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Mounting complexities in the dietary salt & health relationship

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A large prospective study on dietary salt and health has recently been reported in the *New England Journal of Medicine*. While reinforcing extensive past work that a (very) high intake of salt is hazardous to health – an increased hazard was also found for low intakes of salt (i.e., a "J-shaped" or "U-shaped" relationship). This blog post considers this new study in more detail and suggests that we need a high-level international review to clarify the research and policy agenda from here. Our interpretation should be treated as preliminary on what may be an important study; therefore, we welcome and encourage comments on this blog post. *[SEE MULTIPLE COMMENTS ON THIS BLOG BELOW. AND IN PARTICULAR SEE SUBSEQUENT BLOG WHERE WE UPDATE ANALYSIS BELOW BASED ON DISCUSSIONS WITH COLLEAGUES – IMPORTANT.]*

The overall evidence around salt and harm to health (as outlined in two recent systematic reviews (1, 2)) has been described as strong enough to justify public health action to reduce high levels of sodium intake. Indeed, as recently as August 2014 a new study estimated that there were 1.65 million deaths globally from cardiovascular causes in 2010 attributed to sodium consumption above a reference level of 2.0 g per day (3). This study included a new meta-analysis of 107 published trials of sodium reduction and reduced blood pressure (BP).

Furthermore, the risk factor of a "diet high in sodium" has been estimated to be one of the top two dietary risk factors for disease burden identified in the massive Global Burden of Disease Study (4). "Salt reduction" has also been included in the top five priority actions for non-communicable disease (NCD) control internationally (5), and for reducing NCD inequalities (6).

However, the evidence relating to sodium and health has always been controversial to some extent (7). In particular, a recent Institute of Medicine Report (8) highlighted the uncertainty around the health benefits and risks of reducing sodium intakes below the 2300 mg/day level (see the Table below).

Recommendations, actual levels	Sodium (g/day)	Salt (g/day)
Recommended by WHO (9)	<2	<5
Recommended by NZ & Australian authorities (10)	<2.3	<5.8
Minimal level of cardiovascular disease risk used in the Global Burden of Disease 2010 study (4)	1	2.5
Average NZ adult intake (spot urine samples in the National Nutrition Survey 2008/2009) (11)	3.5	8.9
Level associated with *lowest cardiovascular risk* from the O'Donnell et al study discussed in this blog post (12) – see abstracted figure below.	4-5	10-12.5

Most recently, a large study has been reported in the *New England Journal of Medicine* by O'Donnell et al (12). It reports a "U-shaped" relationship for dietary salt intake and all-cause mortality and also for cardiovascular events (see the Figure below). Of note is that the increased cardiovascular risk was estimated to only start increasing from the lowest estimated risk level (4-5g of sodium – see Table above). Other work has also reported such a J-shaped or "U-shaped" relationship (13-16)) but the last two of these cited studies included people with established cardiovascular disease (so reverse causation is possible – see below). But the O'Donnell et al study is by far the largest that has reported such a pattern. Indeed, it involved over 100,000 subjects from 17 countries. It had other desirable

features: 95% follow-up of subjects, 3.7 years of follow-up on average, it considered dietary potassium intake as well, and it undertook various analyses to explore the possibility of reverse causation, sensitivity analyses around potential confounding (array-approach), and propensity-score matched sensitivity analyses.

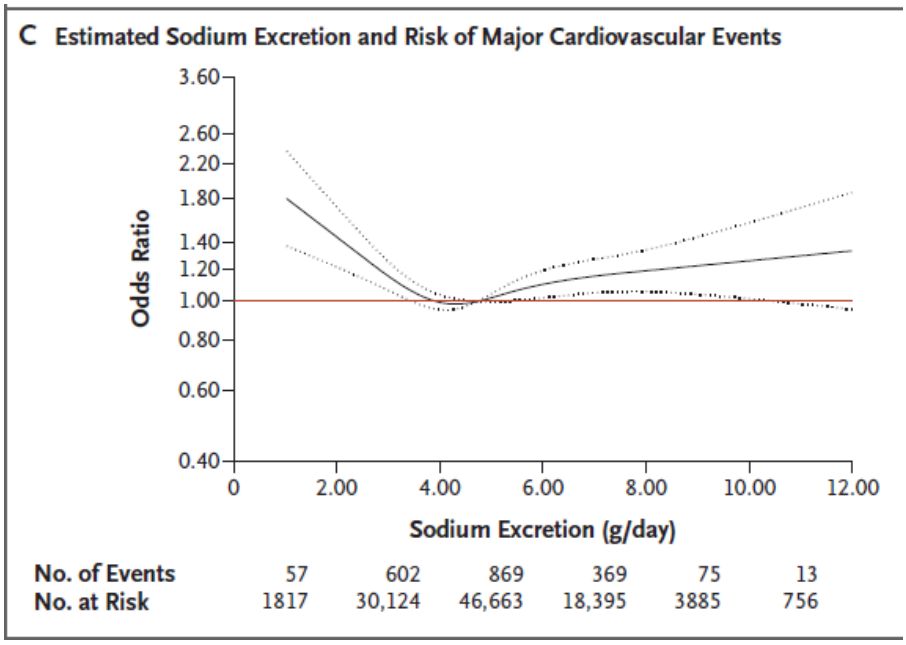

Figure from O'Donnell et al, NEJM 2014

Possible limitations with the new O'Donnell et al study

But no study is perfect, and the limitations with this new study include:

