Comparative Effectiveness Review Disposition of Comments Report

Research Review Title:
Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks

Draft review available for public comment from December 11, 2017 to January 8, 2018.

Research Review Citation: Newberry SJ, Chung M, Anderson CAM, Chen C, Fu Z, Tang A, Zhao N, Booth M, Marks J, Hollands S, Motala A, Larkin JK, Shanman R, Hempel S. Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks. Comparative Effectiveness Review No. 206. (Prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2015-00010-I.) AHRQ Publication No. 18-EHC009-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2018. Posted final reports are located on the Effective Health Care Program search page. DOI: https://doi.org/10.23970/AHRQEPCCER206.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Quality	Superior	Thank you.
TEP Reviewer #2	Quality	Good	We hope we have improved the quality in our revisions.
TEP Reviewer #3	Quality	Good	We hope we have improved the quality in our revisions.
Peer Reviewer #2	Quality	Good	We hope we have improved the quality in our revisions.
Peer Reviewer #3	Quality	Superior	Thank you.
TEP Reviewer #4	Quality	Fair	We hope we have improved the quality in our revisions.
TEP Reviewer #5	Quality	Fair	We hope we have improved the quality in our revisions.
Peer Reviewer #4	Quality	Poor	We hope we have improved the quality in our revisions.
Peer Reviewer #5	Quality	Superior	Thank you.
Peer Reviewer #6	Quality	Superior	Thank you.
Peer Reviewer #7	Quality	Good	We hope we have improved the quality in our revisions.
TEP Reviewer #1	General	Abstract – clear and concise Contents page complete and easy to navigate Executive Summary – clear and helps orient to report Target populations explicitly defined Key questions explicitly stated	Thank you.
Peer Reviewer #1	General	This report is quite well done. The approach to review of the literature based on key questions is quite useful. The approach to evaluate sub populations, such as children and adolescents, is important and useful. The target audience is explicitly defined. The key questions are quite appropriate and are explicitly stated, but some may be unanswerable as the timeline for studies needed for answers is untenable. The report is clinically meaningful to the extent that the published studies with their limitations allow clinical conclusions to be made. The lack of strong evidence is particularly an issue for subpopulations, such as children. While the report does an outstanding job of identifying limitations in the published literature, the readers of this report would benefit from a much more explicit description of the types of studies and methods for assessment of independent and outcome variables needed to advance the field. This future research section appears to be missing.	Thank you. We have added a section to the Discussion chapter that outlines the gaps we identified in the research.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	The report addresses a series of meaningful questions on health effects of sodium and potassium intake in human populations, including vulnerable subgroups, which is important from both a clinical and public health perspective. The report is intended for use by the DRI committee to help set requirements for sodium and potassium intake. I appreciate the huge amount of work by the authors, and their attempts to present the evidence in a systematic way. The statistical methods used seem appropriate. However, I do have some concerns, partly related to the interpretation of findings, which are summarized below.	We describe how we have addressed the specific points below.
TEP Reviewer #2	General	Comment #1 I found the report rather technical at first glance and I had to search for quantitative information that could be used for setting DRIs. The structure let me go back and forth (but maybe this is an AHRQ template that cannot be changed). Numbering of paragraphs or including a header on each page with chapter title may be helpful. It may not be easy for the DRI committee to extract the data they need and (at the same time) judge the reliability and validity of the different pieces of evidence.	We realize the report covers a lot of ground. We tried to summarize the key points (conclusions) in the Executive Summary as well as at the beginning of the response to each key question, along with the kinds of studies used to arrive at each conclusion.
TEP Reviewer #2	Abstract, pg. vii, line 12	Comment #2 The main objective of the report could be phrased more clearly. The following aim is stated in the abstract (p.vii, also elsewhere): "This systematic review synthesized the evidence regarding the effects of dietary sodium reduction and interventions to increase potassium intake on (and their associations with) blood pressure and risk for chronic cardiovascular diseases (CVD)." Why synthesize effects of dietary sodium reduction and interventions to increase potassium intake? What about trials of sodium loading/supplements (e.g. MacGregor et al, Lancet 1989)? The information in parentheses "(and on their associations)" suggests non importance, and grammatically the sentence may be incorrect. What is "chronic cardiovascular diseases"? Is acute myocardial infarction included?	We revised the wording of the overall aim slightly in the abstract and introductions but were required to adhere to the objective provided in our statement of work. We also omitted the difficult phrasing (e.g., chronic CVD). The inclusion/exclusion criteria are further explained in the Methods chapter.
TEP Reviewer #2	Pg. ES-7, line 36	Comment #3 KQ1 (p. ES-7 and elsewhere): "Sodium reduction decreases systolic and diastolic blood pressure significantly in adults (moderate SoE)". I was surprised to read that this is considered (only) moderate SoE. There is overwhelming evidence from well-conducted double-blind placebo-controlled trials (all doses, both dietary and supplemental, even double-blind, e.g. Gijsbers et al, J Hum Hypertens 2015).	We rated the overall strength of evidence (SoE) as moderate for this conclusion, rather than as high because of the inconsistency across study findings. We address this point in the Discussion.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Pg ES-8, line 27 Pg. 59, line 33 Fig 21, pg. 60	Comment #4 KQ3 (p. ES-8, p.59 bottom lines): "In adults, evidence from a small number of RCTs suggests that sodium reduction does not affect risk for CVD mortality, stroke, or composite CVD outcomes (low SoE)". The term low SoE is not very clear, and the conclusion in my opinion is even misleading (because it assumes an outcome's direction, i.e. "does not affect"). When looking at the current evidence for KQ3, I think we cannot draw conclusions on the (nature of the) relationship for sodium reduction and CVD mortality. The findings do not suggest the 2 absence of an effect. There are only a few trials and the number of fatal CVD events in trials is insufficient for drawing conclusions. Similarly for all-cause mortality, the qualification 'low SoE' may not be justified. The conclusion is based on 6 trials, pooled in a random effects model (Figure 21, p.60). Results are largely driven by studies with a low risk of bias, showing causal effects. Because there is no significant heterogeneity, I would also be interested in the RR (95%-CI) from the fixed effects model. In the report, a large-scale trial of sodium reduction and clinical outcomes is recommended, while this is not feasible. A two-step approach is preferred, in which effects of sodium on BP are translated into CVD risk. The relationship between sodium and BP has been proved and quantified, as are the effects of BP on CVD (CHD and stroke) and mortality, based on clinical trials with low risk of bias. This alternative (preferred) method for assessing the effect of sodium on CVD warrants more discussion in the report.	We have reworded a number of the conclusions for KQ3 (CVD and renal outcomes) substantially, both because the conclusions changed when several studies were added and for clarity. However, for most outcomes, we did conclude that evidence was insufficient to draw a conclusion, and we stated that. At your suggestion, we did run a fixed effects model (findings not reported) but the findings did not differ. We also omitted the recommendation for a large-scale RCT on sodium reduction and clinical outcomes.
TEP Reviewer #3	General	A review on the impact of sodium and potassium intake and their effects on blood pressure risks for cardiovascular diseases is clinically relevant and important since the role of dietary sodium and potassium as major risk factors for hypertension and cardiovascular disease (CVD) is highly controversial. Therefore, a systematic review of current available evidence is an important goal that could provide important guidance for future dietary recommendations by multiple organizations. The key questions of this review are appropriate and explicitly stated. Since the relationship between sodium intake and chronic disease outcomes has been especially controversial, the question of whether reducing dietary intake of sodium lowers the risk for disease requires that findings from observational studies be subjected to scrutiny and that they be supported by findings from randomized control trials. The intended audience for this review appears to be a future Dietary Reference Intakes (DRI) committee; the stated purpose of the review is to provide evidence on chronic disease endpoints for consideration in reviewing the DRIs for sodium and potassium.	No response seems to be warranted.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	Comment #6 The report includes usable, quantitative information on the overall BP effects of sodium and potassium intake as addressed in KQ1, KQ2, KQ5, and KQ6. However, the weighing of evidence for KQ1 v. KQ2 and KQ5 v. KQ6 warrants attention and could be made more explicit. In my view, KQ2 is not very relevant because of the overwhelming evidence from sodium reduction trials (with different amounts of sodium, both dietary and supplemental, including longterm effects). Also, I would expect the strength of evidence for KQ1 and KQ5 in adults to be rated as high, not moderate. 'Moderate SoE' raises the suggestion that the effects of sodium and potassium on BP are yet to be proved.	We revised the wording of the conclusions in the abstract and throughout the report to show the contribution of trials and prospective cohort studies to the findings. As stated above, we did not rate the SoE high for the effects of sodium reduction and potassium increase on blood pressure because of substantial inconsistency in the direction of findings.
TEP Reviewer #2	General	Comment #8 In general, the report focuses strongly on results of studies, but less on methodology, e.g. exposure and outcome assessment, confounders, contrast in exposure, duration, bias. For example, the report does not address the quality of BP measurements of different studies. There is high intra-individual variability and the timing, method and number of BP measurements can be important.	In revising the draft report, we have conducted sensitivity analysis to assess the effects of study quality on the findings. We have also calculated the weighted mean differences in sodium intake for randomized controlled trials (RCTs) that contributed to pooled findings, to assess how they relate (reported in the figure legends).Although we do report the methods used to assess blood pressure and included a question on the appropriateness of the method used in our risk of bias assessment, we did not conduct a sensitivity analysis to assess the effect of the methodology. We comment on this point in the LImitations section.
Peer Reviewer #2	General	There are unique clinical issues to consider in potassium intake in patients with kidney disease that are not explored.	We did not identify studies that met our inclusion criteria that assessed effects of increasing potassium intake on populations with kidney disease.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	The purpose of this report is to guide DRIs. Recent reports demonstrate that 13.1% of the US population has CKD (Coresh, JAMA, 2007). These individuals typically already have higher serum potassium concentrations due to their CKD, and often use medications such as ACE inhibitors, ARBs, and aldosterone antagonists for treatment, further increasing their serum potassium concentrations. While increasing potassium intake may be beneficial for blood pressure in the population overall, there may be unique risks to this sizable sub-population to such a strategy.	Unfortunately, we did not identify studies that met our inclusion criteria that assessed effects of increasing potassium intake on populations with kidney disease. In fact we noted in our discussion of research gaps the absence of studies of both sodium reduction and increasing potassium in populations with kidney disease.
Peer Reviewer #2	General	In support of this notion, after reports of beneficial effects of using spironolactone in patients with heart failure, there were marked increases in ER visits, hospitalizations, and deaths related to hyperkalemia (Juurlink DN, NEJM, 2004).	Unfortunately, studies of this type would not have been included as their main focus was beyond the scope of this review.
Peer Reviewer #2	General	The report does very little to examine this risk in the subset of patients with prevalent CKD, and CKD is only haphazardly evaluated in some of the "subgroup" sections. For example, on page 167, the report describes 6 RCTs that reported adverse events associated with potassium supplement interventions (references 73, 197, 251, 59, 115, and 209). Reviewing these in detail, each explicitly excludes persons with renal disease or high potassium concentrations at baseline.	Again, we did not identify studies of potassium supplementation, and few studies on sodium reduction in this population.
Peer Reviewer #2	General	As the purpose of this report is to guide others about setting Dietary Reference Intakes, it must consider the risks to individuals living in the population with chronic diseases who may be harmed, especially if these diseases are highly prevalent like CKD.	We noted the absence of such data in the Research Gaps section of the report.
Peer Reviewer #2	General	The report should be revised to specifically address effects of potassium supplementation on BP and the potential risks associated with it in CKD and in other popualtions where use of ACE/ARB/Aldactone antagonists may be high (for example in heart failure patients). If this can not be done, the report should be explicit about the lack of these data in its limitations section, and the implications this has for public health policy.	Unfortunately, we would have had to change the scope and inclusion/exclusion criteria to have considered this issue. We do discuss the lack of data in the Limitations and Research gap sections.
Peer Reviewer #2	General	"SoE" (presumably Strength of Evidence) and "RoB" (presumably Risk of Bias) are used extensively in the report, but never explicitly spelled out or defined. Or, if they are, not at first use.	We have made sure to spell the terms out at first use, in the Abstract, Executive Summary, and main text, as well as to provide the definitions.
Peer Reviewer #2	General	Page 31 is a repeat of page 12. Please see the two comments above as they are relevant to this page as well.	We have noted the comment and spelled out the terms at first use.
Peer Reviewer #3	General	The report is clinically meaningful on Questions 1 and 2 on sodium intake and BP; and on Questions 5 and 6 on potassium intake and BP.	We regret the lack of strong evidence regarding long-term clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	Questions 3 and 4 that pertain to intervention effect or diet sodium associations with CVD events, morbidity and mortality results in negative findings. This is largely due to lack of studies that attempt to track dietary intake over decades to final endpoints. The same pertains to Questions 7 and 8.	We agree with the reviewer's point. In our revision of the draft, we identified a small number of RCTs that suggest a beneficial effect of sodium reduction on CVD outcomes.
TEP Reviewer #4	General	This encyclopedic document synthesizes evidence on key issues related to the health effects of sodium and potassium intake on health. As a systematic review, it will be best used as a compendium of papers and results. With the exception of BP effects of sodium reduction and increased potassium intake, it will be difficult to use the summary estimates as most of the observational studies had methodologic problems. The DRI committee will need to identify the most robust evidence for decision-making. While I applaud their herculean effort, I have several concerns that should be addressed.	We agree with the reviewer's overall point. We will address the specific concerns below.
TEP Reviewer #4	General	First, it was challenging to read, almost 'legalese' in its prose when there was a low strength of evidence on a topic. [KQ3: "in adults, a low strength of evidence suggests that sodium reduction does not affect risk for CVD mortality". Why not state that "there is insufficient evidence to assess the relationship of sodium reduction with CVD mortality"? My sense is that low SOE and insufficient evidence should be merged as the message is virtually identical and that the direction of the relationship should not be stated for low strength of evidence].	Although we are precluded from merging low and insufficient evidence (because they really do have different implications), we have striven to revise the text to present the conclusions based on low strength of evidence in plain English.
TEP Reviewer #4	General	Second, the document focused on results and made cursory remarks about methods. For this reason, it was hard to distinguish low quality from high quality studies, especially the observational studies. For this reason, I also advise the authors of this report to NOT provide summary quantitative estimates – averaging low quality with high quality evidence does not lead to a more valid result. Unfortunately, summary estimates give the imprimatur of high precision, robust conclusion.	The revised draft includes sensitivity analyses that omit low and unclear quality studies. It also now provides the weighted mean sodium intakes for each pooled analysis to put the findings into perspective. However, for the reason the reviewer states, we included almost no summary estimates in the abstract or executive summary.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	General	Third, because of the focus on meta-regression techniques, which are crude ways to identify effect modifiers, the review missed well-known and well-accepted associations, e.g. greater BP reductions from a reduced sodium intake with advancing age and in blacks compared to whites. This is really important because sodium reduction has great potential to reduce racial disparities in blood pressurerelated disease. My sense is that effect modification relationships are best detected from analyses done within a trial as opposed to across trials. This approach also missed well-accepted adverse effects such as GI discomfort from increased potassium intake from supplements; researchers and the food industry know this.	We have increased our emphasis throughout our responses to the odd-numbered questions on describing the findings of direct (within-study) comparisons. We also note the relative absence of such studies in the Limitations and Research Gaps sections.
TEP Reviewer #4	General	Fourth, the tone of the document is that there should be trials with hard outcomes, yet there are huge logistical obstacles to conducting trials. The authors should not recommend the conduct of such trials or imply that such trials should be done.	We have omitted our recommendation regarding such trials as being impracticable and beyond our charge to recommend.
TEP Reviewer #4	General	Fifth, it makes statements that are hard to reconcile – potential benefit of sodium reduction on total mortality yet no benefit on stroke and CVD events, leaving one to wonder how sodium reduction might reduce mortality given that it is unlikely that a reduced sodium intake prevents cancer (except for gastric cancer) or prevents non-CVD, non-cancer deaths from other causes such as accidents.	In revising the draft report, we repeated the meta-analyses for all-cause mortality and CVD outcomes and revised our conclusions.
TEP Reviewer #4	General	Sixth, its levels of evidence and especially its risk of bias assessment were difficult to understand and will be difficult to use. I am particularly concerned that the report indicates a high risk of bias for the TOHP follow-up studies (appendix page E-24) in which there are several, non-consecutive 24 hour urines used to estimate usual sodium intake. My sense is that it has the lowest risk of bias of the available observational studies of sodium with hard outcomes.	We revised our RoB assessment for TOHP to low; the RoB for the RCT data was low in the review draft, but we had rated it high for the observational data until we could ascertain how intake was validated. We also aimed to explain more clearly the criteria for overall RoB ratings.
TEP Reviewer #4	General	Seventh, the report does not include key quality metrics related to the outcome of blood pressure.Given the high intra-individual variability in blood pressure, it is important to understand how and how often blood pressure was measured at baseline and follow-up. A few studies had rigorous methods (5 sets of BP), but many did not or were unclear. Again, it would be useful to identify trials and studies with strong methods to assess not just exposure but also outcomes.	We abstracted the methods used to assess BP (noted on the Evidence Tables) and we included assessment of methodology in our RoB assessment. But we acknowledge that while we did sensitivity analysis on overall RoB, we did not do a sensitivity analysis based on the method of BP assessment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	General	Eighth, while it is fine to compare results of the Graudal meta-analysis of trials with results in this report (ref 292), it is totally inappropriate to use the Graudal meta-regression analysis of observational studies (reff 293), which is fundamentally flawed; it has an extremely high risk of bias given that it used studies with unrealistically low levels of sodium (e.g. NHANES 1 and 2) for its dose-response analysis.	We simply noted the findings of that review, to compare our findings to those of recent, higher profile reviews.
TEP Reviewer #4	General	Overall, it will be difficult for the DRI committee to use this document, except to dig deeper into individual papers, as it attempts to identify the best evidence to guide policy.	We hope that in redoing critical analyses and revising the text for clarity, we have created a report with usable conclusions.
TEP Reviewer #4	General	Specific points (* indicates major issue) 1) in displaying and stratifying trials, it would be useful to identify those trials in which sodium was controlled through feeding vs advised through behavioral interventions. The former are better for establishing an experimental contrast and determining a true effect, and should be easily identified in this review.	Unfortunately, the number of feeding studies that met inclusion criteria was quite small. However, we have provided a much more detailed description of the findings of the highest quality trials, e.g., DASH Sodium and TOHP.
TEP Reviewer #4	General	2) *The TOHP3 follow-up study with multiple 24 hour urines is perhaps the least biased of all observational studies. It's rating should be 'low' risk of bias (Appendix page E-42)	We revised the RoB for the TOHP followup study to low.
TEP Reviewer #4	General	3) *There is no mention of the (in)accuracy of using 24 hour collections to estimate potassium intake. In contrast to sodium, urinary excretion as a percent of intake is not 100% and is highly variable. See Turban S et al, JASN 2008 Jul;19(7):1396. PMID: 18579642. PMCID: PMC2440302	Thank you. We did not use the same criteria for assessing potassium intake as we used for sodium. We describe the criteria in the Appendix that shows the RoB data.
TEP Reviewer #4	General	4) *The Exeter-Andover trial by Ellison was inappropriately excluded. It is a 2 period cross-over trial with a large sample size and long follow-up. Ironically, the authors lament the lack of studies that took advantage of institutional settings, and this one did. When I reviewed it, I could not find evidence of randomization, but this is a minor issue as the schools were assigned a sequence of usual and low sodium years (and is much less prone to bias than non-parallel arm trials). Ellison RC, Capper AL, Stephenson WP, et al. Effects on blood pressure of a decrease in sodium use in institutional food preparation: the Exeter-Andover Project. J Clin Epidemiol. 1989;42(3):201-8. PMID: 2709080.	Thank you for pointing out this oversight. We reassessed the Ellison study and included it.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	General	5) *The rationale for a moderate SOE as opposed to a strong SOE for BP reduction from sodium reduction is perplexing, as the evidence is much stronger for Na than for potassium which was given a similar SOE. Documentation of the effects of increased K on BP results mostly from meta-analyses of relatively small trials (large trials such as TOHP1 were null), while there are several large and well-done trials of sodium reduction that documented significant BP effects, i.e. documentation of the effects of Na reduction on BP do not rest on just meta-analyses.	We describe our rationale for grading the SoE of the sodium reduction and BP conclusions in the text. Although the effect estimates were certainly significant and the studies had an overall low RoB, the direction of findings was quite inconsistent and many were imprecise.
TEP Reviewer #4	General	6) The Obel trial of potassium supplementation on BP is an extreme outlier with SBP reduction of >30 mmHg. In meta-analyses, this trial is extraordinarily influential and should be noted (and potentially excluded in sensitivity analyses).	We conducted sensitivity analyses that excluded high or unclear RoB studies, but Obel had an overall low RoB. Nevertheless, we believe the effect would have been significant, albeit smaller, with the study omitted.
TEP Reviewer #4	General	7) The authors state that RCTs have highly selected populations, comprising highly motivated individuals (ES-12). While highly selected, the populations turn out to be less motivated than expected. I would drop the clause on highly motivated.	We revised the wording of this limitation.
TEP Reviewer #4	General	8) The authors state that RCTs in academic settings are resource intensive and may have limited practical application (ES-14). This statement is unfounded, based on opinion, and rather derogatory. It should be dropped.	We revised the wording of this limitation.
TEP Reviewer #5	General	I appreciate the breadth and complexity of the task that was assigned to the review group. Most metaanalyses on sodium and potassium focus on one intervention, one outcome and/or one type of study. This review attempts to be very comprehensive and cover a wide area of research, which is very difficult, especially given the complexities involved. I believe there could have been more reliance on other reviews that have been done over decades, some of which take careful account of the nuances and complexities in design and analysis.	We originally hoped to employ existing systematic reviews to cover the earlier studies, but ultimately we had difficulty agreeing on how to assess all the evidence using the same criteria.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	General	The executive summary seems to provide a reasonable summary of the review. It includes a thoughtful discussion of weaknesses and limitations of studies, including possible biases such as measurement error and reverse causation. They also justifiably describe some issues that they could not address in their review. However, they do not carry these observations throughout the review, and appear to insufficiently distinguish studies with more or less bias in the bulk of the report. Studies that exhibit the problems mentioned are not noted in the text and are combined with others in the meta-analyses. Such an analysis is a mechanical summary without stressing important differences between studies, particularly when considering observational data. See specific comments in the sections of this review for some individual examples.	In revising the text, we did conduct sensitivity analyses that omitted high- or unclear-risk of bias studies. We also expanded our discussion of the implications of specific study quality issues for the outcomes (in the Limitations section of the Discussion).
TEP Reviewer #5	General	In general, I believe that the reviewers were tasked with an onerous job, with a limited time frame to address all the complexities. While they seemed to do a reasonable job assembling the vast literature on these topics, the interpretation is lacking. It is very difficult to ascertain all the potential biases in the various studies, especially in observational data, and just summing them into a combined meta-analysis is inadequate.	We hope that in revising the Discussion and Conclusions, we have addressed this problem.
TEP Reviewer #5	General	The authors do separate summaries for trials and observational associations for each outcome and exposure. There are several trials of sodium reduction and BP, and where extensive trial data are available, there should be less focus on the observational results. In general, randomized interventions should be emphasized to get around all the issues surrounding confounding and reverse causation.	The conclusions in the Key Messages and Abstract rely more on RCTs than on the observational studies. We also made sure to clarify the study designs on which each conclusion was based.
TEP Reviewer #5	General	I believe there is one important error in the report. The limitations say that, “No observational studies used multiple 24-hour urinary excretion analyses,” though this is untrue. The TOHP observational followup studies used an average of multiple 24hr urine excretions to assess exposure, then examined risk associated with later long-term follow-up. In fact, there is a discrepancy when summarizing the results for sodium and mortality. The text on page ES-11 says that, “only a small number used multiple 24-hour sodium excretion measures with validation to ensure complete collection,” while that on page 191 says, “none used multiple 24-hour sodium excretion measures with validation to ensure complete collection.” The review should note that TOHP use multiple collections. Quality control data for these are reported in the initial trial reports for TOHP I and II referenced in the papers and included in the appendix.	We reassessed and revised the RoB for the TOHP followup.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	General	In addition, the authors rate observational studies with a single 24hr sodium excretion as high risk of bias. However, some analyses made an effort to correct for measurement error by using repeat collections, sometimes in a subsample, which is not noted in the review. These include, for example, analyses of sodium and BP in Cook (ref 91), of sodium and mortality in Yang (ref 282), and of sodium, potassium and CVD in Prentice (AJE 2017, excluded from this review due to "Intervention not of interest", Appendix B).	We reassessed Rob for all observational studies (as well as RCTs) with these points in mind.
TEP Reviewer #5	General	The authors conclude in several places that there is evidence that sodium reduction does not affect risk when confidence intervals are very wide. These results should be described as inconclusive rather than saying that evidence shows no effect. In other places, the authors make this same conclusion when a beneficial effect is suggested by the point estimates that miss statistical significance, sometime barely. A strict lack of evidence is not evidence of a lack of effect. In general, there is too much emphasis on pvalues and statistical significance rather than effect estimates.	We revised the way we described the findings and the conclusions we drew for the chronic CVD outcomes, to take this point into account.
TEP Reviewer #5	General	The authors note in the limitations the fact that older studies often lack details such that RoB is difficult to assign. Yet these studies are treated the same as the more recent, even larger studies in the syntheses. Several other limitations are noted, such as use of antihypertensive medications, pre-existing health conditions, or other potential residual confounding, yet these are not noted in the review summaries.	We conducted sensitivity analyses that excluded high or unclear RoB studies, but in fact the older studies were not more likely to have high or unclear RoB. In discussing the conclusions we noted where findings might have been affected by failure to account for use of antihypertensives, however, we did not do a sensitivity analysis that specifically omitted such studies or those in which assessment of BP was inadequate.
TEP Reviewer #5	General	It would be very helpful to include the reference numbers for the studies in the forest plots.	Unfortunately, the program we use does not allow us to do that.
TEP Reviewer #5	General	In general, it seems inappropriate to combine studies of children and adults when looking at the effects of sex.	We didn't intend to combine studies of children and adults and have separated them for pooled analyses.
TEP Reviewer #5	General	References 288-295 are out of order.	Thank you! We have checked and revised the references.
TEP Reviewer #5	General	It should be noted whether case-cohort (or case-control) studies are nested within cohort studies.	Thank you; we have done that.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	The report does not provide information useful for clinicians, nor public health. The structure is unsuited to the issues, includes material that has no place, and seems unaware of some biological reality.	The report is intended for the Food and Nutrition Board's DRI Committee to be used as a resource for considering modifying sodium and potassium recommendations. As such, we have revised conclusions to try to make more usable.
Peer Reviewer #4	General	Being an essential nutrient, human life is incompatible with the absence of sodium. Since there are obligatory salt losses, there must be a level of sodium intake below which harm occurs. Other nutrients, like calcium or potassium display a “J” or “U” shaped relation of intake to health outcomes. The report seems content with viewing the sodium relation to health outcomes as a straight line -throughout which low is always better, and more worse.	In keeping with our charge and statement of work, we included existing RCTs and observational studies that assessed normal ranges of intake by humans. We took no position regarding what the shape of the association or relationship should be between sodium intake and health outcomes, and we set no lower limits for sodium intake. Had we identified studies that assessed outcomes of sodium intakes lower than the ones we encountered and that met all other inclusion criteria, we would certainly have included them. We noted this point in the revised introduction.
Peer Reviewer #4	General	Since a straight line cannot explain the relationship of sodium to health outcomes, the DRI committee should assess the evidence derived from an analytic framework that compares health outcomes at the extremes of sodium intake to those of the healthy majority, where intakes are in the middle range of the Gaussian curve. I am unaware of any observational or randomized trial evidence that supports the idea of benefit comparing <2000mg/d to usual intake. Biology demands otherwise. For virtually all essential nutrients, the possibility of harm appears with intakes below the low end of the healthy distribution. This report does not seem to have seriously considered that possibility.	We can't recommend how the DRI committee should use or interpret the findings of our report. We had to base our conclusions on data from existing trials and prospective cohort studies.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	Third, and finally, it is worthwhile to explore all relevant physiological effects associated with changes in sodium intake. It's hard to imagine how a report that leads with, and ignores many adverse physiologic effects can be taken seriously by serious scholars, clinicians, or investigators. The randomized clinical trials that established the effect of sodium on blood pressure, have also established its adverse effect on several other physiological endpoints associated with adverse cardiovascular outcomes.	The statement of work for this report dictated that we focus on BP, kidney stones, all-cause mortality, and CVD, stroke, MI, and renal morbidity and mortality, including efficacy and adverse effects. We reported all adverse effects that were reported in studies that met inclusion criteria.
Peer Reviewer #4	Introduction (General)	The purpose of this review is to assess the evidence provided by the Rand Corporation to support the update of the 2004 DRI recommendations for sodium and potassium. My comments primarily address the sodium issue. The 2004 DRI found the UL for sodium to be 2000mg/d. The IOM/NAM in 2013: Sodium Intake in Populations, concluded that evidence was insufficient to determine whether restricting sodium to <2300mg/d would be harmful or beneficial. The next committee will be charged with reconsidering the previous DRI, while considering the 2013 IOM committee findings, as well material evidence published since then.	No response seems to be warranted. We will address specific comments as they are presented.
Peer Reviewer #5	General	Yes, the report is definitely clinically meaningful.	Thank you.
Peer Reviewer #6	General	Overall, this is an extremely well researched, well organized, and well written systematic review. I concur with the authors conclusions based on the evidence that is presented. I have only minor comments for clarity.	Thank you.
Peer Reviewer #7	General	The association between sodium and potassium intake, blood pressure and cardiovascular outcome is of major clinical and public health relevance, because the dietary intervention in theory might the a cost-effective tool to improve health in the general population. The target population and audience is therefore easy to define.	No response seems warranted.
Peer Reviewer #7	General	In the "world-as-it-was-earlier', the key questions asked here would have been appropriate and explicitly stated. However, things in the sodium research arena today are different from what they were 10 years ago. Today we begin to understand that the physiological concept we apply to study salt and water metabolism in the clinical and public health arena is severely biased; it is more a 150-year old belief than science. In clinical and basic salt research, the generally accepted tools to study the effect of salt on our body thus have become more than shaky. I have addressed this issue in my comments on the methods section.	The key questions were provided in the statement of work. Thus we were obliged to conduct a literature search and review based on those questions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	General	Furthermore, I have the impression that one additional key question is missing here, namely: "Will further research using the same questionable set of tools the community has used for 5 decades result in anything but further inconclusive evidence?"	We were asked not to provide recommendations for future research but to provide a discussion of research gaps, as we did.
Peer Reviewer #7	General	My personal conclusion after having spent time with this paper is that there is no reason to leave things in salt research as they always were. I also think that there is no reason documenting a failing research approach in a systematic review without addressing the perhaps ultimate alternative question: how long can a community neglect the fact that way we are doing salt and water research is simply not good enough?	Again, we can't address this question except within the boundaries of the evidence we identified and assessed.
Peer Reviewer #7	General	This systematic could be different from Graudal's, IOM's, and WHO's work: it could be timely.	Unfortunately, few suggestions were made regarding additional studies to include in our analyses.
TEP Reviewer #1	General: ES-7, line 43: 4th bullet point under KQ1	"Potassium-containing salt substitutes decrease systolic and diastolic BP (moderate SoE)." – K-containing salt substitutes decreased BP when Na intake is decreased or independent of Na intake?	Unfortunately, not all of these studies assessed sodium intake, but to the extent that they did, we report it in the figures.
TEP Reviewer #1	General: ES-9, line 16:1st bullet point under KQ5	Given the traditional link between Na and BP would be helpful when referring to to K intake to indicate whether Na intake was controlled for or not.	We noted when studies of potassium intake controlled for sodium intake.
TEP Reviewer #1	Abstract, pg. viii, line 41. Sentence on that line starts "who achieved a prespecified..."	First define and then consistently use SoE.	We spelled out and defined SoE in the abstract, executive summary, and main text.
TEP Reviewer #1	ES-7, line 43: 4th bullet point under KQ1	"Potassium-containing salt substitutes decrease systolic and diastolic BP (moderate SoE)." – K-containing salt substitutes decreased BP when Na intake is decreased or independent of Na intake? Alluded to, page 27 [ES-15], line 12 [cardiovascular diseases finds that interventions that reduce dietary sodium intake], but not main text.	We reported sodium intakes at followup in the accompanying figures and noted in the text that sodium intake decreased by only 18 mmol overall.
TEP Reviewer #1	ES-9, line 4; KQ 5 header	Question included BP and kidney stone formation – no comment on kidney stones, not even insufficient evidence.	We have added a statement regarding the evidence re kidney stones.
TEP Reviewer #1	ES-9, line 16; 1st bullet point under KQ5	Given the traditional link between Na and BP would be helpful with reference to K-containing salt substitutes to indicate whether Na was controlled for or not.	We reported sodium intakes at followup in the accompanying figures and noted in the text that sodium intake decreased minimally.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	ES-General comment	General comment – Effects are identified in terms of increasing K and decreasing Na intakes but there is no indication of the magnitude of the changes, 1 mg or 1000 mg/day?	We have added details to the figures and text regarding the weighted mean intakes at followup.
Peer Reviewer #2	Exec Summary, pg 12	Executive Summary (page 12), second line of "Background and Objectives"; ....coronary artery disease (such as stroke), and kidney disease..." There is an error here. Stroke is not part of coronary artery disease. Coronary artery disease is specific to heart disease. Stroke is typically classified within cardiovascular disease (CVD), but not coronary artery disease or coronary heart disease.	We have revised the definitions in the introductory sentence.
Peer Reviewer #2	Exec Summary, pg 12	Executive Summary (page 12), "The Dietary Reference Intakes", 8 lines down, "the Food and Nutrition Board of the HMD...." What is HMD? Please define.	We spelled out HMD.
TEP Reviewer #6	Abstract pg vii	Vii – "evidence of a blood-pressure lowering effect of dietary sodium reduction in adults" should be HIGH in this reviewer's opinion not moderate-strength. As stated, this statement refers to evidence of BP lowering effect of sodium reduction where the evidence is very strong (Fig 4a, p. 28, Fig 5a, p.30, and see also the two dose response trials: DASH-sodium trial, and MacGregor et al, Lancet 1989). It may be there is moderate evidence concerning size of effect because of heterogeneity and imprecision, but not for the qualitative question as to whether sodium reduction lowers blood pressure. There seems to me to be confusion on this point when strength of evidence is considered.	In the executive summary and main text, we describe why the evidence supporting these findings was downrated from moderate to high. We can't base the conclusions on only one or two studies, and the many studies that assessed the effects of sodium reduction on BP showed considerable inconsistency in direction of effects.
TEP Reviewer #6	ES-2	– "findings from observational studies be subjected to greater scrutiny and ideally that they be supported by the findings of randomized controlled trials" (Such RCT data not available for cigarette smoking and cancer/CVD, for example)	We purposely drew separate conclusions for RCTs and observational studies and noted where RCTs were not available to address certain questions.
TEP Reviewer #6	ES-7, p.24	NB evidence reported as HIGH in Results on p ES-7, But MODERATE in KQ 1, p ES-7, p24	We have checked and made sure the SoE is consistent throughout.
TEP Reviewer #6	KQ3, ES-8	Should add statement on children (low SoE)	We have added the findings for children.
TEP Reviewer #6	KQ4, ES-8, final bullet point	"A low level of evidence supports a lack of association of…" Re-word as e.g. "We did not find evidence of an association of…with low strength of evidence". (Cannot assert the negative, only absence of the positive.) By the way elsewhere this is "strength of evidence" not "level of evidence" – needs to be consistent throughout.	We have reworded all conclusions regarding negative results, similar to the wording suggested by several reviewers.
TEP Reviewer #6	KQ5, ES-9	Gives numbers of trials on which evidence based – not consistent with wording for other KQ where numbers of studies not given in the ES.	We have provided numbers of studies for all conclusions now.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	KQ6, ES-9	Here talks about potassium “exposure” and “exposure status”, elsewhere “intake”. Intake is better.	We have changed all to "intake."
TEP Reviewer #6	Abstract, ES and Results	The figures are very helpful.	No response warranted.
Peer Reviewer #6	ES-4	Understanding that the difference between KQ1 and KQ2 and KQ 3 vs KQ4 seems to be active efforts to reduce sodium vs association sodium intake with BP and outcomes, it would be helpful to explain in the introduction why outcomes between these two situations should be different.	We actually discuss the differences in findings between the two types of studies in the Discussion section for the full report.
TEP Reviewer #1	Introduction	Complete, no comments	Thank you. No further response is needed.
Peer Reviewer #1	Introduction	The introduction is well done. It is particularly useful to have the explanation regarding dietary reference intakes.	Thank you. No further response is needed.
TEP Reviewer #2	Introduction	Comment #9 Introduction, p.1, line 8: Cardiovascular and circulatory diseases... Are these two distinct categories? CVD is part of circulatory diseases.	We have revised the text that describes the conditions considered in the report.
TEP Reviewer #3	Introduction	The authors may wish to consider a few comments in revising their report. Please note that the page numbers on the pdf at the top of the page differ from those at the bottom of the page. The reference to page numbers in this review refer to page numbers of the report, at the bottom of the pages. 1) Line 12, page 2: There are obviously salt-sensitive and salt-insensitive hypertensive subjects and salt sensitivity is a quantitative trait not a binary phenotype (Circulation. 2016;133:894-906). Therefore, it may be more correct to say the effect of salt or sodium reduction is generally greater in adults with hypertension….	We did in fact provide a conclusion regarding the moderating effect of hypertension on the effects of sodium reduction.
TEP Reviewer #3	Introduction	2) Line 39, page 6: Again, it may be more correct to say “…generally greater in adults with hypertension…”	Thank you for this suggestion
TEP Reviewer #3	Introduction	3) The impact of chloride on the effects of sodium and potassium on blood pressure and cardiovascular risk have not been considered. Previous studies have shown that chloride is a key factor in the blood pressure responses to salt (i.e. sodium chloride) (N Engl J Med. 2013;368:1229-1237; Ann Intern Med. 1983;98:817-822). Although availability of evidence is limited, it may be important to explicitly state that 1) some studies suggest that chloride intake may be a modifier of the blood pressure (and presumably CVD) effects of sodium and potassium, and 2) that future studies are needed.	We realize there is interest in determining whether it is the chloride or the potassium moiety that affects blood pressure; however it was actually beyond the scope of the report to consider this question.
Peer Reviewer #3	Introduction	The introduction is fine. In the Executive Summary it would have been helpful to this reviewer if the term RoB had been defined (page 26 or 257).	We provided the definition in the revised version.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Introduction	9) *The authors state that "since high blood pressure is strongly associated with a higher risk for CVD, stroke, congestive heart failure, and kidney disease and lowering blood pressure lowers these risks, an indirect relationship between sodium intake and CVD has been proposed.15-17 Assessing the relationship between sodium intake and chronic disease outcomes (i.e., CVD, Stroke, MI, and kidney disease), and in particular whether reducing dietary intakes of sodium lowers the risk of these diseases, requires that the findings from observational studies be subjected to greater scrutiny and **that they be supported by the findings of long-term trials.**" The authors should not make such strong statements, as trials with clinical outcomes are impractical (p2, lines 37-44), as evidenced by the fact that none have been done despite calls (by some) for such trials.	We have revised this statement.
TEP Reviewer #6	Introduction	Different units are used in the report e.g. mg, g, mmol and this could be confusing to the reader. At the least a box giving the conversion factors should be provided.	We have tried to include the values in mmol throughout the report
TEP Reviewer #6	Introduction	P4, li 7. Not clear what is meant by "exposures" rather than "intakes" (li 6) Are these used interchangeably (both appear throughout the report)	We have changed all uses of exposure to intake.
Peer Reviewer #5	Introduction	Introduction is clear and I like how it covers the DRI and key questions.	Thank you!
Peer Reviewer #6	Introduction	In the Background the authors refs to definition of hypertension from guideline statements. The definition from the 2017 AHA ACC Guidelines for Hypertension may have been omitted due to the fact that these were just recently released; however, the authors should make note of this definition <130/80 mm Hg.	We have updated the guideline.
Peer Reviewer #6	Introduction	In the Executive Summary and the introduction it would be useful to distinguish the KQs that addressed RCTs from prospective cohort studies as was done in the conclusion (unless I missed it), so the reader better understands the approach that the authors took: "In general, the key questions were organized, first, byexposure: key questions 1 through 4 considered sodium exposure and sodium to potassium ratio,whereas key questions 5 through 8 considered potassium exposures. The questions were then further organized by study design: Key questions 1, 3,5, and 7 assessed the findings of RCTs not he effects of studies intended to reduce sodium or increase potassium intake for the outcomes of interest, whereas the even-numbered questions assessed the associations between sodium or potassium exposures and the outcomes of interest in prospective cohort studies. The questions are then further organized by outcomes."	We have clarified throughout the report where KQs and conclusions are based on RCTs vs. observational studies.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Introduction	Pg 1, line 12: This sentence should be modified in light of new AHA/ACC Blood Pressure Guidelines, in which hypertension is defined as = or >130/80 mmHg.	We have updated the guideline.
Peer Reviewer #7	Introduction	No comments.	No response appears warranted.
TEP Reviewer #1	Methods	Appears complete Inclusion/exclusion criteria appear appropriate Search strategies explicitly stated and logical	No response appears warranted.
Peer Reviewer #1	Methods	The methods are very well described. The inclusion and exclusion criteria are clear and well justified. The search strategy is also clear. The definitions and diagnostic criteria are clearly stated. However, as the authors point out, this can be problematic as the published studies use a variety of different definitions. The statistical methods used appear appropriate.	No response appears warranted.
TEP Reviewer #2	Methods	Comment #10 Methods - Which time period is covered by the literature review? Are recent studies included? - "Crossover trials that did not incorporate a minimum 2-week washout phase between treatment phases ... were excluded". This is a rigid criterion for BP trials, especially for trials with a placebo phase. This criterion is probably the reason why a fully controlled, double-blind feeding study of sodium supplementation and potassium supplementation (Gijsbers et al, J Hum Hypertens 2015) was excluded. This trial included a 4-week phase on placebo and only end-oftreatment BP levels were compared. In my opinion, it should have met the inclusion criteria for this report, to which it would have added valuable information. - A more detailed, systematic overview of in/exclusion criteria would be helpful. I feel not able to replicate the selection of studies for the report (p.23). Also, for each RQ, it would be useful to have an overview of in/excluded studies (references) and the reason why studies were excluded. Will that be added as a Supplemental file? - More attention could be paid to the quality of outcome assessment in different studies.	We revised the description of the searches to incorporate the date limiters. Check Gijsbers. We described the inclusion/exclusion criteria in a table in the Methods and summarized them in the text. Excluded studies are listed in an Appendix. We assume that the reviewer is referring to assessing risk of bias attributable to methods used to measure BP, for example: we described the methods used to assess outcomes for each study in the evidence table, and we included 1 item in the RoB assessment regarding outcome measurement; however, we did not conduct a sensitivity analysis that excluded studies that did use up-to-date methods for measuring BP.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Methods	The criteria for inclusion/exclusion of studies in this review are stringent and generally justified appropriately. The inclusion of studies that reported outcomes of interest in participants at least 4 weeks or more after initiation of the intervention may be appropriate for assessing blood pressure and some metabolic outcomes, but is not long enough to assess cardiovascular mortality and morbidity. Research strategies are explicitly stated and logical and definitions and diagnostic criteria for outcome measures are appropriate. The authors appropriately assess the strength of evidence (SoE) for conclusions that depend on associations separately from those that depend on interventions (e.g. clinical trials in which sodium intake was reduced or potassium intake was increased). The statistical methods used for analysis appear to be appropriate, although this reviewer is not a biostatistician.	No response appears warranted.
