Annex to:

EFSA NDA Panel, 2019. Scientific Opinion on Dietary Reference Values for sodium (EFSA-Q-2011-01224). EFSA Journal 2019;17(8):5778, 210 pp. doi: 10.2903/j.efsa.2019.5778

Annex A - Protocol for sections 5.5 and 6 of the scientific opinion on DRVs for sodium: Assessment of the relationship between sodium intake and pre-specified health outcomes, including dose–response relationships, and integration of different lines of evidence for setting DRVs for sodium

AMENDED VERSION N°1[1]

European Food Safety Authority (EFSA)

[1] The amendments are highlighted throughout the text for easier reference.

Table of Contents

1. Introduction and scope of this document

1.1. Introduction

As part of a series of scientific opinions on dietary references values (DRVs) for micronutrients for the European population,[2] the NDA Panel is reviewing the scientific evidence to set DRVs for sodium.

DRVs are typically developed through a stepwise approach which encompasses: 1) collection of relevant background information on the nutrient of interest, which is used to inform steps 2 and 3; 2) identification of the criteria (endpoints) on which to base DRVs; and 3) synthesis and integration of the available evidence and derivation of DRVs (if possible). Scientific opinions on DRVs are structured accordingly, as follows:

Sections 1-4 provide background information on DRVs for the nutrient set previously by the Scientific Committee for Food (SCF, 1993); the chemistry, function, physiology and metabolism of the nutrient, as well as its interactions with other nutrients, and biomarkers of intake/status; the dietary sources and intake data; and an overview of DRVs and recommendations set by other bodies.

Section 5 depicts possible criteria on which to base DRVs. Specificities of different life stages (e.g. childhood, pregnancy, lactation) are considered. In this section, the NDA Panel assesses the suitability of each criterion to set DRVs for the nutrient on the basis of: i) the quality of the available evidence, ii) the related uncertainties, and iii) the possibility of deriving quantitative estimates.

Section 6 outlines the criterion, or combination of criteria, that is considered by the NDA Panel as the most appropriate for setting DRVs, and provides DRVs for the nutrient (where possible). To that end, the Panel considers the quantitative relationship(s) between the nutrient intake and the selected criterion(a) together with the related uncertainties, and integrates the different lines of evidence, where applicable.

1.2. Scope of this document

To promote quality in its scientific processes and contribute to realising the strategic objectives related to evidence and methods for scientific assessments,[3] EFSA has implemented the PROMETHEUS project (PROmoting METhods for Evidence Use in Scientific assessments[4]). Through this initiative, the Authority defined a set of principles for 'evidence use' (based on its core values), a 4-step approach to fulfil those principles (EFSA, 2015), and carried out an analysis of its 'methodological needs' for evidence use (e.g. methods, tools, procedures, processes) (EFSA, 2016).

The PROMETHEUS 4-step approach consists of: 1) planning upfront (i.e. before initiating any formal data collection, appraisal or synthesis) the strategy for the assessment and detailing it in a protocol. This includes tailoring the methodology for the assessment, to address the trade-off between applying extensive/complex approaches and responsiveness; 2) carrying out the assessment in line with the predefined strategy; 3) verifying compliance with the plan; and 4) thoroughly documenting and reporting the process, results and conclusions, and ensuring accessibility of methods and data. A key point is the recording of any deviations from the planned strategy.

At the time the scientific opinion on DRVs for sodium was selected as a case study for PROMETHEUS, the NDA Panel had already carried out substantial work in relation to Sections 1 to 4 of the scientific opinion, as well as to the parts of Section 5 which refer to biomarkers as indicators of sodium requirement (Section 5.1), balance studies (Section 5.2), and indicators of sodium requirement in

[2] http://www.efsa.europa.eu/en/topics/topic/dietary-reference-values-and-dietary-guidelines
[3] http://www.efsa.europa.eu/en/corporate/pub/strategy2020
[4] http://www.efsa.europa.eu/en/methodology/evidence

children (Section 5.3) and pregnant and lactating women (Section 5.4). Therefore, the protocol presented in this document only applies to the remaining sections of the scientific opinion, namely: i) the assessment of possible relationships between sodium intake and health outcomes, including dose-response relationship(s), where applicable (Section 5.5), and ii) the integration of different lines of evidence for setting DRVs (Section 6).

2. Problem formulation

2.1. Objectives

The objective of Section 5.5 of the scientific opinion is to evaluate possible relationships between sodium intake and selected health-related outcomes in the general population, including a quantitative assessment of the dose–response, where applicable.

The objective of Section 6 of the scientific opinion is to integrate the different lines of evidence and derive DRVs for sodium (if possible).

2.2. Target population

In accordance with the Scientific Opinion on principles for deriving and applying DRVs (EFSA NDA Panel, 2010), DRVs for sodium will be set for the general healthy population.

No DRVs will be set for infants < 6 months, given that requirements for this age group can be covered by the amounts of nutrients provided by breast milk.

DRVs will be set for healthy individuals aged ≥ 6 months. Variations according to life stage, sex groups and genetic polymorphisms will be considered. The choice of life stage groups is based upon differences in requirements related to the velocity of growth, change in endocrine status (such as in puberty), and age-related changes in nutrient absorption and body functions and/or functional capacity, such as renal function.

The following life stages can be defined arbitrarily (SCF, 1993; EFSA NDA Panel, 2010):

- Infants ≥ 6 to < 12 months
- Young children ≥ 1 to < 4 years
- Children ≥ 4 years to < 7 years
- Children ≥ 7 years to < 11 years
- Children ≥ 11 years to < 15 years
- Children ≥ 15 years to < 18 years
- Adults ≥ 18 to < 75 years
- Older adults ≥ 75 years
- Pregnant women
- Lactating women (assuming exclusive breast feeding)

The life stage/age ranges may be modified by the Panel when setting DRVs for sodium, depending on the available data.

Specific DRVs will not be set for subgroups of the population on the basis of, for example, ethnicity, dietary habits (e.g. vegetarians, vegans), level of physical activity (e.g. endurance athletes), disease

conditions (e.g. hypertensive subjects), nutritional status,[5] or environmental conditions (e.g. hot temperatures).

2.3. Sources of intake

The assessment will include sodium from all dietary sources, including foods, beverages and food supplements. Sodium chloride (NaCl, table salt) is used as an ingredient and for technological purposes. It is the main source of sodium in the diet. One gram of sodium chloride consists of 17 mmol of sodium and chloride, and provides 0.4 g sodium and 0.6 g chloride. In addition, sodium occurs naturally in foods/beverages and is also present in some food additives (e.g. sodium bicarbonate, sodium glutamate).

2.4. Selection of health outcomes

The effect of sodium intake on health has been extensively investigated and the literature on this topic is considerable. For the purpose of this assessment, the Panel decided to focus on the health outcomes which meet the following criteria, as they may be the most suitable to inform the setting of DRVs for sodium:

- **Type of evidence**, i.e. health outcomes whose relationship with sodium intake has been reported in randomised controlled trials (RCTs) of sufficient duration and/or observational prospective studies.
- **Biological relevance for the general healthy population**, i.e. health outcomes related to the primary prevention of chronic diseases, including established intermediate markers of disease.
- **Biological plausibility**, i.e. health outcomes likely to be specifically affected by changes in sodium intake (i.e. there is a biologically plausible mechanism for a specific effect of sodium intake on the health outcome).

To inform its decisions, the Panel considered recent reports from national and international bodies (WHO, 2012a, 2012d, 2012c, 2012b; IOM, 2013; Nordic Council of Ministers, 2014), a preparatory systematic review which aimed to identify scientific data for this task (Eeuwijk et al., 2013), and recent systematic reviews and meta-analyses on selected health outcomes (see below).

2.4.1. Selected health outcomes

2.4.1.1. Blood pressure

There is evidence for a positive relationship between sodium intake and blood pressure (EFSA, 2005; WHO, 2012b; IOM, 2013; Nordic Council of Ministers, 2014) and, in turn, there is a positive relationship between blood pressure and risk of cardiovascular disease (CVD) in the general population.

Recent systematic reviews and meta-analyses of RCTs lasting for at least four weeks found that reducing sodium intake decreases SBP and DBP in hypertensive adult subjects and decreases SBP in normotensive adult subjects (Graudal et al., 2011b; WHO, 2012c; He et al., 2013; Australia/New Zealand Expert Working Group for Sodium, 2017). Evidence from RCTs in children was limited (WHO, 2012a).

[5] When setting DRVs for a nutrient, the Panel assumes that the requirements for energy and all other nutrients have already been satisfied (EFSA NDA Panel, 2010).

There is large inter-individual heterogeneity in blood pressure responses to dietary sodium. While high salt intake significantly raises blood pressure in some individuals, it has little or no effect in others. In its latest review, IOM found evidence for a relationship between high dietary sodium and elevated blood pressure in at-risk subgroups, particularly individuals with hypertension or pre-hypertension, while it concluded that data among normotensive individuals were inconsistent (IOM, 2013).

The effect of sodium intake on blood pressure has been attributed to its influence on extracellular volume, although the precise mechanisms linking dietary sodium to blood pressure, in particular the pathophysiological mechanisms of "salt sensitivity" and related environmental and genetic determinants are not completely elucidated (Drenjančević-Perić et al., 2011; Hall, 2016; Iatrino et al., 2016; Morris et al., 2016). Factors which have been associated with "salt sensitive" blood pressure include older age, low-renin hypertension, African American ethnicity and obesity (Kotchen et al., 2013; Hall, 2016). Dietary factors, such as potassium intake, may modulate the relationship between sodium intake and blood pressure levels. Depending on the methods used for assessment and the definition applied, approximately 30 to 50% of persons with hypertension and a smaller percentage of persons with normal blood pressure are thought to have "salt sensitive" blood pressure (Kotchen et al., 2013).

2.4.1.2. Cardiovascular disease related endpoints

Because of the positive relationship between sodium intake and blood pressure, a risk factor for CVD, health professional agencies and organisations recommend a reduction in dietary sodium as a means to prevent CVD (SACN, 2003; Health Council of the Netherlands, 2006; Nordic Council of Ministers, 2014; SINU, 2014; HHS/USDA, 2015; Anses, 2016; Strohm et al., 2016; National Health and Medical Research Council, 2017).

Prospective cohort studies and meta-analyses thereof suggest a positive association between sodium intake and CVD, particularly stroke (WHO, 2012d; IOM, 2013; Nordic Council of Ministers, 2014). However, controversies exist on the nature and shape of the relationship between sodium intake and risk of CVD, particularly in relation to the reported adverse effects associated with low sodium intake (IOM, 2013; Oparil, 2014; Mente et al., 2016).

2.4.1.3. Bone health

There is consistent evidence that an increase in sodium intake increases urinary calcium excretion, while a reduction in sodium intake lowers urinary calcium excretion (Afssa, 2001; EFSA, 2005; IOM, 2005a). The increase in urinary calcium excretion with increasing sodium intake may negatively affect bone calcium balance, even when dietary calcium intake is above the PRI for calcium (see Section 2.5.3 of the scientific opinion). It is biologically plausible that a long-term increase in urinary calcium excretion leading to negative bone calcium balance would both lower bone mineral density (BMD) and increase the risk of osteoporotic bone fractures. However, evidence for a relationship between sodium intake and bone health was considered inconclusive in previous assessments (EFSA, 2005; IOM, 2005a). In 2005, the IOM considered two prospective cohort studies. One reported an inverse association between sodium intake and BMD (Devine et al., 1995), while the other found no relationship (Greendale et al., 1994). The IOM also noted that the effect of reducing sodium intake on the risk of bone fractures had not been investigated. Through a scoping search, the Panel did not retrieve recent systematic reviews of the literature on this issue.

2.4.2. Excluded health outcomes

2.4.2.1. Blood lipid profile

Changes in blood lipid (triglycerides, total, LDL- and HDL-cholesterol) concentrations after sodium restriction have been considered (IOM, 2005b; Graudal et al., 2011a; Aburto et al., 2013; Eeuwijk et al., 2013; He et al., 2013). Despite the fact that they differed in the criteria used for study selection, mostly regarding study duration, the study population (diseased vs non-diseased), the use of concomitant interventions, and the achieved differences in sodium intake between study groups, meta-analyses of trials lasting four to eight weeks showed no significant effect of sodium restriction on blood lipid concentrations (triglycerides, total, LDL- and HDL-cholesterol) (Graudal et al., 2011b; WHO, 2012c; He et al., 2013; Australia/New Zealand Expert Working Group for Sodium, 2017) (Appendix A). In addition, the mechanism by which sodium might affect lipid metabolism remains unclear. Therefore, the Panel considers that blood lipids cannot be used to inform the setting of DRVs for sodium.

2.4.2.2. Catecholamines and the renin-angiotensin-aldosterone system

A reduction in sodium intake activates sodium-sparing mechanisms, which leads to an increase in sodium re-absorption by the kidneys. This response is partly mediated by the sympathetic nervous system (by releasing catecholamines) and the renin-angiotensin-aldosterone system (RAAS) (see Section 2.3.4 of the scientific opinion). In meta-analyses of trials of at least four weeks' duration, a reduction of sodium intake was associated with an increase in plasma aldosterone concentration and renin activity (Graudal et al., 2011b; WHO, 2012c; He et al., 2013) (Appendix B). Data for plasma adrenaline and noradrenaline concentrations were inconsistent. The studies included lasted up to 11 weeks.

Elevated levels of aldosterone and renin have been found in Yanomamo Indians, a culture characterised by life-long low sodium intakes (ca. 20–50 mg (1–2 mmol)/day), which indicates that a chronic activation of the RAAS system is possible (Oliver et al., 1975). Long-term trials in Western populations, however, are lacking. There are no data on long-term effects of low sodium intake on the sympathetic nervous system (plasma catecholamine concentrations). The Panel notes that the observed activation of the sympathetic nervous and RAAS systems in trials investigating the effect of sodium restriction are physiological responses to maintain blood pressure levels. The Panel also notes that the impact of a sustained activation of the sympathetic nervous system and the RAAS system on the risk of CVD or other chronic diseases in the general population is uncertain. Therefore, the Panel considers that these outcomes cannot be used to inform the setting of DRVs for sodium.

2.4.2.3. Glucose tolerance, insulin sensitivity and risk of type 2 diabetes

One prospective cohort study investigated the association between sodium intake and risk of type 2 diabetes in a population of Finnish subjects (1,935 men and women aged 35–64 years) free of diabetes at baseline over a 18.1-year follow-up (129 cases occurred) (Hu et al., 2005). Cut points for quartiles of 24-h urinary sodium excretion at baseline were 165, 212, 270 mmol/24 h in men and 122, 159, 200 mmol/24 h in women. No significant differences in the risk of developing type 2 diabetes were observed between the lowest quartile of 24-hour urinary sodium excretion and the second quartile taken as a reference (HR = 1.61 (95% CI = 0.89, 2.91)). Conversely, an increased risk of type 2 diabetes was found in the fourth quartile compared to the second quartile (HR = 2.24 (95% CI = 1.32, 3.79)).

A number of randomised, cross-over intervention studies have assessed the effect of "low" *vs* "high" sodium intakes on glucose tolerance and/or insulin sensitivity assessed by different methods in non-

diabetic subjects. Appendix C summarises the characteristics of RCTs which used a standard oral glucose tolerance test (OGTT) to assess glucose tolerance (n=3), and of RCTs which used direct measures of insulin sensitivity (i.e. the hyperinsulinaemic-euglycaemic clamp technique (n=6); the insulin suppression test (n=3)). Intervention studies in which the order of the intervention was not randomised (i.e. mostly studies considering "salt sensitive" and "salt resistant" individuals separately in which the low-sodium intervention was administered first) were not considered by the Panel.

Overall, studies were of short duration (most lasted up to one week), and heterogeneous regarding the subjects' characteristics (e.g. age, sex, hypertension status). The washout period ranged from zero to 4 weeks. Most studies compared sodium intake ≤ 50 mmol/day (1,150 mg/day) during the "low-sodium" diet to sodium intake ≥200 mmol/day (4,600 mg/day) during the "high-sodium" diet.

Some studies reported impaired glucose tolerance (Iwaoka et al., 1988), 1988) and lower insulin sensitivity (Gomi et al., 1998; Perry et al., 2003; Townsend et al., 2007) under sodium restriction as compared to the high-sodium period, whereas others found opposite effects on both glucose tolerance (Sharma et al., 1991) and insulin sensitivity (Donovan et al 1993), or no significant differences between study periods on either glucose tolerance (Inoue et al., 1996) or insulin sensitivity (Sharma et al., 1993; Foo et al., 1998; Facchini et al., 1999; Suzuki et al., 2000). In the study by Fliser et al. (1995) insulin sensitivity significantly decreased in normotensive subjects on sodium restriction for 3 days, but not in those on sodium restriction for 7 seven days.

Other studies which have used direct measures of insulin secretion, i.e. the hyperglycaemic clamp (Luther et al., 2014) or the continuous infusion of glucose with model assessment (CIGMA) (Grey et al., 1996) did not report any differences between "low" and "high" (20 vs 160 mmol and 50 vs 185 mmol, respectively) sodium diets in normotensive subjects.

The Panel notes that the effects of sodium restriction on glucose tolerance and insulin sensitivity have only been assessed in studies of short duration (most ≤ 1 week), the results of which are conflicting, and that evidence for a relationship between sodium intake and risk of type 2 diabetes is limited. Therefore, the Panel considers that these outcomes cannot be used to inform the setting of DRVs for sodium.

2.4.2.4. Overweight and obesity

A possible association between sodium intake and overweight and obesity has been addressed in a recent review (Moosavian et al., 2016). Such association has mostly been studied in cross-sectional studies. Prospective cohort studies have failed to find an association between sodium intake and changes in body weight or BMI (Libuda et al., 2012; Larsen et al., 2013). Therefore, the Panel considers that overweight and obesity cannot be used to inform the setting of DRVs for sodium.

2.4.2.5. Gastric cancer

A number of prospective cohort studies have assessed the association between sodium chloride intake and gastric cancer incidence and/or mortality, and have been the subject of several reviews (D'Elia et al., 2012; IOM, 2013; WCRF/AICR, 2016). Many studies used food frequency questionnaires (FFQs) to assess associations with the consumption of selected salted foods, rather than sodium intake as such (Galanis et al., 1998; Ngoan et al., 2002; Kurosawa et al., 2006; Sjodahl et al., 2008; Murata et al., 2010). Other studies were conducted in Japanese populations in which sodium intake was substantially higher than that observed in European populations (Tsugane et al., 2004; Shikata et al., 2006; Takachi et al., 2010). In one study conducted in a European population, in which sodium intake was assessed by means of a semi-quantitative 150-item FFQ validated against 9 dietary records (median intake from 1,640 mg/day in Q1 to 3,240 mg/day in Q5), no association was found between

energy-adjusted sodium intake and gastric cancer (n = 120,852 men and women aged 55–69 years at baseline; 282 incidents of gastric cancer over 6.3 years of follow-up) (van den Brandt et al., 2003). Therefore, the Panel considers that gastric cancer cannot be used to inform the setting of DRVs for sodium.

2.4.2.6. Pre-eclampsia

The effect of a restriction in dietary sodium chloride intake on the risk of pre-eclampsia among pregnant women was assessed in two Cochrane reviews (Duley and Henderson-Smart, 2000; Duley et al., 2005). Both reviews included two multi-centre randomised trials with 603 healthy nulliparous women which were conducted in the Netherlands. Neither study included women with pre-eclampsia, although one included women with mild hypertension (DBP ≥ 85 mmHg at trial entry). Both compared advice to reduce dietary salt intake with advice to continue a normal diet. When sodium chloride intakes of women in the "low sodium chloride" group were compared to an unchanged diet, the relative risk for pre-eclampsia was 1.11 (95 % CI: 0.44–2.66). Compared with "normal dietary intake", a low-salt diet seems no more effective at reducing the risk of pre-eclampsia (Duley, 2011). No further study was identified through the scoping exercise undertaken for this assessment (Eeuwijk et al., 2013). The Panel considers that pre-eclampsia cannot be used to inform the setting of DRVs for sodium for pregnant women.

2.4.2.7. Renal outcomes

The kidneys have a large functional reserve and, although kidney damage can eventually result from conditions mediated by high salt or sodium intakes, manifestations of impaired kidney function are a relatively late event and are usually not apparent until other features of the causative conditions, such as diabetes or high blood pressure, are apparent. In this context, research has focused on the remedial effect of sodium intake on renal outcomes in diseased populations (e.g. diabetic populations and/or populations at risk of CVD). Functional outcome measures of renal disease include serum creatinine, creatinine clearance, estimated glomerular filtration rate (eGFR), proteinuria and albuminuria. Although eGFR values are used to grade chronic kidney disease, eGFR values do not alter until renal function has significantly deteriorated (Stevens et al., 2006). Most published studies have investigated these markers in diseased patients in whom early markers such as albuminuria, and a reduced eGFR (creatinine clearance), are already present, and in whom the possible benefits of a reduced salt intake were being explored (IOM, 2013; Smyth et al., 2014b; Smyth et al., 2014a).

