run-in*		0		
Run-in, Normal Diet	7.9	2.5	0.002	(3.0 to 12.7)
Run-in, Low Na Diet	7.7	3.7	0.037	(0.5 to 15.0)
Constant	55.4	4.8	<0.001	(45.9 to 64.8)

* reference category

Figure 5: Linear dose-response relationship between mean urinary sodium excretion and **mean systolic blood pressure** from meta-regression modelling of trials arms (crude model). Circles represents mean SBP by arm and their size is proportional to weigths from the mixed-effects model. The slope from the full model with moderators did not differ substantially (UNa unadjusted coefficient: 5.2 mm Hg per 100 mmol/day, 95% CI: 3.6-6.9).

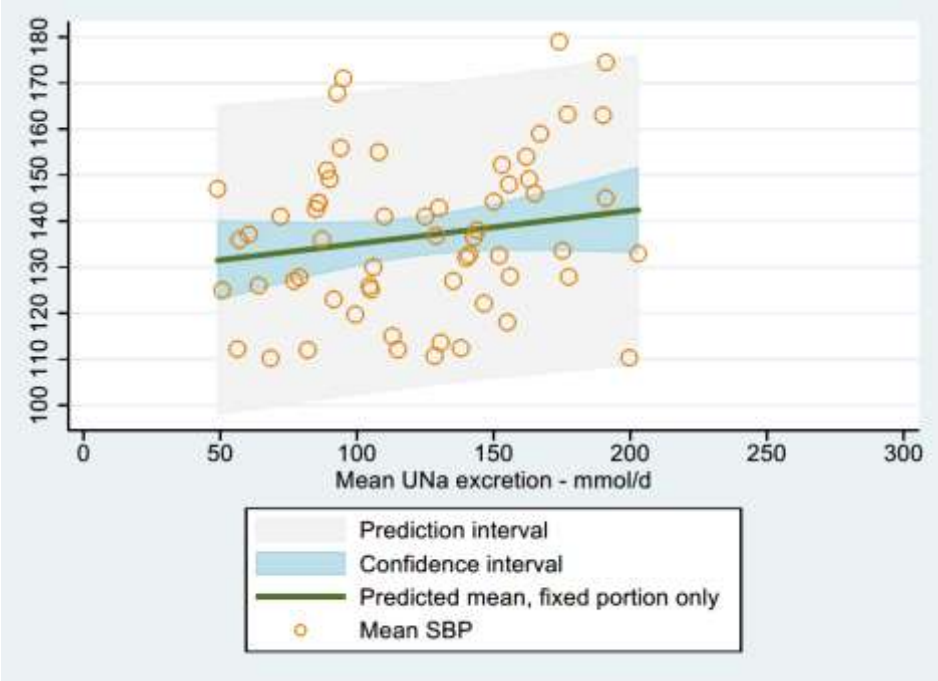
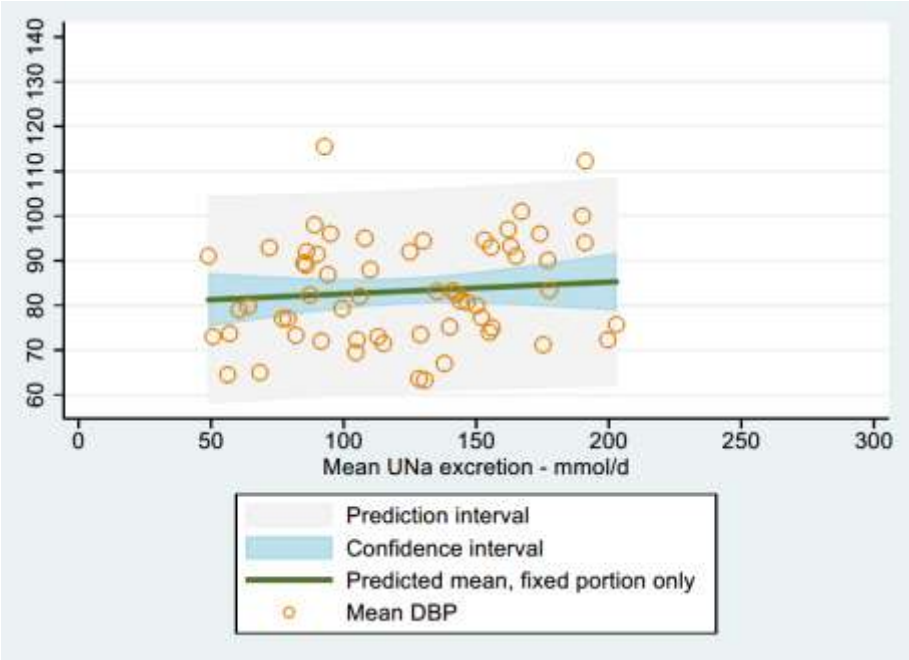


Figure 6: Linear dose-response relationship between mean urinary sodium excretion and **mean diastolic blood pressure** from meta-regression modelling of trials arms (crude model). Circles represents mean DBP by arm and their size is proportional to weigths from the mixed-effects model. The slope from the full model with moderators did not differ substantially (UNa unadjusted coefficient: 2.6 mm Hg per 100 mmol/day, 95% CI: 1.6-3.7).



9. Addressing risk of bias in the analysis

The outcome of the risk of bias assessment (individual dimensions and overall assessment) was used to evaluate whether heterogeneity of results could be attributed to differences in internal validity across individual studies, both in the meta-analyses and in meta-regression models (Appendix C). The following approaches were applied:

- A study-level subgroup analysis based on the overall RoB rating as expressed by different tiers of reliability (tier 1 and 2) was carried out and stratified pooled estimates showed a larger effect in tier 2 trials (Appendix D, Table 3: and Table 4: , Appendix H). Tier of risk of bias was not part of the final set of covariates as its adjusted R^2 was negligible.
- Individual RoB dimensions were evaluated in univariate and multivariable analyses. 'Outcome assessment' was found to play a role in further explaining heterogeneity (Appendix H) while all other dimensions (randomization appropriate, allocation concealment, etc.) did not have a statistically significant impact on the estimates (data not shown). However, outcome assessment was not included in the final models as the stratum showing larger estimates was based on a very few studies, including van Berge-Landry 2004.

10. Sensitivity Analyses

Sensitivity analyses were carried out to evaluate whether the findings were robust to the assumptions made in the systematic review protocols and the analyses.

There were a number of assumptions/decisions/issues provisionally identified that could potentially be tested in sensitivity analyses by comparing the results obtained with alternative input parameters to those from the default model or by restricting to specific sub-sets; none of them raised serious concerns about the robustness of the overall analysis.
The following analyses were considered, and results are reported under section 7.3 and 8.5:

- sitting vs supine measurements;
- use of the average 24-hour urinary sodium collections as opposed to single 24-hour collection;
- van Berge-Landry exclusion with respect to type of intervention in subgroup analyses for SBP and DBP (Appendix F, Figure 9);
- van Berge-Landry inclusion in dose-response models, given its specific UNa values range not covered by all other trials (Appendix F, Figure 10)

Point BP and 24-h BP represent two different biological variables which could be differentially affected by sodium intake. Accordingly, all available measures (point office/home BP, 24-h BP) were extracted from each study but were not evaluated in subgroup analyses due to lack of time.

11. Publication bias

Several systematic reviews of empirical studies have found that studies with statistically significant ($P<0.05$) or positive results are more likely to be published than those with non-significant or negative results and tend to be published earlier.

Publication bias was assessed by visual inspection of the funnel plot (Sterne et al. 2001) and by performing the Egger's test for funnel plot asymmetry (Egger et al. 1997; Sterne et al., 2005) on mean differences in SBP from the 32 RCTs included in the meta-analyses. Contours of statistical significance were superimposed on the funnel plot to help evaluate potential small-study effects (Appendix G, Figure 11).

Egger's test performed a linear regression of the mean difference estimates on their standard errors, weighted by 1 / (variance of the summary estimate) (Appendix G, Figure 12); the test was statistically significant ($p = 0.001$).

Funnel plots investigate the association between study size and effect size; there was a clear indication of funnel plot asymmetry, as trials were missing in the right-hand side of the funnel. Since studies

spread across all areas of significance publication bias was not considered a plausible explanation for the plot asymmetry (Sterne 2011).

12. Analysis uncertainties

Sources of uncertainty specific to the statistical analysis and their potential impact on the final estimates, where possible, were identified and described. Results from the sensitivity analyses further contributed to the interpretation of the dose-response results and together with additional considerations informed the overall assessment of the uncertainty in the body of evidence (see section 6 in the scientific opinion).

- The nature and structure of the dataset introduced specific challenges to model interpretation; there was a strong 'methodological' component (covariates that were linked to the experimental setting) included in the models in order to reach a good fitting and that explained a large part of the heterogeneity between studies (random effects).
- Constants (intercepts) and predictions were difficult to reconcile with 'populations' values (and were substantially influenced by experimental factors).
- The use of data generated in controlled settings was expected to provide a better characterisation of the sodium-blood pressure relationship than using data from observational studies (due to potential confounding); however, the experimental setting was broken to conduct an « observational » type of analysis (with paired points).
- Due to missing information it was not possible to explore important moderators (e.g. BMI, ethnicity, potassium intake and energy intake).
- The model is conditional to the data set and population characteristics of included trials (e.g. relative proportion of trials in normotensives vs. hypertensives, age groups, sex); most studies were of short duration and cross-over by design.
- There was large heterogeneity around the dose-response (I^2 = 99%); the mixed-effects meta-regression models with 2 random effects and 5 fixed effects explained 85%-88% of it, yet 15% remained unexplained.
- Previous analyses on sodium intake and blood pressure have encountered difficulties in taking into account the high inter-individual and intra-individual variability of their measurements. The confidence interval in meta-regression analyses provides only an estimate of the uncertainty about the fitted response line due to sampling; meta-regressions performed on individual participant data could be a better approach to address this limitation, not applicable in the case of the current analysis as no individual data were available.
- General considerations around meta-regression (Thompson 2002) also apply: the model is a representation of the relationship between mean Na and mean BP at 'group' level (aggregated data), it may be different when explored on individual data (aggregation bias); the relationship described is observational in nature, even when is classically modelled on trials effect measures (as opposed to arms absolute values); some factors could not be explored because were not sufficiently variable across studies (e.g. risk of bias from outcome assessment).

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Appendices

Appendix A - Trials main characteristics

Eligibility criteria, relevant contextual and methodological characteristics, and summary data of thirty-two trials (35 comparisons) included in study-level meta-analyses.

Study	Country	N of subjects	Mean age	Age - eligibility criteria	Women %	BP status	Ethnicity
			years	*years*	*%*		
Alli 1992	IT	56	44.3	18+	65	Hypertensive	Not reported
ANHMRCDS 1986	AU	100	52.3	40-65	14	Mixed	Not reported
ANHMRCDS 1989	AU	103	58	18+	16	Hypertensive	Not reported
Benetos 1992	FR	20	41.5	22-55	55	Hypertensive	Not reported
Cappuccio 1997	UK	47	66.8	(60-78)	49	Mixed	Mixed
Cobiac 1992	AU	54	67	60-80	33	Mixed	Not reported
Dickinson 2014	AU	25	56.8	18+	68	Normotensive	Not reported
Erwteman 1984	NL	94	45	20-70	38	Hypertensive	Mixed
Fotherby 1993	UK	17	73	(66-79)	76	Hypertensive	Caucasian
Gates 2004	US	12	63	50+	50	Hypertensive	Caucasian
Gijsbers 2015	NL	36	65.8	40-80	33	Mixed	Caucasian
Grobbee 1987	NL	40	24	(18-28)	15	Hypertensive	Not reported
He 2009	UK	169	50	30-75	33	Hypertensive	Mixed
Jablonski 2013	US	11	60	50-79	27	Mixed	Mixed
Kumanyika 1993 (TOHP I)	US	699	43.4	30-54	28	Normotensive	Mixed
Kumanyika 2005 (TOHP II)	US	1029	44.2	30-54	33	Normotensive	Mixed
MacGregor 1982	UK	19	49	(30-66)	26	Hypertensive	Mixed
MacGregor 1989 100	UK	20	57	(42-72)	45	Hypertensive	Mixed
MacGregor 1989 200	UK	20	57	(42-72)	45	Hypertensive	Mixed
Meland 1997	NO	16	50	20-69	19	Hypertensive	Not reported
Melander 2007	SE	39	53	18+	49	Normotensive	Not reported
Nestel 1993	AU	66	65.5	60-79	50	Normotensive	Not reported
Parijs 1973	BE	17	41.2	18+	55	Hypertensive	Not reported
Puska 1983	FI	72	-	30-50	50	Mixed	Not reported
Richards 1984	NZ	12	-	(19-52)	33	Hypertensive	Not reported
Ruppert 1993	DE	25	47	(19-78)	60	Normotensive	Not reported
Sacks 2001 (DASH) 100	US	192	49	22+	54	Mixed	Mixed
Sacks 2001 (DASH) 150	US	192	49	22+	54	Mixed	Mixed
Santos 2010	PT	17	38.5	(24-53)	53	Normotensive	Not reported
Schorr 1996	DE	16	64.1	(60-72)	56	Normotensive	Not reported
Swift 2005	UK	40	50	18+	57	Hypertensive	African incl. AA
van Berge-Landry 2004	US	48	51	middle-aged adults	21	Hypertensive	Mixed
Watt 1983	UK	18	52	(31-64)	67	Hypertensive	Not reported
Watt 1985 (high/high)	UK	35	22.3	young adults	63	Mixed	Not reported
Watt 1985 (low/low)	UK	31	22.7	young adults	55	Mixed	Not reported

Study	Study design	Specific trial design	Trial duration	Intervention type	Number of urinary collections	BP measure position
			weeks			*point office*
Alli 1992	Cluster-randomized	Run-in - Normal diet	52	Counselling	Single 24h	Supine
ANHMRCDS 1986	Parallel	Run-in - Normal diet	12	Counselling	Single 24h	Sitting
ANHMRCDS 1989	Parallel	Run-in - Normal diet	8	Feeding	Single 24h	Sitting
Benetos 1992	Cross-over	No run-in	4	Feeding	Single 24h	Supine
Cappuccio 1997	Cross-over	Run-in - Low Na diet	4	Feeding	Multiple 24h	Supine
Cobiac 1992	Parallel	Run-in - High Na diet	4	Feeding	Single 24h	Sitting
Dickinson 2014	Cross-over	No run-in	6	Feeding	Multiple 24h	Sitting
Erwteman 1984	Parallel	No run-in	4	Counselling	Multiple 24h	Supine
Fotherby 1993	Cross-over	Run-in - Low Na diet	5	Feeding	Multiple 24h	Supine
Gates 2004	Cross-over	No run-in	4	Feeding	Single 24h	Supine
Gijsbers 2015	Cross-over	Run-in - Low Na diet	6	Feeding	Single 24h	Supine
Grobbee 1987	Cross-over	Run-in - Normal diet	6	Feeding	Multiple 24h	Supine
He 2009	Cross-over	Run-in - Low Na diet	6	Feeding	Multiple 24h	Sitting
Jablonski 2013	Cross-over	No run-in	5	Feeding	Multiple 24h	Supine
Kumanyika 1993 (TOHP I)	Parallel	No run-in	78	Counselling	Single 24h	Sitting
Kumanyika 2005 (TOHP II)	Parallel	No run-in	156	Counselling	Not reported	Sitting
MacGregor 1982	Cross-over	Run-in - Low Na diet	4	Feeding	Multiple 24h	Supine
MacGregor 1989 100	Cross-over	Run-in - Low Na diet	4	Feeding	Multiple 24h	Supine
MacGregor 1989 200	Cross-over	Run-in - Low Na diet	4	Feeding	Multiple 24h	Supine
Meland 1997	Cross-over	Run-in - Normal diet	8	Feeding	Single 24h	Sitting
Melander 2007	Cross-over	No run-in	4	Feeding	Single 24h	Supine
Nestel 1993	Parallel	Run-in - High Na diet	4	Feeding	Single 24h	Sitting
Parijs 1973	Cross-over	Run-in - Normal diet	4	Feeding	Single 24h	Supine
Puska 1983	Parallel	No run-in	6	Counselling	Single 24h	Sitting
Richards 1984	Cross-over	No run-in	5	Feeding	Multiple 24h	Supine
Ruppert 1993	Cross-over	No run-in	4	Feeding	Single 24h	Sitting
Sacks 2001 (DASH) 100	Cross-over	Run-in - High Na diet	4	Feeding	Single 24h	Sitting
Sacks 2001 (DASH) 150	Cross-over	Run-in - High Na diet	4	Feeding	Single 24h	Sitting
Santos 2010	Cross-over	No run-in	7	Feeding	Single 24h	Supine
Schorr 1996	Cross-over	No run-in	4	Feeding	Multiple 24h	NR
Swift 2005	Cross-over	Run-in - Low Na diet	4	Feeding	Not reported	Supine
van Berge-Landry 2004	Cross-over	Run-in - Normal diet	4	Counselling	Single 24h	NR
Watt 1983	Cross-over	Run-in - Low Na diet	4	Feeding	Single 24h	Sitting
Watt 1985 (high/high)	Cross-over	No run-in	4	Feeding	Single 24h	Sitting
Watt 1985 (low/low)	Cross-over	No run-in	4	Feeding	Single 24h	Sitting

Study	Mean BMI	Mean baseline K excretion	Achieved UNa	UNa mean diff.	SBP mean diff.	SBP mean diff. SE	DBP mean diff.	DBP mean diff. SE
	kg/m²	*mmol/day*						
Alli 1992	25	61.2	186.5	13.3	-2.2	3.2	-3.9	1.9
ANHMRCDS 1986	-	66	85.8	-69.8	-4.0	1.5	-4.0	0.9
ANHMRCDS 1989	-	73	90	-63	-3.1	2.7	-3.2	1.1
Benetos 1992	-	70	85	-78	-6.5	3.5	-3.7	2.0
Cappuccio 1997	-	66	94	-83	-7.3	4.4	-3.2	2.0
Cobiac 1992	25	74	79	-73	-4.7	3.7	-0.2	2.8
Dickinson 2014	-	76	113	-42	-3.0	3.8	-1.0	2.0
Erwteman 1984	-	-	72	-58	-1.9	3.3	-1.5	2.3
Fotherby 1993	-	66	95	-79	-8.0	6.7	0.0	3.3
Gates 2004	25.1	72	60.5	-89.6	-7.1	4.6	-0.9	2.9
Gijsbers 2015	27.2	81.8	105.1	-97.8	-7.8	3.9	-3.4	1.8
Grobbee 1987	-	71	57	-72	-0.9	2.5	0.2	2.3
He 2009	29	77	110	-55	-5.0	1.4	-3.0	0.9
Jablonski 2013	27.2	-	77	-67	-11.0	5.8	-4.0	2.8
Kumanyika 1993 (TOHP I)	27.1	61.8	99.4	-47.1	-2.4	0.6	-1.4	0.4
Kumanyika 2005 (TOHP II)	-	66.8	135.2	-42.3	-0.9	0.6	-0.3	0.4
MacGregor 1982	-	59	86	-76	-10.0	5.6	-5.0	2.9
MacGregor 1989 100	-	-	49	-59	-8.0	6.4	-4.0	3.4
MacGregor 1989 200	-	-	49	-141	-16.0	6.9	-9.0	3.4
Meland 1997	-	-	125	-66	-4.0	5.1	-2.0	2.2
Melander 2007	26.3	75	50.7	-89.3	-7.0	3.1	-2.2	1.7
Nestel 1993	24.5	87	91.5	-64.5	-5.0	2.9	-3.0	2.1
Parijs 1973	-	-	92.8	-98.3	-6.7	7.9	3.2	4.9
Puska 1983	-	81	77	-90	1.2	3.4	-0.4	2.3
Richards 1984	-	-	94	-108.8	-5.2	5.8	-1.8	5.0
Ruppert 1993	-	-	82	-117.6	1.7	3.3	1.0	2.3
Sacks 2001 (DASH) 100	30	-	64	-42	-4.0	1.3	-2.2	0.8
Sacks 2001 (DASH) 150	30	-	64	-77	-6.7	1.3	-3.4	0.8
Santos 2010	-	-	115	-23	-0.3	8.6	4.5	3.8
Schorr 1996	26.1	-	104.6	-70.6	-7.7	7.3	-1.7	4.0
Swift 2005	28	63	89	-78	-8.0	2.9	-3.0	1.8
van Berge-Landry 2004	-	-	24	-285	-16.0	2.5	-8.0	1.5
Watt 1983	-	59.2	87.2	-55.6	-0.5	1.5	-0.3	0.8
Watt 1985 (high/high)	-	53.8	56.3	-74.3	-1.4	0.7	1.2	0.9
Watt 1985 (low/low)	-	60	68.4	-60	-0.5	0.8	1.4	0.9

Appendix B – Trial arms summary data

Mean UNa values at baseline and end of trial, mean BP and related standard deviations of 68 arms (from 35 RCTs comparisons) included in arm-level meta-analyses and in the dose-response modelling.

Study arm	Subjects per arm	Baseline mean UNa	Achieved mean UNa	Achieved mean SBP	Achieved SBP SD	Achieved mean DBP	Achieved DBP SD
		mmol/d	*mmol/d*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*
Alli 1992*	26	177.2	186.5	144.4	8.1	90.6	8.2
Alli 1992*	30	174	173.2	146.6	15.1	94.5	5.3
ANHMRCDS 1986	48	142	85.8	144	7.2	89	4.3
ANHMRCDS 1986	52	157	155.6	148	7.4	93	4.5
ANHMRCDS 1989	50	142	90	149.1	13.4	91.4	4.9
ANHMRCDS 1989	53	134	153	152.2	13.8	94.6	6.6
Benetos 1992	20	173	85	142.6	11.6	89.5	6.7
Benetos 1992	20	173	163	149.1	10.3	93.2	5.8
Cappuccio 1997	47	72	94	155.9	21.6	86.9	8.8
Cappuccio 1997	47	72	177	163.2	20.6	90.1	10.5
Cobiac 1992	26	166	79	127.8	10.6	77.1	10.2
Cobiac 1992	28	166	152	132.5	15.9	77.3	10.6
Dickinson 2014	25	154	113	115	10	73	6
Dickinson 2014	25	154	155	118	16	74	8
Erwteman 1984	44		72	141	15.4	92.9	10.4
Erwteman 1984	50		130	142.9	16.4	94.4	12
Fotherby 1993	17	104	95	171	21	96	8
Fotherby 1993	17	104	174	179	18	96	11
Gates 2004	12	134.5	60.5	137.1	9.7	79	7.3
Gates 2004	12	134.5	150.1	144.2	12.8	79.9	6.9
Gijsbers 2015	36	90.8	105.1	125.1	15	72.3	7.7
Gijsbers 2015	36	90.8	202.9	132.9	17.6	75.7	7.5
Grobbee 1987	40	141	57	135.9	11.4	73.7	9.5
Grobbee 1987	40	141	129	136.8	11.4	73.5	11.4
He 2009	169		110	141	12	88	9
He 2009	169		165	146	13	91	8
Jablonski 2013	11	159	77	127	9.9	77	6.6
Jablonski 2013	11	159	144	138	16.6	81	6.6
Kumanyika 1993 (TOHP I)	304	154.6	99.4	119.7	7.94	79.3	5.65
Kumanyika 1993 (TOHP I)	395	156.4	146.5	122.1	8.31	80.7	5.8
Kumanyika 2005 (TOHP II)	515	186.1	135.2	127	9.2	83.1	6.5
Kumanyika 2005 (TOHP II)	514	188	177.5	127.9	8.5	83.4	7
MacGregor 1982	19	83	86	144	17.4	92	6.5
MacGregor 1982	19	83	162	154	17.4	97	10.9
MacGregor 1989 50	20		49	147	17.9	91	8.9
MacGregor 1989 100	20		108	155	13.4	95	8.9
MacGregor 1989 200	20		190	163	17.9	100	

Meland 1997	16	177	125	141	12.2	92	5.1
Meland 1997	16	177	191	145	16.3	94	7.1
Melander 2007	39	165	50.7	125	12.4	73	7.3
Melander 2007	39	165	140	132	14.7	75.2	7.5
Nestel 1993	32	182.5	91.5	123	9	72	8
Nestel 1993	34	162	156	128	14	75	9
Parijs 1973	15		92.8	167.8	24.3	115.5	12.45
Parijs 1973	17		191.1	174.5	20.02	112.3	15.17
Puska 1983*	34	192	77	137.2	15.7	86.5	10.5
Puska 1983*	38	165	167	136	12.9	86.9	9.2
Richards 1984*	12		94	144.7	13.9	90.6	12.5
Richards 1984*	12		202.8	149.9	14.5	92.4	12.1
Ruppert 1993	25		82	112	10.5	73.3	7
Ruppert 1993	25		199.6	110.3	13	72.3	9
Sacks 2001 (DASH) 50	192	152	64	126	10	79.8	6
Sacks 2001 (DASH) 100	192	152	106	130	11.7	82	6.4
Sacks 2001 (DASH) 150	192	152	141	132.7	11.9	83.2	
Santos 2010	17		115	112.1	26.1	71.5	10.1
Santos 2010	17		138	112.4	24.2	67	12.2
Schorr 1996	16	141.8	104.6	125.9	17.3	69.5	10.1
Schorr 1996	16	141.8	175.2	133.6	23.7	71.2	12.2
Swift 2005	40		89	151	13	98	8
Swift 2005	40		167	159	13	101	8
van Berge-Landry 2004*	48		24	128	10	85	7
van Berge-Landry 2004*	48		309	144	14	93	8
Watt 1983	18		87.2	136	4.6	82.3	2.4
Watt 1983	18		142.8	136.5	4.5	82.6	2.4
Watt 1985 (high/high)	35	129.7	56.3	112.2	3.1	64.5	3.89
Watt 1985 (high/high)	35	129.7	130.6	113.6	3.1	63.3	3.89
Watt 1985 (low/low)	31	151.1	68.4	110.2	3.23	65	3.54
Watt 1985 (low/low)	31	151.1	128.4	110.7	3.23	63.6	3.54

*excluded from the dose-response models (van Berge-Landry used in sensitivity analyses)

Appendix C - Outcome of RCTs RoB assessment

References	Risk of bias domains								Tier
	Randomisation	Allocation concealment	Blinding	Attrition	Exposure	Outcome	Reporting	Other threats to internal validity	
Alli 1992	+	- -	- -	- -	++	- -	++	-	2
ANHMRCDS 1986	+	NR	+ +	+	+	+ +	+ +	+	1
ANHMRCDS 1989	+	NR	+	+ +	+	+	++	+	1
Benetos 1992	++	NR	+ +	++	+	++	++	++	1
Cappuccio 1997	+	NR	-	+ +	+	+	+	+	1
Cobiac 1992	NR	NR	++	+	++	+	++	+	2
Dickinson 2014	++	NR	+	-	+	+	++	++	1
Erwteman 1984	+	NR	+	+	+	+ +	+ +	-	1
Fotherby 1993	+	NR	+	+ +	+	+	++	++	1
Gates 2004	+	+	+ +	+ +	+	++	+ +	++	1
Gijsbers 2015	+ +	+ +	+ +	+ +	+	+ +	+ +	+ +	1
Grobbee 1987	+	NR	+	++	+	++	-	++	1
He 2009	++	+	++	+	+	++	++	++	1
Jablonski 2013	++	+	+ +	+	+	+ +	+ +	++	1
Kumanyika 1993 (TOHP I)	+	NR	+ +	+ +	+	+ +	+ +	++	1
Kumanyika 2005 (TOHP II)	++	++	+	++	+	++	++	+	1
MacGregor 1982	++	++	+	++	+	++	++	+	1
MacGregor 1989 100	+	NR	+	+ +	+	+ +	+ +	+ +	1
MacGregor 1989 200	+	NR	+	+ +	+	+ +	+ +	+ +	1
Meland 1997	+	NR	+	+ +	+	+	+ +	++	1
Melander 2007	+	NR	+ +	+	+	+ +	+ +	+ +	1
Nestel 1993	NR	NR	+	+ +	+ +	+	+ +	+	2
Parijs 1973	+	NR	-	+	+	-	+ +	+	1
Puska 1983	+	NR	+	+ +	+ +	+	+ +	-	1
Richards 1984	-	-	-	+	+	+	+	+	2
Ruppert 1993	+	NR	+	+	+	+	++	++	1
Sacks 2001 (DASH) 100	+	+	+	+ +	+	+ +	+ +	++	1
Sacks 2001 (DASH) 150	+	NR	-	+ +	+	+	+ +	+	1
Santos 2010	+	NR	+	+	+	+	++	+	1
Schorr 1996	+	NR	+ +	+ +	+	+	++	+ +	1
Swift 2005	+	NR	-	+ +	+	NR	+ +	+	2
van Berge-Landry 2004	+	NR	+	+ +	+	+	+ +	+ +	1

Appendix D - Summary of meta-analyses results at study-level

Table 3: Subgroup analyses results for **systolic blood pressure** are summarised below and displayed in forest plots in Appendix E. I^2 is the estimated proportion of variance due to heterogeneity in each subgroup; the p value of the test for heterogeneity based on Cochran's Q statistic is reported in the last column.

	Subgroups	N studies	N subjects	Mean diff.	95% CI		I^2	p
All	Adults	35	3407	-3.9	-5.1	-2.8	62%	< 0.001
BP	Hypertensive	17	721	-5.6	-8.1	-3.1	58%	0.001
	Mixed	10	770	-3.5	-5.4	-1.7	67%	0.001
	Normotensive	8	1916	-2.0	-3.3	-0.7	26%	0.218
Age	Adults < 50 yrs	16	632	-2.2	-3.3	-1.1	49%	0.014
	Adults ≥ 50 yrs	19	2775	-6.1	-8.2	-4.1	50%	0.007
Sex	> 55% men	14	2430	-4.5	-6.5	-2.6	74%	< 0.001
	45–55% both genders	14	761	-4.7	-7.0	-2.5	55%	0.007
	> 55% women	7	216	-1.8	-3.6	0.0	20%	0.277
BMI	< 25	1	66	-5.0	-10.6	0.6	-	-
	25–29	10	1132	-4.6	-6.3	-2.8	26%	0.207
	≥ 30	2	384	-5.3	-8.0	-2.7	52%	0.151
	Not reported	**22**	1825	-3.1	-4.7	-1.6	62%	< 0.001
Ethnicity	Caucasian	3	65	-7.6	-12.9	-2.3	0%	0.991
	African (including AA)	1	40	-8.0	-13.7	-2.3	-	-
	Mixed	12	2540	-5.7	-8.0	-3.4	82%	< 0.001
	Not reported	**19**	762	-1.7	-2.5	-0.8	0%	0.578
Potassium	≤ 60 mmol/d	4	103	-1.0	-2.1	0.1	9%	0.346
	>60–≤ 70 mmol/d	8	2008	-3.0	-4.6	-1.4	52%	0.043
	>70–≤ 80 mmol/d	7	442	-4.3	-6.2	-2.5	0%	0.743
	> 80 mmol/d	3	174	-3.8	-8.7	1.2	41%	0.183
	Not reported	**13**	680	-6.4	-9.5	-3.3	59%	0.004
Design	Parallel	8	2217	-2.0	-3.1	-1.0	20%	0.272
	Cross–over	26	1134	-5.0	-6.8	-3.3	67%	< 0.001
	Cluster–randomized	1	56	-2.2	-8.4	4.0	-	-
Specific design	Run-in - Normal diet	7	380	-5.2	-9.6	-0.9	75%	0.001
	Run-in – Low Na diet	9	386	-5.8	-8.6	-2.9	43%	0.083
	Run-in – High Na diet	4	504	-5.3	-7.0	-3.6	0%	0.552
	No run-in	15	2137	-1.6	-2.5	-0.8	18%	0.254
Duration	1 month	20	1005	-5.1	-7.0	-3.1	72%	< 0.001
	2-3 months	12	618	-4.0	-5.5	-2.5	0%	0.755
	≥ 1 year	3	1784	-1.6	-2.8	-0.4	40%	0.191
Intervention type	Feeding	28	1309	-4.0	-5.3	-2.7	44%	0.007
	Counselling	7	2098	-3.7	-6.2	-1.1	85%	< 0.001
Position	Supine	17	517	-5.6	-7.5	-3.6	0%	0.762
	Seated	16	2826	-2.5	-3.6	-1.5	57%	0.003
	Not reported	**2**	64	-14.7	-20.6	-8.8	13%	0.284

UNa difference	<=50 mmol	6	2018	-2.0	-3.0	-0.9	23%	0.26
	51–75 mmol	14	773	-2.4	-3.6	-1.2	27%	0.169
	76–100 mmol	11	511	-6.5	-8.3	-4.7	0%	0.814
	> 100 mmol	4	105	-8.6	-19.0	1.7	85%	< 0.001
Tier	Tier 1	30	3171	-3.3	-4.4	-2.2	50%	0.001
	Tier 2	5	236	-6.9	-12.8	-1.1	75%	0.003
RoB outcome	Definitively low RoB	18	2788	-3.4	-4.6	-2.1	62%	0
	Probably low RoB	14	498	-3.1	-4.6	-1.6	0%	0.48
	High or NR RoB	3	121	-8.7	-19.4	2.0	83%	0.003
Baseline SBP	<140 mmHg	14	2497	-2.9	-4.1	-1.6	61%	0.001
	>=140 mmHg	14	581	-4.2	-5.9	-2.4	0%	0.787
	Not reported	**7**	329	-5.2	-9.9	-0.6	82%	0
Baseline UNa	<100 mmol/d	3	102	-8.1	-13.1	-3.0	0%	0.926
	100-149 mmol/d	7	323	-2.1	-3.3	-0.9	0%	0.486
	>=150 mmol/d	14	2502	-3.1	-4.5	-1.7	59%	0.003
	Not reported	**11**	480	-5.7	-9.4	-1.9	73%	0
Achieved Una in High Na group	<=3 g/day	6	412	-1.6	-2.8	-0.4	19%	0.291
	>3 & <=3.6 g/day	12	1336	-3.8	-5.3	-2.3	34%	0.116
	>3.6 & <4.4 g/day	10	1485	-4.2	-6.7	-1.6	56%	0.015
	>4.4 g/day	7	174	-7.6	-13.8	-1.4	71%	0.002
Achieved Una in Low Na group	<=1.7 g/day	10	629	-5.4	-8.2	-2.6	84%	0
	>1.7 & <=2 g/day	10	453	-3.3	-5.6	-1.0	38%	0.109
	>2 & <=2.3 g/day	7	961	-2.7	-3.8	-1.6	0%	0.799
	>2.3 g/day	8	1364	-3.1	-5.4	-0.8	39%	0.117
N of urinary collections	Multiple 24h	21	1848	-4.8	-6.7	-3.0	0%	0.629
	Single 24h	12	490	-3.8	-5.3	-2.3	68%	0
	Not reported	**2**	1069	-3.9	-10.7	3.0	83%	0.016
Year of publication	Before 1995	20	1518	-2.0	-2.9	-1.1	11%	0.314
	After 1995	15	1889	-6.3	-8.8	-3.8	78%	0
Funding	Public	13	2613	-4.4	-6.3	-2.6	77%	0
	Profit	3	104	-5.6	-10.0	-1.3	0%	0.739
	Non-profit	7	221	-1.7	-4.9	1.4	18%	0.299
	Mixed	2	101	-2.1	-3.9	-0.4	35%	0.159
	Not reported	**10**	368	-5.2	-8.8	-1.6	24%	0.241

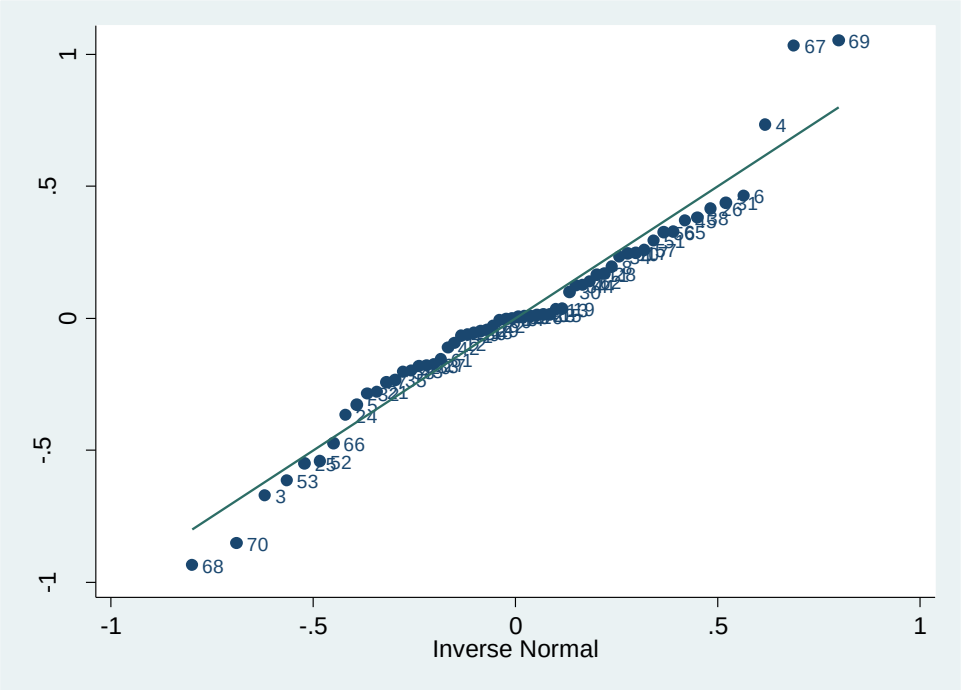
Table 4: Subgroup analyses results for **diastolic blood pressure** are summarised below and displayed in forest plots in Appendix E. I^2 is the estimated proportion of variance due to heterogeneity in each subgroup; the p value of the test for heterogeneity based on Cochran's Q statistic is reported in the last column.

	Subgroups	N studies	N subjects	Mean diff.	95% CI		I^2	p
All	Adults	35	3407	-2.0	-2.8	-1.2	61%	< 0.001
BP	Hypertensive	17	721	-2.9	-4.2	-1.6	47%	0.016
	Mixed	10	770	-1.7	-3.3	-0.2	75%	< 0.001
	Normotensive	8	1916	-0.9	-1.6	-0.2	9%	0.365
Age	Adults < 50 yrs	16	632	-1.0	-2.0	0.0	61%	0.001
	Adults ≥ 50 yrs	19	2775	-2.9	-4.0	-1.9	40%	0.036
Sex	> 55% men	14	2430	-2.7	-3.9	-1.5	70%	< 0.001
	45–55% both genders	14	761	-1.9	-3.3	-0.5	53%	0.01
	> 55% women	7	216	-0.6	-2.0	0.8	33%	0.173
BMI	< 25	1	66	-3.0	-7.1	1.1	-	-
	25–29	10	1132	-1.9	-2.6	-1.2	0%	0.739
	≥ 30	2	384	-2.8	-4.0	-1.6	16%	0.276
	Not reported	**22**	1825	-1.7	-2.8	-0.5	69%	< 0.001
Ethnicity	Caucasian	3	65	-2.2	-4.9	0.5	0%	0.579
	African (including AA)	1	40	-3.0	-6.5	0.5	-	-
	Mixed	12	2540	-3.0	-4.2	-1.7	74%	< 0.001
	Not reported	**19**	762	-1.2	-2.3	0.0	54%	0.003
Potassium	≤ 60 mmol/d	4	103	0.4	-1.1	1.9	51%	0.105
	>60–≤ 70 mmol/d	8	2008	-2.2	-3.4	-0.9	66%	0.005
	>70–≤ 80 mmol/d	7	442	-2.4	-3.5	-1.3	0%	0.742
	> 80 mmol/d	3	174	-2.5	-4.8	-0.2	0%	0.573
	Not reported	**13**	680	-2.9	-4.5	-1.2	51%	0.017
Design	Parallel	8	2217	-1.8	-3.0	-0.7	63%	0.009
	Cross–over	26	1134	-2.0	-3.1	-0.9	61%	< 0.001
	Cluster–randomized	1	56	-3.9	-7.6	-0.2	-	-
Specific design	Run-in – Normal diet	7	380	-3.6	-5.4	-1.7	55%	0.036
	Run-in – Low Na diet	9	386	-2.7	-4.1	-1.2	38%	0.119
	Run-in – High Na diet	4	504	-2.7	-3.7	-1.7	0%	0.57
	No run-in	15	2137	-0.5	-1.3	0.3	30%	0.131
Duration	1 month	20	1005	-2.1	-3.4	-0.8	67%	< 0.001
	2-3 months	12	618	-2.8	-3.7	-1.9	0%	0.501
	≥ 1 year	3	1784	-1.1	-2.3	0.1	66%	0.052
Intervention type	Feeding	28	1309	-1.7	-2.6	-0.9	46%	0.004
	Counselling	7	2098	-2.7	-4.4	-1.0	83%	< 0.001
Position	Supine	17	517	-2.7	-3.8	-1.5	0%	0.66
	Seated	16	2826	-1.4	-2.3	-0.5	70%	< 0.001
	Not reported	**2**	64	-5.9	-11.7	-0.1	55%	0.138
UNa difference	<=50 mmol	6	2018	-1.3	-2.3	-0.2	52%	0.063

	51–75 mmol	14	773	-1.5	-2.8	-0.2	64%	0.001
	76–100 mmol	11	511	-2.9	-3.9	-1.9	0%	0.869
	> 100 mmol	4	105	-4.6	-10.1	0.8	76%	0.006
Tier	Tier 1	30	3171	-1.7	-2.4	-0.9	56%	< 0.001
	Tier 2	5	236	-4.1	-7.0	-1.2	52%	0.081
RoB outcome	Definitively low RoB	18	2788	-1.8	-2.7	-0.9	64%	0
	Probably low RoB	14	498	-1.7	-2.8	-0.5	23%	0.209
	High or NR RoB	3	121	-4.5	-9.2	0.3	69%	0.039
Baseline SBP	<90 mmHg	17	2596	-1.2	-2.1	-0.4	53%	0.005
	>=90 mmHg	11	482	-3.5	-4.6	-2.4	0%	0.677
	Not reported	**7**	329	-2.1	-4.7	0.4	77%	0
Baseline UNa	<100 mmol/d	3	102	-3.6	-6.0	-1.2	0%	0.868
	100-149 mmol/d	7	323	-1.4	-3.6	0.8	69%	0.004
	>=150 mmol/d	14	2502	-1.6	-2.5	-0.7	55%	0.007
	Not reported	**11**	480	-2.4	-4.5	-0.3	68%	0.001
Achieved Una in High Na group	<=3 g/day	6	412	-0.3	-2.1	1.5	64%	0.017
	>3 & <=3.6 g/day	12	1336	-2.1	-3.1	-1.1	46%	0.043
	>3.6 & <4.4 g/day	10	1485	-2.2	-3.6	-0.9	44%	0.067
	>4.4 g/day	7	174	-3.4	-6.6	-0.2	65%	0.009
Achieved Una in Low Na group	<=1.7 g/day	10	629	-2.3	-4.3	-0.3	82%	0
	>1.7 & <=2 g/day	10	453	-2.1	-3.5	-0.7	40%	0.093
	>2 & <=2.3 g/day	7	961	-1.7	-2.4	-0.9	0%	0.62
	>2.3 g/day	8	1364	-1.8	-3.3	-0.2	50%	0.053
N of urinary collections	Multiple 24h	21	1848	-1.9	-2.9	-0.9	69%	0
	Single 24h	12	490	-2.7	-3.9	-1.5	0%	0.733
	Not reported	**2**	1069	-1.1	-3.5	1.3	54%	0.142
Year of publication	Before 1995	20	1518	-1.5	-2.6	-0.4	57%	0.001
	After 1995	15	1889	-2.6	-3.8	-1.4	65%	0
Funding	Public	13	2613	-2.4	-3.5	-1.4	73%	0
	Profit	3	104	-3.4	-6.2	-0.5	0%	0.808
	Non-profit	7	221	-0.5	-1.9	0.9	0%	0.464
	Mixed	2	101	-0.9	-2.7	1.0	57%	0.03
	Not reported	**10**	368	-2.4	-4.3	-0.5	11%	0.344

Appendix E - Dose-response models: diagnostics and fitting

Figure 7: Quantiles of Pearson standardised residuals for mean SBP (first plot) and DBP (second plot) are plotted against quantiles of the normal distribution to assess potential outliers and goodness-of-fit.