TEP Reviewer #3	Methods	The authors might consider the following comments: 1) Page 25, line 15-17: It is unlikely that "impaired renal function could potentially affect urinary sodium excretion in response to changes in sodium potassium intake…" Even patients with severe impairment of kidney function rapidly achieve sodium balance (i.e. balance between intake and urinary excretion) within a few days. Therefore, measured sodium excretion depends more on intake than on renal function if steady-state conditions are achieved.	We have revised the text accordingly.
TEP Reviewer #3	Methods	2) Page 26, lines 36-40: It is also unlikely that "…differences of sodium excretion or failure to see differences in sodium excretion might be due to use of drugs that effect sodium excretion". Again, chronic changes and sodium excretion are determined by intake, not by medications, if sufficient time (generally 3-6 days) is permitted to achieve sodium balance.	We have revised the text accordingly.
Peer Reviewer #2	Methods	Regarding inclusion and exclusion criteria, evaluation of populations with prevalent CKD are haphazardly addressed. For example, CKD in not included in "subgroups" in sections 1c, 2b, 6b, or 8c, yet it is considered for 3c, 4c, and 7c. Often kidney disease is evaluated as an outcome, rather than a risk factor for adverse outcomes. There are unique considerations of potassium supplementation in this subgroup (see below).	Unfortunately, few studies on populations with kidney disease met inclusion criteria. We have added a section to the response to Key question 1 on blood pressure outcomes in studies of populations with kidney disease.
Peer Reviewer #3	Methods	The methods are clearly stated and appear to be rigorous and correct.	No response appears warranted.
TEP Reviewer #6	Methods	P21, line 30-34. "If overall risk of bias..". I don't understand this sentence – is it correct?	We have revised the wording of the sentence.
TEP Reviewer #6	Methods	P21-22. Not clear what happened if the two reviewers had different views on strength of evidence etc	We revised our description of the reconciliation of judgements.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	The ratio of sodium and potassium is totally irrelevant to the deliberations of the DRI. It has no practical application. Both intakes are important and influence each other, and can be measured. Proper analyses of evidence must include, for example, that the association of sodium intake to mortality is significantly influenced by the coincidental potassium intake. Thus, any analysis of sodium must take into account the concurrent potassium intake. The inclusion of these questions reflects upon the capability of those who composed the questions.	We assessed findings with respect to sodium/potassium ratio for relevant outcomes because it was part of the statement of work.
Peer Reviewer #4	Methods	Since the objective of the review is to provide information for the DRI committee, it must be based upon knowledge of the population distribution of sodium intake, and, to the extent possible, the relation of intake to health outcome. That was defined by the 2013 IOM Committee Report. Physiological effects are not health outcomes. Exclusive focus on one of many physiological consequences of variation in dietary sodium intake may have been of primary interest to those who constructed the questions, but reflects an inexcusable focus one, instead of all potential consequences. The health effect of changes in sodium intake integrates of all its physiological consequences. Perhaps someone else would focus on another - and find the same association with health outcomes.	Unfortunately, we are bound to adhere to the outcomes set forth in the statement of work.
Peer Reviewer #4	Methods	As with blood pressure, there is a rich body of evidence describing the effect of sodium on the renin angiotensin system, triglycerides, glucose, aldosterone, etc. The initial questions can most generously be ascribed to unfamiliarity with conventional biomedical science practice. Nevertheless, these findings are of secondary importance to the task of the DRI. The association of sodium intake with CVD and all-cause mortality integrates all recognized and unrecognized physiologic effects.	Again, we assessed the literature that addressed the outcomes of interest to the Committee within the limitations of the literature that met the inclusion criteria.
Peer Reviewer #5	Methods	Yes, all are clear and explicitly stated. Tables are helpful.	Thank you.
Peer Reviewer #6	Methods	Yes to all of these questions.	Thank you.
Peer Reviewer #7	Methods	Formally, exclusion and exclusion criteria and search strategies explicitly stated are logical and justifiable.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Methods	In contrast, I do not agree that the diagnostic criteria (single 24h urine collections, spot urine collections) reported here are appropriate to measure an individual's salt intake. The idea that 24-h urine sodium is useful to measure salt intake in a human derives from Carl Ludwig and Wilhelm Wundt, who studied chloride excretion in humans on the short-term and in response to dietary extremes (very low salt intake to very high salt intake and reverse within one week (Ludwig, C. (1861). Veränderlichkeit der Chloridausscheidung mit der Zufuhr. In: Physiologie des Menschen. Leipzig & Heidelberg, Wintersche Verlagshandlung pages: 398-400.) Clinicians have used this methodological approach for more than 100 years without questioning its validity (Kidney Int. 1985 Jun;27(6):837-41), and have transferred it into the current public health research arena.	We agree that the single 24-hour and spot urine methods are not appropriate, based on the evidence, and we went to great lengths to downgrade the quality of observational studies that relied on this method to assess intake/status. However, increasing evidence appears to have validated the use of multiple days measurements, and they are the best we have.
Peer Reviewer #7	Methods	The underlying theory is that all salt that enters the body will inevitably be accompanied by water (Assumption 1). Therefore, body sodium content is kept constant (Assumption 2). This is achieved by transferring excess dietary salt into the urine within 24 hours (Assumption 3).	No response appears warranted.
Peer Reviewer #7	Methods	Was it appropriate to transfer this diagnostic tool into the public health arena, and define Assumption 3 as a gold standard measurement for dietary salt intake in populations? Opinion suggests that it was not, because humans do not live lives in response to dietary extremes, and because life is longer than 7 days.	We agree with the reviewer's assessment, which is why we excluded studies with duration less than 4 weeks, which essentially excludes sodium loading or depletion studies.
Peer Reviewer #7	Methods	Furthermore, science suggests that these assumptions are flawed. Under daily life conditions, 9 repetitive accurate 24-h urine collections are necessary to predict salt intake, and morning collections are of no value (Hypertension 1982;4:805–808). These findings were confirmed in long-term controlled feeding studies. 24-h salt excretion in the urine underlies half-weekly, weekly, and monthly rhythmical change patterns (Cell Metab. 2013 Jan 8;17(1):125-31).	We had to include studies regardless of assessment method, but we were clear about including only studies with the more valid methods in support of conclusions. We would have had no studies to include, had we limited exclusion to studies with 9 repeated measures.
Peer Reviewer #7	Methods	The long-term biological pattern reduces the predictive value of an accurately collected single 24-h urine to diagnose a 3-g difference in real salt intake to 50% (Hypertension. 2015 Oct;66(4):850-7). The predictive value of single 24-h potassium and chloride collections is not any better (Am J Clin Nutr. 2016 Jul;104(1):49-57).	We have addressed this problem in the Discussion.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Methods	What is the predictive value of a spot urine to predict real 24-h excretion? In a recently reported Chinese population study, another 50% of spot urine samples did not correctly estimate a 3 g difference in real 24-h sodium excretion (Am J Clin Nutr 2017;105: 1291–6).	Thank you! We had already considered and cited the reviewer's commentary! We are not suggesting that spot urine assessment is a valid indicator of sodium intake and believe we have addressed this issue in the report.
Peer Reviewer #7	Methods	To summarize the experimental evidence: using accurately collected 24-h urine samples, 50% of the single 24-h urine samples with misclassify a 3-g difference in real salt intake, and 50% of the single spot urine samples with misclassify a 3-g difference in real 24-h sodium excretion. Combining the experimental evidence mathematically, we can anticipate that only 25% of single spot urine samples will correctly classify real salt intake.	No further response needed.
Peer Reviewer #7	Methods	Liffert Vogt's group has recently addressed this problem in an observational study. Multiple urine collections not only significantly changed information on assumed salt intake level, but also provided with very different information on the relationship between urinary salt excretion and later cardiovascular outcome (Circulation. 2017 Sep 5;136(10):917-926).	No further response needed.
Peer Reviewer #7	Methods	Is it of any relevance for public health research that the biology of urinary salt excretion is very different from what doctors and physiologists believed for more than 100 years? 1. At the population level, the gold-standard 24-h urine collection will diagnose how much salt a community eats, because rhythmical release and storage of sodium in the tissues the results in systematic over- and underestimation of real salt intake, ultimately resulting in a correct measure of average salt intake. 2. In the individual study participant, 50% of the single 24-h urine collections will misclassify a 3-g difference in real salt intake. This systemic error persists independent of cohort or study sample size.	We have addressed this indirectly in the introduction and Discussion.
Peer Reviewer #7	Methods	The resulting misclassification inevitably leads to misinterpretation. 24-h sodium excretion does not necessarily represent an individual's sodium intake. Correlating single 24-h sodium excretion with later health outcome therefore cannot provide with information on the relationship between long-term salt intake and health outcomes in observational studies.	No additional response.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	The results are presented in a clear and understandable manner. There is sufficient detail presented to provide understanding. The characteristics of the studies, including design and risk of bias, are well presented. The associated tables and figures are clear and complement the other aspects of the presentation of results. The key messages are explicit. I can find no studies that were overlooked and no studies that were mistakenly included.	Thank you. No response needed.
TEP Reviewer #1	Results, pg. 23, line 11	"...assessing effects of sodium or sodium to potassium ratios." – The Na/K ratio is of current interest. First time in report noted. If there are insufficient data should be stated in Executive Summary.	
TEP Reviewer #1	Results, pg. 23, line 13	"<.of the sodium-to-potassium ration .." – ration should probably be changed to ratio.	Revised. Thank you.
TEP Reviewer #1	Results, pg. 24, line 4	Flow diagram important yet too small to read.	Unfortunately, we were not able to make it larger.
TEP Reviewer #1	Results, pg. 24, line 41	Key points summary helpful.	Thank you
TEP Reviewer #1	Results, pg. 25, line 19	"Increasing potassium intake does not modify the effect of reducing dietary sodium on blood pressure compared with sodium reduction alone (low SoE)." – relates to issue of Na/K ratio. Should be tied together and consistently addressed in report.	We addressed this issue in the Discussion
TEP Reviewer #1	Results, pg. 25, line 21	"Potassium-containing salt substitutes decrease systolic and diastolic BP (moderate SoE)." – State whether the benefits from the K-containing substitute was related to Na reduction.	We added text to the report regarding the inconsistency of changes in sodium intake with use of the potassium-containing salt substitutes.
TEP Reviewer #1	Results, pg. 27, line 15, sentence starting with "foods."	Would be valuable to include some indication of the absolute change in Na intake, in this case, or in other cases throughout report in terms of Na excreted (mmol/d).	We have added the weighted mean difference in sodium intake for all pooled analyses.
TEP Reviewer #1	Results, pg. 39, line 30, sentence starting with "studies of normotensive.."	Again, throughout report, hard to put results into context without some idea of the estimated Na intake.	Sodium intakes now added.
TEP Reviewer #1	Results, pg. 44, line 25, sentence starting with "of potassium on the effects."	Per prior comments the following statement was helpful "(we do not define reduced dietary sodium or low sodium in this review, as definitions and target goals differed across studies, and some provided no definition or goal)", however, this limitation limits the value of the review.	We agree. We hope that by provided the achieved intakes, that will help
TEP Reviewer #1	Results, pg. 44, line 32	Per prior comments, the following is helpful and should be used consistently when appropriate; "Thirteen studies assess the effects of using potassium salt substitutes **in place of** sodium chloride table salt..'	We have added the numbers of studies throughout.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Results, pg. 44, line 43	The findings, "Comparison of low sodium diet with or without increased potassium intake" were not adequately captured in the summary.	We did not include the conclusion in the original key points but have added it.
TEP Reviewer #1	Results, pg. 50, line 34; Key Points for KQ2	Key points clearly stated	Thank you
TEP Reviewer #1	Results, pg. 57, line 11; Key Points for KQ3	Key points clearly stated	Thank you
TEP Reviewer #1	Results, pg. 65, line 13 Key Points for KQ4	Key points clearly stated	Thank you
TEP Reviewer #1	Results, pg. 128, line 12 Key Points for KQ5	Key points clearly stated	Thank you
TEP Reviewer #1	Results, pg. 144, line 10 Key Points for KQ6	Key points clearly stated	Thank you
TEP Reviewer #1	General results	No additional comments on subsequent key points Results section contained an adequate amount of detail to support the key points. Figures are particularly helpful. Not aware of any additional studies that should have been included.	Thank you
TEP Reviewer #2	Results, KQ4, pg 66 Fig. 24, pg. 67	Comment #5 KQ4 (p.66): The results from observational studies of sodium intake and (CVD) mortality can only be understood when accompanied by a critical appraisal of the methodological aspects of these studies. Studies with selection and/or information bias, as extensively discussed in the scientific literature, should be placed out of order first. Final conclusions should be based only on the (limited) number of studies with multiple, reliable 24-hour urinary collections that do not include people with a poor prognosis (i.e. with low urinary sodium because of clinical disorders, medication use, old age, urine collection problems, etc.). Graphs with categorical analysis of the associations (e.g. Figure 24) are not informative because they lack context. For every graph a detailed legend is needed to explain exposure and outcome assessment, type of population, nature of the association, covariables in the model, etc. Some graphs show 'optimal' values for sodium intake of 200-250 mmol/24h (~5000 mg/d), which cannot go without explanation in the accompanying text.	In addition to describing the methodological details for each of the observational studies and ordering them by method of sodium intake assessment, we have labeled the figures with the assessment method.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results, KQ5c, pg 139	Comment #7 KQ5c (p.139): Overall BP effects of potassium intake in healthy people are compared with effects in people with prehypertension or hypertension. First, I have difficulty with the dichotomy (healthy-unhealthy) based on BP level, because of the dose-response relation between BP and risk of CVD (starting at SBP of 115 mmHg). Second, trials cannot easily be divided as such. The 'inclusion BP level' depends on the number of BP measurements before randomization (regression to the mean phenomenon). Older trials used higher cut-off values for defining hypertension. Also, trial populations have (largely) overlapping BP distributions, i.e. trials in socalled (pre) hypertensives also include normotensives and v.v. When drawing conclusions on effect modification by initial BP, I would prefer individual subject data (e.g. subgroup analysis in DASH-trial). This allows also for covariable adjustment (e.g. differences in age, sex, BMI, 3 mineral dose and other factors associated with BP). When comparing at the higher aggregation level, one may even introduce bias ('ecological fallacy') if not analysed properly. Third, BP trials in patients on antihypertensive medication should be addressed separately (or excluded) because of interaction between medication and mineral intakes, and also for translation of finding to the general population. In principle, DRIs are set for healthy (i.e. non-medicated, nondiseased) populations.	We also struggled with how to divide studies. Ideally we would have compared outcomes within studies by BP level, but few studies made these comparisons for sodium, and none did so for potassium, so we were left with needing to conduct metaregressions. We also realize the categorizations depend on the numbers of BP measures, which we note in the evidence tables but did not try to control for in sensitivity analyses.
TEP Reviewer #2	Results	Comment #11 Results - In my opinion, studies of poor methodological quality should have been excluded from the analysis when drawing conclusions, especially for observational studies on sodium intake and (CVD) mortality (see also comment #7). Also, more attention should be paid to bias and confounding. For me it is not clear how covariable adjustment was done in individual studies, and which people were in/excluded from the population of analysis. For example, in the Results section "Dietary Sodium Intake and CVD Mortality" (p.80), no potential confounders are mentioned in the text. Also for graphs (e.g. Figure 28) it is unclear which (multivariable) models were used. - I miss a number of studies (see also comment #10) but there is no full list of references to check whether these have be deliberately excluded or whether they have indeed been overlooked.	In drawing conclusions from observational studies, we did not include high RoB studies. For RCTs, we conducted sensitivity analyses to omit studies of high or unclear quality.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	The amount of information presented in the results section is appropriate. The authors have clearly described studies that were included and the key messages are explicit. However, they may want to consider stating some of the key messages differently as discussed below. The figures, tables, and appendices are adequate and descriptive. I am not aware of any major studies that the investigators overlooked or that should be included or excluded.	Thank you.
TEP Reviewer #3	Results	1) Page 54, lines 45-46: The evidence presented may not warrant the statement that "sodium reduction does not affect blood pressure in children." Although the authors indicate that there is a low strength of evidence to support this statement, it seems inappropriate to make this general statement in light of the fact that the effects of long-term reductions in sodium have not been ascertained. Experimental studies show that high sodium intake early in life can have adverse long-term blood pressure effects during adulthood. Similar qualifications may be considered for statements on lines 7-8, page 55 and 19-20, page 55. It may be more appropriate to say "increasing potassium intake "may not" modify…" rather than "…does not modify…"	We have revised the wording to consider the low strength of evidence. We also conducted sensitivity analyses to assess the effects of omitting high and unclear RoB studies from the analyses.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	2) It is interesting that Figure 7 shows that the risk for incident hypertension was reduced in all of the trials of sodium reductions, although statistical significance was not achieved in some trials. This seems to contradict the statement that "…..these finding suggest a lack of beneficial effect of sodium reduction on the risk for incident hypertension in adults" (Lines 20-21, page 63). I recognize the challenge presented by the inconsistency of the data, but perhaps it might be more prudent to state that "…these findings do not provide clear evidence of a beneficial effect of sodium reduction on the risk of incident hypertension in adults (low SoE)." Throughout the text the authors seem to make definitive statements when the results are ambiguous and inconsistent. I recommend that the authors find a more circumspect way of presenting these data to indicate that the results are inconsistent, unclear, and therefore the conclusions are unclear. This lack of clarity is also demonstrated in Figures 8 and 9 which illustrate that most studies show beneficial effects of sodium reduction, although in several cases the results are not statistically significant. In these cases, it might be prudent to indicate that the evidence was insufficient to draw conclusions. The authors have appropriately indicated that the SoE was insufficient to make conclusions about CVD morbidity and mortality. The main point that needs to be emphasized, perhaps more vigorously, is that the SoE is insufficient due to the limitations and the time of sodium exposure in most cases, the assessment methods, and the variability in outcome definitions.	In light of the non-statistically significant effect of sodium reduction on risk for HTN, we did reconsider the conclusion as suggested.
Peer Reviewer #2	Results	Page 53, "Results" section, 6th line of introduction, "sodium-to-potassium ration" "Ration" is a typo (should be "ratio").	Corrected, thank you!
Peer Reviewer #2	Results	Page 79, "Adverse Events Associated with Use of Salt Substitutes", 3rd line, "The China Salt Substitute Study Collaborative Group compared risk of hyperkalemia between the salt substitute group and the control group. No incidents of hyperkalemia were reported (low RoB)." It should be noted that this study excluded anyone with kidney disease or using drugs that might increase serum potassium concentrations. Please see main comment above.	We have noted this in the text.
Peer Reviewer #2	Results	Page 85, "Renal Health Status" subsection, 5th line, "...was significantly associated with reduced SBP and DBP (RoB)." The assessment of Risk of Bias is missing.	Added, thank you.
Peer Reviewer #2	Results	These aspects look good.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	The studies are clearly described. Some key messages are difficult to understand. An example is on page 79 or 257 where it states "A low strength of evidence supports a lack of association of sodium exposure with systolic or diastolic BP in adults based on observational studies. All studies had high risk of bias based on the methods used to assess sodium intake (typically single 24- hour urine excretion with or without validation)." I had to read this several times to understand the meaning. I could be written more clearly.	We have revised the wording considerably for clarity.
TEP Reviewer #4	Results	10) Page 33, the text states just 2 trials assessed the effects of Na reduction on headaches. There are at least 2 others – DASH-Na (Sacks, 2001; in detail, Amer M, Effects of dietary sodium and the DASH diet on the occurrence of headaches: results from randomized multicenter DASHSodium clinical trial. BMJ Open. 2014 Dec 11:4(12):e006671 PMID: 25500372 PMCID:PMC4265150]. A second study is the TONE trial which reported on the relationship of sodium with headaches, Chen L. Lower Sodium Intake and Risk of Headaches: Results from the Trial of Nonpharmacologic Interventions in the Elderly. Am J Public Health. 2016 Apr 14:e1-e6.[PubMed] PMID:27077348. Hence, there are 4 trials on this topic.	We have added the findings from DASH-Na to the findings we had already included. Thank you.
TEP Reviewer #4	Results	11) Page 43, lines 26-32 - incoherent formatting to text.	Revised. Thank you.
TEP Reviewer #4	Results	12) Page 50, lines 3-4. Incomplete and inaccurate sentence, 'Evidence is insufficient to draw conclusions about the moderating effects of age on blood pressure'.	We have revised the text.
TEP Reviewer #4	Results	13) Page 50, lines 7-8. Inaccurate statement, 'Evidence is insufficient to draw conclusions regarding the moderating effect of hypertension on the association between sodium exposure and blood pressure'. This statement is inconsistent with prior conclusions and key messages.	We have revised the text. It refers the findings of prospective cohort studies, whereas prior conclusions had pertained to RCTs.
TEP Reviewer #4	Results	14) Key Question 6 is poorly worded, '.. what is the association between potassium intake and blood pressure and kidney stone formation?'	BP and kidney stones were intended to be separate outcomes. We clarified in the response (Results).
TEP Reviewer #4	Results	15) Page 187, conclusion is poorly worded ' A low strength of evidence suggests higher potassium exposure status is not associated with lower adjusted BP ..'	We reworded the conclusion.
TEP Reviewer #5	Results	KQ1 – Trials of Na and BP The report includes all trials of sodium and blood pressure, but some trials have very small net sodium differences by intervention group. Some go down even as far as less than 5 mmol/24hr. The authors could consider a sensitivity analysis looking at the effects by difference in sodium achieved.	Although we were precluded from doing this analysis by time and resources, we do show the achieved sodium for each study on the forest plots and provide mean differences.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	KQ1 – Trials of Na and BP The results for TOHP Phases I and II are unclear and may be mixed up. The labelling should be clarified. Note that reference 139 should be authored by "The Trials of Hypertension Prevention Collaborative Research Group" rather than "Hypertension Prevention Collaborative Research Group" and represents Phase II, similar to reference 256 which represents Phase I. It's not clear which study is in the table for normotensives on page 40, though from the year (1997) it looks like TOHP II. The paper by Kumanyika in 2005 provides the same data from TOHP II, so these results are duplicated. To clarify, references 256 and 166 present data from TOHP I and references 139 and 165 present data from TOHP II.	We checked and reran the analyses with the correct findings for each study. Thank you!
TEP Reviewer #5	Results	KQ2 – Observational studies of Na and BP While there is a comprehensive body of work on this topic, including from cross-sectional studies not included in this review, this question should be greatly overshadowed by the RCT results in KQ1. There are enough trials of this question to provide fairly definitive evidence of the relationship of sodium to blood pressure.	We were asked to include a review of observational studies, but we distinguished conclusions based on each and relied primarily on the RCTs.
TEP Reviewer #5	Results	KQ2 – Observational studies of Na and BP The observational analyses of BP can be very strongly biased by use of anti-hypertensive medications. Adjustment for this is often inadequate. For example, in Singer 2015 (ref 240) participants were recruited from a worksite hypertension program between 1978 and 1999. Those on medication were instructed to go off it. Then they were free to start taking these again as prescribed, and by final followup 77% were on medication. The dose and type and its impact on BP is ignored, even though medication effects on BP are likely larger than differences by sodium intake.	We noted this detail in the description of the study, and again, did not base our primary conclusions on observational studies.
TEP Reviewer #5	Results	KQ2 – Observational studies of Na and BP The measurement of sodium also differs greatly across studies, and may not even be adequately captured by type of measurement. For example, in the same study by Singer 2015 (ref 240) an 24hr excretion was used, but "Subjects were instructed to follow their usual diet while avoiding 'excessively salty foods' for a period of 4–5 days preceding the collection." This is not a usual diet and will distort the estimates of baseline sodium consumption. This study has a much higher risk of bias than others considered, leading to results that are opposite to the others. The study should be discounted due to the above flaws.	We noted this problem with the study in the text.
TEP Reviewer #5	Results	KQ2 – Observational studies of Na and BP Given all the potential for bias in observational studies, the dose-response analyses from trials are likely to be less distorted and more reliable than those from observational cohorts.	No further response warranted.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	KQ2 – Observational studies of Na and BP The presentation of results for KQ2a starting on page 50 seem out of order. Why are results by sex presented before the overall results in adults?	We have revised the order of the text.
TEP Reviewer #5	Results	KQ3 – Trials of Na and CVD/KD/Mort The follow-up time for several of the studies varies quite a bit. It would be helpful to make this more explicit in the summary tables and text. For example, the TOHP interventions were followed up to 20 years for mortality, which may have reduced the intervention effect by diminution over time. Some of the others assess endpoints only during a short time interval, during which an effect on mortality or CVD or KD outcomes is very unlikely. Some studies also report results at more than one time. For example, the TOHP trial report outcomes at the end of the interventions, then at 9-12 years and again at 20+ years. The time horizons for each outcome should be noted, since they may be different for BP, CVD, and mortality.	We do note followup times in the evidence tables, and where possible in the text. For the TOHP findings, we noted which outcomes were assessed at which followup times.
TEP Reviewer #5	Results	KQ3 – Trials of Na and CVD/KD/Mort It looks like only the crude proportions of events were used in all the meta-analyses of the trials. Some of these were stratified by design, or imbalanced by important factors. In the TOHP studies, for example, there was a significant baseline difference in age, which was important for later CVD and mortality, though less so for the change in blood pressure levels.	Unfortunately, we did not try to take the baseline age differences into account in our analyses because of the small numbers of studies.
TEP Reviewer #5	Results	KQ3 – Trials of Na and CVD/KD/Mort The conclusions in KQ3 say that there is a low strength of evidence that sodium reduction does not affect risk for either stroke or a composite measure of CVD. However, the pooled CI for stroke is 0.09-19.26 which is very wide and suggests a complete lack of evidence. On the other hand, the CI for any CVD is 0.69-1.05 with an overall RR=0.86, which, while not significant, is leaning towards a beneficial effect. It does not seem appropriate to interpret either as showing there is evidence that sodium does NOT affect stroke or CVD. The absence of evidence is not evidence of absence of effect.	We reconsidered our overall conclusions based on this comment and revised them as well as the strengths of evidence, accordingly.
TEP Reviewer #5	Results	KQ3 – Trials of Na and CVD/KD/Mort As is well-known, random effects analyses give more weight to smaller studies, even though these may be less rigorous for the endpoints of interest or have shorter follow-up. A fixed effects analysis could be considered for a sensitivity analysis. For example, the paper by Morgan et al reports mortality among only 77 patients. The CSSS reports only 13 deaths occurring over one year. These small studies receive disproportionate weight compared to studies that are much longer and over 20 times larger in the random effects analyses.	We reran the analyses as fixed effects analyses and although we don't show the findings in the report, they did not differ.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	KQ3 – Trials of Na and CVD/KD/Mort In addition, most of the small trials were not designed to study these hard outcomes. Other potential biases, such as use of medications or inadequate endpoint adjudication, could be hidden. The small trials with a post hoc report of adverse events should not be simply combined with trials that are much larger and longer with more complete and intentional follow-up for CVD or mortality.	Although we did leave all of the studies in question in the analyses, we emphasize this concern in the Limitations section of the Discussion chapter.
TEP Reviewer #5	Results	KQ3 – Trials of Na and CVD/KD/Mort In the Morgan study, there were 4 deaths (8.0/100,000 person-days) in the low sodium group (N=35) and 5 (9.25/100,000 person-days) in the control group (N=42). How was the RR of 1.20 derived? It looks like there are fewer deaths in the low sodium group no matter how it is calculated. The crude rate ratio is 0.96 while the ratio of rates is 0.86. Is this a mistake?	We rechecked the numbers and revised them.
TEP Reviewer #5	Results	KQ3 – Trials of Na and CVD/KD/Mort The authors mention that they exclude one trial that was included in the Cochrane review by Adler (2014), but a reference for which one would be helpful. It looks like there may be several differences between the two reviews and it would be helpful to see why the discrepancies occur. For example, I don't see studies by Chang (2006), Kwok (2012), HPT (1990), or TONE (1998) that are in the Cochrane meta-analysis for mortality. Both the study by Chang et al and the CSSS used a potassium salt substitute but CSSS is included while Chang et al is not. More detail on how and why the included studies differ from the Cochrane review would be helpful.	We actually reran our analyses and included the study we had excluded; the analysis now includes Chang (2006), as well as HPT and TONE. We also revised our discussion of how the present review differs from that of the reviews of Aburto and Adler.
TEP Reviewer #5	Results	KQ3 – Results for KQ3 seem to be a bit disorganized on pages 58-62. It would seem that the results for all (adults) should be presented before subgroups by age among adults. When the included studies are described, doesn't that include all studies reporting these outcomes, not just those with subgroup information?	We presented the overall findings (for all adults) first, before presenting findings for potential effect modifiers (subgroups).
TEP Reviewer #5	Results	Some statements in the text seem unsupported by reference or results. For example, on page 59, under CVD Mortality, it says, "A random-effects meta-analysis of the three found no significant effect." Either the effect estimate and CI should be shown or a reference cited. The text should be checked for other occurrences of this.	We have added the forest plot and findings throughout.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	KQ4 – Obs Na and CVD/KD/Mort There are many potential biases in observational studies of sodium and CVD or mortality. First, the study population is crucial. If there is baseline CVD or even hypertension, there may be reverse causation. In the Scottish Heart Health Study (ref 262) about 20% had evidence of coronary heart disease at baseline. While the review notes that the Scottish study only controls for age and thus may be biased, it nevertheless includes this study when it notes that the analysis with all 5 studies would have led to a smaller effect, which seems inconsistent since it gives this study equal weight to the others. In general, there seems to be a lack of appreciation of the differences in quality between studies in the summaries.	We did not include the study but did not consider its findings in drawing conclusions. We tried to address the quality issues for each of the cohort studies.
TEP Reviewer #5	Results	KQ4 – Obs Na and CVD/KD/Mort In the combined FLEMENGHO and EPOGH cohorts (ref 247) 26% and in PREVEND (ref 155) roughly 13% were on anti-hypertensive medication at baseline (in PREVEND about 30% had hypertension, not all on meds), which could lead participants to reduce their sodium intake. They may still be at higher risk of CVD due to their hypertension, which could induce an apparent inverse relationship of sodium and CVD due to reverse causation.	We note these concerns in the Discussion chapter.
TEP Reviewer #5	Results	KQ4 – Obs Na and CVD/KD/Mort As noted above, the TOHP study (not TOPH) was based on multiple 24hr urine excretions, which seems to be missed. While the review notes the importance of multiple measurements in the overview, this is not carried throughout the document and no mention of this is made in the text describing results for the observational analyses. The presence of multiple measures in TOHP is not noted in Table 5, which presents a summary of the individual studies. It is included, though, in Tables C1 and C2 in the appendix. Note that quality control for the follow-up for endpoints was reported for the TOHP interventions included in Table C1 and this was referenced in the observational studies in Table C2. These quality control measures were not noted in Table C2.	We revised our assessment of the risk of bias for this study to low and considered the study in drawing conclusions for observational studies.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	KQ4 – Obs Na and CVD/KD/Mort In fact, the conclusion (page 223) states that, "No observational studies used multiple 24-hour urinary excretion analyses, although increasing evidence demonstrates that multiple, non-consecutive 24-hour urinary sodium excretion needs to be used as the indicator of compliance in RCTs and exposure in observational studies." The TOHP trials collected multiple 24hr urines throughout the trial periods, and these formed the basis of the exposure assessment for the observational analysis of sodium and potassium in the TOHP Follow-up Study. A total of 3-7 24hr urine specimens were carefully collected over either 18 months or 3-4 years during the two interventions, and the average of these was used as the exposure over the much longer follow-up period. Table F2 in Appendix E rates the ascertainment of sodium exposure in the TOHP observational analyses as having a high risk of bias but it's not clear why it is given this rating. This may be an error.	Again, we revised the risk of bias rating for this study.
TEP Reviewer #5	Results	KQ4 – Obs Na and CVD/KD/Mort The sodium data from NHANES were based on a single 24hr diet recall. While that may be able to assess the average population intake, it is a grossly inadequate measure for usual sodium intake in an individual. This was used in NHANES I (ref 41) and II (ref 87), studies which have other methodologic flaws such as failing to adjust for total energy intake, adjusting for blood pressure which is in the causal pathway, and adjusting for table salt which is part of total sodium intake. The paper by Yang using NHANES III data (ref 282) helps to ameliorate the imprecision by applying an adjustment for regression dilution bias developed at NCI. This uses a subsample with a second recall and provides a much less biased estimate. These important differences are not mentioned in the review.	We distinguished NHANES I from NHANES III in our assessment of risk of bias, and based conclusions on findings from NHANES III only.
TEP Reviewer #5	Results	KQ4 – Obs Na and CVD/KD/Mort The authors show plots for studies that present a categorical analysis, but many of the publications show a spline curve. It would be more informative to include these.	We were trying to show the figures in a way that would enable some cross-comparison in spite of differences in intake ranges.
TEP Reviewer #5	Results	KQ4 – Obs Na and CVD/KD/Mort In several sections, the review presents data from a pooled analysis of four cohorts (PURE, EPIDREAM, ONTARGET and TRANSCEND), as well as data from the PURE cohort and the PURE South America cohort. While they do mention that there is overlap, they also present these results separately. This is misleading since the duplicate results are thus given more weight, objectively and/or subjectively. The duplicate results should not be repeated.	Realizing that it would appear we would be double counting findings from the same cohorts, we actually did not consider these studies in our conclusions. We clarified this in the text.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	KQ4 – Obs Na and CVD/KD/Mort The PURE cohorts (ref 204) included 8% with prior CVD and 42% with hypertension, which could lead to reverse causation. The same is true of the four-cohort analysis (ref 184).	We address this issue in the Results text and Discussion (Limitations) section.
TEP Reviewer #5	Results	KQ4 - Table 5 lists the exposure assessment as "24-hour urinary potassium excretion" for several studies, but this should be "24-hour urinary sodium and potassium excretion" or just "24-hour urinary excretion".	Revised.
TEP Reviewer #5	Results	KQ5 – Trials of Potassium and BP More care needs to be taken to define groups according to hypertensive status at baseline. For example, TOHP is listed as a trial in hypertensives in Figure 43, but the participants had high normal BP at baseline. Conversely, pre-hypertensives in TOHP were included as normotensives in the review of trials of sodium. These should be relabeled. There are even enough trials of potassium to separate out those with prehypertension from those with actual hypertension.	We struggled with how to classify studies of individuals with high-normal BP or "mild HTN," and had to make some possibly arbitrary decisions. We at least tried to make sure we were consistent throughout. Ideally, we would have had enough trials with internal comparisons not to have to do meta-regressions.
TEP Reviewer #5	Results	KQ5 – Trials of Potassium and BP In fact, the trial by Naismith and Braschi, which is labeled as a trial in normotensives, had 20% and 7% hypertensive (BP>140/90) in the K and placebo groups at baseline, resp., while none in TOHP were hypertensive. In the study by Braschi, two (7%) of those in the K-citrate group were hypertensive. They found an association of change in SBP with average SBP level, such that the potassium effect was greater in those with higher baseline BP.	We did not describe these findings but did address this issue in the Discussion.
TEP Reviewer #5	Results	KQ5 – Trials of Potassium and BP In general, it seems that much of the evidence appears to support a larger effect of increased K in those with higher baseline BP, but that is not reflected here.	We did note a greater effect on BP for those with HTN.
TEP Reviewer #5	Results	KQ6 – Observational Studies of Potassium and BP/Kidney Stones I have similar comments as to KQ2 re sodium above. In particular, this question should be greatly overshadowed by the RCT results in KQ5. There are enough trials of this question to provide sufficient evidence of the relationship of potassium to blood pressure. Given all the potential for bias in observational studies, the dose-response analyses from trials are likely to be less distorted than data from observational cohorts.	We do provide separate conclusions for the observational studies and RCTs and rely more heavily on the RCTs, as we note in the executive summary and Discussion.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	KQ7 - Trials of K intake and CVD The only trial of K supplementation and CVD or mortality was that by Chang et al. This, though, substituted potassium salt for sodium salt, so the effects cannot be disentangled. It provides evidence for both the questions on increased potassium and for reduced sodium.	Yes, we noted that this study addressed both the effects of potassium and that of reduced sodium, and we included it in the analysis of the effects of sodium reduction on CVD outcomes.
TEP Reviewer #5	Results	KQ8 – Observational studies of K and CVD/KD/mortality There is a difference in the ability to assess potassium vs. sodium intake from dietary questionnaires. While it is particularly difficult for sodium due to the presence of sometimes extreme quantities in processed foods and the addition of salt at the table, this is less of a problem for potassium. While the calibration may be far off, the ranking of individuals may be more appropriate for dietary measures of potassium. This should be noted when discussing the quality of data.	We noted this point and assessed the risk of bias for intake assessment differently depending on whether the study outcomes were reflecting sodium or potassium intake.
TEP Reviewer #5	Results	KQ8 – Observational studies of K and CVD/KD/mortality Studies of potassium are also likely less subject to reverse causation since dietary recommendations are not as strong for potassium as for sodium among those with CVD or hypertension.	No response warranted.
TEP Reviewer #5	Results	KQ8 – Observational studies of K and CVD/KD/mortality The results for potassium seem strongest for stroke. Five of 11 studies showed significant inverse relationships, while another 6 did not. Reliance should not be just on p-values, though, but the effect estimates should be considered. The term “inconsistent” suggests that some studies show an increased risk with increased K intake. The ones that did should be separated from those that were in the direction of protection but non-significant.	Because we did not do quantitative analysis, we did not try to assess potential differences that might account for differences in the outcomes or base conclusions on a subset of the studies.
TEP Reviewer #6	Results	General point – sometimes refers to sodium reduction (e.g p.43, line 19, line 36, line 40), and sometimes sodium restriction, e.g. p.43, line 12, line15 – which also states the study “imposed” a sodium restricted diet. “reduction” is preferred throughout - “impose”, “restricted”, etc. are pejorative terms and should be avoided.	We have revised all to "sodium reduction," and have tried to eliminate use of words such as imposed or restricted.
TEP Reviewer #6	Results	Same point	We have revised the wording to be consistent throughout.
TEP Reviewer #6	Results	p.49, line 36, line 40. “A low strength of evidence supports a lack of association of…” Re-word as e.g. “We did not find evidence of an association of…with low strength of evidence” . Similar point, p.54, line 28, p.59, line 45-46, p.60, line 42-43, p.61, line 30-31, p.65, line 21-22, p. 128, line 44, p.144, line 12, p.148, line 38, 42, etc. (see above re absence of positive).	We revised wording of the conclusions.
TEP Reviewer #6	Results	p.55, line 50-51. “53 mmol higher sodium concentration was associated with SBP higher by..” Similar point, heading Fig 26, p.73, line5. P.74, line 32. p.80, line12, line 26,	We are not sure of the requested revision.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	Results	p.57, line 15 et seq.(line 17, 22, 26…) Re-word as e.g. “no evidence that sodium reduction affects risk for CVD mortality, with low strength of evidence”.	Reworded as suggested.
TEP Reviewer #6	Results	p.66, line26-27, “50 mmol higher sodium… associated with 9% higher risk..” Similar, p.62, line 24.	Reworded as suggested.
TEP Reviewer #6	Results	p.59, line 8-9, re-word “all cause mortality was lower, but not significantly so, in the reduced sodium group” (15% lower mortality for ~40 mmol lower sodium in a trial 20 years earlier is not “slightly”).	We removed all such descriptive words.
TEP Reviewer #6	Results	p.147, line 44-47 re-word, e.g. “higher potassium intake was associated with lower....eliminated the association with potassium” . Similar point, p.163, line 36, line 46 “higher” rather than “increased”	We have reworded.
TEP Reviewer #6	Results	p.170, line 40, typo “potassium intake” instead of “sodium”	Corrected.
TEP Reviewer #6	Results	p.174, line 9, “lower” rather than “decreased”	Revised.
Peer Reviewer #4	Results	Since the objective of the review is to provide information for the DRI committee, it must be based upon knowledge of the population distribution of sodium intake, and, to the extent possible, the relation of intake to health outcome. That was defined by the 2013 IOM Committee Report. Physiological effects are not health outcomes. Exclusive focus on one of many physiological consequences of variation in dietary sodium intake may have been of primary interest to those who constructed the questions, but reflects an inexcusable focus one, instead of all potential consequences. The health effect of changes in sodium intake integrates of all its physiological consequences. Perhaps someone else would focus on another - and find the same association with health outcomes.	We were required to adhere to the statement of work in conducting the review.
Peer Reviewer #4	Results	As with blood pressure, there is a rich body of evidence describing the effect of sodium on the renin angiotensin system, triglycerides, glucose, aldosterone, etc. The initial questions can most generously be ascribed to unfamiliarity with conventional biomedical science practice. Nevertheless, these findings are of secondary importance to the task of the DRI. The association of sodium intake with CVD and all-cause mortality integrates all recognized and unrecognized physiologic effects.	We addressed the key questions as presented in the statement of work.
Peer Reviewer #5	Results	Yes, all one well. I do like Figure 4a. I like how adults and children are separated in the results. I appreciate sex differences in results/	Thank you!
Peer Reviewer #6	Results	The answer to the first 3 questions is yes. In the txt and in then tables describing the effects of sodium on BP, the units for MD are never provided..presumably it is mm Hg.This hold be added in all relevant places.	We have added the units at the first report of findings and stated that they are the same throughout.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	I am not aware of any relevant studies that were missed. However, I ask that the authors look more closely at whether there is data on the effect of sodium reduction or sodium intake on blood pressure reduction by race in hypertensive (not just combined normotensive and hypertensive) Black vs nonBlack populations.	We have now described the findings of several studies that assessed these differences within studies (notable TOHP and DASH Sodium).
Peer Reviewer #7	Results	RCTs: No objections. Observational studies: see methodological comments above.	No further response warranted.
Peer Reviewer #7	Results	Circulation 2017 Sep 5;136(10):917-926 demonstrates how the linkage between urine excretion parameters and outcome changes with the use of repetitive versus single 24-h sodium excretion samples, while average sodium excretion remains unchanged. The study may serve as an example of the major methodological limitations in this area of research, and sheds new light on the value of accepted diagnostic gold standards in the epidemiological-observational study of the effects of salt on health.	Thank you for providing the additional references. We have addressed the point in the Discussion.
Peer Reviewer #6	Results	Pg. 27, line 3: Is MD in mmHG. Please specify.	We have clarified the units
Peer Reviewer #6	Results	Pg. 28, Fig 4a: Indicate that Systolic Blood pressure forest plot and MD is in mmHg if that is intended	We have indicated that these are the units throughout the report
Peer Reviewer #6	Results	Pg. 29, line 9: As above - indicate MD in appropriate units, i.e. mmHg	We have indicated that these are the units throughout the report
Peer Reviewer #6	Results	Pg. 29, line 10: Which, or how many, of these 8 parallel RCTS studied both children and adults, and note that there was a decrease in SBP in the audts if that is accurate	We noted the number that studies both.
Peer Reviewer #6	Results	Pg. 29, line 19: If the effect of sodium reduction in both children and adults in this one randomized trial (ref 4) were not significant, how do the findings (alluded to on this section on children) suggest a difference in the effect so sodium reduction on systolic BP in adults and children	We based the finding on meta-regression and note that this is not preferred.
Peer Reviewer #6	Results	Pg. 29, line 43: As above, indicate MD is in mmHg	We have indicated that these are the units throughout the report
Peer Reviewer #6	Results	Pg. 30, line 8: Indicate units	We have indicated that these are the units throughout the report
Peer Reviewer #6	Results	Pg. 33, line 8: Insert units mmHg	We have indicated that these are the units throughout the report
Peer Reviewer #6	Results	Pg. 33, line 14: With these CI, confirm that the RR for incident hypertension is not significant	We revised the wording.
Peer Reviewer #6	Results	Pg. 34, line 17: MD is mm Hg?	We have indicated that these are the units throughout the report
Peer Reviewer #6	Results	Pg. 37, line 3, Fig. 11: Here and elsewhere in document when referring to BP, specify that MD is mm Hg	We have indicated that these are the units throughout the report