1. It was a prospective study and these all suffer from the possibility of **residual confounding** (unmeasured and mismeasured variables). But the authors did analyses to explore this and point out the level of confounding by a single confounder would need to be large to nullify their findings – and peculiar to generate the U-shape. Nevertheless, if there are multiple confounders on many separate "backdoor paths" (epidemiological jargon for considering other causal pathways) then several modest confounding processes could conceivably sum up to create such a relationship (but, again, we have difficulty seeing how this might result in a "U-shaped" relationship). Unlike with alcohol whereby confounding may generate a J-shaped curve, it is difficult to posit that people with average salt consumption have better profiles on other risk factors than either low and high salt consumers, *and* that this is not measured or known.
2. "**Reverse causation** cannot be completely ruled out" as the authors' state. Reverse causation would arise if early CVD disease caused a lowering of salt intake. The authors excluded people with any pre-existing CVD, and it made no substantive difference to findings. But, it would have been ideal to have even longer follow-up.
3. They used **spot urine measures** (and only a single measure) rather than the gold standard of 24-hour urines to measure sodium. There are still uncertainties with the utility of the spot urine measure (see this systematic review of 20 studies (17)). Nevertheless, any such measurement error would tend to weaken the association with sodium intake and health outcomes. Again, it would seem to take a very odd correlation of measurement error processes to generate a "U-shaped" association. Furthermore, the study found the expected relationship with salt and higher BP which

suggests that this is unlikely to be problematic (i.e., BP results can be seen as functioning as a sort of internal control on the validity of the study).
4. There was some dominance of Chinese subjects (42% of the total) – though there was adjustment for Asian vs non-Asian in the analyses.

There are also some limitations with generalising the findings from this study:

1. It is still **just one study** (albeit large and apparently well designed).
2. It is still **just an observational study**. A large RCT with an intervention to lower sodium intake would be scientifically superior.
3. There is **no obvious mechanism** for why low sodium intakes might be hazardous (given the very small amounts that are thought to be required for normal physiological functioning). Nevertheless, some other studies have also suggested this U-shaped relationship (see above) and many nutrients follow J-shaped relationships of both too little and too much being problematic for health (e.g., selenium, vitamin A, and total intake of dietary energy).

Our overall interpretation

The new O'Donnell et al study is large and appears to be fairly robust. As such it probably needs to be considered as a serious challenge to certain aspects of the current prevailing view around the level at which the intake of dietary salt impacts on health outcomes. While there is no doubt that very high salt intakes are hazardous – it is now somewhat uncertain if too little salt is also hazardous and what the threshold is before the hazard starts to appear (for both too little and too much).

This blog post should be treated as our preliminary perspective. This new study will probably generate much academic discussion and probing. We plan to update our perspective in the future (keep checking *Public Health Expert blog*).

What could be done now?

1. The World Health Organization (WHO) could establish a **high-level review panel** and clarify the state of the evidence and the future research agenda. Such a panel may have maximum credibility if it just had scientists with no past publications relating to dietary salt and health. If this is widely seen as the most efficient option – the NZ Government could request that WHO takes on this task.
2. Health authorities could just wait until a **large cluster-randomised trial** in China is completed (18) (it includes replacing some sodium chloride [NaCl] intake with potassium chloride [KCl]). But perhaps it will still not be clear if any benefit is due to the higher potassium or the lower sodium (or a mix of both).
3. Health authorities **could proceed with certain sodium reduction actions** that still have a high probability of being favourable. That is the reformulation of various high salt products to replace some of the NaCl with KCl in some other processed foods (as has already been happening for some foods in NZ e.g., some soup products). The evidence that increased dietary potassium is good for cardiovascular health is now fairly strong (e.g., these two meta-analyses (19, 20), as well as the O'Donnell et al study for lower risk of death and major cardiovascular events combined (12)). A recent meta-analysis of 5 RCTs using salt substitutes has also reported a benefit for reducing systolic and diastolic blood pressures (21). Furthermore – the health advice to eat more whole foods and to avoid a high intake of processed foods (usually high in all three of: salt, sugar and saturated fat) still stands. Indeed, a junk food tax (as

recently introduced by Mexico) could well be justified on numerous health grounds and not just on sodium levels.

Conclusion

The relationship between dietary salt and poorer health is still fairly certain for very high intakes – but given recent research findings there is less confidence about the associations for other levels of intake. Given this uncertainty there appears to be a reasonable case for a WHO-led expert review.

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