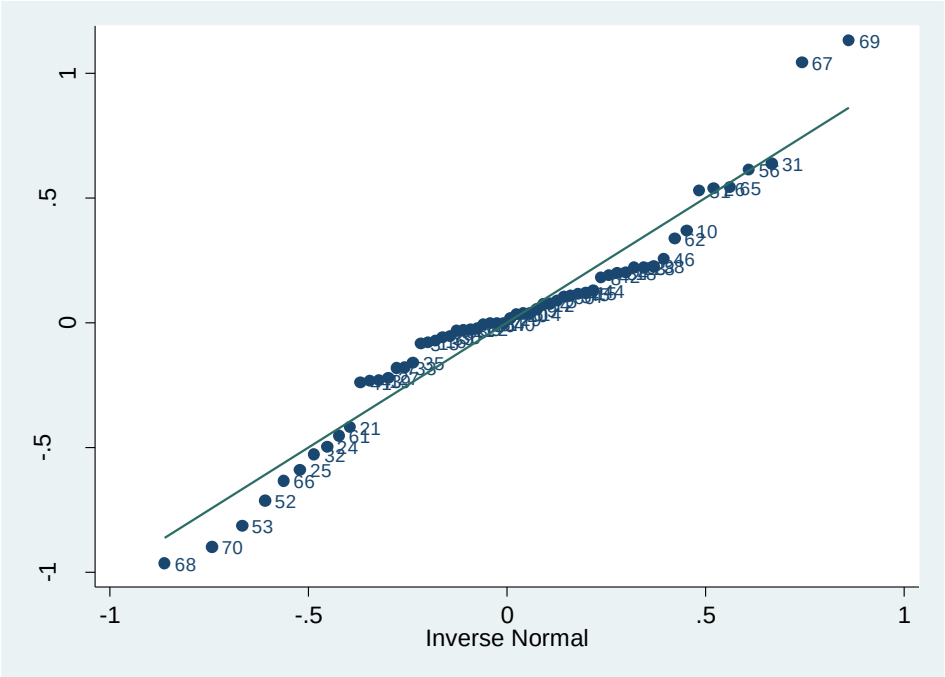
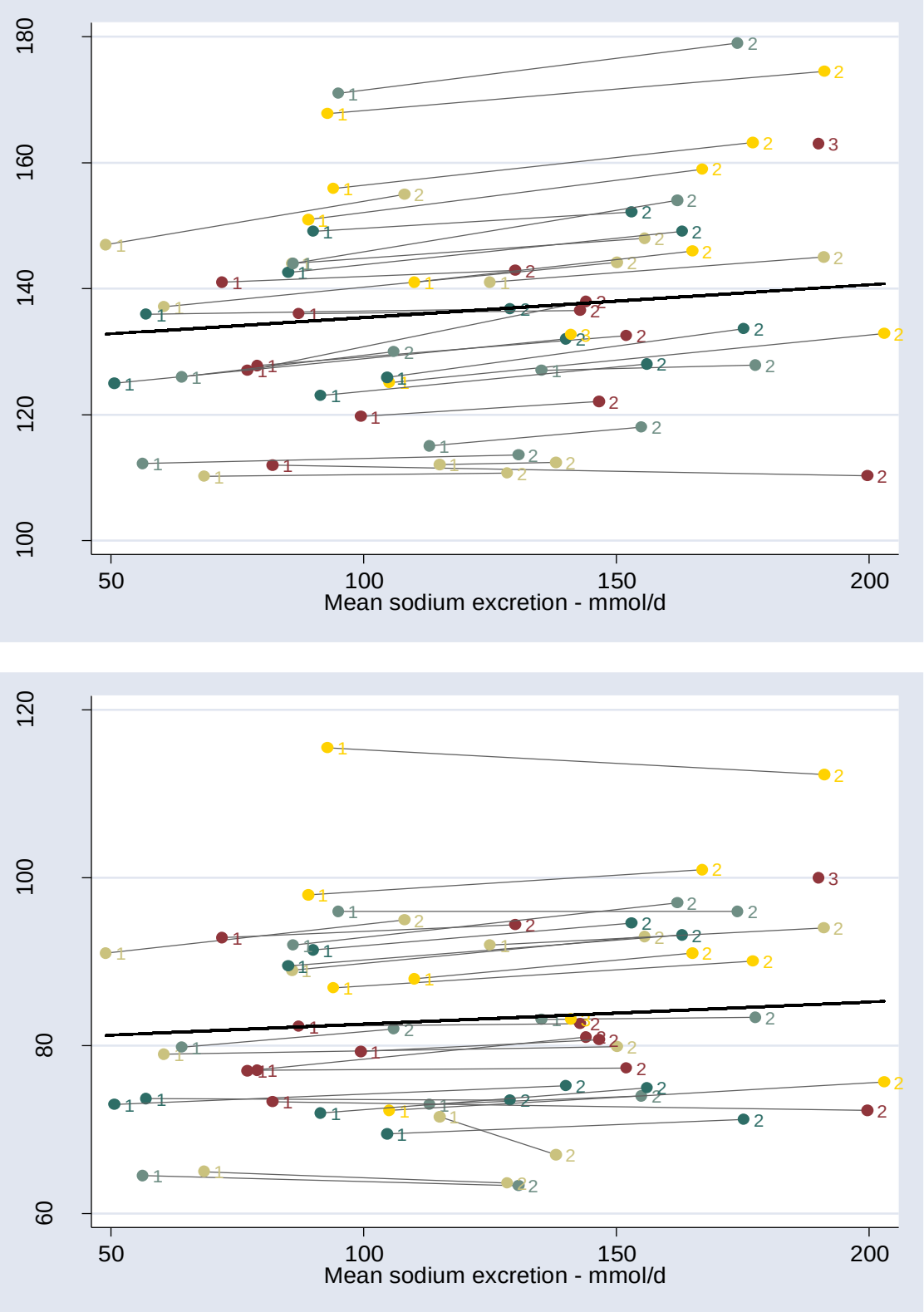


Table 5: Regression coefficients of model covariates from nested meta-regression models on mean SBP (first column: null model; second column: mean UNa excretion; last column: fully adjusted model); related Tau^2, adjusted R^2 and residual I^2 value changes are reported at the bottom.

Covariates	Categories	Null Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Mean UNa excretion - 100 mmol/d			5.224***	5.199***	5.159***	5.188***	5.247***	5.284***
Age at baseline	Age < 40 yrs old*			0	0	0	0	0
	Age 40-49 yrs old			17.62	11.43*	12.89*	15.20**	18.24***
	Age 50-59 yrs old			22.39*	9.252	8.913	13.56*	11.55*
	Age >= 60 yrs old			20.44*	14.11*	15.93**	16.12**	12.44**
BP status	Normotensive*				0	0	0	0
	Hypertensive				24.99***	26.80***	21.72***	11.35*
Mean UNa excretion at baseline	<100 mmol/d*					0	0	0
	100-149 mmol/d					10.06	12.93*	25.16***
	>=150 mmol/d					8.601	9.36	18.69**
	Not reported					7.845	7.555	13.38*
BP measure method	Point office, supine*						0	0
	Point office, sitting						-8.419*	-13.23***
Specific trial design	No Run-in*							0
	Run-in, Normal Diet							11.93***
	Run-in, Low Na Diet							19.73***
	Constant	136.6***	132.7***	115.3***	109.0***	99.30***	103.4***	95.50***
	Tau^2	275	268	216	76	70	59	33
	Adj R^2	0	3%	22%	72%	75%	79%	88%
	Res I^2	99%	99%	98%	94%	94%	94%	90%

* p < 0.5; ** p < 0.01; *** p < 0.001

Figure 8: Mean SBP and DBP responses against mean urinary sodium excretion - Each line represents a trial, where low sodium (1) and high sodium (2) arms are connected (SBP: first plot; DBP: second plot).



Appendix F - Sensitivity analyses

Figure 9: Forest plot of the effect of salt reduction on SBP difference in means (study level) by type of intervention. Sensitivity analysis on the impact of van Berge-Landry's estimate on SBP difference in means in the Counselling group.

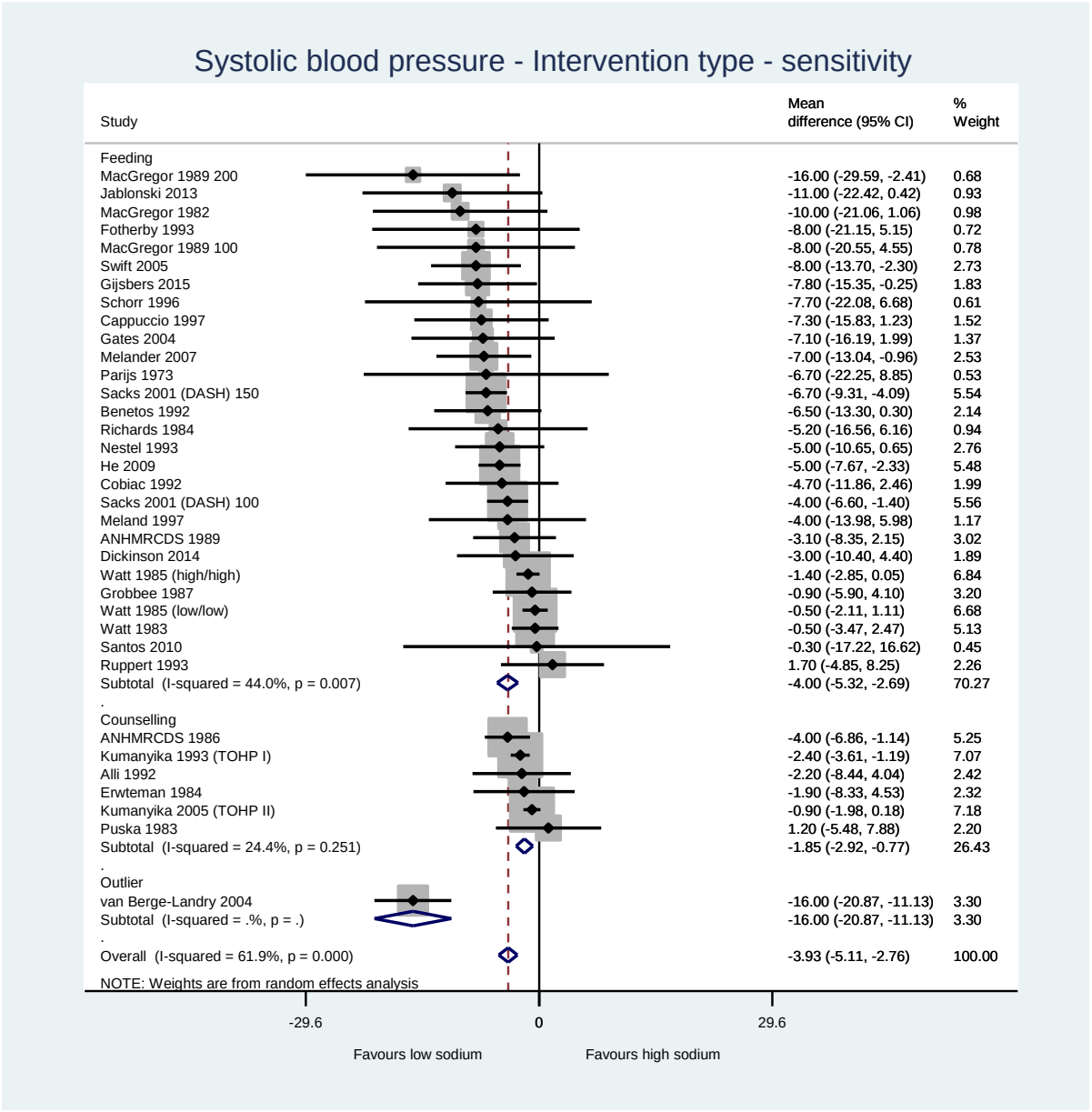
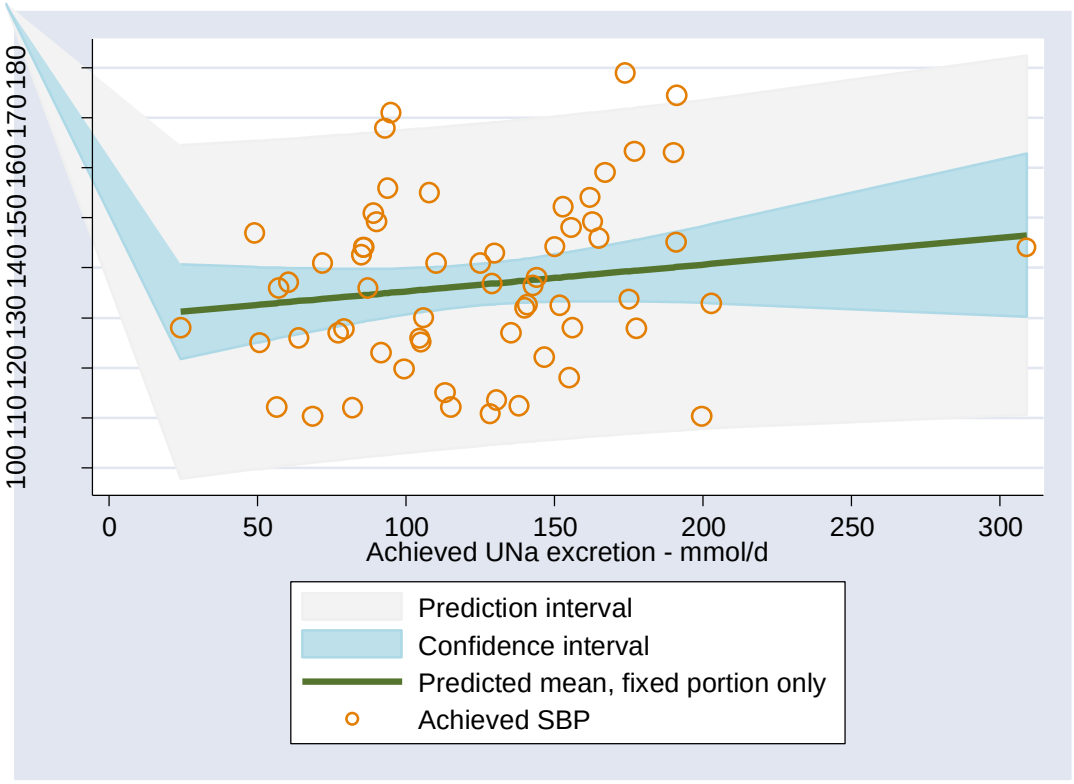


Figure 10: Linear dose-response relationship between mean urinary sodium excretion and mean systolic blood pressure from meta-regression modelling of trials' arms (crude model) **with inclusion of van Berge-Landry's arms**. Circles represents mean SBP by arm and their size is proportional to weights from the mixed-effects model. The slope from the full model with moderators did not differ substantially (UNa unadjusted coefficient: 5.4 mm Hg, 95% CI: 4.1-6.6).



Appendix G - Funnel plots

Figure 11: Contour funnel plot of mean SBP difference effect estimates against their standard error and with superimposed areas of statistical significance.

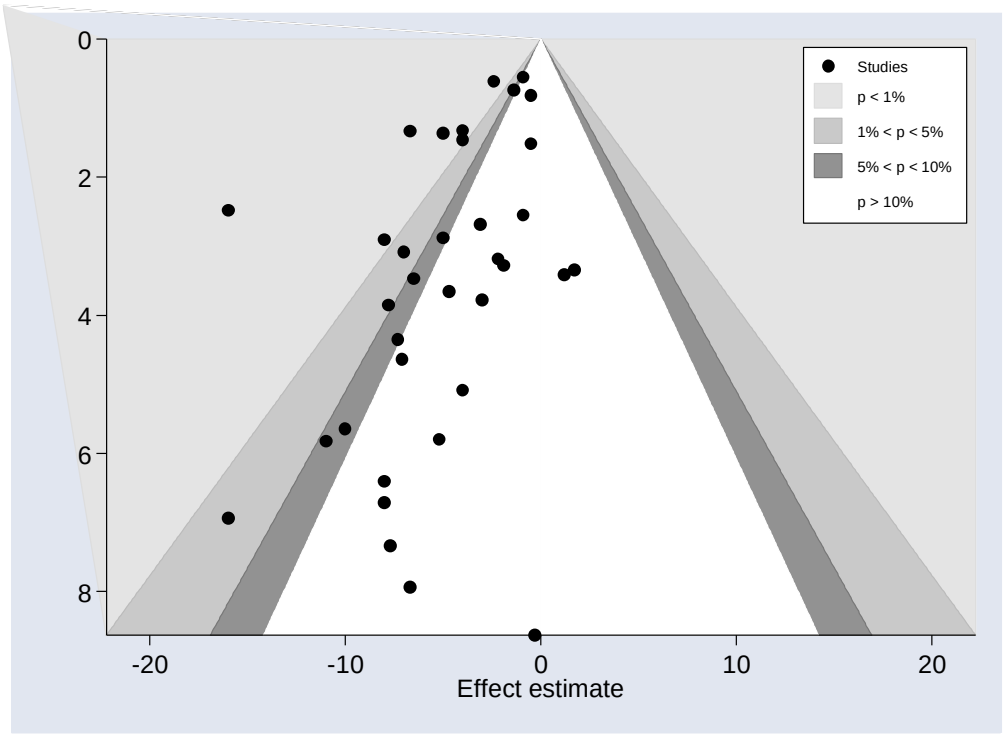
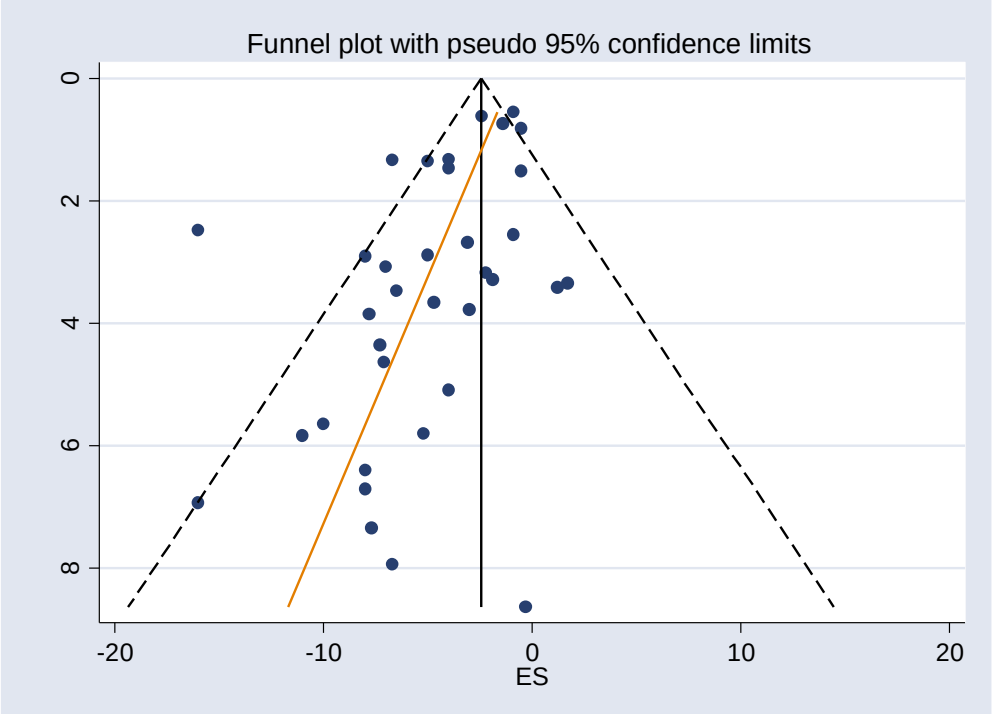
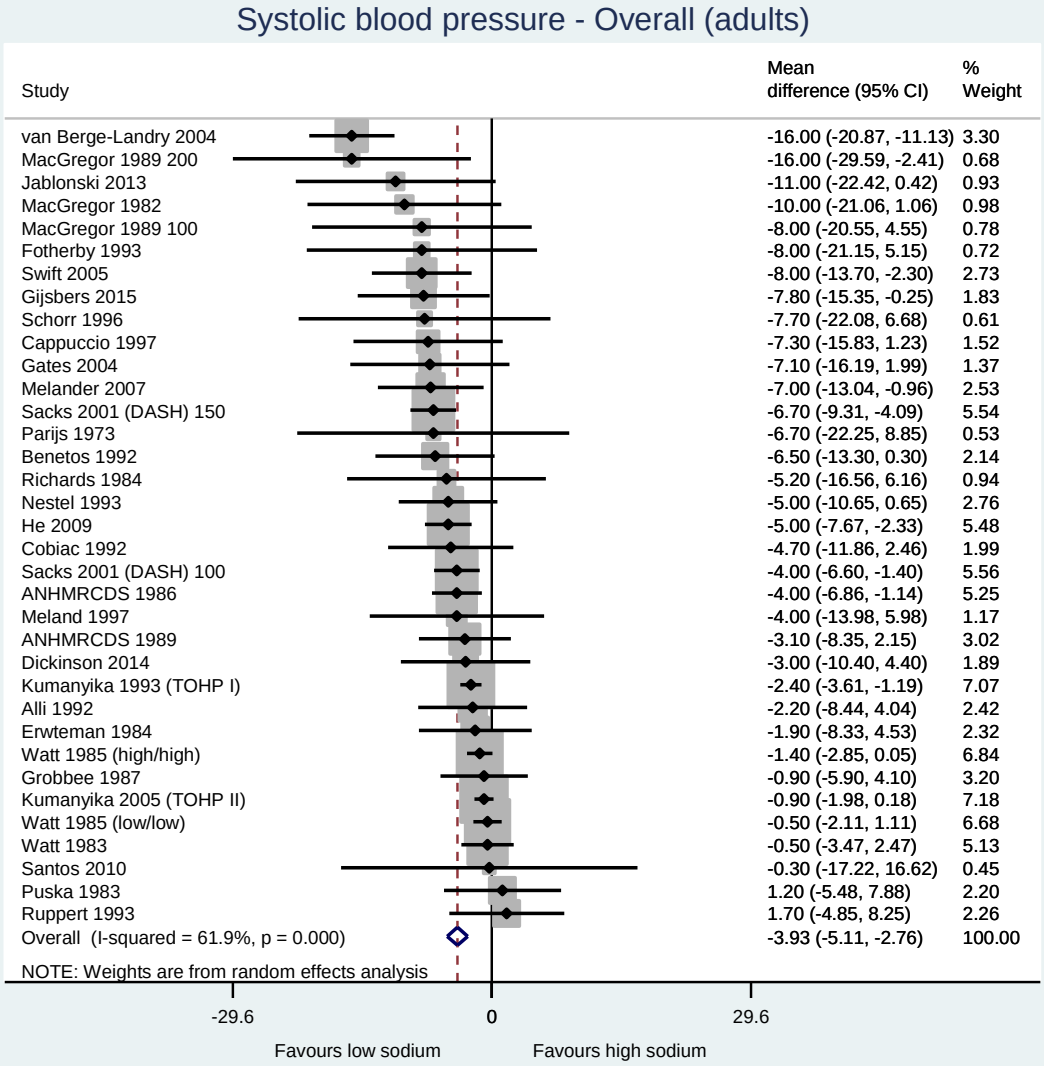
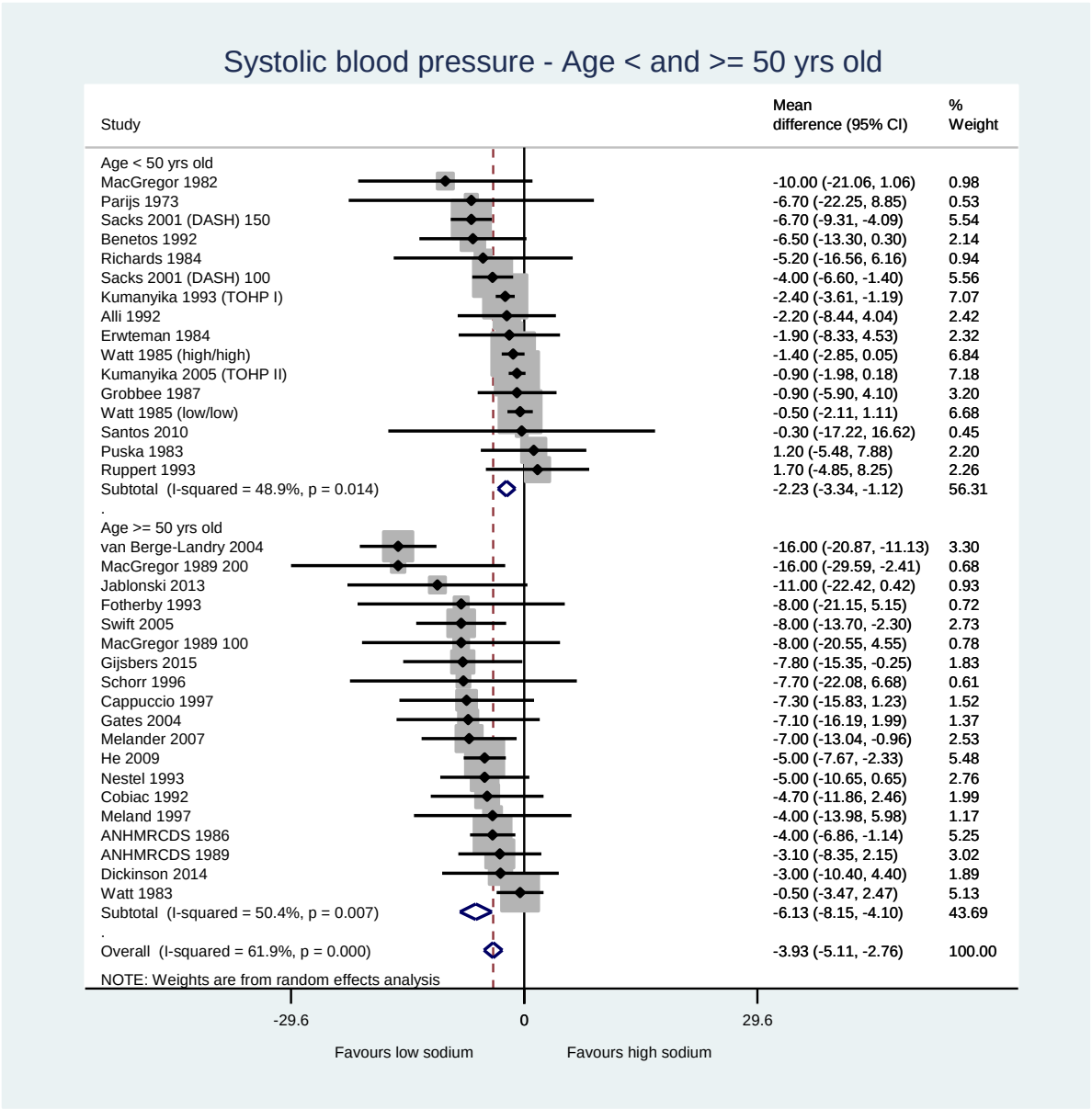


Figure 12: Funnel plot of mean SBP difference effect estimates against their standard error and with Egger regression line to test for plot asymmetry (p = 0.001).

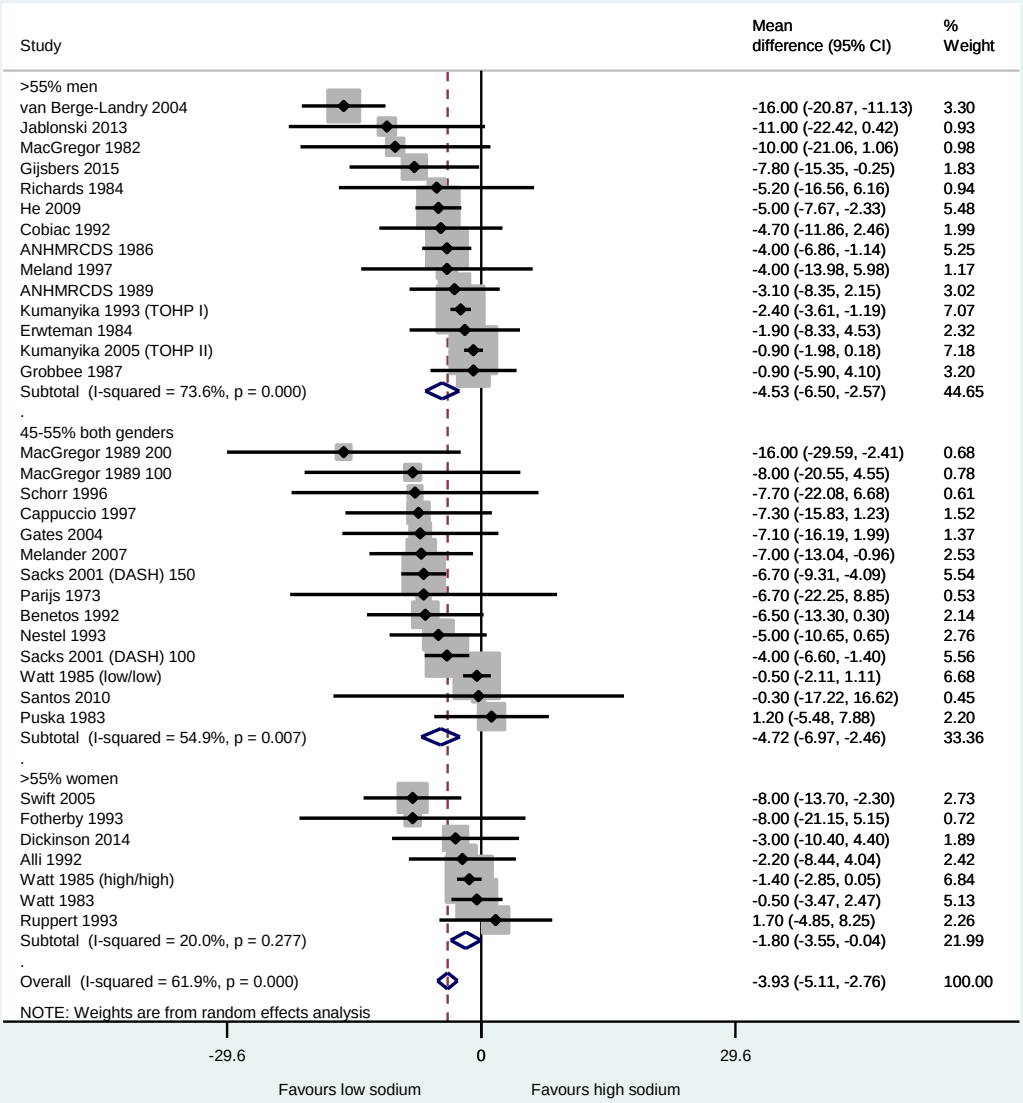


Appendix H - Forest plots at study level: subgroup analyses

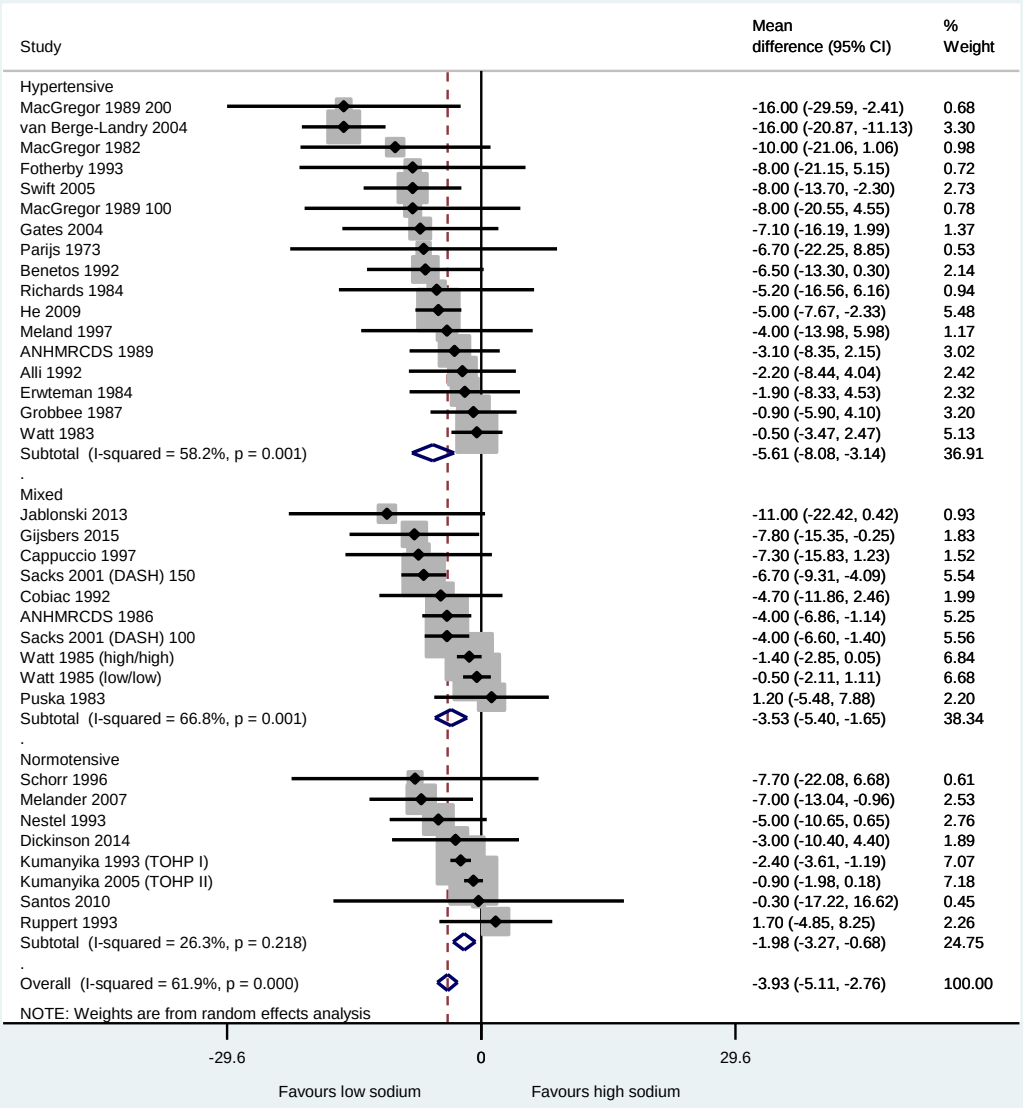



Systolic blood pressure - Age < and >= 50 yrs old
Study
Mean difference (95% CI)
% Weight
Age < 50 yrs old
MacGregor 1982 -10.00 (-21.06, 1.06) 0.98
Parijs 1973 -6.70 (-22.25, 8.85) 0.53
Sacks 2001 (DASH) 150 -6.70 (-9.31, -4.09) 5.54
Benetos 1992 -6.50 (-13.30, 0.30) 2.14
Richards 1984 -5.20 (-16.56, 6.16) 0.94
Sacks 2001 (DASH) 100 -4.00 (-6.60, -1.40) 5.56
Kumanyika 1993 (TOHP I) -2.40 (-3.61, -1.19) 7.07
Alli 1992 -2.20 (-8.44, 4.04) 2.42
Erwteman 1984 -1.90 (-8.33, 4.53) 2.32
Watt 1985 (high/high) -1.40 (-2.85, 0.05) 6.84
Kumanyika 2005 (TOHP II) -0.90 (-1.98, 0.18) 7.18
Grobbee 1987 -0.90 (-5.90, 4.10) 3.20
Watt 1985 (low/low) -0.50 (-2.11, 1.11) 6.68
Santos 2010 -0.30 (-17.22, 16.62) 0.45
Puska 1983 1.20 (-5.48, 7.88) 2.20
Ruppert 1993 1.70 (-4.85, 8.25) 2.26
Subtotal (I-squared = 48.9%, p = 0.014) -2.23 (-3.34, -1.12) 56.31
Age >= 50 yrs old
van Berge-Landry 2004 -16.00 (-20.87, -11.13) 3.30
MacGregor 1989 200 -16.00 (-29.59, -2.41) 0.68
Jablonski 2013 -11.00 (-22.42, 0.42) 0.93
Fotherby 1993 -8.00 (-21.15, 5.15) 0.72
Swift 2005 -8.00 (-13.70, -2.30) 2.73
MacGregor 1989 100 -8.00 (-20.55, 4.55) 0.78
Gijsbers 2015 -7.80 (-15.35, -0.25) 1.83
Schorr 1996 -7.70 (-22.08, 6.68) 0.61
Cappuccio 1997 -7.30 (-15.83, 1.23) 1.52
Gates 2004 -7.10 (-16.19, 1.99) 1.37
Melander 2007 -7.00 (-13.04, -0.96) 2.53
He 2009 -5.00 (-7.67, -2.33) 5.48
Nestel 1993 -5.00 (-10.65, 0.65) 2.76
Cobiac 1992 -4.70 (-11.86, 2.46) 1.99
Meland 1997 -4.00 (-13.98, 5.98) 1.17
ANHMRCDS 1986 -4.00 (-6.86, -1.14) 5.25
ANHMRCDS 1989 -3.10 (-8.35, 2.15) 3.02
Dickinson 2014 -3.00 (-10.40, 4.40) 1.89
Watt 1983 -0.50 (-3.47, 2.47) 5.13
Subtotal (I-squared = 50.4%, p = 0.007) -6.13 (-8.15, -4.10) 43.69
Overall (I-squared = 61.9%, p = 0.000) -3.93 (-5.11, -2.76) 100.00
NOTE: Weights are from random effects analysis
-29.6
0
29.6
Favours low sodium
Favours high sodium

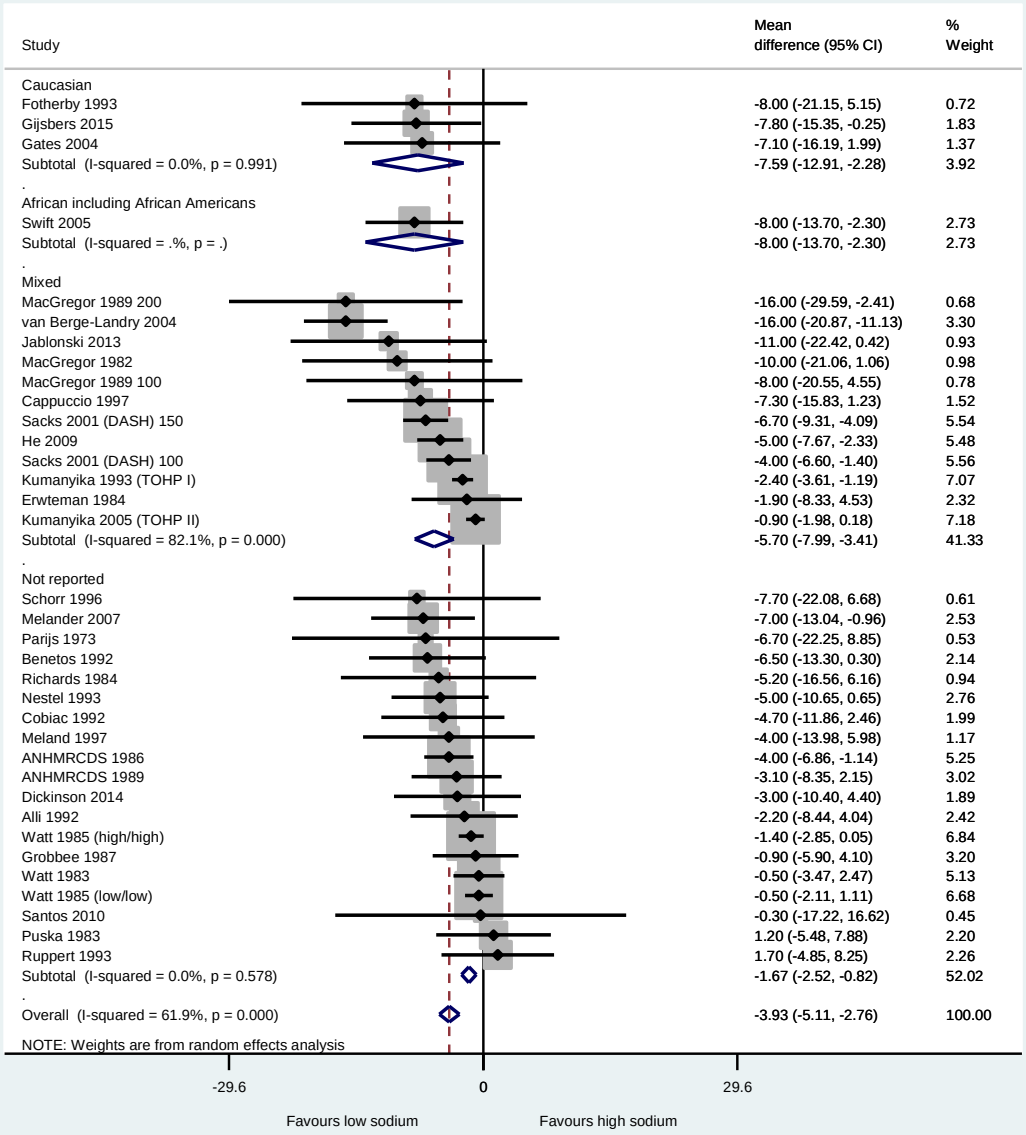
Systolic blood pressure - Sex proportion



