Letter to the Editor

Dissidents and dietary sodium: concerns about the commentary by O’Donnell et al.

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O’Donnell et al. claim that there are few individuals with extreme perspectives on both sides of the sodium controversy and that there are ‘few areas in public health that elicit more strident, polemic interpretations of the research literature’. Yet numerous independent health and scientific organizations have reviewed the totality of evidence and have reached very consistent recommendations to reduce dietary sodium. Further, mainstream health practitioners and scientists, including the World Health Organization, have strongly supported reductions in dietary sodium. In Canada, where O’Donnell and his co-authors have academic affiliations, 26 national health and scientific organizations endorsed a position to reduce dietary sodium to <2300 mg/day, the federal and provincial governments set a target to reduce dietary sodium to 2300 mg/day by the end of 2016 and leaders of organizations representing most health care professionals and about 70% of the Canadian population supported a regulatory approach to reducing dietary sodium: Hypertension Canada [http://www.hypertension.ca/images/pdf/Sodium_Fact_Sheet_2016_Final2.pdf], accessed 30 March 2016; and Consumer Science in the Public Interest [http://cspinet.org/canada/pdl/online.salty-to-a-fault.2013-update.pdf], accessed 30 March 2016. The Canadian Hypertension Education Program recommends considering reducing dietary sodium to 2000 mg/day to reduce blood pressure. High levels of support are seen in many other countries. World Action of Salt and Health, an organization of scientists and health professionals concerned about excess dietary sodium, has over 500 members from 95 countries [http://www.worldactiononsalt.com/about/], accessed 31 March 2016. There are similar local networks of concerned scientists in other areas of the world [ALASS, http://www.alass.net/], accessed 31 March 2016. Most national hypertension organizations and the World Hypertension League and the International Society of Hypertension support dietary sodium reduction. Consumers International (an umbrella organization of 240 national civil society organizations in 120 countries) supports reductions in dietary sodium as a key project [http://www.consumersinternational.org/our-work/food/key-projects/salt-reduction/], accessed 1 April 2016. I am not aware of any credible health, scientific or civil society organization that supports the views expressed in O’Donnell’s commentary or those of other dissenting scientists. The debate is generated by a small but highly vocal group of dissenting scientists advocating against mainstream science and public health.

Financial conflicts of interest can have a major impact on the interpretation of nutritional evidence. Several of the vocal dissenting scientists have had long-term associations with the food and/or salt industry, for example Integrity in Science [http://www.cspinet.org/integrity/], accessed 31 March 2016, search site under ‘sodium’). O’Donnell et al. do not indicate any potential conflicts of interest, but Drs Yusuf and Mente were on the organizing committee of a food policy meeting that raised funds from food companies where their own controversial research findings on dietary sodium were presented by Dr O’Donnell [http://www.nutritioncnd2014.com], accessed 25 July 2016. There was no public disclosure of how the food industry funds were dispersed. A recent Lancet article with Drs O’Donnell, Yusuf and Mente as co-authors also lists the Sugar Institute as a funder of their research, and they also have published manuscripts advocating against dietary sodium reduction while...
advocating for antihypertensive therapies in settings where Dr Yusuf holds one or more patents and has made multiple patent applications (United States Patent and Trademark Office, Patent number 736469 and application publication numbers 20110263619, 20100267798, 20090258919, 20080287403, 20080188538, 20080125472, 20080114046, 20070093541, 20070021491, 20060194868, 20050101658, 20050065203, 20040248968, 20040229934, 2004087645, 20030158223). These may represent potential conflicts of interest.

