Systematic review of the evidence for a relationship between potassium and blood pressure

Prepared by Food Standards Australia New Zealand

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Executive summary

Does potassium intake affect blood pressure?	
Food-health relationship	Increased potassium intake reduces blood pressure
Degree of certainty (GRADE rating)	Moderate in normotensive population (no change in resting blood pressure) ⊕⊕⊕ High in hypertensive population (reduced resting blood pressure) ⊕⊕⊕⊕
Component	**Notes**
Body of evidence	The updated WHO systematic review and meta-analysis of randomised controlled trials (RCTs) is consistent with three previous meta-analyses which support the relationship in hypertensive people.
Consistency	The majority of RCTs, and the high quality RCTs, demonstrate unchanged (in normotensives) or decreased (in hypertensives) blood pressure with increased potassium intake.
Causality	RCTs are a strong study design for causal evidence. The WHO meta-analysis of 22 RCTs supports a causal relationship between increased intake and reduced blood pressure in hypertensive people. The one new study in normotensive people does not alter this conclusion.
Plausibility	Potassium can plausibly decrease or maintain normal blood pressure through effects on vasodilation, natriuresis and modulation of the renin-angiotensin system.
Generalisability	The meta-analysis included studies from Australia, New Zealand, Asia, Europe and the Americas.

FSANZ has critically appraised and updated a 2012 World Health Organization (WHO) systematic review and meta-analysis on potassium and blood pressure. In doing this review, FSANZ has followed the requirements of the *Application Handbook* and of Schedule 6 of Standard 1.2.7 – Nutrition, Health and Related Claims, for updates to existing systematic reviews.

Twenty-two relevant randomised controlled trials (RCTs) investigating the relationship between potassium intake and blood pressure were identified by WHO, with one additional study identified in the FSANZ update process. Including this study in the review did not change the outcome. During critical appraisal FSANZ identified and corrected a number of errors in the WHO meta-analyses. These corrections did not alter the outcomes of the meta-analyses.

The relationship between potassium intake and blood pressure has been shown to be consistent and causal in hypertensive people. There are multiple mechanisms by which it is plausible for potassium to maintain normal or decrease blood pressure. The effect of increased potassium intake reducing resting blood pressure was substantiated in hypertensive populations, but not in populations with normal blood pressure. In normotensives, there was no change in resting blood pressure with increasing potassium intake (with a 'Moderate' degree of certainty – see Appendix 2). The RCTs considered were conducted in a number of countries with similar population characteristics to Australia and New Zealand.

Contents

1 Introduction

In 2012, the European Union authorised a claim that 'Potassium contributes to the maintenance of normal blood pressure' under Article 13(1) which permits function claims (European Commission regulation (EU) No 432/2012 of 16/05/2012). FSANZ notes that the review by the European Food Safety Authority (EFSA), on which this claim was based (EFSA, 2010), referred to four systematic reviews published between 1991 and 2006 which concluded that increased potassium intake lowered blood pressure. New studies are now available.

FSANZ is considering whether a relationship between potassium and blood pressure can be incorporated into Schedule 2 of Standard 1.2.7 – Nutrition, Health and Related Claims. FSANZ considers that 'maintain' is part of the wording specifications for the EU claim. Therefore, the relationship to be investigated by FSANZ is that increased potassium intake reduces blood pressure. The purpose of this paper is to systematically review the evidence for this relationship.

At the time FSANZ commenced this work, the most recent relevant existing review, commissioned by the World Health Organization (WHO), was reported by Aburto et al. (2013). The WHO review is the summary of three separate systematic reviews, one of which assessed the relationship between potassium intake and blood pressure in adults (World Health Organisation 2012a). The WHO review was assessed by Nutrition Guidance Expert Advisory Group which concluded that there was high quality evidence to support a relationship between increased potassium intakes and reduced resting systolic and diastolic blood pressures (World Health Organisation 2012b; Aburto et al. 2013).

Like the review by WHO (2012a), three prior reviews had included studies in normotensive and hypertensive adults (Cappuccio and MacGregor 1991; Whelton et al. 1997; Geleijnse et al. 2003;). A fourth review had examined studies in hypertensive populations (Dickinson et al. 2006). As WHO (2012a) had formally considered the prior systematic reviews in their literature searching, FSANZ selected it as the most recent and comprehensive existing systematic review of the literature which would be updated to assess the scientific evidence for the relationship between potassium and blood pressure. FSANZ notes that the WHO guideline document contains other material that is relevant to the guideline recommendation but is not relevant to the current assessment of the relationship between potassium and blood pressure.

1.1 Property of food

In almost all foods, particularly fruit, vegetables, nuts, meat and fish, potassium is usually present in the form of an organic salt such as potassium citrate and/or potassium malate. In addition to food, other potassium salts, such as potassium gluconate, may also be consumed as a dietary supplement. Potassium may also be consumed as an excipient in multivitamins, in some complementary medicines, and as a prescribed medicine by some individuals. In water, organic potassium salts readily dissociate into electrolytes, e.g. (K^+) and (citrate; $C_6H_5O_7^{3-}$). For the purpose of this report, potassium refers to potassium as an electrolyte.

1.2 Health effect

Blood pressure is a measure of the force exerted on the vessel (typically artery) wall by blood as it is pumped around the body. It is measured in millimetres of mercury (mm Hg) using a sphygmomanometer (manual or automated), and is usually presented as systolic blood pressure over diastolic blood pressure. Systolic blood pressure is the measure of force

exerted on vessels immediately after the ventricles of the heart contract to eject blood from the heart, while diastolic blood pressure is the measure of force as the vessels relax while the heart refills with blood.

Blood pressure can be measured at rest or as ambulatory blood pressure. Measurement of ambulatory blood pressure involves a device that takes blood pressure measures repeatedly throughout a 24-hour period. Due to its more invasive nature it is less commonly measured than resting blood pressure. Both ambulatory and resting blood pressure measures are reliable and appropriate measures of blood pressure.

Elevated blood pressure is associated with increased risk of heart attack and stroke. As such, reductions in blood pressure or the maintenance of normal blood pressure (generally regarded to be <140/90 mm Hg[1]) are considered to be beneficial health effects. Specifically, sustained reductions in blood pressure are considered to be the beneficial health effect, rather than acute or transient effects that may occur with short-term interventions.

1.3 Proposed relationship

The food-health relationship being assessed in this report is that increased potassium intake reduces blood pressure in the adult population.

2 Summary and critical appraisal of existing systematic review

2.1 Methods used in the existing review

The property of food (the electrolyte potassium), the health effect (blood pressure measured in mm Hg using a sphygmomanometer) and the direction of effect investigated in the WHO review are identical to those that FSANZ has specified above.

As previously indicated, the methods and results of the WHO systematic review are reported in three separate documents. There is a summary in the guideline document (WHO 2012b), a full report of the systematic review (WHO 2012a) and an abbreviated report in the British Medical Journal (Aburto et al. 2013). The latter publication also summarises the results of two other systematic reviews (on potassium and cardiovascular disease, and potassium and blood pressure in children).

In the WHO (2012a) review, literature was searched in two phases. The initial search sought to identify existing systematic reviews examining the relationship between potassium intake and blood pressure. The reference lists of these studies were used to select studies for inclusion in the review. In the second phase, literature searches were performed to update the identified reviews with more recent publications.

The following databases were searched between 25 August 2011 and 6 September 2011:

- Cochrane register of controlled trials
- MEDLINE (through PubMed)
- EMBASE

[1] Australian Heart Foundation blood pressure classifications: normal <120/80 mm Hg, high-normal 120-139/80-89, hypertensive >140/90

- Latin American and Caribbean Health Science Literature Database
- WHO International Clinical Trials Registry Platform (for ongoing trials).

The EMBASE search was limited to studies published after 2004, to update the identified systematic reviews. The PubMed search was conducted for the 180 days prior to the search date to identify any publications recently added to the Medline database that may not have been identified through the EMBASE search which is updated less frequently. Date restrictions were not applied to the other searches.

The basis for study selection, summarised under the PICOT headings, is detailed in Table 1. In this review only adults were included, with a separate review performed for children. To be included, studies had to be an RCT with a documented increase in potassium intake in the intervention group. As such, a measure of 24-hour urinary potassium was required for inclusion.

Table 1 *PICOTS criteria for study selection*

Population	Male and female adults (≥16) Apparently healthy (with or without hypertension)
Intervention	Increased potassium intake through diet, dietary advice or supplementation (ascertained by measures of urinary potassium)
Comparator	Normal or lower potassium intake Placebo (for supplementation studies)
Outcome	Blood pressure (systolic, diastolic or both; resting or ambulatory)
Time	≥4 weeks

Studies were excluded if they involved a concomitant intervention, unless the same intervention was also applied to the control group. Studies with a monitoring duration of less than 4 weeks were excluded so that acute effects of changes in potassium intake were not considered. Studies in acutely ill subjects were also excluded.