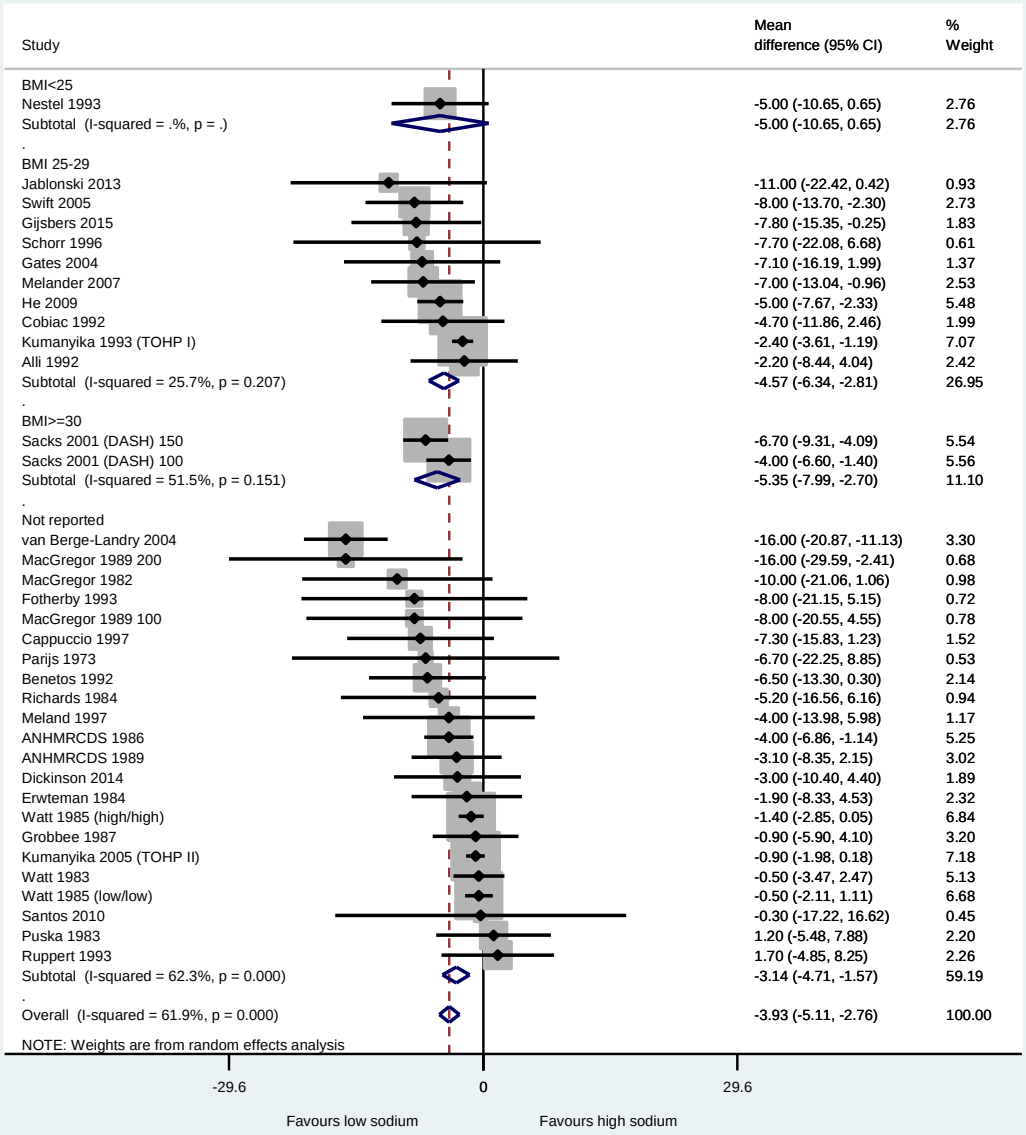
Systolic blood pressure - Blood pressure status



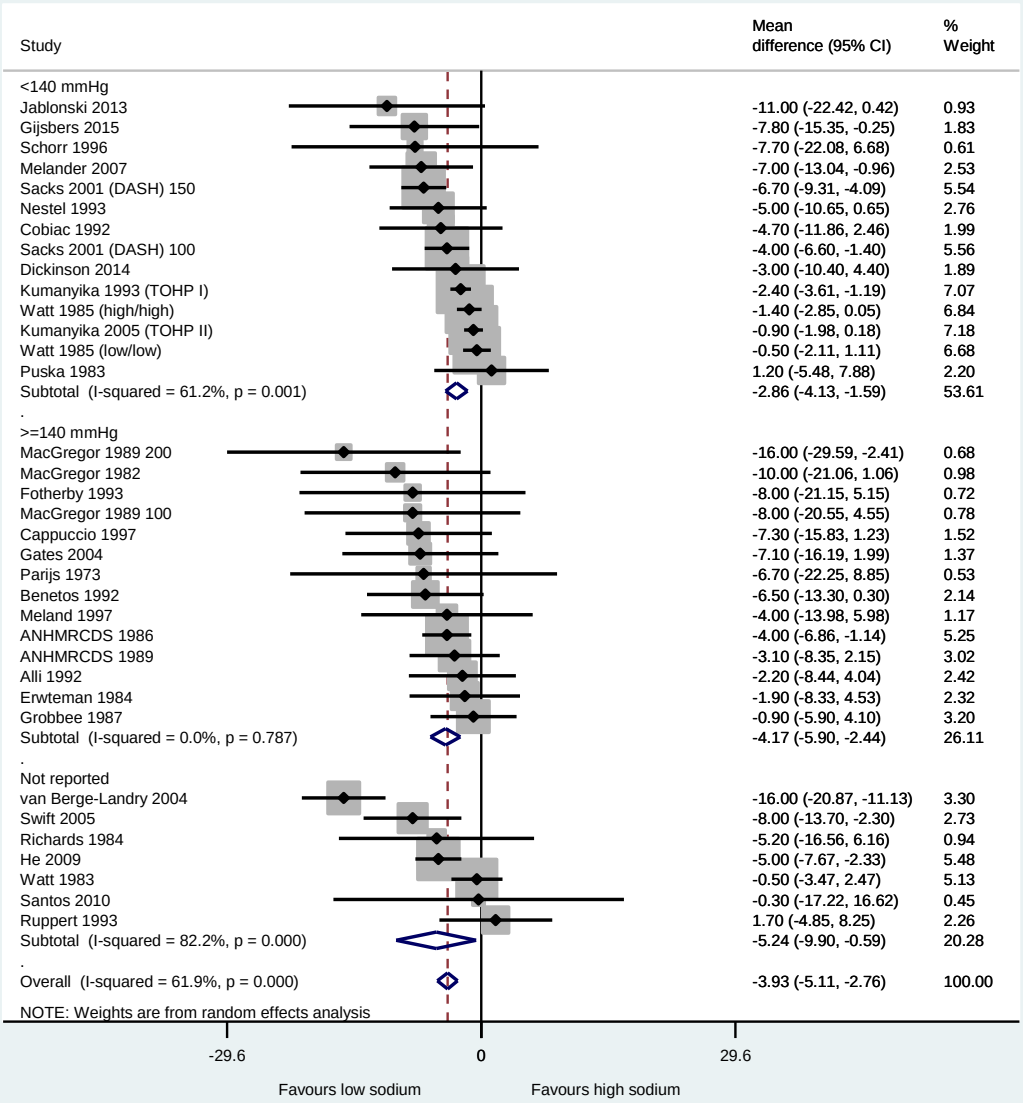
Systolic blood pressure - Ethnicity



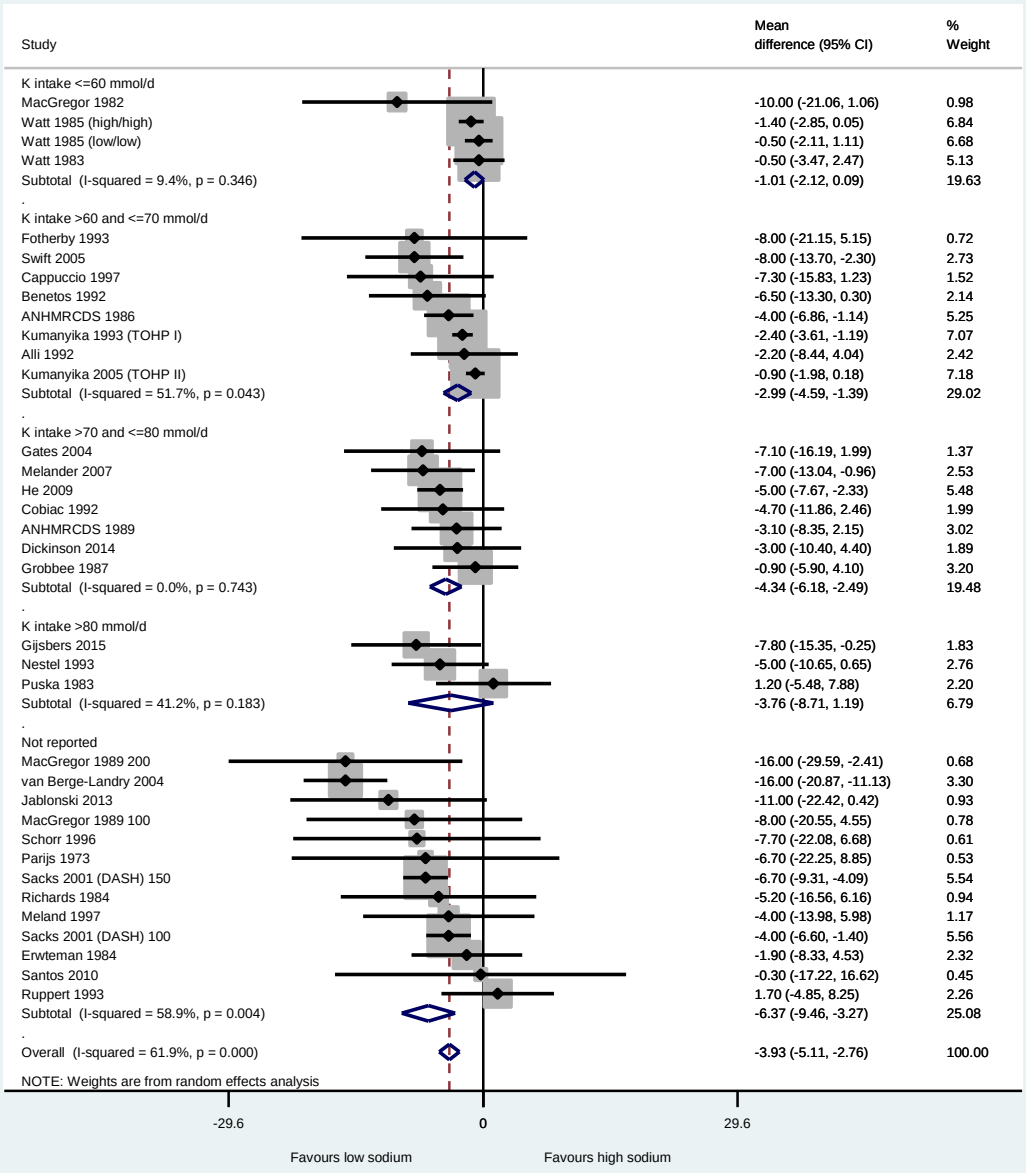
Systolic blood pressure - BMI



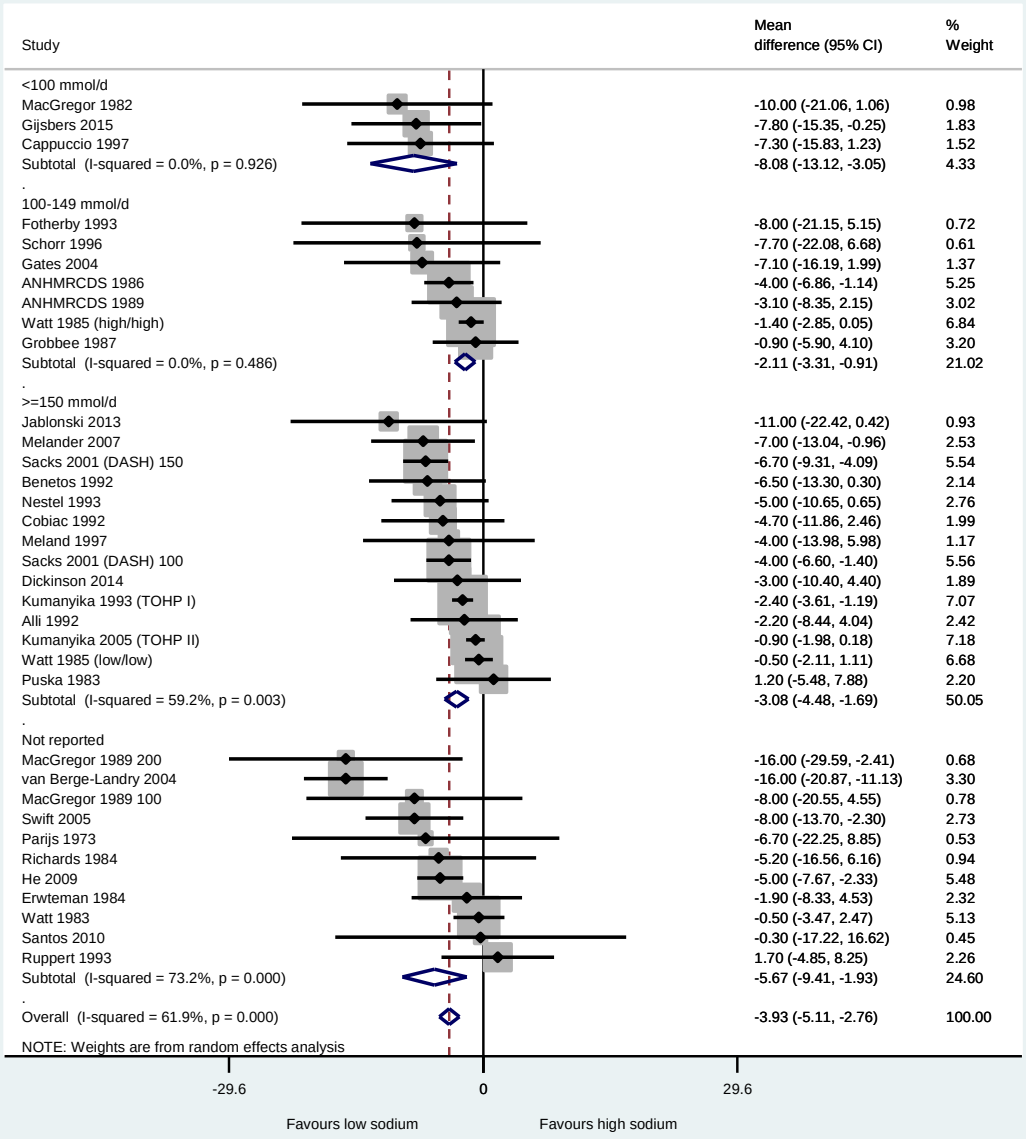
Systolic blood pressure - Baseline SBP



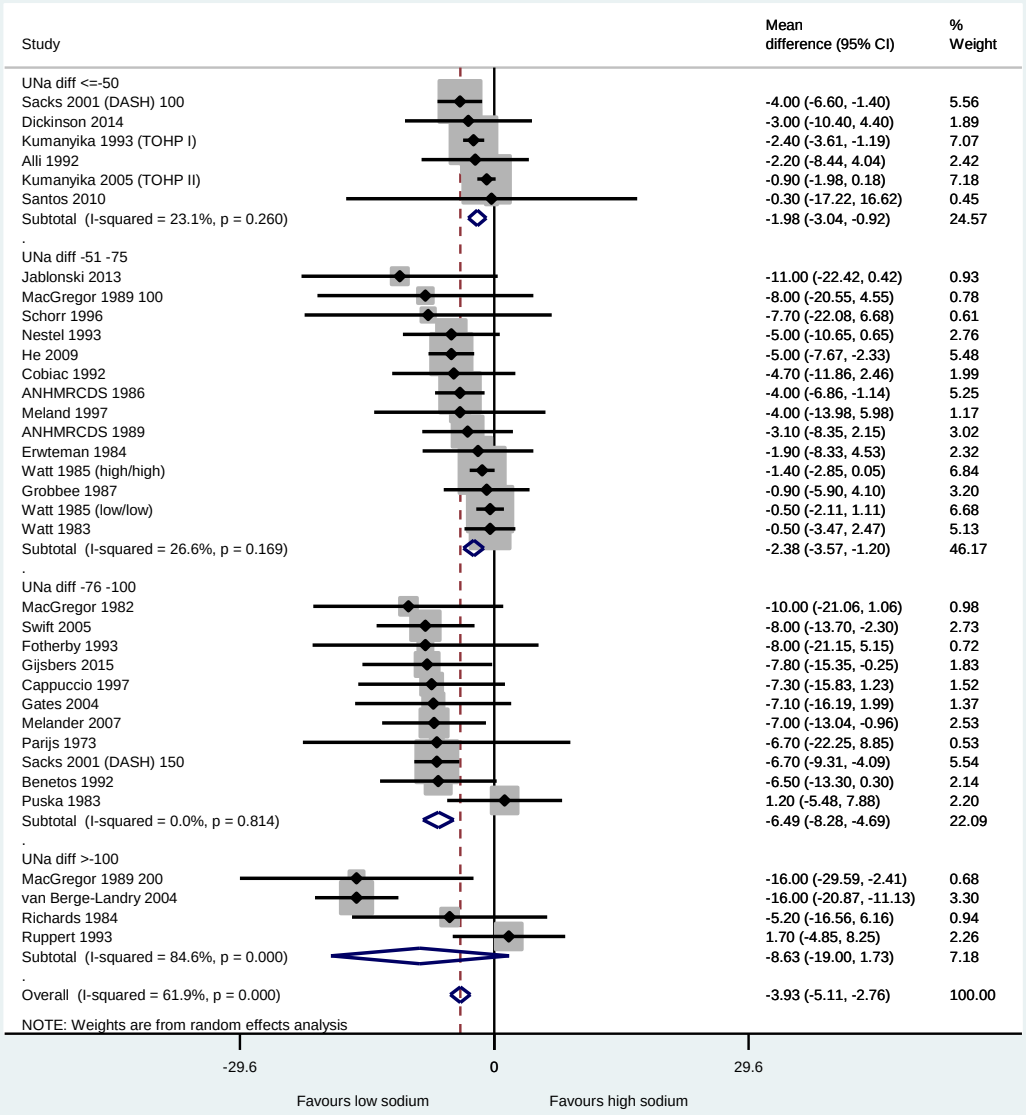
Systolic blood pressure - Baseline potassium intake



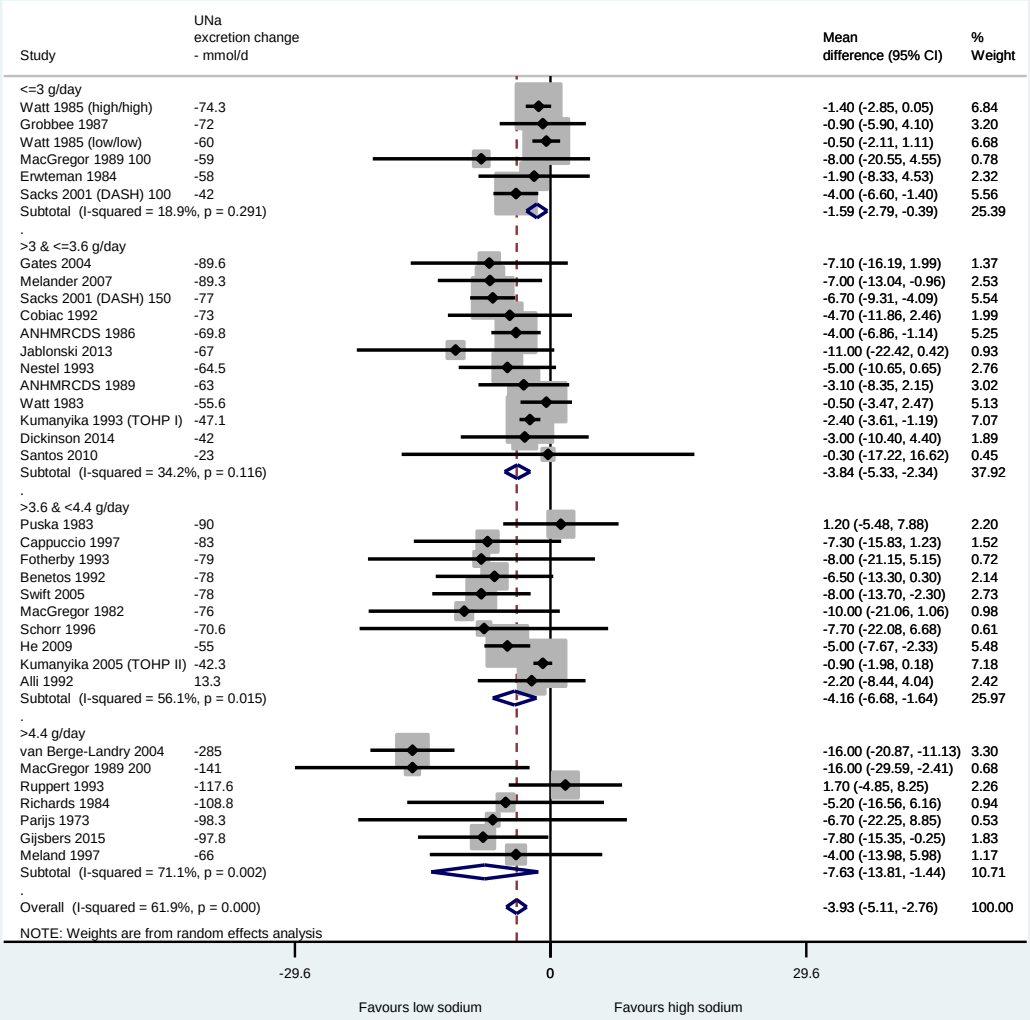
Systolic blood pressure - Sodium excretion at baseline



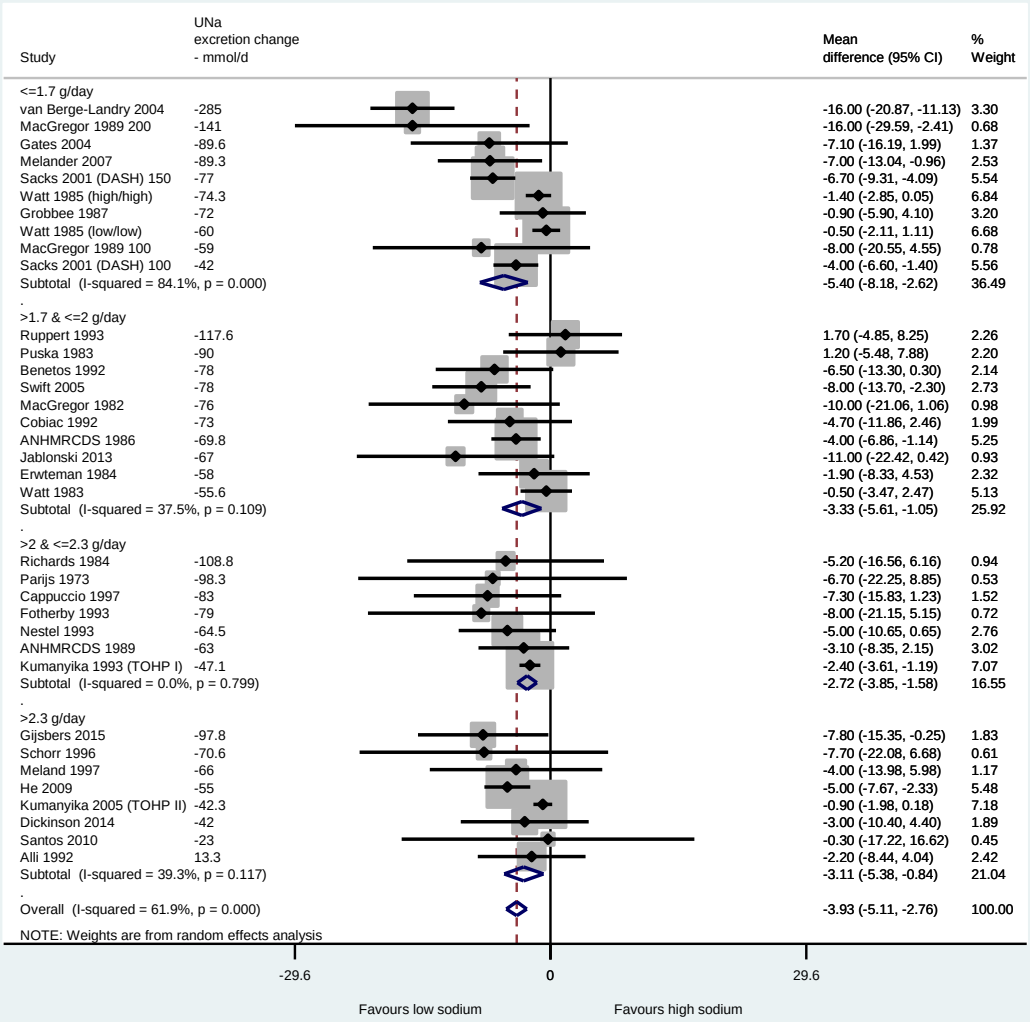
Systolic blood pressure - Sodium excretion difference across arms



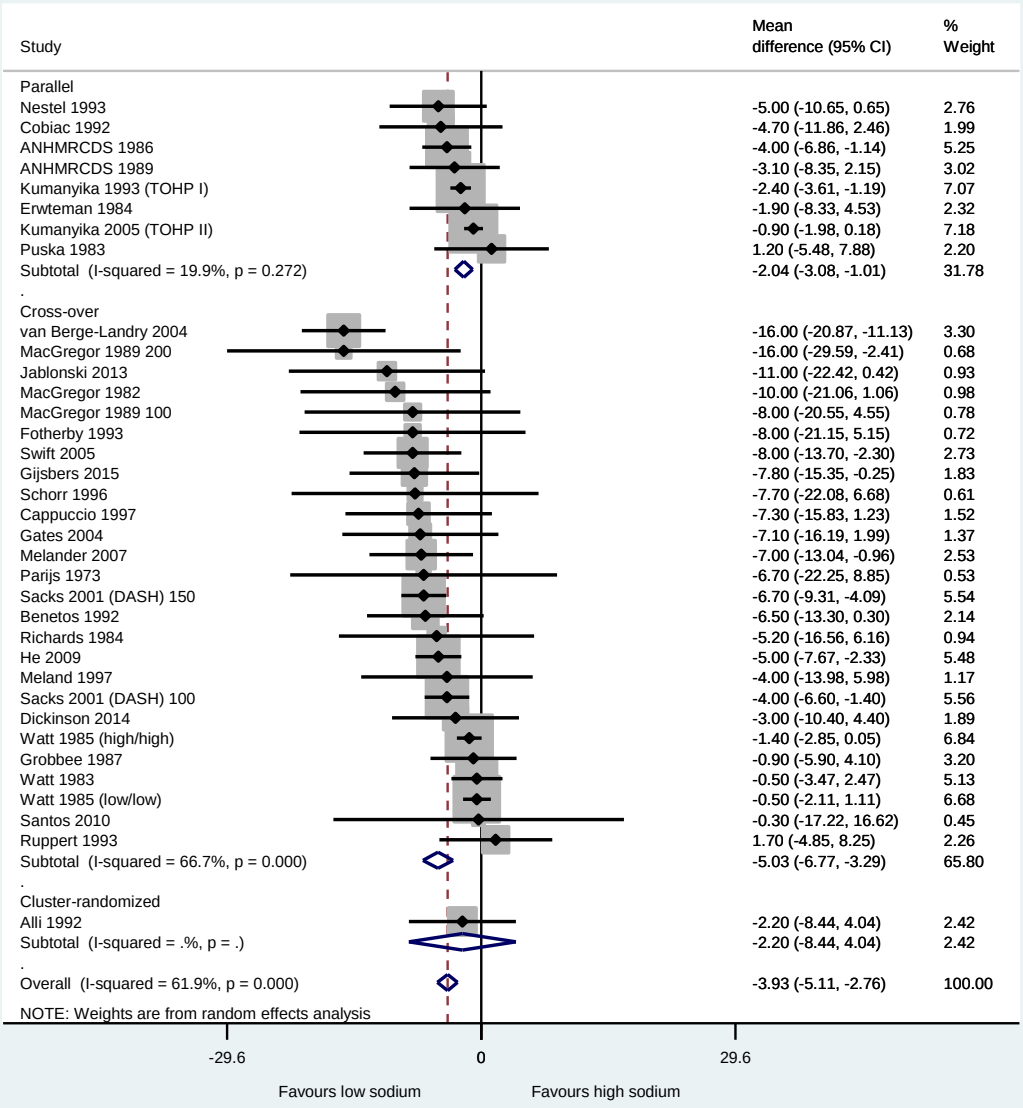
Systolic blood pressure - Achieved sodium excretion in high Na group



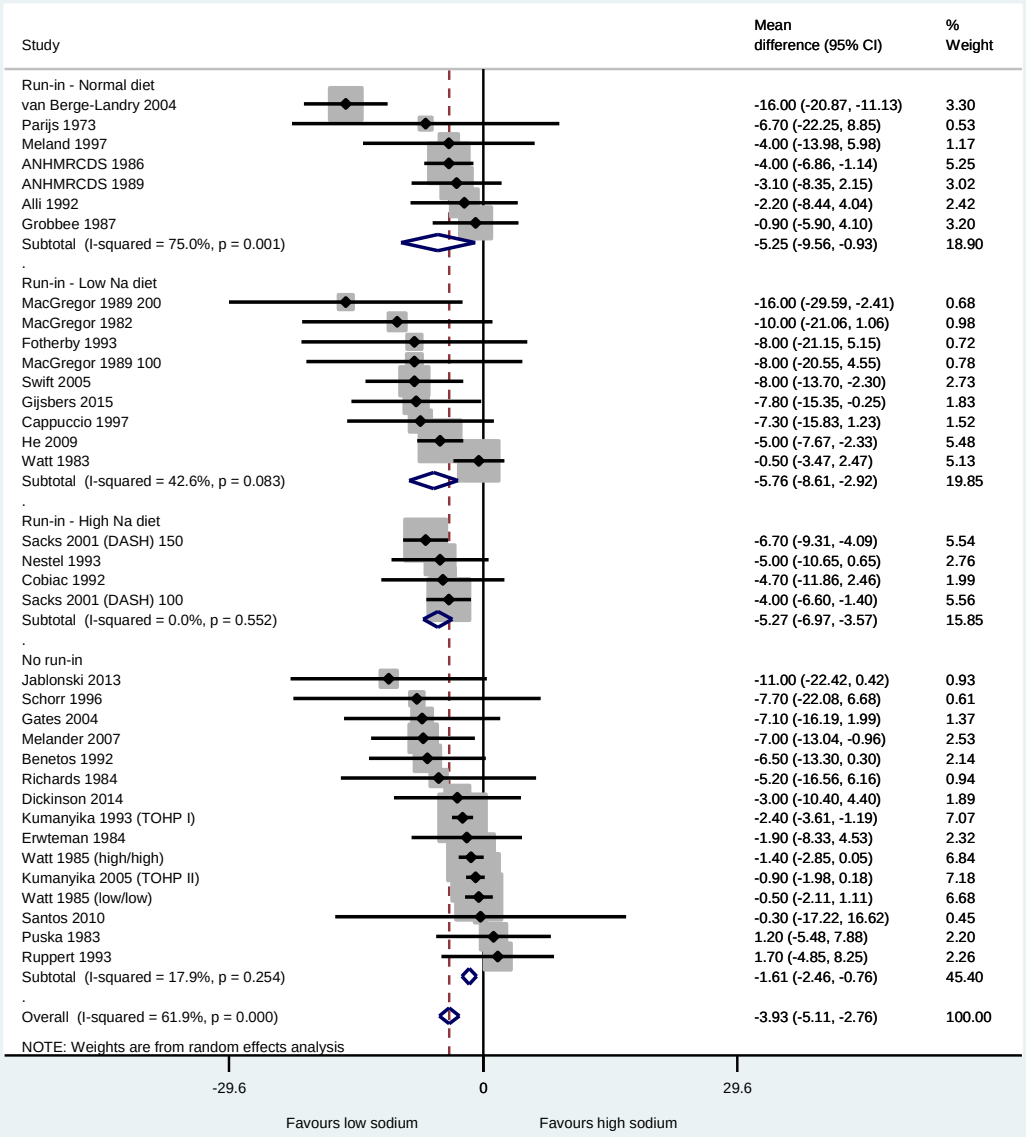
Systolic blood pressure - Achieved sodium excretion in low Na group



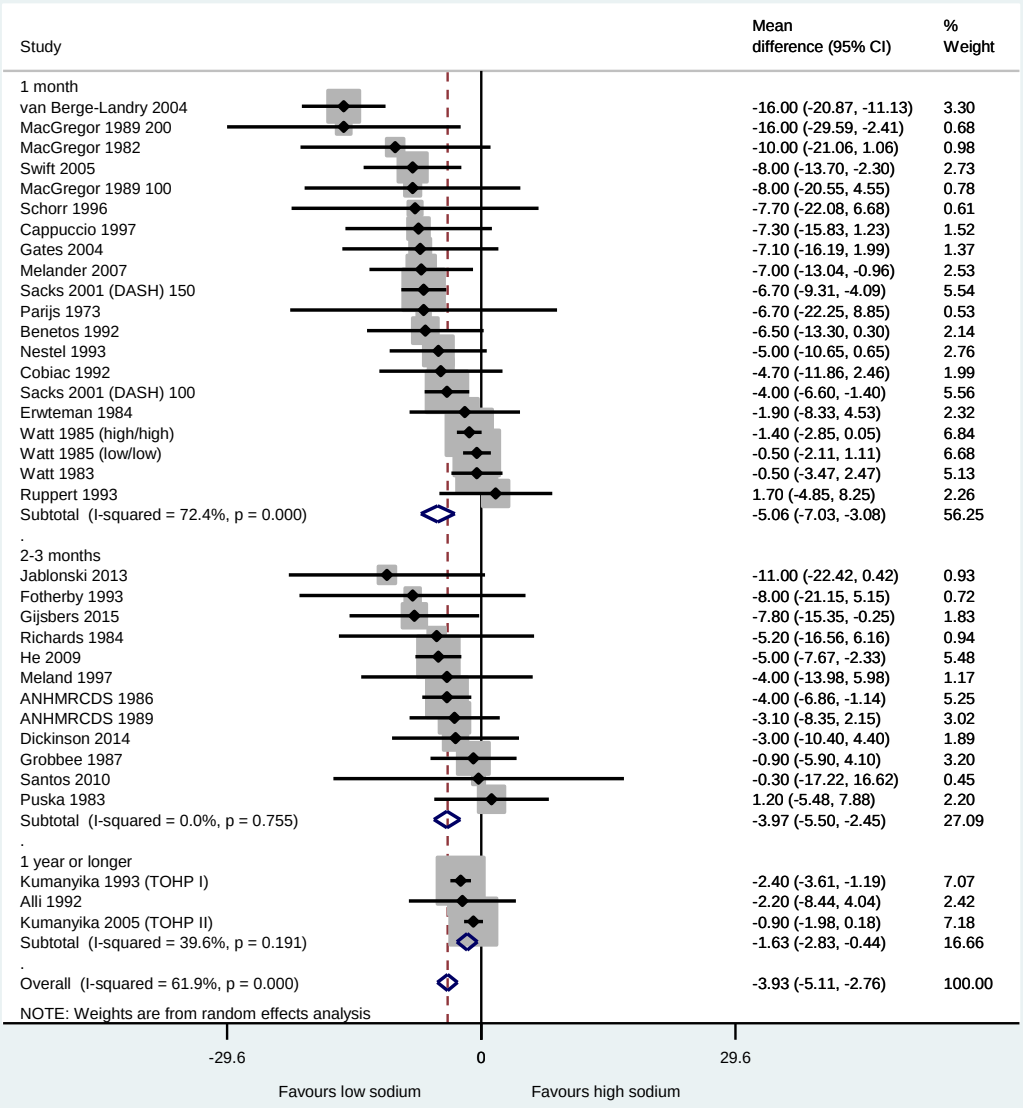
Systolic blood pressure - Study design



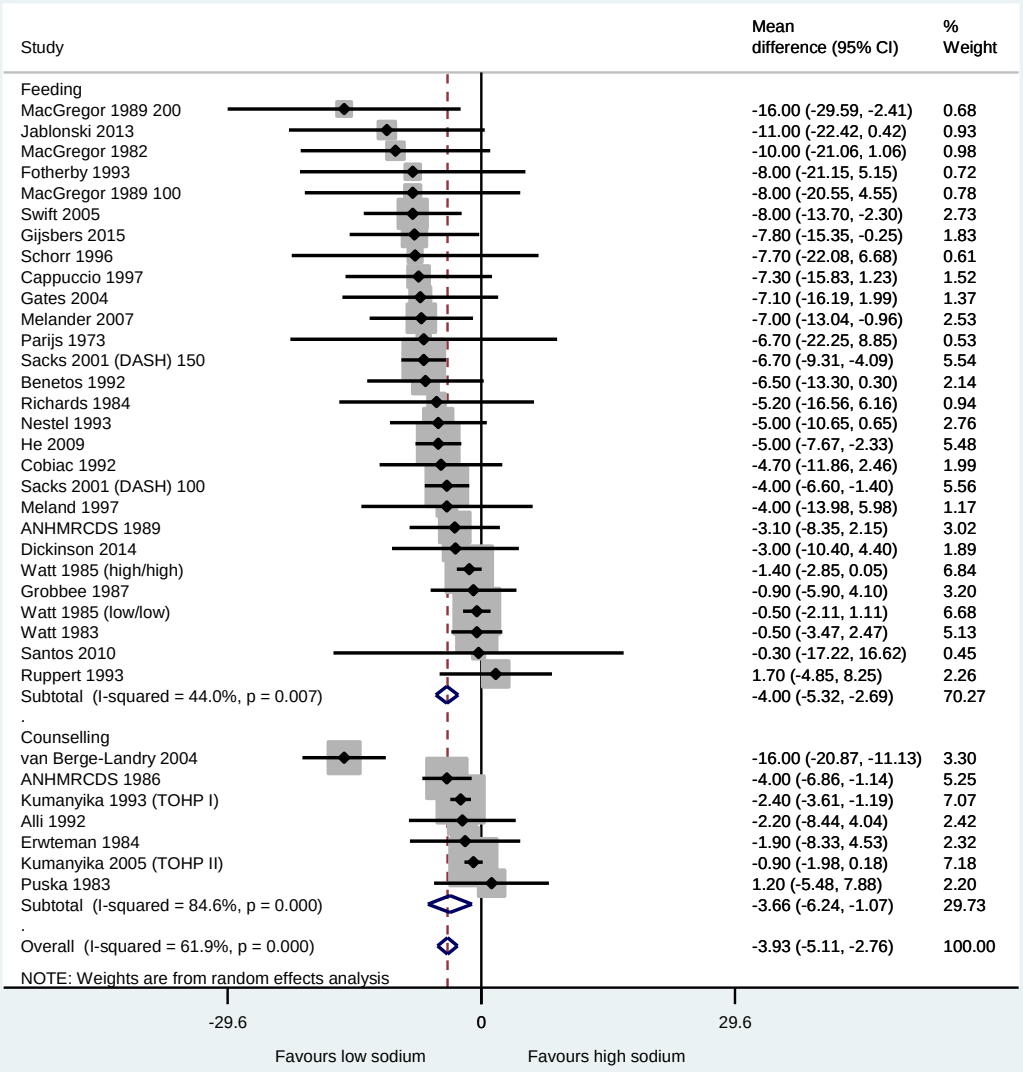
Systolic blood pressure - Specific design



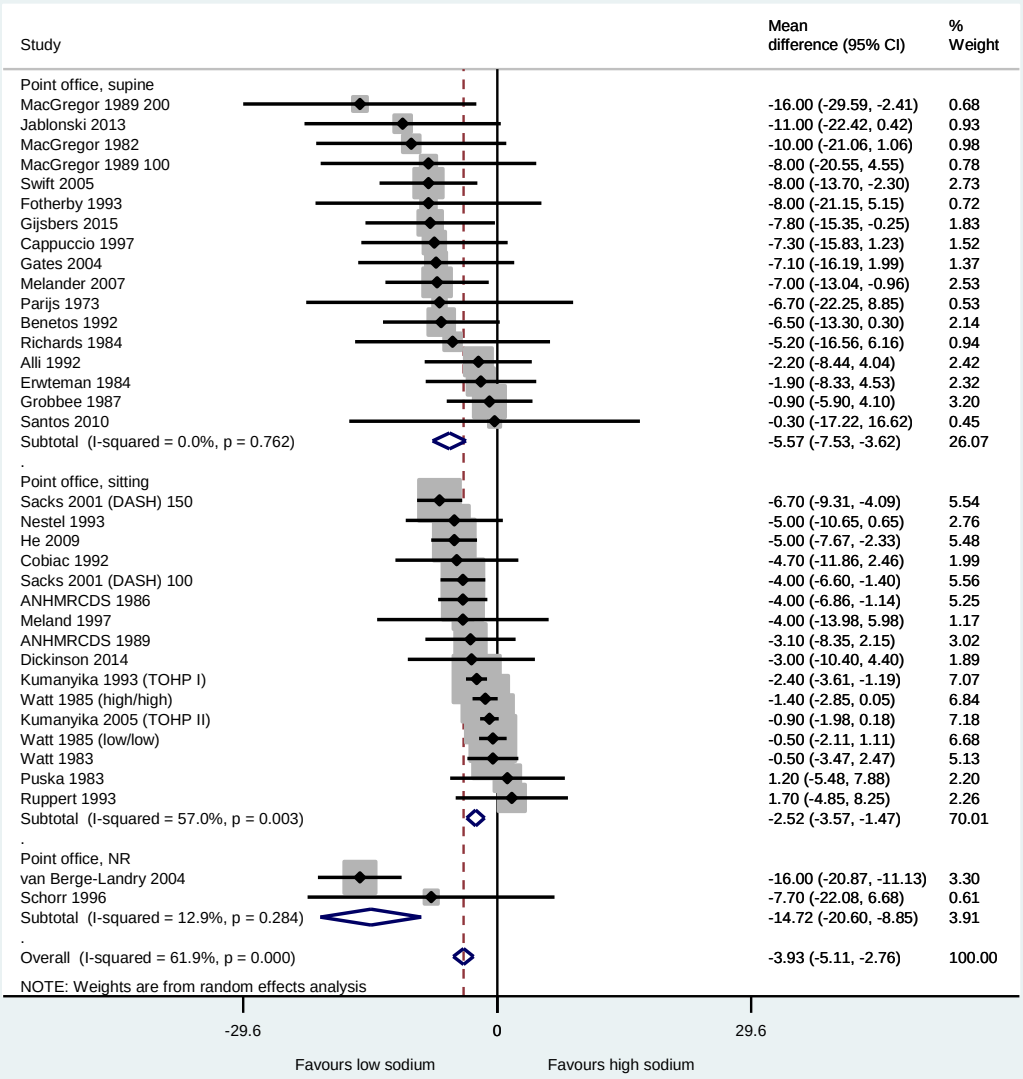
Systolic blood pressure - Trial duration



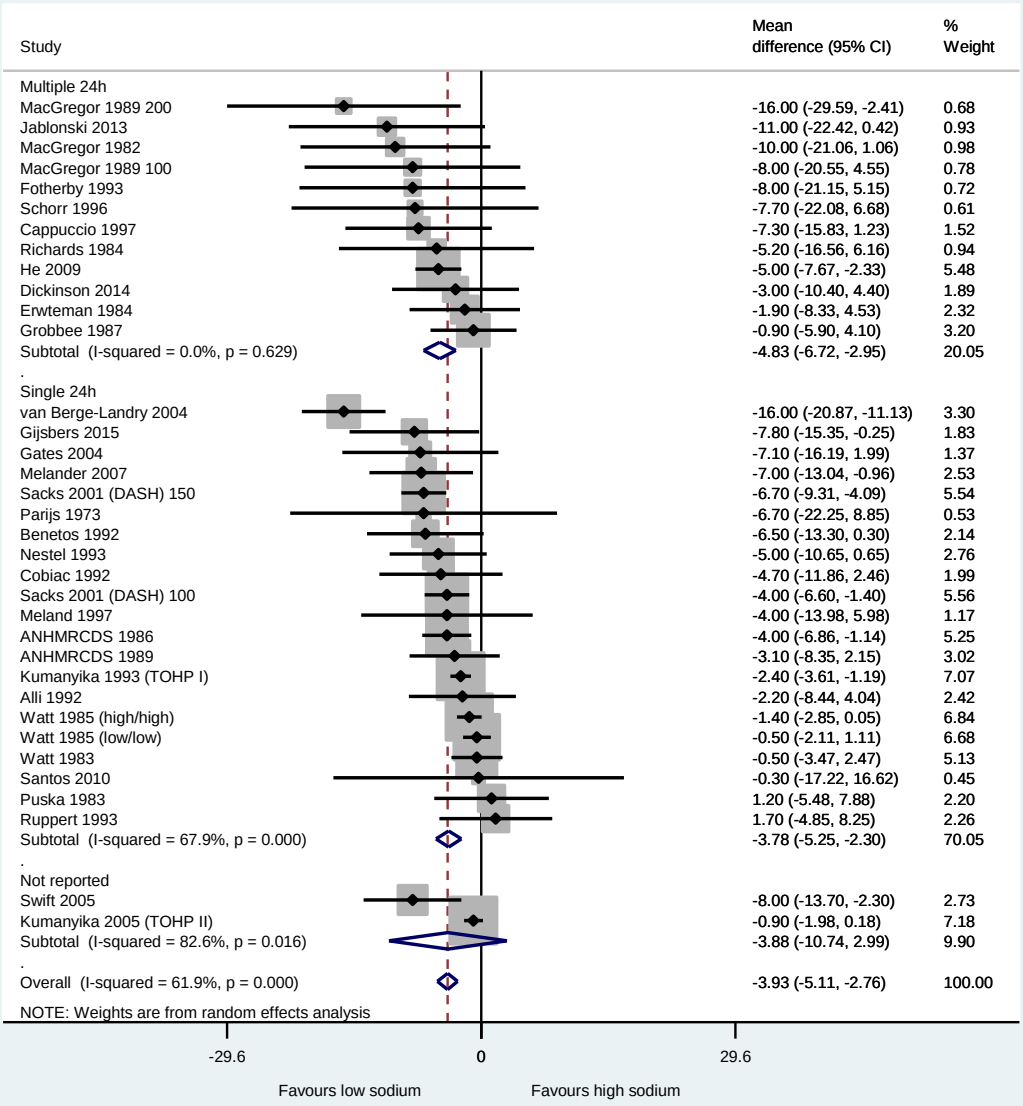
Systolic blood pressure - Intervention type



