Digesting things further: High dietary salt intakes are almost certainly problematic

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We recently did a blog post on dietary salt and health, particularly with regard to a new large prospective study (the PURE Study). This facilitated useful feedback from others, along with input from colleagues in a journal club we ran. Based on these discussions, we now have stronger concerns about remaining reverse causation in the PURE Study (and persisting concerns regarding other aspects). Here we update some of our thinking and conclude that the totality of the available evidence is sufficient for health authorities to continue taking a range of evidence-based actions to reduce the hazard of high salt intakes. Again however we invite critical comment on our assessment and suggestions on where to from here.

The new observational study – the PURE Study by O'Donnell et al – was the focus of the former blog post. Although it was large multi-country study, it is vital to place the PURE Study in context and consider the **total** body of evidence around salt intake. And not just in terms of quantity, but also quality.

In our previous blog post we alluded to the overall evidence around salt being harmful to health – and undoubtedly so at high levels. Additionally, our colleagues have also emphasised that the evidence from randomised controlled trials should be weighted more heavily than the results of the PURE Study by itself. We agree with this, and highlight the following key findings from randomised trial data that preceded the PURE Study:

- The randomised trial data show that reducing dietary sodium reduces blood pressure (e.g., a meta-analysis of 34 trials lasting more than 4 weeks (1)).
- The randomised trial data show that reducing blood pressure reduces disease outcomes (e.g., a meta-analysis of 147 randomised trials (2)).
- Long-term follow-up of the randomised trial data around reducing sodium intakes provides some of the strongest scientific evidence available. E.g., the TOHP study followed up their participants for 10-15 years and used relatively reliable methods for measuring sodium (averaging 3 to 7 twenty-four hour urinary excretions of sodium and potassium per subject). It found the "risk of a cardiovascular event was 25% lower among those in the intervention group" (relative risk 0.75, 95% confidence interval 0.57 to 0.99, p=0.04) [3]. Similarly for low levels of sodium intake: "Spline curves supported a linear association of sodium with cardiovascular events, which continued to decrease from 3600 to 2300 and 1500 mg/d" (4). (That is, a linear dose-response (not a U-shaped curve) of CVD risk down to sodium intakes way below the nadir found in the O'Donnell et al PURE Study.) Furthermore, CVD risk was particularly elevated when the sodium to potassium excretion ratio was high (RR, 1.24; 95%CI, 1.05-1.46; p=0.01) (5).

Further thoughts on the limitations with the "PURE" Study

1. Our discussions with colleagues also generated more in-depth discussion on the limitations of the PURE Study: As noted previously the authors of the PURE Study used **spot urine measures** (and only a single measure) rather than the gold standard of 24-hour urines to measure sodium (see also this systematic review of 20 studies (6)). Our colleagues reiterated the limitations with this measure (though we still doubt that this potential source of measurement error could contribute to the U-shaped relationship found in the PURE Study).

2. Limitations with the **Kawasaki formula** used in the PURE Study to estimate 24-hour sodium intake from spot urines – in particular with this potentially causing substantial over-estimates in sodium intake in the PURE Study (see comments by Professor Bruce Neal in the "Comments" part of the previous blog post). Again, though, we struggle to see how this formula could generate a spurious U-shape curve – possible, but unlikely.

3. "**Reverse causation** cannot be completely ruled out" as the PURE authors' state. Reverse causation would arise if early CVD or other diseases caused a lowering of salt intake or excretion. The authors did adjust in their analyses for various known diseases and certain risk factors, and exclude CVD events in the first two years post-diagnosis in sensitivity analyses (although this greatly reduced the number of events given only a median 3.7 year follow-up). If these adjustments and exclusion were inadequate to completely rule out reverse causation, it could be that undiagnosed pathological processes

were reducing their sodium excretion and contributing to the higher death rate in this group (the left side of the reported U-shaped association) or that medications were reducing sodium intake. Indeed, the PURE Study reports that the group found to have the lowest sodium excretion also had the highest: LDL levels, prevalence of a history of CVD, prevalence of diabetes, alcohol intake and medication use for each of 4 types of CVD medication (other differences were the lowest male to female ratio and highest calorie intake which may also be relevant; see Table 1 of O'Donnell et al). It is our view, now, that reverse causation is the most likely spurious cause of a U-shaped association. One way to resolve this is with longer follow-up of the PURE Study – which is frustrating in that we are now waiting another five years or so for a more definitive answer.