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	Pg. 39, comment below line 37: DId the auhtors examine the effectg of sodium intake by hypertension x race? Specifically, were there studies that enable examination of a difference in BP response in hypertensive Blacks compared with hypertensive nonBlacks?	We have qualitatively described studies that performed internal comparisons as well as doing a meta-regression.
Peer Reviewer #6	Results	Pg. 62, line 35: This is confusing. Above, the authors found no effect of sodium reduction on CV outcomes, yet here, there is implication that sodium reduction does improve outcomes, at least when looking at the TONE study; whereas in the TOHP studoes , it was significant in whtes	We have substantially revised the text.
Peer Reviewer #6	Results	Pg. 138, line17: What units is MD here?	We have indicated that the units are mm Hg throughout the report
Peer Reviewer #1	Discussion/ Conclusion	The implications of the results are clearly stated. This includes the limitations of the available evidence. The conclusions appear to be well grounded in the evidence available. I do not find a clearly stated section on future research, either in the main report or the Executive Summary. I may have missed something, but I find this to be the biggest limitation of this report.	We have added a section identifying research gaps.
TEP Reviewer #2	Discussion/ Conclusion	Comment #12 Discussion/Conclusion - The Discussion/Conclusion section, in general, gives a comprehensive overview of the implications of the major findings and the limitations of the review. The results from wellcontrolled sodium reduction trials (e.g. follow-up of TOHP) could be more emphasized, because they are non-biased. The authors emphasize the need of a large clinical trial to prove the effects of sodium reduction on CVD, which is not feasible. Alternative methods for evidence synthesis (e.g. two-step approach for sodium-CVD) could be explained.	We have tried to increase emphasis on the findings of the RCTs and the conclusions based on them. We removed our suggestion for a large clinical trial.
TEP Reviewer #3	Discussion/ Conclusion	The overall conclusions are generally stated appropriately. For Key Question 1, would it be appropriate to mention that there is no evidence that reduction of sodium intake had harmful/adverse effects on blood pressure?	We inferred that but did not believe it was appropriate to state it directly, based on the evidence
TEP Reviewer #3	Discussion/ Conclusion	Page 182, lines 44-45: The statement that “Evidence suggests that sodium reduction does not lower blood pressure in children” seems too definitive based on the low SoE. It seems more prudent to indicate that the evidence for blood pressure effects of sodium reduction is insufficient to make conclusions.	We have revised this conclusion.
TEP Reviewer #3	Discussion/ Conclusion	Page 214, lines 15-16: The statement appears too definitive in light of the low SoE. It seems more prudent to indicate that the evidence is insufficient to determine whether sodium reduction affects risk for CVD mortality.	We have revised the conclusion as suggested.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion/ Conclusion	The most important implication of this review is briefly stated in the last sentence, "The effects of sodium reduction and increased potassium intake on mortality and morbidity due to CVD, CHD, and renal disease need more research." It seems appropriate that this point should be more extensively discussed to point out that randomized controlled of trials of sodium reduction or increases in potassium intake should be conducted to determine if there is harm or benefit. Moreover, there is little discussion of the levels of sodium reduction or increases in potassium intake that have been achieved in previous trials and the implications of the findings. If the data are inadequate to make definitive statements about the levels of sodium and potassium intake, then this implies that there is a need to determine what levels of sodium and potassium are optimal.	We were requested not to advocate for more research but to address the gaps we identified so we have now done that. We also now provide the mean changes in sodium achieved across trials in analyses as well as in the individual trials.
TEP Reviewer #3	Discussion/ Conclusion	Although the limitations of the evidence base are discussed, there is little discussion of the future research that is needed to address these limitations. A more extensive discussion of the gaps in knowledge and current literature would enhance the overall impact of this report and perhaps provide some guidance for future research needs.	We have added a section that enumerates research gaps we identified.
Peer Reviewer #2	Discussion/ Conclusion	Limitations need to address the lack of any safety data of using potassium supplements or increasing potassium intake in CKD patients	We have noted this.
Peer Reviewer #3	Discussion/ Conclusion	This section is excellent. It is written clearly and provides an very readable summary of the results and explains where there is insufficient evidence to provide a clear conclusion.	Thank you.
TEP Reviewer #6	Discussion/ Conclusion	p. 182, line34-35. Macgregor et al Lancet 1989 dose response trial similarly found large effects.	Thank you. Noted.
TEP Reviewer #6	Discussion/ Conclusion	p.182, line 44. Re-word, e.g. "The evidence did not suggest that sodium reduction lowers BP in children…"	We have reworded.
TEP Reviewer #6	Discussion/ Conclusion	p.184, line16, 21, 24 "The evidence did not suggest that sodium reduction affects..(low SoE)". Similarly p.85, line 4-5.	We have reworded.
TEP Reviewer #6	Discussion/ Conclusion	Similar point re potassium, p.187, lines 40-45.	We have reworded.
TEP Reviewer #6	Discussion/ Conclusion	p.192, lines 13-14. I don't understand this sentence.	We have tried to clarify the wording.
TEP Reviewer #6	Discussion/ Conclusion	p.195, line 28 delete "slightly". (We do not know enough about the size of any effect because of the various biases and measurement error described in the report).	We have deleted all such adjectives.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion/ Conclusion	Interesting, in the first sentence of the report, the authors note that decreasing sodium intake is greater in persons with hypertension than others. In fact the difference is 1 vs 5 . - a highly important fact to clincians, investigators, and public health authorities. Thoise figures derive from ddefining hypertension at 140 mmHg systolic. Thus, for about 2/3ds of the population 1 mmHg would not be of any practical significance. Of course, leading with this bit can only reflect a misunderstanding of the importance of the blood pressure in terms of the DRI's task - or any assessment of the health consequences of sodium and health.	Response not warranted.
Peer Reviewer #4	Discussion/ Conclusion	The reviewers obviously did not have new guidelines defining "hypertension" down. The calculation presented here is based upon a previous blood pressure level. An analysis based upon the 2017 definitions would generate different results and implications.	We have added the new guidelines, which were issued while the report was undergoing review.
Peer Reviewer #4	Discussion/ Conclusion	The reviewers report that the impact of sodium on health is uncertain. The reviewers correctly identify the absence of adequate evidence of causality – or benefit or harm from intervention. There is, however, a rich body of observational evidence linking sodium directly to morbidity and mortality	We do not believe we reported that the impact is uncertain, based on the findings of RCTs, at least.
Peer Reviewer #4	Discussion/ Conclusion	Skilled investigators have produced more than 30 observational studies with more than>400,000 participants. The results have been remarkably consistent. Concerns about measurement error and reverse causality have been addressed. In fact, sodium can be precisely measured. The problem is with intra-individual variation. That, of course, is why population studies are needed to account for individual variety. This is also seen in blood pressure, and for a similar reason. The possibility of reverse causality has been addressed through censoring events, and/or comparison of outcomes in persons at high and low cardiovascular risk. Here, low sodium intakes have been associated with greatest adverse impact on mortality among the healthiest subjects.	The evidence from these observational studies is less strong than that from RCTs because of numerous sources of bias. Thus, we were guarded in any conclusions we drew from these studies., even those that attempted to adjust for known sources of bias.
Peer Reviewer #4	Discussion/ Conclusion	All of this notwithstanding, observational studies are still subject to the possibility of unrecognized confounding. Although the evidence associating the middle range of intakes to optimal health outcomes is convincing, and consistent with experience with other essential nutrients, (associations do not establish causality, and are not a basis for intervention.	No response warranted.
Peer Reviewer #5	Discussion/ Conclusion	Yes, on all points.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion/ Conclusion	The major finds are stated clearly in the summaries of each major section and in the conclusion. Major findings of subsections are not always summarized or clearly stated. The limitations are described adequately. I am not aware of any literature omissions. The future research section is clear, but suggestions for new research are implied rather than explicitly stated.	We have tried to clarify the language and wording of the conclusions.
Peer Reviewer #7	Discussion/ Conclusion	I am restricting my comments to observational studies. The relationship between salt intake and blood pressure has been clarified with the DASH sodium trials and does not require much further evidence.	No response warranted.
Peer Reviewer #7	Discussion/ Conclusion	Major findings clearly stated? Yes. It is clearly stated that a reduction in salt intake lowers blood pressure, and that increasing potassium intake lowers blood pressure, and that the effects of sodium reduction and/or increased potassium intake on mortality and morbidity are inconsistent and require more research.	No response warranted.
Peer Reviewer #7	Discussion/ Conclusion	Limitations clearly stated? Page 182, Association between dietary sodium intake and blood pressure: The author(s) might want to make clear that the evident relationship between sodium excretion and blood pressure which is typical for RCTs does not come through in observational population studies. In this context, it might be important to discuss that single 24-h urine collection, even if accurately collected, do not necessarily represent a good diagnostic tool to access dietary sodium exposure status.	We have addressed this point in the study Limitations.
Peer Reviewer #7	Discussion/ Conclusion	Page 184, Key question 3, RCT intervention and long-term clinical outcomes: The use of the term RCT in this context could be misleading. Conducting long-term controlled feeding studies that are sufficiently long to correlate real salt intake with cardiovascular or other hard endpoints is impossible. The problem with all “RCTs” in the outcome research arena is the difficulty in tracking people’s sodium intake over extended periods and then accurately correlating that information to people’s health. It is impossible/unfundable to conduct landmark studies such as the DASH sodium trial long enough to test for hard endpoints.	We address this point in the study limitations.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Discussion/ Conclusion	Page 184, Key question 4, association between dietary sodium intake and hard endpoints in observational studies. As stated in the methods section, neither an accurately collected 24-h urine sample, nor a spot urine sample is a reliable tool to measure real sodium intake in a subject. The assumption that a single urine sample is representative for the individual's salt intake over a long period of time is most likely invalid. I therefore find it misleading to discuss an "association of sodium intake levels with CVD mortality", a "lack of association of sodium intake levels and risk for stroke", etc. – because real salt intake of the followed-up individuals was not been measured and most likely has been misclassified (see methods section). Not surprisingly, the evidence on the association between sodium excretion (not: sodium intake, which has not been measured in these studies) and mortality, stroke, myocardial infarction, combined CVD morbidity and mortality, progression of renal disease, and left ventricular hypertrophy is insufficient to draw conclusions. A more critical evaluation of the limitations would be helpful, especially with respect to future research directions: the problem is that it is impossible to track people's sodium intake over extended periods and then accurately correlate that information to people's health. To my view, one of the major outcomes of this review is that future research using the same analytical tools to study the effect between salt and health will not contribute information that goes beyond what is already known.	We attempted to base any conclusions we drew from observational studies regarding sodium intake only on studies that conducted multiple 24-hour urines, or noted that the conclusions were based on moderate RoB studies and accounted for this.
Peer Reviewer #7	Discussion/ Conclusion	Is the future research section clear and easily translated into new research? A future research section is missing. This is unfortunate, because this systemic review documents the inability of traditional epidemiological research approaches to measure a valid relationship between salt intake and cardiovascular outcome at the population level, despite the clearly established relationship between salt intake and blood pressure.	We have added a section that enumerates research gaps we identified.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Discussion/ Conclusion	Doesn't that mean that it is high time to question the accepted methodological tools to assess the relationship between salt and health in populations? Research in humans and in experimental animals during the last decade has shown that the 3 basic physiological assumptions on salt and water metabolism are invalid: - sodium is stored in tissue without parallel water retention (contradicts Assumption 1, see methods section); therefore - body sodium content is not constant (contradicts Assumption 2) and, thus, - dietary salt is not immediately transferred into the urine (contradicts Assumption 3 and thereby the theoretical basis of the value of a 24-h urine sample as a measure of salt intake).	No response warranted.
Peer Reviewer #7	Discussion/ Conclusion	Could direct measurements of tissue sodium content be a better research strategy to diagnose the relationship between salt and health? The apparent shortcoming of the currently available methods used for clinical and epidemiological investigation of salt in health has prompted us to search for an alternative diagnostic tool. We have implemented novel 23Na magnetic resonance imaging (23NaMRI) technology to non-invasively detect and measure tissue Na+ levels in humans [1, 2]. Introducing 23NaMRI in clinical and population studies, we have found that humans store large amounts of Na+ in their skin and in muscle as they age [2-5]. We have found that Na+ storage in skin and muscle increases with high aldosterone levels in humans [2] and animals [6-8]. Additional published and unpublished data suggest that high salt intake increases glucocorticoid levels [9, 10]. The unexpected finding that humans store large amounts of Na+ in tissues brought about a novel view on the principles of salt and water metabolism [11-17], which we could rapidly transfer into the clinical arena.	Unfortunately, assessing alternative methods for more accurate Na assessment was beyond the scope of the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Discussion/ Conclusion	(cont'd from above)Our clinical studies indicate that skin Na+ storage is linked with primary [2] and secondary hypertension [4], while muscle Na+ storage is coupled with insulin resistance [18]. The findings have opened new research avenues on the pathogenesis of arterial hypertension [2, 4, 19-21], diabetes mellitus [9, 18], immune regulation, and autoimmune disease [19-23]. The first clinical studies suggest that the adverse effect of Na+ on human health goes beyond the well-established salt-blood pressure relationship. We now aim to test the hypothesis that humans with increased tissue Na+ storage may have increased CVD risk, even independent of blood pressure. Application of 23NaMRI technology for detection of Na+ storage in cohort studies provides a powerful tool for understanding its epidemiological and functional significance. In participants of the Multi-Ethnic Study of Atherosclerosis (MESA), our preliminary data indicate that African Americans, Chinese Americans and Caucasians store Na+ with age, with more pronounced Na+ storage in men than in women. Recent biopsy studies corroborate these findings (Hypertension. 2017 Nov; 70(5): 930–937).	No further response warranted.
Peer Reviewer #7	Discussion/ Conclusion	In addition, we recently demonstrated that skin Na+ is associated with left ventricular hypertrophy in a cohort of patients with early stage renal disease [24]. It only took 99 patients to demonstrate a clear association between salt and a hard endpoint marker for cardiovascular morbidity and mortality. This is in sharp contrast to the thousands of urine sodium excretion samples that could not demonstrate any relationship between single urinary Na+ excretion measurements from spot urine samples and LVH (page 187), most likely because single urinary Na+ spot urine measurements provide neither a reliable estimate of Na+ intake, nor information on changes in body Na+ content.	No response warranted.
Peer Reviewer #7	Discussion/ Conclusion	I am surprised that the author(s) neither had a suggestion for future research, nor found it worthy to mention this already existing precision medicine alternative for future sodium research in populations.	We have added a section that identifies research gaps.
Peer Reviewer #6	Discussion/ Conclusion	Pg. 181, line 15: It would be useful to have this statement in the introduction: "Key questions 1, 3,5, and 7 assessed the findings of RCTs on the effects of studies intended to reduce sodium or increase potassium intake for the outcomes of interest, whereas the even-numbered questions assessed the associations between sodium or potassium exposures and the outcomes of interest in prospective cohort studies."	We have added it to the text that precedes the descriptions of findings.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	References	References: 1. Kopp, C., et al., Seeing the sodium in a patient with hypernatremia. Kidney Int, 2012. 82(12): p. 1343-4. 2. Kopp, C., et al., (23)Na magnetic resonance imaging of tissue sodium. Hypertension, 2012. 59(1): p. 167-72. 3. Dahlmann, A., et al., Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. Kidney Int, 2015. 87(2): p. 434-41. 4. Kopp, C., et al., 23Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients. Hypertension, 2013. 61(3): p. 635-40. 5. Linz, P., et al., Skin sodium measured with (23) Na MRI at 7.0 T. NMR Biomed, 2015. 28(1): p. 54-62. 6. Titze, J., et al., Internal sodium balance in DOCA-salt rats: a body composition study. Am J Physiol Renal Physiol, 2005. 289(4): p. F793-802. 7. Ziomber, A., et al., Sodium-, potassium-, chloride-, and bicarbonate-related effects on blood pressure and electrolyte homeostasis in deoxycorticosterone acetate-treated rats. Am J Physiol Renal Physiol, 2008. 295(6): p. F1752-63. 8. Rakova, N., et al., Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. Cell Metab, 2013. 17(1): p. 125-31. 9. Kitada, K., et al., High salt intake reprioritizes osmolyte and energy metabolism for body fluid conservation. J Clin Invest, 2017. 127(5): p. 1944-1959. 10. Rakova, N., et al., Increased salt consumption induces body water conservation and decreases fluid intake. J Clin Invest, 2017. 127(5): p. 1932-1943. 11. Schatz, V., et al., Elementary immunology: Na+ as a regulator of immunity. Pediatr Nephrol, 2017. 32(2): p. 201-210.	We appreciate the provision of these background studies for reference.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	References	(More references from above) 12. Titze, J., et al., Balancing wobbles in the body sodium. Nephrol Dial Transplant, 2016. 31(7): p. 1078-81. 13. Johnson, R.S., J. Titze, and R. Weller, Cutaneous control of blood pressure. Curr Opin Nephrol Hypertens, 2016. 25(1): p. 11-5. 14. Titze, J., A different view on sodium balance. Curr Opin Nephrol Hypertens, 2015. 24(1): p. 14-20. 15. Titze, J., D.N. Muller, and F.C. Luft, Taking another "look" at sodium. Can J Cardiol, 2014. 30(5): p. 473-5. 16. Titze, J., et al., Spooky sodium balance. Kidney Int, 2014. 85(4): p. 759-67. 17. Titze, J., Sodium balance is not just a renal affair. Curr Opin Nephrol Hypertens, 2014. 23(2): p. 101-5. 18. Deger, S.M., et al., Tissue sodium accumulation and peripheral insulin sensitivity in maintenance hemodialysis patients. J Cachexia Sarcopenia Muscle, 2017. 8(3): p. 500-507. 19. Machnik, A., et al., Mononuclear phagocyte system depletion blocks interstitial tonicity-responsive enhancer binding protein/vascular endothelial growth factor C expression and induces salt-sensitive hypertension in rats. Hypertension, 2010. 55(3): p. 755-61. 20. Wiig, H., et al., Immune cells control skin lymphatic electrolyte homeostasis and blood pressure. J Clin Invest, 2013. 123(7): p. 2803-15. 21. Machnik, A., et al., Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med, 2009. 15(5): p. 545-52.	We appreciate the provision of these background studies for reference.
		(More references from above) 22. Kleinewietfeld, M., et al., Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature, 2013. 496(7446): p. 518-22. 23. Binger, K.J., et al., High salt reduces the activation of IL-4- and IL-13-stimulated macrophages. J Clin Invest, 2015. 125(11): p. 4223-38. 24. Schneider, M.P., et al., Skin Sodium Concentration Correlates with Left Ventricular Hypertrophy in CKD. J Am Soc Nephrol, 2017. 28(6): p. 1867-1876.	We appreciate the provision of these background studies for reference.
TEP Reviewer #6	References	Repetition of references eg Aburto et al #3, #10 ES-15 and ES-16, also p196	
TEP Reviewer #6	Appendix	CIs better given as X to Y rather than X-Y as confusion with minus sign.	
TEP Reviewer #1	Clarity and Usability	Report logically structured, easy to follow.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Clarity and Usability	Conclusions reflect the data presented. Without any indication of what actual increases and decreases in Na intake are and relationship to change in BP it is difficult to relate to policy or practice decisions.	Thank you. We have added the mean achieved sodium intakes for all RCTs.
Peer Reviewer #1	Clarity and Usability	The report is well constructed and clearly written. The main points are clear. The key questions were well designed. However, the authors should address the question of whether any of the key questions are impossible to answer because of the difficulty in designing and carrying out studies that would answer them. If it is not possible for key questions to be answered (this may be particularly relevant for children and adolescents) the authors should address alternative approaches to come closest to a usable answer. This is especially important as policy or clinical practice decisions are considered. Overall, the analyses and the presentation contribute new information. However, the overwhelming conclusion is the less-than-optimum evidence base from which to draw firm conclusions. This report must define the future need for research so that, in the future, appropriate policy and practice decisions can be based on the evidence, rather than needing to focus on gaps in the evidence.	We have added a section to the Discussion that enumerates the gaps in the literature that hindered our addressing many of the questions of interest.
TEP Reviewer #2	Clarity and Usability	Comment #13 Clarity and Usability - The report is organized in such a way that it takes time to extract the relevant information needed for setting DRIs. Most conclusions (e.g. in Executive Summary) are qualitative, while quantitative information is needed. The conclusions will be relevant to researchers in general (knowledge gaps are well indicated) but for policy makers and guideline committees, it may be hard to find the high quality pieces of evidence. The report contributes some new information (e.g. on potassium supplements) but it does not advance understanding, which would need a more critical appraisal of (particularly observational) studies.	We have tried to organize the key findings more clearly in the executive summary, along with effect estimates.
TEP Reviewer #3	Clarity and Usability	The report is well organized and the main results are, in general, presented clearly. However, as noted in my previous comments, some statements seem too definitive based on the low SoE. Lack of adequate evidence for an effect does not necessarily imply that there is no effect, especially when SoE is insufficient due to the limitations and the time of sodium exposure in most cases, the assessment methods, and the variability in outcome definitions.	We have extensively revised the wording to make the conclusions more accessible.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Clarity and Usability	The conclusions will not provide clear guidance for clinical practice decisions or for future Dietary Reference Intakes (DRI) committees to make recommendations. This is due partly to the limitations of available evidence. The authors have sifted through a large amount of evidence but have not arrived at clear conclusions. This report will not resolve current controversies in the field or provide new understanding of the role of potassium and sodium intake in chronic diseases. Revision of the manuscript may be able to better articulate the needs for future research.	We did in fact add a section on research gaps and have reorganized the findings to be more clearly presented.
Peer Reviewer #2	Clarity and Usability	This looks okay.	Thank you.
Peer Reviewer #3	Clarity and Usability	The report is well organized and provides a clear description of methodology. The method for ascertaining the strength of the evidence is clearly described. The conclusions on questions 1, 2, 5, and 6. are relevant to policy and practice decisions. Interventions to lower sodium intake (Key question 1) and to increase potassium intake (Key question 5) lower BP, especially among individuals with hypertension. This should be very useful to clinicians and inform policy.	Thank you.
Peer Reviewer #4	Clarity and Usability	It is poorly structured. The issues that need to be presented include 1st, the distribution of blood pressure in the general, healthy population. 2nd should be a full, and meaningful analysis of the information on the relation of intakes to outcomes. As noted above, the report seemed unaware that sodium is an essential nutrient. The final shortcoming of the organization was to have presented evidence linking sodium to blood pressure. Its hard to believe that the reviewers were unaware of other and sometimes adverse consequences caused by changes in sodium intake. The inclusion of the sodium/potassium ratio is of no help to the DRI and should not have been included. Ratios have no practical application in forming health policy.	We reviewed studies that met the inclusion criteria approved by the sponsors in keeping with the statement of work. In addition, we present the findings in the most organized manner we could identify, and we hope the Committee will be able to use the report as needed.
Peer Reviewer #4	Clarity and Usability	This review has failed to deliver on the task at hand. The questions have influenced the outcome. Failure to establish the distribution of sodium in the general population; focusing on but one of many physiological outcomes; presenting the ratio of sodium/potassium; failure to appreciate the need for some level of sodium – above zero; are the most egregious shortcomings of this report.	As stated, we analyzed all studies that met our inclusion criteria, regardless of achieved or baseline sodium intakes (which were not among the inclusion criteria). Insofar as the questions are the charge, we had to address them and rely on them in structuring the review.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Clarity and Usability	The DRI should receive scientifically sound answers to: What is the distribution intakes of sodium and potassium in the healthy population; what are the observed relations to health outcomes in the population; and what are the physiological consequences of varying sodium and potassium intake.	The studies included in the report do actually provide a fair assessment of the ranges of sodium intake in healthy populations. However, prospective cohort studies don't present a clear picture of the association between those intakes and the outcomes of interest, nor do trials consistently demonstrate the expected effects.
Peer Reviewer #5	Clarity and Usability	Yes, this really is a well-written and clear paper. Detailed and a lot of hard work put into this report.	Thank you.
Peer Reviewer #6	Clarity and Usability	Yes to all of these questions.	Thank you.
Peer Reviewer #7	Clarity and Usability	To my understanding, the main point is that after more than 5 decades of population research on the relationship between urine sodium excretion and disease, the research community is still unable to demonstrate a compelling relationship between salt and hard endpoint outcome at the population level.	In re-reviewing the literature, we attempted to clarify the challenges that exist in constructing and interpreting the findings of studies.
Peer Reviewer #7	Clarity and Usability	Despite of the fact that methodological limitations in this research area are obvious and limiting, the author(s) did not inform about alternative diagnostic precision approaches for future research.	Unfortunately, we were not charged with providing research recommendations, but did identify the shortcomings of the existing research.
Peer Reviewer #7	Clarity and Usability	The current version of this report does not contribute significant new information or understanding that goes beyond current other reports (page 190-191).	No further response.
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	We are scientists and medical researchers at McMaster University and the Population Health Research Institute in Hamilton, Canada who have spent 3 decades working on approaches to prevent cardiovascular disease globally. Our research involves over 100 countries and about a million persons. We are writing to bring to your attention that the recent draft systematic review ("Effects of Dietary Sodium and Potassium Intake on Chronic Disease Outcome and Related Risk Factors"), appears to have ignored substantial scientific evidence. These data indicate the following:	We will address the specific points below.