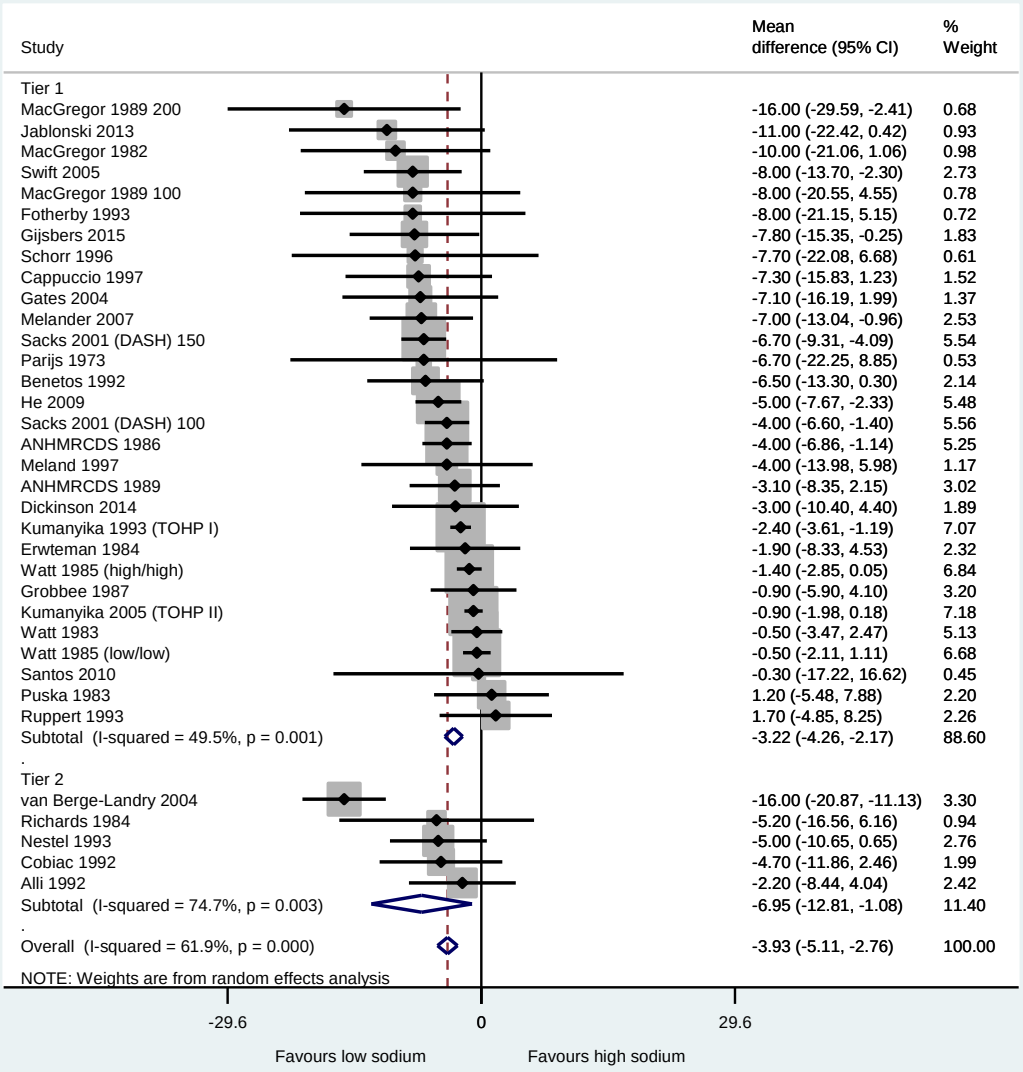
Systolic blood pressure - BP measurement method



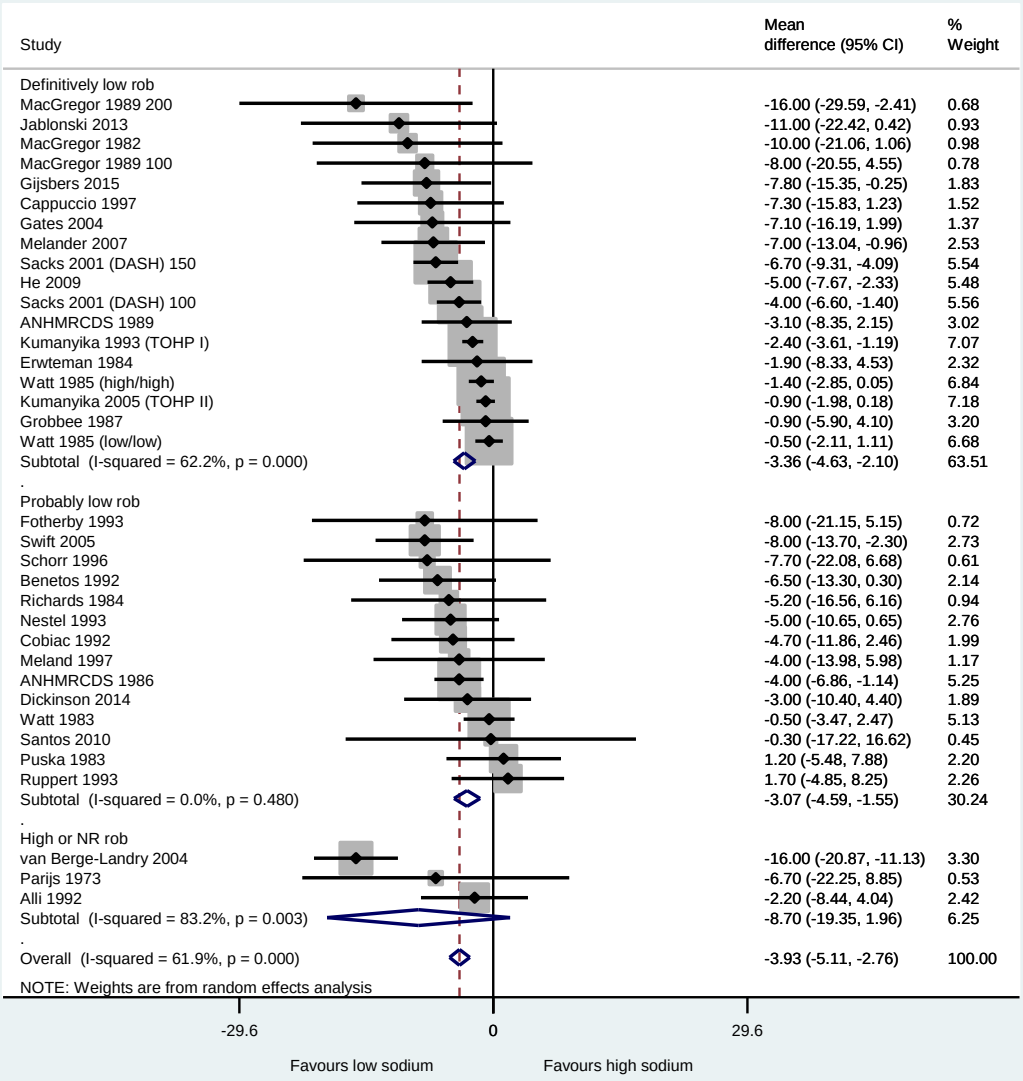
Systolic blood pressure - Number of urinary collections

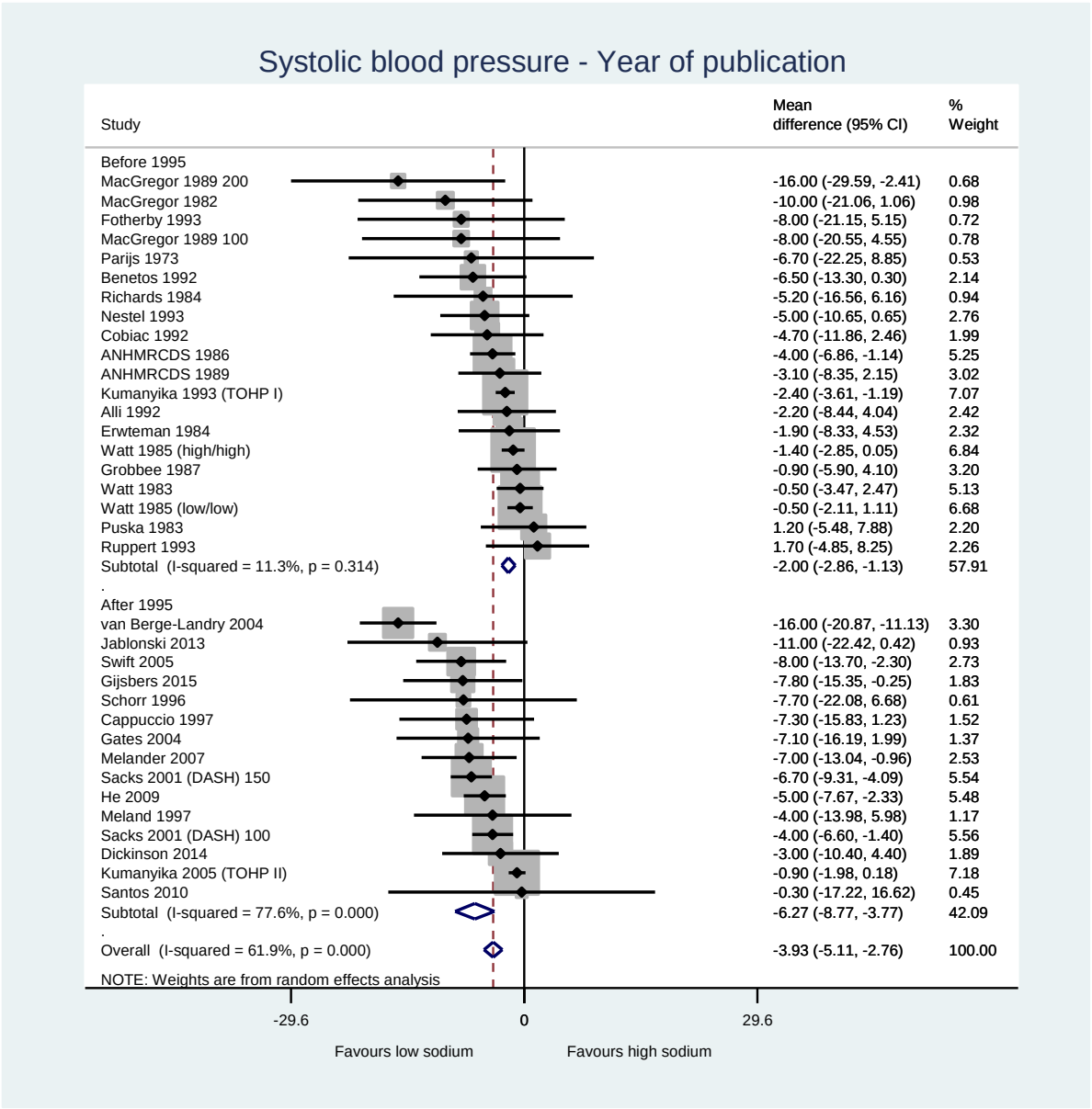


Systolic blood pressure - Risk of Bias TIER

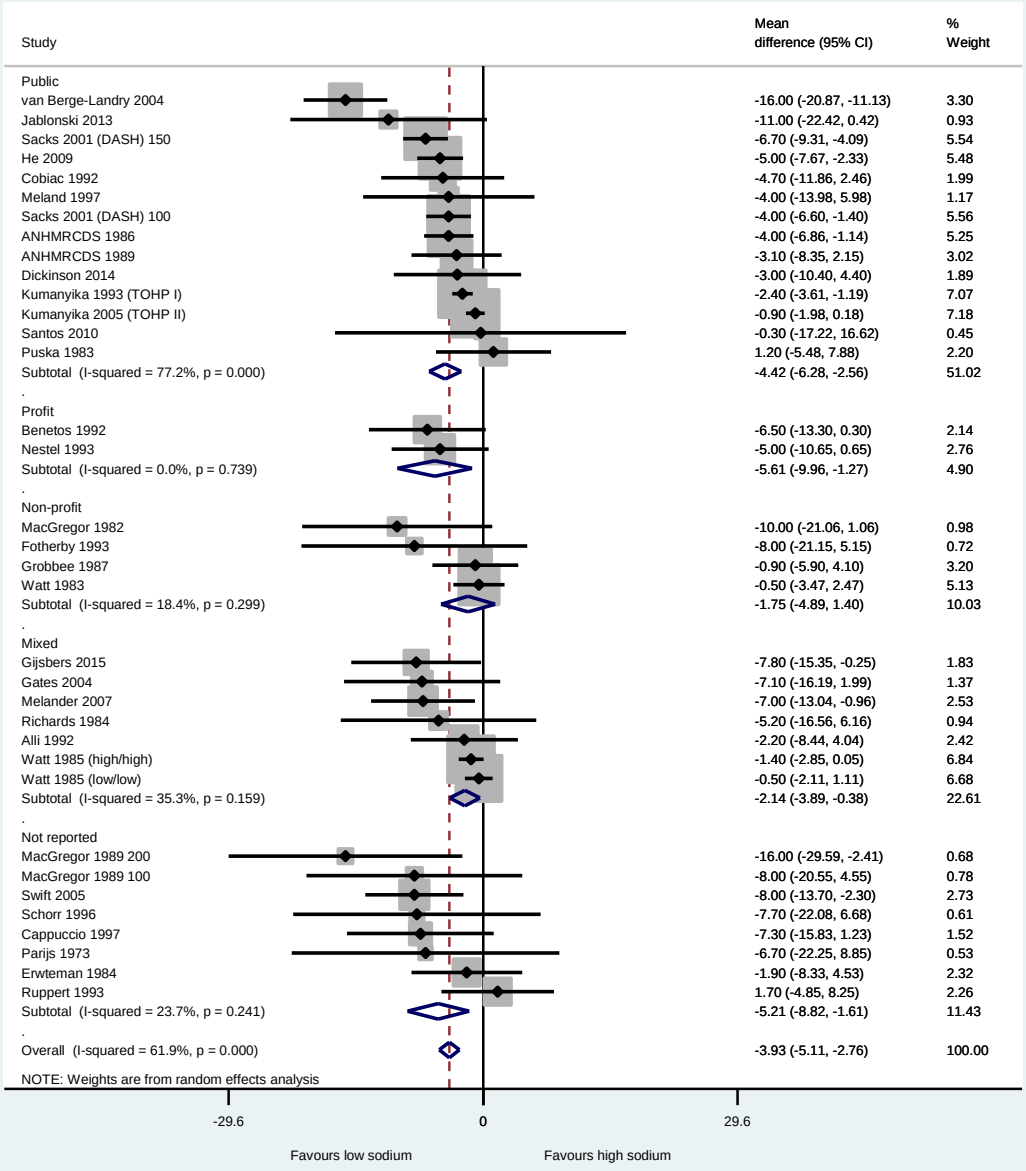


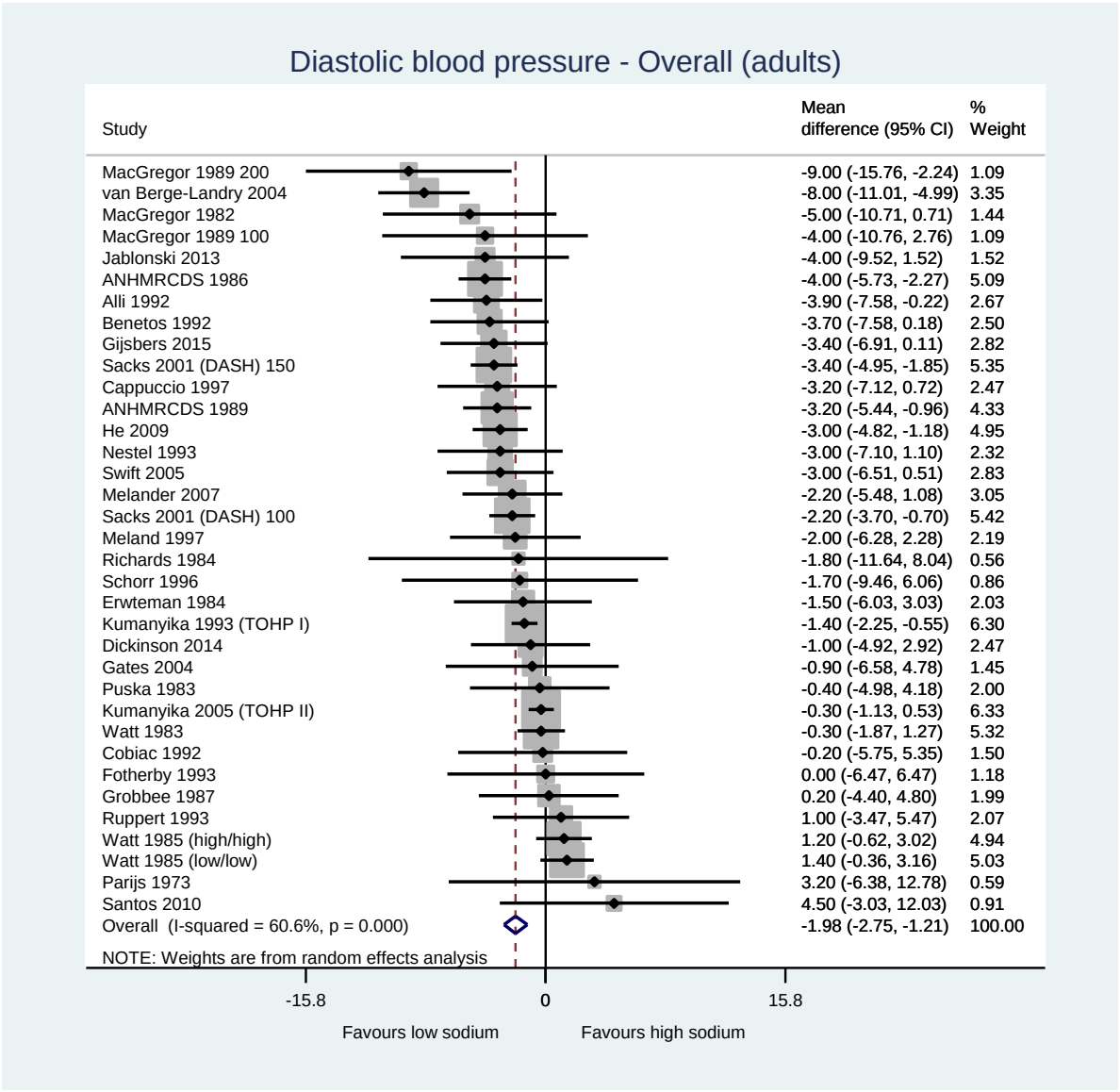
Systolic blood pressure - Risk of Bias OUTCOME



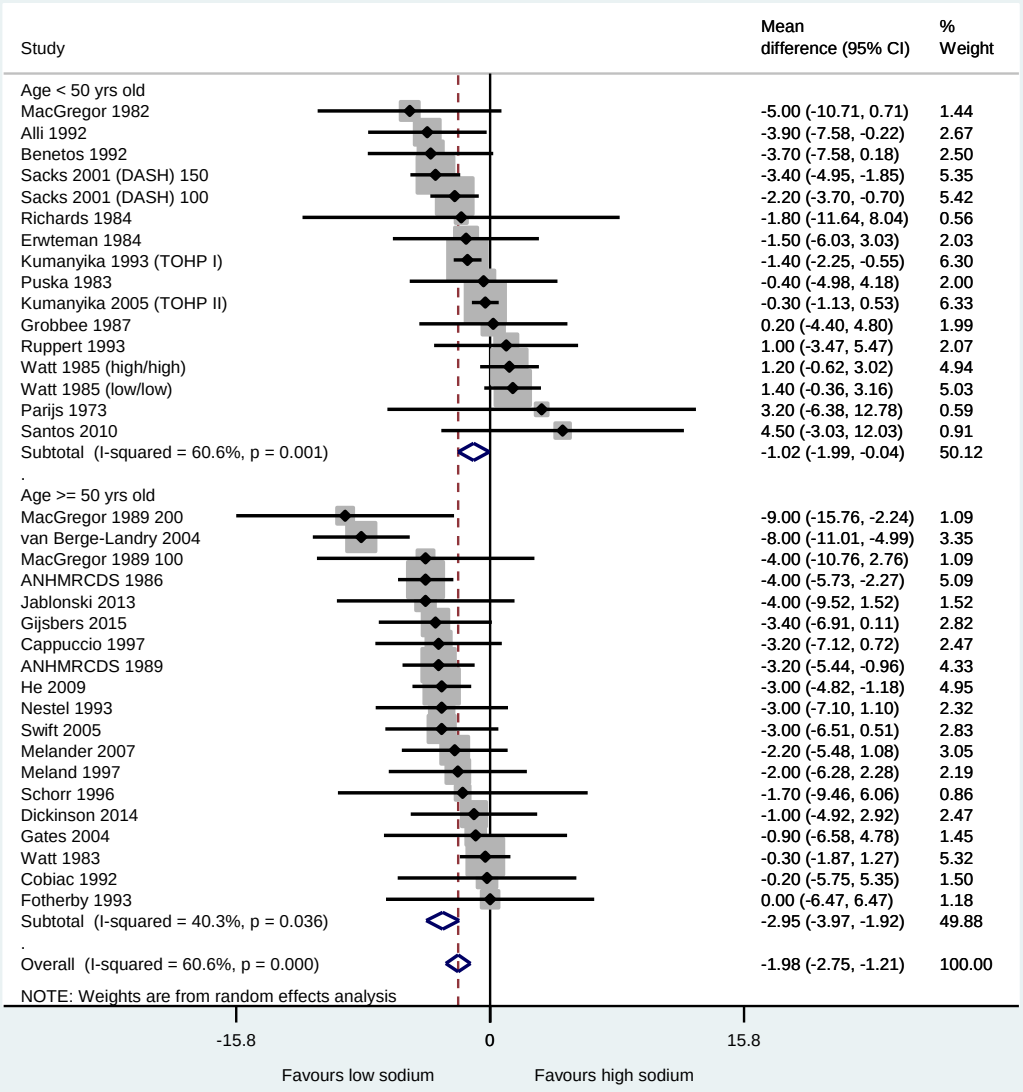

Systolic blood pressure - Year of publication
Study
Mean difference (95% CI)
% Weight
Before 1995
MacGregor 1989 200 -16.00 (-29.59, -2.41) 0.68
MacGregor 1982 -10.00 (-21.06, 1.06) 0.98
Fotherby 1993 -8.00 (-21.15, 5.15) 0.72
MacGregor 1989 100 -8.00 (-20.55, 4.55) 0.78
Parijs 1973 -6.70 (-22.25, 8.85) 0.53
Benetos 1992 -6.50 (-13.30, 0.30) 2.14
Richards 1984 -5.20 (-16.56, 6.16) 0.94
Nestel 1993 -5.00 (-10.65, 0.65) 2.76
Cobiac 1992 -4.70 (-11.86, 2.46) 1.99
ANHMRCDS 1986 -4.00 (-6.86, -1.14) 5.25
ANHMRCDS 1989 -3.10 (-8.35, 2.15) 3.02
Kumanyika 1993 (TOHP I) -2.40 (-3.61, -1.19) 7.07
Alli 1992 -2.20 (-8.44, 4.04) 2.42
Erwteman 1984 -1.90 (-8.33, 4.53) 2.32
Watt 1985 (high/high) -1.40 (-2.85, 0.05) 6.84
Grobbee 1987 -0.90 (-5.90, 4.10) 3.20
Watt 1983 -0.50 (-3.47, 2.47) 5.13
Watt 1985 (low/low) -0.50 (-2.11, 1.11) 6.68
Puska 1983 1.20 (-5.48, 7.88) 2.20
Ruppert 1993 1.70 (-4.85, 8.25) 2.26
Subtotal (I-squared = 11.3%, p = 0.314) -2.00 (-2.86, -1.13) 57.91
After 1995
van Berge-Landry 2004 -16.00 (-20.87, -11.13) 3.30
Jablonski 2013 -11.00 (-22.42, 0.42) 0.93
Swift 2005 -8.00 (-13.70, -2.30) 2.73
Gijsbers 2015 -7.80 (-15.35, -0.25) 1.83
Schorr 1996 -7.70 (-22.08, 6.68) 0.61
Cappuccio 1997 -7.30 (-15.83, 1.23) 1.52
Gates 2004 -7.10 (-16.19, 1.99) 1.37
Melander 2007 -7.00 (-13.04, -0.96) 2.53
Sacks 2001 (DASH) 150 -6.70 (-9.31, -4.09) 5.54
He 2009 -5.00 (-7.67, -2.33) 5.48
Meland 1997 -4.00 (-13.98, 5.98) 1.17
Sacks 2001 (DASH) 100 -4.00 (-6.60, -1.40) 5.56
Dickinson 2014 -3.00 (-10.40, 4.40) 1.89
Kumanyika 2005 (TOHP II) -0.90 (-1.98, 0.18) 7.18
Santos 2010 -0.30 (-17.22, 16.62) 0.45
Subtotal (I-squared = 77.6%, p = 0.000) -6.27 (-8.77, -3.77) 42.09
Overall (I-squared = 61.9%, p = 0.000) -3.93 (-5.11, -2.76) 100.00
NOTE: Weights are from random effects analysis
-29.6
0
29.6
Favours low sodium
Favours high sodium

Systolic blood pressure - Funding

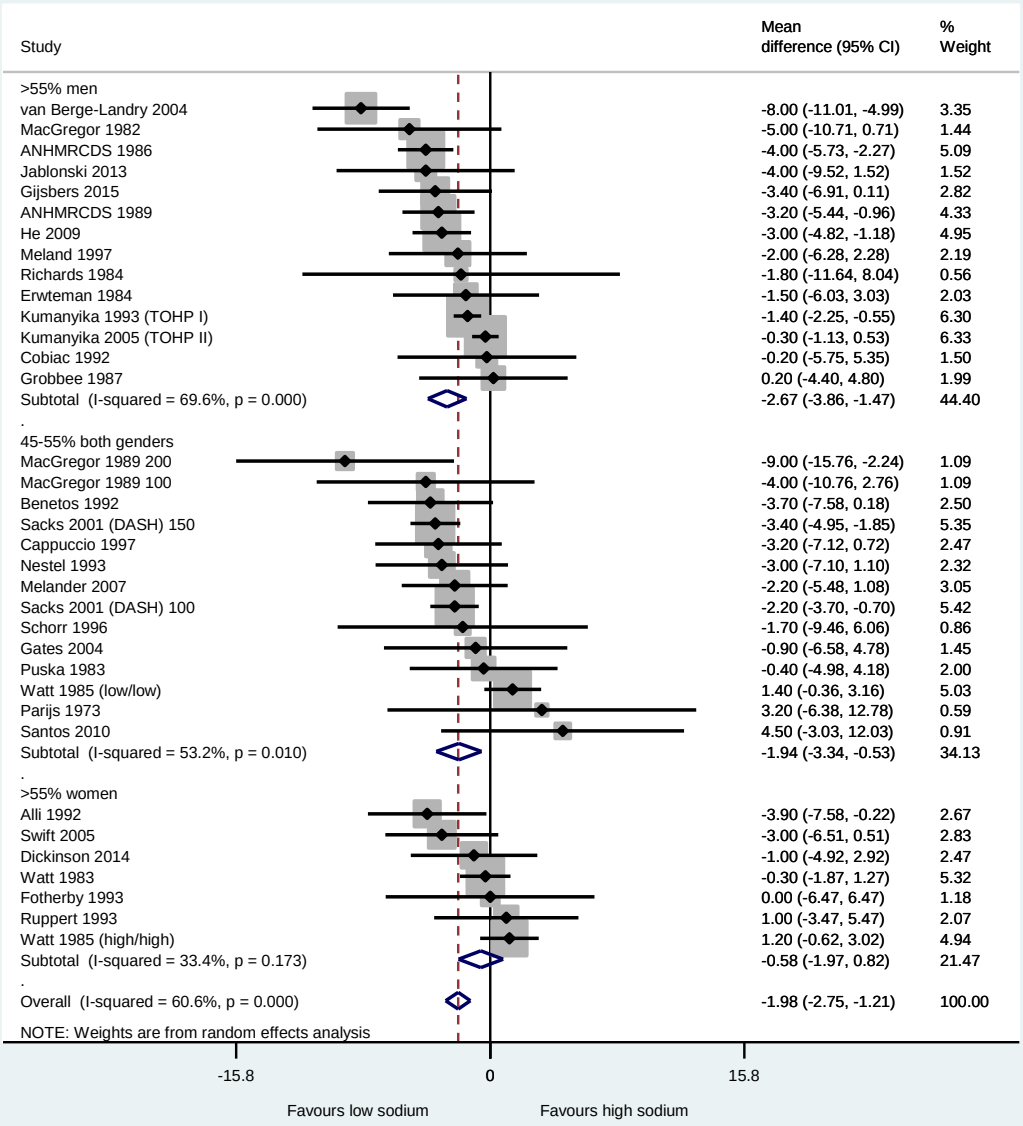



Diastolic blood pressure - Overall (adults)
Study
Mean difference (95% CI)
% Weight
MacGregor 1989 200 -9.00 (-15.76, -2.24) 1.09
van Berge-Landry 2004 -8.00 (-11.01, -4.99) 3.35
MacGregor 1982 -5.00 (-10.71, 0.71) 1.44
MacGregor 1989 100 -4.00 (-10.76, 2.76) 1.09
Jablonski 2013 -4.00 (-9.52, 1.52) 1.52
ANHMRCDS 1986 -4.00 (-5.73, -2.27) 5.09
Alli 1992 -3.90 (-7.58, -0.22) 2.67
Benetos 1992 -3.70 (-7.58, 0.18) 2.50
Gijsbers 2015 -3.40 (-6.91, 0.11) 2.82
Sacks 2001 (DASH) 150 -3.40 (-4.95, -1.85) 5.35
Cappuccio 1997 -3.20 (-7.12, 0.72) 2.47
ANHMRCDS 1989 -3.20 (-5.44, -0.96) 4.33
He 2009 -3.00 (-4.82, -1.18) 4.95
Nestel 1993 -3.00 (-7.10, 1.10) 2.32
Swift 2005 -3.00 (-6.51, 0.51) 2.83
Melander 2007 -2.20 (-5.48, 1.08) 3.05
Sacks 2001 (DASH) 100 -2.20 (-3.70, -0.70) 5.42
Meland 1997 -2.00 (-6.28, 2.28) 2.19
Richards 1984 -1.80 (-11.64, 8.04) 0.56
Schorr 1996 -1.70 (-9.46, 6.06) 0.86
Erwteman 1984 -1.50 (-6.03, 3.03) 2.03
Kumanyika 1993 (TOHP I) -1.40 (-2.25, -0.55) 6.30
Dickinson 2014 -1.00 (-4.92, 2.92) 2.47
Gates 2004 -0.90 (-6.58, 4.78) 1.45
Puska 1983 -0.40 (-4.98, 4.18) 2.00
Kumanyika 2005 (TOHP II) -0.30 (-1.13, 0.53) 6.33
Watt 1983 -0.30 (-1.87, 1.27) 5.32
Cobiac 1992 -0.20 (-5.75, 5.35) 1.50
Fotherby 1993 0.00 (-6.47, 6.47) 1.18
Grobbee 1987 0.20 (-4.40, 4.80) 1.99
Ruppert 1993 1.00 (-3.47, 5.47) 2.07
Watt 1985 (high/high) 1.20 (-0.62, 3.02) 4.94
Watt 1985 (low/low) 1.40 (-0.36, 3.16) 5.03
Parijs 1973 3.20 (-6.38, 12.78) 0.59
Santos 2010 4.50 (-3.03, 12.03) 0.91
Overall (I-squared = 60.6%, p = 0.000) -1.98 (-2.75, -1.21) 100.00
NOTE: Weights are from random effects analysis
-15.8
0
15.8
Favours low sodium
Favours high sodium

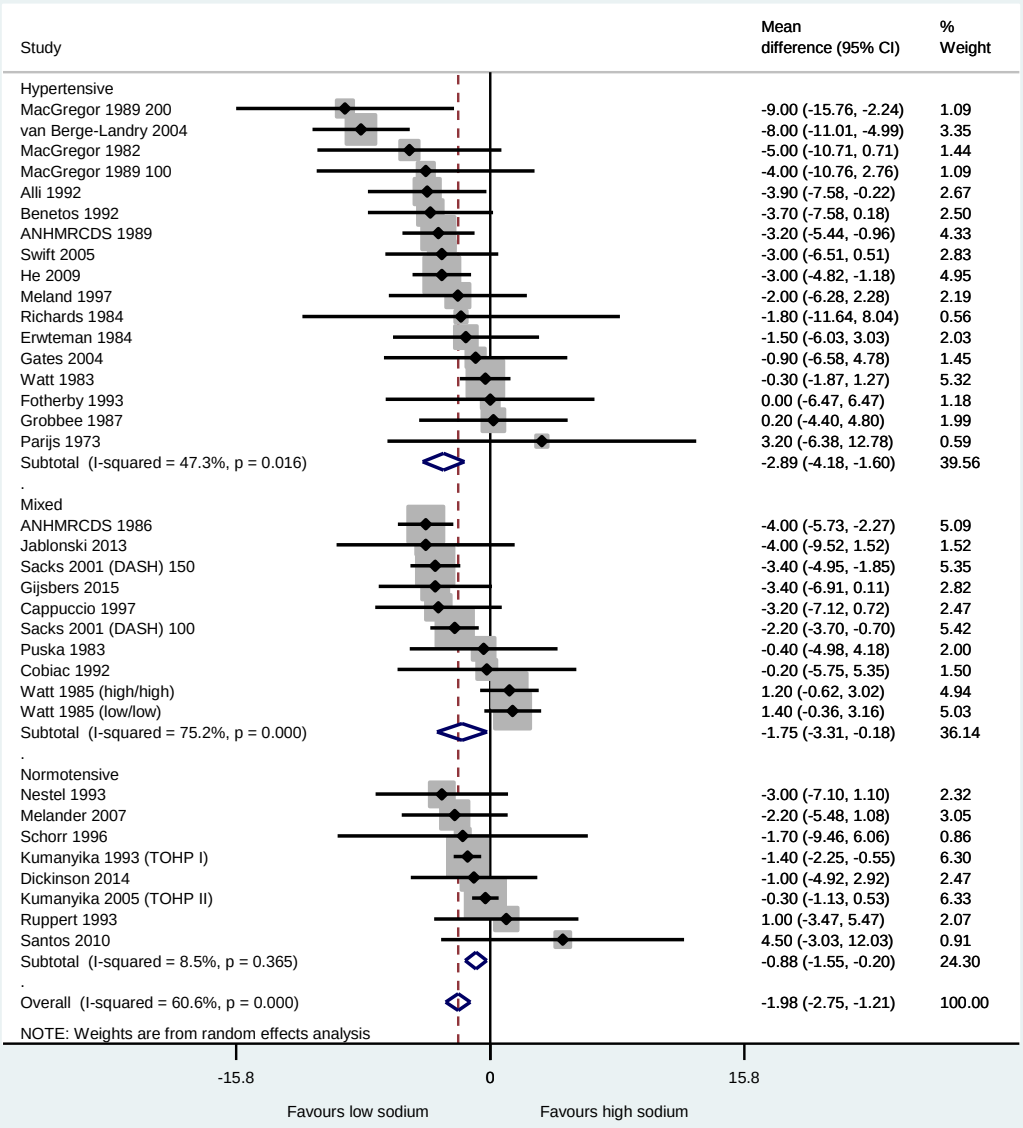
Diastolic blood pressure - Age < and >= 50 yrs old



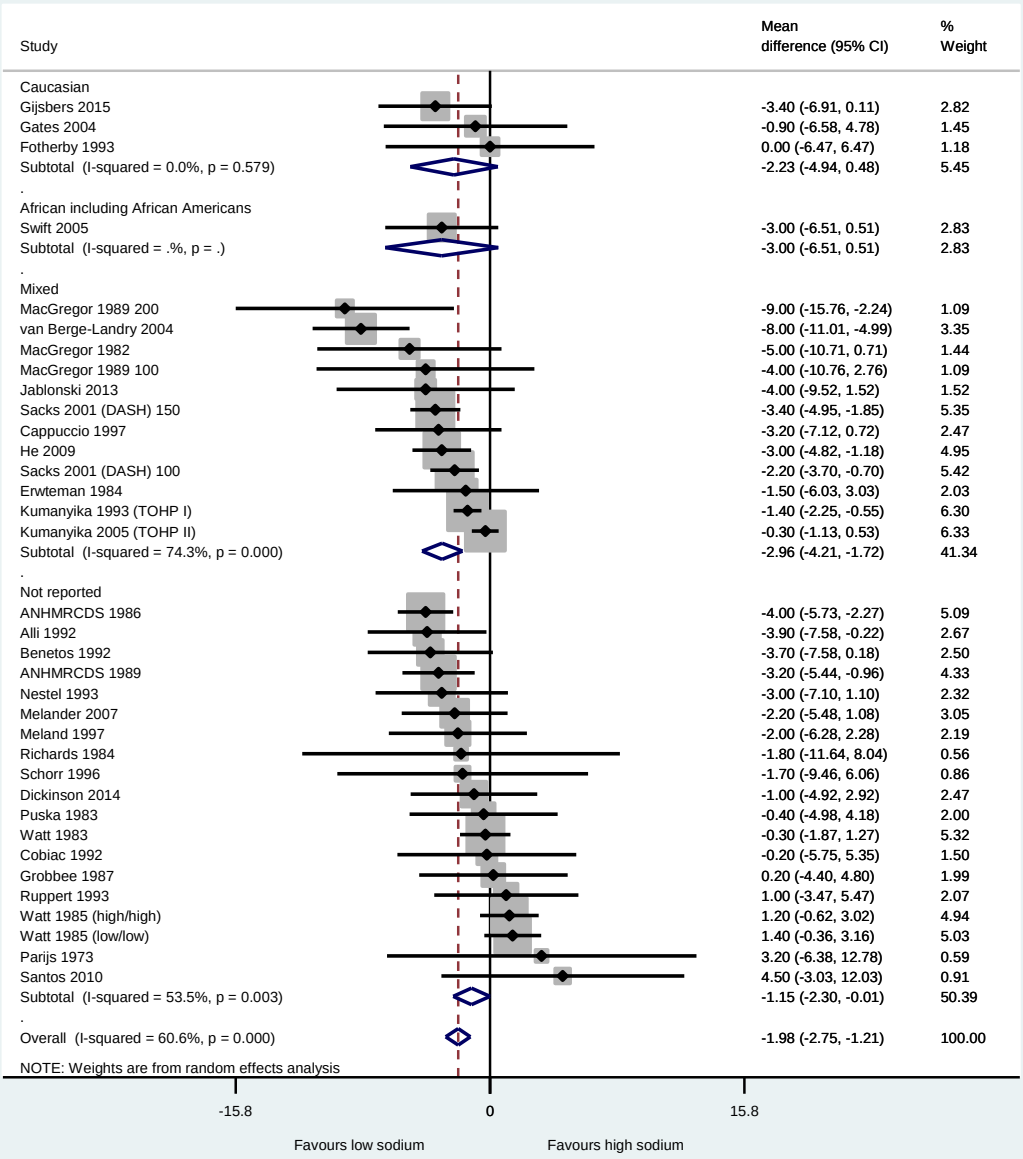
Diastolic blood pressure - Sex proportion



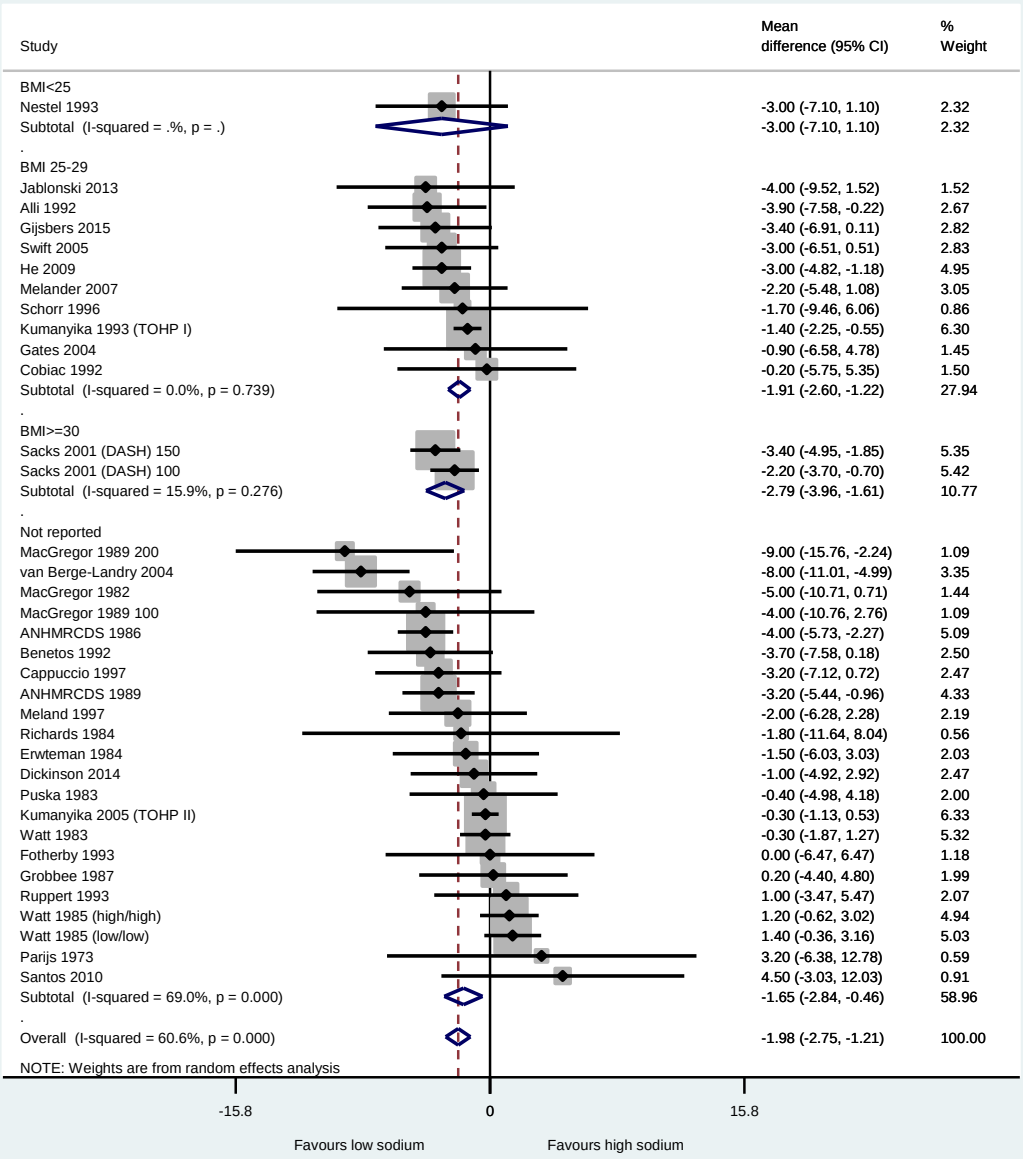
Diastolic blood pressure - Blood pressure status