Data were extracted from the selected studies by two reviewers. Risk of bias was assessed based on the criteria specified in the *Cochrane handbook for systematic reviews of interventions 5.0.2* (The Cochrane Collaboration 2009). The quality of the body of evidence was assessed using the GRADE methodology (Guyatt et al. 2008).

Meta-analyses[2] were performed for resting and ambulatory systolic and diastolic blood pressure using Review Manager (RevMan), the systematic review software developed by The Cochrane Collaboration (The Nordic Cochrane Centre 2014). It was decided, *a priori*, that subgroup analyses would be performed, where possible, based on:

- gender
- blood pressure status
- achieved potassium intake
- achieved difference in potassium intake
- duration of intervention
- baseline potassium and sodium intake

[2] Meta-analysis is a statistical method in which data from similar studies are pooled to calculate an average effect

- hypertensive medication status
- type of intervention
- type of blood pressure device
- method of blood pressure measurement
- trial design.

2.2 Summary of results

The electronic literature searches and hand-searching of reference lists identified 4926 records for screening. Twenty-two studies were included in the quantitative meta-analysis of the relationship of interest. Table 2 presents selected findings which achieved a 'Moderate' or 'High' GRADE rating for evidence quality (Guyatt et al. 2008). Sub-group analyses that revealed apparent differences in the effect of potassium intake on blood pressure are also included in Table 2. The discrepancy in GRADE for some relationships is discussed in Section 2.3.4. As indicated in Table 2, FSANZ believes that there are some errors in data extraction. These errors are addressed in Section 2.3.

Most studies reported resting systolic and diastolic blood pressures. The outcome of meta-analyses demonstrated that increased potassium intake was associated with decreased resting systolic and diastolic blood pressure in adults. The effects were generally more pronounced on systolic compared to diastolic blood pressure.

Sub-analyses of effects of increased potassium intake on resting systolic blood pressure showed:

- the effect was restricted to hypertensive populations
- the effect was greater in studies of less than 4 months duration[3]
- the effects were greater in populations with higher sodium intake
- there was no dose-response relationship for either absolute intake in the intervention group or for the difference in potassium intake between intervention and control group
- the effect was present in studies using supplements and also dietary advice.

[3] it should be noted that the studies with longer duration were in either normotensive populations or in a study where blood pressure medication levels were also manipulated

Table 2 *Selected results summary from WHO systematic review of relationship between potassium and blood pressure (WHO, 2012a)*

Outcome		No. of studies (participants)	Mean difference mmHg (95% CI)	GRADE rating	Comments[1]
Resting systolic BP		**21 (1892)**	**-3.49 (-5.15, -1.82)**	**Moderate (preliminary) High (final)**	*Inconsistency: 95% CI do not always overlap between studies*
K intake (mmol/day) *[equivalent urinary K excretion (mmol/day)]*	<90 [*<70*]	2 (183)	-3.65 (-6.69, -0.62)	High	
	91-117* *[≥70 to <90]*	5 (286)	-7.16 (-12.41, -1.91)	Moderate	*Inconsistency: 95% CI do not always overlap*
	117-156^# *[≥90 to <120]*	11 (1187)	-1.71 (-3.42, 0.00)	Moderate	*Imprecision: 95%CI reaches zero*
	>156 *[≥120]*	4 (236)	-3.00 (-6.28, 0.27)	Moderate	*Imprecision: 95%CI crosses zero*
Achieved difference in K intake (mmol/day)	<30	6 (501)	-4.89 (-7.59, -2.20)	Sub-analyses without individual GRADE rating	
	30-60	12 (1169)	-1.97 (-3.85, -0.09)		
	>60	4 (222)	-3.01 (-7.03, 1.02)		
BP status	Normotensive#	3 (757)	0.09 (-0.77, 0.95)		Greatest effect in hypertensive population
	Hypertensive*^	16 (818)	-5.53 (-7.56, -3.51)		
	Mixed	2 (233)	-2.95 (-5.65, -0.26)		
Duration	<2 months	15 (933)	-3.36 (-4.94, -1.78)		
	2-4 months^	8 (1074)	-3.83 (-6.72, -0.95)		
	>4 months*#	3 (718)	0.02 (-0.85, 0.90)		
Baseline Na intake	< 2g/d	1 (40)	-2.00 (-11.70, 7.70)		
	2-4 g/d*^	16 (1470)	-1.97 (-3.41, -0.52)		
	>4 g/d	5 (382)	-6.91 (-11.53, -2.29)		
Intervention type	Supplement	20 (1744)	-3.31 (-5.07, -1.55)		
	Dietary advice	3 (244)	-4.19 (-6.46, -1.92)		
Resting diastolic BP		**21 (1857)**	**-3.02 (-4.86, -1.17)**	**Moderate (preliminary) High (final)**	*Inconsistency: 95% CI do not always overlap*
K intake (mmol/day) *[equivalent urinary K excretion (mmol/day)]*	<90 [*<70*]	2 (183)	-1.35 (-5.31, 2.60)	Moderate	*Imprecision: 95%CI cross zero*
	91-117* *[≥70 to <90]*	5 (212)	-4.01 (-8.44, 0.42)	Moderate	*Imprecision: 95%CI cross zero*
	117-156^# *[≥90 to <120]*	10 (1051)	-0.83 (-1.82, 0.17)	Moderate	*Imprecision: 95%CI cross zero*
	>156 *[≥120]*	4 (236)	-1.76 (-4.23, 0.74)	Moderate	*Imprecision: 95%CI cross zero*
Achieved difference in K intake (mmol/day)	<30	6 (427)	-1.87 (-4.11, 0.37)	Sub-analyses without individual GRADE rating	
	30-60	12 (1134)	-1.63 (-3.04, -0.21)		
	>60	4 (222)	-3.57 (-6.32, -0.82)		
BP status	Normotensive#	3 (722)	-0.56 (-1.55, 0.42)		Greatest effect in hypertensive population
	Hypertensive*^	17 (902)	-3.91 (-6.54, -1.28)		
	Mixed	2 (233)	-0.17 (-1.82, 1.48)		
Duration	<2 months	15 (933)	-1.99 (-3.11, -0.87)		
	2-4 months^	8 (1074)	-1.86 (-3.75, 0.02)		
	>4 months*#	3 (718)	-0.35 (-1.06, 0.35)		
Baseline Na intake	< 2g/d	1 (40)	0.00 (-6.12, 6.12)		
	2-4 g/d*^	16 (1435)	-1.96 (-3.16, -0.76)		
	>4 g/d	5 (308)	-2.87 (-6.96,1.22)		
Intervention type	Supplement	20 (1709)	-3.04 (-5.09, -0.99)		
	Dietary advice	3 (244)	-2.44 (-7.12, 0.17)		

Outcome	No. of studies (participants)	Mean difference mmHg (95% CI)	GRADE rating	Comments[1]
Ambulatory systolic BP	**4 (322)**	**-3.04 (-5.4, -0.7)**	**Moderate**	*Imprecision: 95%CI very near zero*
Hypertensive	3 (226)	-3.37 (-6.05, -0.69)	No GRADE rating	No studies in normotensives
Mixed BP status	1 (96)	-1.80 (-7.02, 3.42)		
Ambulatory diastolic BP	**4 (322)**	**-1.24 (-3.1, +0.7)**	**Moderate**	*Imprecision: 95%CI very near zero*
Hypertensive	3 (226)	-1.18 (-3.38, 1.02)	No GRADE rating	No studies in normotensives
Mixed BP status	1 (96)	-1.40 (-5.14, 2.34)		

[1] Reason for down-rating of evidence using GRADE.
**Includes Siani 1991 in which medication for hypertension was manipulated during study, and data extraction was inversed (Siani et al. 1991). ^Includes Chalmers 1986 in which data were extracted for incorrect group (Chalmers et al. 1986). [#]The inclusion of results from the TOHP1 study is duplicated in these publications (Trial Hyp Prv Col 1992; Whelton et al. 1995)*

2.3 Critical appraisal of the existing review

2.3.1 Study identification and selection

The search strategy enabled the authors to retrieve a comprehensive list of records for screening. The inclusion and exclusion criteria used were appropriate for selecting relevant studies for the meta-analysis. Critical trials were included in the systematic review, and the exclusion of studies was appropriate. Potential records for inclusion were screened on title, abstract and key words by two of the review authors. Remaining records were then screened on full-text, of which 22 studies were included in the meta-analyses (MacGregor et al. 1982; Richards et al. 1984; Bulpitt et al. 1985; Kaplan et al. 1985; Smith et al. 1985; Chalmers et al. 1986; Matlou et al. 1986; Barden et al. 1987; Grobbee et al. 1987; Siani et al. 1987; Forrester and Grell 1988; Obel 1989; Patki et al. 1990; Siani et al. 1991; Valdes et al. 1991; Fotherby and Potter 1992; Trial Hyp Prv Col 1992; Whelton et al. 1995; Kawano et al. 1998; Gu et al. 2001; Berry et al. 2010; He et al. 2010).