Commentator & Affiliation	Section	Comment	Response
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	A) There is absolutely NO robust evidence that lowering sodium below an intake of 3 g/day is likely to lead to a reduction in cardiovascular events or mortality compared to sodium intake between 3 to 5 g/day. Twelve recent studies and two recent meta-analyses of all observational studies involving >400,000 people indicate that while sodium intake above 5 g/day is associated with higher mortality and cardiovascular disease event rates compared to sodium intake between 3 and 5 g/day, there is no evidence that lowering sodium further (<3 g/day) is associated with better health (see references below).	We assessed the evidence from all RCTs and observational studies that met inclusion criteria regardless of the levels of sodium intake sought or achieved. Large RCTs that conducted dose-response analyses have noted linear relationships between sodium intake and mortality or morbidity risk at all intake levels.Only a small number of observational studies have reported increases in mortality or morbidity risk at low sodium intakes, and these findings can be attributed to reverse causality, invalid intake measures, or other residual causes of bias.
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	References 1. Thomas MC, Moran J, Forsblom C, et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. Diabetes Care 2011; 34: 861–66. 2. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. Diabetes Care 2011; 34: 703–09. 3. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA 2011; 305: 1777–85. 4. O'Donnell MJ, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. JAMA 2011; 306: 2229–38.	Thank you for the list of references.