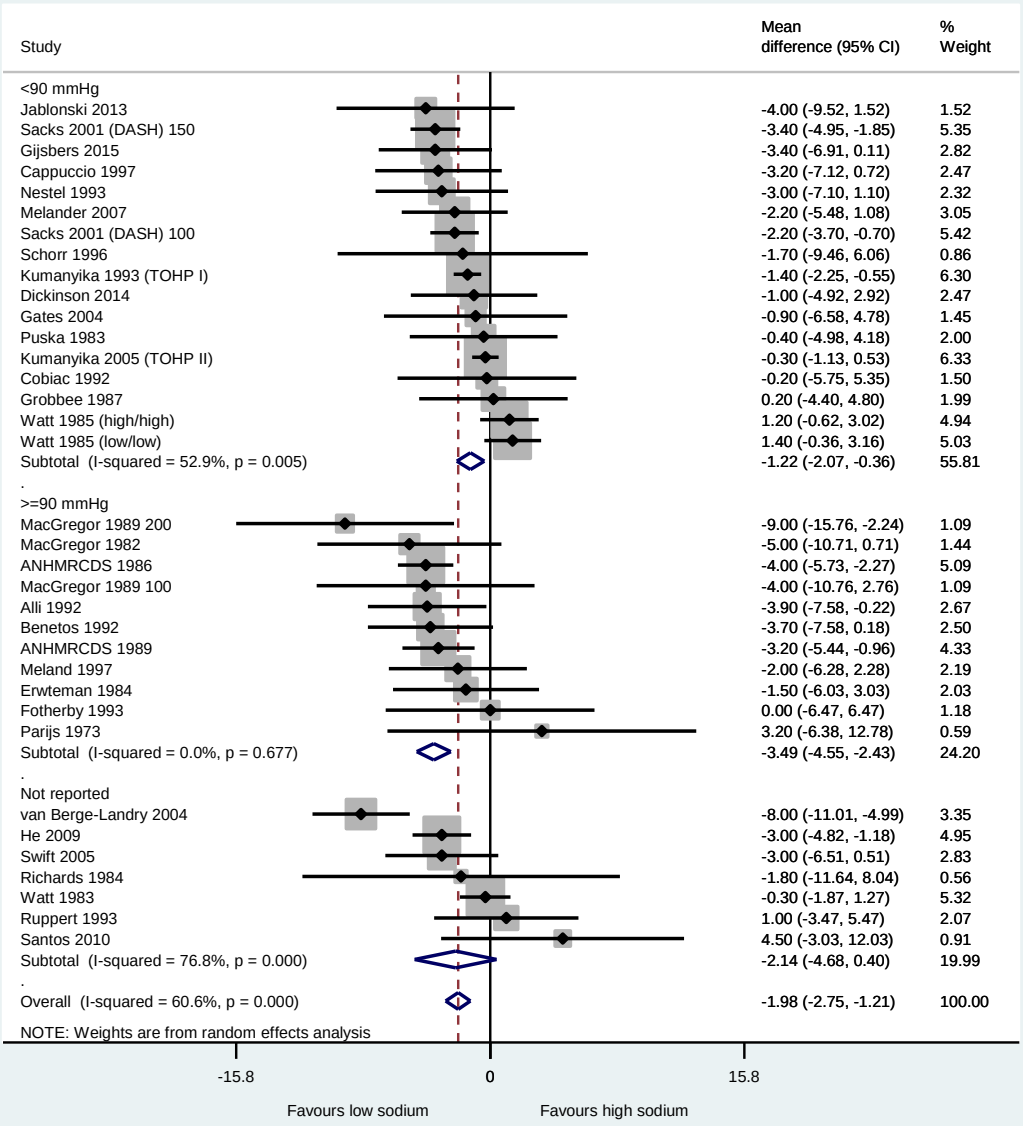
Diastolic blood pressure - Ethnicity



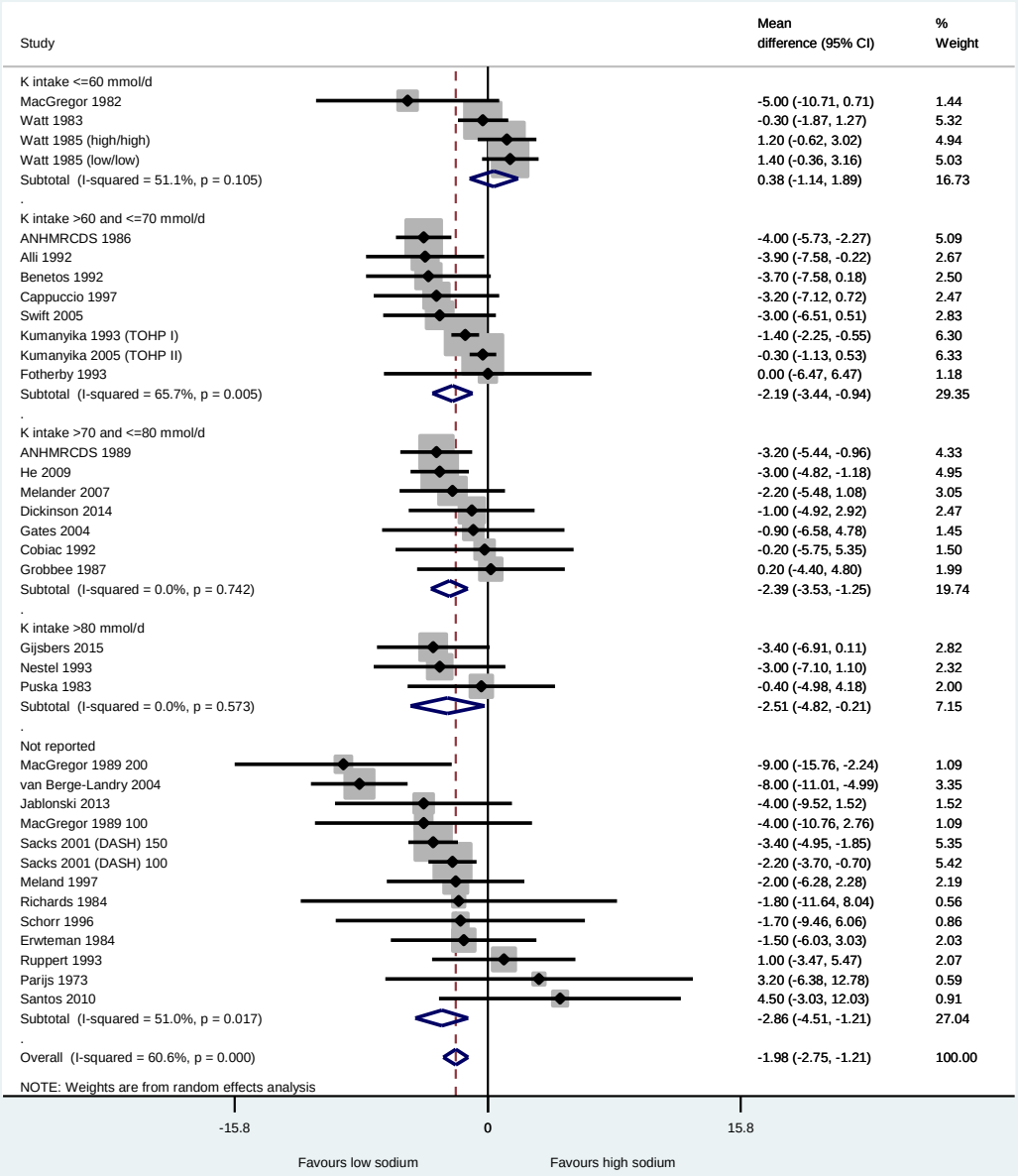
Diastolic blood pressure - BMI



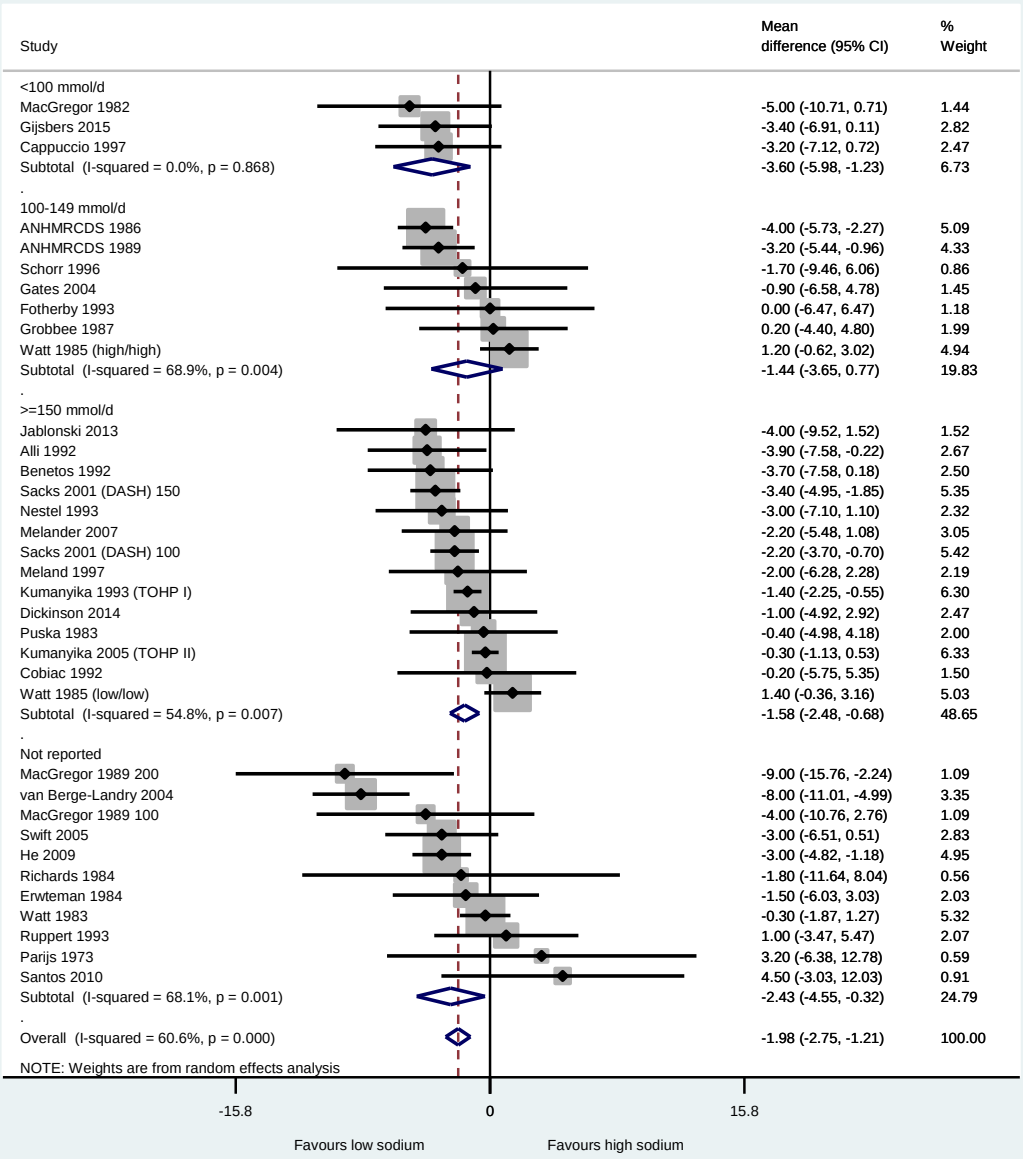
Diastolic blood pressure - Baseline DBP



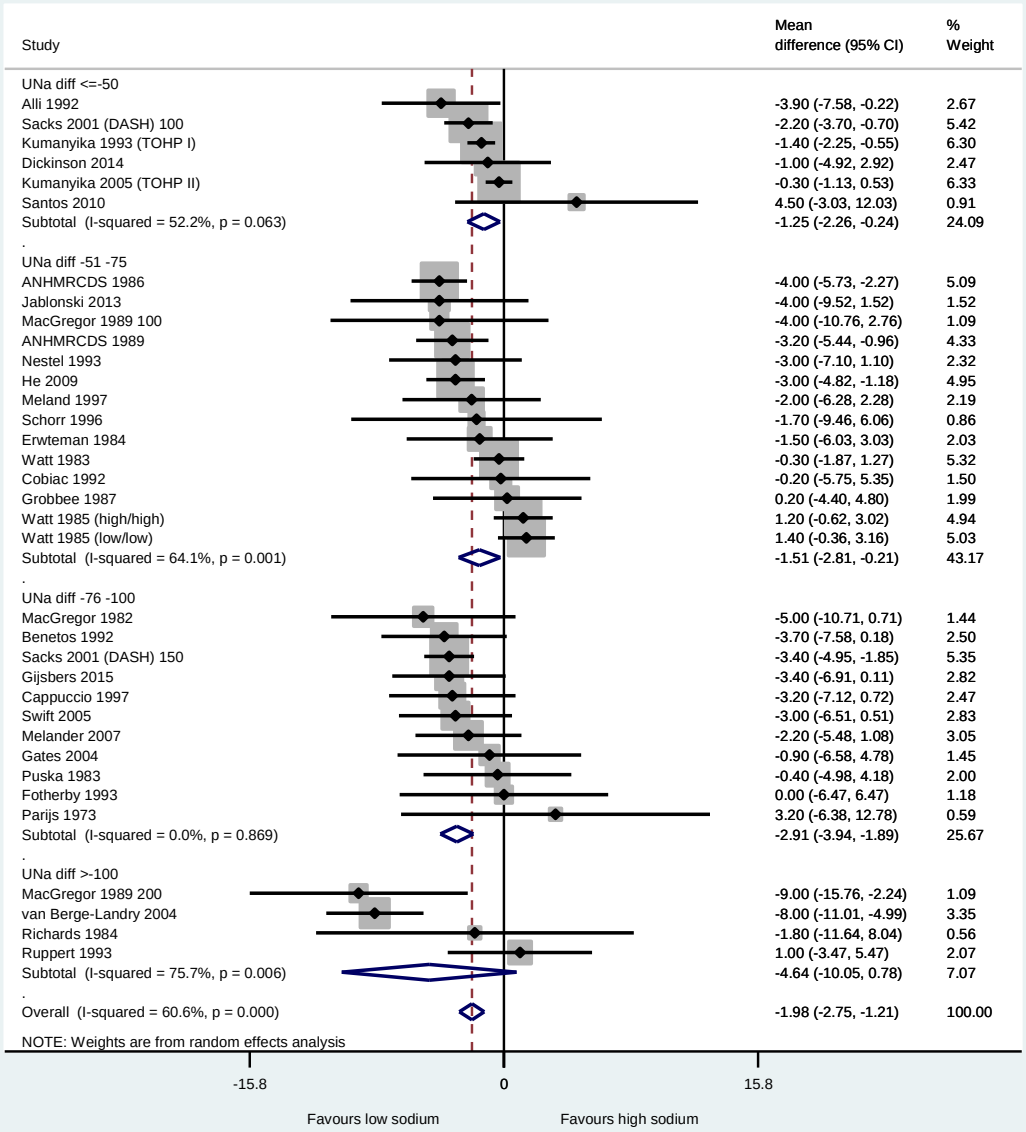
Diastolic blood pressure - Baseline potassium intake



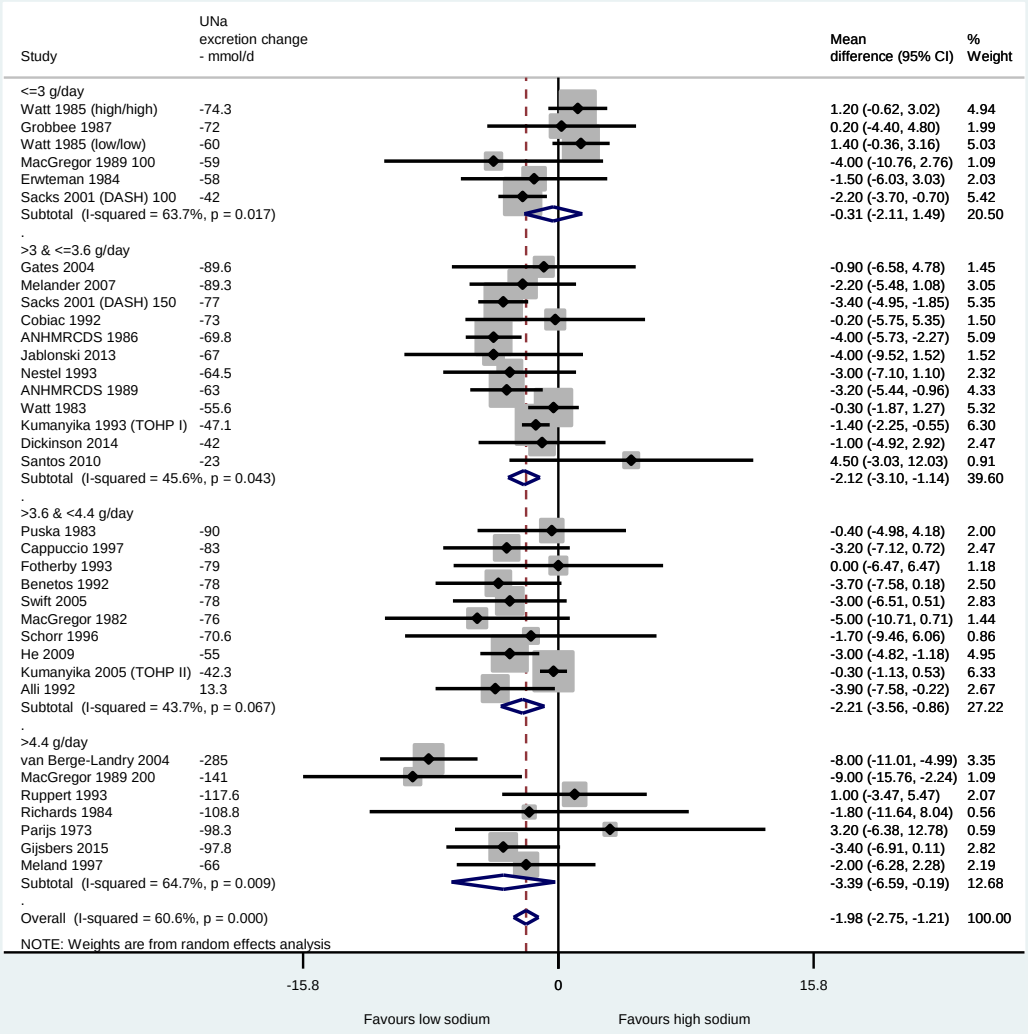
Diastolic blood pressure - Sodium excretion at baseline



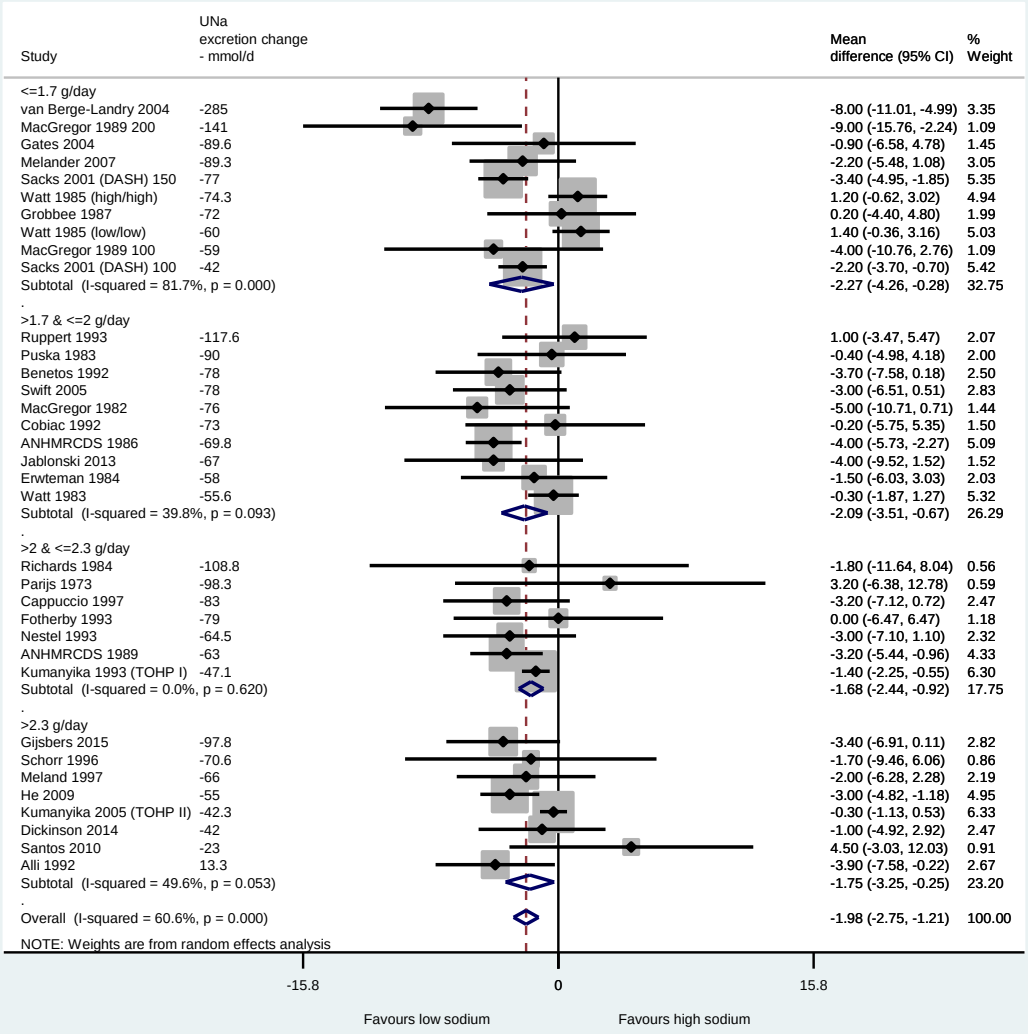
Diastolic blood pressure - Sodium excretion difference across arms



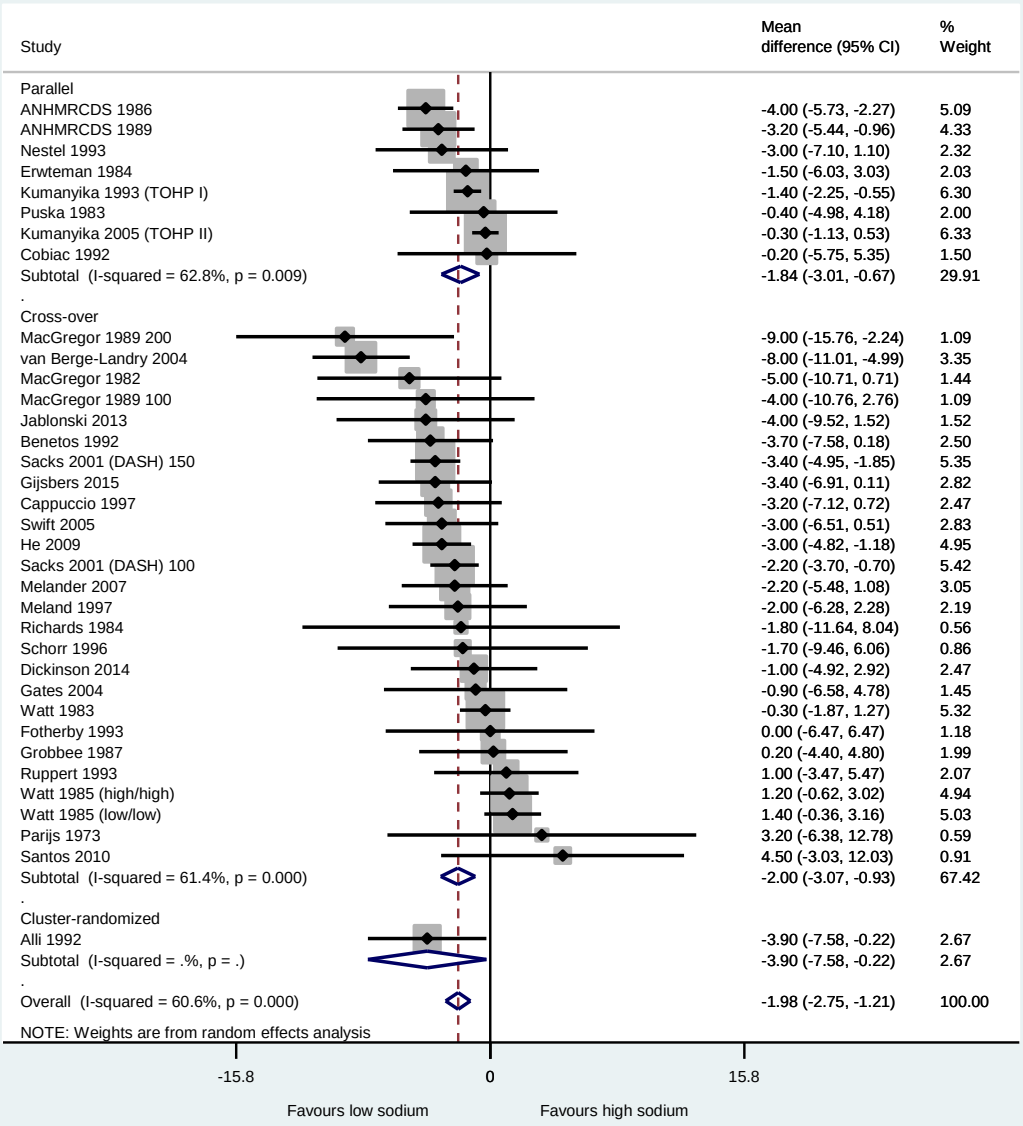
Diastolic blood pressure - Achieved sodium excretion in high Na group



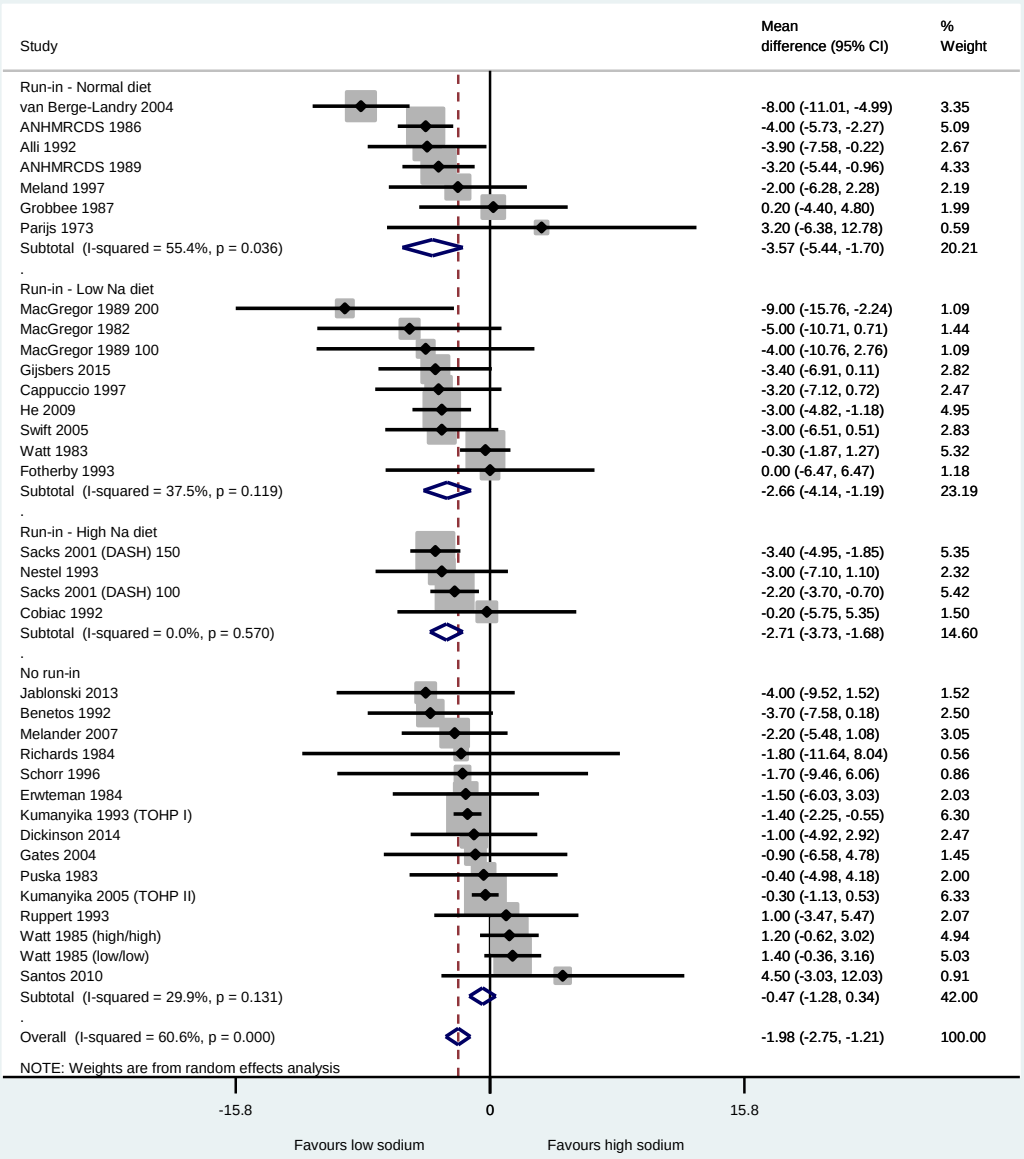
Diastolic blood pressure - Achieved sodium excretion in low Na group



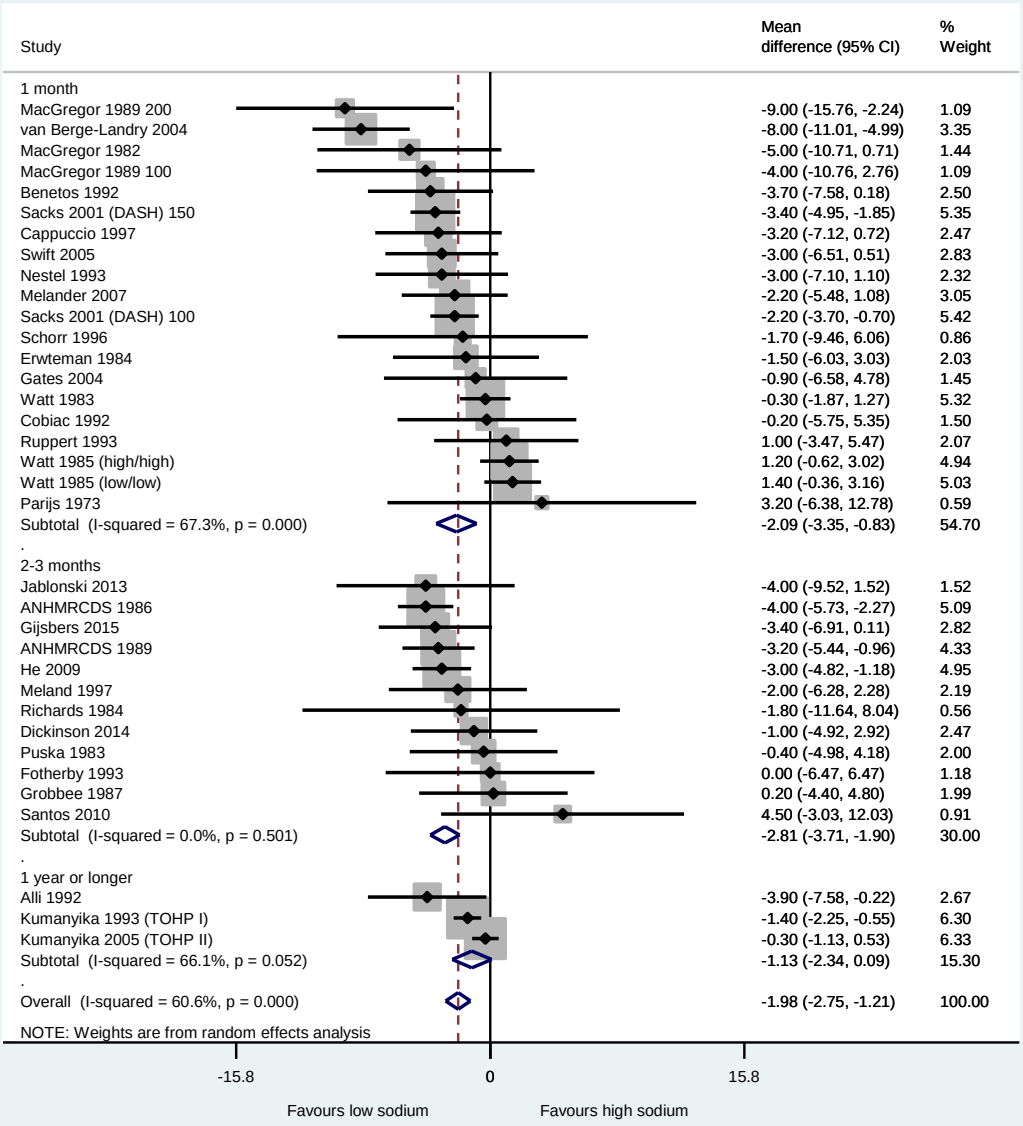
Diastolic blood pressure - Study design



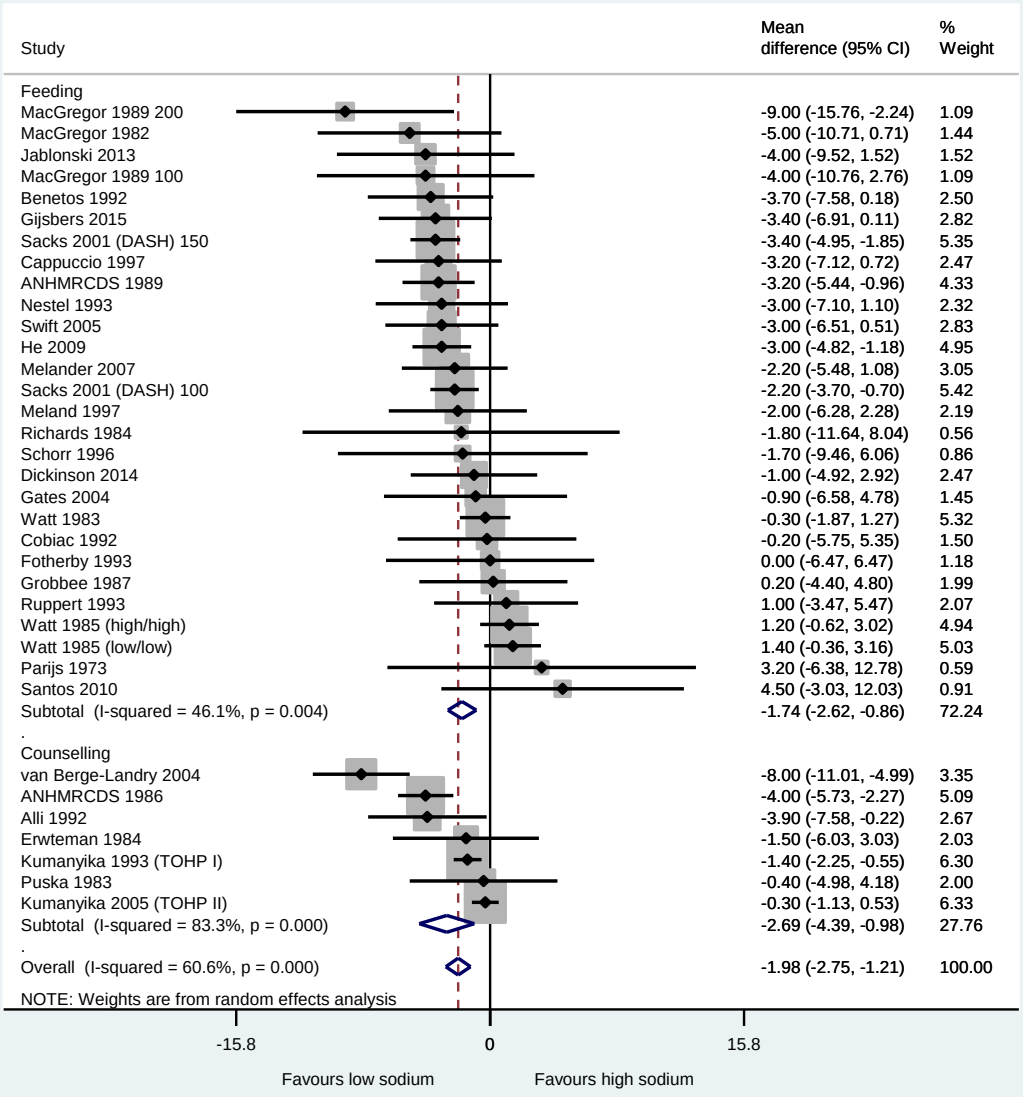
Diastolic blood pressure - Specific design



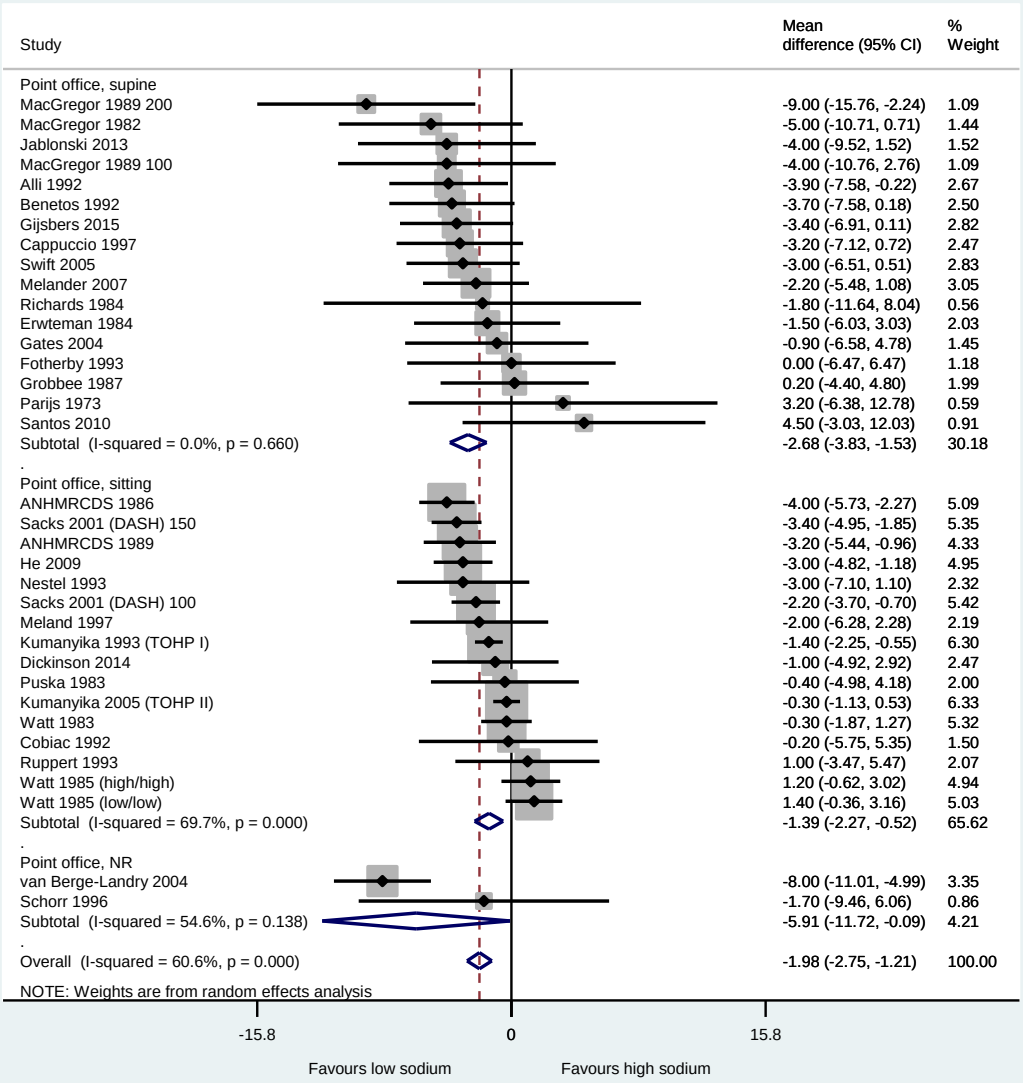
Diastolic blood pressure - Trial duration



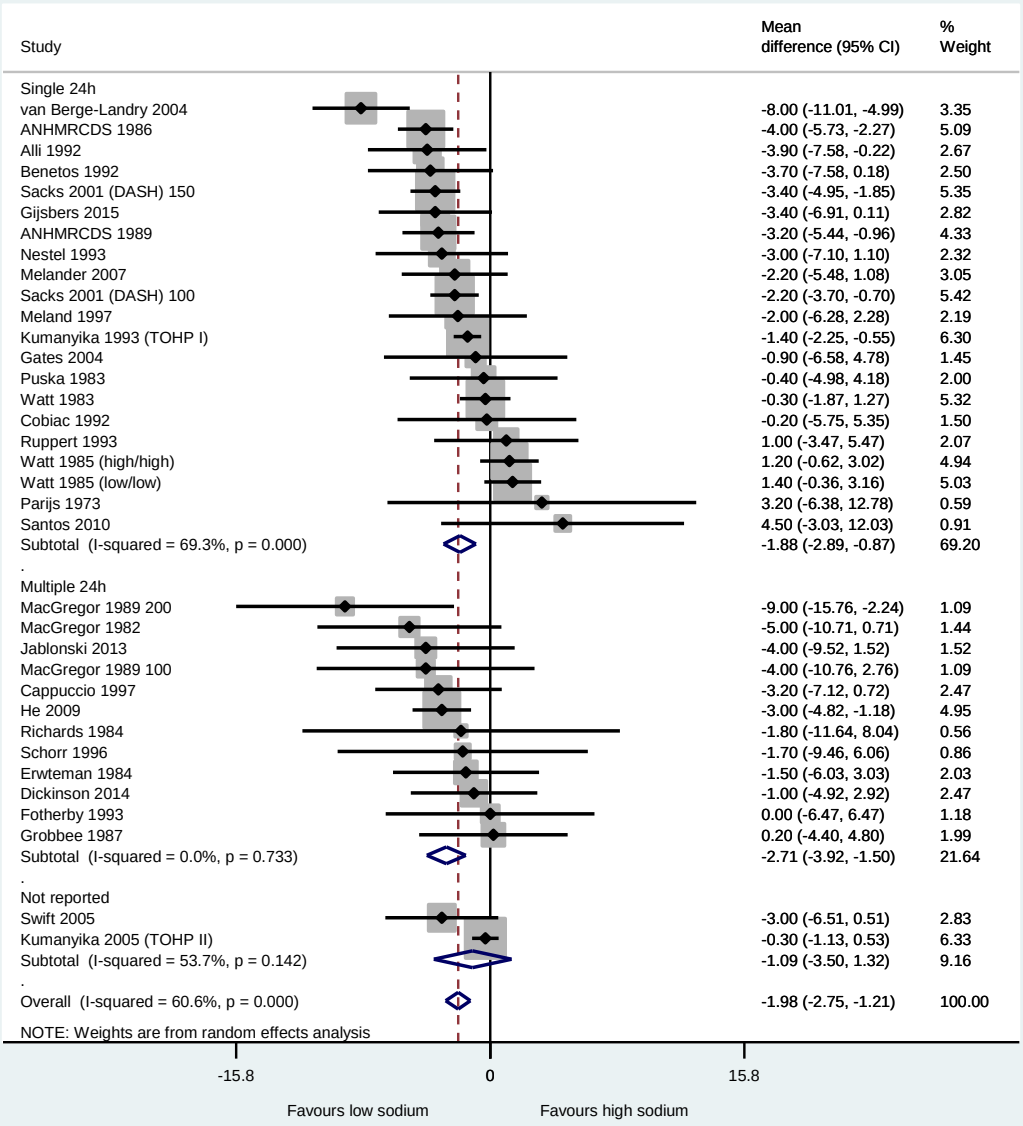
Diastolic blood pressure - Intervention type