The Panel considers that the relationship between sodium intake and chronic kidney disease progression in specific subgroups of the population cannot be used to inform the setting of DRVs for sodium for the general population. The Panel also notes that, despite the well-established effect of sodium intake on blood pressure, the relationship between sodium intake and impaired renal function and the risk of chronic kidney disease has not been studied in the general population. The Panel therefore considers that renal outcomes cannot be used to inform the setting of DRVs for sodium.

2.4.2.8. All-cause mortality

Several prospective cohort studies and meta-analyses thereof have investigated the association between sodium intake and all-cause mortality (WHO, 2012d; Adler et al., 2014; Graudal et al., 2014). The Panel notes that overall mortality clusters death from diseases which may be unrelated to sodium intakes. The Panel thus considers that any relationship between sodium intake and overall mortality would be difficult to interpret. The Panel considers that overall mortality is not an appropriate health outcome to inform the setting of DRVs for sodium.

2.4.2.9. Other health outcomes

Some RCTs or cohort studies have studied the relationship between sodium intake and various health outcomes in diseased populations, ascites in patients with liver cirrhosis (Gu et al., 2012), bronchial responsiveness in asthmatic patients (Gotshall et al., 2004; Mickleborough et al., 2005) and kidney stone formation in susceptible patient groups (Eisner et al., 2009; Yun et al., 2010) (reviewed by IOM, 2013). The Panel notes that these studies in patient populations cannot inform the setting of DRVs for the general healthy population.

2.5. Sub-questions that will be answered for achieving the objective of Section 5.5 of the scientific opinion

A series of sub-questions will be answered to evaluate possible relationships between sodium intake and the selected health outcomes in the general population, including, where applicable, a quantitative assessment of the dose–response (i.e. objective of section 5.5 of the scientific opinion).

The sub-questions identified by the Panel are reported in Table 1. The assessment of the relationships between sodium intake and the selected health outcomes will include an investigation of related dose–responses and influencing factors. Of particular relevance to the setting of DRVs is the potential influence of sex and age on the relationship (see 2.2. target population).

Table 1: Sub-questions that will be answered for achieving the objective of Section 5.5 of the scientific opinion on DRVs for sodium

No	Sub-question
1	What is the relationship between sodium intake and blood pressure in humans?
2	What is the relationship between sodium intake and cardiovascular disease-related outcomes in humans?
3	What is the relationship in children[(a)] between sodium intake and bone mineral density (BMD) and/or bone mineral content (BMC)?
4	What is the relationship in adults[(b)] between sodium intake and BMD?
5	What is the relationship in adults[(b)] between sodium intake and the risk of osteoporotic fractures?

(a): 6 months to < 18 years
(b): ≥ 18 years

3. Method for answering the individual sub-questions

The five sub-questions formulated in 2.5. will be answered through systematic reviews. A systematic review is a well-established, stepwise process for reviewing evidence, based on the use of a standardised approach to identify and critically appraise relevant research, and to collect, synthesise and report data from the studies that are included in the review (EFSA, 2010; Higgins and Green, 2011).

3.1. General principles

The Panel will base its assessment on studies on humans. Basic research in animal models can produce valuable knowledge on mechanisms and/or dose–response relationships, for instance in relation to the physiology and metabolism of sodium. However, due to inter-species differences, extrapolation from animal models to humans is subject to considerable uncertainties, and data from animal models are rarely used in the setting of DRVs (EFSA NDA Panel, 2010).

The Panel will focus on evidence provided by observational prospective studies and RCTs. These study designs are preferred over retrospective case–control and cross-sectional studies because of the lower risk of recall bias and reverse causality.

3.2. Eligibility criteria for study selection

Studies will be selected for inclusion in the review based on pre-defined eligibility criteria. These cover aspects related to studies' internal validity, i.e. the degree to which bias or 'a systematic error, or deviation from the truth, in results or inferences' (Higgins and Green, 2011) is minimised in the study of interest, and external validity (or directness, generalisability, applicability, transferability), i.e. the extent to which the study findings can be generalised to the population of interest.

In particular, the following elements were considered for setting the eligibility criteria related to study characteristics:

- **The health status of the study subjects.** DRVs are set for the general healthy population. The Panel considers that studies restricted to diseased individuals under treatment should be excluded from the review because the relationship between sodium intake and health outcomes may be affected by the disease condition and/or medication use. Thus, observational studies focused on the secondary prevention of diseases or trials which selected diseased people under treatment will be excluded. In addition, observational prospective studies which did not explicitly exclude prevalent CVD cases at baseline will not be considered in answering sub-questions 1 and 2, in order to avoid bias due to reverse causality.
- **The duration of the study.** Studies will be included/excluded depending on their duration, the suitability of which is outcome-dependent (3.2.1., 3.2.2., 3.2.3 and 3.2.4.)
- **The intake assessment method.** Because of the limitations of the assessment of daily sodium intake through dietary questionnaires, and uncertainties associated with daily sodium intake estimated from casual spot and timed spot urine collections (see Sections 2.6.1 and 3.2.1 of the scientific opinion), studies which rely on these measures only will be excluded. Studies which assess sodium intake through 24-h urinary sodium excretion (from single or multiple collections) will be included.

The studies meeting the eligibility criteria for inclusion in the assessment will present varying degrees of internal and external validity, which will be addressed as possible sources of heterogeneity and uncertainty (3.6., 3.7. and 3.8.).

With respect to the report characteristics, the criteria listed in Table 2 will be applied.

Table 2: Eligibility criteria related to report characteristics (all sub-questions)

Language	Full-text document in English Articles with abstract in English and full-text in another European language will be screened against the eligibility criteria (3.2.1., 3.2.2., 3.2.3 and 3.2.4.). If based on the abstract the study seems eligible, the full-text document will be dealt with in EFSA and a summary given to the working group on Dietary References Values for minerals.
Publication type In	Primary research papers (i.e. studies generating new data) published in journals or available in clinical trial registers and master/theses registers. PhD theses and letters to the editor in case they report original investigations.

	Out	Expert opinions, editorials Articles from the popular media Extended abstracts, conference proceedings Other grey literature

3.2.1. Eligibility criteria related to study characteristics for sub-question 1

The studies relevant to sub-question 1 will be selected using the eligibility criteria related to study characteristics outlined in Table 3.

Table 3: Eligibility criteria related to study characteristics for sub-question 1

Sub-question 1	**What is the relationship between sodium intake and blood pressure in humans?**	
RCTs		
Study populations	In	Adults (≥ 18 years) and children (6 months to < 18 years) from the general population, including overweight and obese subjects and subjects with hypertension (as defined by the authors) who are not on pharmacological treatment with blood pressure-lowering medications during the intervention [(a)]
	Out	Trials on diseased individuals (e.g. with diabetes mellitus, congestive heart failure, chronic kidney disease), individuals on a therapeutic diet (including weight loss diet), or hypertensive subjects on blood pressure-lowering medications [(b)] Trials in pregnant women Trials with specialised exercise (e.g. athletes, militaries) and extreme environmental conditions (e.g. prolonged exposure to unusually high temperature)
Study design	In	Randomised controlled parallel or crossover trials, which: - lasted at least 4 weeks (28 days) - assessed the effect of different levels of sodium intake - assessed 24-h urinary sodium excretion ~~both at baseline and~~[6] at the end of each intervention/period - cross-over trials with a wash out period of any duration
	Out	Other study designs
Intervention	In	Intervention: change in sodium intake Method to measure sodium intake: urinary sodium excretion from 24-h urinary sodium excretion calculated from single or multiple 24-h urine collection(s)
	Out	Intervention: with concomitant intervention which is deemed to affect blood pressure[(c)] Intervention consisting in replacing table salt with potassium salts Method to measure sodium intake: FFQs, food records, diet recalls, spot urine collections or urine collections lasting less than 24-h
Comparator	In	Comparison: usual diet, no intervention, placebo Method to measure sodium intake: as for the intervention
	Out	Comparison: any concomitant intervention deemed to affect blood pressure Method to measure sodium intake: as for the intervention
Outcomes of interest	In	• Point blood pressure (SBP, DBP) (home/office)[7] • Incidence of hypertension
	Out	Other outcomes

[6] Protocol amemdment: DELETION. This criteria was found to be too restrictive and was not justified by the type of analyses foreseen (section 3.7).

[7] Protocol amendment: ADDITION. Ambulatory blood pressure measurements could not be integrated with point blood pressure measurements in the analyses foreseen (section 3.7) and eligible outcome measures were restricted to home/office point BP measurements.

OBSERVATIONAL PROSPECTIVE STUDIES		
Study populations	In	Adults (≥ 18 years) and children (6 months to < 18 years) from the general population Studies which explicitly excluded prevalent CVD cases
	Out	Studies which did not explicitly exclude prevalent CVD cases Adults selected on the basis of a disease condition, including hypertensive subjects on blood pressure-lowering medications Studies in pregnant women
Study design	In	Prospective studies including cohort studies, nested case-control studies and case-cohort studies and follow-up of trials
	Out	Case series/reports, retrospective case-control, cross-sectional studies
Exposure	In	Exposure: Dietary sodium intake Route of exposure: oral Method to assess sodium intake: 24-h urinary sodium excretion measured on the basis of single or multiple 24-h urine collections. Levels/Doses: Any range of Na intake
	Out	Exposure: data do not allow quantification of sodium intake Method to assess sodium intake: • 24-h urinary sodium excretion calculated from urine collections less than 24-h or spot urine collections • FFQs, food records, diet recalls or other dietary questionnaires
Outcomes of interest	In	• Point blood pressure (SBP, DBP) (home/office)[8] • Incidence of hypertension
	Out	• Other outcomes

DBP: diastolic blood pressure; CVD: cardiovascular disease; FFQ: food frequency questionnaire; SBP: systolic blood pressure

(a): Blood pressure is a continuous variable related to the risk of cardiovascular disease in a dose-dependent manner across a wide range of values, both below and above the cut-off values used for the diagnosis of hypertension. Therefore, the Panel considers that studies in subjects with hypertension who are not on pharmacological treatment with blood pressure-lowering medication may inform the relationship between sodium intake and blood pressure in the context of deriving DRVs for sodium. Trials which involved subjects with hypertension who were requested to stop their antihypertensive treatment before the start of the intervention will be included.

(b): Some trials may have mixed populations and provide results by sub-population groups. In such cases, the study will be included if it provides results for the subgroup without disease/therapeutic diet/blood pressure-lowering medications. Only data from this subgroup will be considered in the assessment.

(c): Some trials may have several sodium reduction arms, with or without concomitant interventions. In such cases, the study will be included and only data from arms without a concomitant intervention or with a concomitant intervention which is deemed not to affect blood pressure will be considered in the assessment.

3.2.2. Eligibility criteria related to study characteristics for sub-question 2

The studies relevant to sub-question 2 will selected using the eligibility criteria related to study characteristics outlined in Table 4.

Table 4: Eligibility criteria related to study characteristics for sub-question 2

Sub-question 2		**What is the relationship in humans between sodium intake and CVD-related outcomes?**
RCTs		
Study populations	In	Adults (≥ 18 years) and children (6 months to < 18 years) from the general population, including overweight and obese subjects and subjects with

[8] Protocol amendment: ADDITION. Ambulatory blood pressure measurements could not be integrated with point blood pressure measurements in the analyses foreseen (section 3.7) and eligible outcome measures were restricted to home/office point BP measurements.

		hypertension (as defined by the authors) who are not on pharmacological treatment with blood pressure-lowering medications during the intervention [a]
	Out	Trials on diseased individuals (e.g. with diabetes mellitus, congestive heart failure, chronic kidney disease), individuals on a therapeutic diet (including weight loss diet) or hypertensive subjects on blood pressure-lowering medications [b] Trials in pregnant women Trials with specialised exercise (e.g. athletes, militaries) and extreme environmental conditions (e.g. prolonged exposure to unusually high temperature)
Study design	In	Randomised controlled parallel, which: - lasted at least 6 months - assessed the effect of different levels of sodium intake - assessed 24-h sodium urinary sodium excretion ~~both at baseline and~~[9] at the end of each intervention/period
	Out	Other study designs
Intervention	In	Intervention: change in sodium intake Method to measure sodium intake: urinary sodium excretion from 24-h urinary sodium excretion calculated from single or multiple 24-h urinary sodium
	Out	Intervention: with concomitant intervention which is deemed to affect CVD [c] Intervention consisting in replacing table salt with potassium salts Method to measure sodium intake: FFQs, food records, diet recalls, spot urine collections or urine collections lasting less than 24-h
Comparator	In	Comparison: usual diet, no intervention, placebo Method to measure sodium intake: as for the intervention
	Out	Comparison: any concomitant intervention deemed to affect CVD Method to measure sodium intake: as for the intervention
Outcomes of interest	In	• Incidence of stroke [haemorrhagic (intracerebral, subarachnoid) and/or ischaemic; fatal and/or non-fatal] • Incidence of myocardial infarction (fatal and/or non-fatal) • Incidence of congestive heart failure • Fatal and/or non-fatal cardiovascular events (composite outcome)
	Out	• all-cause mortality • Other outcomes
OBSERVATIONAL PROSPECTIVE STUDIES		
Study populations	In	Adults (≥ 18 years) and children (6 months to < 18 years) from the general population Studies which explicitly excluded prevalent CVD cases
	Out	Studies which did not explicitly exclude prevalent CVD cases Adults selected on the basis of a disease condition, including hypertensive subjects on blood pressure-lowering medications Studies in pregnant women
Study design	In	Prospective studies including cohort studies, nested case-control and case-cohort studies, and follow-up of trials
	Out	Case series/reports, retrospective case-control, cross-sectional studies
Exposure	In	Exposure: Dietary sodium intake Route of exposure: oral Method to assess sodium intake: 24-h urinary sodium excretion measured on the basis of single or multiple 24-h urine collections. Levels/Doses: Any range of Na intake
	Out	Exposure: data do not allow quantification of sodium intake Method to assess sodium intake: • 24-h urinary sodium excretion calculated from urine collections less than 24-h

[9] Protocol amemdment: DELETION. This criterion was found to be too restrictive and was not justified by the type of analyses foreseen (section 3.7).

		or spot urine collections • FFQs, food records, diet recalls or other dietary questionnaires
Outcomes of interest	In	• Incidence of stroke [haemorrhagic (intracerebral, subarachnoid) and/or ischaemic; fatal and/or non-fatal] • Incidence of myocardial infarction (fatal and/or non-fatal) • Incidence of congestive heart failure • Fatal and/or non-fatal cardiovascular events (composite outcome)
	Out	• Death from all causes. • Other outcomes

CVD: cardiovascular disease; FFQ: food frequency questionnaire

(a): Blood pressure is a continuous variable related to the risk of cardiovascular disease in a dose-dependent manner across a wide range of values, both below and above the cut-off values used for the diagnosis of hypertension. Therefore, the Panel considers that studies in subjects with hypertension who are not on pharmacological treatment with blood pressure-lowering medication may inform the relationship between sodium intake and risk of CVD in the context of deriving DRVs for sodium. Trials which involved subjects with hypertension who were requested to stop their antihypertensive treatment before the start of the intervention will be included.

(b): Some trials may have mixed populations and provide results by sub-population groups. In such cases, the study will be included if it provides results for the subgroup without disease/therapeutic diet/blood pressure-lowering medications. Only data from this subgroup will be considered in the assessment.

(c): Some trials may have several sodium reduction arms, with or without concomitant interventions. In such cases, the study will be included and only data from arms without a concomitant intervention or with a concomitant intervention which is deemed not to affect blood pressure will be considered in the assessment.

3.2.3. Eligibility criteria related to study characteristics for sub-question 3

The studies relevant to sub-question 3 will be selected using the eligibility criteria related to study characteristics outlined in Table 5.

Table 5: Eligibility criteria related to study characteristics for sub-question 3

Sub-question 3		**What is the relationship in children between sodium intake and BMD and/or BMC?**
RCTs		
Study populations	In	Children (6 months to < 18 years) from the general population, including overweight and obese subjects
	Out	Trials including diseased individuals (e.g. with diabetes mellitus) or individuals on a therapeutic diet (including weight loss diet) [(a)]
Study design	In	Randomised controlled parallel, which: - assessed the effect of different levels of sodium intake - assessed 24-h sodium urinary sodium excretion ~~both at baseline and~~[10] at the end of each intervention/period
	Out	Other study designs
Intervention	In	Intervention: change in sodium intake Method to measure sodium intake: urinary sodium excretion from 24-h urinary sodium excretion calculated from single or multiple 24-h urinary sodium
	Out	Intervention: with concomitant intervention which differed between the control and intervention groups ~~which is deemed to affect BMD or the risk of osteoporotic fractures~~[(b)] [11]Method to measure sodium intake: FFQs, food records, diet recalls, spot urine collections or urine collections lasting less than 24-h
Comparator	In	Comparison: usual diet, placebo

[10] Protocol amemdment: DELETION. This criterion was found to be too restrictive and was not justified by the type of analyses foreseen (section 3.7).

[11] Protocol amendment: DELETION. This criterion was found to be too restrictive in view of the scarcity of the literature available.

		Method to measure sodium intake: as for the intervention
	Out	Comparison: any concomitant intervention deemed to affect BMD and/or BMC Method to measure sodium intake: as for the intervention
Outcomes of interest	In	• BMD at any skeletal site, measured by DXA Whole body BMC/BMD normalized by body size, measured by DXA
	Out	• Other outcomes
OBSERVATIONAL PROSPECTIVE STUDIES		
Study populations	In	Children (6 months to < 18 years) from the general population
	Out	Population selected on the basis of a disease condition.
Study design	In	Prospective studies including cohort studies, nested case-control and case-cohort studies and follow-up of trials
	Out	Case series/reports, retrospective case-control, cross-sectional studies
Exposure	In	Exposure: Dietary sodium intake Route of exposure: oral Method to assess sodium intake: 24-h urinary sodium excretion measured on the basis of single or multiple 24-h urine collections. Levels/Doses: Any range of Na intake
	Out	Exposure: data do not allow quantification of sodium intake Method to assess sodium intake: • 24-h urinary sodium excretion calculated from urine collections less than 24-h or spot urine collections • FFQs, food records, diet recalls or other dietary questionnaires
Outcomes of interest	In	• BMD at any skeletal site, measured by DXA • Whole body BMC/BMD normalized by body size, measured by DXA
	Out	• Other outcomes

BMC: bone mineral content; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; FFQ: food frequency questionnaire

(a): Some trials may have mixed populations and provide results by sub-population groups. In such cases, the study will be included if it provides results for the subgroup without disease/therapeutic diet. Only data from this subgroup will be considered in the assessment.

~~(b): Some trials may have several sodium reduction arms, with or without concomitant interventions. In such cases, the study will be included and only data from arms without a concomitant intervention or with a concomitant intervention which is deemed not to affect blood pressure will be considered in the assessment.~~

3.2.4. Eligibility criteria related to study characteristics for sub-questions 4 and 5

The studies relevant to sub-question 4 and 5 will be selected using the eligibility criteria related to study characteristics outlined in Table 6.