Commentator & Affiliation	Section	Comment	Response
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	5. Pfister R, Michels G, Sharp SJ, et al. Estimated urinary sodium excretion and risk of heart failure in men and women in the EPIC-Norfolk study. Eur J Heart Fail 2014; 16: 394–402. 6. Saulnier PJ, Gand E, Hadjadj S; SURDIAGENE Study Group.Sodium and cardiovascular disease. N Engl J Med 2014; 371: 2135–36. 7. O'Donnell M, Mente A, Rangarajan S, et al; PURE Investigators. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 2014; 371: 612–23. 8. Mente A, O'Donnell M, Rangarajan S, et al, EPIDREAM and ONTARGET/TRANSCEND Investigators. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet 2016;388:465-75. 9. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I). Lancet 1998;351:781-5. 10. Cohen HW, Hailpern SM, Fang J, et al. Sodium intake and mortality in the NHANES II follow-up study. Am J Med 2006;119:275.e7-14.	No further response seems warranted.
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	11. Cohen HW, Hailpern SM, Alderman MH. Sodium intake and mortality follow-up in the Third National Health and Nutrition Examination Survey (NHANES III). J Gen Intern Med 2008;23:1297-302. 12. Mills KT, Chen J, Yang W, et al. Sodium Excretion and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease. JAMA 2016;315:2200-10. 13. Graudal N, Jürgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. Am J Hypertens 2014;27:1129-37. 14. Graudal N. A Radical Sodium Reduction Policy is not Supported by Randomized Controlled Trials or Observational Studies: Grading the Evidence. Am J Hypertens 2016;29:543-8.	No further response seems warranted.