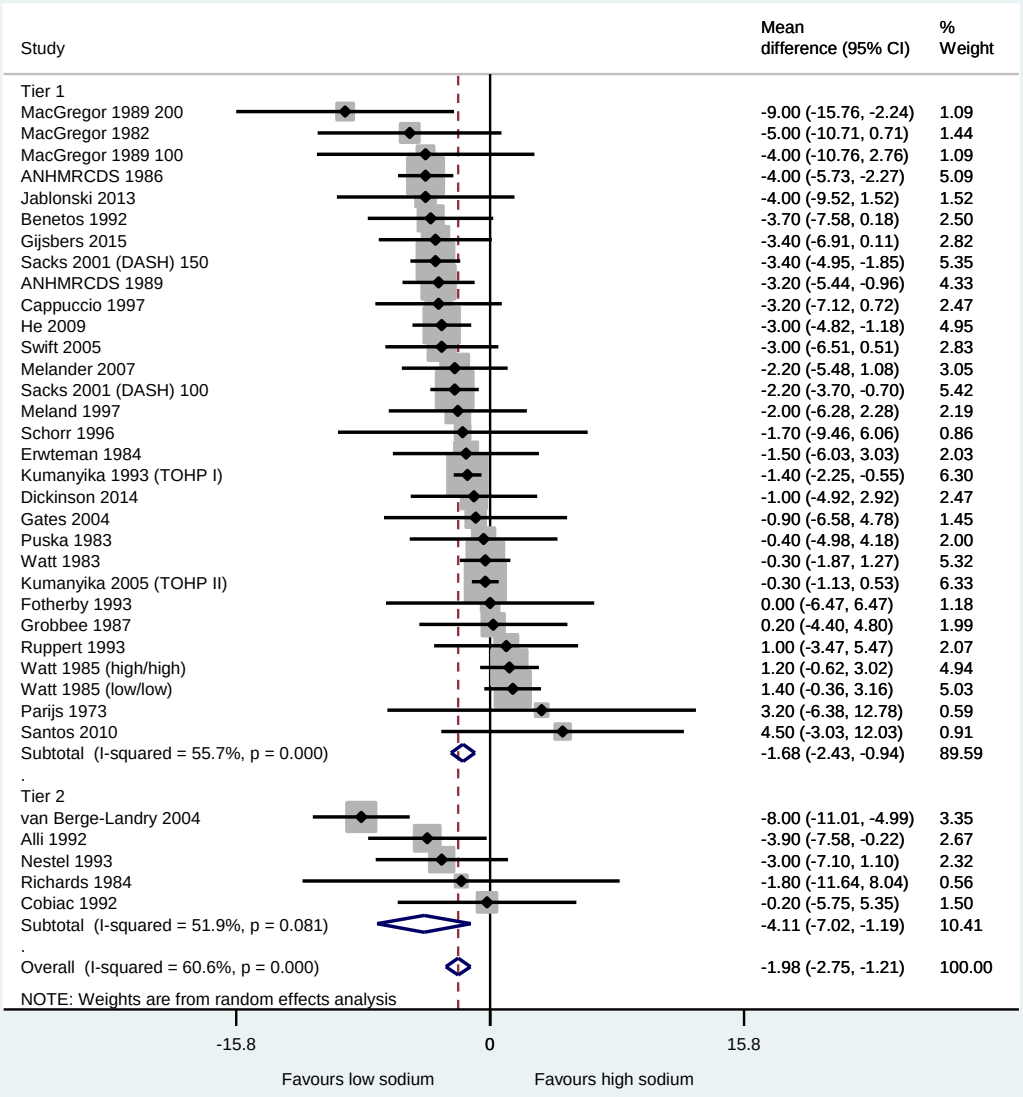
Diastolic blood pressure - BP measurement method



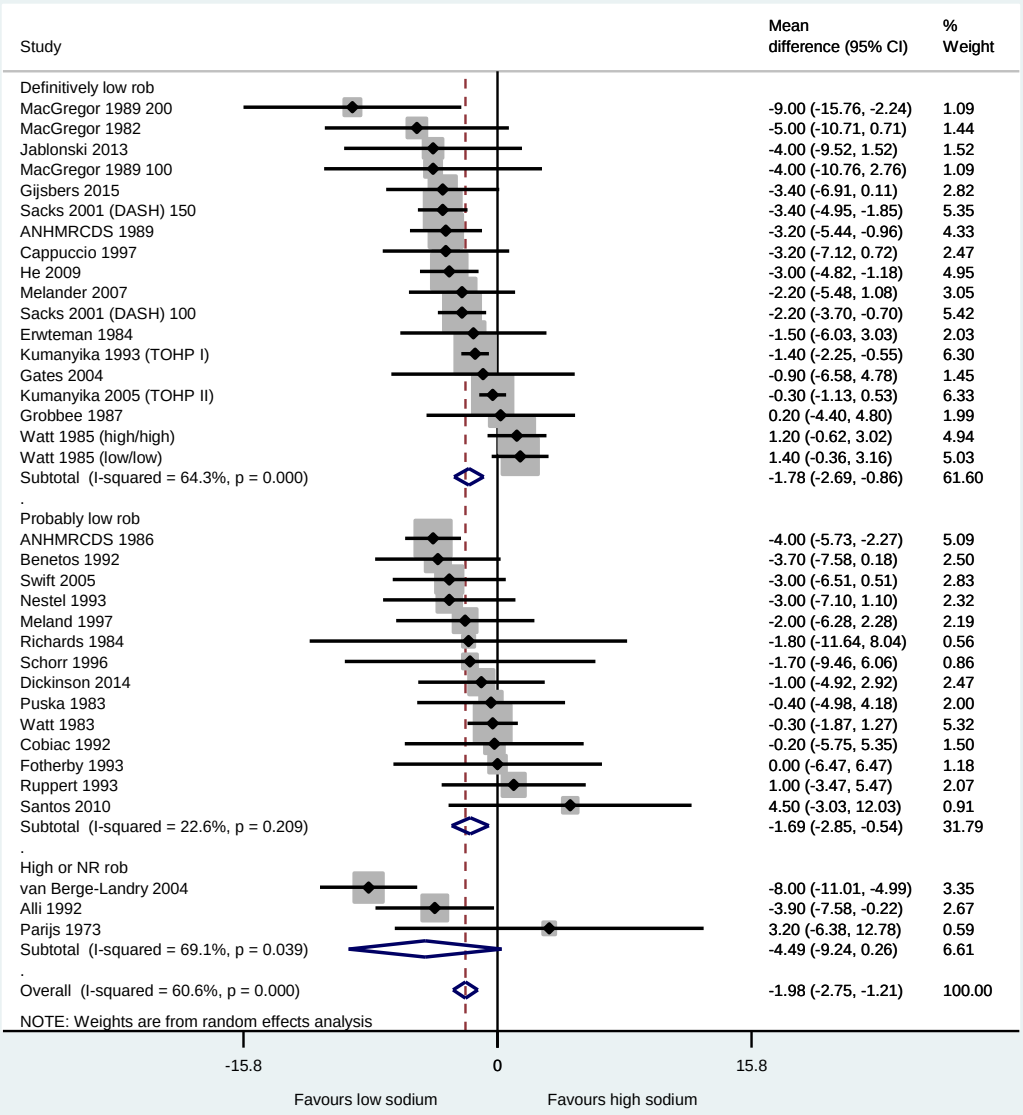
Diastolic blood pressure - Number of urinary collections



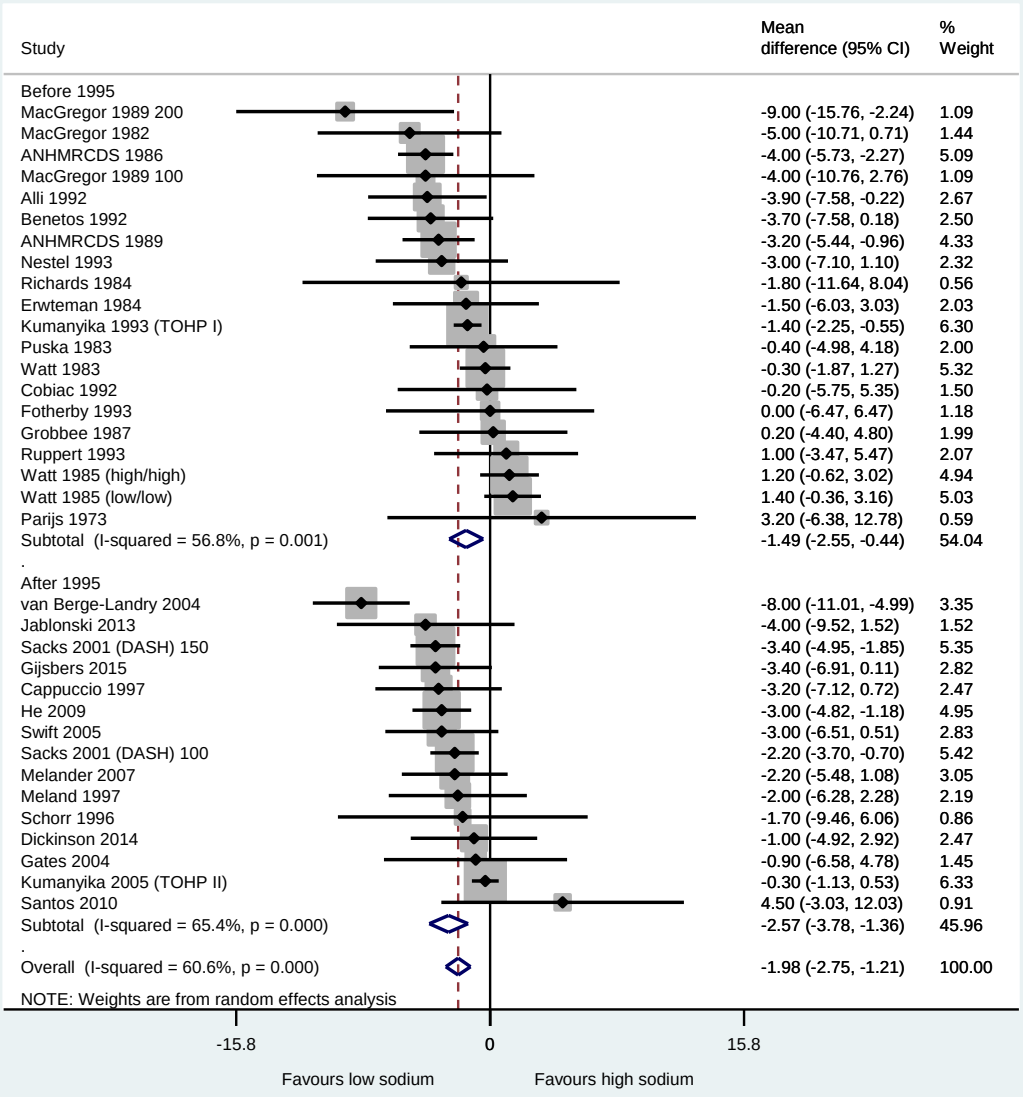
Diastolic blood pressure - Risk of Bias TIER



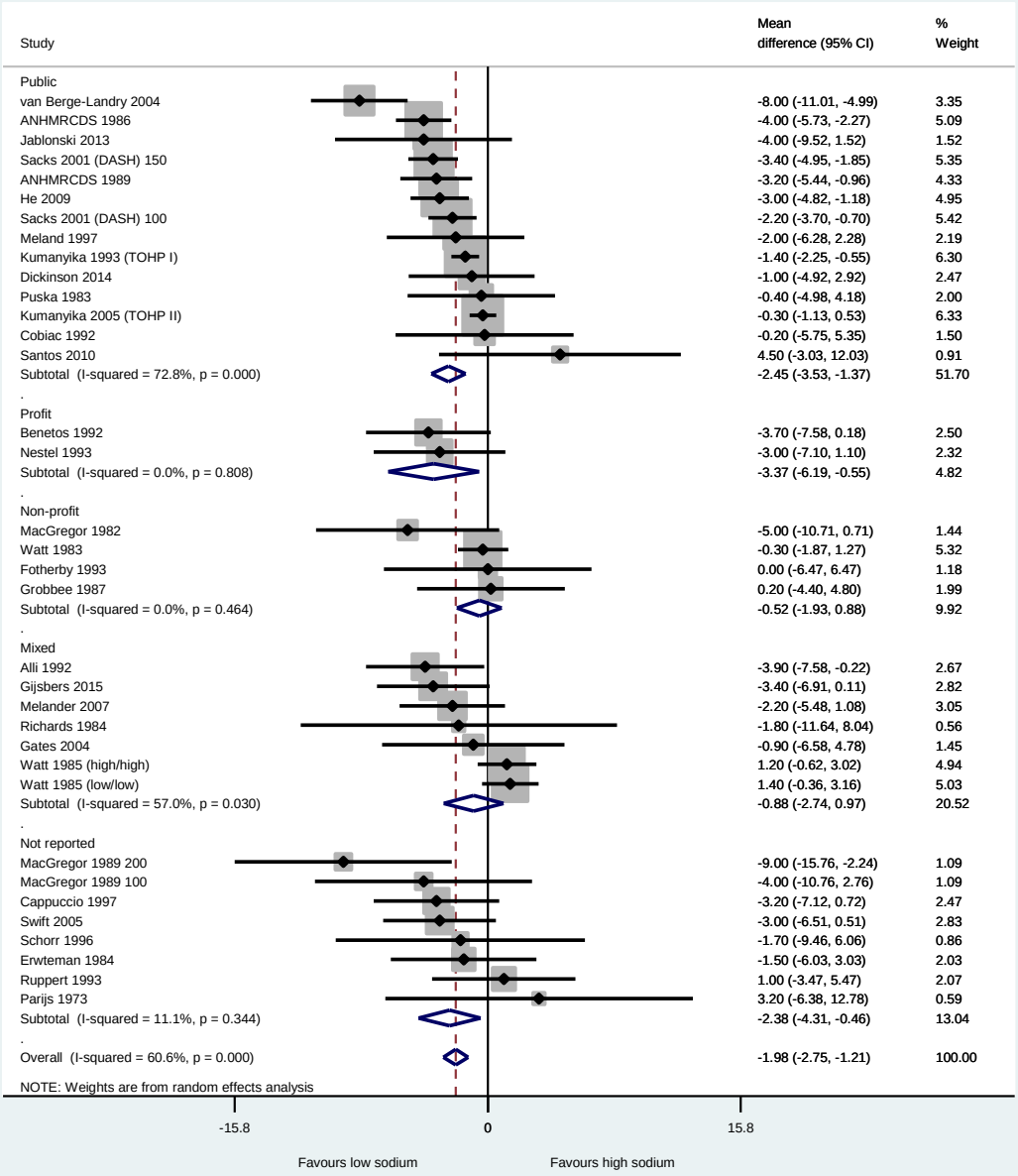
Diastolic blood pressure - Risk of Bias OUTCOME



Diastolic blood pressure - Year of publication

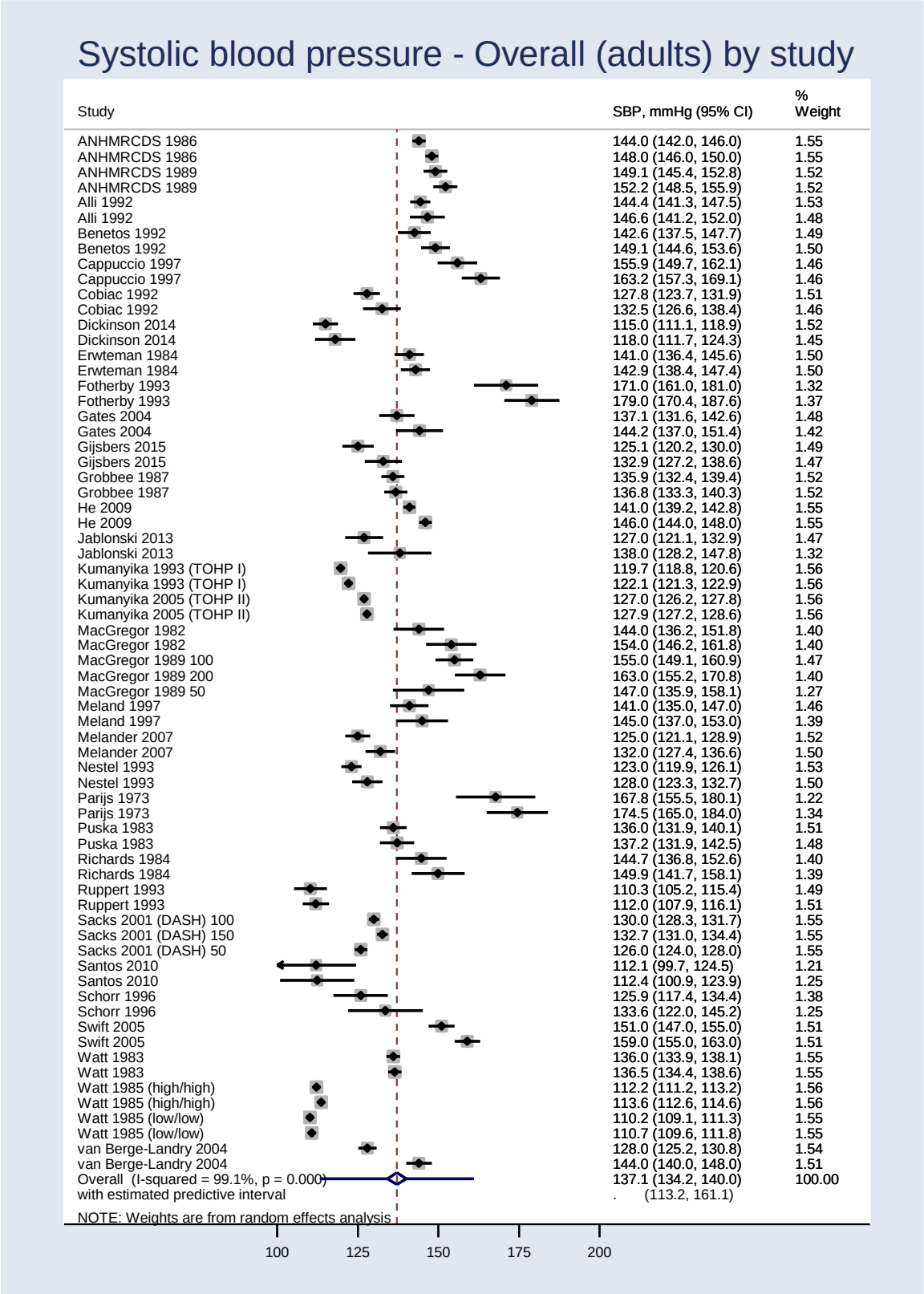


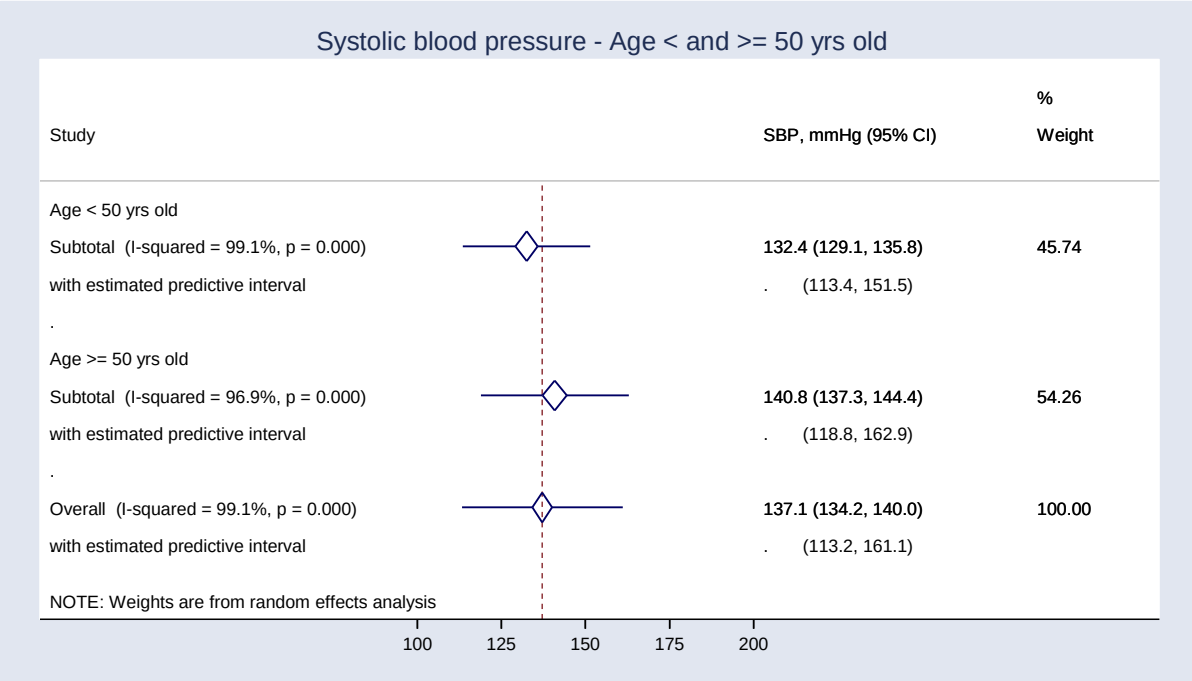
Diastolic blood pressure - Funding

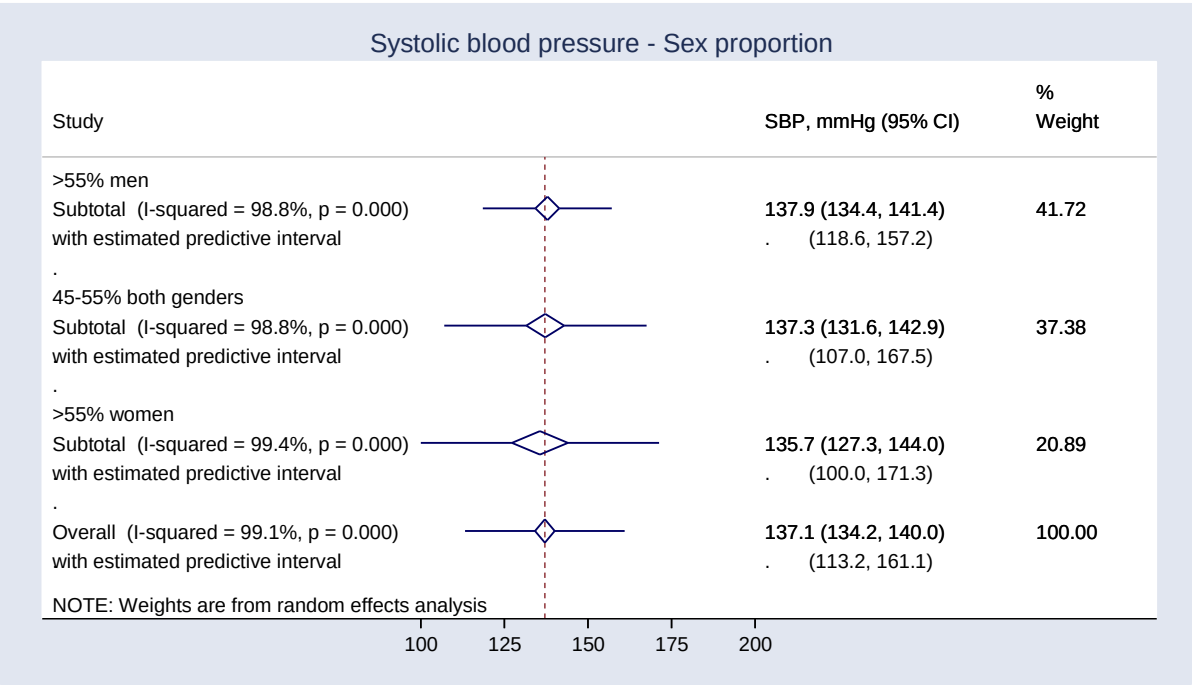


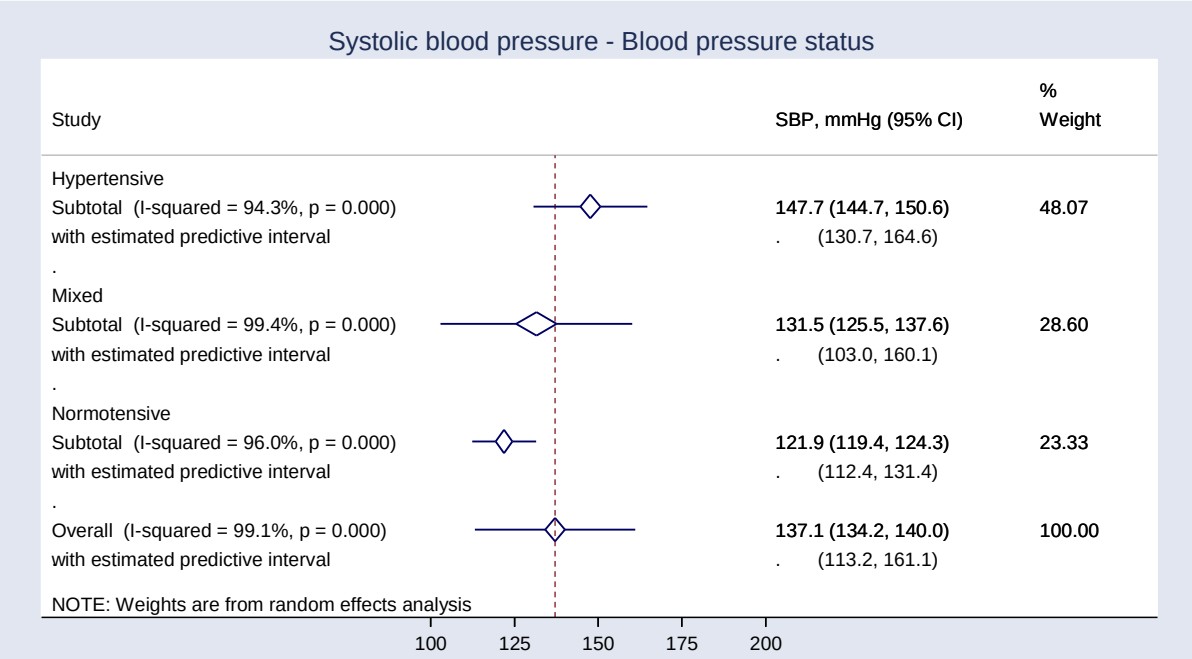
Appendix I - Forest plots at arm level: subgroup analyses

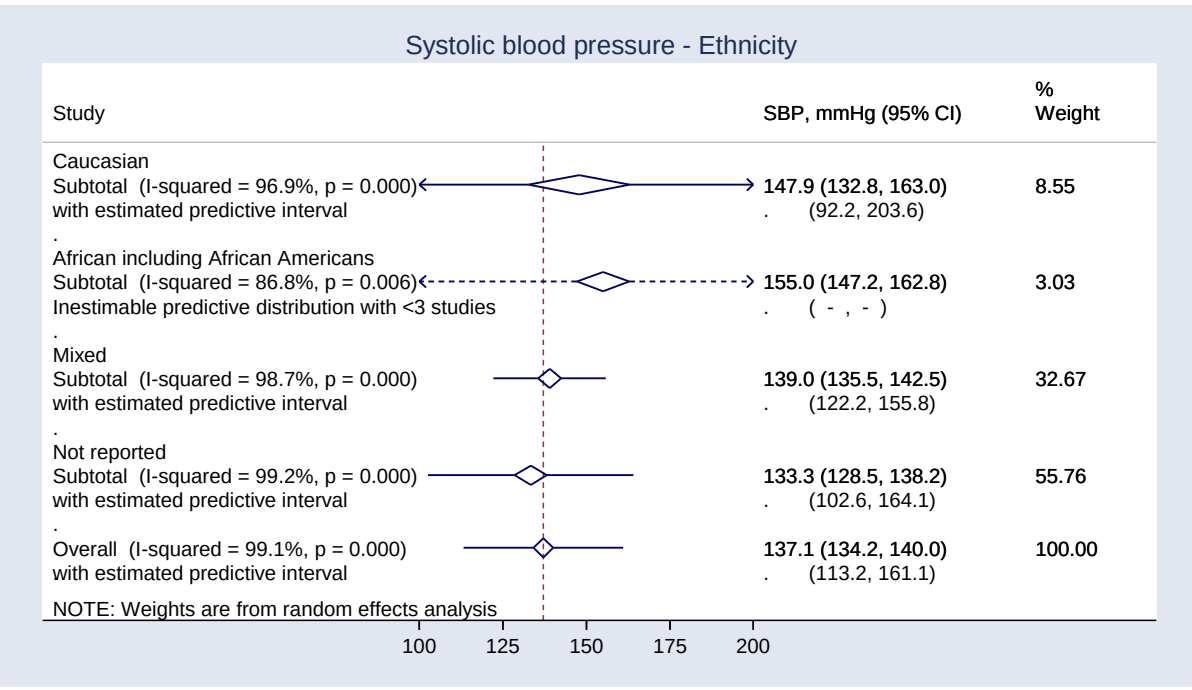
The first overall plot reports all mean BP absolute values by trial's arm, while in the subgroup analyses plots only pooled estimates by subgroup are reported together with their 95% confidence and prediction intervals (arms not reported for sake of visualisation). Correspondent subgroup variable values can be found in Appendix A, where study-level characteristics are described.

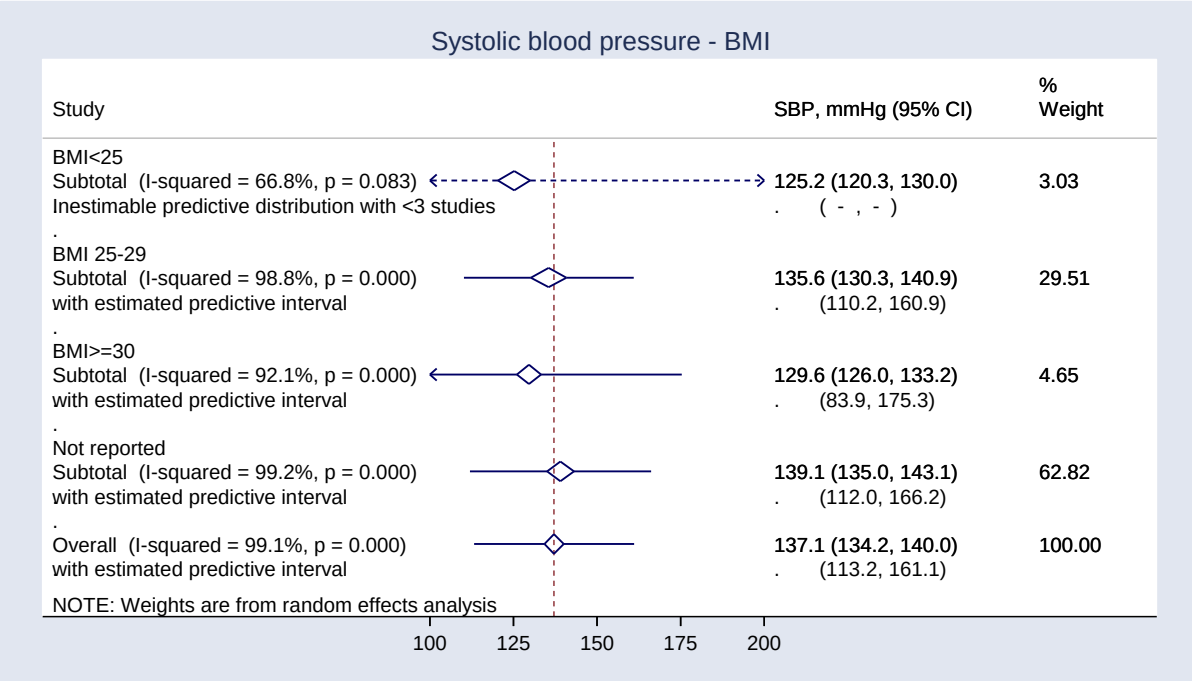


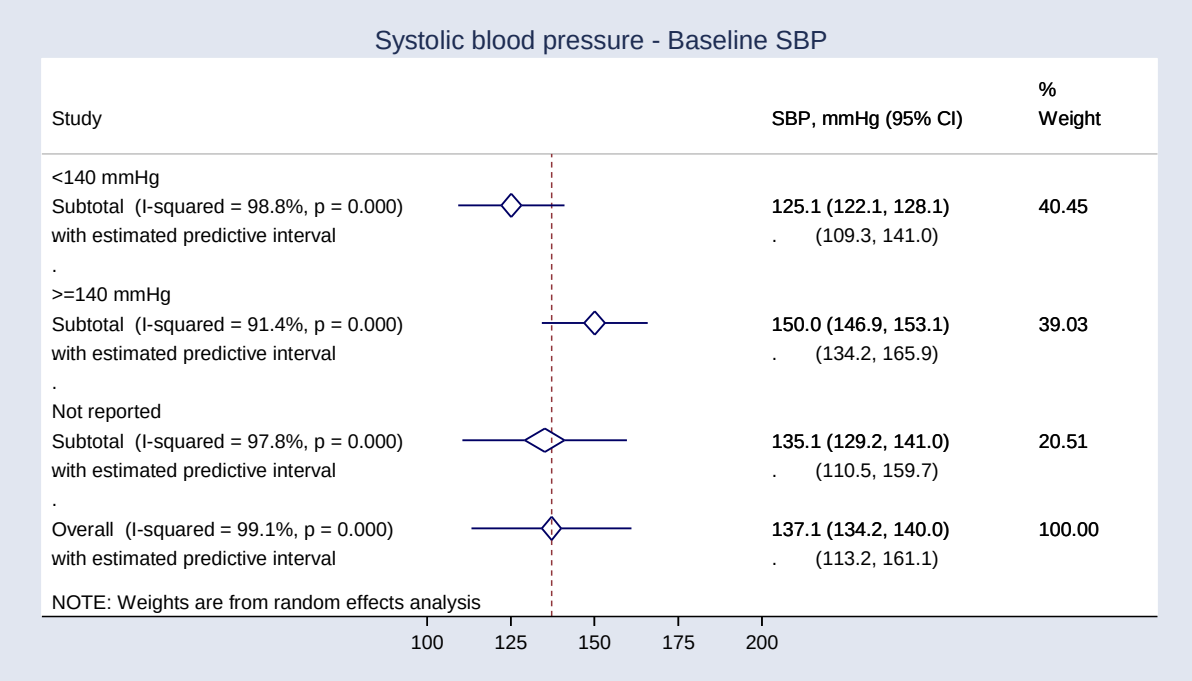

Systolic blood pressure - Age < and >= 50 yrs old
Study
SBP, mmHg (95% CI)
% Weight
Age < 50 yrs old
Subtotal (I-squared = 99.1%, p = 0.000)
132.4 (129.1, 135.8)
45.74
with estimated predictive interval
(113.4, 151.5)
Age >= 50 yrs old
Subtotal (I-squared = 96.9%, p = 0.000)
140.8 (137.3, 144.4)
54.26
with estimated predictive interval
(118.8, 162.9)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200


Systolic blood pressure - Sex proportion
Study
SBP, mmHg (95% CI)
% Weight
>55% men
Subtotal (I-squared = 98.8%, p = 0.000)
137.9 (134.4, 141.4)
41.72
with estimated predictive interval
(118.6, 157.2)
45-55% both genders
Subtotal (I-squared = 98.8%, p = 0.000)
137.3 (131.6, 142.9)
37.38
with estimated predictive interval
(107.0, 167.5)
>55% women
Subtotal (I-squared = 99.4%, p = 0.000)
135.7 (127.3, 144.0)
20.89
with estimated predictive interval
(100.0, 171.3)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

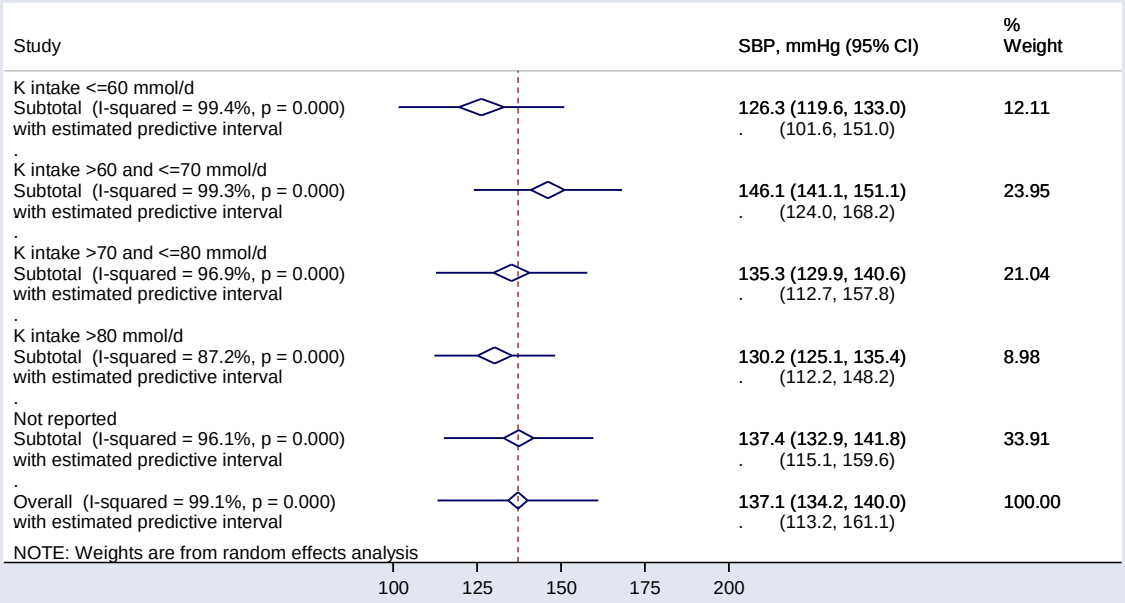

Systolic blood pressure - Blood pressure status
Study
SBP, mmHg (95% CI)
% Weight
Hypertensive
Subtotal (I-squared = 94.3%, p = 0.000)
147.7 (144.7, 150.6)
48.07
with estimated predictive interval
(130.7, 164.6)
Mixed
Subtotal (I-squared = 99.4%, p = 0.000)
131.5 (125.5, 137.6)
28.60
with estimated predictive interval
(103.0, 160.1)
Normotensive
Subtotal (I-squared = 96.0%, p = 0.000)
121.9 (119.4, 124.3)
23.33
with estimated predictive interval
(112.4, 131.4)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200


Systolic blood pressure - Ethnicity
Study
SBP, mmHg (95% CI)
% Weight
Caucasian
Subtotal (I-squared = 96.9%, p = 0.000)
147.9 (132.8, 163.0)
8.55
with estimated predictive interval
(92.2, 203.6)
African including African Americans
Subtotal (I-squared = 86.8%, p = 0.006)
155.0 (147.2, 162.8)
3.03
Inestimable predictive distribution with <3 studies
(- , -)
Mixed
Subtotal (I-squared = 98.7%, p = 0.000)
139.0 (135.5, 142.5)
32.67
with estimated predictive interval
(122.2, 155.8)
Not reported
Subtotal (I-squared = 99.2%, p = 0.000)
133.3 (128.5, 138.2)
55.76
with estimated predictive interval
(102.6, 164.1)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

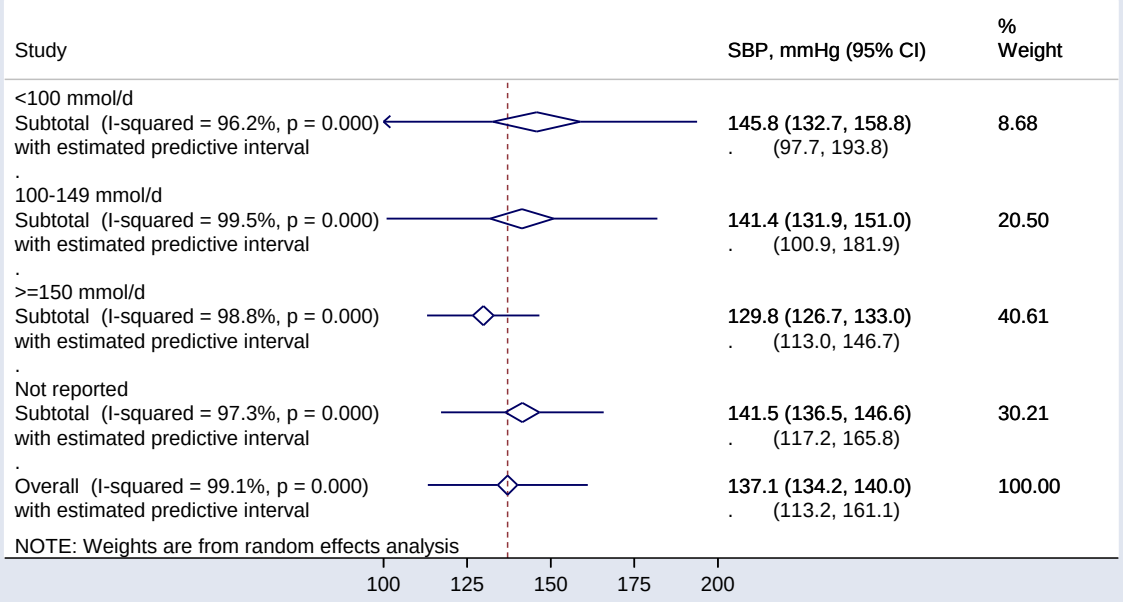

Systolic blood pressure - BMI
Study
SBP, mmHg (95% CI)
% Weight
BMI<25
Subtotal (I-squared = 66.8%, p = 0.083)
125.2 (120.3, 130.0)
3.03
Inestimable predictive distribution with <3 studies
. (- , -)
BMI 25-29
Subtotal (I-squared = 98.8%, p = 0.000)
135.6 (130.3, 140.9)
29.51
with estimated predictive interval
. (110.2, 160.9)
BMI>=30
Subtotal (I-squared = 92.1%, p = 0.000)
129.6 (126.0, 133.2)
4.65
with estimated predictive interval
. (83.9, 175.3)
Not reported
Subtotal (I-squared = 99.2%, p = 0.000)
139.1 (135.0, 143.1)
62.82
with estimated predictive interval
. (112.0, 166.2)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
. (113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