Table 6: Eligibility criteria related to study characteristics for sub-questions 4 and 5

Sub-question 4		**What is the relationship in adults between sodium intake and BMD?**
Sub-question 5		**What is the relationship in adults between sodium intake and the risk of osteoporotic fractures?**
RCTs		
Study populations	In	Adults (≥ 18 years) from the general population, including overweight and obese subjects
	Out	Trials including diseased individuals (e.g. with diabetes mellitus, congestive heart failure, chronic kidney disease, osteoporotic fractures, under antiosteoporotic treatment, under hormone replacement therapy) or individuals on a therapeutic diet (including weight loss diet)[(a)]
Study design	In	Randomised controlled parallel, which: - lasted at least 1 year

		- assessed the effect of different levels of sodium intake - assessed 24-h sodium urinary sodium excretion ~~both at baseline and~~[12] ~~at~~ the end of each intervention/period
	Out	Other study designs
Intervention	In	Intervention: change in sodium intake Method to measure sodium intake: urinary sodium excretion from 24-h urinary sodium excretion calculated from single or multiple 24-h urinary sodium
	Out	Intervention: with concomitant intervention which differed between the control and intervention groups ~~which is deemed to affect BMD or the risk of osteoporotic fractures~~[(b)] [13] Method to measure sodium intake: FFQs, food records, diet recalls, spot urine collections or urine collections lasting less than 24-h
Comparator	In	Comparison: usual diet, placebo Method to measure sodium intake: as for the intervention
	Out	Comparison: any concomitant intervention deemed to affect BMD or the risk of osteoporotic fractures Method to measure sodium intake: as for the intervention
Outcomes of interest	In	• BMD at any skeletal site, measured by DXA • Incidence of osteoporosis • Incidence of osteoporotic fracture at any skeletal site
	Out	• Biochemical markers of bone turnover • Incidence of bone fractures due to other causes (e.g. trauma, genetic diseases, etc) • Other outcomes
OBSERVATIONAL PROSPECTIVE STUDIES		
Study populations	In	Adults (≥ 18 years) from the general population
	Out	Adults selected on the basis of a disease condition.
Study design	In	Prospective studies including cohort studies, nested case-control and case-cohort studies and follow-up of trials
	Out	Case series/reports, retrospective case-control, cross-sectional studies
Exposure	In	Exposure: Dietary sodium intake Route of exposure: oral Method to assess sodium intake: 24-h urinary sodium excretion measured on the basis of single or multiple 24-h urine collections. Levels/Doses: Any range of Na intake
	Out	Exposure: data do not allow quantification of sodium intake Method to assess sodium intake: • 24-h urinary sodium excretion calculated from urine collections less than 24-h or spot urine collections • FFQs, food records, diet recalls or other dietary questionnaires
Outcomes of interest	In	• BMD measurement at any skeletal site, measured by DXA • Incidence of osteoporosis • Incidence of osteoporotic fracture at any skeletal site
	Out	• Incidence of bone fractures due to other causes (e.g. trauma, genetic diseases, etc.) • Other outcomes

BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; FFQ: food frequency questionnaire

(a): Some trials may have mixed populations and provide results by sub-population groups. In such cases, the study will be included if it provides results for the subgroup without disease/therapeutic diet. Only data from this subgroup will be considered in the assessment.

~~(b): Some trials may have several sodium reduction arms, with or without concomitant interventions. In such cases, the study will be included and only data from arms without a concomitant intervention or with a concomitant intervention which is deemed not to affect blood pressure will be considered in the assessment.~~

[12] Protocol amendment: DELETION. This criterion was found to be too restrictive and was not justified by the type of analyses foreseen (section 3.7).

[13] Protocol amendment: DELETION. This criterion was found to be too restrictive in view of the scarcity of the literature available.

3.3. Search for studies meeting the eligibility criteria

The bibliographic databases listed in Table 7 will be searched in order to identify relevant studies.

Table 7: Bibliographic databases searched for relevant studies

Database	Platform	Types of studies
Cochrane Library. Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley	Clinical trials
Cochrane Library. Cochrane Database of Systematic Reviews (CDSR)	Wiley	Systematic reviews
Cochrane Library. Database of Abstracts of Reviews of Effects	Wiley	Systematic reviews
Embase	Embase.com	Systematic reviews, clinical trials, observational studies
PubMed	PubMed (NLM)	Systematic reviews, clinical trials, observational studies

Additional searches will be performed to identify PhD theses in the resources listed in Table 8.

Table 8: Resources searched for relevant PhD thesis

Resource	Website link	Type of publication
PQDT Open	http://pqdtopen.proquest.com/search.html	Thesis and dissertations
DART-Europe E-theses Portal	http://www.dart-europe.eu/basic-search.php	Thesis and dissertations

Databases have been identified in line with the defined scope of the systematic reviews and based on the EFSA inventory of information sources (www.metaxis.com/EFSAINVENTORY).

The specific search strategies have been created by an information specialist with input from the working group. Controlled vocabulary, when available, (i.e. MeSH and Emtree terms) and natural vocabulary have been used to represent the concepts in the search strings, and they have been tailored to capture the studies meeting the eligibility criteria illustrated in the various sub-questions. The references included in previous systematic reviews have been used to assess the sensitivity of the search strategies.

Language of the original studies will be limited to European languages for bibliographic databases; the retrieval of PHD theses will be limited to English.

During the scoping searches, previous systematic reviews of RCTs with review questions similar to sub-question 1 (Graudal et al., 2011a; WHO, 2012c; He et al., 2013; Graudal et al., 2017) and sub-question 2 (Adler et al., 2014) have been identified. They were found to have similar or broader inclusion criteria than the present systematic review and appropriate search strategies. In relation to sub-question 1, the list of studies included in the most recent systematic review from Graudal et al. (2017) was checked and found to include all pertinent studies included in the other reviews (Graudal et al., 2011a; WHO, 2012c; He et al., 2013). Therefore, date limits will be applied to the searches for RCTs in relation to these sub-questions (Table 9). RCTs published before these dates will be retrieved from the reference lists of Graudal et al. (2017) (sub-question 1) and Adler et al. (2014) (sub-question 2). No date limits will be applied for the retrieval of observational studies pertinent to these sub-questions. Date limits might be changed should new systematic reviews on the topic be identified which are considered to adequately cover the relevant literature.

Table 9: Date limits applied to the searches and systematic reviews used as sources of relevant studies

Sub-question	Date limits	Systematic reviews
1	RCTs: as of the 1st of January 2016	(Graudal et al., 2017)[(a)]
	Observational studies : no time restriction	
2	RCTs : as of the 1st of January 2013	(Adler et al., 2014)[(b)]
	Observational studies : no time restriction	
3–5	RCTs: no time restriction	
	Observational studies : no time restriction	

(a): Graudal et al., 2017 searched Medline, Embase, Cochrane CENTRAL, the Cochrane Hypertension Specialised Register and Clinicaltrials.gov until March 2016.

(b): Adler et al., 2014 searched Cochrane CENTRAL, Medline, Embase and CINAHL until April 2013.

The search strings are available in Appendix D.

The output of the searches, i.e. records retrieved from bibliographic databases and additional search resources, together with the relevant metadata (e.g. title, authors, abstract) will be exported into separate Endnote X8 libraries (Clarivate Analytics). All RCTs included in the two above-mentioned systematic reviews will be added to specific Endnote X8 libraries. This will allow a count of the individual hits per database and source. Duplicates retrieved within the same database will be removed. Then, the files for all the sources will be combined and duplicate records will be removed.

The files obtained will be uploaded onto DistillerSR® (Evidence Partners, Ottawa, Canada), a web-based systematic review software that will be used for supporting some of the following steps in the systematic review process.

Reference lists of the eligible studies resulting from the searches will be checked in order to identify possibly relevant studies not retrieved in other sources. Systematic reviews published in journals or available in grey literature on a similar review question will also be used as a source of primary research papers.

The final search processes and strategies will be documented and reported in the scientific opinion, i.e. the date of the search, sources of information, search string for each bibliographic database and additional sources, and the number of records before and after de-duplication. Should modifications in the search strings be considered after the publication of the protocol, they will be also reported.

3.4. Selection of studies for inclusion in the assessment

The eligibility criteria described above will be transferred to the software DistillerSR® (Evidence Partners, Ottawa, Canada) and applied to each individual record retrieved by the literature searches, in order to identify the studies that meet the eligibility criteria defined for this assessment.

A step-wise procedure is foreseen, as follows:

- **Screening of titles and abstracts,** to identify: i) studies that obviously do not meet the eligibility criteria, to be excluded from the assessment; ii) studies that potentially meet the eligibility criteria or unclear studies, to proceed with the full-text screening. Each title/abstract will be screened for relevance by two EFSA staff. If there are doubts or divergences between the two reviewers, the record will be moved to full-text screening (next step). Articles excluded at this step will be stored in DistillerSR®.
- **Screening of full-text documents**, to identify studies relevant to the assessment. Each full-text document will be screened by two EFSA staff. Possible divergences between the two

reviewers that cannot be solved via discussion or studies deemed unclear by both reviewers will be discussed with the members of the working group on Dietary References Values for minerals (WG).

Eligibility criteria will be pilot tested on a subset of records, and refined if prone to misinterpretation.

Duplicate publications will be flagged to the WG and considered only once in the assessment.

The results of the different steps of the study selection process will be reported in the scientific opinion using a flowchart as recommended in the PRISMA statement on preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2010).

The list of studies excluded after full-text screening will be published as an Annex to the scientific opinion, along with the reasons for excluding them at this stage.

3.5. Data extraction from the included studies

Data will be extracted from the studies using pre-defined forms that comprise data on the characteristics of the studies (e.g. study design), their key-elements (e.g. population, intervention/exposure, comparator, outcomes, setting and duration), results and aspects related to the internal validity of the studies (e.g. confounders, randomisation).

The data will be extracted in the original units of measurement, which will be subsequently harmonised to allow data analysis. The authors will be contacted to retrieve additional data if needed.

Clear instructions for extracting data will be developed. The data extraction forms will be created in DistillerSR® (Evidence Partners, Ottawa, Canada) (sub-question 1) or Excel (sub-questions 2 to 5)[14] and pilot tested on a subset of studies. The piloting will also be used to identify sources of contextual (i.e. related to the key elements of the studies) heterogeneity. The forms and instructions will be refined if needed.

Data will be extracted from each individual study by one EFSA staff member. In the piloting phase, extracted data will be validated by another EFSA staff member, in order to identify sources of possible errors. Once fine-tuned, the data extraction will be conducted by one EFSA staff member.

If a full-text document reports on more than one study, the individual studies will be identified at this step to allow for data extraction and appraisal at individual study level (3.6.).

3.6. Appraisal of the internal validity of the included studies

The internal validity or risk of bias (RoB) of each individual study included in the assessment will be appraised using a customised version of the OHAT/NTP RoB tool, which is suitable for both RCTs and observational studies.[15] This tool was developed based on guidance from the Agency for Healthcare Research and Quality (Viswanathan et al., 2012, 2013), the Cochrane risk-of-bias tool for non-randomised studies of interventions (Sterne et al., 2014), Cochrane Handbook (Higgins and Green, 2011), CLARITY Group at McMaster University (2013), and other sources. The OHAT/NTP RoB tool was developed to provide a parallel approach to the evaluation of the risk of bias in the context of hazard identification for human risk assessment of chemicals, and to facilitate consideration of risk of bias across evidence streams (i.e. human, animal and mechanistic studies) with common terms and

[14] Protocol amendment: ADDITION. In view of the small number of eligible studies, data relevant to sub-questions 2 to 5 were extracted in Excel.
[15] https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

categories for risk of bias rating. For this assessment, the use of the tool will be limited to the aspects relevant to RCTs and prospective observational studies in humans.

For each study, the appraisal will be done at outcome level, because for the same study the design and conduct may affect the risk of bias differently depending on the outcomes measured. Each study will be appraised by two mutually independent experts from the WG ('the reviewers'). Possible discrepancies will be discussed by the whole WG. If, upon further discussion, the WG cannot reach an agreement on a risk of bias rating for a particular domain, the more conservative judgment will be selected.

For the appraisal of human studies, the OHAT/NTP RoB tool outlines 10 risk-of-bias questions, grouped by 6 bias domains (selection, confounding, performance, attrition/exclusion, detection, and selective reporting) - plus 'other sources of bias' -, which help identify the practices that may introduce bias (Table 10). Each risk-of-bias question addresses aspects relevant to specific study designs, i.e. 8 questions apply to RCTs and 7 questions apply to prospective observational (cohort, nested case–control and case–cohort) studies (Table 10). Reviewers are required to answer risk-of-bias questions by applying a 4-level rating scale (Figure 1).

The risk-of-bias questions and rating instructions provided in the tool will be tailored to the specific sub-questions illustrated in this protocol.

Table 10: Extracted from OHAT/NTP RoB tool (source: OHAT Handbook - January 9, 2015)[16]

Bias Domains and Questions	RCT	Prospective observational
Selection Bias		
1. Was administered dose or exposure level adequately randomized?	X	
2. Was allocation to study groups adequately concealed?	X	
3. Did selection of study participants result in appropriate comparison groups?		X
Confounding Bias		
4. Did the study design or analysis account for important confounding and modifying variables?		X
Performance Bias		
5. Were the research personnel and human subjects blinded to the study group during the study?	X	
Attrition/Exclusion Bias		
6. Were outcome data complete without attrition or exclusion from analysis?	X	X
Detection Bias		
7. Can we be confident in the exposure characterization?	X	X
8. Can we be confident in the outcome assessment?	X	X
Selective Reporting Bias		
9. Were all measured outcomes reported?	X	X
Other Sources of Bias		
10. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	X	X

[16] https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf

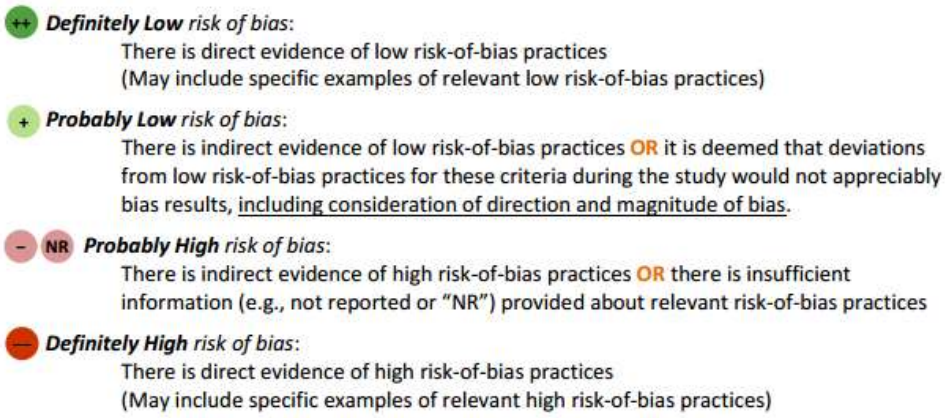


Figure 1: Answer format for the RoB questions (source: OHAT/NTP RoB tool)[17]

The OHAT/NTP RoB tool encourages judging the direction of bias, when possible. Empirical evidence about the direction of bias is discussed for each of the risk-of-bias questions. If there is no clear rationale for judging the likely direction of bias, reviewers are invited to simply outline the evidence and not to attempt a guess. The Panel will follow this approach.

The tool will be created in the review management software DistillerSR® to allow web-based appraisal of the studies.

Specific elements identified *a priori* and that will be considered in the assessment of confounding and biases related to exposure and outcome characterisation are discussed below.

3.6.1. Consideration of potential confounders

Confounding occurs when the relationship between the exposure and disease is to some extent attributable to the effect of another risk factor, i.e., the confounder. There are several requirements for a factor to actually act as a confounder, as described by McNamee (2003) and illustrated below. The factor must:

• be a cause of the disease, or a surrogate measure of the cause, in unexposed people; factors satisfying this condition are called 'risk factors'; and

• be correlated, positively or negatively, with exposure in the study populations. If the study population is classified into exposed and unexposed groups, this means that the factor has a different distribution (prevalence) in the two groups; and

• not be an intermediate step in the causal pathway between the exposure and the disease.

Based on recent publications, the Panel identified *a priori* an indicative list of potential factors that could confound the relationship between sodium intake and blood pressure, and the relationship between sodium intake and cardiovascular disease-related endpoints: age, sex, race/ethnicity, education, smoking habits, physical activity, alcohol consumption, daily energy intake, potassium intake/fruit and vegetable consumption, body weight/body mass index (BMI) (Figure 2).

The Panel also identified *a priori* an indicative list of potential factors that could confound the relationship between sodium intake and BMD / risk of osteoporotic fracture: age, sex, race/ethnicity, smoking habits, education, physical activity, alcohol consumption, daily energy intake, dietary intake of protein, dietary intake of calcium, body weight/BMI, menopausal status (Figure 2).

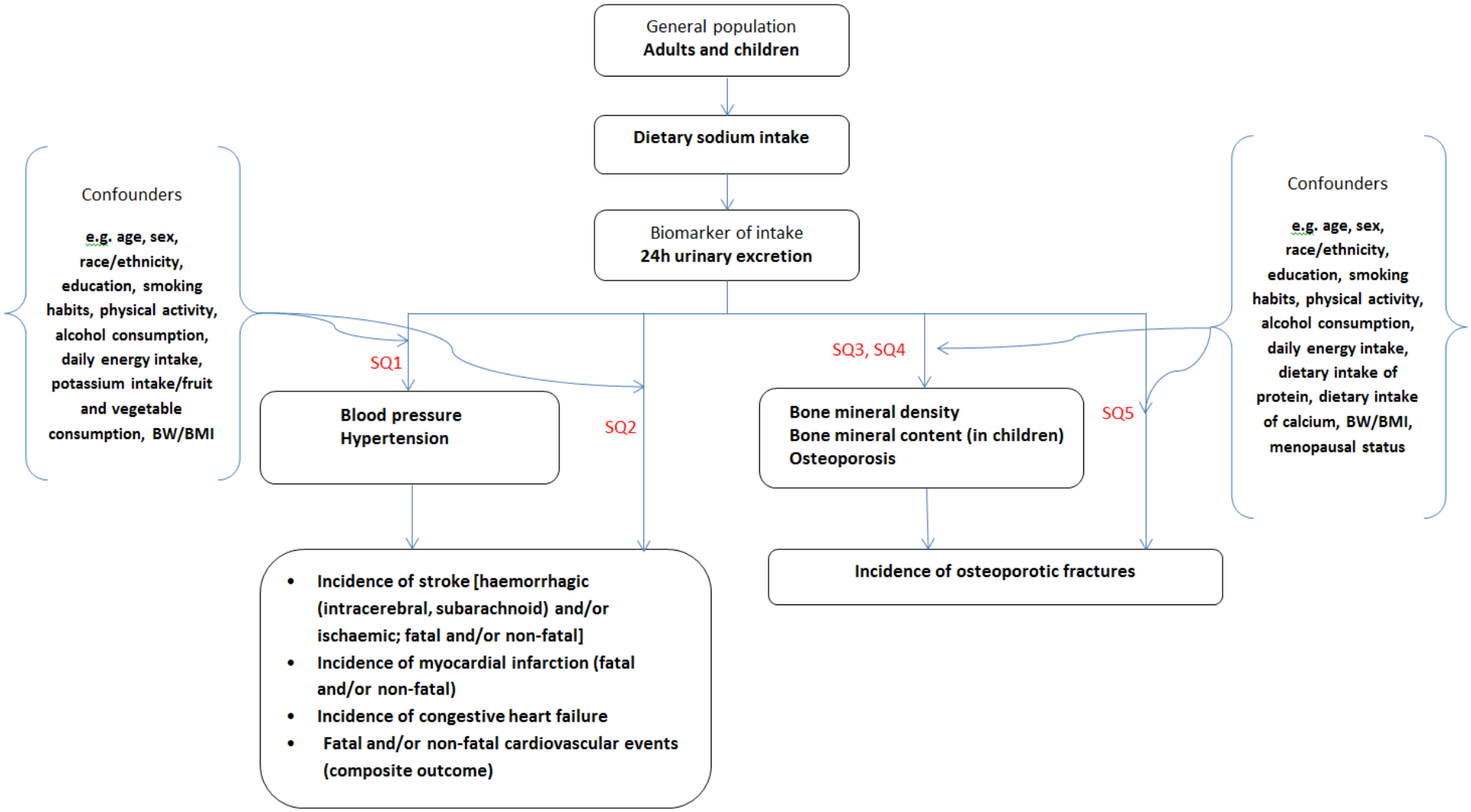
[17] https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

When assessing risk of bias in observational studies, the reviewers will consider, for each study, whether these factors can confound the association on a case-by-case basis. Additional confounders may be identified by the reviewers. The reviewers will consider whether the confounding variables were measured reliably and consistently within each study and whether the design and/or the data analysis adequately accounted for potential confounding (e.g. multivariable analysis, stratification).

Blood pressure is considered a mediator in the causal pathway between sodium intake and cardiovascular disease-related endpoints. Adjustment for BP will be considered a potential source of over-adjustment bias.

The OHAT/NTP RoB tool does not include a separate question for confounding in experimental human studies because randomization and allocation concealment should adequately address the issue of confounding. It recognizes, however, that in some cases appropriate procedures for randomisation and allocation concealment may fail in accounting for confounding. For example, in the context of this assessment, confounding could be a concern if there are important differences in characteristics at baseline. In accordance with the OHAT/NTP guidance, for experimental studies where confounding is strongly suspected despite the fact that randomisation and allocation concealment are rated at "probably low" or "definitely low risk of bias", confounding will be addressed under "other potential threats to internal validity" (OHAT/NTP, 2015).

Figure 2. Conceptual framework for the systematic reviews on sodium intake and selected health outcomes



BMI, body mass index; BW, body weight; SQ, sub-question

3.6.2. Confidence in the exposure characterisation

As described above (3.2.), the assessment will include studies that estimate sodium intake through 24-h urinary sodium excretion, from single or multiple collections. Other intake assessment methods are excluded.

In assessing risk of bias, reviewers will consider the risk of errors in the estimate of habitual sodium intake for individuals, and related risks of misclassification of individuals according to their exposure. The accuracy of habitual sodium intake estimates may be affected by i) the number of urinary samples collected (single vs multiple collections); ii) the completeness of 24-hour urine collections; iii) systematic changes in habitual diet prior to the urinary collection (see Section 2.6.1 of the scientific opinion). The reviewers will consider the resulting misclassification in appraising the studies.