The WHO identified four systematic reviews with meta-analyses that assessed the relationship between potassium intake and blood pressure (Cappuccio and MacGregor 1991; Whelton et al. 1997; Geleijnse et al. 2003; Dickinson et al. 2006). These reviews were used in combination with literature searches to identify studies for inclusion. Three of these reviews found a significant relationship between increased potassium intake and decreased blood pressure, with the estimated effect ranging from -2.4 to -5.9 mm Hg systolic blood pressure (Cappuccio and MacGregor 1991; Whelton et al. 1997; Geleijnse et al. 2003). These meta-analyses included studies of less than four weeks duration, which may bias the results towards larger, acute effects of increased potassium intake on blood pressure. Therefore, the WHO review only included studies with a minimum duration of four weeks.

In contrast to the other systematic reviews, the Dickinson meta-analysis only included trials in hypertensive populations that were of eight weeks duration or longer (Dickinson et al. 2006). These more stringent inclusion criteria resulted in inclusion of only five RCTs in the meta-analysis, which found large but non-significant reductions in blood pressure following potassium supplementation. In contrast, as the WHO review included studies of at least four weeks duration, 16 RCTs of hypertensive participants were included. This resulted in the decreases in blood pressure following increased potassium intake being statistically significant.

The above systematic reviews were also used by FSANZ to cross-check included studies included in the WHO review. From this process, FSANZ believes all relevant trials published at the time were considered by the WHO.

2.3.2 Assessment of bias

The WHO assessed the risk of bias for each study included in the systematic review. For the majority of studies there was an unclear risk of selection bias due to inadequate information on the methods of randomisation and allocation concealment. The majority of included studies blinded participants and personnel, but 25% of studies had a high risk of performance bias.[4] Detection bias was minimised in half of the included studies, while in all except one of the remaining studies it was unclear whether outcome assessors were blinded. No reporting bias was identified, and the majority of studies had a low risk for attrition bias. Despite the relatively large proportion of studies with 'unclear risk' of bias, the authors concluded that 'the entire body of evidence is not at risk of serious problems due to bias'. Sensitivity analysis was performed in which the one study with high overall risk of bias was removed (Forrester and Grell 1988), and this had little effect on the meta-analysis results. In addition, funnel plot analysis was used to assess publication bias, with little risk shown.

2.3.3 Data extraction and analysis

Two review authors independently extracted data from included trials using a standard data extraction form, with a third author checking for accuracy. Despite this, FSANZ notes the following inaccuracies:

- Duplicate inclusion of results from the Trials of Hypertension Prevention Phase 1 (TOHP1) study (Trial Hyp Prv Col 1992; Whelton et al. 1995)
- Data extraction inverted for control and intervention groups (Siani et al. 1991)
- Data extracted for incorrect intervention group (Chalmers et al. 1986).

To determine the effect of these errors FSANZ repeated the meta-analysis. First, because the WHO used RevMan to analyse their data whereas FSANZ used StatsDirect (England: StatsDirect Ltd. 2008), FSANZ replicated the WHO analysis without data correction. This produced the same mean differences and confidence intervals for both individual studies and pooled effects as those obtained by the WHO. Therefore any differences in analytical results are not related to use of different statistical software packages.

Following correction of data extraction for two studies (Siani et al. 1991; Chalmers et al. 1986) and excluding the duplicated data from TOHP1 (Whelton et al. 1995), the results for resting systolic and diastolic blood pressure were not substantially altered and differences remained significant (see Table 3). The re-analysed forest plots are presented in Figures 1 and 2. The re-analysis does not impact on the conclusions of the WHO review.

It should be noted that the WHO meta-analysis included eight studies with a parallel design and 14 with a cross-over design. The effects of trial design were assessed in the sub-group analyses, with both study types showing a significant effect of increased potassium intake reducing blood pressure. However, when describing the number of participants in the summary tables, the WHO document had counted the subjects in cross-over studies once as intervention subjects, and once as control subjects. The revised participant numbers in Table 3 were derived by FSANZ counting cross-over study participants only once, as well as the removal of the duplicated TOHP1 results (Whelton et al. 1995) from the analysis.

[4] Performance bias can arise if participants and or investigators are not blinded to the intervention

Table 3 *Comparison of the results of the original WHO and revised meta-analyses for effects of increased potassium intake on resting systolic and diastolic blood pressure*

	N Studies (N participants)	Mean Difference (mmHg)	Lower 95% CI	Upper 95% CI	p-value
Resting systolic blood pressure					
WHO report	21 (1892*)	-3.49	-5.15	-1.82	p<0.0001
FSANZ re-analysis of WHO report	20 (708 parallel, 433 cross-over)	-3.54	-5.44	-1.65	p=0.0002
Resting diastolic blood pressure					
WHO report	21 (1857*)	-3.02	-4.86	-1.17	p=0.001
FSANZ re-analysis of WHO report	20 (673 parallel, 433 cross-over)	-3.03	-5.13	-0.92	p=0.005

**Participants in cross-over studies counted twice*

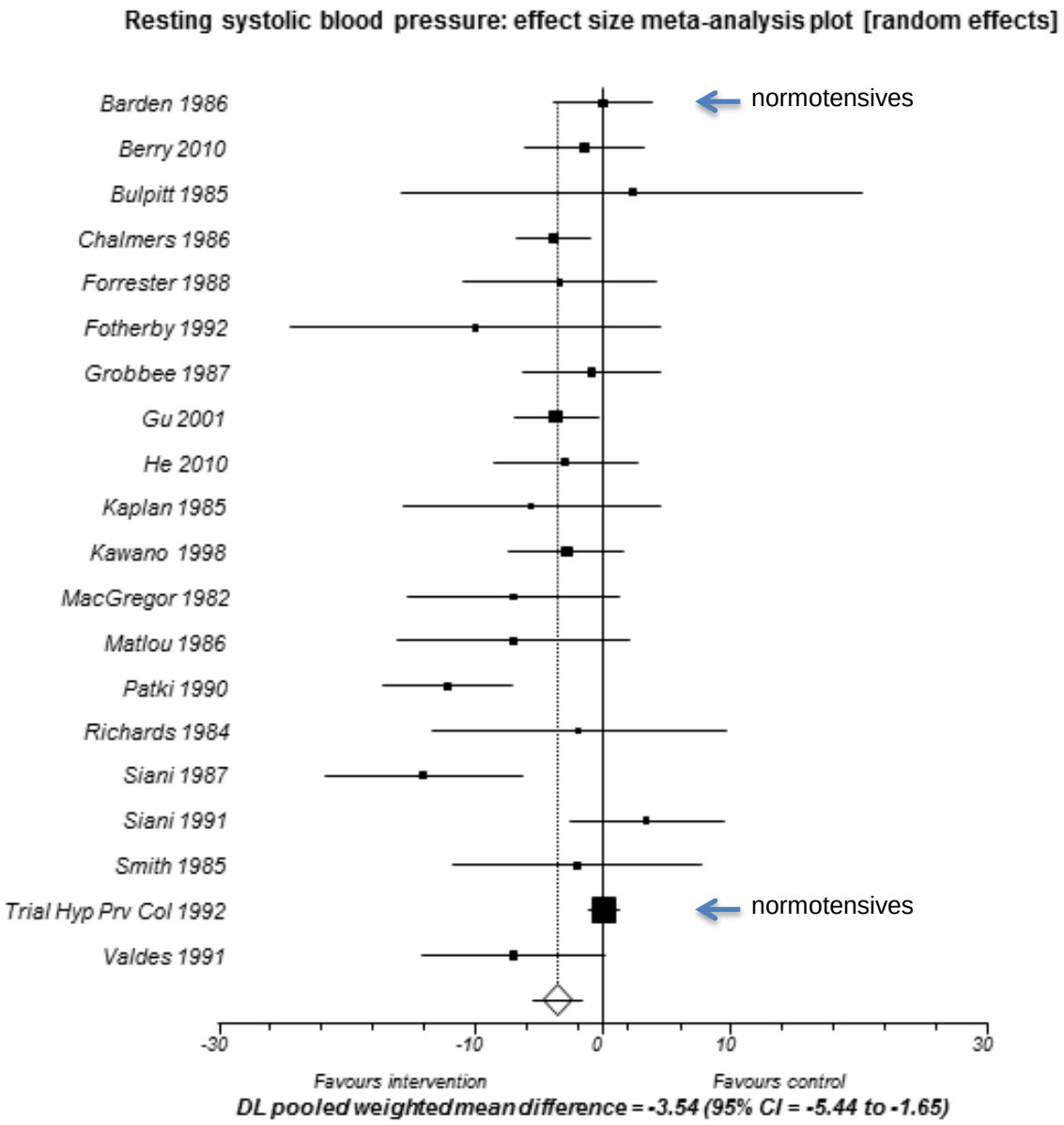

Figure 1 *Re-analysis of WHO meta-analysis. Forest plot for relationship between increased potassium intake and resting systolic blood pressure (all studies, studies in normotensive populations are indicated). Data from two studies have been corrected and a duplicate inclusion of data from one study deleted.*