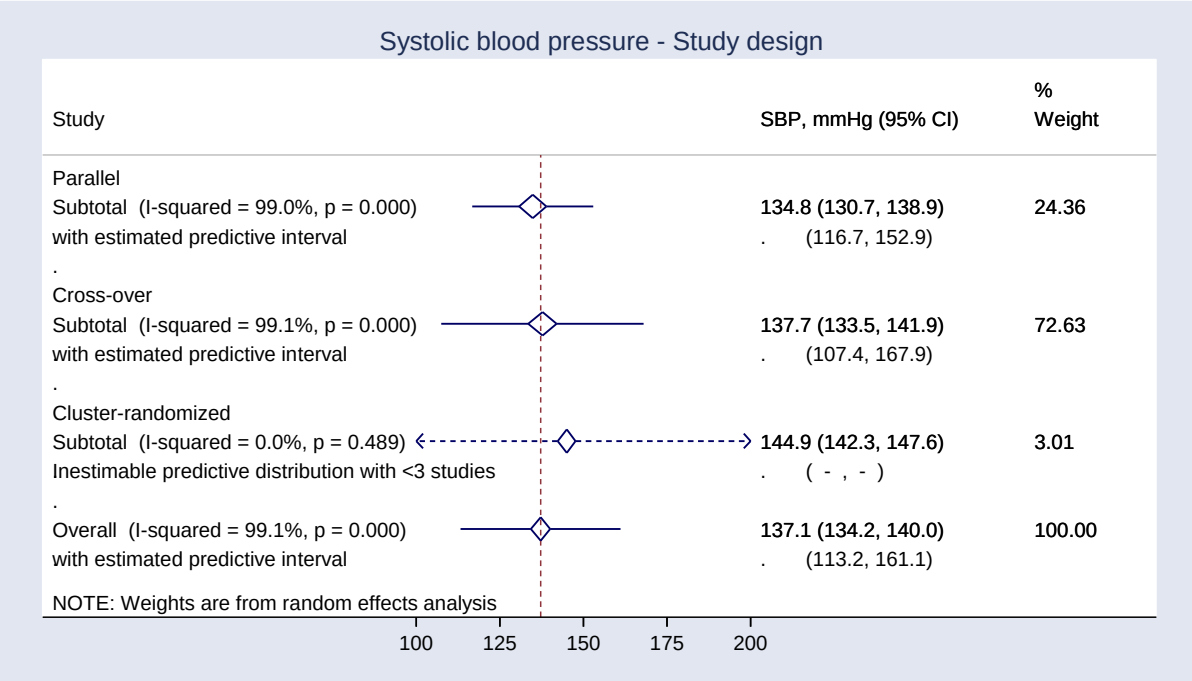

Systolic blood pressure - Baseline SBP
Study
SBP, mmHg (95% CI)
% Weight
<140 mmHg
Subtotal (I-squared = 98.8%, p = 0.000)
125.1 (122.1, 128.1)
40.45
with estimated predictive interval
. (109.3, 141.0)
>=140 mmHg
Subtotal (I-squared = 91.4%, p = 0.000)
150.0 (146.9, 153.1)
39.03
with estimated predictive interval
. (134.2, 165.9)
Not reported
Subtotal (I-squared = 97.8%, p = 0.000)
135.1 (129.2, 141.0)
20.51
with estimated predictive interval
. (110.5, 159.7)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
. (113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

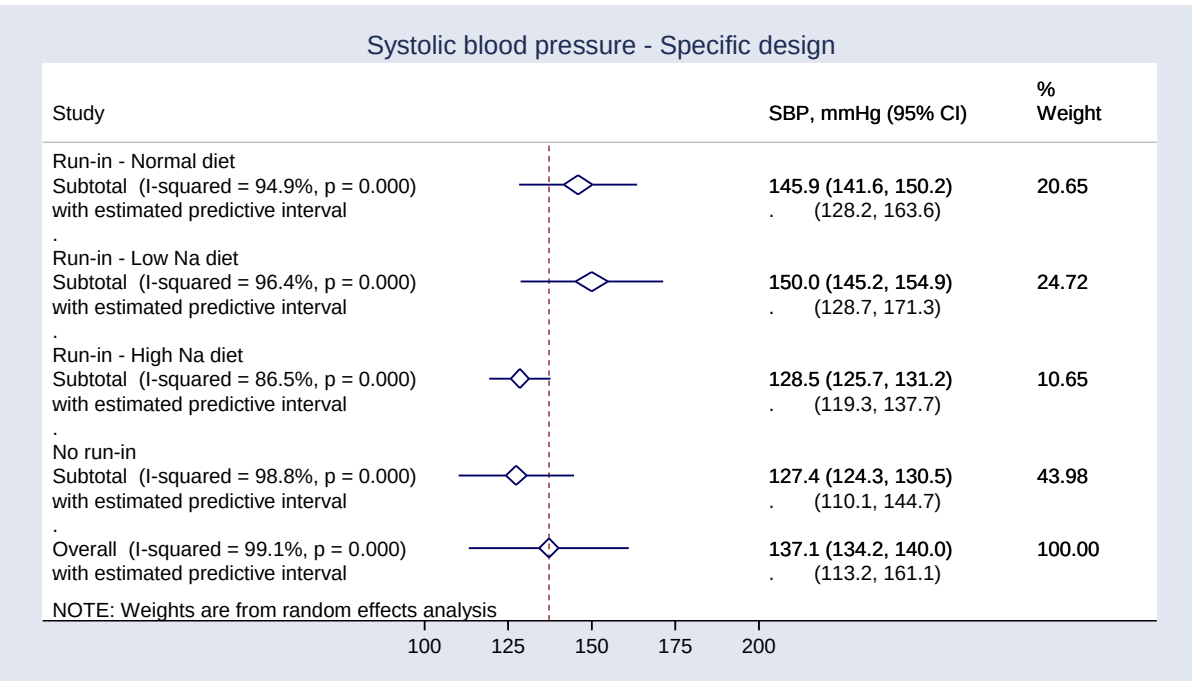
Systolic blood pressure - Baseline potassium intake

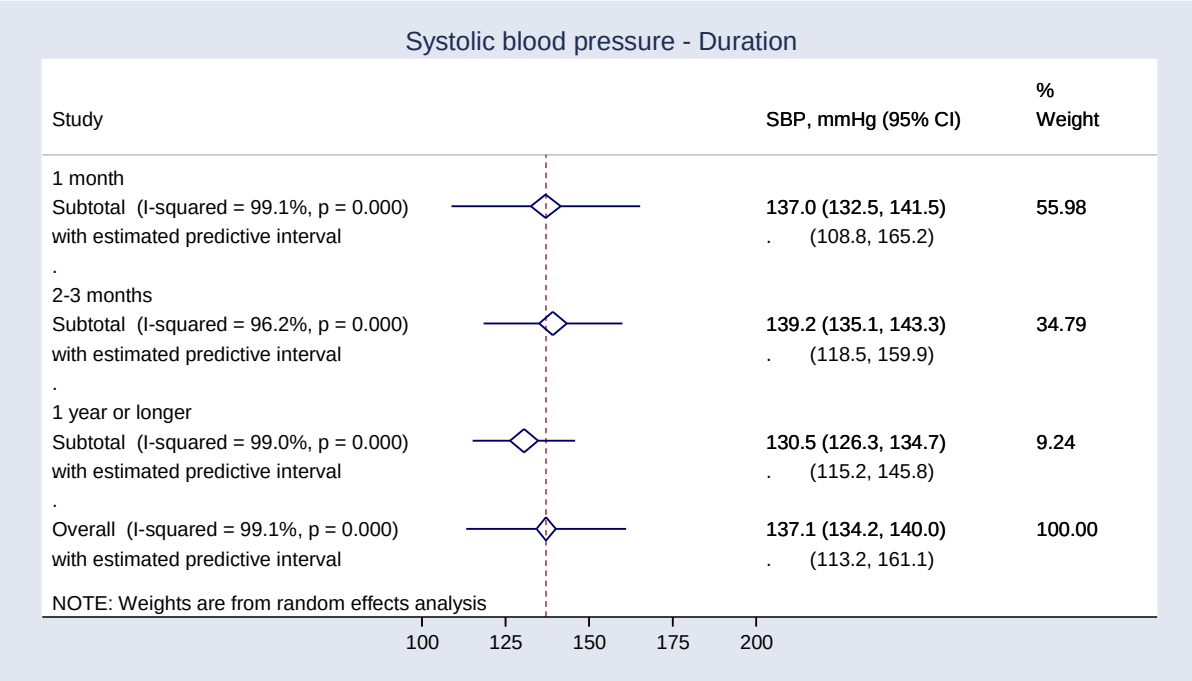


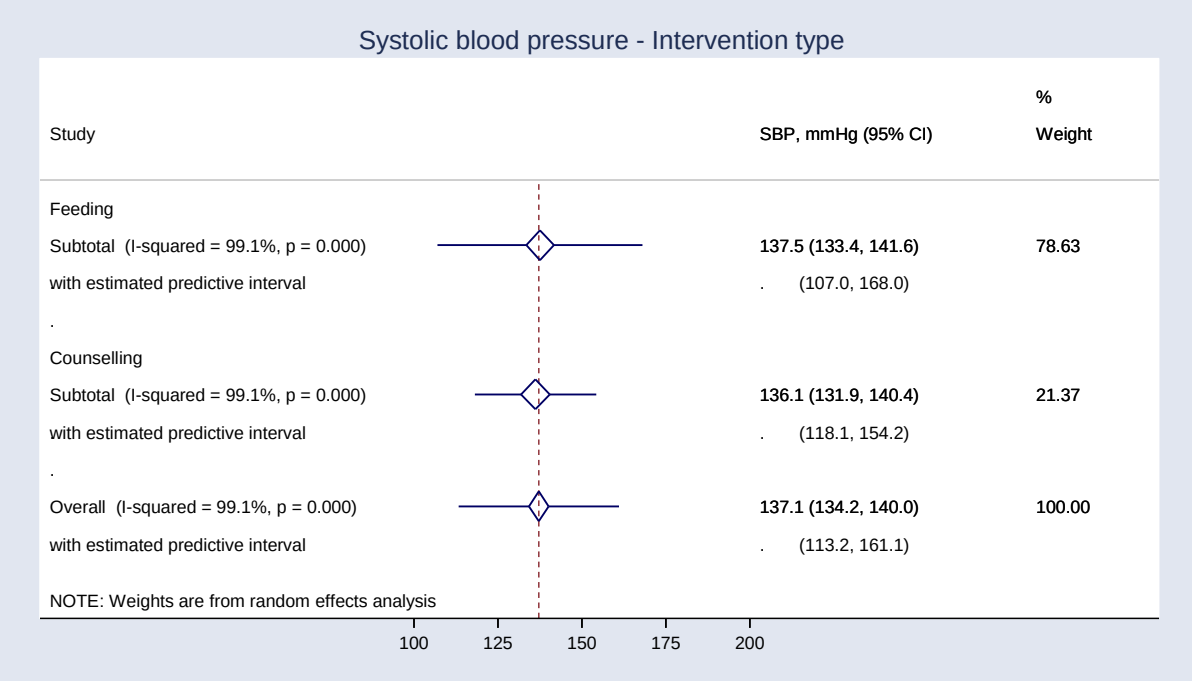
Systolic blood pressure - UNa excretion at baseline



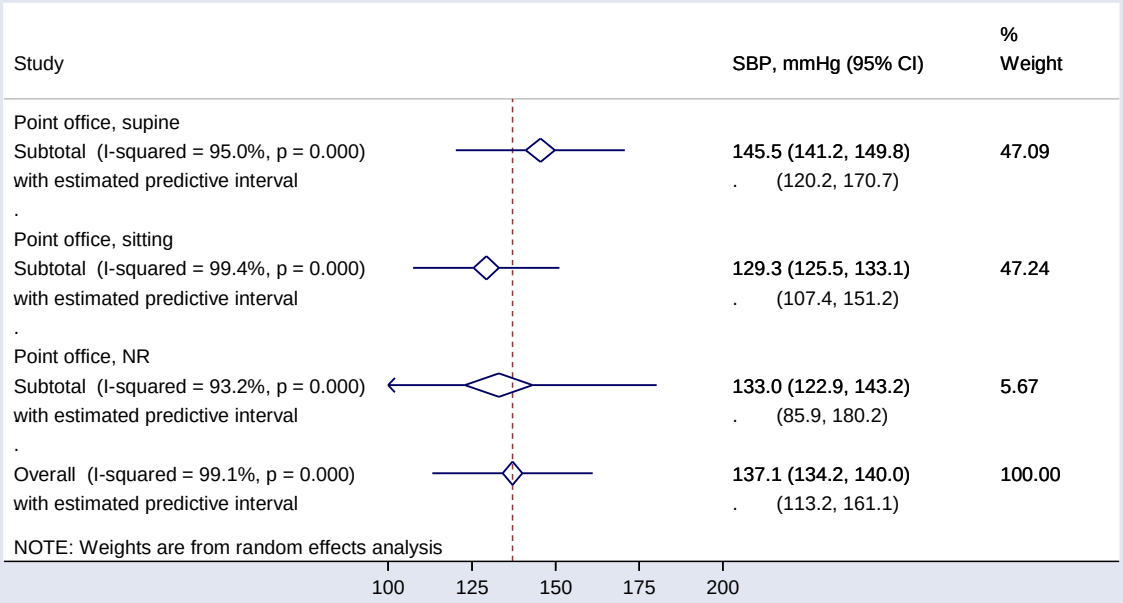

Systolic blood pressure - Study design
Study
SBP, mmHg (95% CI)
% Weight
Parallel
Subtotal (I-squared = 99.0%, p = 0.000)
134.8 (130.7, 138.9)
24.36
with estimated predictive interval
(116.7, 152.9)
Cross-over
Subtotal (I-squared = 99.1%, p = 0.000)
137.7 (133.5, 141.9)
72.63
with estimated predictive interval
(107.4, 167.9)
Cluster-randomized
Subtotal (I-squared = 0.0%, p = 0.489)
144.9 (142.3, 147.6)
3.01
Inestimable predictive distribution with <3 studies
(- , -)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200


Systolic blood pressure - Specific design
Study
SBP, mmHg (95% CI)
% Weight
Run-in - Normal diet
Subtotal (I-squared = 94.9%, p = 0.000)
145.9 (141.6, 150.2)
20.65
with estimated predictive interval
(128.2, 163.6)
Run-in - Low Na diet
Subtotal (I-squared = 96.4%, p = 0.000)
150.0 (145.2, 154.9)
24.72
with estimated predictive interval
(128.7, 171.3)
Run-in - High Na diet
Subtotal (I-squared = 86.5%, p = 0.000)
128.5 (125.7, 131.2)
10.65
with estimated predictive interval
(119.3, 137.7)
No run-in
Subtotal (I-squared = 98.8%, p = 0.000)
127.4 (124.3, 130.5)
43.98
with estimated predictive interval
(110.1, 144.7)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

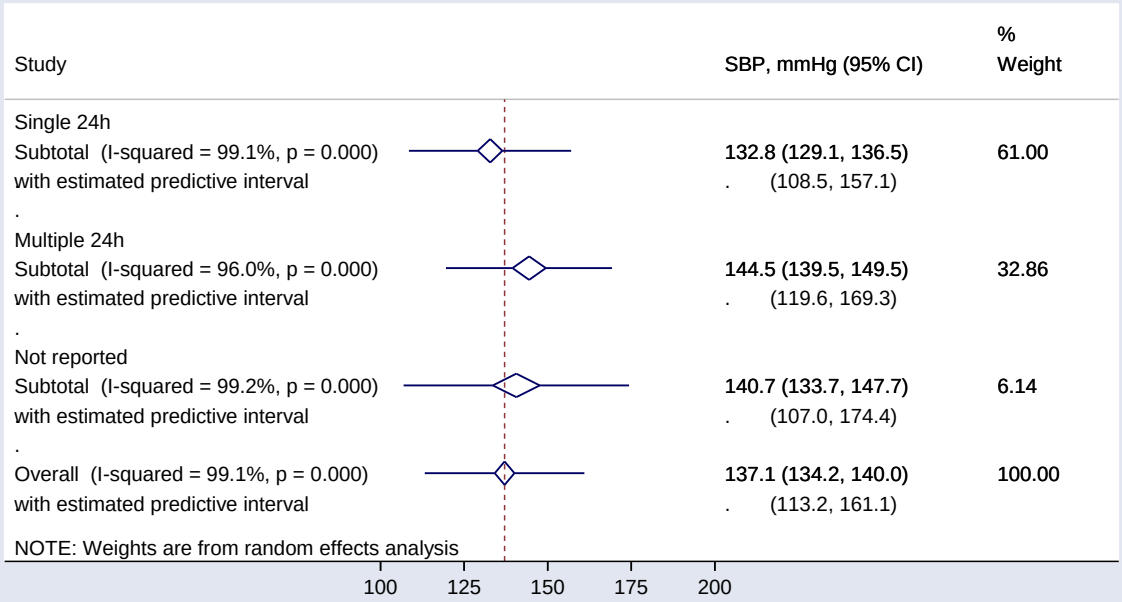

Systolic blood pressure - Duration
Study
SBP, mmHg (95% CI)
% Weight
1 month
Subtotal (I-squared = 99.1%, p = 0.000)
137.0 (132.5, 141.5)
55.98
with estimated predictive interval
(108.8, 165.2)
2-3 months
Subtotal (I-squared = 96.2%, p = 0.000)
139.2 (135.1, 143.3)
34.79
with estimated predictive interval
(118.5, 159.9)
1 year or longer
Subtotal (I-squared = 99.0%, p = 0.000)
130.5 (126.3, 134.7)
9.24
with estimated predictive interval
(115.2, 145.8)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

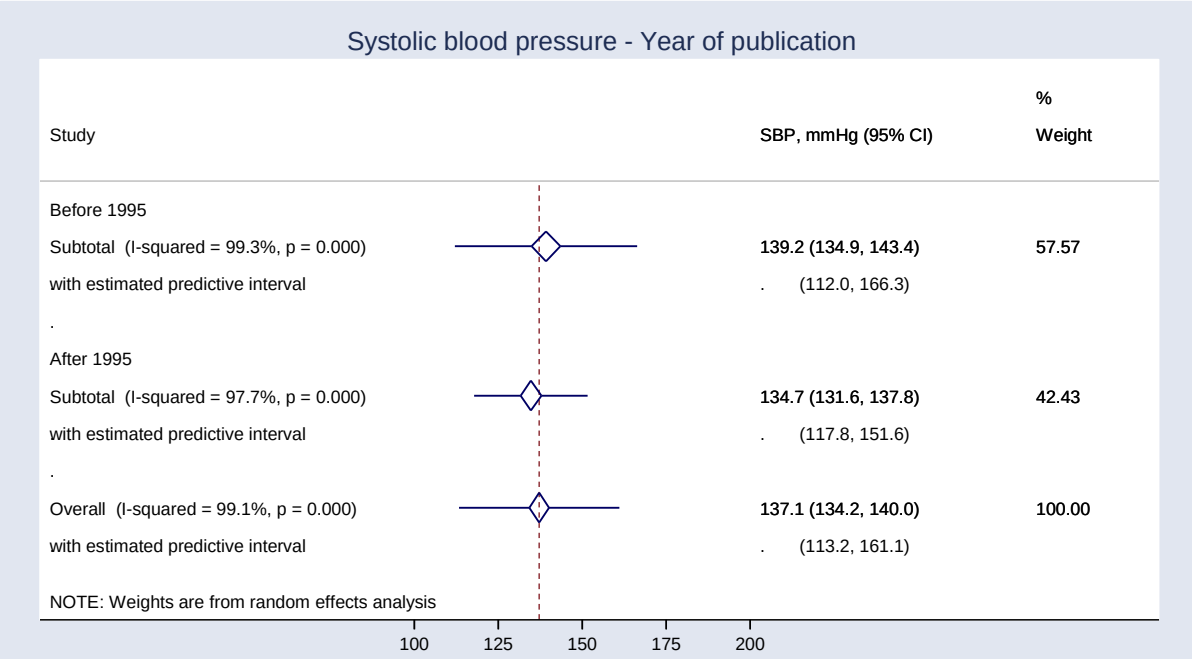

Systolic blood pressure - Intervention type
Study
SBP, mmHg (95% CI)
% Weight
Feeding
Subtotal (I-squared = 99.1%, p = 0.000)
137.5 (133.4, 141.6)
78.63
with estimated predictive interval
(107.0, 168.0)
Counselling
Subtotal (I-squared = 99.1%, p = 0.000)
136.1 (131.9, 140.4)
21.37
with estimated predictive interval
(118.1, 154.2)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

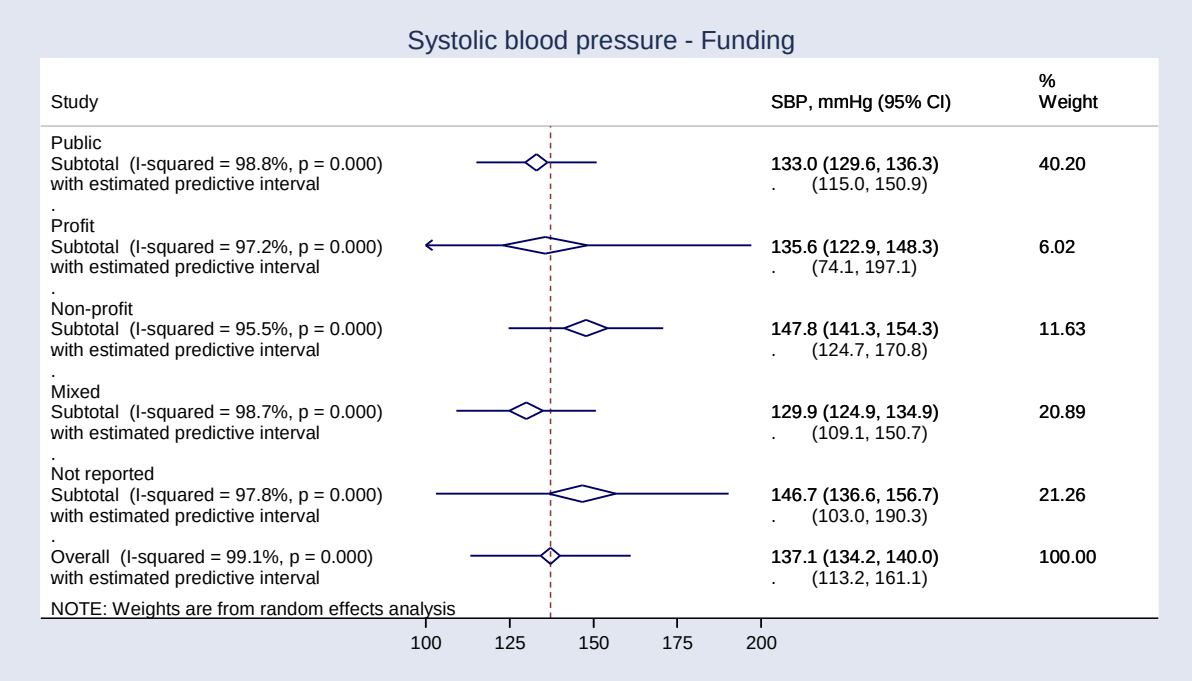
Systolic blood pressure - BP measurement method

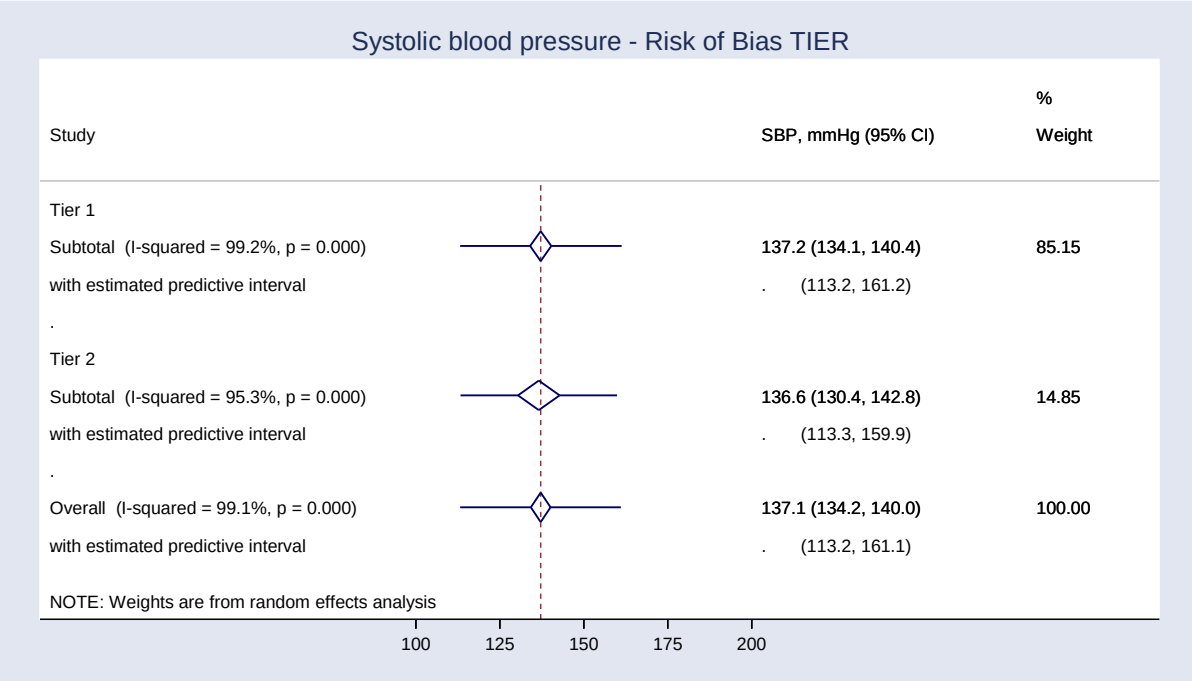


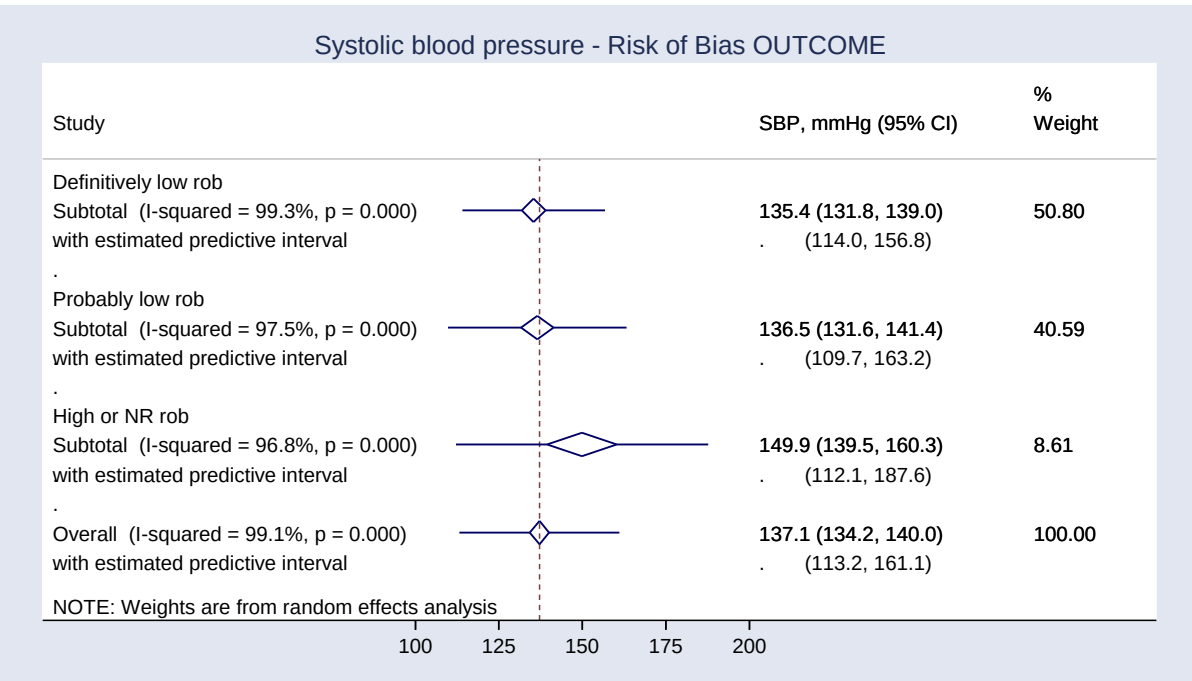
Systolic blood pressure - Number of urinary collections



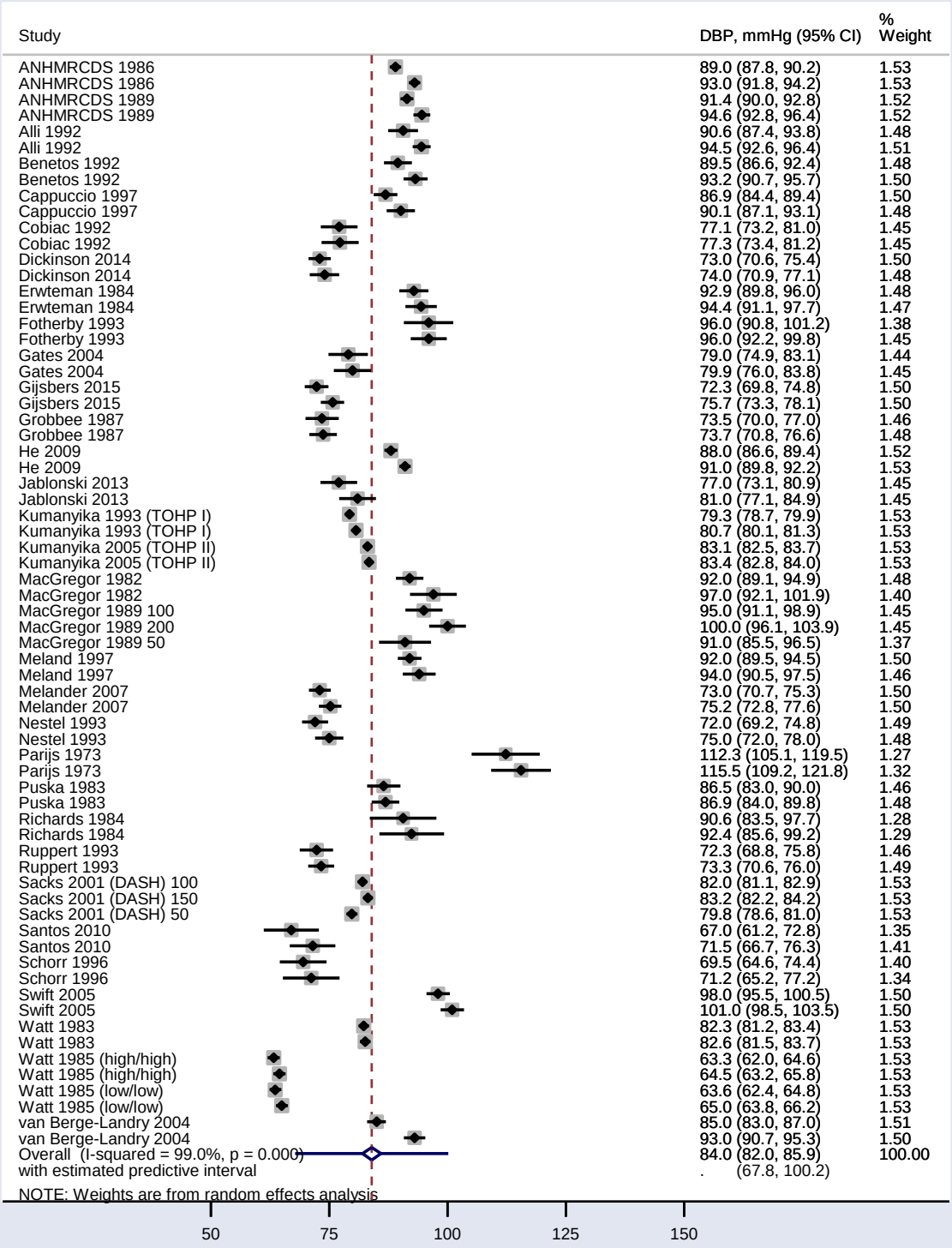

Systolic blood pressure - Year of publication
Study
SBP, mmHg (95% CI)
% Weight
Before 1995
Subtotal (I-squared = 99.3%, p = 0.000)
139.2 (134.9, 143.4)
57.57
with estimated predictive interval
(112.0, 166.3)
After 1995
Subtotal (I-squared = 97.7%, p = 0.000)
134.7 (131.6, 137.8)
42.43
with estimated predictive interval
(117.8, 151.6)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

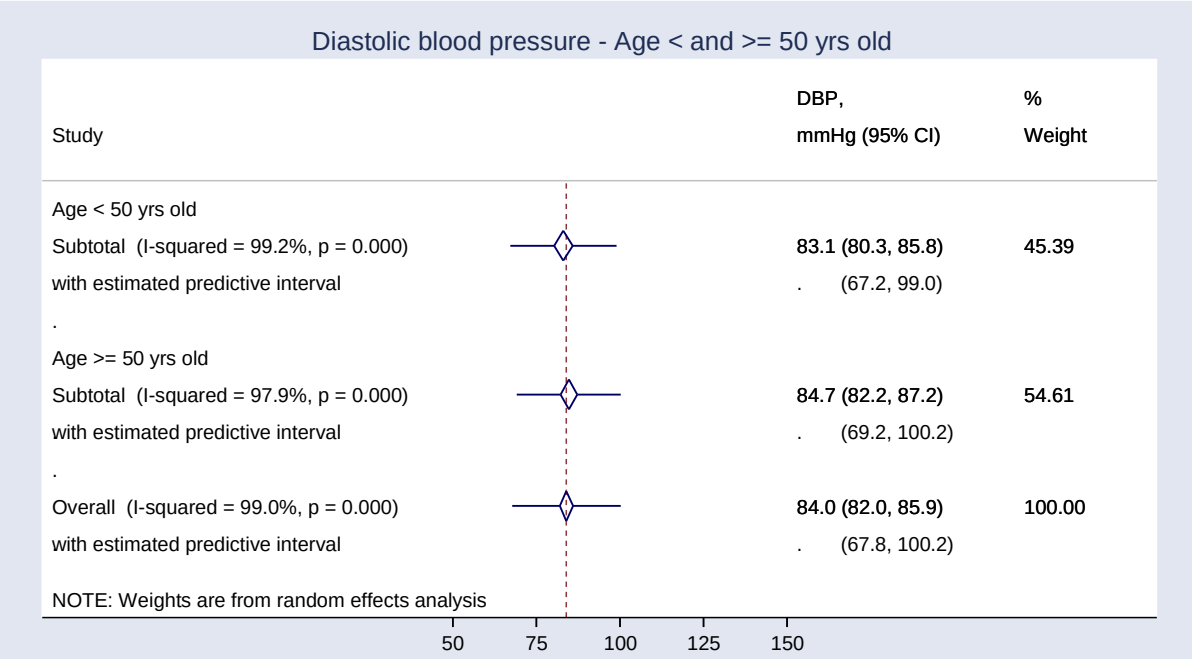

Systolic blood pressure - Funding
Study
SBP, mmHg (95% CI)
% Weight
Public
Subtotal (I-squared = 98.8%, p = 0.000)
133.0 (129.6, 136.3)
40.20
with estimated predictive interval
(115.0, 150.9)
Profit
Subtotal (I-squared = 97.2%, p = 0.000)
135.6 (122.9, 148.3)
6.02
with estimated predictive interval
(74.1, 197.1)
Non-profit
Subtotal (I-squared = 95.5%, p = 0.000)
147.8 (141.3, 154.3)
11.63
with estimated predictive interval
(124.7, 170.8)
Mixed
Subtotal (I-squared = 98.7%, p = 0.000)
129.9 (124.9, 134.9)
20.89
with estimated predictive interval
(109.1, 150.7)
Not reported
Subtotal (I-squared = 97.8%, p = 0.000)
146.7 (136.6, 156.7)
21.26
with estimated predictive interval
(103.0, 190.3)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

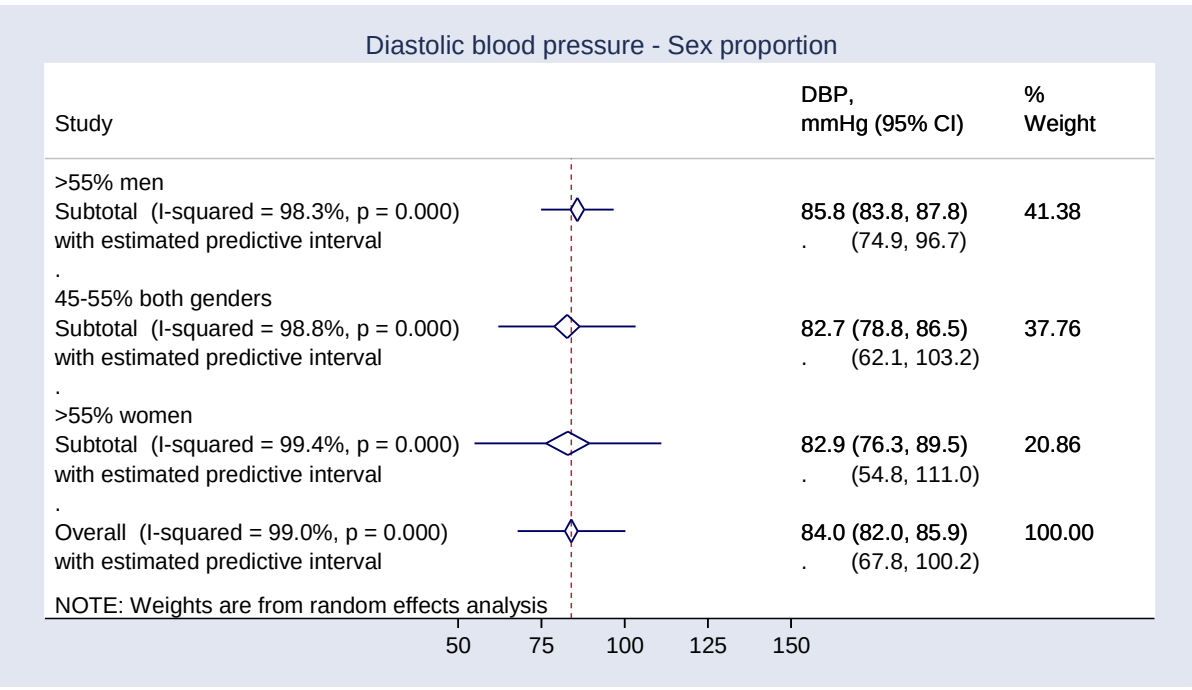

Systolic blood pressure - Risk of Bias TIER
Study
SBP, mmHg (95% CI)
% Weight
Tier 1
Subtotal (I-squared = 99.2%, p = 0.000)
137.2 (134.1, 140.4)
85.15
with estimated predictive interval
(113.2, 161.2)
Tier 2
Subtotal (I-squared = 95.3%, p = 0.000)
136.6 (130.4, 142.8)
14.85
with estimated predictive interval
(113.3, 159.9)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

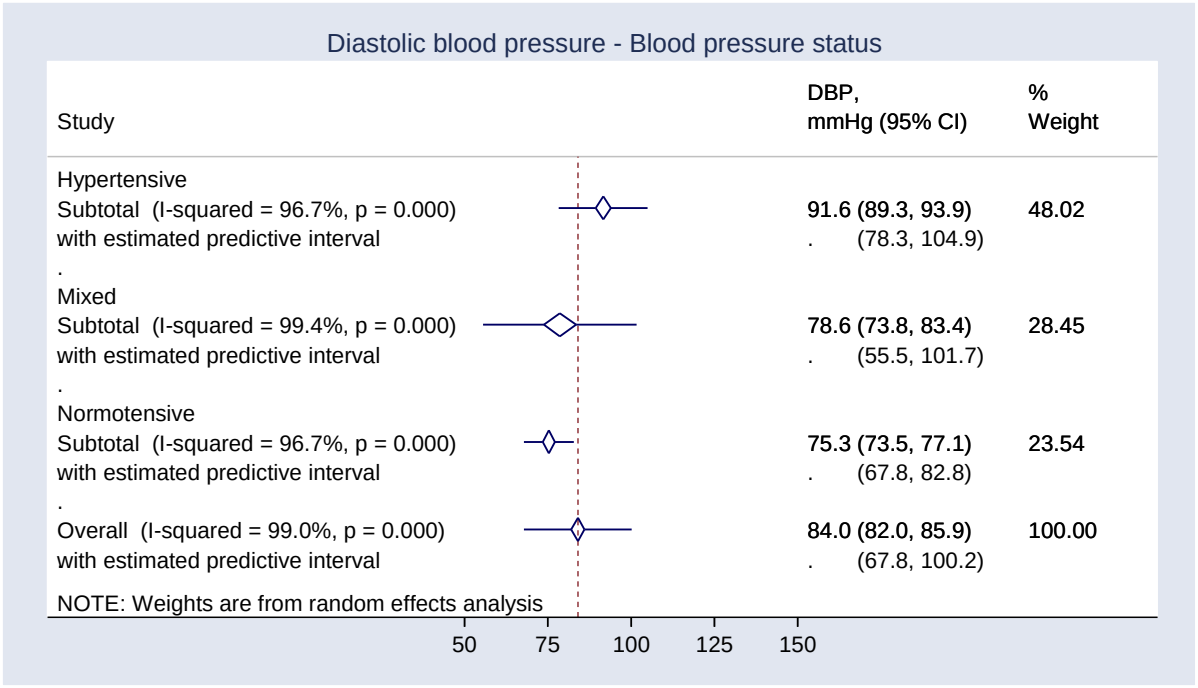

Systolic blood pressure - Risk of Bias OUTCOME
Study
SBP, mmHg (95% CI)
% Weight
Definitively low rob
Subtotal (I-squared = 99.3%, p = 0.000)
135.4 (131.8, 139.0)
50.80
with estimated predictive interval
(114.0, 156.8)
Probably low rob
Subtotal (I-squared = 97.5%, p = 0.000)
136.5 (131.6, 141.4)
40.59
with estimated predictive interval
(109.7, 163.2)
High or NR rob
Subtotal (I-squared = 96.8%, p = 0.000)
149.9 (139.5, 160.3)
8.61
with estimated predictive interval
(112.1, 187.6)
Overall (I-squared = 99.1%, p = 0.000)
137.1 (134.2, 140.0)
100.00
with estimated predictive interval
(113.2, 161.1)
NOTE: Weights are from random effects analysis
100
125
150
175
200