3.6.3. Confidence in the outcome assessment

Confidence in the outcome requires valid, reliable, and sensitive methods to assess the outcome applied consistently across groups (OHAT/NTP, 2015). Outcome misclassification or measurement error may be unrelated to the exposure (non-differential) or related to the exposure (differential).

Factors that will be considered by the reviewers while assessing bias in relation to the outcome assessment include: 1) the objectivity of the outcome assessment, 2) the consistency in measurement of outcomes, and 3) the blinding of the outcome assessors (for knowledge of the exposure) (OHAT/NTP, 2015).

3.6.4. Summarising the internal validity of each individual study

Each study will be reported using a tabular summary form which will include the key elements of the study and a summary of the results of the critical appraisal.

An algorithm will be defined in order to combine the judgements to the risk-of-bias questions into an overall risk-of-bias judgment for each individual study (by outcome). To this end, key-questions (or criteria) within the list of risk-of-bias questions will be identified. This will result in each study being allocated to a different 'tier of risk of bias' (by outcome).

The foreseen approach to accounting for risk-of-bias judgements in the analysis is presented below (3.7.5.).

3.7. Synthesis of the evidence

Information on inclusion criteria, risk-of-bias assessment and outcomes as extracted from the individual studies will be summarised in evidence tables.

In the context of the current dose–response analysis on aggregated data, a high statistical heterogeneity across included studies is expected; it will be incorporated in meta-analyses and meta-regressions under a random-effects model, which considers both within-study and between-study variations. Heterogeneity will be quantified, and methodological and/or contextual sources will be identified and evaluated (Borenstein et al., 2010).

3.7.1. Meta-analyses

Continuous outcomes (i.e. SBP, DBP, BMD, BMC) will be analysed using mean differences if the same measurement scales are used across included studies or have been converted during data extraction; SBP and DBP will also be analysed separately as absolute achieved mean values in the dose–response analysis with absolute sodium intake.

Dichotomous outcomes (i.e. incidence of hypertension, incidence of fatal and/or non-fatal stroke, incidence of fatal and/or non-fatal myocardial infarction, incidence of congestive heart failure, fatal

and/or non-fatal cardiovascular events (composite outcome), incidence of osteoporosis, incidence of osteporotic fractures) will be analysed using relative risks (RRs) as estimated by the risk measures reported in the original studies (i.e. risk ratios, rate ratios, odds ratios or hazard ratios).

Mean differences and RRs with related standard errors will be calculated based on summary data extracted from the original individual studies. Specific formulae will be applied to derive summary data where not directly extracted/available; if no indirect calculation/estimation is possible, the missing data will be imputed according to the approach proposed by Furukawa et al. (2006).

Random-effects meta-analyses of mean differences and relative risks will be carried out using the approach from DerSimonian and Laird (DerSimonian and Laird, 1986) to complement the results from the multivariable dose–response models.

Statistical heterogeneity will be tested using a χ^2 test (Cochrane's Q test; significance level: 0.10) and quantified by calculating the I^2 statistic.

3.7.2. Dose–response models

In a two-stage approach, study-specific dose–response relationships between sodium intake and the selected outcomes will be estimated (first stage) and combined (second stage) to produce pooled intake–outcome curves (Greenland and Longnecker, 1992; Berlin et al., 1993; Liu et al., 2009; Orsini et al., 2012; Crippa and Orsini, 2016).

Sodium intake will be modelled with restricted cubic splines in multivariate random-effects dose–response models if the study-specific estimated trends show or suggest non-linear relationships (i.e. statistically significant estimates for the slopes of second or higher order).

The advantages of applying restricted cubic splines, both at the first or second stage, will be to ensure more flexibility in modelling (no assumptions on dose–response curve shape are required) and to maximise the number of studies that can be included (the minimum number of intakes categories needed beyond the control group can be as low as 2). Also, non-linear non-monotonic functional relationships (e.g. J-shaped, U-shaped curves) can be accommodated by restricted splines using only two parameters.

Bias deriving from dependencies in error terms (e.g. RR estimates from the same study are correlated) will be dealt with in the first stage by adjusting for the covariances approximated by suitable methods upon availability of the required information (Orsini et al., 2012). Centered dose levels (i.e. each original non-reference dose minus the reference dose within a study) will be used for model fitting, as it is expected that both mean differences and RRs will not have zero as a reference sodium intake value.

If the number of intake categories is not sufficient to estimate the study-specific trends (i.e. less than 3), a one-stage (or 'pool-first') approach will be taken, where study-specific data are combined first and then one summary dose–response model is fitted. It is likely that only the latter will be suitable for the sodium–blood pressure dose–response modelling (as most studies will have just a "low" sodium intake group and a "control" sodium intake group).

If the number of included studies is too low (as could be the case for observational studies across all sub-questions) and a suitable dose–response function is not reported by the authors, consideration will be given to trend estimation in individual studies by the application of the first stage of the approach.

The generalized least square method will allow estimation of the dose–response trend from the intake-specific relative risks (or mean differences) to describe the overall functional relation and predict the change in the lnRR (or mean differences) per unit change of sodium intake.

Hypothesis testing, identification of statistical heterogeneity, predictions and graphical presentation of the pooled dose–response curves will be carried out according to the methods described by Crippa and Orsini (2016) and Orsini et al. (2012).

Outliers and influential studies will be detected (Berlin et al., 1993). Statistics obtained from random permutations will be used to adjust for the issue of multiple testing (Higgins and Thompson, 2004).

Goodness-of-fit of models on means and RRs will be assessed applying the approach described in (Crippa and Orsini, 2016) and (Discacciati et al., 2017), respectively.

For all dichotomous outcomes (e.g. CVD-related endpoints) the modelling approach will produce estimates of the relative risk of having the disease at relevant sodium intake levels as compared with a reference value of interest (e.g. the minimum usual intake across populations; the median intake across European populations).

For all continuous outcomes (e.g. BMD, BMC), the modelling approach will produce estimates of the mean changes in the endpoints at relevant sodium intake levels as compared with a suitable reference value. In addition, the modelling of absolute achieved mean values of SBP and DBP vs. absolute sodium intake could allow the identification of a range of sodium intakes for which the predicted blood pressure values would be associated with the lowest risk of CVD.

3.7.3. Subgroup analyses

A number of factors potentially influencing the dose–response relationships have been identified *a priori* both from the literature and by the Panel. Sub-group analyses (and corresponding modelling in meta-regressions) will be 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 include: exposure and outcome measurement methods (e.g. number of 24-h urinary collections; point office blood pressure vs. 24-h ambulatory blood pressure; subject's position (e.g. supine, sitting); study design (e.g. cross-over vs. parallel trials, duration, type of intervention (e.g. dietary counselling, Na tablet)). Contextual sources of heterogeneity include: age, sex, BMI, hypertension status, baseline and/or achieved values of sodium intake, baseline values of SBP and DBP.

3.7.4. Sensitivity analyses

A number of sensitivity analyses will be carried out to evaluate whether the findings are robust to the assumptions made in the systematic review protocols and the analyses (e.g. meta-regression models). There are a number of assumptions/decisions/issues provisionally identified that can potentially be tested in sensitivity analyses: on data cleaning issues (e.g. implausible values; missing data); on quality dimensions (e.g. incomplete follow-up; confounding adjustments); on analytical approaches (e.g. data imputation; choice of categories); on eligibility criteria (e.g. study design; exposure and outcome measurement methods); on risk of bias ratings (see following section on how risk-of-bias is dealt with in the analysis).

3.7.5. Addressing risk of bias in the analysis

The outcome of the individual studies appraisal will be used in the analysis as recommended by the Cochrane Collaboration (Higgins and Green, 2011) to evaluate whether heterogeneity of results can be attributed to differences in internal validity. The following approaches will be considered: to run the analysis on low-moderate-risk studies only (restriction - depending on a suitable number of studies that fall in this category); to run a subgroup analysis (or meta-regression) by risk of bias categories (stratification - depending on sub-group size); to integrate a qualitative (narrative) evaluation of the risk-of-bias in the discussion of the analysis results (e.g. in case the number of studies is small).

All statistical analyses will be performed with STATA version 13.1 (StataCorp, 2013) and R version 3.3.2 (R Core Team, 2013). Unless otherwise specified, all estimates will be presented with 95% confidence intervals and all analyses will be carried out at the level of statistical significance of 0.05.

3.8. Evaluating the uncertainty in the body of evidence

Once the individual studies are appraised for internal validity and after synthesising the evidence, for each sub-question, outcome and line of evidence (i.e. RCTs separately from observational studies), the uncertainty in the body of evidence will be discussed, by considering factors such as the consistency of results, the precision of effect/association estimates and/or dose–response models, the internal validity and external validity (directness, generalisability, applicability) of the included studies.

3.9. Plans for updating the literature searches and dealing with newly available evidence

The literature searches performed as detailed above (3.3.) will be repeated approximately 3 months before the planned date of endorsement of the opinion by the Panel.

The papers retrieved by these additional searches will be screened for relevance, applying the same criteria.

Relevant studies will be narratively reviewed by the Working Group experts, and where controversial issues are identified (e.g. conflicting conclusions) these will be discussed in the Working Group, which will prepare a proposal on how to deal with the issues. The controversial issues and the proposed solutions will be brought to the attention of the Panel, which will take the final decision.

4. Method for combining the evidence and setting the DRVs for sodium (section 6 of the scientific opinion)

The Dietary Reference Values for sodium will be set according to the principles for deriving DRVs established by the Panel (EFSA NDA Panel, 2010). DRVs are typically set by population subgroups, according to lifestage and sex.

4.1. Selection of the criterion(a) to be used to derive DRVs for sodium

The Panel has identified the following possible criteria to derive DRVs for sodium: i) sodium balance (see Section 5.2 of the scientific opinion); ii) risk of diseases (i.e. CVD; osteoporotic fractures); iii) relationship with intermediate endpoints (i.e. blood pressure, BMC and BMD).

Which criterion, or combination of criteria, is the most appropriate to set DRVs for sodium will be a matter of scientific judgement, taking into account all available data and weighing of the evidence. The possibility to identify a quantitative dose–response relationship between sodium intake and the envisaged criterion(a) is a key element of the selection process.

In relation to chronic diseases, the outcome of the systematic reviews will be used to evaluate:

- whether there is a relationship between sodium intake and the selected diseases;
- in which population subgroups it exists (e.g. age, sex) and if it differs across them;
- whether a quantitative dose–response relationship can be identified and characterised.

In weighing the evidence, the Panel will then consider i) the uncertainty in the body of evidence for each sub-question, outcome and line of evidence (3.8.); ii) whether the observed relationship(s) relates to disease outcome or intermediate endpoints. A quantitative dose–response relationship between sodium intake and a disease outcome would provide the strongest level of evidence to set DRVs for sodium based on the risk of chronic diseases. However, should such evidence not be available, the Panel considers that evidence on a relationship between sodium intake and intermediate endpoints such as blood pressure, BMD or BMC (in children) could be sufficient to derive DRVs for sodium, because of the well-established relationships between these markers and diseases (i.e. CVD and osteoporotic fractures, respectively).

4.2. Identification of the type of DRVs to be set

The Panel anticipates that Average Requirements (ARs) cannot be determined for sodium based on the evidence reviewed in the draft Opinion (see Section 5 of the scientific opinion). The Panel also notes that the setting of an AR based on chronic disease endpoints is particularly challenging.

The Panel will consider whether an adequate intake (AI) can be set based on observed, or experimentally determined, approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people. For example, the Panel considers that an AI may be set at the level of sodium intake associated with the lowest risk of chronic disease(s).[18] However, depending on the available evidence and shape(s) of the dose–response relationship(s), it may not be possible to identify a single value. In such a case, a range of adequate intakes may be proposed.

4.3. Bridging data gaps

In instances where no data are available to set DRVs for specific age and sex group, interpolation or extrapolation could be used (EFSA NDA Panel, 2010). To that end, the Panel will consider whether the extrapolation of the relationship observed in a certain subgroup to another subgroup of the population is scientifically justified.

5. Human resources, software and timelines for undertaking the scientific assessment

Tasks for performing the different steps in the assessment are shown in Table 11.

Table 11: Human resources, software and timelines.

What	Who	Software
Search process	EFSA information specialist	Endnote
Study selection for relevance	EFSA staff	Distiller SR
Data extraction	EFSA staff	Distiller SR/Excel[19]
Appraisal of relevant studies	WG experts	Distiller SR
Uncertainty analysis	WG experts + EFSA staff[20]	n.a.
Synthesis of results	EFSA staff	Stata, R
Opinion drafting	WG experts + EFSA staff	n.a.
Update of the searches	EFSA information specialist	Endnote
Study selection for relevance	EFSA staff	Distiller SR
Narrative review of relevant additional studies	WG experts + EFSA staff	n.a.
Endorsement of draft opinion	NDA panel experts	n.a.
Public consultation on draft opinion	Interested parties	n.a.
Technical report of the PC	WG experts + EFSA staff	n.a.
Opinion finalisation	WG experts + EFSA staff	n.a.
Adoption of final opinion	NDA panel experts	n.a.

6. Plan for reviewing the protocol

The draft protocol was published for public consultation from 29 September to 12 November 2017. The members of the WG on DRVs for minerals and the NDA Panel considered the comments received and amended the protocol, where appropriate. A technical report, summarising the comments received and considerations from the Panel, was published in December 2017 (EFSA, 2017).

[18] Such approach was previously taken to set DRVs for potassium (EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. Scientific opinion on dietary reference values for potassium. EFSA Journal, 14(10):4592, 56 pp.)
[19] Protocol amendment: ADDITION
[20] Protocol amendment: ADDITION

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Abbreviations

AI	Adequate Intake
AR	Average Requirement
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CIGMA	continuous infusion of glucose with model assessment
CVD	cardiovascular disease
DBP	diastolic blood pressure
DRV	Dietary Reference Value
DXA	dual-energy X-ray absorptiometry
FFQ	food frequency questionnaire
HDL	high density lipoprotein
IOM	US Institute of Medicine of the National Academy of Sciences
LDL	low density lipoprotein
OGTT	oral glucose tolerance test
OHAT/NTP	office of health assessment and translation/national toxicology program
PRI	Population Reference Intake
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RAAS	renin-angiotensin-aldosterone system
RCT	randomised controlled trial
RoB	risk of bias
RR	relative risk
SBP	systolic blood pressure
SQ	sub-question
WG	working group
WHO	World Health Organization

Appendix A – Effect of sodium intake on blood lipids – meta-analyses of trials of at least four weeks.

Ref	Inclusion criteria						Included studies																N	Pooled effect (95% CI)
	Study type	Achieved sodium difference between experimental groups	Intervention duration	Participants	Co-intervention		(Kirkendall et al., 1976)	(Grobbee et al., 1987)	(Sciarrone et al., 1992)	(Fotherby and Potter, 1993)	(Ruppert et al., 1993)	(Muhlhauser et al., 1996)	(Schorr et al., 1996)	(McCarron et al., 1997)	(Meland et al., 1997)	(Fotherby and Potter, 1997)	(Ames, 2001)	(Cappuccio et al., 1997)	(van Berge-Landry and James, 2004)	(Gates et al., 2004)	(Harsha et al., 2004)	(Voat et al., 2008)	(Meland and Aamland, 2009)	(Jablonski et al., 2013)		
(He et al., 2013)	RCTs allocating to a modestly reduced salt intake or usual salt intake.	A reduction in 24-h urinary sodium within the range of 40 to 120 mmol.	At least 4 weeks.	• Adults (≥18 years) (trials in children or pregnant women excluded), irrespective of ethnicity • With normal or raised BP • Trials in patients with other diseases than hypertension were excluded.	Studies with concomitant interventions (i.e. nonpharmacological interventions, antihypertensive or other medications) were excluded.	TC	X			X	X		X		X			X			X	X			8	0.05 (–0.02, 0.11) mmol/L
						TG				X	X		X					X		X	X				6	0.04 (–0.02, 0.09) mmol/L
						HDL				X	X		X		X					X	X				6	–0.02 (–0.06, 0.01) mmol/L
						LDL				X	X		X							X	X				5	0.05 (–0.01, 0.12) mmol/L
(Graudal et al., 2011b)	RCTs allocating subjects to either a low or a high sodium diet.	Any.	Any. Subgroup analysis restricted to studies ≥ 4 weeks.	• Any age, irrespective of ethnicity • With normal or raised BP • Trials in patients with other diseases than elevated blood pressure were excluded.	Studies with concomitant interventions were included if the co-intervention was identical during the low and high sodium diet.	TC	X						X	X	X	X	X		X	X	X				9	3.21 (–2.51, 8.93) mg/dL
						TG							X	X		X	X		X	X	X				7	8.37 (–1.43, 18.18) mg/dL
						HDL							X	X	X	X	X			X	X		X		8	–0.14 (–2.58, 2.30) mg/dL
						LDL							X	X		X	X			X	X				6	3.72 (–2.67, 10.11) mg/dL
(WHO, 2012c)	RCTs which included an intervention that planned to or achieved a reduced sodium intake.	A reduction in 24-h urinary sodium > 40 mmol/day .	At least 4 weeks.	• Adults (≥16 years), irrespective of ethnicity • With normal or raised BP • Trials in patients with chronic conditions (e.g. overweight or obesity, diabetes, chronic nephrolithiasis) were included. • Studies targeting patients who were acutely ill or infected with HIV were excluded.	Studies with concomitant interventions (e.g. physical activity, medical treatment (e.g. diuretics or beta blockers)) were included if the co-intervention was identical in the intervention and control groups.	TC		X	X	X	X		X	X			X			X	X	X	X		11	0.02 (–0.03, 0.07) mmol/L
						TG		X	X	X			X				X			X	X		X		8	0.04 (–0.01, 0.09) mmol/L
						HDL		X	X	X	X		X	X						X	X		X		9	–0.01 (–0.03, 0.00) mmol/L
						LDL		X	X	X			X							X	X				6	0.03 (–0.02, 0.08) mmol/L

Ref	Inclusion criteria						Included studies																N	Pooled effect (95% CI)
	Study type	Achieved sodium difference between experimental groups	Intervention duration	Participants	Co-intervention		(Kirkendall et al., 1976)	(Grobbee et al., 1987)	(Sciarrone et al., 1992)	(Fotherby and Potter, 1993)	(Ruppert et al., 1993)	(Muhlhauser et al., 1996)	(Schorr et al., 1996)	(McCarron et al., 1997)	(Meland et al., 1997)	(Fotherby and Potter, 1997)	(Ames, 2001)	(Cappuccio et al., 1997)	(van Berge-Landry and James, 2004)	(Gates et al., 2004)	(Harsha et al., 2004)	(Voqt et al., 2008)	(Meland and Aamland, 2009)	(Jablonski et al., 2013)		
(Australia/New Zealand Expert Working Group for Sodium, 2017)	RCTs allocating subjects to either a low or a high sodium diet.	Any.	At least 4 weeks.	• Adults (≥18 years) (trials in children or pregnant women excluded), irrespective of ethnicity • With normal or raised BP • Trials in patients with other diseases than hypertension and diabetes (type 1 or 2; that has not progressed to nephropathy or CKD) were excluded.	Studies with concomitant interventions (simultaneous interventions) were included if the role of sodium could be isolated.	TC	X	X	X	X	X		X	X	X		X	X	X	X		X	X	14	0.03 (–0.02, 0.08) mmol/L
						HDL			X	X	X		X	X	X					X	X		X	X	10	–0.01 (–0.02, 0.01) mmol/L
						LDL			X	X	X		X	X						X	X			X	8	0.01 (–0.06, 0.09) mmol/L

CKD: chronic kidney disease; HIV: human immunodeficiency virus; LDL: low density lipoproteins; HDL: high density lipoproteins; TC: total cholesterol; TG: triglycerides

Appendix B – Effect of sodium intake on blood catecholamines and aldosterone concentrations and renin activity – meta-analyses of trials of at least four weeks.