DL; DerSimonian-Laird method for random effects meta-analysis

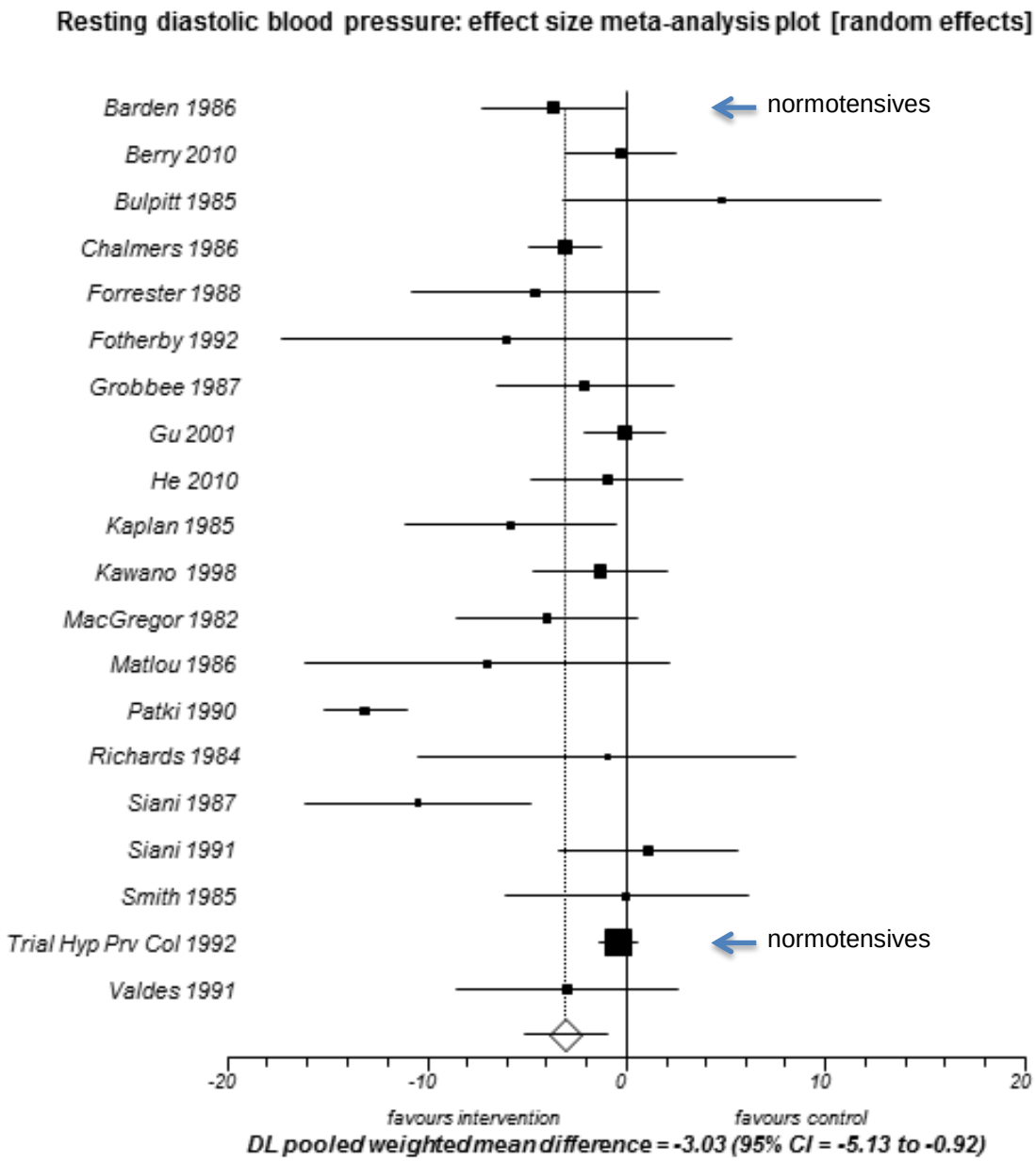

Figure 2 *Re-analysis of WHO meta-analysis. Forest plot for relationship between increased potassium intake and resting diastolic blood pressure (all studies, studies in normotensive populations are indicated). Data from two studies have been corrected and a duplicate inclusion of data from one study deleted.*

Two studies within the FSANZ re-analysis had mean differences in blood pressure that were greater than zero, indicating the intervention increased blood pressure. However, both these studies were in hypertensive subjects on medication. In the study by Siani et al. 1991, the dose of blood pressure medication was reduced during the trial in both groups. At the completion of the study, participants with increased potassium intake required significantly less hypertensive medication than the control group. Therefore, the apparently higher blood pressure in the intervention group may be in part due to the difference in medication levels (Siani et al. 1991). In the Bulpitt 1985 study, subjects were on a potassium losing diuretic (Bulpitt et al. 1985). The effects of increased potassium intake in these subjects may be limited by the action of this medication. Removal of these two studies from the meta-analysis strengthened the relationship between potassium intake and resting systolic blood pressure, resulting in a mean difference of -3.99 mm Hg ([-5.95, -2.03] p<0.0001).

Subgroup analyses

Blood pressure status was also used in subgroup analyses, with studies separated by normotensive, hypertensive or mixed populations. The greatest effect was seen in hypertensive populations (see Table 2). Only two trials were performed in normotensive subjects, and blood pressure was not affected by increased potassium intake. It should be noted the TOHP1 subjects were selected to have high-normal diastolic blood pressure (80-89 mm Hg). Two studies were performed in populations with mixed blood pressure status. Analysis of these trials found increased potassium intake decreased systolic, but not diastolic, blood pressure. There was a significant sub-group effect of baseline blood pressure status on systolic blood pressure (p=0.0005)[5].

The WHO performed subgroup analyses with studies stratified into four groups by the potassium intake achieved by the intervention. The groups were defined according to 24 hour potassium urinary excretion and the corresponding dietary intake was calculated (see Table 2). The cut-offs for the potassium intake levels were in part based on a joint WHO/FAO consultation (70 mmol/day, (World Health Organisation 2003)) and an IOM report (120 mmol/day (Institute of Medicine 2005)). For ease of reading, the dietary intakes will be referred to when describing these analyses.[6] In all four strata of increased potassium intake, there was a reduction in blood pressure but there was not a consistent dose-response in effect across the strata. The greatest effect on systolic blood pressure was achieved with potassium intakes of 91-117 mmol/day (-7.16 mm Hg [95%CI: -12.41, -1.91]). The smallest effect occurred in the studies achieving a potassium intake of 117-156[6] mmol/day (-1.71 mm Hg [95% CI: -3.42, -0.00]. However, this subgroup included the duplicated results from the TOHP1, as well as the Bulpitt study in which participants were on a potassium-losing diuretic and both studies in normotensives. Removal of the trials in normotensives and the Bulpitt trial from the analysis alters the pooled effect to -4.11 mm Hg [-6.31, -1.90]. Consequently, it can be concluded that the mean reduction in blood pressure ranged from -3 to -7 mm Hg in hypertensive populations across the intake strata available. This might indicate that all studies used intakes greater than the lowest amount needed to achieve the maximal effect and that more studies testing lower intakes are needed to determine the exact shape of the dose-response relationship.