Commentator & Affiliation	Section	Comment	Response
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	B) There are concerns that sodium intake below 3 g/day may be associated with a higher risk of death compared to those with intakes between 3 to 5 g/day. This has been repeatedly observed in most large studies despite extensive statistical adjustments for confounders and extensive efforts to avoid “reverse causation”. This excess risk in mortality has been seen in studies done by several different investigators from over 50 countries (i.e., PURE, ONTARGET, TRANSCEND, EPIDREAM, EPIC-Norfolk, NHANES-I, II and III, FLEMENGHO/EPOGH, SURDIAGENE, and CRIC studies), and has been observed in those with and without vascular disease, those with and without diabetes and those with and without hypertension. They have also been seen in studies with different approaches to measuring sodium intake (dietary questionnaire, random urine measures, first morning urine measures, single 24 hour urine measures and repeated 24 hour urine measures).	Please see our responses to the prior comments.
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	In the largest study of this question, the PURE study of 100,000 people (93% without vascular diseases) followed for 7 years (the 4 year results which are similar have been published, NEJM and Lancet), and recording 4682 cardiovascular events and 4501 deaths, found an increased risk of cardiovascular disease or mortality in those with sodium intake below 3 g/day was observed. These results remained significant and strong after excluding those with diabetes, those with hypertension, or those with any risk factors. The results also remained significant and strong after excluding those events that occurred in the first 3 years. These analyses do not support the possibility that the excess in mortality seen in those who consume less than 3g/day is due to measurable confounders or due to reverse causation.	Please see our responses to the prior comments.
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	While confounding and reverse causation can never be completely ruled out in any observational study, the current data are consistent with the expected associations between an essential nutrient and health. In general, for essential nutrients, too low intakes will lead to adverse health outcomes related to undernutrition and too high intakes would lead to toxicity from over nutrition. Sodium is an essential nutrient as it is integrally involved in homeostasis and numerous physiologic pathways. Therefore, it is not at all surprising that both high and low intakes of sodium is associated with increased risk of death as there is an optimal range (which is widely accepted for all physiologic and essential variables) or “sweet spot”.	Please see our responses to the prior comments.

Commentator & Affiliation	Section	Comment	Response
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	Therefore the totality of the observational data is consistent with our knowledge of the physiology of essential nutrient (which sodium is). Before any recommendations to reduce sodium below 3 g/day is made, robust data proving that it is beneficial and safe is essential. This can only be achieved by the completion of large, well designed, adequately powered randomized trials. In the absence of such data, it is premature to recommend reducing sodium to such low levels (a level that few people in the world currently consume) to avoid a large waste of resources (which can be used more effectively for other approaches to improve health) or potentially risking the lives of several million people in the US and worldwide.	Please see our responses to the prior comments.
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	An international committee of experts (with a range of views and backgrounds) convened by the World Heart Federation came to a similar conclusion (report attached).	Please see our responses to the prior comments.
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	Similarly the Cochrane collaboration report and a previous report from the Institute of Medicine concluded that there is currently no good evidence to support reducing sodium intake to below 3 g/day.	Please see our responses to the prior comments. It is not within our charge to make recommendations regarding sodium intake levels.
Salim Yusuf, MBBS, DPhil Population Health Research Institute	General	The totality of the observational data are supportive that high sodium intake (more than 5 grams of sodium per day) is associated with a modestly higher risk (by about 30%) of death and cardiovascular disease compared to an intake between 3 and 5 g/day). However there are no robust randomized controlled trials that have tested whether reducing sodium intakes at any level would reduce cardiovascular disease or deaths. In their absence some may wish to still advocate reducing sodium intake to levels between 3 and 5 g/day while we await the results of ongoing large trials. However, at present there is absolutely no data to support the claim that reducing sodium intake below 3 g/day in entire populations is effective or safe.	We do review the 20-year followup outcomes for the largest trial to date for these outcomes.
Center for Science in the Public Interest	General	The Center for Science in the Public Interest (CSPI) is a non-profit consumer education and advocacy organization that since 1971 has been working to improve the public's health through better nutrition and food safety policies. CSPI is an independent organization that does not accept any government or corporate funding. We appreciate the opportunity to submit comments on the draft sodium report.	No response is warranted.

Commentator & Affiliation	Section	Comment	Response
Center for Science in the Public Interest	General	Overall, several aspects of the draft report bring much-needed clarity to the broad body of evidence on sodium and potassium. For example, the draft makes it clear that observational studies have a high risk of bias if they assess sodium intake with a spot urine, a timed urine, a single 24-hour urine, or a 24-hour urine collection without quality control measures, instead of multiple 24-hour urine collections with quality control measures (Appendix E-7). AHRQ's recognition that measurement error can create bias may resolve some of the confusion and inconsistency in this body of evidence.	No response seems warranted.
Center for Science in the Public Interest	General	However, the draft report could further resolve confusion and inconsistency in the sodium literature by basing its conclusions on only the highest-quality randomized trials and observational studies, even if these are few in number. For example, the draft report might have found high-strength, rather than moderate, evidence that reducing sodium lowers blood pressure (BP) if it had relied only on randomized controlled trials (RCTs) that documented a sufficient difference (e.g., 40 mmol/day) between people consuming a higher vs. a lower sodium intake. Including less well-conducted studies adds imprecision and creates a perception of less certainty than may be justified.	We do not exclude studies from reviews based on quality (risk of bias). However we did conduct sensitivity analyses that excluded studies with high or unclear risk of bias and provide those findings in the report.
Center for Science in the Public Interest	General	Similarly, the draft report would have reached stronger conclusions if it had excluded studies at high risk of bias. The draft states, "Although we hoped to exclude prospective cohort studies that used methods other than multiple nonconsecutive measures of 24-hour urinary sodium excretion to assess status, doing so would have excluded most large cohort studies. Therefore, we included these studies but their risk of bias is higher" (ES-14). Instead of including those studies, AHRQ could have limited its review to studies at low risk of bias, even if the remaining, higher-quality studies were few. At a minimum, AHRQ could have looked separately at the evidence from studies with a high vs. low risk of bias and based its conclusions on studies at low risk of bias.	Again, we do not exclude studies from reviews based on quality (risk of bias). However we did conduct sensitivity analyses that excluded studies with high or unclear risk of bias and provide those findings in the report.

Commentator & Affiliation	Section	Comment	Response
Center for Science in the Public Interest	KQ1	Below, we comment in more detail on the draft's strengths and limitations: KQ 1. Effect of interventions to reduce dietary sodium intake on blood pressure. The AHRQ review concludes that reducing sodium intake lowers blood pressure in adults, but rates the evidence as moderate-strength, rather than high-strength, because of "some inconsistency across study outcomes and high heterogeneity" (p. 27). AHRQ should conduct additional analyses to determine how much of the inconsistency and heterogeneity is due to inadequate reduction or measurement of sodium intake. For example, only 27 of the 48 RCTs included in AHRQ's analysis reported that the mean difference in sodium intake between groups was at least 40 mmol/day, the minimum difference required for inclusion in a 2013 WHO systematic review and meta-analysis.(1) The remaining studies achieved a mean difference in sodium intake as low as 2 mmol/day. (The low differences likely reflect the failure of study subjects to comply with the intake recommendations for the study arm to which they were assigned.) AHRQ could further clarify the impact of lowering sodium intake on blood pressure by looking separately at RCTs that achieved sufficient differences in sodium intake (e.g., 40 mmol/day or more) based on at least one 24-hour urinary sodium level. AHRQ should give the greatest weight to trials such as DASH-Sodium, which had the most tightly controlled sodium intake because all foods were provided by the investigators. Including poorly controlled studies obscures the impact of lowering sodium intake on blood pressure. (1) Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: systematic review and metaanalyses. BMJ. 2013 Apr 3;346:f1326. doi: 10.1136/bmj.f1326.	We have conducted the additional analyses and now report their findings.
Center for Science in the Public Interest	KQ2	KQ 2. Among adults and children, what is the association between dietary sodium intake and blood pressure? The AHRQ review concludes that "a low strength of evidence supports a lack of association of sodium exposure with systolic or diastolic BP in adults based on observational studies. All studies had high risk of bias based on the methods used to assess sodium intake (typically single 24-hour urine excretion with or without validation)" (p. 49). We question AHRQ's conclusion that the observational evidence supports a lack of association between sodium and BP in adults.	We did not conduct meta-analyses on observational studies in this report, and most of our overarching conclusions are based on trials (KQ1, 3, and 5).

Commentator & Affiliation	Section	Comment	Response
Center for Science in the Public Interest	KQ2	AHRQ's summary of studies using 24-hour urinary excretion—which is a better measure than estimated 24-hour urinary excretion—relies on only two studies. One has a high risk of bias.(2) The second is TOHP-1, which has a low risk of bias.(3) TOHP-1 reported that both systolic and diastolic blood pressure were significantly lower in the sodium-reduction group. Given that TOHP, the only study reviewed in this section with a low risk of bias, found a significant association between 24-sodium excretion and systolic BP, it is inappropriate to conclude that sodium exposure is not associated with BP. (Furthermore, stronger evidence from randomized trials makes it clear that lowering sodium intake reduces blood pressure.) (2) Singer P, Cohen H, Alderman M. Assessing the associations of sodium intake with long-term all-cause and cardiovascular mortality in a hypertensive cohort. American Journal of Hypertension. 2015 1;28(3):335-42. (3) The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA. 1992 Mar 4;267(9):1213-20. AHRQ incorrectly identified TOHP as having a high overall ROB and a high ROB for sodium ascertainment (p. 52, Appendix E-41, E-42). In fact, the TOHP studies used multiple 24-hour urine analyses with validation (Appendix C-84) and were rated as having a low risk of bias (Appendix E-20, E-34).	We based our conclusions from observational studies on the totality of the evidence.
Center for Science in the Public Interest	KQ3	KQ 3. Among adults, what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on CVD and kidney disease morbidity and mortality and on total mortality? <u>Total mortality</u> AHRQ appropriately concludes that sodium reduction decreases the risk of all-cause mortality (low strength of evidence). This conclusion is bolstered by the TOHP Follow-up studies, which reported a nonsignificant 15 percent lower risk of mortality in the sodium reduction group (HR 0.85, CI 0.66, 1.09).(4) A meta-analysis combining TOHP with other studies found a borderline significant benefit (RR 0.92, CI 0.84, 1.00). (4) Cook NR, Appel LJ, Whelton PK. Sodium Intake and All-Cause Mortality Over 20 Years in the Trials of Hypertension Prevention. J Am Coll Cardiol. 2016 Oct 11;68(15):1609-1617.	We actually reconsidered and determined that the strength of evidence was insufficient to draw a conclusion, given the small number of controlled trials; our conclusion is based solely on observational studies.

Commentator & Affiliation	Section	Comment	Response
Center for Science in the Public Interest	KQ3	CVD mortality We question AHRQ's conclusion that sodium reduction does not affect the risk of CVD mortality (low strength of evidence). As AHRQ notes, the TOHP Follow-up studies—which contributed two of the three studies used to reach this conclusion—reported 10 CVD deaths in the reduced sodium groups and 15 CVD deaths in the comparison groups. While that difference was not quite statistically significant, it suggests that a larger sample size might have yielded significant results. It is inappropriate for AHRQ to conclude that sodium reduction does not affect the risk of CVD mortality when the available studies may be underpowered to detect an effect.	We need to consider the totality of the evidence when drawing a conclusion.
Center for Science in the Public Interest	KQ3	Stroke We question AHRQ's conclusion that sodium reduction does not affect the risk of stroke (low strength of evidence). AHRQ based this conclusion on only 3 RCTs. One reported a mean difference of only 15 mmol/day in sodium consumption in an 8-week study on only 80 people.(5) (One person in the reduced-sodium group and none in the control group suffered a stroke.) Another reported a difference of only 7 mmol/day in sodium consumption in a 9-month study on only 40 people.(6) Clearly, these studies are too small, too short, and achieved too small a reduction in sodium intake to constitute a reasonable test of whether lowering sodium intake reduces the risk of stroke. Only one RCT (TONE) reported a mean difference of 24-hour sodium excretion of at least 40 mmol/day in a trial that involved 681 people and lasted an average of nearly 28 months.(7) (One person in the reduced-sodium group and two in the control group had a stroke.) It is inappropriate for AHRQ to conclude that sodium reduction does not affect the risk of stroke when the available studies may be underpowered to detect an effect. (5) Charlton KE, Steyn K, Levitt NS, et al. A food-based dietary strategy lowers blood pressure in a low socioeconomic setting: a randomized study in South Africa. Public Health Nutr. 2008 Dec;11(12):1397-406. (6) Gilleran G, O'Leary M, Bartlett WA, et al. Effects of dietary sodium substitution with potassium and magnesium in hypertensive type II diabetics: a randomised blind controlled parallel study. J Hum Hypertens. 1996 Aug;10(8):517-21. (7) Appel LJ, Espeland MA, Easter L, et al. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). Arch Intern Med. 2001 Mar 12;161(5):685-93.	We agree that the achieved sodium intakes in the studies of stroke that met our inclusion criteria fell short of the intended goals. A low strength of evidence is intended to indicate the conclusion has a high likelihood of changing with additional research findings.

Commentator & Affiliation	Section	Comment	Response
Center for Science in the Public Interest	KQ3	Any CVD Event We question AHRQ's conclusion that sodium reduction does not affect the risk of any CVD event (low strength of evidence). As AHRQ notes, the TOHP I and II Follow-up studies found a statistically significant 25 percent reduction in the adjusted relative risk of CVD outcomes.(8) Furthermore, AHRQ found a non-statistically significant beneficial effect of sodium reduction when it pooled the (unadjusted) TOHP results with the only three other trials, two of which did not report a difference in achieved sodium (RR 0.85, CI 0.69, 1.05). Based on the highest-quality available studies, AHRQ should conclude that sodium reduction decreases the risk of a CVD event. (8) Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ. 2007 Apr 28;334(7599):885-8.	We conducted this analysis with several additional studies and concluded that evidence was sufficient to conclude that the risk for any CVD event was decreased with sodium reduction.
Center for Science in the Public Interest	KQ 4	KQ 4. Among adults, what is the association between dietary sodium intake and CVD, CHD, stroke and kidney disease morbidity and mortality and between dietary sodium intake and total mortality? All-cause mortality AHRQ concludes that "a low level of evidence supports the association between higher sodium levels and higher risks for all-cause mortality (data are insufficient to determine the linearity)" (ES-8). We question whether the data are insufficient to determine whether the association is linear. In the TOHP Follow-up studies, there was a direct linear relationship between intake and later mortality, with no evidence of a J-shaped or nonlinear relationship.(4) These studies are the only observational studies with a low risk of bias considered in this section.(9) Therefore, AHRQ should conclude that the available studies at low risk of bias support a linear association between sodium levels and all-cause mortality. (4) Cook NR, Appel LJ, Whelton PK. Sodium Intake and All-Cause Mortality Over 20 Years in the Trials of Hypertension Prevention. J Am Coll Cardiol. 2016 Oct 11;68(15):1609-1617. (9) The risk of bias for the TOHP Follow-up studies appears to be incorrectly identified as high in the Appendix, pp. E-41, 42.	For several reasons, observations of morbidity or mortality at very low sodium intakes are highly susceptible to bias.

Commentator & Affiliation	Section	Comment	Response
Center for Science in the Public Interest	KQ 4	CVD morbidity and mortality We question whether it is appropriate for AHRQ to conclude that "a low level of evidence supports a lack of association of sodium intake levels and risk for combined CVD morbidity and mortality" (ES-8). As noted above, the TOHP I and II Follow-up studies, two of the few observational studies with a low risk of bias, found a statistically significant 25 percent reduction in the adjusted relative risk of CVD outcomes and a non-significant 15 percent reduction in the risk of total mortality.(4,8) Given that all the other observational evidence in this section was at high risk of bias—and given the well-established relationship between blood pressure and stroke and CVD—it is inappropriate to conclude that an association is lacking. (4) Cook NR, Appel LJ, Whelton PK. Sodium Intake and All-Cause Mortality Over 20 Years in the Trials of Hypertension Prevention. J Am Coll Cardiol. 2016 Oct 11;68(15):1609-1617. (8) Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ. 2007 Apr 28;334(7599):885-8.	We cannot draw a conclusion based on the findings of only one study, however high in quality; however we do discuss the implications of the TOHP findings for long-term outcomes.
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	The National Kidney Foundation appreciates the consideration of chronic kidney disease (CKD), cardiovascular disease (CVD) and kidney stones in its assessment of the health impacts of sodium and potassium intake in the general population and in populations with chronic conditions, including CKD. We also appreciate that the report focuses on CVD endpoints for which CKD is known to be an independent risk factor.(1) The National Kidney Foundation is the largest, most comprehensive and longstanding, patient centric organization dedicated to the awareness, prevention and treatment of kidney disease in the US. In addition, the National Kidney Foundation has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD), including transplantation since 1997 through the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI). We offer the following comments and additional literature on the impacts of sodium and potassium in people at risk and with CKD. (1) Matsushita K, Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data Lancet Diabetes Endocrinology; (2015)	No response is warranted.

Commentator & Affiliation	Section	Comment	Response
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	Given the growing prevalence of individuals at risk of and with CKD and the established role of diet in CKD progression, we believe it is important for public health to include the best-characterized CKD endpoints, the rate of decline of estimated glomerular filtration rate (eGFR), and the level of albuminuria measured by albumin to creatine ratio (ACR), in dietary reference intake (DRI) reviews. We appreciate that this review takes into consideration both of these endpoints, which we previously recommended in response to the March 2015 Workshop and a Request for Public Comment on Questions Regarding Dietary Reference Intakes and Chronic Disease Endpoints. The evidence for these endpoints has been reviewed and forms the basis for clinical practice guidelines strongly recommending their use in the evaluation and management of CKD.(2) Longitudinal data including these endpoints, and serial measurements of serum levels of at least some of the micronutrients of concern, is maintained on approximately 11 million subjects, and can be accessed through the CKD Prognosis Consortium.(3) (2) Inker, Lesley, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD, AJKD, 63:5, 713–735, May 2014. (3) Matsushita et al., Cohort Profile: The Chronic Kidney Disease Prognosis Consortium, Int J Epidemiology 2013; 42:1660-68.	We did seek to include studies that reported on the endpoints mentioned, however, few observational studies and no RCTs that met our inclusion criteria reported on these outcomes.
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	**Dietary Sodium and incident CKD** Low-sodium diets that have been shown to reduce incident or new onset CKD are the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets. Observational data and randomized trials also show these diets significantly reduce blood pressure and cardiovascular disease in the general population.(4, 5) (4) Khatri M, Moon YP, Scarmeas N, et al. The association between a Mediterranean-style diet and kidney function in the Northern Manhattan Study cohort. Clin J Am Soc Nephrol. 2014;9(11):1868-1875. (5) Rebholz CM, Crews DC, Grams ME, et al. DASH (Dietary Approaches to Stop Hypertension) Diet and Risk of Subsequent Kidney Disease. Am J Kidney Dis. 2016;68(6):853-861.	