Ref	Inclusion criteria						Included studies																	N	Pooled effect (95% CI)
	Study type	Achieved sodium difference between experimental groups	Intervention duration	Participants	Co-intervention		(MacGregor et al., 1982)	(Watt et al., 1983)	(Andersson et al., 1984)	(Richards et al., 1984)	(Grobbee et al., 1987)	(MacGregor et al., 1989)	(Carney et al., 1991)	(Singer et al., 1991)	(Benetos et al., 1992)	(Fotherby and Potter, 1993)	(Ruppert et al., 1993)	(Schorr et al., 1996)	(Ames, 2001)	(Cappuccio et al., 1997)	(Nowson et al., 2003)	(Gates et al., 2004)	(Swift et al., 2005)	(Melander et al., 2007)	(He et al., 2009)		
(He et al., 2013)	RCTs allocating to a modestly reduced salt intake or usual salt intake.	A reduction in 24-h urinary sodium within the range of 40 to 120 mmol.	At least 4 weeks.	• Adults (≥18 years) (trials in children or pregnant women excluded), irrespective of ethnicity • With normal or raised BP Trials in patients with other diseases than hypertension were excluded.	Studies with concomitant interventions (i.e. nonpharmacological interventions, antihypertensive or other medications) were excluded.	RA	X	X		X	X	X			X	X	X	X		X		X	X		X	13	0.26 (0.17, 0.36) ng/mL/h
						ALD	X			X		X				X		X	X			X	X		X	8	73.20 (44.92, 101.48) pmol/L
						NOR				X	X	X			X		X					X				6	31.67 (6.57, 56.77) pg/mL
						ADR				X	X				X							X				4	6.70 (−0.25, 13.64) pg/mL
(Graudal et al., 2011b)	RCTs allocating subjects to either a low or a high sodium diet.	Any.	Any. Subgroup analysis restricted to studies ≥ 4 weeks.	• Any age, irrespective of ethnicity • With normal or raised BP Trials in patients with other diseases than elevated blood pressure were excluded.	Studies with concomitant interventions were included if the co-intervention was identical during the low and high sodium diet.	RA[a]	?	?		?	?	?	?	?	?	?		?			?	?	?	?	?	14	0.47 (0.35, 0.60) [b]
						ALD	X			X		X	X	X	X	X		X					X		X	9	0.70 (0.37, 1.04) [b]
						NOR				X	X	X			X				X			X				6	0.06 (−0.19, 0.32) [b]
						ADR				X	X				X				X			X				5	0.24 (−0.04, 0.52) [b]
(WHO, 2012c)	RCTs which included an intervention that planned to or achieved a reduced sodium intake.	A reduction in 24-h urinary sodium > 40 mmol/day .	At least 4 weeks.	• Adults (≥16 years), irrespective of ethnicity • With normal or raised BP • Trials in patients with chronic conditions (e.g. overweight or obesity, diabetes, chronic nephrolithiasis) were included. Studies targeting patients who were acutely ill or infected with HIV were excluded.	Studies with concomitant interventions (e.g. physical activity, medical treatment (e.g. diuretics or beta blockers)) were included if the co-intervention was identical in the intervention and control groups.	RA														Not assessed						
						ALD														Not assessed						
						NOR			X	X	X	X			X		X					X				7	8.23 (−27.84, 44.29) pg/mL
						ADR				X	X				X							X				4	6.90 (−2.17, 15.96) pg/mL

ADR: adrenaline; ALD: aldosterone; NOR: noradrenaline; RA: renin activity

(a): Through their systematic review, Graudal et al., 2011b retrieved 15 trials lasting ≥ 4 weeks which reported on RA. However, the paper indicates that the pooled analysis for the subgroup of studies lasting ≥ 4 weeks included 14 trials. The list of references included in the pooled analysis is not provided.
(b): Standardised mean difference, calculated for outcome measures with different units. The difference in effect between two treatments is divided by the standard deviation of the measurements.

Appendix C – RCTs assessing the effect of sodium intake on direct measures of insulin sensitivity and glucose tolerance

C1. Insulin sensitivity assessed using the hyperinsulinaemic-euglycaemic clamp technique

Reference	Population	Design	Insulin infusion rate	Na intake (mg(mmol)/d)	FPG	FPI	Insulin sensitivity indexes	
							M	M/I
(Donovan et al., 1993)	8 NT Both sexes	5-d cross-over, variable washout	40 mU/m^2/min	230 (10) 4,600 (200)	mean ± SEM mg/dL 96±2 97±2 NS	mean ± SEM µU/mL 5±2 5±1 NS	mean ± SEM mg/m^2/min 334±24 279±19 p < 0.01	mean ± SEM µmol/m^2/min per µU/mL 5.92±0.45 4.98±0.42 p < 0.05
(Fliser et al., 1995)	7 healthy young NT men	3-d cross-over, no washout	40 mU/m^2/min	460 (20) 4,600 (200)	mean ± SD mmol/L 4.6±0.3 4.7±0.2 NS	mean ± SD uU/mL 9.7±2.7 7.3±2.4 p < 0.05	mean ± SD mg/kg/min 7.4±1.2 8.6±1.1 p < 0.01	
	7 healthy young NT men	7-d cross-over, no washout			4.4±0.4 4.4±0.2 NS	8.4±3.8 6.1±2.9 p < 0.05	7.8±1.8 7.6±1.3 NS	
(Gomi et al., 1998)	12 HT, both sexes	1-week run-in (4,600 Na intake) + 1-week cross-over, no washout	1.5 mU/kg/min	690 (30) 2,300 (100)	mean±SD mmol/L 4.66±0.39 4.67±0.23 NS	mean±SD µU/mL 10.90±3.50 7.75±2.55 p < 0.01	mean±SD µmol/m^2/min 1,057±173 1,318±189 p < 0.01 NS compared to the 4,600 Na intake run-in	mean±SD µmol/m^2/min per µU/mL 13.2±1.9 16.6±2.1 p < 0.01
(Foo et al., 1998)	18 NT, both sexes	6-d cross-over, ≥ 1 week washout	2-step clamp 40 and 600 mU/min/m^2	920 (40) 5,060 (220)	mean±SD pmol/L 4.8±0.3 4.9±0.3 NS	geometric mean x/SD pmol/L 18.2 x/ 1.9 22.2 x/ 1.7 NS	geometric mean x/SD dL/min* Low-dose insulin 5.13 (SD x/1.35) 4.94 (SD x/1.37) p = 1.0 High-dose insulin 9.68 (SD x/1.30) 9.68 (SD x/1.27) p = 0.69 *Clearance rate of glucose at steady state not adjusted by body size	

Reference	Population	Design	Insulin infusion rate	Na intake (mg(mmol)/d)	FPG	FPI	Insulin sensitivity indexes	
							M	M/I
(Perry et al., 2003)	15 NT men	5-d cross-over, ≥ 1 week washout, placebo vs 100 mmol/d Na in addition to usual diet	1.5 mU/kg/min	24-h urinary Na (mg/24h (mmol/24h)) 1,610±1,035 (70±45) 4,025±1,656 (175±72)	mean±SD mmol/L 4.5±0.33 4.5±0.45 NS	mean±SD µU/mL 11.6±3.24 11.4±3.02 NS	median (IQR) mg/kg/min 10.2 (9.5–13.8) 12.8 (9.6–14.3) $p < 0.05$	mean±SD mg/kg/min per µU/mL 0.08±0.033 0.10±0.049 $p < 0.05$
(Townsend et al., 2007)	20 NT sexes (10 SS, 10 SR), both	6-d cross-over, 4-week washout	40 mU/m^2/min	460 (20) 4,600 (200)			mean±SEM mg/kg/min 6.11±0.40 7.41±0.41 $p = 0.03$ NS between SS and SR subjects	

FPG = fasting plasma glucose; FPI= fasting plasma insulin; HT= hypertensives; LBM = lean body mass; M = mean glucose infusion rate at steady state; M/I = mean glucose infusion rate at steady state/ steady-state insulin concentration; NS = not significantly different from the "low sodium" diet; NT = Normotensives; SR = salt resistant; SS = salt sensitive

C2. Insulin sensitivity assessed using insulin suppression tests

Reference	Population	Design	Insulin infusion rate	Somatostatin/ analogue infusion rate	Glucose infusion rate	Na intake (mg(mmol)/d)	SSPG (mmol/L)	SSPI (pmol/L)
(Sharma et al., 1993)	18 NT healthy young men, 7 SS, 11 SR	1-week cross-over, no washout, placebo vs 220 mmol/d Na in addition to diet	24 mU/m^2/min	Somatostatin, 350 μg/h	150 mg/m^2/min	24- urinary Na mean±SD SR (mmol/24h) 12±3 230 ± 16 SS (mmol/24h) 25±3 242±14	mean±SD Low-Na SR: 3.9±0.9 SS: 6.7±2.0 p = 0.001 High-Na SR: 3.8±1.1 SS: 5.9+1.6 p = 0.005 NS between low-Na and high-Na within either SR or SS	Similar results for SPSPG/SSPI as for SSPG for SR vs SS and for low-Na vs high-Na.
(Facchini et al., 1999)	19 healthy NT, both sexes	5- cross-over, no washout	25 mU/m^2/min	Ocreotide, 5 μg/min	240 mg/m^2/min	575 (25) 4,600 (200)	mean±SEM 8.25±1.01 7.83±1.00 NS	mean±SEM 306±42 330±49 NS
(Suzuki et al., 2000)	20 HT, both sexes	1-week cross-over, no washout	0.77 mU/kg/ min	Ocreotide, 73.5 pmol/h	6 mg/kg/ min	1,150 (50) 5,175 (225)	mean±SEM 12.2±0.6 11.2±0.7 NS	mean±SEM 312±16 293±15 NS

HT= hypertensives; NS = not significantly different from the "low sodium" diet; NT = Normotensives; SS = salt sensitive; SSPG – steady-state plasma glucose; SSPI = steady state plasma insulin; SR = salt resistant

C3. Glucose tolerance using a standard oral glucose tolerance test

Reference	Population	Design	Na intake (mg(mmol)/d)	FPG (mean ± SEM)	FPI (mean ± SEM)	OGTT iAUC glucose (mean ± SEM)	OGTT iAUC insulin (mean ± SEM)
Iwaoka et al., (1988)	15 HT, both sexes	8-d cross-over, no washout	2,000 (87) 20,000 (870)	mg/dL 96.2±4.2 91.4±3.3 p<0.05	µU/mL 7.8±1.0 6.2±0.5 p<0.05	mg · h/dL 153.4±16.7 110.3±11.5 p<0.005	µU· h/mL 97.1±18.4 69.2±12.1 p<0.025
Sharma et al., 1991	23 NT young lean males; 10 SS, 13 SR	6-d cross-over, no washout	460 (20) 5,980 (260)	mmol/L SR 4.4±0.4 4.1±0.3 NS SS 4.2±0.1 4.2±0.1 NS	mU/L SR 11.4 ± 1.5 10.4 ± 1.4 NS SS 10.8±1.5 11.6±1.8 NS	min · mmol/L SR 867 ± 61 801 ± 59 NS SS 864±76 1,140±96* p < 0.02 *p <0.008 vs SR	min · mU/L SR 4,835 ± 455 3,911 ± 347 p ≤0.05 SS 6,258±1,216 8,567±1,147* p = 0.003 *p < 0.02
Inoue et al., 1996	14 HT middle-age, both sexes	7-d cross-over, no washout	230 (10) 8,050 (350)	NS (values reported in a figure only)	mU/L 10.6±1.6 8.1±1.3 8.7±1.5* NS *High-Na value corrected for haemodilution	Analysis by two-way ANOVA of values at 0, 1 and 2-h during the OGTT NS	Analysis by two-way ANOVA of values at 0, 1 and 2-h during the OGTT; Significantly higher response during the high-NA, p = 0.020; NS when high-NA values were corrected for haemodilution

FPG = fasting plasma glucose; FPI= fasting plasma insulin;HT= hypertensives; NS = not significantly different from the "low sodium" diet; NT = Normotensives; SS = salt sensitive; iAUC = incremental area under the curve; SR = salt resistant

Appendix D – Search strings

D.1. Sub-question 1. Systematic reviews, clinical trials

Cochrane Library. Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects

ID	Search
#1	([mh Sodium] or [mh "sodium chloride"]) and ([mh Diet] or diet:ti,ab,kw or diets:ti,ab,kw or dieta*:ti,ab,kw or diete*:ti,ab,kw or intak*:ti,ab,kw or consum*:ti,ab,kw or ingest*:ti,ab,kw or added:ti,ab,kw or restrict*:ti,ab,kw or limit*:ti,ab,kw or low:ti,ab,kw or lower*:ti,ab,kw or reduc*:ti,ab,kw or excess*:ti,ab,kw or free:ti,ab,kw or high:ti,ab,kw or higher:ti,ab,kw or chang*:ti,ab,kw)
#2	(salt:ti,ab,kw or NaCl:ti,ab,kw or natrium:ti,ab,kw or sodium:ti,ab,kw) and [mh diet]
#3	(salt:ti,ab,kw or NaCl:ti,ab,kw or natrium:ti,ab,kw or sodium:ti,ab,kw) near/3 (diet:ti,ab,kw or diets:ti,ab,kw or dieta*:ti,ab,kw or diete*:ti,ab,kw or intak*:ti,ab,kw or consum*:ti,ab,kw or ingest*:ti,ab,kw or added:ti,ab,kw or restrict*:ti,ab,kw or limit*:ti,ab,kw or low:ti,ab,kw or lower*:ti,ab,kw or reduc*:ti,ab,kw or excess*:ti,ab,kw or free:ti,ab,kw or high:ti,ab,kw or higher:ti,ab,kw or chang*:ti,ab,kw)
#4	[mh "Sodium, Dietary"] or [mh "Diet, Sodium-Restricted"]
#5	#1 or #2 or #3 or #4
#6	[mh "Blood Pressure"] or "Blood pressure":ti,ab,kw or "arterial pressure":ti,ab,kw or diastolic:ti,ab,kw or systolic:ti,ab,kw or bloodpressure:ti,ab,kw or [mh Hypertension] or hypertensi*:ti,ab,kw or [mh Hypotension] or hypotensi*:ti,ab,kw or [mh Prehypertension] or prehypertensi*:ti,ab,kw or "brachial pressure":ti,ab,kw or " aortic pressure":ti,ab,kw or normotens*:ti,ab,kw or "normo tension":ti,ab,kw or "normo tensive":ti,ab,kw or "normo tensives":ti,ab,kw
#7	#6 and #5 Publication Year from 2016 to 2018

Embase

Search	Query
#16	#15 AND [2016-2018]/py
#15	#14 NOT ([conference abstract]/lim OR [editorial]/lim) AND ([basque]/lim OR [bulgarian]/lim OR [catalan]/lim OR [croatian]/lim OR [czech]/lim OR [danish]/lim OR [dutch]/lim OR [english]/lim OR [estonian]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [greek]/lim OR [hungarian]/lim OR [icelandic]/lim OR [italian]/lim OR [latvian]/lim OR [lithuanian]/lim OR [norwegian]/lim OR [polish]/lim OR [portuguese]/lim OR [romanian]/lim OR [scottish gaelic]/lim OR [slovak]/lim OR [slovenian]/lim OR [spanish]/lim OR [swedish]/lim)
#14	#13 AND #12
#13	#8 NOT #11
#12	'clinical trial'/exp OR 'clinical trial' OR randomized:ti,ab OR randomised:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab OR 'clinical trial (topic)'/exp OR 'clinical trial (topic)' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR ((singl* OR doubl* OR trebl* OR tripl*) NEAR/10 (mask* OR blind* OR dumm*)):ti,ab OR 'crossover procedure'/exp OR 'crossover procedure' OR ((crossover OR 'cross over') NEAR/10 (study OR studies OR design* OR method* OR procedure OR comparison)):ti,ab OR 'meta analysis'/exp OR 'meta analysis' OR 'meta analysis (topic)'/exp OR 'meta analysis (topic)' OR 'systematic review'/exp OR 'systematic review' OR 'systematic review (topic)'/exp OR 'systematic review (topic)' OR 'biomedical technology assessment'/exp OR 'biomedical technology assessment' OR (systematic* NEAR/3 (review* OR overview*)):ti,ab OR (methodologic* NEAR/3 (review* OR overview*)):ti,ab OR (quantitative NEAR/3 (review* OR overview* OR synthes*)):ti,ab OR (research NEAR/3 (integrati* OR overview*)):ti,ab OR (integrative NEAR/3 (review* OR overview*)):ti,ab OR (collaborative NEAR/3 (review* OR overview*)):ti,ab OR (pool* NEAR/3 analy*):ti,ab OR (data NEAR/1 (synthes* OR extraction* OR abstraction*)):ti,ab OR handsearch*:ti,ab OR 'hand search':ti,ab OR 'hand searches':ti,ab OR 'hand searching':ti,ab OR 'mantel haenszel':ti,ab OR peto:ti,ab OR 'der simonian':ti,ab OR dersimonian:ti,ab OR 'fixed effect':ti,ab OR 'fixed effects':ti,ab OR 'latin square':ti,ab OR 'latin squares':ti,ab OR 'meta analysis':ti,ab OR 'meta analyses':ti,ab OR 'met analysis':ti,ab OR 'met analyses':ti,ab OR metaanaly*:ti,ab OR metanaly*:ti,ab OR 'meta

	regression':ti,ab OR 'meta regressions':ti,ab OR metaregression*:ti,ab OR medline:ti,ab OR cochrane:ti,ab OR pubmed:ti,ab OR medlars:ti,ab OR embase:ti,ab OR cinahl:ti,ab OR cochrane:jt OR 'evidence report':jt OR (comparative NEAR/3 (efficacy OR effectiveness)):ti,ab OR 'outcomes research':ti,ab OR 'relative effectiveness':ti,ab OR ((indirect OR 'indirect treatment' OR 'mixed treatment') NEAR/3 comparison):ti,ab
#11	#9 NOT#10
#10	'human'/exp OR 'human experiment'/de
#9	'animal'/exp OR 'animal experiment'/exp
#8	#6 AND #7
#7	'blood pressure'/exp OR ((blood OR arterial OR brachial OR aortic) NEAR/2 pressure):ti,ab OR diastolic:ti,ab OR systolic:ti,ab OR bloodpressure:ti,ab OR 'hypertension'/exp OR hypertensi*:ti,ab OR 'hypotension'/exp OR hypotensi*:ti,ab OR prehypertensi*:ti,ab OR normotensi*:ti,ab OR (normo NEAR/1 tensi*):ti,ab
#6	#1 OR #2 OR #3 OR #4 OR #5
#5	'sodium'/exp/mj OR 'sodium chloride'/exp/mj AND ('dietary intake'/de OR 'dietary reference intake'/exp OR 'diet restriction'/de OR 'diet'/de OR diet:ti,ab OR diets:ti,ab OR dieta*:ti,ab OR diete*:ti,ab OR intak*:ti,ab OR consum*:ti,ab OR ingest*:ti,ab OR added:ti OR restrict*:ti OR limit*:ti OR low:ti OR lower*:ti OR reduction*:ti OR excess*:ti OR high:ti OR higher:ti OR change*:ti OR free:ti)
#4	sodium:ti OR salt:ti OR natrium:ti OR nacl:ti AND ('dietary intake'/de OR 'dietary reference intake'/exp OR 'diet'/de OR 'diet restriction'/de)
#3	((sodium OR salt OR nacl OR natrium) NEAR/3 (intak* OR consum* OR ingest* OR added OR restrict* OR limit* OR low OR lower* OR reduction* OR excess* OR free OR high OR higher OR change*)):ti,ab
#2	diet:ti,ab OR diets:ti,ab OR dieta*:ti,ab OR diete*:ti,ab AND (sodium:ti,ab OR salt:ti,ab OR natrium:ti,ab OR nacl:ti,ab)
#1	'sodium intake'/exp OR 'salt intake'/exp OR 'sodium restriction'/exp

Search string to identify systematic reviews and clinical trials adapted from CADTH's Database Search Filters:

CADTH database search filters [Internet]. Ottawa: CADTH; 2016. Available from: /resources/finding-evidence

Pubmed

Search	Query
#15	Search #13 AND #12 Filters: Publication date from 2016/01/01
#14	Search #13 AND #12
#13	Search (Bulgarian[lang] OR Croatian[lang] OR Czech[lang] OR Danish[lang] OR Dutch[lang] OR English[lang] OR Estonian[lang] OR Finnish[lang] OR French[lang] OR German[lang] OR Greek, Modern[lang] OR Hungarian[lang] OR Italian[lang] OR Latvian[lang] OR Lithuanian[lang] OR Norwegian[Lang] OR Polish[lang] OR Portuguese[lang] OR Romanian[lang] OR Scottish gaelic[lang] OR Slovak[lang] OR Slovenian[lang] OR Spanish[lang] OR Swedish[lang] OR "multiple languages"[Lang] OR "undetermined"[Lang])
#12	Search #10 AND #11
#11	Search "clinical trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Clinical Trials as Topic"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) AND (mask*[tiab] OR blind*[tiab] OR dumm*[tiab])) OR "Cross-Over Studies"[Mesh] OR ((crossover[tiab] OR "cross over"[tiab]) AND (study[tiab] OR studies[tiab] OR design*[tiab] OR method*[tiab] OR procedure[tiab] OR comparison[tiab])) OR systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab]

	OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal:__jrid21711]
#10	Search #9 NOT "Editorial" [Publication Type]
#9	Search #7 NOT #8
#8	Search (rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR rodent[ti] OR rodents[ti] OR hamster[ti] OR hamsters[ti] OR pig[ti] OR pigs[ti] OR porcine[ti] OR rabbit[ti] OR rabbits[ti] OR animal[ti] OR animals[ti] OR dogs[ti] OR dog[ti] OR cats[ti] OR cow[ti] OR bovine[ti] OR sheep[ti] OR ovine[ti] OR monkey[ti] OR monkeys[ti]) NOT medline[sb]
#7	Search #5 NOT #6
#6	Search "Animals"[Mesh] NOT "Humans"[Mesh]
#5	Search ((((("Sodium, Dietary"[Mesh] OR "Diet, Sodium-Restricted"[Mesh])) OR ((("Sodium"[Mesh] OR "Sodium Chloride"[Mesh] OR sodium[tiab] OR salt[tiab] OR NaCl[tiab] OR natrium[tiab]) AND ("Diet"[Mesh] OR diet[tiab] OR diets[tiab] OR dieta*[tiab] OR diete*[tiab] OR intak*[tiab] OR consum*[tiab] OR ingest*[tiab] OR added[ti] OR restrict*[ti] OR limit*[ti] OR low[ti] OR lower*[ti] OR reduct*[ti] OR excess*[ti] OR free[ti] OR high[ti] OR higher[ti] OR chang*[ti])) OR "added sodium"[tiab] OR "added dietary sodium"[tiab] OR "added salt"[tiab] OR salt restrict*[tiab] OR sodium restrict*[tiab] OR sodium chloride restrict*[tiab] OR "restricted salt"[tiab] OR "restricted sodium"[tiab] OR " restricted dietary sodium"[tiab] OR "restricting dietary sodium"[tiab] OR "restricting salt"[tiab] OR sodium limit*[tiab] OR salt limit*[tiab] OR "limited salt"[tiab] OR "limited sodium"[tiab] OR "limiting salt"[tiab] OR "limiting sodium"[tiab] OR "limited dietary sodium"[tiab] OR "limiting dietary sodium"[tiab] OR "low sodium"[tiab] OR "low dietary sodium"[tiab] OR "low salt"[tiab] OR "lowering sodium"[tiab] OR "lowering dietary sodium"[tiab] OR "lowering salt"[tiab] OR salt low*[tiab] OR sodium low*[tiab] OR "lower sodium"[tiab] OR "lower dietary sodium"[tiab] OR "lower salt"[tiab] OR "salt reduction"[tiab] OR "sodium reduction"[tiab] OR "sodium chloride reduction"[tiab] OR "reduced salt"[tiab] OR "reduced sodium"[tiab] OR "reduced dietary sodium"[tiab] OR "reducing dietary sodium"[tiab] OR "reducing sodium"[tiab] OR "reducing salt"[tiab] OR "reduce sodium"[tiab] OR "reduce salt"[tiab] OR "reduce dietary sodium"[tiab] OR "salt excess"[tiab] OR "sodium excess"[tiab] OR "excessive sodium"[tiab] OR "excessive salt"[tiab] OR "excessive dietary sodium"[tiab] OR "high sodium"[tiab] OR "high salt"[tiab] OR "high dietary sodium"[tiab] OR "higher sodium"[tiab] OR "higher salt"[tiab] OR "higher dietary sodium"[tiab] OR sodium high*[tiab] OR salt high*[tiab] OR sodium chang*[tiab] OR salt chang*[tiab])))) AND ("Blood Pressure"[Mesh] OR "Blood pressure" [tiab] OR "arterial pressure"[tiab] OR diastolic[tiab] OR systolic[tiab] OR bloodpressure[tiab] OR "Hypertension"[Mesh] OR hypertensi*[tiab] OR "Hypotension"[Mesh] OR hypotensi*[tiab] OR "Prehypertension"[Mesh] OR prehypertensi*[tiab] OR "brachial pressure"[tiab] OR " aortic pressure"[tiab] OR normotens*[tiab] OR normo tens*[tiab])
#4	Search "Blood Pressure"[Mesh] OR "Blood pressure" [tiab] OR "arterial pressure"[tiab] OR diastolic[tiab] OR systolic[tiab] OR bloodpressure[tiab] OR "Hypertension"[Mesh] OR hypertensi*[tiab] OR "Hypotension"[Mesh] OR hypotensi*[tiab] OR "Prehypertension"[Mesh] OR prehypertensi*[tiab] OR "brachial pressure"[tiab] OR " aortic pressure"[tiab] OR normotens*[tiab] OR normo tens*[tiab]
#3	Search (("Sodium, Dietary"[Mesh] OR "Diet, Sodium-Restricted"[Mesh])) OR ((("Sodium"[Mesh] OR "Sodium Chloride"[Mesh] OR sodium[tiab] OR salt[tiab] OR NaCl[tiab] OR natrium[tiab]) AND ("Diet"[Mesh] OR diet[tiab] OR diets[tiab] OR dieta*[tiab] OR diete*[tiab] OR intak*[tiab] OR consum*[tiab] OR ingest*[tiab] OR added[ti] OR restrict*[ti] OR limit*[ti] OR low[ti] OR lower*[ti] OR reduct*[ti] OR excess*[ti] OR free[ti] OR high[ti] OR higher[ti] OR chang*[ti])) OR "added sodium"[tiab] OR "added dietary sodium"[tiab] OR "added salt"[tiab] OR salt restrict*[tiab] OR sodium restrict*[tiab] OR sodium chloride restrict*[tiab] OR "restricted salt"[tiab] OR "restricted sodium"[tiab] OR " restricted dietary sodium"[tiab] OR "restricting dietary sodium"[tiab] OR "restricting salt"[tiab] OR sodium limit*[tiab] OR salt limit*[tiab] OR "limited salt"[tiab] OR "limited sodium"[tiab] OR "limiting salt"[tiab] OR "limiting sodium"[tiab] OR "limited dietary sodium"[tiab] OR "limiting dietary sodium"[tiab] OR "low sodium"[tiab] OR "low dietary sodium"[tiab] OR "low salt"[tiab] OR "lowering sodium"[tiab] OR "lowering dietary sodium"[tiab] OR "lowering salt"[tiab] OR salt low*[tiab] OR sodium low*[tiab] OR "lower sodium"[tiab] OR "lower dietary sodium"[tiab] OR "lower salt"[tiab] OR "salt reduction"[tiab] OR "sodium reduction"[tiab] OR "sodium chloride reduction"[tiab] OR "reduced salt"[tiab] OR "reduced sodium"[tiab] OR "reduced dietary sodium"[tiab] OR "reducing dietary sodium"[tiab] OR "reducing sodium"[tiab] OR "reducing salt"[tiab] OR "reduce sodium"[tiab] OR "reduce salt"[tiab] OR "reduce dietary sodium"[tiab] OR "salt

	excess"[tiab] OR "sodium excess"[tiab] OR "excessive sodium"[tiab] OR "excessive salt"[tiab] OR "excessive dietary sodium"[tiab] OR "high sodium"[tiab] OR "high salt"[tiab] OR "high dietary sodium"[tiab] OR "higher sodium"[tiab] OR "higher salt"[tiab] OR "higher dietary sodium"[tiab] OR sodium high*[tiab] OR salt high*[tiab] OR sodium chang*[tiab] OR salt chang*[tiab])
#2	Search "Sodium, Dietary"[Mesh] OR "Diet, Sodium-Restricted"[Mesh]
#1	Search (("Sodium"[Mesh] OR "Sodium Chloride"[Mesh] OR sodium[tiab] OR salt[tiab] OR NaCl[tiab] OR natrium[tiab]) AND ("Diet"[Mesh] OR diet[tiab] OR diets[tiab] OR dieta*[tiab] OR diete*[tiab] OR intak*[tiab] OR consum*[tiab] OR ingest*[tiab] OR added[ti] OR restrict*[ti] OR limit*[ti] OR low[ti] OR lower*[ti] OR reduct*[ti] OR excess*[ti] OR free[ti] OR high[ti] OR higher[ti] OR chang*[ti])) OR "added sodium"[tiab] OR "added dietary sodium"[tiab] OR "added salt"[tiab] OR salt restrict*[tiab] OR sodium restrict*[tiab] OR sodium chloride restrict*[tiab] OR "restricted salt"[tiab] OR "restricted sodium"[tiab] OR " restricted dietary sodium"[tiab] OR "restricting dietary sodium"[tiab] OR "restricting salt"[tiab] OR sodium limit*[tiab] OR salt limit*[tiab] OR "limited salt"[tiab] OR "limited sodium"[tiab] OR "limiting salt"[tiab] OR "limiting sodium"[tiab] OR "limited dietary sodium"[tiab] OR "limiting dietary sodium"[tiab] OR "low sodium"[tiab] OR "low dietary sodium"[tiab] OR "low salt"[tiab] OR "lowering sodium"[tiab] OR "lowering dietary sodium"[tiab] OR "lowering salt"[tiab] OR salt low*[tiab] OR sodium low*[tiab] OR "lower sodium"[tiab] OR "lower dietary sodium"[tiab] OR "lower salt"[tiab] OR "salt reduction"[tiab] OR "sodium reduction"[tiab] OR "sodium chloride reduction"[tiab] OR "reduced salt"[tiab] OR "reduced sodium"[tiab] OR "reduced dietary sodium"[tiab] OR "reducing dietary sodium"[tiab] OR "reducing sodium"[tiab] OR "reducing salt"[tiab] OR "reduce sodium"[tiab] OR "reduce salt"[tiab] OR "reduce dietary sodium"[tiab] OR "salt excess"[tiab] OR "sodium excess"[tiab] OR "excessive sodium"[tiab] OR "excessive salt"[tiab] OR "excessive dietary sodium"[tiab] OR "high sodium"[tiab] OR "high salt"[tiab] OR "high dietary sodium"[tiab] OR "higher sodium"[tiab] OR "higher salt"[tiab] OR "higher dietary sodium"[tiab] OR sodium high*[tiab] OR salt high*[tiab] OR sodium chang*[tiab] OR salt chang*[tiab]

Search string to identify systematic reviews and clinical trials adapted from CADTH's Database Search Filters:

CADTH database search filters [Internet]. Ottawa: CADTH; 2016. Available from: /resources/finding-evidence

D.2. Sub-question 2. Systematic reviews and clinical trials

Cochrane Library. Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects

ID	Search
#1	([mh Sodium] or [mh "sodium chloride"]) and ([mh Diet] or diet:ti,ab,kw or diets:ti,ab,kw or dieta*:ti,ab,kw or diete*:ti,ab,kw or intak*:ti,ab,kw or consum*:ti,ab,kw or ingest*:ti,ab,kw or added:ti,ab,kw or restrict*:ti,ab,kw or limit*:ti,ab,kw or low:ti,ab,kw or lower*:ti,ab,kw or reduc*:ti,ab,kw or excess*:ti,ab,kw or free:ti,ab,kw or high:ti,ab,kw or higher:ti,ab,kw or chang*:ti,ab,kw)
#2	(salt:ti,ab,kw or NaCl:ti,ab,kw or natrium:ti,ab,kw or sodium:ti,ab,kw) and [mh diet]
#3	(salt:ti,ab,kw or NaCl:ti,ab,kw or natrium:ti,ab,kw or sodium:ti,ab,kw) near/3 (diet:ti,ab,kw or diets:ti,ab,kw or dieta*:ti,ab,kw or diete*:ti,ab,kw or intak*:ti,ab,kw or consum*:ti,ab,kw or ingest*:ti,ab,kw or added:ti,ab,kw or restrict*:ti,ab,kw or limit*:ti,ab,kw or low:ti,ab,kw or lower*:ti,ab,kw or reduc*:ti,ab,kw or excess*:ti,ab,kw or free:ti,ab,kw or high:ti,ab,kw or higher:ti,ab,kw or chang*:ti,ab,kw)
#4	[mh "Sodium, Dietary"] or [mh "Diet, Sodium-Restricted"]
#5	#1 or #2 or #3 or #4
#6	[mh ^"Cardiovascular Diseases"] or [mh ^" Vascular diseases "] or ((cardiovascular or vascular) near/3 (disease* or disorder* or event or events or complication* or risk* or outcome* or morbidity or mortality or death*)):ti,ab,kw or (cv near/1 disease*):ti,ab,kw or cvd:ti,ab,kw or cvds:ti,ab,kw
#7	[mh ^" Cerebrovascular Disorders "] or [mh stroke] or [mh "brain ischemia"] or stroke:ti,ab,kw or (('cerebro vascular' or 'cerebral vascular' or 'brain vascular' or cerebrovascular) near/3 (accident* or injur* or arrest* or disease* or disorder*)):ti,ab,kw or (brain near/3 (accident* or attack*)):ti,ab,kw or cva:ti,ab,kw or cvas:ti,ab,kw or ((brain or cerebral) near/3 infarct*):ti,ab,kw or apoplexy*:ti,ab,kw or ischaemic*:ti,ab,kw or ischemi*:ti,ab,kw or thrombos*:ti,ab,kw or thrombot*:ti,ab,kw or emboli*:ti,ab,kw or hypoxia:ti,ab,kw or anoxaemi*:ti,ab,kw or anoxi*:ti,ab,kw and (cerebral:ti,ab,kw or

	cerebellar:ti,ab,kw or brain:ti,ab,kw or vertebrobasilar:ti,ab,kw or intracranial:ti,ab,kw or 'intra craneal':ti,ab) or thromboembolism:ti,ab,kw or (trans*:ti,ab,kw and isch*emic:ti,ab,kw and attack*:ti,ab) or ((cerebral or cerebellar or intracerebral or 'intra cerebral' or 'intracranial' or 'intra cranial' or brain or subarachnoid or subdural or extradural or epidural) near/3 (hemorrhagic or haemorrhagic or haemorrhage* or hemorrhage* or haematoma* or hematoma* or aneurysm* or bleed*)):ti,ab,kw or atherosclero* or ((arterial or artery) near/3 (disease* or obliterate* or occlus* or obstruct*)):ti,ab,kw or ((peripheral or vascular) near/3 (occlus* or obstruct* or obliterate*)):ti,ab,kw or [mh thromboembolism] or thromboembolism*:ti,ab,kw
#8	[mh "Heart Failure"] or [mh "Myocardial Infarction"] or ((myocardi* or heart or cardia*) near/3 (infarct* or attack* or failure*)):ti,ab,kw or [mh ^"Myocardial Ischemia"] or (('heart muscle' or 'cardiac muscle' or myocardial or myocardium or cardiac or coronary or heart or transient or cardiomyophath*) near/3 (ischemi* or ischaem*)):ti,ab,kw or [mh "Acute Coronary Syndrome"] or "coronary syndrome":ti,ab,kw
#9	[mh "Coronary Disease"] or ((coronary or heart) near/3 (aneurysm* or disease*)):ti,ab,kw or (coronary near/3 (occlusion* or stenos* or obstruction* or thrombos*)):ti,ab,kw
#10	[mh "Heart Arrest"] or ((heart or cardiac or cardiopulmonary or circulatory) near/1 (arrest or arrests)):ti,ab,kw or asystole:ti,ab,kw or asystolia:ti,ab,kw or asystoly:ti,ab,kw
#11	(('congestive heart' or 'congestive cardiac' or 'cardiac congestive') near/3 (failure or insufficienc* or disease*)):ti,ab,kw
#12	#6 or #7 or #8 or #9 or #10 or #11
#13	#12 and #5 in Cochrane Reviews (Reviews and Protocols), Other Reviews and Trials
#14	#13 Publication Year from 2013 to 2018

Embase

Search	Query
#26	#24 NOT ([conference abstract]/lim OR [editorial]/lim) AND [2013-2018]/py
#25	#24 NOT ([conference abstract]/lim OR [editorial]/lim)
#24	#21 AND #22 AND #23
#23	'clinical trial'/exp OR 'clinical trial' OR randomized:ti,ab OR randomised:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab OR 'clinical trial (topic)'/exp OR 'clinical trial (topic)' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR ((singl* OR doubl* OR trebl* OR tripl*) NEAR/10 (mask* OR blind* OR dumm*)):ti,ab OR 'crossover procedure'/exp OR 'crossover procedure' OR ((crossover OR 'cross over') NEAR/10 (study OR studies OR design* OR method* OR procedure OR comparison)):ti,ab OR 'meta analysis'/exp OR 'meta analysis' OR 'meta analysis (topic)'/exp OR 'meta analysis (topic)' OR 'systematic review'/exp OR 'systematic review' OR 'systematic review (topic)'/exp OR 'systematic review (topic)' OR 'biomedical technology assessment'/exp OR 'biomedical technology assessment' OR (systematic* NEAR/3 (review* OR overview*)):ti,ab OR (methodologic* NEAR/3 (review* OR overview*)):ti,ab OR (quantitative NEAR/3 (review* OR overview* OR synthes*)):ti,ab OR (research NEAR/3 (integrati* OR overview*)):ti,ab OR (integrative NEAR/3 (review* OR overview*)):ti,ab OR (collaborative NEAR/3 (review* OR overview*)):ti,ab OR (pool* NEAR/3 analy*):ti,ab OR (data NEAR/1 (synthes* OR extraction* OR abstraction*)):ti,ab OR handsearch*:ti,ab OR 'hand search':ti,ab OR 'hand searches':ti,ab OR 'hand searching':ti,ab OR 'mantel haenszel':ti,ab OR peto:ti,ab OR 'der simonian':ti,ab OR dersimonian:ti,ab OR 'fixed effect':ti,ab OR 'fixed effects':ti,ab OR 'latin square':ti,ab OR 'latin squares':ti,ab OR 'meta analysis':ti,ab OR 'meta analyses':ti,ab OR 'met analysis':ti,ab OR 'met analyses':ti,ab OR metaanaly*:ti,ab OR metanaly*:ti,ab OR 'meta regression':ti,ab OR 'meta regressions':ti,ab OR metaregression*:ti,ab OR medline:ti,ab OR cochrane:ti,ab OR pubmed:ti,ab OR medlars:ti,ab OR embase:ti,ab OR cinahl:ti,ab OR cochrane:jt OR 'evidence report':jt OR (comparative NEAR/3 (efficacy OR effectiveness)):ti,ab OR 'outcomes research':ti,ab OR 'relative effectiveness':ti,ab OR ((indirect OR 'indirect treatment' OR 'mixed treatment') NEAR/3 comparison):ti,ab
#22	[basque]/lim OR [bulgarian]/lim OR [catalan]/lim OR [croatian]/lim OR [czech]/lim OR [danish]/lim OR [dutch]/lim OR [english]/lim OR [estonian]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [greek]/lim OR [hungarian]/lim OR [icelandic]/lim OR [italian]/lim OR [latvian]/lim OR [lithuanian]/lim OR [norwegian]/lim OR [polish]/lim OR [portuguese]/lim OR [romanian]/lim OR [scottish gaelic]/lim OR [slovak]/lim OR [slovenian]/lim OR [spanish]/lim OR [swedish]/lim
#21	#17 NOT #20
#20	#18 NOT #19