Subgroup analyses were also performed stratifying studies by baseline sodium intake. Only one trial included subjects with sodium intake <2 g per day, and it showed a small non-significant decrease in systolic blood pressure. Increased potassium intake decreased systolic blood pressure by an average of 1.97 mm Hg in subjects with a baseline sodium

[5] The statistical analysis for the subgroup difference was performed using Review Manager version 5.2, the systematic review software developed by The Cochrane Collaboration. FSANZ acknowledges The Cochrane Collaboration's generosity in making this software available to FSANZ.
[6] Dietary intakes were converted from urinary potassium excretion by multiplying the value by 1.3.

intake of 2-4 g/day. A larger effect was seen in trials where baseline sodium intake was greater than 4 g per day, with an average decrease in systolic blood pressure of 6.91 mm Hg.

In summary, although a number of sub-group analyses were examined, these were done one at a time. The difference in effect in the two trials that included only normotensive subjects means that there will be uneven distribution of baseline blood pressure status across strata of other factors, for example potassium and sodium intake. This makes it difficult to directly compare effects between the subgroups. Furthermore, the populations differ in characteristics other than potassium intake. It may be possible to overcome this limitation by a multivariate meta-regression, but this was not performed.

Ambulatory blood pressure

The direction of effect was the same for ambulatory systolic and diastolic blood pressures although the effect size was smaller and there were few studies (Table 2). All four studies reporting ambulatory blood pressure outcomes were conducted in hypertensive (three trials) or mixed (one trial) populations.

2.3.4 Data interpretation

Only the main results and the sub-analyses by achieved intake of potassium were given a GRADE rating. As shown in Table 2, the reported GRADE ratings for the overall resting systolic and diastolic blood pressure relationships are not consistent across the three documents describing the WHO review. They are rated as 'Moderate' in the WHO systematic review (World Health Organisation 2012a) and 'High' in the guideline report and paper (World Health Organisation 2012b; Aburto et al. 2013). Communication with the WHO clarified that evidence for each outcome was given a preliminary GRADE rating by the systematic review authors (World Health Organisation 2012a). As a part of the WHO guideline development process, the WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and Health subsequently adjusted the GRADE rating based on further review of the evidence, in this case grading up from 'Moderate' to 'High' (J Montez, personal communication 2013).

Although all included studies were RCTs, the review authors had proposed that the relationship be down-graded to 'Moderate' due to inconsistency, in that the confidence intervals of some studies did not overlap the pooled effect 95% confidence interval. In the reanalysed meta-analysis of systolic blood pressure (Figure 1), the same result occurs. Both the Patki 1990 and Siani 1987 studies have confidence intervals below the pooled effect, while the TOHP1 study also does not overlap the pooled effect, but lies above it (Patki et al. 1990; Siani et al. 1991; Trial Hyp Prv Col 1992). For diastolic blood pressure, only Patki 1990 does not overlap the pooled effect confidence intervals (Figure 2). The 'High' GRADE rating indicates that WHO's advisory group did not consider the inconsistency of some studies (only three of 20 studies did not overlap with the pooled effect and that the results of two of these studies were in the same direction as the pooled effect) to be sufficient to warrant down-grading of the evidence as had been proposed by the review authors.

The subgroup analysis indicated that the effects of increased potassium intake on blood pressure are greater in subjects that are hypertensive and /or have a higher sodium intake, but the WHO did not rate the evidence in individual population groups. However, this is a relevant consideration for assessing the applicability of the relationship to underpin a health claim on food labels. FSANZ needs to examine the evidence in the normotensive and hypertensive population subgroups. FSANZ considered the re-analysed evidence to show a 'High' degree of certainty in the relationship between increased potassium intake and reduced blood pressure in hypertensive populations. However, in normotensive populations,

there was only a ‘Moderate’ degree of certainty and the effect estimate indicated no change in blood pressure with increased potassium intake. Therefore, when rating the evidence, FSANZ regards the significant difference in the effect between normotensive and hypertensive people to be an important factor and has down-rated the certainty in the relationship for all studies (in hypertensive and normotensive participants combined).

The WHO also investigated different levels of potassium intake, and from this developed a guideline recommending potassium intake of at least 90 mmol/day, equivalent to 3510 mg/day (World Health Organisation 2012b). However, the sub-group analysis demonstrates potassium intakes lower than this cut-point also have a beneficial effect on blood pressure. These data, together with the known physiological functions of potassium, indicate that increased intake of potassium reduces blood pressure, at least in hypertensive populations.

2.4 Consideration of validity and strength of evidence

Some inconsistencies and errors were noted in the WHO systematic review, and have been listed in Section 2.3.3. However, these errors did not impact on the outcome of meta-analyses, as demonstrated in Table 3. As such, the results of the WHO reviews are valid.

The strength of evidence supporting a relationship that increased potassium intake reduces systolic and diastolic resting blood pressure was rated as ‘High’ by the WHO following advice from their Advisory Group (World Health Organisation 2012b; Aburto et al. 2013). Based on this relationship, the WHO recommended a daily potassium intake of at least 90 mmol/day for adults (equivalent to 3510 mg/day) (World Health Organisation 2012b). However, as discussed, there was a significant effect for potassium intakes of less than 90 mmol/day on resting systolic blood pressure in hypertensive populations. Based on this evidence, FSANZ concludes that the beneficial effect of increased potassium intake on blood pressure in hypertensive people is not restricted to intakes of greater than 90 mmol/day. FSANZ notes that the two studies with normotensive populations did not show a benefit. FSANZ rated the degree of certainty in the evidence as ‘High’ for potassium intake reducing blood pressure in hypertensive populations. In normotensive populations, the evidence provided a ‘Moderate’ degree of certainty that increased potassium intake had no effect on blood pressure.

3 Evaluation of new evidence

In this section the WHO review is updated to determine whether any new studies meeting the criteria may have altered the conclusions drawn by the WHO.

3.1 Methods

3.1.1 Search strategy

Searches to update the WHO review were performed in June 2013. Search terms from the WHO systematic reviews were used, but those for EMBASE were modified to correct some numbering inconsistencies within the WHO report. Detailed search strategies are presented in Appendix 1.

3.1.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria used by WHO were applied (section 2.1).

3.1.3 Databases searched

Searches were conducted in EMBASE, PubMed, The Cochrane Library and LILACS. Date restrictions were applied to only retrieve articles published in 2011 or later, in order to update the WHO searches. EMBASE accesses the Medline database, but it is not updated as frequently as PubMed. Therefore, the PubMed search was performed with the date restricted from 1/12/12, as publications from 2011 and 2012 would be identified by the EMBASE search.

3.1.4 Unpublished material

The WHO International Clinical Trials Registry Platform and PROSPERO were searched for trials or reviews which could have been completed during 2013 (see Appendix 1). Searches of EMBASE included conference abstracts that were considered for relevance.

3.1.5 Study selection, data extraction and statistical analyses

Records identified during the search process were imported in EPPIreviewer 4 (http://eppi.ioe.ac.uk/cms/er4). Following removal of duplicates, records were screened on title and abstract. Candidate full-text articles were retrieved and assessed against the selection criteria. Screening was conducted by one investigator.

StatsDirect statistical software (England: StatsDirect Ltd. 2008) was used to update meta-analyses with data from studies identified by the literature search.

3.2 Results

3.2.1 Search results

Repeating the WHO search strategies generated 173 records. The screening of these results is detailed in Figure 3, with search details in Appendix 1. Twelve records were screened on full text, with only one study meeting the selection criteria. Hand-searching of reference lists of records screened on full-text did not yield any additional records for inclusion. No upcoming trials or reviews were identified that were expected to be completed during 2013. Conference abstracts identified through the EMBASE searches did not yield any reports of research relevant to this review.