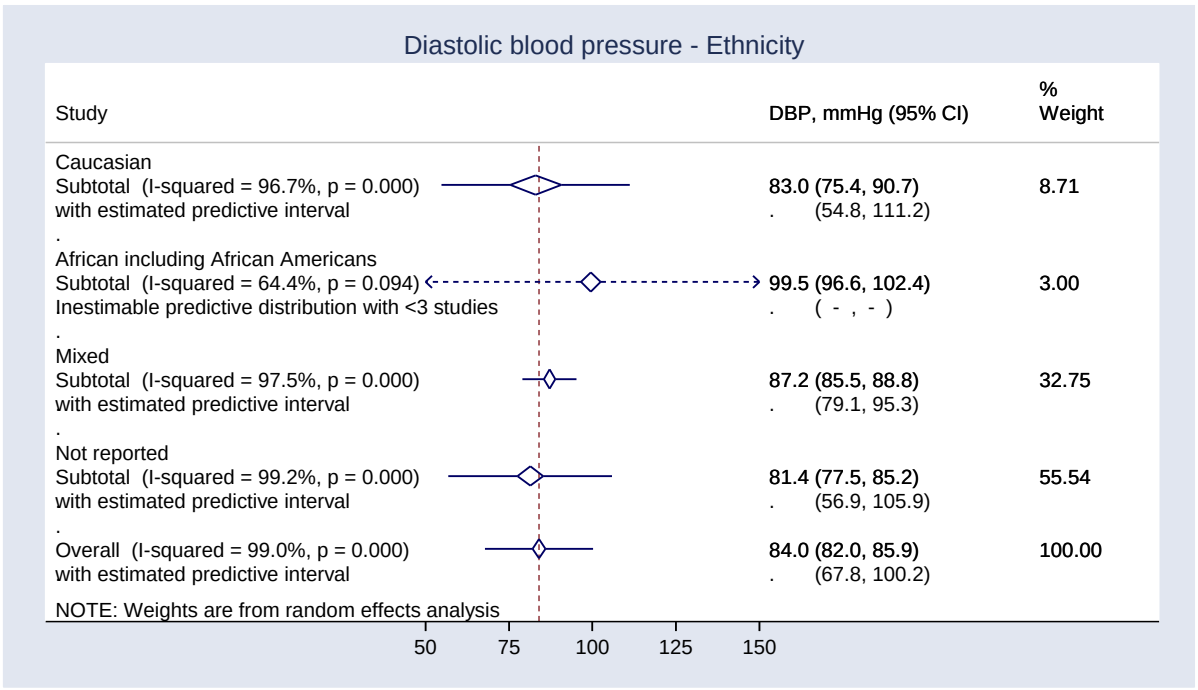
Diastolic blood pressure - Overall (adults) by study



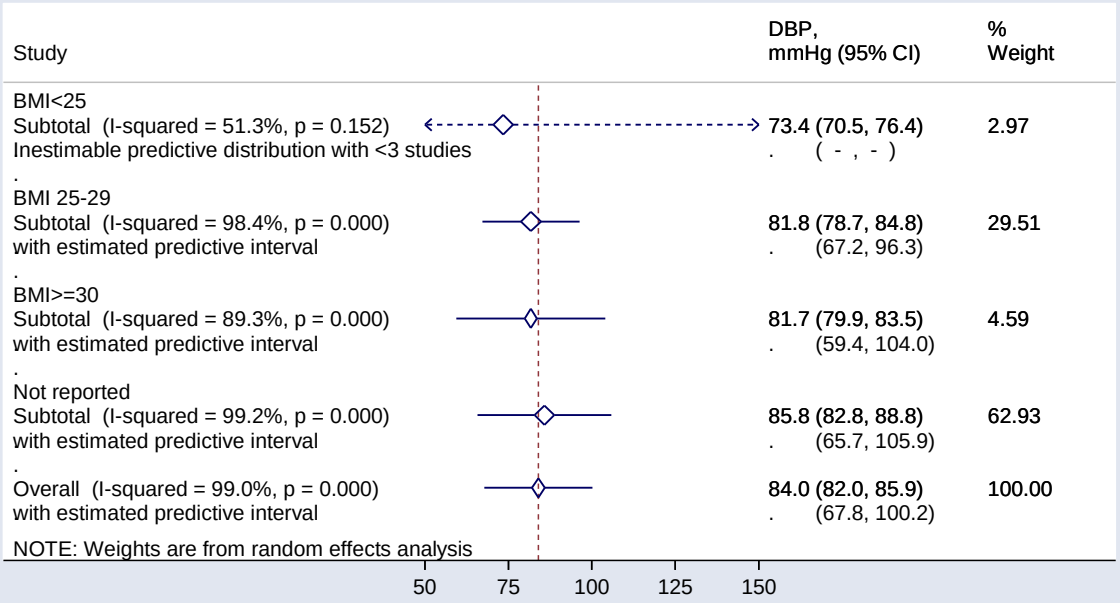

Diastolic blood pressure - Age < and >= 50 yrs old
Study
DBP, mmHg (95% CI)
% Weight
Age < 50 yrs old
Subtotal (I-squared = 99.2%, p = 0.000)
83.1 (80.3, 85.8)
45.39
with estimated predictive interval
. (67.2, 99.0)
Age >= 50 yrs old
Subtotal (I-squared = 97.9%, p = 0.000)
84.7 (82.2, 87.2)
54.61
with estimated predictive interval
. (69.2, 100.2)
Overall (I-squared = 99.0%, p = 0.000)
84.0 (82.0, 85.9)
100.00
with estimated predictive interval
. (67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150


Diastolic blood pressure - Sex proportion
Study
DBP, mmHg (95% CI)
% Weight
>55% men
Subtotal (I-squared = 98.3%, p = 0.000)
85.8 (83.8, 87.8)
41.38
with estimated predictive interval
. (74.9, 96.7)
45-55% both genders
Subtotal (I-squared = 98.8%, p = 0.000)
82.7 (78.8, 86.5)
37.76
with estimated predictive interval
. (62.1, 103.2)
>55% women
Subtotal (I-squared = 99.4%, p = 0.000)
82.9 (76.3, 89.5)
20.86
with estimated predictive interval
. (54.8, 111.0)
Overall (I-squared = 99.0%, p = 0.000)
84.0 (82.0, 85.9)
100.00
with estimated predictive interval
. (67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150

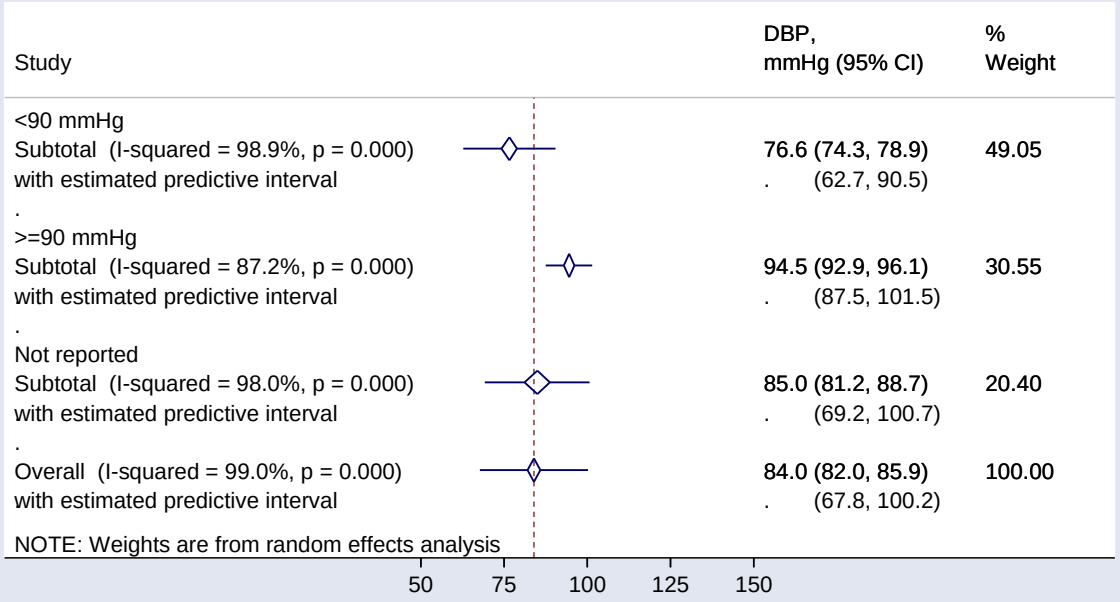

Diastolic blood pressure - Blood pressure status
Study
DBP, mmHg (95% CI)
% Weight
Hypertensive
Subtotal (I-squared = 96.7%, p = 0.000)
91.6 (89.3, 93.9)
48.02
with estimated predictive interval
(78.3, 104.9)
Mixed
Subtotal (I-squared = 99.4%, p = 0.000)
78.6 (73.8, 83.4)
28.45
with estimated predictive interval
(55.5, 101.7)
Normotensive
Subtotal (I-squared = 96.7%, p = 0.000)
75.3 (73.5, 77.1)
23.54
with estimated predictive interval
(67.8, 82.8)
Overall (I-squared = 99.0%, p = 0.000)
84.0 (82.0, 85.9)
100.00
with estimated predictive interval
(67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150

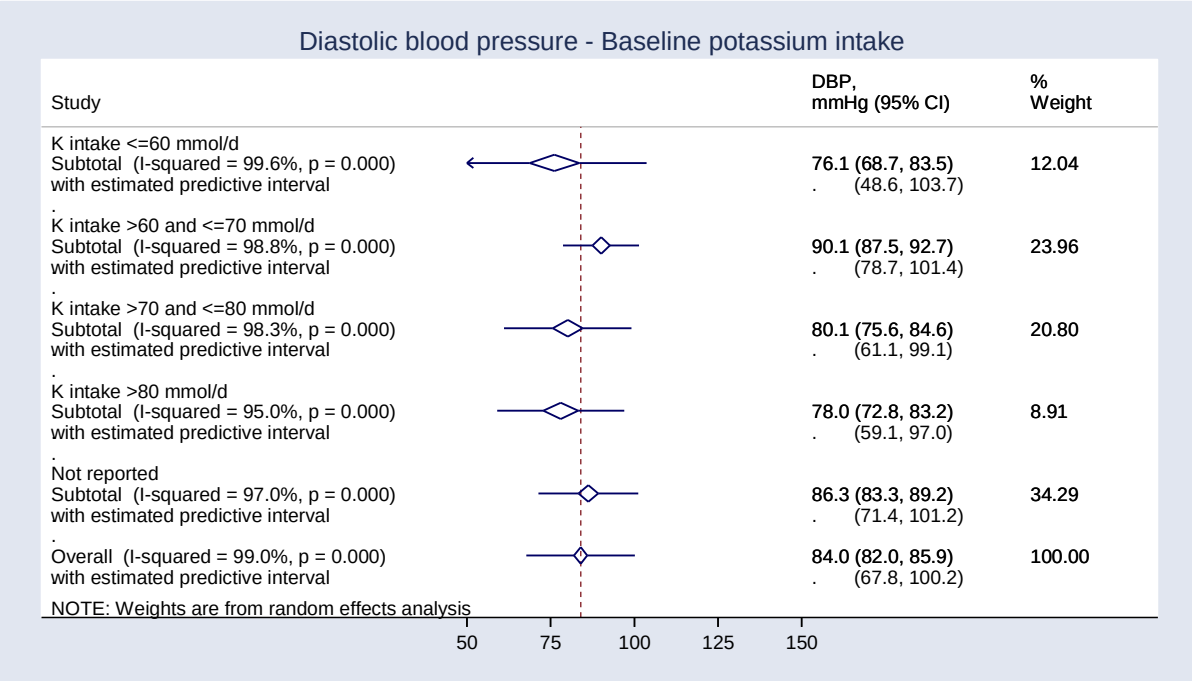

Diastolic blood pressure - Ethnicity
Study
DBP, mmHg (95% CI)
% Weight
Caucasian
Subtotal (I-squared = 96.7%, p = 0.000)
83.0 (75.4, 90.7)
8.71
with estimated predictive interval
(54.8, 111.2)
African including African Americans
Subtotal (I-squared = 64.4%, p = 0.094)
99.5 (96.6, 102.4)
3.00
Inestimable predictive distribution with <3 studies
(- , -)
Mixed
Subtotal (I-squared = 97.5%, p = 0.000)
87.2 (85.5, 88.8)
32.75
with estimated predictive interval
(79.1, 95.3)
Not reported
Subtotal (I-squared = 99.2%, p = 0.000)
81.4 (77.5, 85.2)
55.54
with estimated predictive interval
(56.9, 105.9)
Overall (I-squared = 99.0%, p = 0.000)
84.0 (82.0, 85.9)
100.00
with estimated predictive interval
(67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150

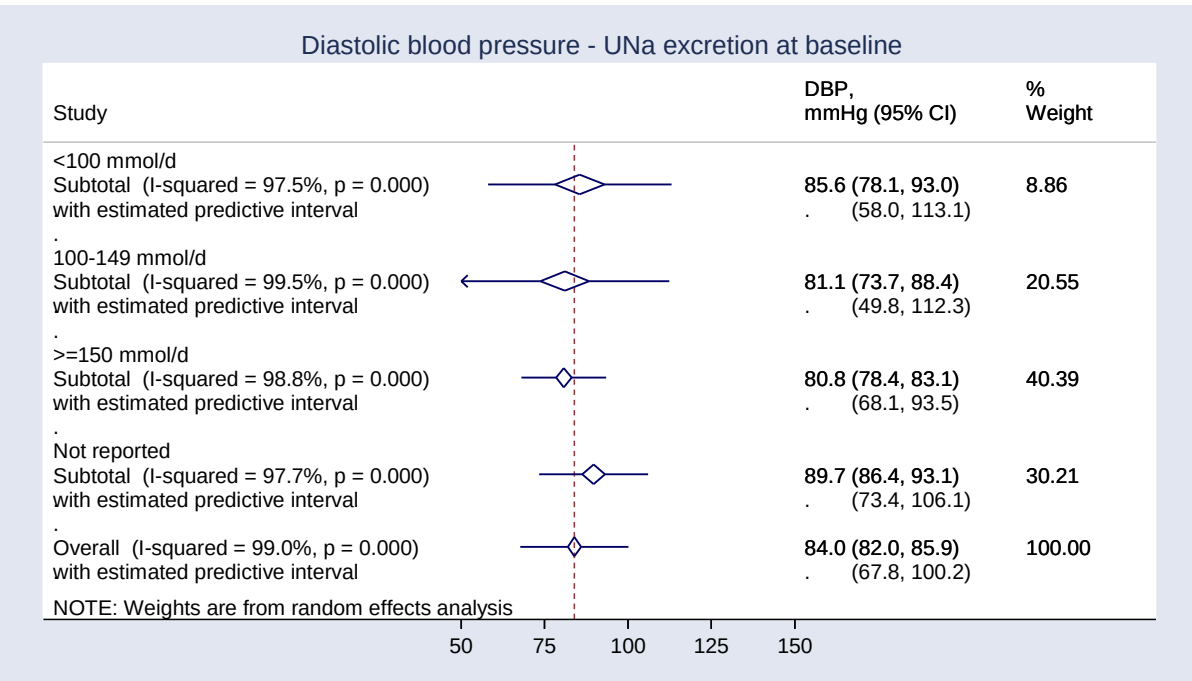
Diastolic blood pressure - BMI

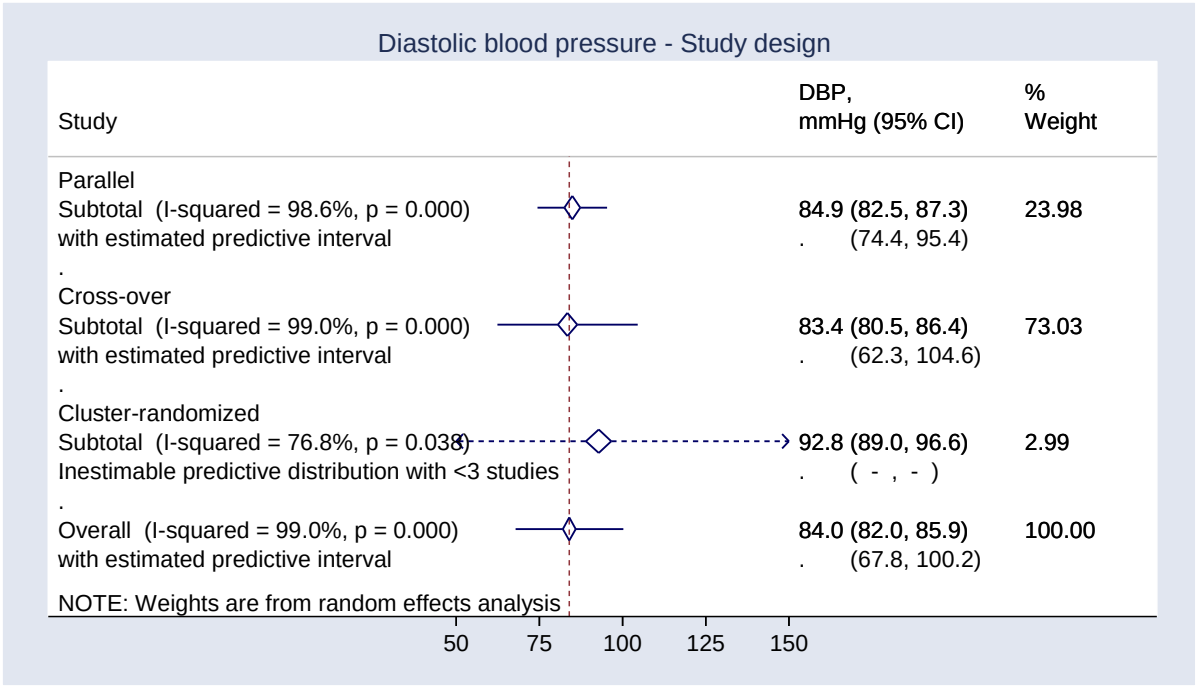


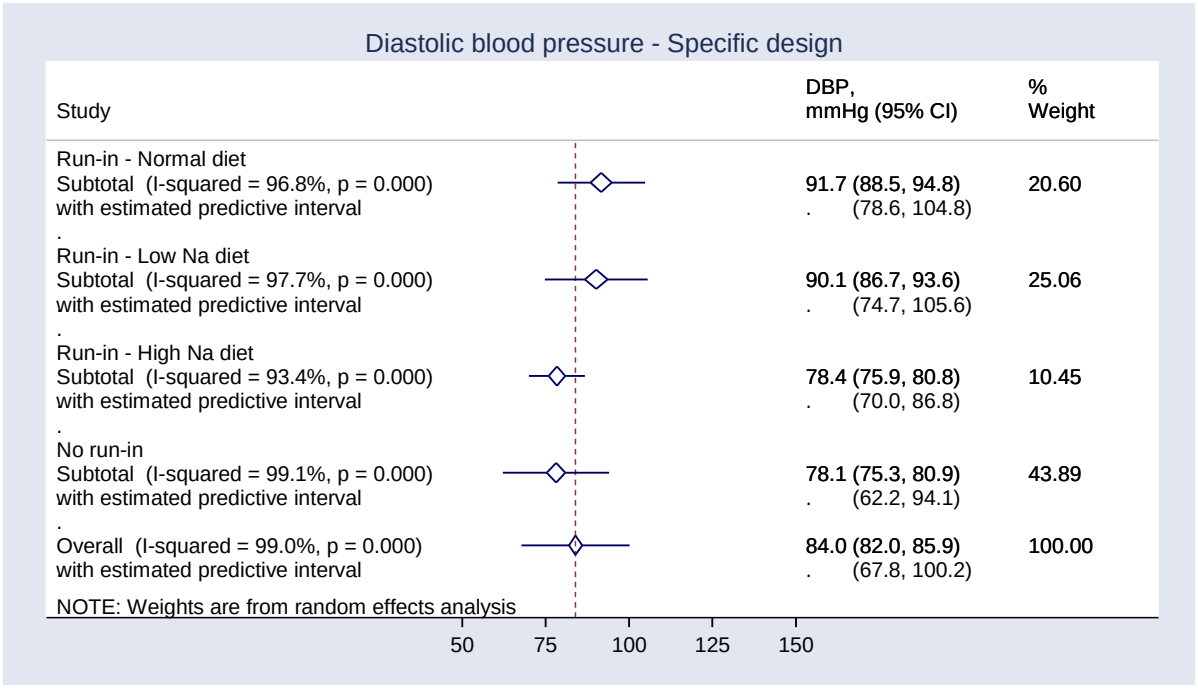
Diastolic blood pressure - Baseline DBP



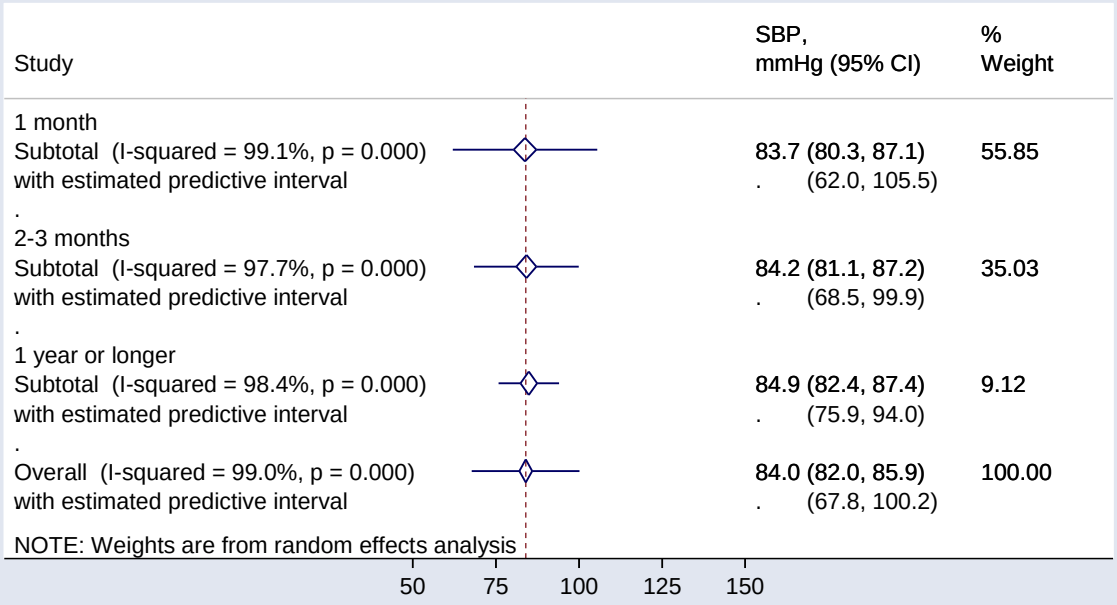

Diastolic blood pressure - Baseline potassium intake
Study
DBP, mmHg (95% CI)
% Weight
K intake <=60 mmol/d
Subtotal (I-squared = 99.6%, p = 0.000)
with estimated predictive interval
76.1 (68.7, 83.5)
(48.6, 103.7)
12.04
K intake >60 and <=70 mmol/d
Subtotal (I-squared = 98.8%, p = 0.000)
with estimated predictive interval
90.1 (87.5, 92.7)
(78.7, 101.4)
23.96
K intake >70 and <=80 mmol/d
Subtotal (I-squared = 98.3%, p = 0.000)
with estimated predictive interval
80.1 (75.6, 84.6)
(61.1, 99.1)
20.80
K intake >80 mmol/d
Subtotal (I-squared = 95.0%, p = 0.000)
with estimated predictive interval
78.0 (72.8, 83.2)
(59.1, 97.0)
8.91
Not reported
Subtotal (I-squared = 97.0%, p = 0.000)
with estimated predictive interval
86.3 (83.3, 89.2)
(71.4, 101.2)
34.29
Overall (I-squared = 99.0%, p = 0.000)
with estimated predictive interval
84.0 (82.0, 85.9)
(67.8, 100.2)
100.00
NOTE: Weights are from random effects analysis
50
75
100
125
150


Diastolic blood pressure - UNa excretion at baseline
Study
DBP, mmHg (95% CI)
% Weight
<100 mmol/d
Subtotal (I-squared = 97.5%, p = 0.000)
with estimated predictive interval
85.6 (78.1, 93.0)
(58.0, 113.1)
8.86
100-149 mmol/d
Subtotal (I-squared = 99.5%, p = 0.000)
with estimated predictive interval
81.1 (73.7, 88.4)
(49.8, 112.3)
20.55
>=150 mmol/d
Subtotal (I-squared = 98.8%, p = 0.000)
with estimated predictive interval
80.8 (78.4, 83.1)
(68.1, 93.5)
40.39
Not reported
Subtotal (I-squared = 97.7%, p = 0.000)
with estimated predictive interval
89.7 (86.4, 93.1)
(73.4, 106.1)
30.21
Overall (I-squared = 99.0%, p = 0.000)
with estimated predictive interval
84.0 (82.0, 85.9)
(67.8, 100.2)
100.00
NOTE: Weights are from random effects analysis
50
75
100
125
150

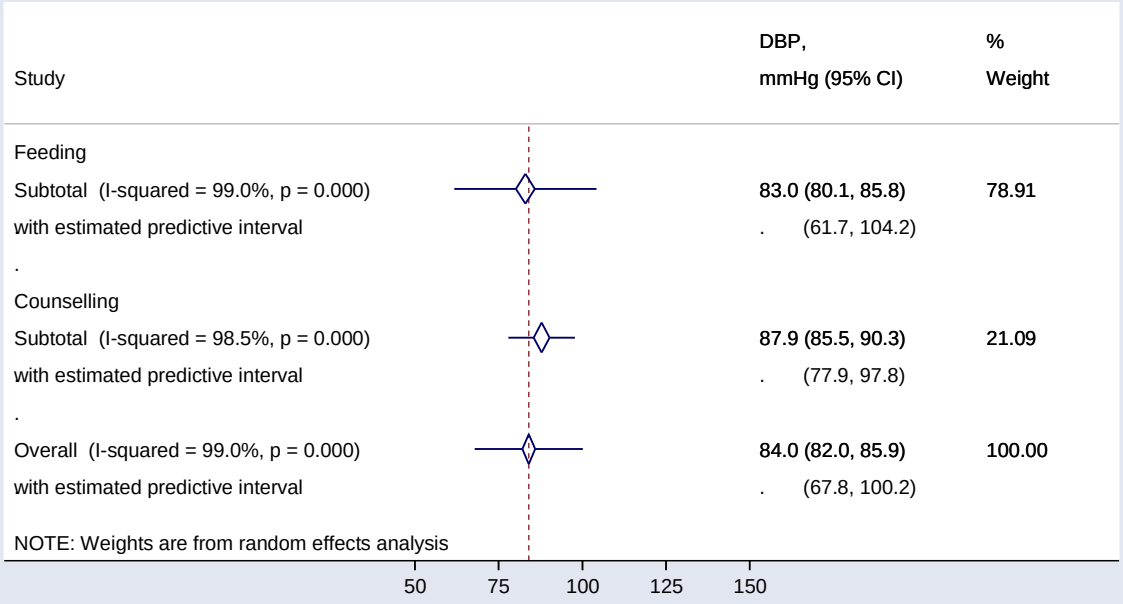

Diastolic blood pressure - Study design
Study
DBP, mmHg (95% CI)
% Weight
Parallel
Subtotal (I-squared = 98.6%, p = 0.000)
84.9 (82.5, 87.3)
23.98
with estimated predictive interval
(74.4, 95.4)
Cross-over
Subtotal (I-squared = 99.0%, p = 0.000)
83.4 (80.5, 86.4)
73.03
with estimated predictive interval
(62.3, 104.6)
Cluster-randomized
Subtotal (I-squared = 76.8%, p = 0.038)
92.8 (89.0, 96.6)
2.99
Inestimable predictive distribution with <3 studies
(- , -)
Overall (I-squared = 99.0%, p = 0.000)
84.0 (82.0, 85.9)
100.00
with estimated predictive interval
(67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150

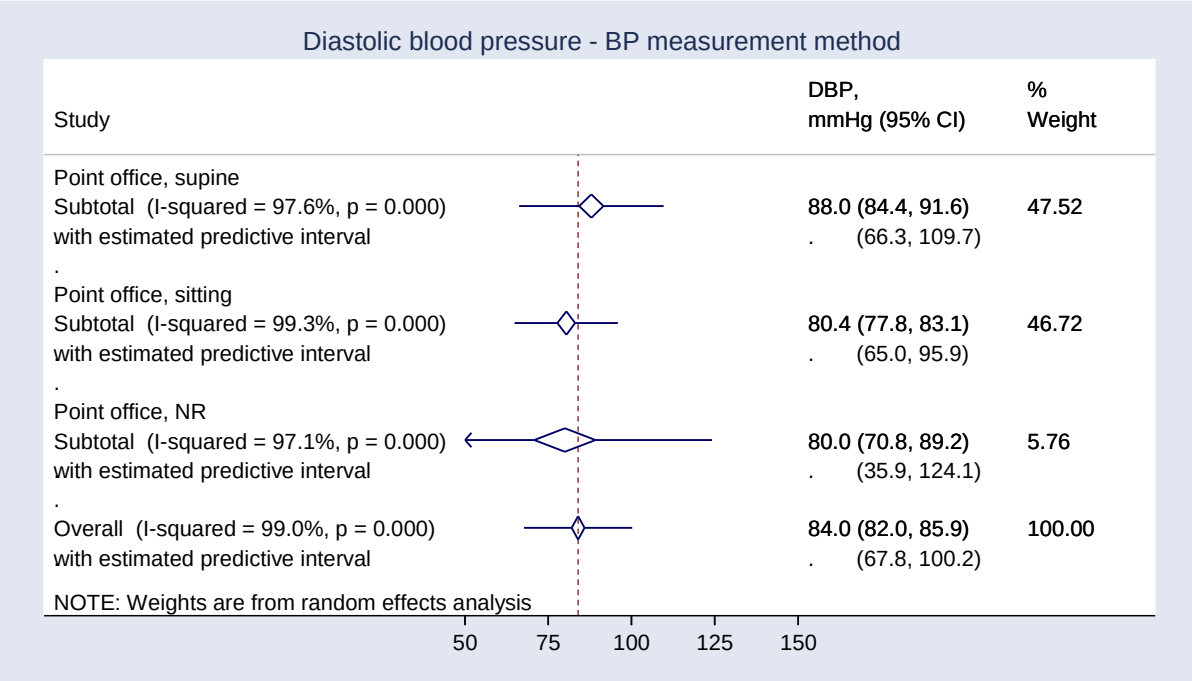

Diastolic blood pressure - Specific design
Study
DBP, mmHg (95% CI)
% Weight
Run-in - Normal diet
Subtotal (I-squared = 96.8%, p = 0.000)
91.7 (88.5, 94.8)
20.60
with estimated predictive interval
(78.6, 104.8)
Run-in - Low Na diet
Subtotal (I-squared = 97.7%, p = 0.000)
90.1 (86.7, 93.6)
25.06
with estimated predictive interval
(74.7, 105.6)
Run-in - High Na diet
Subtotal (I-squared = 93.4%, p = 0.000)
78.4 (75.9, 80.8)
10.45
with estimated predictive interval
(70.0, 86.8)
No run-in
Subtotal (I-squared = 99.1%, p = 0.000)
78.1 (75.3, 80.9)
43.89
with estimated predictive interval
(62.2, 94.1)
Overall (I-squared = 99.0%, p = 0.000)
84.0 (82.0, 85.9)
100.00
with estimated predictive interval
(67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150

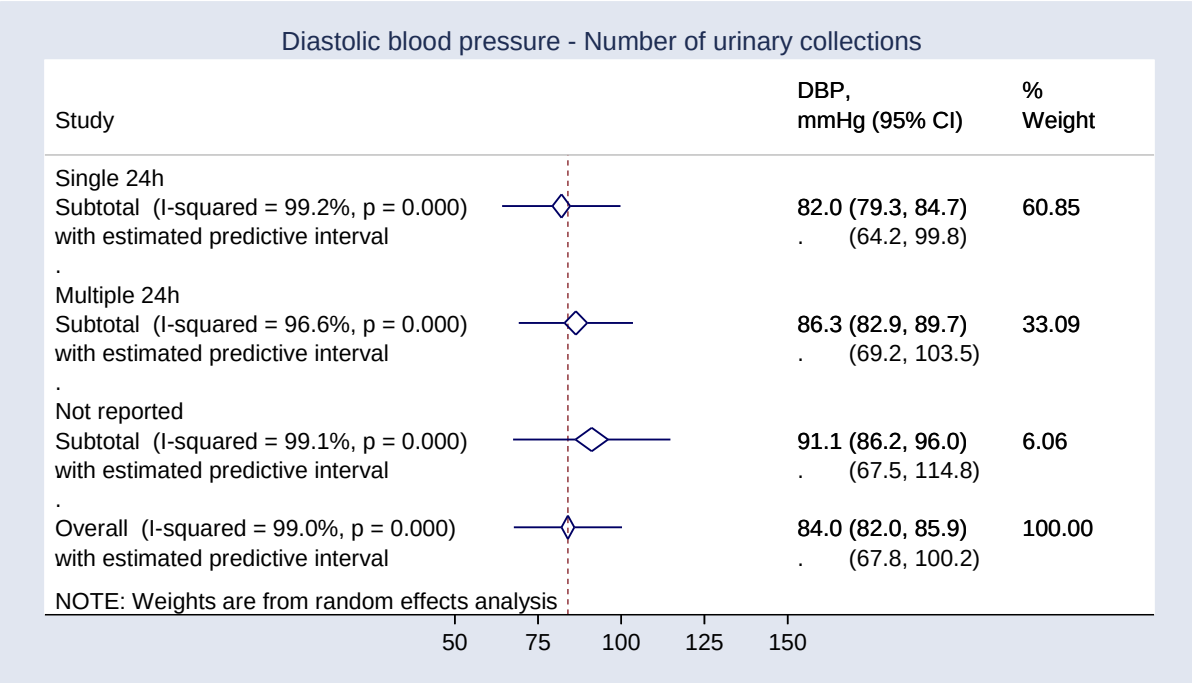
Diastolic blood pressure - Duration

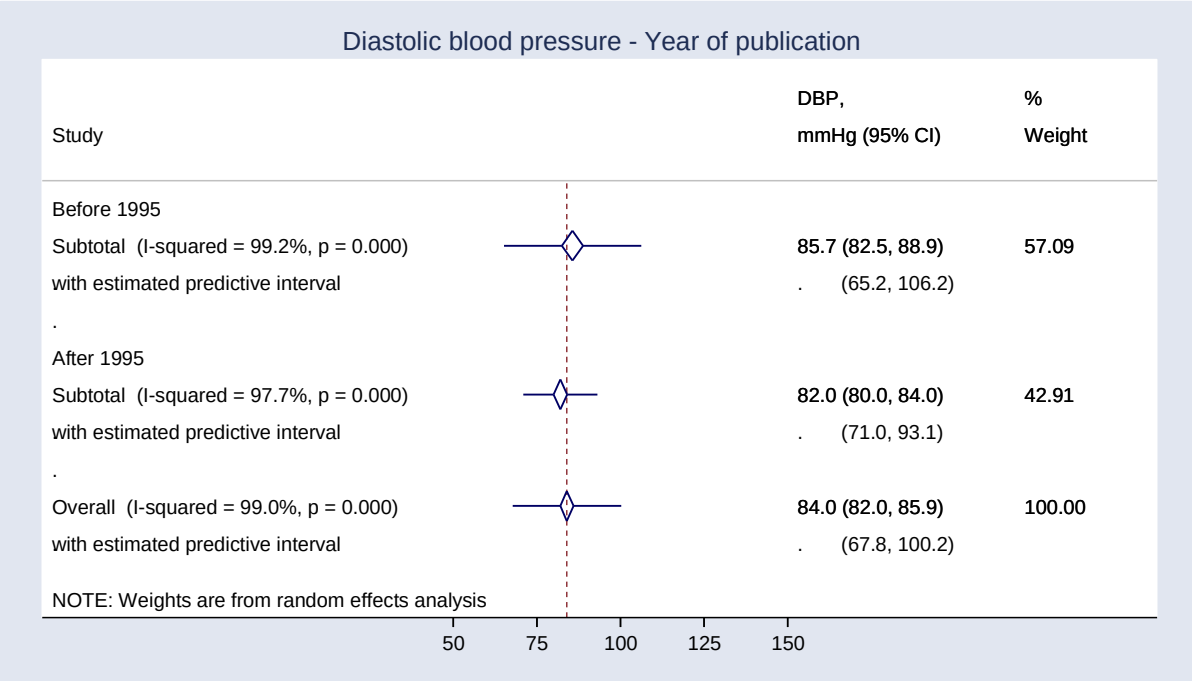


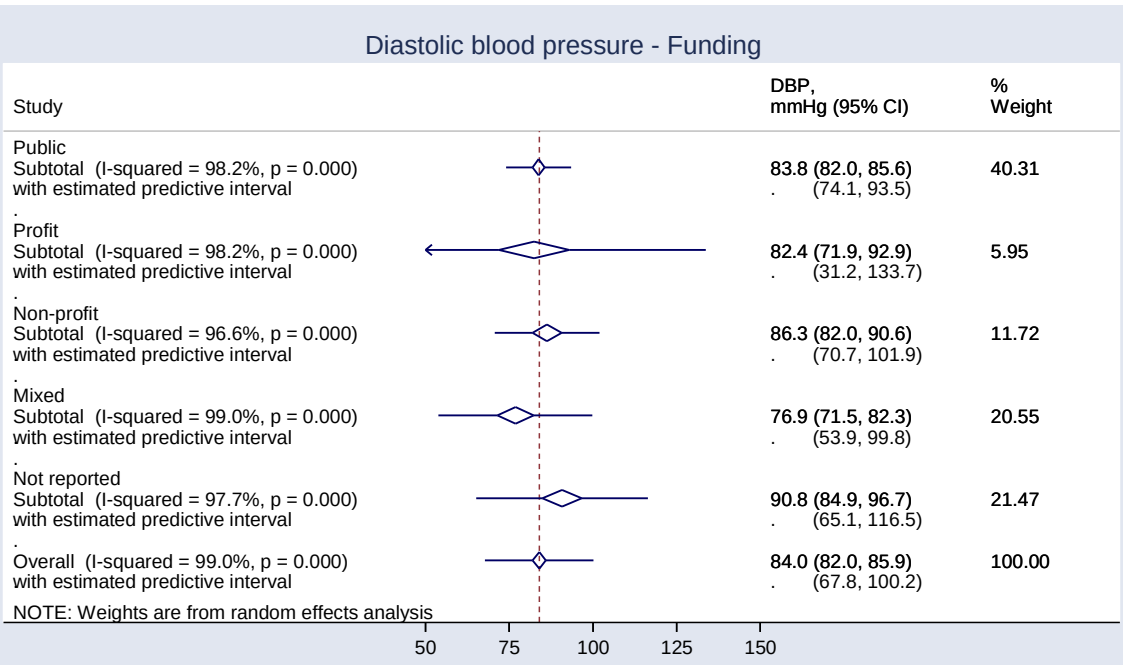
Diastolic blood pressure - Intervention type



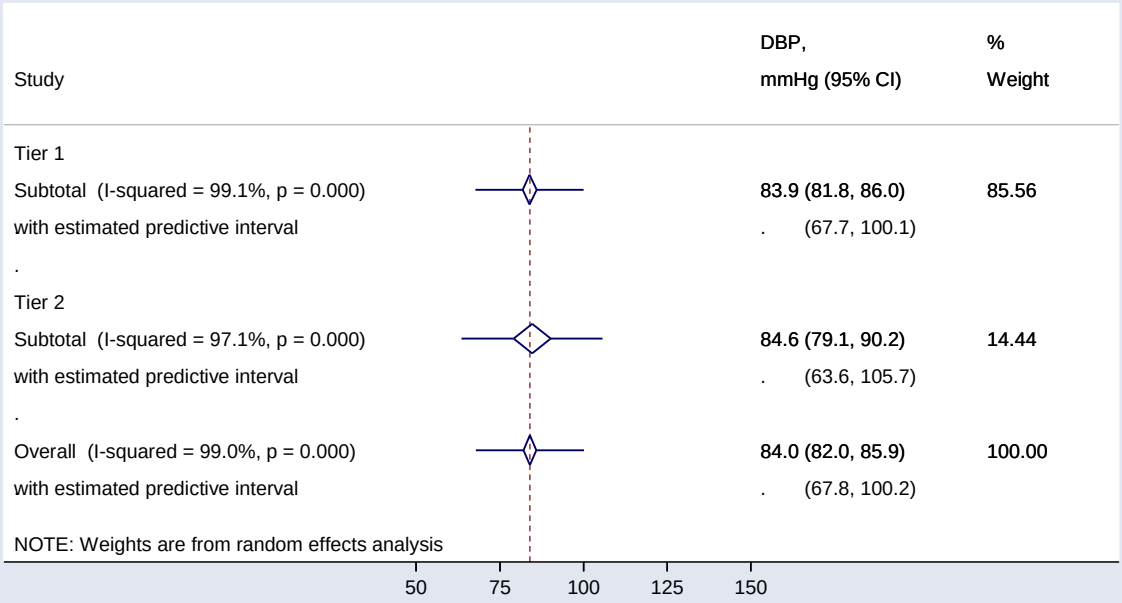

Diastolic blood pressure - BP measurement method
Study
DBP, mmHg (95% CI)
% Weight
Point office, supine
Subtotal (I-squared = 97.6%, p = 0.000)
88.0 (84.4, 91.6)
47.52
with estimated predictive interval
. (66.3, 109.7)
Point office, sitting
Subtotal (I-squared = 99.3%, p = 0.000)
80.4 (77.8, 83.1)
46.72
with estimated predictive interval
. (65.0, 95.9)
Point office, NR
Subtotal (I-squared = 97.1%, p = 0.000)
80.0 (70.8, 89.2)
5.76
with estimated predictive interval
. (35.9, 124.1)
Overall (I-squared = 99.0%, p = 0.000)
84.0 (82.0, 85.9)
100.00
with estimated predictive interval
. (67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150


Diastolic blood pressure - Number of urinary collections
Study
DBP, mmHg (95% CI)
% Weight
Single 24h
Subtotal (I-squared = 99.2%, p = 0.000)
82.0 (79.3, 84.7)
60.85
with estimated predictive interval
. (64.2, 99.8)
Multiple 24h
Subtotal (I-squared = 96.6%, p = 0.000)
86.3 (82.9, 89.7)
33.09
with estimated predictive interval
. (69.2, 103.5)
Not reported
Subtotal (I-squared = 99.1%, p = 0.000)
91.1 (86.2, 96.0)
6.06
with estimated predictive interval
. (67.5, 114.8)
Overall (I-squared = 99.0%, p = 0.000)
84.0 (82.0, 85.9)
100.00
with estimated predictive interval
. (67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150


Diastolic blood pressure - Year of publication
Study
DBP, mmHg (95% CI)
% Weight
Before 1995
Subtotal (I-squared = 99.2%, p = 0.000) 85.7 (82.5, 88.9) 57.09
with estimated predictive interval . (65.2, 106.2)
After 1995
Subtotal (I-squared = 97.7%, p = 0.000) 82.0 (80.0, 84.0) 42.91
with estimated predictive interval . (71.0, 93.1)
Overall (I-squared = 99.0%, p = 0.000) 84.0 (82.0, 85.9) 100.00
with estimated predictive interval . (67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150


Diastolic blood pressure - Funding
Study
DBP, mmHg (95% CI)
% Weight
Public
Subtotal (I-squared = 98.2%, p = 0.000) 83.8 (82.0, 85.6) 40.31
with estimated predictive interval . (74.1, 93.5)
Profit
Subtotal (I-squared = 98.2%, p = 0.000) 82.4 (71.9, 92.9) 5.95
with estimated predictive interval . (31.2, 133.7)
Non-profit
Subtotal (I-squared = 96.6%, p = 0.000) 86.3 (82.0, 90.6) 11.72
with estimated predictive interval . (70.7, 101.9)
Mixed
Subtotal (I-squared = 99.0%, p = 0.000) 76.9 (71.5, 82.3) 20.55
with estimated predictive interval . (53.9, 99.8)
Not reported
Subtotal (I-squared = 97.7%, p = 0.000) 90.8 (84.9, 96.7) 21.47
with estimated predictive interval . (65.1, 116.5)
Overall (I-squared = 99.0%, p = 0.000) 84.0 (82.0, 85.9) 100.00
with estimated predictive interval . (67.8, 100.2)
NOTE: Weights are from random effects analysis
50
75
100
125
150

Diastolic blood pressure - Risk of Bias TIER



Diastolic blood pressure - Risk of Bias OUTCOME