#19	'human'/exp OR 'human experiment'/de
#18	'animal'/exp OR 'animal experiment'/exp
#17	#6 AND #16
#16	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#15	trans*:ti,ab AND isch*emic:ti,ab AND attack*:ti,ab OR atherosclero*:ti,ab OR ((arterial OR artery) NEAR/3 (disease* OR obliterat* OR occlus* OR obstruct*)):ti,ab OR ((peripheral OR vascular) NEAR/3 (occlus* OR obstruct* OR obliterat*)):ti,ab OR ((cerebral OR cerebellar OR intracerebral OR 'intra cerebral' OR 'intracranial' OR 'intra cranial' OR brain OR subarachnoid OR subdural OR extradural OR epidural) NEAR/3 (hemorrhagic OR haemorrhagic OR haemorrhage* OR hemorrhage* OR haematoma* OR hematoma* OR aneurysm* OR bleed*)):ti,ab
#14	((apoplexy* OR ischaemi* OR ischemi* OR thrombos* OR thrombot* OR emboli* OR hyp oxia OR anoxaemi* OR anoxi*) NEAR/3 (cerebral OR cerebellar OR brain OR vertebrobasilar OR intracranial OR 'intra craneal')):ti,ab OR thromboembolism*:ti,ab
#13	stroke*:ti,ab OR (('cerebro vascular' OR 'cerebral vascular' OR 'brain vascular' OR cerebrovascular) NEAR/3 (accident* OR injur* OR arrest* OR disease* OR disorder*)):ti,ab OR (brain NEAR/3 (accident* OR attack*)):ti,ab OR cva:ti,ab OR cvas:ti,ab OR ((brain OR cerebral) NEAR/3 infarct*):ti,ab
#12	'cerebrovascular disease'/de OR 'cerebrovascular accident'/exp OR 'brain hemorrhage'/exp OR 'brain hematoma'/exp OR 'intracranial aneurysm'/exp OR 'brain ischemia'/de OR 'transient ischemic attack'/exp OR 'occlusive cerebrovascular disease'/exp OR 'brain embolism'/exp OR 'brain atherosclerosis'/exp OR 'thromboembolism'/exp
#11	'congestive heart failure'/exp OR (('congestive heart' OR 'congestive cardiac' OR 'cardiac congestive') NEAR/3 (failure OR insufficienc* OR disease*)):ti,ab
#10	'heart arrest'/exp OR ((heart OR cardiac OR cardiopulmonary OR circulatory) NEAR/1 (arrest OR arrests)):ti,ab OR asystole:ti,ab OR asystolia:ti,ab OR asystoly:ti,ab
#9	'coronary artery disease'/exp OR 'heart aneurysm'/de OR 'coronary artery thrombosis'/exp OR 'coronary artery obstruction'/exp OR ((coronary OR heart) NEAR/3 (aneurysm* OR disease*)):ti,ab OR (coronary NEAR/3 (occlusion* OR stenos* OR obstruction* OR thrombos*)):ti,ab
#8	'heart failure'/de OR 'acute heart failure'/exp OR 'heart infarction'/exp OR ((myocardi* OR heart OR cardia*) NEAR/3 (infarct* OR attack* OR failure*)):ti,ab OR 'ischemic heart disease'/de OR 'heart muscle ischemia'/exp OR 'ischemic cardiomyopathy'/exp OR (('heart muscle' OR 'cardiac muscle' OR myocardial OR myocardium OR cardiac OR coronary OR heart OR transient O R cardiomyophath*) NEAR/3 (ischemi* OR ischaem*)):ti,ab OR 'acute coronary syndrome'/exp OR 'coronary syndrome':ti,ab
#7	'cardiovascular disease'/de OR 'vascular disease'/de OR ((cardiovascular OR vascular OR cardiac) NEAR/3 (disease* OR disorder* OR event OR events OR complication* OR risk* OR outcome* OR morbidity OR mortality OR death*)):ti,ab OR (cv NEAR/1 disease*):ti,ab OR cvd:ti,ab OR cvds:ti,ab
#6	#1 OR #2 OR #3 OR #4 OR #5
#5	'sodium'/exp/mj OR 'sodium chloride'/exp/mj AND ('dietary intake'/de OR 'dietary reference intake'/exp OR 'diet restriction'/de OR 'diet'/de OR diet:ti,ab OR diets:ti,ab OR dieta*:ti,ab OR diete*:ti,ab OR intak*:ti,ab OR consum*:ti,ab OR ingest*:ti,ab OR added:ti OR restrict*:ti OR limit*:ti OR low:ti OR lower*:ti OR reduction*:ti OR excess*:ti OR high:ti OR higher:ti OR change*:ti OR free:ti)
#4	sodium:ti OR salt:ti OR natrium:ti OR nacl:ti AND ('dietary intake'/de OR 'dietary reference intake'/exp OR 'diet'/de OR 'diet restriction'/de)
#3	((sodium OR salt OR nacl OR natrium) NEAR/3 (intak* OR consum* OR ingest* OR added OR restrict* OR limit* OR low OR lower* OR r eduction* OR excess* OR free OR high OR higher OR change*)):ti,ab
#2	diet:ti,ab OR diets:ti,ab OR dieta*:ti,ab OR diete*:ti,ab AND (sodium:ti,ab OR salt:ti,ab OR natrium:ti,ab OR nacl:ti,ab)
#1	'sodium intake'/exp OR 'salt intake'/exp OR 'sodium restriction'/exp

Search string to identify systematic reviews and clinical trials adapted from CADTH's Database Search Filters:

CADTH database search filters [Internet]. Ottawa: CADTH; 2016. Available from: /resources/finding-evidence

Pubmed

Search	Query
#29	Search #26 NOT #27 Filters: Publication date from 2013/01/01
#28	Search #26 AND #27
#27	Search (Bulgarian[lang] OR Croatian[lang] OR Czech[lang] OR Danish[lang] OR Dutch[lang] OR English[lang] OR Estonian[lang] OR Finnish[lang] OR French[lang] OR German[lang] OR Greek, Modern[lang] OR Hungarian[lang] OR Italian[lang] OR Latvian[lang] OR Lithuanian[lang] OR Norwegian[Lang] OR Polish[lang] OR Portuguese[lang] OR Romanian[lang] OR Scottish gaelic[lang] OR Slovak[lang] OR Slovenian[lang] OR Spanish[lang] OR Swedish[lang] OR "multiple languages"[Lang] OR "undetermined"[Lang])
#26	Search #24 AND #25
#25	Search "clinical trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Clinical Trials as Topic"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) AND (mask*[tiab] OR blind*[tiab] OR dumm*[tiab])) OR "Cross-Over Studies"[Mesh] OR ((crossover[tiab] OR "cross over"[tiab]) AND (study[tiab] OR studies[tiab] OR design*[tiab] OR method*[tiab] OR procedure[tiab] OR comparison[tiab])) OR systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal:__jrid21711]
#24	Search #22 NOT #23
#23	Search "Editorial" [Publication Type]
#22	Search #20 NOT #21
#21	Search (rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR rodent[ti] OR rodents[ti] OR hamster[ti] OR hamsters[ti] OR pig[ti] OR pigs[ti] OR porcine[ti] OR rabbit[ti] OR rabbits[ti] OR animal[ti] OR animals[ti] OR dogs[ti] OR dog[ti] OR cats[ti] OR cow[ti] OR bovine[ti] OR sheep[ti] OR ovine[ti] OR monkey[ti] OR monkeys[ti]) NOT medline[sb]
#20	Search #18 NOT #19
#19	Search "Animals"[Mesh] NOT "Humans"[Mesh]
#18	Search #9 AND #17
#17	Search #10 OR #11 OR #12 OR #13 OR #14 OR #15
#15	Search "Cerebrovascular Disorders"[Mesh:noexp] OR "Stroke"[Mesh] OR "Brain Ischemia"[Mesh] OR stroke*[tiab] OR (("cerebro vascular"[tiab] OR "cerebral vascular"[tiab] OR "brain vascular"[tiab] OR cerebrovascular[tiab]) AND (accident*[tiab] OR injur*[tiab] OR arrest*[tiab] OR disorder*[tiab])) OR brain accident*[tiab] OR CVA[tiab] OR CVAs[tiab] OR brain infarction*[tiab] OR cerebral infarction*[tiab] OR brain attack*[tiab] OR ((apoplexia[tiab] OR apoplexy[tiab] OR ischaemi*[tiab] OR ischemi*[tiab] OR thrombos*[tiab] OR thrombot*[tiab] OR emboli*[tiab] OR hypoxia[tiab] OR anoxaemi*[tiab] OR anoxi*[tiab]) AND (cerebral[tiab] OR cerebellar[tiab] OR brain[tiab] OR vertebrobasilar[tiab] OR intracranial[tiab] OR "intra cranial"[tiab])) OR "Thromboembolism"[Mesh] OR thromboembolism*[tiab] OR ((cerebral[tiab] OR cerebellar[tiab] OR intracerebral[tiab] OR intracranial[tiab] OR "intra cranial"[tiab] OR brain[tiab] OR subarachnoid[tiab] OR subdural[tiab] OR extradural[tiab] OR epidural[tiab]) AND (haemorrhagic[tiab] OR hemorrhagic[tiab] OR haemorrhage*[tiab] OR haemorrhage*[tiab] OR bleed*[tiab] OR haematoma*[tiab] OR hematoma*[tiab] OR aneurysm[tiab])) OR atherosclero*[tiab] OR arterial disease*[tiab] OR arterial obliterat*[tiab] OR arterial occlus*[tiab] OR arterial obstruct*[tiab] OR artery disease*[tiab] OR artery obliterat*[tiab] OR artery occlus*[tiab] OR artery obstruct*[tiab] OR

	((peripheral[tiab] OR vascular[tiab]) AND (occlus*[tiab] OR obstruct*[tiab] OR obliterat*[tiab]))
#14	Search (("congestive heart"[tiab] AND (insufficienc*[tiab] OR disease*[tiab])) OR (congestive cardia*[tiab] AND (disease*[tiab] OR insufficienc*[tiab])))
#13	Search "Heart Arrest"[Mesh] OR heart arrest*[tiab] OR cardiac arrest*[tiab] OR asystole[tiab] OR asystolia[tiab] OR asystoly[tiab] OR cardiopulmonary arrest*[tiab]
#12	Search "Coronary Disease"[Mesh] OR coronary disease*[tiab] OR heart disease*[tiab] OR cardiac disease*[tiab] OR ((coronary[tiab] OR heart[tiab]) AND aneurysm*[tiab]) OR (Coronary[tiab] AND (occlusion[tiab] OR stenos*[tiab] OR obstruction*[tiab] OR thrombos*[tiab]))
#11	Search "Heart Failure"[Mesh] OR "Myocardial Infarction"[Mesh] OR Myocardial infarct*[tiab] OR myocardium infarct*[tiab] OR heart attack*[tiab] OR heart infarct*[tiab] OR heart failure*[tiab] OR cardiac infarct*[tiab] OR cardial infarct*[tiab] OR cardiac failure*[tiab] OR "Myocardial Ischemia"[Mesh:noexp] OR (("heart muscle"[tiab] OR "cardiac muscle"[tiab] OR myocardial[tiab] OR myocardium[tiab] OR cardiac[tiab] OR coronary[tiab] OR heart[tiab] OR transient[tiab] OR cardiomyophath*[tiab]) AND (ischemi*[tiab] OR ischaem*[tiab])) OR "Acute Coronary Syndrome"[Mesh] OR "coronary syndrome"[tiab]
#10	Search ("Cardiovascular Diseases"[Mesh:NoExp] OR "Vascular diseases"[Mesh:NoExp] OR cardiovascular disease*[tiab] OR CV disease*[tiab] OR CVD[tiab] OR CVDs[tiab] OR cardiovascular disorder*[tiab] OR cardiovascular event*[tiab] OR cardiovascular complication*[tiab] OR cardiovascular risk*[tiab] OR cardiovascular outcome*[tiab] OR cardiovascular morbidity[tiab] OR cardiovascular mortality[tiab] OR vascular disease*[tiab] OR vascular disorder*[tiab] OR vascular event*[tiab] OR vascular complication*[tiab] OR vascular risk*[tiab] OR vascular outcome*[tiab] OR vascular morbidity[tiab] OR vascular mortality[tiab] OR cardiac death*[tiab])
#9	Search #7 OR #8
#8	Search "Sodium, Dietary"[Mesh] OR "Diet, Sodium-Restricted"[Mesh]
#7	Search (("Sodium"[Mesh] OR "Sodium Chloride"[Mesh] OR sodium[tiab] OR salt[tiab] OR NaCl[tiab] OR natrium[tiab]) AND ("Diet"[Mesh] OR diet[tiab] OR diets[tiab] OR dieta*[tiab] OR diete*[tiab] OR intak*[tiab] OR consum*[tiab] OR ingest*[tiab] OR added[ti] OR restrict*[ti] OR limit*[ti] OR low[ti] OR lower*[ti] OR reduct*[ti] OR excess*[ti] OR free[ti] OR high[ti] OR higher[ti] OR chang*[ti])) OR "added sodium"[tiab] OR "added dietary sodium"[tiab] OR "added salt"[tiab] OR salt restrict*[tiab] OR sodium restrict*[tiab] OR sodium chloride restrict*[tiab] OR "restricted salt"[tiab] OR "restricted sodium"[tiab] OR " restricted dietary sodium"[tiab] OR "restricting dietary sodium"[tiab] OR "restricting salt"[tiab] OR sodium limit*[tiab] OR salt limit*[tiab] OR "limited salt"[tiab] OR "limited sodium"[tiab] OR "limiting salt"[tiab] OR "limiting sodium"[tiab] OR "limited dietary sodium"[tiab] OR "limiting dietary sodium"[tiab] OR "low sodium"[tiab] OR "low dietary sodium"[tiab] OR "low salt"[tiab] OR "lowering sodium"[tiab] OR "lowering dietary sodium"[tiab] OR "lowering salt"[tiab] OR salt low*[tiab] OR sodium low*[tiab] OR "lower sodium"[tiab] OR "lower dietary sodium"[tiab] OR "lower salt"[tiab] OR "salt reduction"[tiab] OR "sodium reduction"[tiab] OR "sodium chloride reduction"[tiab] OR "reduced salt"[tiab] OR "reduced sodium"[tiab] OR "reduced dietary sodium"[tiab] OR "reducing dietary sodium"[tiab] OR "reducing sodium"[tiab] OR "reducing salt"[tiab] OR "reduce sodium"[tiab] OR "reduce salt"[tiab] OR "reduce dietary sodium"[tiab] OR "salt excess"[tiab] OR "sodium excess"[tiab] OR "excessive sodium"[tiab] OR "excessive salt"[tiab] OR "excessive dietary sodium"[tiab] OR "high sodium"[tiab] OR "high salt"[tiab] OR "high dietary sodium"[tiab] OR "higher sodium"[tiab] OR "higher salt"[tiab] OR "higher dietary sodium"[tiab] OR sodium high*[tiab] OR salt high*[tiab] OR sodium chang*[tiab] OR salt chang*[tiab]

Search string to identify systematic reviews and clinical trials adapted from CADTH's Database Search Filters:

CADTH database search filters [Internet]. Ottawa: CADTH; 2016. Available from: /resources/finding-evidence

D.3. Sub-questions 1 and 2. Observational studies

Embase

Search	Query
#27	#25 AND #26
#26	[basque]/lim OR [bulgarian]/lim OR [catalan]/lim OR [croatian]/lim OR [czech]/lim OR [danish]/lim OR [dutch]/lim OR [english]/lim OR [estonian]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [greek]/lim OR [hungarian]/lim OR [icelandic]/lim OR

	[italian]/lim OR [latvian]/lim OR [lithuanian]/lim OR [norwegian]/lim OR [polish]/lim OR [portuguese]/lim OR [romanian]/lim OR [scottish gaelic]/lim OR [slovak]/lim OR [slovenian]/lim OR [spanish]/lim OR [swedish]/lim
#25	#24 NOT ([conference abstract]/lim OR [editorial]/lim)
#24	#22 AND #23
#23	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR cohort*:ti,ab OR 'observational study'/exp OR prospective:ti,ab OR longitudinal:ti,ab OR observational:ti,ab OR followup:ti,ab OR 'follow up':ti,ab OR 'case control study'/exp OR 'control group'/exp OR (nested NEAR/3 (stud* OR analys*)):ti,ab OR (case*:ti,ab AND control*:ti,ab) OR ((participant* OR group) NEAR/3 follow*):ti,ab OR 'control group':ti,ab OR 'control groups':ti,ab
#22	#18 NOT #21
#21	#19 NOT #20
#20	'human'/exp OR 'human experiment'/de
#19	'animal'/exp OR 'animal experiment'/exp
#18	#6 AND #17
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#16	'blood pressure'/exp OR ((blood OR arterial OR brachial OR aortic) NEAR/2 pressure):ti,ab OR diastolic:ti,ab OR systolic:ti,ab OR bloodpressure:ti,ab OR 'hypertension'/exp OR hypertensi*:ti,ab OR 'hypotension'/exp OR hypotensi*:ti,ab OR prehypertensi*:ti,ab OR normotensi*:ti,ab OR (normo NEAR/1 tensi*):ti,ab
#15	trans*:ti,ab AND isch*emic:ti,ab AND attack*:ti,ab OR atherosclero*:ti,ab OR ((arterial OR artery) NEAR/3 (disease* OR obliterat* OR occlus* OR obstruct*)):ti,ab OR ((peripheral OR vascular) NEAR/3 (occlus* OR obstruct* OR obliterat*)):ti,ab OR ((cerebral OR cerebellar OR intracerebral OR 'intra cerebral' OR 'intracranial' OR 'intra cranial' OR brain OR subarachnoid OR subdural OR extradural OR epidural) NEAR/3 (hemorrhagic OR haemorrhagic OR haemorrhage* OR hemorrhage* OR haematoma* OR hematoma* OR aneurysm* OR bleed*)):ti,ab
#14	((apoplexy* OR ischaemi* OR ischemi* OR thrombos* OR thrombot* OR emboli* OR hyp oxia OR anoxaemi* OR anoxi*) NEAR/3 (cerebral OR cerebellar OR brain OR vertebrobasilar OR intracranial OR 'intra craneal')):ti,ab OR thromboembolism*:ti,ab
#13	stroke*:ti,ab OR (('cerebro vascular' OR 'cerebral vascular' OR 'brain vascular' OR cerebrovascular) NEAR/3 (accident* OR injur* OR arrest* OR disease* OR disorder*)):ti,ab OR (brain NEAR/3 (accident* OR attack*)):ti,ab OR cva:ti,ab OR cvas:ti,ab OR ((brain OR cerebral) NEAR/3 infarct*):ti,ab
#12	'cerebrovascular disease'/de OR 'cerebrovascular accident'/exp OR 'brain hemorrhage'/exp OR 'brain hematoma'/exp OR 'intracranial aneurysm'/exp OR 'brain ischemia'/de OR 'transient ischemic attack'/exp OR 'occlusive cerebrovascular disease'/exp OR 'brain embolism'/exp OR 'brain atherosclerosis'/exp OR 'thromboembolism'/exp
#11	'congestive heart failure'/exp OR (('congestive heart' OR 'congestive cardiac' OR 'cardiac congestive') NEAR/3 (failure OR insufficienc* OR disease*)):ti,ab
#10	'heart arrest'/exp OR ((heart OR cardiac OR cardiopulmonary OR circulatory) NEAR/1 (arrest OR arrests)):ti,ab OR asystole:ti,ab OR asystolia:ti,ab OR asystoly:ti,ab
#9	'coronary artery disease'/exp OR 'heart aneurysm'/de OR 'coronary artery thrombosis'/exp OR 'coronary artery obstruction'/exp OR ((coronary OR heart) NEAR/3 (aneurysm* OR disease*)):ti,ab OR (coronary NEAR/3 (occlusion* OR stenos* OR obstruction* OR thrombos*)):ti,ab
#8	'heart failure'/de OR 'acute heart failure'/exp OR 'heart infarction'/exp OR ((myocardi* OR heart OR cardia*) NEAR/3 (infarct* OR attack* OR failure*)):ti,ab OR 'ischemic heart disease'/de OR 'heart muscle ischemia'/exp OR 'ischemic cardiomyopathy'/exp OR (('heart muscle' OR 'cardiac muscle' OR myocardial OR myocardium OR cardiac OR coronary OR heart OR transient O R cardiomyophath*) NEAR/3 (ischemi* OR ischaem*)):ti,ab OR 'acute coronary syndrome'/exp OR 'coronary syndrome':ti,ab
#7	'cardiovascular disease'/de OR 'vascular disease'/de OR ((cardiovascular OR vascular OR cardiac) NEAR/3 (disease* OR disorder* OR event OR events OR complication* OR risk* OR outcome* OR morbidity OR mortality OR death*)):ti,ab OR (cv NEAR/1 disease*):ti,ab OR cvd:ti,ab OR cvds:ti,ab

#6	#1 OR #2 OR #3 OR #4 OR #5
#5	'sodium'/exp/mj OR 'sodium chloride'/exp/mj AND ('dietary intake'/de OR 'dietary reference intake'/exp OR 'diet restriction'/de OR 'diet'/de OR diet:ti,ab OR diets:ti,ab OR dieta*:ti,ab OR diete*:ti,ab OR intak*:ti,ab OR consum*:ti,ab OR ingest*:ti,ab OR added:ti OR restrict*:ti OR limit*:ti OR low:ti OR lower*:ti OR reduction*:ti OR excess*:ti OR high:ti OR higher:ti OR change*:ti OR free:ti)
#4	sodium:ti OR salt:ti OR natrium:ti OR nacl:ti AND ('dietary intake'/de OR 'dietary reference intake'/exp OR 'diet'/de OR 'diet restriction'/de)
#3	((sodium OR salt OR nacl OR natrium) NEAR/3 (intak* OR consum* OR ingest* OR added OR restrict* OR limit* OR low OR lower* OR r eduction* OR excess* OR free OR high OR higher OR change*)):ti,ab
#2	diet:ti,ab OR diets:ti,ab OR dieta*:ti,ab OR diete*:ti,ab AND (sodium:ti,ab OR salt:ti,ab OR natrium:ti,ab OR nacl:ti,ab)
#1	'sodium intake'/exp OR 'salt intake'/exp OR 'sodium restriction'/exp