4. **Residual confounding** remains a possibility – although it would probably take a mis-measured or mis-specified confounder with a U-Shape association with CVD risk and a linear association with sodium intake to generate such a pattern. Such a situation would normally be unlikely…. but BMI does have a U-shape association with CVD risk in many studies. The PURE Study adjusted for BMI, but we suspect as a linear term rather than categorical or non-linear (it is not clear in the paper) which could generate some spurious U-shape association of sodium with CVD risk. We consider this residual source of error as possible, but (as best we can tell) probably not as important as the above reverse causation concern.

Collectively these limitations should raise suggestions that the various findings from the PURE Study (no harm until very high sodium intakes and a U-shaped relationship) should be treated cautiously and seen as less important that the randomised trial evidence detailed above.

Where to from here?

1. **Watch** for the inevitable correspondence regarding this paper in the NEJM that addresses the above concerns, and any other arising critiques.

2. **Wait** for longer follow-up of the PURE Study – although this is not that helpful for policy-makers now! Alternatively, we could wait until the large cluster-randomised trial in China is completed (7).

3. Although many public health and nutritional scientists may be reassured by the overall state of the evidence – we suspect that some policy makers might not be. Therefore there might still be a case for the World Health Organization (WHO) to establish a **high-level review panel** and re-clarify the state of the evidence and the future research agenda (as we suggested previously). Such a panel may have maximum credibility if it just had scientists with no past publications relating to dietary salt and health.

4. In the **meantime** public health policy is, we believe justified to continue **with sodium reduction actions** that target the high end of the salt intake spectrum and are unlikely to impact on those with very low salt intake. These include:

i) Regulations on setting **maximum levels** of sodium in the very saltiest of foods e.g., sauces and processed meats. This may also encourage more manufacturers to replace sodium with potassium (NaCl with KCl) in these products (see this recent meta-analysis of 5 RCTs using salt substitutes and the benefits for lowering blood pressure (8)).

ii) Improving **front of pack nutrition labelling** – e.g., traffic light type systems, or the "warning high salt" style of label used in Finland (9).

iii) Encouraging the food industry to **reformulate their processed foods** (possibly one of the reasons for the success of a recent UK salt reduction campaign (10)). Indeed, this is a focus for the Heart Foundation in NZ, which had had success with reducing sodium in NZ bread, breakfast cereals and margarine in the past (11). The Foundation is now working with other food manufacturers e.g., Continental products such as soups and spreads (12).

5. **Probably justified** to consider a wider range of options:

i) A tax on junk food (as recently introduced in Mexico) – which would target foods high in sugar, saturated fat and sodium. Revenue from such a tax could fund nutrition interventions such as healthy school lunches.

ii) A tax on salt itself eg, at the point at which it leaves the salt production facility. Of note is that Hungary has a tax on salty snacks.

iii) Regulations on maximum salt levels in a wide range of foods e.g., as in some European countries (13) and recently South Africa (14).

All these options could be considered in the NZ context – given the high levels of intake in this country (see Appendix). In particular reducing population salt intakes would probably be pro-equity given higher background CVD rates among Māori.

Conclusions

It seems that the totality of evidence – and particularly the randomised trial data, suggests it would be beneficial for health authorities to continue acting to reduce dietary salt intakes. Many options exist, from more cautious approaches to bolder ones such as junk food taxes.

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Recommendations, actual levels	Sodium (g/day)	Salt (g/day)
"Adequate intake" for health as defined by NZ & Australian authorities [15].	0.46–0.92	1.15–2.3
Minimal level of CVD risk used in the Global Burden of Disease 2010 study [16]. The risk factor of a "diet high in sodium" was estimated in this study to be one of the top two dietary risk factors for disease burden globally.	1	2.5
Recommended by WHO [17]. A very recent meta-analysis estimates that there were 1.65 million deaths globally from CVD causes in 2010 attributed to sodium consumption above this 2.0 g per day level [18].	<2	<5
Recommended by NZ & Australian authorities [15].	<2.3	<5.8
Levels at which the US Institute of Medicine highlighted uncertainty around – in terms of any extra benefit [19]	<2.3	<5.8
Levels of intake for UK adults after a campaign (ie, intakes changed from 9.5 to 8.1 g/d in daily salt intake) [10].	3.2	8.1
Level of average NZ adult intake (spot urine samples in the National Nutrition Survey 2008/2009) [20]	3.5	8.9

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