Commentator & Affiliation	Section	Comment	Response
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	**Dietary Sodium and CKD progression** A randomized trial of low sodium diet in patients with CKD showed significantly improved blood pressure control as well as lower levels of albuminuria.(6) Certain blood pressure medications (ACE inhibitors, Angiotensin II Receptor Blockers) help reduce protein in the urine of CKD patients, which slows progressive kidney damage, and delays the onset of kidney failure. High sodium diets have been shown to blunt the protective effects of these medications on reducing urine protein.(7) In patients with heavy urine protein loss, a high sodium diet was associated with significantly increased risks of end stage renal disease (ESRD).(8) (6) McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, Campbell KL. A randomized trial of dietary sodium restriction in CKD, J Am Soc Nephrol. 2013;24(12):2096-103. (7) Slagman MC, et al., Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial, BMJ 2011;343:d4366. (8) Vegter, S, et al., Sodium intake, ACE inhibition, and progression to ESRD, J Am Soc Nephrol, 2012 Jan;23(1):165-73.	
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	**Dietary Sodium and Kidney stones** We note that an evaluation of the relationship between sodium intake and kidney stones was not conducted in this review as was done for the relationship between potassium and kidney stones. The American Urological Association guideline recommendations, which relied on a previous systematic review by AHRQ notes that sodium chloride is linked to urinary calcium excretion. The guideline cites "[A] randomized trial demonstrated that a lower salt diet, in conjunction with the recommended calcium intake and low animal protein consumption, reduced urinary calcium excretion in hypercalciuric stone formers." This was cited as support for the guideline panel's recommended daily sodium intake target of 2,300 mg.(9) (9) Pearle, Margaret S. et al., Medical Management of Kidney Stones: AUA Guideline The Journal of Urology, 2014 Aug;192(2):316-24.	Assessing the relationship between potassium intake and kidney stone incidence was part of the original charge. However, we identified only one RCT and four cohort studies that assessed the relationship between potassium and kidney stones. In addition, we were charged to assess the relationship between sodium intake and kidney disease, but kidney stones were not considered one of the outcomes for this question.

Commentator & Affiliation	Section	Comment	Response
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	The National Kidney Foundation is a partner in the National Sodium Reduction Initiative and recommends that the dietary reference intakes upper limit be no more than 2300 mg of sodium per day, but ideally intake should be 1500mg, which is also recommended by the American Heart Association (AHA). There are strong links between blood pressure and sodium intake, and a high prevalence of high blood pressure(10) (one-third of Americans have hypertension with another third in the prehypertension range)(11). Most recently the AHA and the American College of Cardiologists recommend an ideal daily target of 1,500mg of sodium in the general population to prevent and treat hypertension or at least a reduction in sodium intake of 1,000mg for most adults.(12) (10) Whelton, Paul K., et al. AHA Presidential Advisory Sodium, Blood Pressure, and Cardiovascular Disease Further Evidence Supporting the American Heart Association Sodium Reduction Recommendations. Circulation, 2012; 126:2880-2889. (11) Centers for Disease Control and Prevention High Blood Pressure Facts http://www.cdc.gov/bloodpressure/facts.htm (12) Whelton, Paul K., et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017; Nov 13:[Epub ahead of print].	No response is warranted.
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	Additionally, despite the lack of high quality studies in people with CKD the KDIGO guidelines recommend limiting intake to 2g of sodium (Grade 1C).(13) However, using potassium salt alternatives is not a safe option for CKD patients for reasons we elaborate on below. (13) Taler, SJ, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Management of Blood Pressure in CKDAm J Kidney Dis. 62(2):201-213.	No response is warranted.
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	Reducing sodium intake is also a cost-effective approach to cardiovascular disease risk reduction. The National Kidney Foundation and many other organizations believe more needs to be done to encourage food producers to lower sodium content and consumers to lower their intake. This is particularly important for people with chronic conditions, like chronic kidney disease, who are already at higher risk for hypertension and cardiovascular events.	No response is warranted.

Commentator & Affiliation	Section	Comment	Response
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	**Dietary Potassium and Chronic Kidney Disease** As noted in the current DRI report, individuals with kidney disease also need to limit their intake of potassium to reduce risk of hyperkalemia, which is associated with irregular heart beat and heat attack. As kidney function declines the kidneys lose the ability to excrete excess potassium. Additionally, taking Angiotensin converting enzyme inhibitors (ACEi) or Angiotensin II receptor blockers (ARB), which are the most effective medications available to delay progression of CKD, increases the risk of hyperkalemia, and hence the need to lower potassium intake as a modifiable risk factor.(14) (14) Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin aldosterone system inhibitors. Clin J Am Soc Nephrol. 2010;5:531-548.	Unfortunately, we did not identify studies that met the inclusion criteria that assessed potassium intake in populations with kidney disease.
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	In contrast, most Americans need to increase their potassium, which has been strongly associated with decreases in blood pressure. The NKF-KDOQI Clinical Practice Guidelines on Hypertension recommended potassium intake identical to the general population in patients with CKD stages 1 and 2, and reduced intake of 2 to 4 g/d (51-102 mmol/d) in patients with CKD stages 3 and 4.(15,16) (15) National Kidney Foundation. KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004; 43 (5) (suppl 1): S1-S290. (16) Fried LF, Emanuele N, Zhang JH, et al; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892-1903.	No response is warranted.
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	While we concur that additional research in this area is needed, the risk of high potassium intake, when combined with reduced ability to excrete potassium, and taking ACEi or ARBs, necessitates advising CKD patients to limit potassium intake. Therefore, we believe that including a warning in the DRIs that individuals with CKD need to limit their potassium intake is important. Given that many individuals with CKD also have hypertension, and may be inclined to follow general health advice that increasing potassium is beneficial, appropriate warnings need to be communicated to them.	Again, we did not identify literature that would have allowed us to address this important issue.
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	**Dietary Potassium and Kidney Stones** The National Kidney Foundation concurs with the lack of evidence of a relationship between potassium intake and the formation of kidney stones concluded in this review.	No response is warranted.

Commentator & Affiliation	Section	Comment	Response
Joseph Vassalotti, MD and Kerry Willis, PhD of the National Kidney Foundation	General	**Conclusion** Although much remains to be learned about the effects sodium and potassium intake have on morbidity, mortality and CKD progression, there remains a great need to highlight the potential risks that high intake of these nutrients poses, which is supported by recent ACC/AHA guideline recommendations to reduce sodium intake generally, and KDIGO recommendations for sodium and potassium intake specifically in advanced CKD patients.	We noted the lack of research evidence in the area of sodium reduction and increased potassium intake among populations with kidney disease.
American Heart Association	Methods	**Assessment of Methodological Risk of Bias of Individual Studies** Assessment of sodium and potassium intake: To distinguish low- from high- quality studies, the American Heart Association (AHA) believes that an in-depth focus on study methodology is imperative. Unfortunately, the report has a fairly cursory approach to methodologic issues, especially the measurement of sodium intake which is challenging and fraught with risk of error. While the report cites a major AHA scientific statement on the methodologic limitations of observational studies,(i) it should include and emphasize (beyond this mention and Appendix E) that spot urine collections do not provide an accurate estimate of usual sodium intake and more recent evidence that 24-hour urine sodium excretion may be significantly different from the actual long-term intake.(ii) AHA also recommends that the report mention the inaccuracy of the use of 24-hour urine collection methods to estimate potassium intake. Urinary excretion of potassium as a percent of intake is variable.(iii) (i) Cobb LK, Anderson CA, Elliott P, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. Circulation. 2014 Mar 11;129(10):1173-86. (ii) Olde Engberink RHG, van den Hoek TC, van Noordenne ND, et al. Use of a Single Baseline Versus Multiyear 24-Hour Urine Collection for Estimation of Long-Term Sodium Intake and Associated Cardiovascular and Renal Risk. Circulation. 2017; 136:917-926. (iii) Turban S, Miller ER 3rd, Ange B, et al. Racial differences in urinary potassium excretion. J Am Soc Nephrol. 2008 Jul;19(7):1396-402.	We were extremely careful to take the method used to assess sodium intake into account in our appraisal of observational studies. For trials, sodium intake was assessed primarily to assess compliance but we noted the methods used for these as well in our measurement of study quality, albeit with less stringent criteria. We did note in our description of the criteria for quality that 24-hour measures are not appropriate for potassium assessment.

Commentator & Affiliation	Section	Comment	Response
American Heart Association	Methods	Measurement of blood pressure: The highest quality studies obtain multiple sets of blood pressure at baseline and follow-up, given the high intra-individual variability of blood pressure. Therefore, when assessing risk of bias, the report should not only assess sodium or potassium exposure, but also assess the number and quality of blood pressure measurements.	We did note the methods used to measure blood pressure and the number of measurements; these data are in the evidence tables, and were included in the overall risk of bias assessment.
American Heart Association	Methods	Types of trials: AHA recognizes the logistical challenges of conducting randomized controlled trials, especially those that intervene on aspects of nutrition. We recommend distinguishing between trials in which sodium or potassium are controlled through feeding, and trials in which sodium or potassium exposure are influenced through behavioral interventions. Trials in which sodium or potassium are controlled through feeding are best suited for establishing and maintaining an experimental contrast and identifying the actual effects of these nutrients.	Unfortunately, the number of feeding studies was too small on which to conduct separate meta-analyses. However, we now describe in detail the findings of the largest, highest quality feeding studies in the text.
American Heart Association	Methods	**Data Synthesis/Analysis** Inappropriate data synthesis: Many if not most of the observational studies that relate sodium intake (or excretion) to hard clinical outcomes are fundamentally flawed. The studies are so problematic that it is inappropriate to synthesize evidence. The AHA strongly recommends that the report present results using the current graphic but without summary estimates.	We considered the quality of the observation studies when drawing our conclusions. No meta-analyses were conducted on observational studies, and we no longer provide summary estimates.
American Heart Association	Methods	Because the report relied on meta-regression techniques, which use group data to identify potential effect modifiers, the report is not well positioned to identify factors associated with greater or lesser BP reduction. These factors, which are well documented, include greater blood pressure reduction from a reduced sodium intake in a) older compared to younger persons and b) black/African American persons compared with non-black persons.(iv) Ideally, the report should identify those studies which have an adequate design and statistical power to identify differences. At a minimum, the report should mention this limitation. (iv) Elijovich F, Weinberger MH, Anderson CA, et al. Salt Sensitivity and Blood Pressure. Hypertension. 2016 Sep;68(3): e7-e46.	The conclusions regarding potential effect modifiers were based on a combination of meta-regressions and direct, within-study comparisons. Unfortunately, few studies conducted these comparisons.

Commentator & Affiliation	Section	Comment	Response
American Heart Association	Methods	**Grading the Strength of Evidence (SoE) for Major Comparisons and Outcomes** AHA has three concerns regarding the assessment of bias and strength of evidence: 1. The Trials of Hypertension Prevention follow-up studies, (v,vi,vii) are listed as high risk for bias in ascertainment of sodium exposure in Appendix E. AHA recommends that these studies be listed as low risk for bias because the studies used multiple, 24-hour urine samples to assess sodium intake. (v) Cook NR, Obarzanek E, Cutler JA, et al. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: The Trials of Hypertension Prevention follow-up study. Arch Intern Med. 2009 Jan 12;169(1):32-40. (vi) Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. Circulation. 2014 Mar 4;129(9):981-9. (vii) Cook NR, Appel LJ, Whelton PK. Sodium Intake and All-Cause Mortality Over 20 Years in the Trials of Hypertension Prevention. J Am Coll Cardiol. 2016 Oct 11;68(15):1609-17.	We have graded TOHP as low RoB; however study quality is only one factor in grading strength of evidence, and no conclusions were based on one study alone.
American Heart Association	Methods	**Grading the Strength of Evidence (SoE) for Major Comparisons and Outcomes (cont'd)** 2. A Cochrane review by Graudal (viii) is included in the report. This review includes studies that lasted less than one week and that had extreme and rapid changes in sodium intake. Therefore, this review is regarded as having little relevance to public health. It should not be used in the report. (viii) Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of Low-Sodium Diet vs. High-Sodium Diet on blood Pressure, Renin, Aldosterone, Catecholamines, Cholesterol, and Triglyceride (Cochrane Review). Am J Hypertens 2011.	We included the Graudal review only as a point of reference, as we were requested to do, and noted its flaws.

Commentator & Affiliation	Section	Comment	Response
American Heart Association	Methods	**Grading the Strength of Evidence (SoE) for Major Comparisons and Outcomes (cont'd)** 3. The rationale for moderate strength of evidence as opposed to strong strength of evidence for blood pressure reduction from sodium reduction is perplexing. There are several large and well-done trials of sodium reduction that documented significant effects on blood pressure. (ix,x,xi,xii) Interestingly, the report rates the strength of evidence as moderate for the effects of increased potassium on blood pressure effects, but this evidence is largely based on meta-analysis of relatively smaller trials. The AHA believes that the strength of evidence for the effect of sodium reduction on reducing blood pressure should be rated as strong. (ix) Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001 Jan 4;344(1):3-10. (x) The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA. 1992 Mar 4;267(9):1213-20.	We describe within the text why we rated the SoE for the conclusions on sodium reduction and BP as moderate, rather than high (downgrading), namely that inconsistency in the direction of findings was considerable. We can't base the SoE on only one or two studies.
American Heart Association	Methods	(References continued from above comment) (xi) Whelton PK, Kumanyika SK, Cook NR, Cutler JA, Borhani NO, Hennekens CH, Kuller LH, Langford H, Jones DW, Satterfield S, Lasser NL, Cohen JD. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group. Am J Clin Nutr. 1997 Feb;65(2 Suppl):652S-660S. (xii) Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with highnormal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. Arch Intern Med. 1997 Mar 24;157(6):657-67.	No further response warranted.
American Heart Association	Methods	**Key Question 2. Among adults and children, what is the association between dietary sodium intake and blood pressure?** AHA recommends the following study be included in the report: • Ellison RC, Capper AL, Stephenson WP, et al. Effects on blood pressure of a decrease in sodium use in institutional food preparation: the Exeter-Andover Project. J Clin Epidemiol. 1989;42(3):201-8.	We added the study by Ellison to our analysis.

Commentator & Affiliation	Section	Comment	Response
American Heart Association	Results	**Key Question 3. Among adults, what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on CVD and kidney disease morbidity and mortality and on total mortality?** To avoid misrepresentation of what low strength of evidence indicates, the report should rewrite the findings in which the strength of evidence is low. The current wording for many of these statements is unclear and potentially misleading. For example, the statement "in adults, a low strength of evidence suggests that sodium reduction does not affect risk for CVD mortality" can be misinterpreted to mean that there is no effect between sodium and mortality from cardiovascular disease. Alternatively, the report could state "there is insufficient evidence to assess the relationship of sodium reduction with CVD mortality."	We greatly revised the wording of the conclusions for low strength of evidence.
American Heart Association	Results	AHA notes the potential benefit of sodium reduction on all-cause mortality. However, it is difficult to reconcile the report's finding that no evidence shows the benefit of sodium reduction on mortality from stroke or cardiovascular event, while there was evidence on all-cause mortality. Apart from gastric cancer,(xiii) how does sodium reduction impact allcause mortality if not from a stroke or cardiovascular event? It is well-known that hypertension is a risk factor for cardiovascular disease and stroke.(xiv) Therefore, if "moderate-strength evidence supports a blood-pressure lowering effect of dietary sodium reduction in adults," then sodium reduction should translate to a reduction in rates of cardiovascular disease and stroke. (xiii) Appel LJ, Frohlich ED, Hall JE, Pearson TA, Sacco RL, Seals DR, Sacks FM, Smith SC, Vafiadis DK, Van Horn LV. The importance of populationwide sodium reduction as a means to prevent cardiovascular disease and stroke: a call for action from the American Heart Association. Circulation. 2011; 123:1138-1143. (xiv) He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. Journal of Human Hypertension. 2009 Jun;23(6):363-84.	We repeated our analyses and now report a significant beneficial effect of sodium reduction on several of the long term clinical outcomes; however we did not find this for all-cause mortality or stroke risk and we note possible reasons in the text.
American Heart Association	Discussion	Addition: AHA recommends adding to the discussion the emerging theories about the harm of extravascular sodium that occurs with a diet high in sodium intake.(xv) (xv) Wang, TJ, DK Gupta. Is a DASH of salt all we need? J Am Coll Cardiol. 2017 Dec 12;70(23):2849-2851.	We did not include commentaries in the literature we considered, although we have included several post hoc analyses of the DASH sodium trial.

Commentator & Affiliation	Section	Comment	Response
American Heart Association	Discussion	Call for More Research: The tone of this report implies that there should be randomized controlled trials of sodium reduction with cardiovascular and stroke mortality. While AHA supports the need for more research funding, it is important to recognize the major practical obstacles of conducting randomized controlled trials with a long duration. Elevated blood pressure is a chronic risk factor that leads to cardiovascular disease and stroke over years or decades of exposure.(xvi) (xvi) Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. JAMA. 2002; 287:1003-1010.	We agree that the recommendation for more long-term trials is impractical and unlikely to answer the questions, and we have withdrawn that. We have added a section to the Discussion that describes the research gaps we identified.
American Heart Association	Discussion	However, trials that last more than a few years are impractical, especially those that test lifestyle modifications. In this context, it is appropriate to rely on the results of high quality trials that test the effect of sodium reduction on blood pressure as well as those observational studies with high quality methods, such as the Trials of Hypertension Prevention studies.(xvii) In the current version of the report, rigorously conducted epidemiological and observational studies do not get ranked highly enough, and therefore the findings are undervalued. (xvii) National Heart, Lung, and Blood Institute (NHLBI). Trials of Hypertension Prevention (TOHP). Website updated 16 Mar 2016. Accessed online 8 Jan 2018: https://clinicaltrials.gov/ct2/show/NCT00000528.	Again, we agree that the recommendation for more long-term trials is impractical and unlikely to answer the questions, and we have withdrawn that. We have added a section to the Discussion that describes the research gaps we identified.
American Assn of Meat Processors; American Bakers Assn; American Frozen Food Institute; Grocery Manufacturers Assn; Independent Bakers Assn; International Dairy Foods Assn; National Milk Producers Federation; North American Meat Institute; North American Millers' Assn; SNAC International; Wheat Foods Council	General	We, the undersigned, thank you for accepting comments on the recently released draft systematic review "Effects of Dietary Sodium and Potassium Intake on Chronic Disease Outcomes and Related Risk Factors." We fully support an update of the Dietary Reference Intakes (DRIs) for sodium and potassium and are pleased to see this first step of the DRI process is nearing completion. The DRIs are the basis for dietary recommendations and public health policies and, therefore, the DRIs must be credible and reflect new scientific developments over the past decade.	No response warranted.

Commentator & Affiliation	Section	Comment	Response
American Assn of Meat Processors; American Bakers Assn; American Frozen Food Institute; Grocery Manufacturers Assn; Independent Bakers Assn; International Dairy Foods Assn; National Milk Producers Federation; North American Meat Institute; North American Millers' Assn; SNAC International; Wheat Foods Council	General	Though we have some questions regarding the analysis, we will be focusing our comments on the draft key messages. Of importance, we are troubled by the fact that the key messages as currently written do not accurately reflect the results and conclusions of the actual review. As drafted, the key messages imply that, at least in some cases, the evidence is stronger than the research supports. The key to public trust is transparency and accuracy. Though this report is not meant for the general public, trusting the information and its interpretation is critical as efforts are underway to update the DRI for sodium and potassium. We are concerned that the current key messages are neither transparent nor accurate in that they do not adequately confer the true state of the science as articulated in the report.	No response warranted.
American Assn of Meat Processors; American Bakers Assn; American Frozen Food Institute; Grocery Manufacturers Assn; Independent Bakers Assn; International Dairy Foods Assn; National Milk Producers Federation; North American Meat Institute; North American Millers' Assn; SNAC International; Wheat Foods Council	General	Of note, none of the findings within this systematic review were given a high Strength of Evidence (SoE) rating. In fact, of the 17 key findings that are highlighted in the results section of the Executive Summary text, seven (41%) were moderate strength of evidence (answering only two of eight key questions), seven (41%) were low strength of evidence, and the rest (18%) were listed as having insufficient evidence to answer. Nutrition policies and programs must be based upon the strongest available science, and it is misleading to have such strongly worded key messages when they are based on such limited evidence. Given this is a scientific, evidence-based report, we believe it is critical to include the SoE in the key messages.	We did not rate any of the conclusions as having high strength of evidence, because the literature on which each was based showed inconsistencies in direction across studies. We explain this in the key points and the Discussion. EPC policy is not to include the SoE ratings in the Key Messages, to keep them in plain language.
American Assn of Meat Processors; American Bakers Assn; American Frozen Food Institute; Grocery Manufacturers Assn; Independent Bakers Assn; International Dairy Foods Assn; National Milk Producers Federation; North American Meat Institute; North American Millers' Assn; SNAC International; Wheat Foods Council	General	Additionally, we note that one of the report's main conclusion statements is that more research is needed to determine the effects of dietary sodium reduction, increased potassium intake, and use of potassium-containing salt substitutes on longer term chronic disease outcomes, particularly CVD and CHD morbidity and mortality; yet, this is not included in the key messages. We are especially troubled considering less definitive statements were included. Given the fact that these messages reflect the issues considered important to the authors, we strongly urge a revision to include this key conclusion of the systematic review.	We did not rate any of the conclusions as having high strength of evidence, because the literature on which each was based showed inconsistencies in direction across studies. We explain this in the key points and the Discussion. EPC policy is not to include SoE in the key messages, to keep them in plain language.

Commentator & Affiliation	Section	Comment	Response
American Assn of Meat Processors; American Bakers Assn; American Frozen Food Institute; Grocery Manufacturers Assn; Independent Bakers Assn; International Dairy Foods Assn; National Milk Producers Federation; North American Meat Institute; North American Millers' Assn; SNAC International; Wheat Foods Council	General	Given the importance of sodium in the diet as well as the lack of consensus among the scientific community, the topic of sodium intake has become a contentious one. This means more people will be tuned into the DRI process as it unfolds, especially in light of the fact that, as mentioned earlier, the DRI is the basis for all federal nutrition policies and programs. For public health safety, the entire process needs to be done in the most rigorous and scientifically sound manner possible. Given the scientific esteem of both the AHRQ and the National Academies of Science, Engineering, and Medicine, we appreciate your thorough review and thoughtful consideration of our suggestions.	We did not include a key message regarding future research, and in fact, removed that recommendation. We now include a Research Gaps section in the report.
Grocery Manufacturers Association	General	The Grocery Manufacturers Association is grateful for the opportunity to comment on the Draft Systematic Review of the effects of dietary sodium and potassium intake on chronic disease outcomes and related risk factors. We appreciate the thoroughness of the review and compilation of the evidence. In view of the timing and duration of the response period, our comments are largely limited to the "DRAFT Key Messages" section and are offered in the spirit of constructive input.	No response is warranted.
Grocery Manufacturers Association	General	It is unclear why a "key messages" section is needed in a report that is primarily designed to provide a technical review and summary of the evidence for a committee of scientific experts rather than for direct application by health care professionals or the general public. (We note that there was no key messages section in the 2009 review of vitamin D and calcium that had a similar purpose). Our recommendation is to remove the key messages as they do not provide the detail and nuance so critical to accurately summarize this technical review. The Abstract and Executive Summary adequately summarize the report.	It is EPC policy to include a Key Messages section.
Grocery Manufacturers Association	General	If the section is retained, we offer that a more appropriate heading is "key findings". Additionally, the following revisions are critical to move toward a more accurate summary of the report. Specifically: 1. Strength of evidence for each summary point should be included. A reader who does not peruse the report beyond the key messages section could be left with the impression that all points are supported by a similar high level of evidence. This is not the case as most of the key points have moderate or low strength of evidence.	It is also EPC policy not to include SoE in the Key Messages but to use plain language instead.