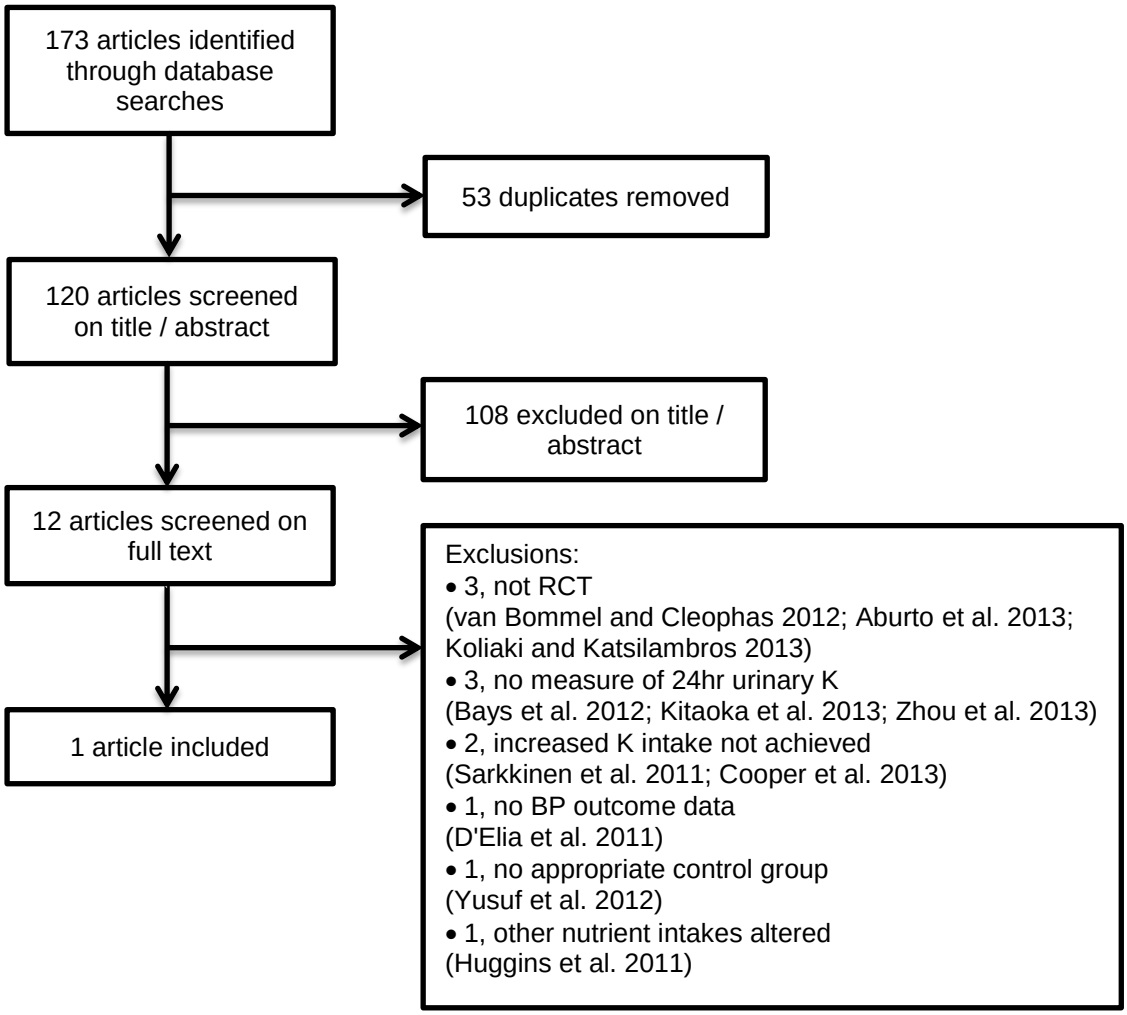

Figure 3 *PRISMA diagram for selection of studies*

3.2.2 Included studies

One study was identified for inclusion in the update of the WHO systematic review. The details of the included study are provided in Table 4, with the assessment of bias in Table 5.

The identified study tested the effects of supplementation with 100 mmol/day potassium as potassium chloride in a randomised, placebo-controlled cross-over trial (Matthesen et al. 2012). The study was conducted in Denmark and used healthy volunteers. Twenty four-hour ambulatory blood pressure was measured after a 4 week intervention, and following 4 days of a controlled diet with standardised energy, sodium and water content. Additional information was provided by Dr Solveig Klok Matthesen regarding the blinding of participants and outcome assessors (personal communication, 2013).

3.2.3 Extracted data

Data were extracted using the template in the WHO review and are summarised in Table 5.

Table 4 *Matthesen et al. (2012) study details*

Reference	Matthesen et al. 2012
Study design	Randomised, placebo-controlled cross-over trial
Objectives	Determine the effects of daily supplementation with 100 mmol potassium on renal tubular function and blood pressure in healthy participants
Sample size	29 participants randomised, 8 excluded from analysis (5 unwilling to continue, 2 no intravenous access, 1 lack of compliance) Final n = 21 (20-22 required by power calculation for effect on aquaporin2)
Participants	Healthy volunteers, all normotensive. 43% male, mean age 26 (range 18-40 years), Body mass index of 18.5–30 kg/m^2
Interventions	Participants were randomly allocated to receive 100 mmol K per day as 2x 50 mmol doses, or placebo, for 28 days. Following the first intervention period, participants underwent a 2-week wash-out, followed by the alternate intervention.
Methods	Intervention: Potassium intake measured by 24-hour urinary potassium excretion Outcome: Ambulatory blood pressure measured every 15 or 30 minutes during the day / night
Confounders	Diet standardised for energy, sodium and water content provided for 4 days at end of intervention periods prior to biochemical and physiological measurements
Results	24-hour urinary potassium: intervention, 168±37 vs. placebo 76±20 mmol/24 hours Ambulatory blood pressure: placebo, 116±8 / 69±7 vs. intervention, 116±8 / 70±6 mm Hg
Notes (including adverse effects)	Potassium supplementation increased aldosterone and arterial stiffness

3.2.4 Quality assessment of individual studies

The Matthesen et al. 2012 study sought to test the hypothesis that potassium supplementation would reduce blood pressure through changes in renal tubular function. As a cross-over randomised placebo-controlled trial the effect of confounders was minimised. Similarly, the risk of selection bias, attrition bias and reporting bias were low. However, as neither participants nor outcome assessors were blinded there was a high risk of performance bias (see Table 5). The duration of the study was adequate to detect an effect, and the wash-out period between intervention arms was suitable. Power calculations were performed, but for an outcome other than blood pressure.

Table 5 *Risk of bias in Matthesen et al. (2012) study*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear	Limited impact due to cross-over design
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding
Incomplete outcome data (attrition bias)	Low	28% subjects did not complete trial, but due to cross-over design this affected both groups to the same extent
Selective reporting (reporting bias)	Low	All outcomes reported

3.2.5 Outcome data

The effects of including the Matthesen et al. 2012 study in the meta-analyses for ambulatory blood pressure were calculated.

In the WHO review, four studies measured ambulatory blood pressure, three of which were in hypertensive populations and the fourth in a mixed population. The evidence for the relationship between increased potassium intake and **ambulatory** systolic blood pressure was rated as 'Moderate' in the WHO review. This was rated down from 'High' due to imprecision, as the 95% CI was near zero. Inclusion of the Matthesen et al. 2012 study supports this rating as the upper confidence interval remains close to zero (see Tables 6 and 7 and Figures 4 and 5). However, the WHO recommendations are based on **resting** blood pressure. This was not measured in the current study, and therefore this study does not alter the conclusions made by the WHO in relation to potassium intake and blood pressure.

Table 6 *Updated meta-analysis of ambulatory systolic blood pressure*

Study	N (exptl.)	N (ctrl.)	Mean difference (mmHg)	Approximate 95% CI	
Berry 2010	48	48	-1.8	-7.02	3.42
Fotherby 1992	16	16	-6	-17.48	5.48
He 2010	42	42	-3	-7.07	1.07
Kawano 1998	55	55	-3.4	-7.15	0.35
Matthesen 2012	21	21	0	-4.84	4.84
Overall (WHO review)	***p=0.01***		***-3.04***	***-5.42***	***-0.66***
Overall (updated)	***p=0.025***		***-2.45***	***-4.59***	***-0.31***

Table 7 *Updated meta-analysis of ambulatory diastolic blood pressure*

Study	N (exptl.)	N (ctrl.)	Mean difference (mmHg)	Approximate 95% CI	
Berry 2010	48	48	-1.4	-5.14	2.34
Fotherby 1992	16	16	-2	-10.67	6.67
He 2010	42	42	-1	-4.64	2.64
Kawano 1998	55	55	-1.2	-4.11	1.71
Matthesen 2012	21	21	1	-2.94	4.94
Overall (WHO review)	***p=0.20***		***-1.24***	***-3.13***	***0.66***
Overall (updated)	***p=0.35***		***-0.82***	***-2.54***	***0.89***