Pubmed

Search	Query
#29	Search (((#25 AND #26))) AND (Bulgarian[lang] OR Croatian[lang] OR Czech[lang] OR Danish[lang] OR Dutch[lang] OR English[lang] OR Estonian[lang] OR Finnish[lang] OR French[lang] OR German[lang] OR Greek, Modern[lang] OR Hungarian[lang] OR Italian[lang] OR Latvian[lang] OR Lithuanian[lang] OR Norwegian[Lang] OR Polish[lang] OR Portuguese[lang] OR Romanian[lang] OR Scottish gaelic[lang] OR Slovak[lang] OR Slovenian[lang] OR Spanish[lang] OR Swedish[lang] OR "multiple languages"[Lang] OR "undetermined"[Lang])
#28	Search (Bulgarian[lang] OR Croatian[lang] OR Czech[lang] OR Danish[lang] OR Dutch[lang] OR English[lang] OR Estonian[lang] OR Finnish[lang] OR French[lang] OR German[lang] OR Greek, Modern[lang] OR Hungarian[lang] OR Italian[lang] OR Latvian[lang] OR Lithuanian[lang] OR Norwegian[Lang] OR Polish[lang] OR Portuguese[lang] OR Romanian[lang] OR Scottish gaelic[lang] OR Slovak[lang] OR Slovenian[lang] OR Spanish[lang] OR Swedish[lang] OR "multiple languages"[Lang] OR "undetermined"[Lang])
#27	Search (#25 AND #26)
#26	Search "Cohort Studies"[Mesh] OR cohort*[tiab] OR "follow up"[tiab] OR followup[tiab] OR prospective[tiab] OR longitudinal[tiab] OR "epidemiologic methods"[Mesh:noexp] OR "Observational Study" [Publication Type] OR observational[tiab] OR "Case-Control Studies"[Mesh] OR "Control Groups"[Mesh] OR nested stud*[tiab] OR nested analys*[tiab] OR (case*[tiab] AND control*[tiab]) OR control group*[tiab]
#25	Search #23 NOT #24
#24	Search "Editorial" [Publication Type]
#23	Search #21 NOT #22
#22	Search (rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR rodent[ti] OR rodents[ti] OR hamster[ti] OR hamsters[ti] OR pig[ti] OR pigs[ti] OR porcine[ti] OR rabbit[ti] OR rabbits[ti] OR animal[ti] OR animals[ti] OR dogs[ti] OR dog[ti] OR cats[ti] OR cow[ti] OR bovine[ti] OR sheep[ti] OR ovine[ti] OR monkey[ti] OR monkeys[ti]) NOT medline[sb]
#21	Search #19 NOT #20
#20	Search "Animals"[Mesh] NOT "Humans"[Mesh]
#19	Search #18 AND #9
#18	Search #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#16	Search "Blood Pressure"[Mesh] OR "Blood pressure" [tiab] OR "arterial pressure"[tiab] OR diastolic[tiab] OR systolic[tiab] OR bloodpressure[tiab] OR "Hypertension"[Mesh] OR hypertensi*[tiab] OR "Hypotension"[Mesh] OR hypotensi*[tiab] OR "Prehypertension"[Mesh] OR prehypertensi*[tiab] OR "brachial pressure"[tiab] OR " aortic pressure"[tiab] OR normotens*[tiab] OR normo tens*[tiab]
#15	Search "Heart Failure"[Mesh] OR "Myocardial Infarction"[Mesh] OR Myocardial infarct*[tiab] OR myocardium infarct*[tiab] OR heart attack*[tiab] OR heart infarct*[tiab] OR heart failure*[tiab] OR cardiac infarct*[tiab] OR cardial infarct*[tiab] OR cardiac failure*[tiab] OR "Myocardial Ischemia"[Mesh:noexp] OR (("heart muscle"[tiab] OR "cardiac muscle"[tiab] OR myocardial[tiab] OR myocardium[tiab] OR cardiac[tiab] OR coronary[tiab] OR heart[tiab] OR transient[tiab] OR cardiomyophath*[tiab]) AND (ischemi*[tiab] OR ischaem*[tiab])) OR "Acute Coronary Syndrome"[Mesh] OR "coronary syndrome"[tiab]
#14	Search "Cerebrovascular Disorders"[Mesh:noexp] OR "Stroke"[Mesh] OR "Brain Ischemia"[Mesh] OR stroke*[tiab] OR (("cerebro vascular"[tiab] OR "cerebral vascular"[tiab]

	OR "brain vascular"[tiab] OR cerebrovascular[tiab]) AND (accident*[tiab] OR injur*[tiab] OR arrest*[tiab] OR disorder*[tiab])) OR brain accident*[tiab] OR CVA[tiab] OR CVAs[tiab] OR brain infarction*[tiab] OR cerebral infarction*[tiab] OR brain attack*[tiab] OR ((apoplexia[tiab] OR apoplexy[tiab] OR ischaemi*[tiab] OR ischemi*[tiab] OR thrombos*[tiab] OR thrombot*[tiab] OR emboli*[tiab] OR hypoxia[tiab] OR anoxaemi*[tiab] OR anoxi*[tiab]) AND (cerebral[tiab] OR cerebellar[tiab] OR brain[tiab] OR vertebrobasilar[tiab] OR intracranial[tiab] OR "intra cranial"[tiab])) OR "Thromboembolism"[Mesh] OR thromboembolism*[tiab] OR ((cerebral[tiab] OR cerebellar[tiab] OR intracerebral[tiab] OR intracranial[tiab] OR "intra cranial"[tiab] OR brain[tiab] OR subarachnoid[tiab] OR subdural[tiab] OR extradural[tiab] OR epidural[tiab]) AND (haemorrhagic[tiab] OR hemorrhagic[tiab] OR haemorrhage*[tiab] OR haemorrhage*[tiab] OR bleed*[tiab] OR haematoma*[tiab] OR hematoma*[tiab] OR aneurysm[tiab])) OR atherosclero*[tiab] OR arterial disease*[tiab] OR arterial obliterat*[tiab] OR arterial occlus*[tiab] OR arterial obstruct*[tiab] OR artery disease*[tiab] OR artery obliterat*[tiab] OR artery occlus*[tiab] OR artery obstruct*[tiab] OR ((peripheral[tiab] OR vascular[tiab]) AND (occlus*[tiab] OR obstruct*[tiab] OR obliterat*[tiab]))
#13	Search (("congestive heart"[tiab] AND (insufficienc*[tiab] OR disease*[tiab])) OR (congestive cardia*[tiab] AND (disease*[tiab] OR insufficienc*[tiab])))
#12	Search "Heart Arrest"[Mesh] OR heart arrest*[tiab] OR cardiac arrest*[tiab] OR asystole[tiab] OR asystolia[tiab] OR asystoly[tiab] OR cardiopulmonary arrest*[tiab]
#11	Search "Coronary Disease"[Mesh] OR coronary disease*[tiab] OR heart disease*[tiab] OR cardiac disease*[tiab] OR ((coronary[tiab] OR heart[tiab]) AND aneurysm*[tiab]) OR (Coronary[tiab] AND (occlusion[tiab] OR stenos*[tiab] OR obstruction*[tiab] OR thrombos*[tiab]))
#10	Search ("Cardiovascular Diseases"[Mesh:NoExp] OR "Vascular diseases"[Mesh:NoExp] OR cardiovascular disease*[tiab] OR CV disease*[tiab] OR CVD[tiab] OR CVDs[tiab] OR cardiovascular disorder*[tiab] OR cardiovascular event*[tiab] OR cardiovascular complication*[tiab] OR cardiovascular risk*[tiab] OR cardiovascular outcome*[tiab] OR cardiovascular morbidity[tiab] OR cardiovascular mortality[tiab] OR vascular disease*[tiab] OR vascular disorder*[tiab] OR vascular event*[tiab] OR vascular complication*[tiab] OR vascular risk*[tiab] OR vascular outcome*[tiab] OR vascular morbidity[tiab] OR vascular mortality[tiab] OR cardiac death*[tiab])
#9	Search #7 OR #8
#8	Search "Sodium, Dietary"[Mesh] OR "Diet, Sodium-Restricted"[Mesh]
#7	Search (("Sodium"[Mesh] OR "Sodium Chloride"[Mesh] OR sodium[tiab] OR salt[tiab] OR NaCl[tiab] OR natrium[tiab]) AND ("Diet"[Mesh] OR diet[tiab] OR diets[tiab] OR dieta*[tiab] OR diete*[tiab] OR intak*[tiab] OR consum*[tiab] OR ingest*[tiab] OR added[ti] OR restrict*[ti] OR limit*[ti] OR low[ti] OR lower*[ti] OR reduct*[ti] OR excess*[ti] OR free[ti] OR high[ti] OR higher[ti] OR chang*[ti])) OR "added sodium"[tiab] OR "added dietary sodium"[tiab] OR "added salt"[tiab] OR salt restrict*[tiab] OR sodium restrict*[tiab] OR sodium chloride restrict*[tiab] OR "restricted salt"[tiab] OR "restricted sodium"[tiab] OR " restricted dietary sodium"[tiab] OR "restricting dietary sodium"[tiab] OR "restricting salt"[tiab] OR sodium limit*[tiab] OR salt limit*[tiab] OR "limited salt"[tiab] OR "limited sodium"[tiab] OR "limiting salt"[tiab] OR "limiting sodium"[tiab] OR "limited dietary sodium"[tiab] OR "limiting dietary sodium"[tiab] OR "low sodium"[tiab] OR "low dietary sodium"[tiab] OR "low salt"[tiab] OR "lowering sodium"[tiab] OR "lowering dietary sodium"[tiab] OR "lowering salt"[tiab] OR salt low*[tiab] OR sodium low*[tiab] OR "lower sodium"[tiab] OR "lower dietary sodium"[tiab] OR "lower salt"[tiab] OR "salt reduction"[tiab] OR "sodium reduction"[tiab] OR "sodium chloride reduction"[tiab] OR "reduced salt"[tiab] OR "reduced sodium"[tiab] OR "reduced dietary sodium"[tiab] OR "reducing dietary sodium"[tiab] OR "reducing sodium"[tiab] OR "reducing salt"[tiab] OR "reduce sodium"[tiab] OR "reduce salt"[tiab] OR "reduce dietary sodium"[tiab] OR "salt excess"[tiab] OR "sodium excess"[tiab] OR "excessive sodium"[tiab] OR "excessive salt"[tiab] OR "excessive dietary sodium"[tiab] OR "high sodium"[tiab] OR "high salt"[tiab] OR "high dietary sodium"[tiab] OR "higher sodium"[tiab] OR "higher salt"[tiab] OR "higher dietary sodium"[tiab] OR sodium high*[tiab] OR salt high*[tiab] OR sodium chang*[tiab] OR salt chang*[tiab]

D.4. Sub-questions 3, 4 and 5. All type of studies

Cochrane Library. Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects

ID	Search
#2	([mh Sodium] or [mh "sodium chloride"]) and ([mh Diet] or diet:ti,ab,kw or diets:ti,ab,kw or dieta*:ti,ab,kw or diete*:ti,ab,kw or intak*:ti,ab,kw or consum*:ti,ab,kw or ingest*:ti,ab,kw or added:ti,ab,kw or restrict*:ti,ab,kw or limit*:ti,ab,kw or low:ti,ab,kw or lower*:ti,ab,kw or reduc*:ti,ab,kw or excess*:ti,ab,kw or free:ti,ab,kw or high:ti,ab,kw or higher:ti,ab,kw or chang*:ti,ab,kw)
#3	(salt:ti,ab,kw or NaCl:ti,ab,kw or natrium:ti,ab,kw or sodium:ti,ab,kw) and [mh diet]
#4	(salt:ti,ab,kw or NaCl:ti,ab,kw or natrium:ti,ab,kw or sodium:ti,ab,kw) near/3 (diet:ti,ab,kw or diets:ti,ab,kw or dieta*:ti,ab,kw or diete*:ti,ab,kw or intak*:ti,ab,kw or consum*:ti,ab,kw or ingest*:ti,ab,kw or added:ti,ab,kw or restrict*:ti,ab,kw or limit*:ti,ab,kw or low:ti,ab,kw or lower*:ti,ab,kw or reduc*:ti,ab,kw or excess*:ti,ab,kw or free:ti,ab,kw or high:ti,ab,kw or higher:ti,ab,kw or chang*:ti,ab,kw)
#5	[mh "Sodium, Dietary"] or [mh "Diet, Sodium-Restricted"]
#6	#2 or #3 or #4 or #5
#7	[mh ^"Bone and Bones"] or [mh "bone density"] or [mh ^"bone diseases"] or [mh "Fractures, Bone"] or [mh osteoporosis] or BMC:ti,ab,kw or BMD:ti,ab,kw or ((bone* or skelet* or osseous) near/5 (content or demineral* or densit* or health or mass or volume or loss* or resorption*)):ti,ab,kw or ((bone or skelt* or osseus) and mineral and concentration):ti,ab,kw or decalcification*:ti,ab,kw or fracture*:ti,ab,kw or (broken near/5 bone*):ti,ab,kw or osteoporo*:ti,ab,kw
#8	#24 and #6

Embase

Search	Query
#16	#14 AND #15
#15	[basque]/lim OR [bulgarian]/lim OR [catalan]/lim OR [croatian]/lim OR [czech]/lim OR [danish]/lim OR [dutch]/lim OR [english]/lim OR [estonian]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [greek]/lim OR [hungarian]/lim OR [icelandic]/lim OR [italian]/lim OR [latvian]/lim OR [lithuanian]/lim OR [norwegian]/lim OR [polish]/lim OR [portuguese]/lim OR [romanian]/lim OR [scottish gaelic]/lim OR [slovak]/lim OR [slovenian]/lim OR [spanish]/lim OR [swedish]/lim
#14	#12 NOT #13
#13	[conference abstract]/lim OR [editorial]/lim OR [conference review]/lim
#12	#8 NOT #11
#11	#9 NOT #10
#10	'human'/exp OR 'human experiment'/de
#9	'animal'/exp OR 'animal experiment'/exp
#8	#6 AND #7
#7	'bone health'/exp OR 'bone density'/exp OR 'bone disease'/de OR 'bone mass'/exp OR 'bone mineral'/exp OR 'fracture'/exp OR 'osteoporosis'/exp OR (((bone* OR skelet* OR osseous) NEAR/5 (content OR demineral* OR densit* OR health OR mass OR volume OR loss* OR resorption*)):ti,ab) OR ((bone*:ti,ab OR osseous:ti,ab OR skelet*:ti,ab) AND mineral:ti,ab AND concentration:ti,ab) OR decalcification*:ti,ab OR fracture*:ti,ab OR ((broken NEAR/5 bone*):ti,ab) OR osteoporo*:ti,ab
#6	#1 OR #2 OR #3 OR #4 OR #5
#5	('sodium'/exp/mj OR 'sodium chloride'/exp/mj) AND ('dietary intake'/de OR 'dietary reference intake'/exp OR 'diet restriction'/de OR 'diet'/de OR diet:ti,ab OR diets:ti,ab OR dieta*:ti,ab OR diete*:ti,ab OR intak*:ti,ab OR consum*:ti,ab OR ingest*:ti,ab OR added:ti OR restrict*:ti OR limit*:ti OR low:ti OR lower*:ti OR reduction*:ti OR excess*:ti OR high:ti OR higher:ti OR change*:ti OR free:ti)
#4	(sodium:ti OR salt:ti OR natrium:ti OR nacl:ti) AND ('dietary intake'/de OR 'dietary reference intake'/exp OR 'diet'/de OR 'diet restriction'/de)
#3	((sodium OR salt OR nacl OR natrium) NEAR/3 (intak* OR consum* OR ingest* OR added OR restrict* OR limit* OR low OR lower* OR reduction* OR excess* OR free OR high OR higher OR change*)):ti,ab
#2	(diet:ti,ab OR diets:ti,ab OR dieta*:ti,ab OR diete*:ti,ab) AND (sodium:ti,ab OR salt:ti,ab

	OR natrium:ti,ab OR nacl:ti,ab)
#1	'sodium intake'/exp OR 'salt intake'/exp OR 'sodium restriction'/exp

Pubmed

Search	Query
#13	Search #11 AND #12
#12	Search (Bulgarian[lang] OR Croatian[lang] OR Czech[lang] OR Danish[lang] OR Dutch[lang] OR English[lang] OR Estonian[lang] OR Finnish[lang] OR French[lang] OR German[lang] OR Greek, Modern[lang] OR Hungarian[lang] OR Italian[lang] OR Latvian[lang] OR Lithuanian[lang] OR Norwegian[Lang] OR Polish[lang] OR Portuguese[lang] OR Romanian[lang] OR Scottish gaelic[lang] OR Slovak[lang] OR Slovenian[lang] OR Spanish[lang] OR Swedish[lang] OR "multiple languages"[Lang] OR "undetermined"[Lang])
#11	Search #9 NOT #10
#10	Search "Editorial" [Publication Type]
#9	Search #7 NOT #8
#8	Search (rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR rodent[ti] OR rodents[ti] OR hamster[ti] OR hamsters[ti] OR pig[ti] OR pigs[ti] OR porcine[ti] OR rabbit[ti] OR rabbits[ti] OR animal[ti] OR animals[ti] OR dogs[ti] OR dog[ti] OR cats[ti] OR cow[ti] OR bovine[ti] OR sheep[ti] OR ovine[ti] OR monkey[ti] OR monkeys[ti]) NOT medline[sb]
#7	Search #5 NOT #6
#6	Search "Animals"[Mesh] NOT "Humans"[Mesh]
#5	Search #3 AND #4
#4	Search ("Bone and Bones"[Mesh:NoExp] OR "Bone Density"[Mesh] OR "Bone Diseases"[Mesh:NoExp] OR "Fractures, Bone"[Mesh] OR "Osteoporosis"[Mesh] OR "Bone Resorption"[Mesh] OR BMC[tiab] OR BMD[tiab] OR ((bone*[tiab] OR osseus[tiab] OR skeleto*[tiab] OR skeleta*[tiab]) AND (content[tiab] OR demineralis*[tiab] OR demineraliz*[tiab] OR densit*[tiab] OR health[tiab] OR mass[tiab] OR volume[tiab] OR loss*[tiab] OR resorption*[tiab])) OR ((bone*[tiab] OR skeleto*[tiab] OR skeletal*[tiab] OR osseus[tiab]) AND (mineral[tiab] AND concentration*[tiab])) OR decalcification*[tiab] OR fracture*[tiab] OR broken bone*[tiab] OR osteoporo*[tiab])
#3	Search #1 OR #2
#2	Search "Sodium, Dietary"[Mesh] OR "Diet, Sodium-Restricted"[Mesh]
#1	Search (("Sodium"[Mesh] OR "Sodium Chloride"[Mesh] OR sodium[tiab] OR salt[tiab] OR NaCl[tiab] OR natrium[tiab]) AND ("Diet"[Mesh] OR diet[tiab] OR diets[tiab] OR dieta*[tiab] OR diete*[tiab] OR intak*[tiab] OR consum*[tiab] OR ingest*[tiab] OR added[ti] OR restrict*[ti] OR limit*[ti] OR low[ti] OR lower*[ti] OR reduct*[ti] OR excess*[ti] OR free[ti] OR high[ti] OR higher[ti] OR chang*[ti])) OR "added sodium"[tiab] OR "added dietary sodium"[tiab] OR "added salt"[tiab] OR salt restrict*[tiab] OR sodium restrict*[tiab] OR sodium chloride restrict*[tiab] OR "restricted salt"[tiab] OR "restricted sodium"[tiab] OR " restricted dietary sodium"[tiab] OR "restricting dietary sodium"[tiab] OR "restricting salt"[tiab] OR sodium limit*[tiab] OR salt limit*[tiab] OR "limited salt"[tiab] OR "limited sodium"[tiab] OR "limiting salt"[tiab] OR "limiting sodium"[tiab] OR "limited dietary sodium"[tiab] OR "limiting dietary sodium"[tiab] OR "low sodium"[tiab] OR "low dietary sodium"[tiab] OR "low salt"[tiab] OR "lowering sodium"[tiab] OR "lowering dietary sodium"[tiab] OR "lowering salt"[tiab] OR salt low*[tiab] OR sodium low*[tiab] OR "lower sodium"[tiab] OR "lower dietary sodium"[tiab] OR "lower salt"[tiab] OR "salt reduction"[tiab] OR "sodium reduction"[tiab] OR "sodium chloride reduction"[tiab] OR "reduced salt"[tiab] OR "reduced sodium"[tiab] OR "reduced dietary sodium"[tiab] OR "reducing dietary sodium"[tiab] OR "reducing sodium"[tiab] OR "reducing salt"[tiab] OR "reduce sodium"[tiab] OR "reduce salt"[tiab] OR "reduce dietary sodium"[tiab] OR "salt excess"[tiab] OR "sodium excess"[tiab] OR "excessive sodium"[tiab] OR "excessive salt"[tiab] OR "excessive dietary sodium"[tiab] OR "high sodium"[tiab] OR "high salt"[tiab] OR "high dietary sodium"[tiab] OR "higher sodium"[tiab] OR "higher salt"[tiab] OR "higher dietary sodium"[tiab] OR sodium high*[tiab] OR salt high*[tiab] OR sodium chang*[tiab] OR salt chang*[tiab]