Commentator & Affiliation	Section	Comment	Response
Grocery Manufacturers Association	General	2. The key messages as drafted seem to assume that the relationship between sodium and potassium intakes and all outcomes is linear. The final point in key messages states that linearity could not be determined for some relationships Linearity should not be assumed unless there is convincing evidence that sodium and potassium behave differently as compared to other nutrients.	We have revised the conclusions, in part to ensure that we do not give the impression that we assumed linearity.
Grocery Manufacturers Association	General	3. Relative terms, such as increase, decrease, higher or lower should be anchored to a reference point, e.g., current recommendations/DRIs, normal intake, level reported in a study, etc. For instance, what are the levels of sodium intake that are associated with increased risk for developing hypertension? Baseline intakes should be included in statements such as increasing potassium intake decreases blood pressure.	We now note several times throughout the report that we cannot provide a definition or benchmark for low or high sodium or potassium, as each study used its own definition, and not all studies met their goals.
Grocery Manufacturers Association	General	4. The limitations of the evidence base and consequent need for additional targeted research seems to be an important conclusion of the review and worthy of inclusion under key messages.	We have added a section that describes research gaps we identified.
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Insttitute of Alberta at the University of Calgary	General	Thank you for the opportunity to comment. I would like to bring to the attention of the committee several issues relating to the lack of validity of using estimates of long term sodium ingestion from spot urine samples and specifically major methodological issues with the validation study used to support the PURE and ONTARGET studies.	Thank you. We agree with this assessment.
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Insttitute of Alberta at the University of Calgary	General	**1) There is little theoretical basis for estimates of long term sodium intake from a single spot urine sample to be valid.** In most societies, sodium intake varies meal to meal, day to day and season to season while the sodium concentration in a single spot urine sample mainly reflects the sodium and water ingested within 6 hrs. of the urine being produced that is in the spot urine sample [1, 2]. 1. Cogswell, M.E., et al., Use of Urine Biomarkers to Assess Sodium Intake: Challenges and Opportunities. Annu.Rev Nutr, 2015. 35: p. 349-387. 2. Strauss, M.B., et al., Surfeit and deficit of sodium; a kinetic concept of sodium excretion. AMA.Arch Intern Med, 1958. 102(4): p. 527-536.	We reinforce this point in the introduction and limitations sections of the report.

Commentator & Affiliation	Section	Comment	Response
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Instittute of Alberta at the University of Calgary	General	**2) Several factors impacting short term sodium excretion (that would affect the spot urine sodium concentration) are potential confounding risks for cardiovascular outcomes.** Other than diet, several confounding factors that impact sodium excretion in the non-steady state circumstances of a spot urine sample include aldosterone, cortisol, sympathetic stimulation, potassium, renal function [3, 4]. Several of these factors are known risk factors for cardiovascular disease. Most of the counter regulatory hormones that impact sodium excretion will have a more prominent affect in the early morning when their levels rise, and sodium excretion increases. The PURE study used a first or second morning voided sample where the sodium concentration would be most impacted by the counter regulatory hormones. A 24 hr urine sample represents an overall daily steady state of the various factors influencing sodium excretion. Sodium concentration in a spot urine sample is confounded by various factors that regulate short term sodium excretion and are risks for cardiovascular disease. 3. Rakova, N., et al., Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. Cell.Metab, 2013. 17(1): p. 125-131. 4. Titze, J., D.N. Muller, and F.C. Luft, Taking another "look" at sodium. Can J Cardiol, 2014. 30(5):p. 473-475.	We reinforce this point in the introduction and limitations sections of the report.
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Instittute of Alberta at the University of Calgary	General	**3) The accuracy and reproducibility of a single spot urine estimate of 24 hr urine sodium vs a single 24 hr urine sodium is variable and mostly low.** A meta-analysis of single spot urine estimates of 24 hr urine sodium vs a single 24 hr urine sodium found a wide range of correlations (0.17 to 0.94) with the high correlations not being reproducible [5]. Few studies in the meta-analysis had Bland Altman analysis that are recommended for validation. The authors recommended that spot urine sodium samples not be used to estimate sodium intake. A subsequent meta-analysis found the Kawasaki equation (that was used in the PURE study to relate spot urine sodium to 24 hr urine sodium) to be particularly poor [6]. 5. Ji, C., et al., Systematic review of studies comparing 24-hour and spot urine collections for estimating population salt intake. Rev Panam Salud Publica, 2012. 32(4): p. 307-315. 6. Huang, L., et al., Mean population salt intake estimated from 24-h urine samples and spot urine samples: a systematic review and meta-analysis. Int.J Epidemiol., 2016. 45(1): p. 239-250.	No further response warranted.

Commentator & Affiliation	Section	Comment	Response
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Institttute of Alberta at the University of Calgary	General	3) continued: When the second meta-analysis was done, there were more Bland Altman analysis performed in recent studies. The Bland Altman plots showed poor agreement of spot urine estimates of 24 hr urine sodium and 24 hr urine samples at higher and lower than average sodium intake. At lower than average 24 hr urine sodium, the spot urine samples over estimated 24 hr urine sodium and at higher 24 hr urine sodium, spot urine underestimated 24 hr urine sodium. The spot urine estimates of 24 hr urine sodium were inaccurate by over 8000 mg in individuals. The second meta-analysis concluded that an average population salt intake less than or greater than 5 gm/day could be estimated from spot urine samples but neither meta-analysis supported use of single spot urine samples to predict an individual's usual sodium intake.	No further response warranted.
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Institttute of Alberta at the University of Calgary	General	**4) Single 24 hr urine sodium vs multiple days of 24 hr urine sodium.** Because sodium intake varies day to day, there is not a strong theoretical basis for a single 24 hr urine to accurately represent usual sodium intake. A series of studies have confirmed that a single 24 hr urine is not an accurate reflection of usual intake and that 3-7 24 hr urine sodium are needed to accurately classify sodium intake[1, 7-9]. The weak and inconsistent association of a single spot urine sodium estimate of 24 hr urine sodium to a single 24 hr urine sodium is further weakened by the need for multiple 24 hr hr urine collections to accurately classify and individuals' usual sodium consumption. 1. Cogswell, M.E., et al., Use of Urine Biomarkers to Assess Sodium Intake: Challenges and Opportunities. Annu.Rev Nutr, 2015. 35: p. 349-387. 7. Birukov, A., et al., Ultra-long-term human salt balance studies reveal interrelations between sodium, potassium, and chloride intake and excretion. Am J Clin Nutr, 2016. 104(1): p. 49-57. 8. Olde Engberink, R.H.G., et al., Use of a Single Baseline Versus Multiyear 24-Hour Urine Collection for Estimation of Long-Term Sodium Intake and Associated Cardiovascular and Renal Risk. Circulation, 2017. 136(10): p. 917-926. 9. Sakaki, M., et al., Long-term variability of urinary salt excretion and blood pressure in hypertensive patients. Hypertens Res, 2014. 37(10): p. 939-43.	No further response warranted.

Commentator & Affiliation	Section	Comment	Response
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Instittute of Alberta at the University of Calgary	General	**5) The formula used to estimate 24 hr urine sodium from a spot sample contain confounding variables that are likely to impact associations with blood pressure, cardiovascular disease and mortality independent of the urine sodium concentration.** Sodium intake varies by age, gender and activity level. The Kawasaki and other equations use age, gender and creatinine to better predict 24 hr urine sodium. The output of these formula therefore reflect age, gender, creatinine as well as sodium concentration. Urine creatinine is closely correlated with muscle mass and physical activity in a healthy population. Age, gender and physical activity (and renal function) are some of the strongest correlates with change in blood pressure, cardiovascular disease and death. Hence it is implausible that an equation that contains age, gender and creatinine as three of 4 variables will not be related to blood pressure, cardiovascular disease and death. It is not logical to attribute an outcome to an inaccurate estimate of sodium intake in a formula that contains also contains accurate data on very well-established risks of age, gender and creatinine. The output of formula that contain well established cardiovascular risk factors should not be used to associate a less established risk factor to outcomes. This is akin to inserting a spot urine sodium estimate into a Framingham risk equation and attributing any association with outcome to the spot urine sodium estimate.	No further response warranted.

Commentator & Affiliation	Section	Comment	Response
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Institute of Alberta at the University of Calgary	General	**6) The PURE validation study was methodologically unsound and prone to artefactual inflation of the association of the spot urine sodium estimate of 24 hr urine sodium and the 24 hr urine sodium.** The PURE validation study had a very low proportion of 'complete' 24 hr. urine samples to compare with spot urine samples [10, 11]. In the PURE validation study, only 50% of 24 hr urine samples were complete by the criteria provided by the investigators. However, the PURE investigators without overt disclosure included 24 hr urine samples within 25% of predicted 24 hr. excretion of creatinine as being complete even though the original method called for excluding urines that exceeded 15% of predicted creatinine excretion [10-13]. The revised formula resulted in the inclusion of many incomplete 24 hr urines (at least 20% of those classified as complete by the altered formula)[13]. 10. Mente, A., et al., Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries. Journal of Hypertension, 2014. 32(5): p. 1005-1014. 11. Campbell, N., Validation and comparision of three formulae to estimate sodium and potasium excretion from a single morning fasting urin compared to 24-h measures in 11 countries. Correspondence. Journal of Hypertension, 2014. 32(12): p. 2499-2500. 12. He, J. and K. Obst, Estimating dietary sodium intake using spot urine samples: correlation and bias. J Hypertens, 2017. 35(3): p. 466-467. 13. Mente, A., M.J. O'Donnell, and S. Yusuf, Reply to both letters. J Hypertens, 2014. 32(12): p. 2501-3.	We note the flaws in the study and do not include it in any conclusions.

Commentator & Affiliation	Section	Comment	Response
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Institute of Alberta at the University of Calgary	General	**6) cont'd:** Hence there was no 'standard' to compare to the spot urine samples (incomplete 24 hr urines do not represent a standard of comparison). This is accentuated by the observation that in the setting of a high proportion of incomplete 24 hr urine samples, the formula for assessing if the urines are complete do not accurately discriminate between complete and incomplete collections and using different formula in this setting can remarkably alter the estimates of 24 hr urine sodium [14, 15]. The high correlation between spot and 24 hr urine sodium in the PURE validation study is plausibly an artifact of comparing a sample to itself. The spot samples in the validation study were first morning (i.e. overnight) and were compared to incomplete 24 hr urine samples [10]. This is a setting where the overnight collection would represent a large proportion of the incomplete 24 hr sample. It is concerning that independent spot and 24 hr urine collections were collected in the PURE validation study but the comparisons of spot samples to independent 24 hr urine samples have not been released although the analysis has been requested several times [16]. 10. Mente, A., et al., Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries. Journal of Hypertension, 2014. 32(5): p. 1005-1014. 14. John, K.A., et al., Accuracy and Usefulness of Select Methods for Assessing Complete Collection of 24-Hour Urine: A Systematic Review. J Clin Hypertens (Greenwich), 2016. 18(5): p. 456-467. 15. Wielgosz, A., et al., The Impact of Using Different Methods to Assess Completeness of 24-Hour Urine Collection on Estimating Dietary Sodium. J Clin Hypertens (Greenwich), 2016. 18(6): p.581-584. 16. Campbell, N.R., Dissidents and dietary sodium: concerns about the commentary by O'Donnell et al. Int J Epidemiol, 2016.	

Commentator & Affiliation	Section	Comment	Response
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Institute of Alberta at the University of Calgary	General	**6) cont'd:** The lack of reproducibility of the PURE validation is also concerning. The PURE China subsample published their validation and found a higher average error (bias) and low correlation (Pearson r=.19, ICC r= 0.28) between the spot urine sodium estimates and 24 hr urine sodium [17]. Most events in the PURE study came from China. The lack of rigor in the PURE validation study was also evident in 4 erratum in the published Kawasaki equation [10, 12] and in a lack of comparability of the blood pressures in the PURE study to rigorous blood pressure surveys in the same populations [16]. It is also concerning that the authors of the PURE validation study have in publications and presentations misrepresented their research results and those of other other authors [16] 10. Mente, A., et al., Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries. Journal of Hypertension, 2014. 32(5): p. 1005-1014. 12. He, J. and K. Obst, Estimating dietary sodium intake using spot urine samples: correlation and bias. J Hypertens, 2017. 35(3): p. 466-467. 16. Campbell, N.R., Dissidents and dietary sodium: concerns about the commentary by O'Donnell et al. Int J Epidemiol, 2016. 17. Peng, Y., et al., Validation and Assessment of Three Methods to Estimate 24-h Urinary Sodium Excretion from Spot Urine Samples in Chinese Adults. PLoS.One., 2016. 11(2): p. e0149655.	
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Institute of Alberta at the University of Calgary	General	**7) Financial COI are strongly associated with results that favor the commercial interest.** We note that some of the authors of the PURE sodium studies and the validation study were raising funds from the food industry at the time of the PURE study and the validation study but often do not disclose these interests (http://www.nutritioncvd2014.com/) and are inconsistent in disclosing other potential conflicts of interest [16]. 16. Campbell, N.R., Dissidents and dietary sodium: concerns about the commentary by O'Donnell et al. Int J Epidemiol, 2016.	Again, we did not consider the PURE study in any conclusions.

Commentator & Affiliation	Section	Comment	Response
Norm Campbell, MD Professor of Medicine, Community Health Sciences and Physiology and Pharmacology, O'Brien Institute of Public Health and Libin Cardiovascular Instittute of Alberta at the University of Calgary	General	We have also published an analysis of a prior IOM report on dietary sodium's relationship with various outcomes [18]. We noted in our analysis and other analyses, a tendency for high quality studies to show associations with adverse outcomes while lower quality studies were a mix of no association and positive or a negative association [19-22]. We are disappointed that two of studies of the NHANES database with Dr Alderman as the senior author are included in your analysis when the same data bases were reanalyzed by other investigators with different findings. These are not independent studies but studies with findings that were refuted but subsequent analyses. 18. Lucko, A., C.T.A. Doktorchik, and N.R.C. Campbell, Impact of quality of research on patient outcomes in the Institute of Medicine 2013 report on dietary sodium. J Clin Hypertens. In press. 19. Arcand, J., et al., The Science of Salt: A Regularly Updated Systematic Review of Salt and Health Outcomes (June and July 2015). J Clin Hypertens (Greenwich), 2016. 18(5): p. 371-377. 20. Arcand, J., et al., More evidene that salt increases blood pressure and risk of kidney disease from the Science of Salt: A regularly updated systematic review of salt and health outcomes (April-July 2016). J Clin Hypertens (Greenwich), 2017. 19(8): p. 813-823. 21. Johnson, C., et al., The Science of Salt: A Systematic Review of Quality Clinical Salt Outcome Studies June 2014 to May 2015. J Clin Hypertens, 2016. 18(9): p. 832-839. 22. Johnson, C., et al., The science of salt: a systematic review of clinical salt studies 2013 to 2014. J Clin Hypertens (Greenwich), 2015. 17(5): p. 401-411.	
Norman Campbell University of Calgary	Executive Summary	Upload Document 04 comments for Agency for Health Care Research and Quality.docx I accept the disclosure policy. My comments relate mainly to the inclusion of studies based on spot urine samples. Please see the attachment for details. I was also concerned that there are 4 studies reporting analyses of two databases. The report presumes they are 4 independent studies but in fact are two NHANES studies that were conducted by a Senior Author who was a consultant to the Salt Institute and two refuting studies of the same NHANES studies. One of the references is in press but if there is interest I can forward the galley proof (your website allows only one upload)	

Commentator & Affiliation	Section	Comment	Response
kok phin chian **Knowing please just**	??	No comments or attachments. Contact information submitted is questionable. Presumably, Rhode Island is in place of the Republic of Indonesia I accept the disclosure policy.	Thank you
Jessica Hixson **SNAC International**	??	Upload Document: 03_Sodium Coalition Extension Request_AHRQ report_12-20-2017.docx I accept the disclosure policy.	Thank you
Jessica Hixson **SNAC International**		Upload Document 06_AHRQ comments Final 1-8-8.docx I accept the disclosure policy.	Thank you
Robert Burns **Grocery Manufacturers Association**		Upload Document 05_2018-01-08 GMA comments on AHRQ draft report.docx I accept the disclosure policy.	Thank you
American Heart Association		Upload Document 07_AHA Comments on Sodium Potassium Review.docx I accept the disclosure policy.	Thank you
Agnès de Sesmaisons **European Food Safety Authority (EFSA)**	Results	Upload Document 08_Potassium_stroke.pdf (??) I accept the disclosure policy. With respect to the association between dietary potassium and stroke (Key Question 8), the draft report concludes "No RCTs assessed the effect of increased potassium intake on the risk for stroke. Among thirteen prospective cohort studies that assessed associations of potassium status with stroke risk among healthy cohorts, findings were inconsistent and could not be predicted by method used to assess potassium status (insufficient evidence)." (p 189)	We did not identify trials that met our inclusion criteria regarding potassium supplementation and risk for stroke. We also did not identify enough observational studies that met our inclusion criteria to conduct a dose response analysis.

Commentator & Affiliation	Section	Comment	Response
Agnès de Sesmaisons European Food Safety Authority (EFSA)	Results	This statement contradicts the results of several meta-analyses (Larsson et al., 2011; WHO, 2012; Aburto et al., 2013; D'Elia et al., 2014; Adebamowo et al., 2015; Vinceti et al., 2016), which reported an inverse association between potassium intake and risk of stroke. Notably, those conducting a dose-response analysis found a roughly linear decrease in the risk of total stroke with increasing potassium intake up to around 3,500 mg/day (Vinceti et al, 2016; Larsson et al, 2011). Above this value, the inverse association is weakened and more uncertain. In stratified analyses by subgroups of dietary potassium intake (<90, 90–120, and ≥120 mmol/day; 90 mmol/day corresponds to 3,500 mg/day), Vinceti et al. (2016) found that the summary RRs for the highest versus the lowest potassium exposure category increased with increasing exposure, as did the statistical imprecision of the estimate: 0.87 (95% CI 0.82–0.93), 0.92 (95% CI 0.82–1.04), and 1.02 (95% CI 0.83–1.24) for the respective subgroups.	No further response warranted.
Agnès de Sesmaisons European Food Safety Authority (EFSA)	Results	(continued from above) In spline regression analysis, a decrease in the pooled RR up to around 90 mmol/day potassium intake was observed, based on the most adjusted model. At this cutpoint of intake, the RR was 0.78 (95% CI 0.70–0.86), while above it the RR flattened. There was substantial uncertainty in this upper range of the distribution. Based on RRs not adjusted for blood pressure, a U-shaped dose–response curve was observed. With respect to the methods used to assess potassium intake, summary RRs obtained when pooling studies based on urinary assessment methods (4 studies) were higher and more statistically unstable (wider confidence intervals) than those obtained when pooling studies based on dietary questionnaires.	No further response warranted.
Agnès de Sesmaisons European Food Safety Authority (EFSA)	Results	When assessing the consistency across studies, the AHRQ draft report does not appear to account for the fact that the association between potassium intake and risk of stroke may vary according to the level of potassium intake. Consideration could also be given to the possible lack of power (small number of cases) in some of the cohort studies. Rather than being “inconsistent,” we argue that the body of evidence consistently points to an inverse association between potassium intake and risk of stroke for potassium intakes up to around 3,500 mg/day (EFSA NDA Panel, 2016).	Responses presented to individual comments

Commentator & Affiliation	Section	Comment	Response
Agnès de Sesmaisons European Food Safety Authority (EFSA)	Results	References (from above): Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P and Cappuccio FP, 2013. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. British Medical Journal (Clinical Research Edition), 346, f1378. Adebamowo SN, Spiegelman D, Willett WC and Rexrode KM, 2015b. Association between intakes of magnesium, potassium, and calcium and risk of stroke: 2 cohorts of US women and updated meta-analyses. American Journal of Clinical Nutrition, 101, 1269–1277. D'Elia L, Iannotta C, Sabino P and Ippolito R, 2014. Potassium-rich diet and risk of stroke: updated meta-analysis. Nutrition, Metabolism and Cardiovascular Diseases, 24, 585–587. EFSA NDA Panel (EFSA Panel on Dietetic Products Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle H, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, Tomé D, Van Loveren H, Vinceti M, Willatts P, Aggett P, Martin A, Przyrembel H, Brönstrup A, Ciok J, Gómez Ruiz JA, de Sesmaisons-Lecarré A and Naska A, 2016. Scientific opinion on Dietary Reference Values for potassium. EFSA Journal 2016;14(10):4592, 56 pp. doi:10.2903/j.efsa.2016.4592 Larsson SC, Orsini N and Wolk A, 2011a. Dietary potassium intake and risk of stroke: a dose-response meta-analysis of prospective studies. Stroke, 42, 2746–2750 Vinceti M, Filippini T, Crippa A, de Sesmaisons A, Wise L and Orsini N, 2016. A meta-analysis of potassium intake and the risk of stroke. Journal of the American Heart Association, 5, e004210. doi: 10.1161/JAHA.116.004210 WHO (World Health Organisation), 2012d. Effect of increased potassium intake on cardiovascular disease, coronary heart disease and stroke. World Health Organisation, Geneva, Switzerland, 42 pp.	Responses presented to individual comments
Tonya Saffer National Kidney Foundation		Please see comments from the National Kidney Foundation attached. Upload Document 09_20180112 NKF comments on sodium and potassium on chronic disease endpoints.pdf I accept the disclosure policy.	Responses presented to individual comments

Commentator & Affiliation	Section	Comment	Response
Bonnie Liebman **Center for Science in the Public Interest**		Upload Document 10_CSPI Comments on AHRQ Draft Sodium Report Final.pdf I accept the disclosure policy.	Responses presented to individual comments