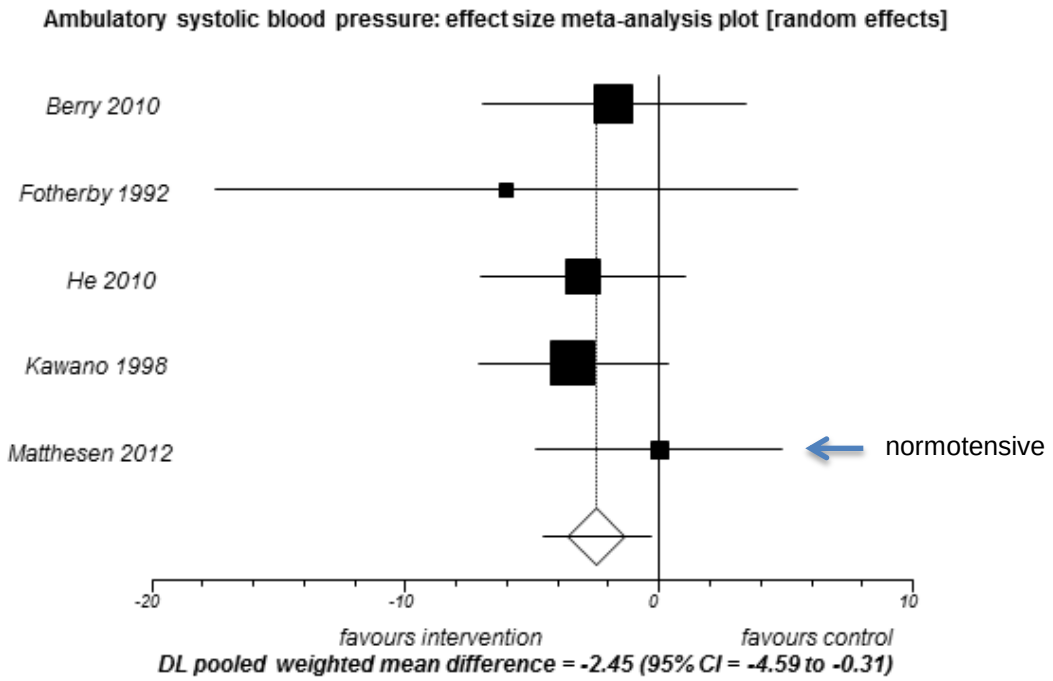

Figure 4 *Updated meta-analysis of effect of increased potassium intake on ambulatory systolic blood pressure*

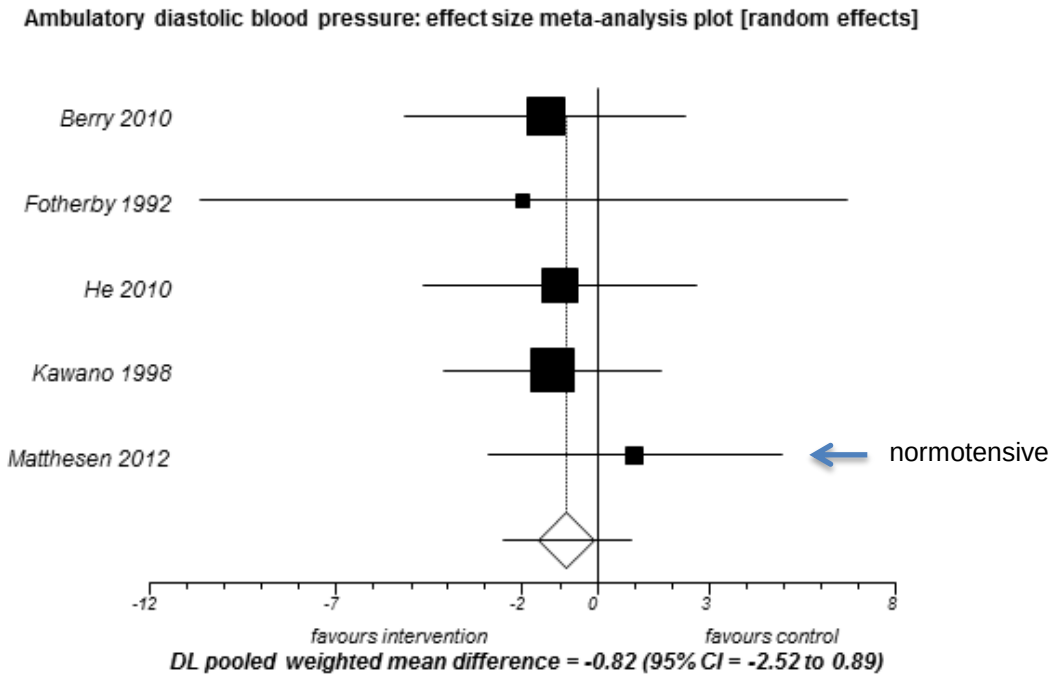

Figure 5 *Updated meta-analysis of effect of increased potassium intake on ambulatory diastolic blood pressure*

3.3 Summary of new evidence

From 173 records identified through the search strategy only one met the inclusion criteria. This study measured the effects of potassium supplementation on ambulatory blood pressure in normotensive subjects, but found no effect of increased potassium intake. As participants and outcome assessors were not blinded the study was at high risk of bias. The results of the trial did not significantly alter the results of the meta-analyses performed within the WHO review. Taken together with the high risk of bias, the results of this study do not alter the conclusions made by the WHO on the relationship between potassium intake and ambulatory blood pressure, with the quality of evidence rating remaining at 'Moderate'. Additionally, as no measures of resting blood pressure were reported in this trial, the results do not affect the WHO's conclusions on the relationship between potassium and resting blood pressure overall. This study was conducted in normotensives and so is consistent with the difference of effect observed between hypertensive and normotensive populations found in the studies measuring resting blood pressure.

4 Weight of evidence

4.1 Assessment of body of evidence

4.1.1 Consistency and Causality

The WHO systematic review, and earlier systematic reviews, included only RCTs which are a strong study design for detecting causal relationships. As such, the results of the WHO meta-analysis demonstrate a causal relationship between increased potassium intake and decreased blood pressure. In the WHO meta-analysis one study was considered to be of 'low' quality (high risk of bias). The effect estimate was similar following removal of this study from the meta-analysis. These analyses demonstrate a consistent effect of increased potassium intake on blood pressure across high quality studies.

In addition to the WHO systematic review, three earlier meta-analyses found the same relationship overall. The results of a fourth meta-analysis, which was restricted to hypertensive subjects and durations of ≥8 weeks, had a large favourable effect although it was not significant (Dickinson et al. 2006). Therefore its results are consistent with the other meta-analyses. Together these reviews have shown consistent evidence for a causal relationship between potassium and blood pressure over time despite ongoing inclusion of additional relevant studies and differences in eligibility criteria between reviews such as minimum study duration.

4.1.2 Plausibility

Evidence from RCTs demonstrated a causal relationship between potassium intake and blood pressure. This direct evidence is also indicative of plausibility. Furthermore, observational studies have shown an inverse correlation between potassium intake and blood pressure (Intersalt Cooperative Research Group 1988; Ascherio et al. 1996; Geleijnse et al. 1996).

In addition to clinical data, laboratory studies have demonstrated that there are multiple modes of action by which potassium can modulate blood pressure, including:

- enhanced natriuresis
- increased urinary volume
- modulation of renin-angiotensin system
- stimulating vasodilation (reviewed in (Haddy et al. 2006)).

Therefore, it is biologically plausible that increased potassium intake can reduce blood pressure.

4.2 Applicability to Australia and New Zealand

4.2.1 Potassium intake required for effect

The mean potassium intakes of Australians aged 14 years or more from the 2011-12 Australian Health Survey were (Australian Bureau of Statistics 2014):

- Males: 2,830–3,306 mg/day (73–85 mmol/day)
- Females: 2,466–2,700 mg/day in (63–69 mmol/day)

The mean potassium intakes of New Zealanders aged 15 year of over from the 2008/09 New Zealand Adult Nutrition Survey (University of Otago and Ministry of Health 2011) were:

- Males: 3,176–3,785 mg/day (81–97 mmol/day)
- Females: 2,306–2,933 mg/day in (59–75 mmol/day)

Given the current potassium intakes, the amount required to achieve a beneficial effect is reasonable for Australian and New Zealand hypertensive populations. Example of potassium contents in foods are[7]:

- 1 banana; 11 mmol (440 mg)
- 1 medium cooked potato; 16 mmol (610 mg)
- ½ cup broccoli; 6 mmol (229 mg)
- 1 serve beef steak; 17 mmol (550 mg)
- 1 serve fish (hoki) fillet; 10 mmol (400 mg)
- 2 slices wholegrain bread; 5 mmol (188 mg)

These values indicate that by increasing intake of fruits, vegetables, wholegrain foods, meat or fish it would be possible to increase potassium intakes by an amount required for the health effect observed in hypertensive subjects.

4.2.2 Target population

The food-health relationship has been assessed in adults, with sub-analyses conducted on blood pressure status. In analyses of all adults, combining both hypertensive and normotensive populations, increased potassium intake significantly reduced blood pressure. When stratified for blood pressure status, however, increased potassium intake:

- significantly decreased blood pressure in hypertensive subjects,
- did not affect blood pressure in normotensive subjects (and blood pressure remained in the normal range).

In the WHO meta-analysis there were studies from Australia, New Zealand, Asia, Europe and the Americas. As such, the results from these studies are directly applicable to Australian and New Zealand adult populations.

In addition, the WHO prepared an additional systematic review assessing the relationship between potassium intake and blood pressure in children. Four studies were identified, and due to bias the quality of evidence for the relationship was rated as low.

[7] Based on data from The Concise New Zealand Food Composition Tables, 9th Edition 2012

4.2.3 Extrapolation from supplements

In the WHO review, sub-analyses were performed to assess the effect of method by which increased potassium intake was achieved. Twenty studies used a supplement to achieve increased potassium intake, while three studies used dietary interventions (one study used both). The majority of the supplement trials used potassium chloride, with one using a mix of potassium chloride and potassium bicarbonate (He et al. 2010), and another trial using potassium citrate supplementation (Berry et al. 2010).

Trials involving potassium supplementation or dietary advice both achieved significant reductions of a similar magnitude in resting systolic blood pressure (see Table 2). It is therefore reasonable to extrapolate data from supplementation studies to support a relationship between increased dietary potassium intake and reduced blood pressure (in hypertensive people). Furthermore, there is direct evidence from dietary interventions supporting this food-health relationship.

The trials which gave supplemental potassium were conducted in generally healthy populations under medical supervision. It should be noted that in this critical appraisal and update of the review a safety assessment has not been performed on the use of supplemental potassium.

4.2.4 Adverse effects

Adverse effects of increased potassium intake were also considered in the WHO review of the relationship between potassium and blood pressure. The review concluded that there were no adverse effects of increased potassium intake on blood cholesterol or triglyceride levels, renal function or catecholamine levels. However, there is a risk of potassium accumulation in individuals with impaired renal function. Elevated serum potassium (hyperkalaemia) can impair cardiac conduction which can result in ventricular fibrillation or asystole that may ultimately be fatal. As the two trials with the longest duration were conducted for only 6 and 12 months, mortality and other disease outcomes could not be examined.

5 Conclusion

The results of the WHO meta-analysis concluded that increased potassium intake compared with lower intake decreases resting systolic and diastolic blood pressure in adults. However, this result is driven by studies in hypertensive populations, and the effect was not evident in the two trials of normotensive populations. The searches to update this review identified one study in which the effects of potassium intake on ambulatory blood pressure in normotensive subjects were investigated. This new evidence was consistent with other studies in the WHO review. It can therefore be concluded that there is sufficient high quality scientific evidence to substantiate the food-health relationship that increased potassium intake reduces blood pressure only in hypertensive people.

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Appendix 1 – Search terms

PubMed

Search performed 13/6/13, 29 results (search dates restricted to 1/12/2012 to 13/6/13)

(("blood pressure"[MeSH Terms] OR "blood pressure determination"[MeSH Terms] OR "arterial pressure"[MeSH Terms]) OR "hypertension"[MeSH Terms] OR blood pressure[tiab] OR hypertension[tiab]) AND (("potassium, dietary"[MeSH Terms] OR "potassium"[MeSH Terms]) OR "potassium chloride"[MeSH Terms] OR potassium[tiab] OR potassium chloride[tiab]) AND ("diet"[MeSH Terms] OR "diet"[MeSH Terms] OR diet[tiab] OR dietary[tiab] OR intake[tiab] OR restriction[tiab] OR reduction[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) AND ("2012/12/01"[PDAT] : "3000/12/31"[PDAT])

EMBASE

Note: Search terms adjusted to enable search to be performed.
Restricted search (20/6/13, 36 results):

ID Search
1 potassium/ or potassium chloride/ 107639
2 exp hypertension/ or exp blood pressure/ 690680
3 exp dietary intake/ or exp diet/ or restrict$.ab,ti. or reduction.ab,ti. or intake.ab,ti. or diet.ab,ti. or dietary.ab,ti. 1735003
4 1 and 2 and 3 3021
5 limit 4 to (randomized controlled trial or controlled clinical trial) 315
6 limit 4 to cochrane library 5
7 limit 4 to (meta analysis or systematic review) 54
8 5 or 6 or 7 367
9 limit 8 to (yr="2011 - 2013") 36

Broad search (20/6/13, 76 results)

ID Search
1 potassium/ or potassium chloride/ or potassium.ab,ti. 183825
2 exp hypertension/ or exp blood pressure/ or hypertension.ab,ti. or blood pressure,ab.ti. or hypertensive.ab,ti. or intravascular pressure.ab,ti. or normotension.ab,ti. or vascular pressure.ab,ti. or exp blood pressure monitoring/ 798580
3 exp dietary intake/ or exp diet/ or restrict$.ab,ti. or reduce$.ab,ti. or reduction.ab,ti. or intake.ab,ti. or diet.ab,ti. or dietary.ab,ti. 3007805
4 1 and 2 and 3 7212
5 limit 4 to cochrane library 9
6 limit 4 to (randomized controlled trial or controlled clinical trial) 675
7 limit 4 to (meta analysis or systematic review) 86
8 5 or 6 or 7 755
9 limit 8 to (yr="2011 - 2013") 76

LILACS

Search performed 13/6/13, 8 results (restricted to 2011, no papers identified for 2012 and 2013)

(potassium AND blood pressure) OR (potassium AND hypertension)

Cochrane CENTRAL

Search performed 17/6/13, 24 results
Search Name: potassium and blood pressure WHO strategy
ID Search
#1 MeSH descriptor: [Blood Pressure] explode all trees
#2 MeSH descriptor: [Hypertension] explode all trees
#3 MeSH descriptor: [Potassium] explode all trees
#4 MeSH descriptor: [Potassium Chloride] explode all trees
#5 MeSH descriptor: [Diet] explode all trees
#6 #1 or #2 or (blood and pressure) or hypertension
#7 #3 or #4 or potassium or (potassium and chloride)
#8 #5 or diet or dietary or intake or restriction or reduction
#9 (randomized and controlled and trial) or (controlled and clinical and trial) or randomized or placebo or (drug and therapy) or randomly or trial or groups
#10 #6 and #7 and #8 and #9 from 2011 to 2013, in Trials

WHO International Clinical Trials Registry Platform

Search performed 23/10/13, no relevant trials identified as registered since the WHO search sate of September 2011.
Search terms: (potassium AND blood pressure) OR (potassium AND hypertension)

PROSPERO

Search performed 17/6/13, no relevant upcoming reviews identified.
Search term: “potassium”

Appendix 2 – GRADE summary of findings table

GRADE summary of findings table of FSANZ's updated systematic review (adapted from WHO systematic review)
Question: What is the effect of increased potassium intake relative to lower potassium intake on blood pressure in adults (≥16 years of age)?

Quality Assessment of body of evidence							Participants		Effect	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Considerations**	**Parallel studies**	**Cross-over studies**	**Mean difference mmHg (95% CI)**	**Quality (degree of certainty in relationship)**
Resting systolic blood pressure – all included studies										
20	RCTs	No serious risk	No serious inconsistency[1]	Some[2]	None	None	708	433	-3.54 (-5.44, -1.65)	⊕⊕⊕ Moderate[2]
Resting systolic blood pressure – studies in normotensive participants										
2	RCTs	No serious risk	None	None	Serious[3]	Small number of studies	353	43	0.05* (-1.11, 1.22)	⊕⊕⊕ Moderate[4]
Resting systolic blood pressure – studies in hypertensive participants										
16	RCTs	No serious risk	No serious inconsistency[1]	None	None	None	355	390	-4.68* (-6.97, -2.40)	⊕⊕⊕⊕ High
Resting diastolic blood pressure – all included studies										
20	RCTs	No serious risk	No serious inconsistency[1]	Some[2]	None	None	673	433	-3.03 (-5.13, -0.92)	⊕⊕⊕ Moderate[2]
Resting diastolic blood pressure – studies in normotensive participants										
2	RCTs	No serious risk	None	None	Serious[3]	Small number of studies	318	43	-1.55 (-4.58, 1.48)	⊕⊕⊕ Moderate
Resting diastolic blood pressure – studies in hypertensive participants										
16	RCTs	No serious risk	No serious inconsistency[1]	None	None	None	355	390	-3.65 (-6.42, -0.88)	⊕⊕⊕⊕ High

[1]95%CI for majority of studies overlap, therefore inconsistency was not considered to be serious
[2]FSANZ judged that the quality of evidence for all studies combined should be down-rated based on extrapolation from hypertensive to normotensive populations, as the evidence indicates no effect in normotensive populations.
[3]95% CI crosses zero
[4]Note that the 'Moderate' quality of evidence supports no effect of increased potassium on systolic blood pressure in the two trials of normotensive participants
**p=0.005 for sub-group difference*