Rather than being cautious in advocating against a major public health policy, several dissenting scientists have conducted low-quality research, taken research out of context, made factual errors or misinterpreted results, altered scientific formulae/protocols in a fashion that makes their controversial research appear more robust and used low-quality evidence to trump higher quality. For example, Dr O’Donnell has recently claimed, based on the Prospective Urban Rural Epidemiology (PURE) study observational data, that there is a non-linear lowering of blood pressure with less blood pressure lowering at the lower levels of sodium intake, rather than using data from randomized controlled trials which show a linear relationship, see the Canadian Cardiovascular Society [https://eccs.eventkaddy.net/video_player], accessed 31 March 2015, and search the ‘The Great Salt Debate’. The PURE study assessed long-term sodium intake based on a single fasting morning spot urine sample, and the reported blood pressure data from the PURE study are markedly different from those of high-quality national surveys. A sub-study of the PURE study from China did not confirm the high correlation of the single morning fasting spot urine estimate of sodium intake to 24-h urine sodium that the main PURE study analysis reported [intraclass correlation (ICC) 0.71 vs 0.28 (Pearson Correlation r=-.19)] and plots from both studies showed up to 8000 mg/day differences between estimated 24-h urine sodium from spot samples and measured 24-h urine sodium.

Systematic analysis of the association of spot urine estimates of 24-h urine sodium to 24-h urine sodium showed marked variation with correlations as low as 0.19, yet publications with Drs O’Donnell, Yusuf and Mente as authors only mention high correlations. Mente et al. did not respond to a request to provide the correlation of independent spot urine samples to 24-h urine although the PURE study had these samples to evaluate. When recently challenged, Dr Mente claimed that the China validation used afternoon rather than morning sampling, whereas both the overall and the China subsample of PURE assessed morning fasting spot urine samples: World Congress of Cardiology 2016 [https://www.pathlms.com/world-heart-federation/events/532/video_presentations/31122], accessed 31 July 2016. Dr Mente also claimed that the PURE study did not use a spot urine sample but a fasting morning sample (a spot urine sample is defined as a spontaneously voided un timed urine sample and hence includes fasting morning samples). Regardless fasting morning urine samples suffer all the problems of inaccuracy and lack of reproducibility of other spot urine samples. The main validation study for PURE spot urine samples had substantive methodological issues including four errata, over 50% incomplete 24-h urine samples and an undisclosed change to the published formula that makes the study appear more robust. Dr O’Donnell has also claimed that there are no randomized controlled trials lasting longer than 6 months that showed reductions in blood pressure, see the Canadian Cardiovascular Society [https://eccs.eventkaddy.net/video_player], accessed 31 March 2016. There are several randomized controlled trials that have lasted over 6 months and show the predicted degree of blood pressure lowering with reduced dietary sodium.

Notwithstanding the scientific inadequacies repeatedly reported in appraisals and reviews of their studies, dissenters ignore the critique and do not strengthen their methods of investigation. Some dissenters have conducted underpowered sub-group or irrelevant analyses to conclude that there is little to no impact from sodium reduction or potential harm. For example, Graudal et al. conducted a meta-analysis examining the dose response to sodium reduction. The meta-analysis found no reduction in blood pressure in people with normal blood pressure and concluded that there was no dose response to sodium reduction. The analysis included only 83 people with normal blood pressure. Multiple independent meta-analyses of randomized controlled trials confirm that sodium reduction lowers blood pressure in people with normotension. Graudal et al. have also conducted a meta-analysis of the impact of sodium reduction on renin and aldosterone levels that is heavily weighted by short-term large reductions in dietary sodium. The study finding of increased renin and aldosterone levels were critiqued as irrelevant to public health due to the extensive short-term changes in dietary sodium. Nevertheless, Graudal updated the meta-analysis twice using the same approach. The largest of the meta-analyses of Graudal had an average reduction in dietary sodium of 3440 mg/day, and a median duration of 7 days in those with normal blood pressure. Meta-analysis of only longer-term studies show little impact on renin and aldosterone levels from sodium reduction, and the effect of sodium reduction on renin and aldosterone dissipates in studies lasting just over 1 month.
Other problems that have been observed in the research of dissenting scientists include lack of reproducibility of research results, inability to provide original data to explain duplicate findings in different trials, inaccuracies in data extraction and an analytical design of a meta-analysis that misclassified data.

O’Donnell et al. imply that a modest short-term ‘stimulation’ of the renin aldosterone axis (RAS) is a viable mechanism for long-term harm in current efforts to reduce dietary sodium. Apart from the fact that long-term gradual reductions in dietary sodium to current recommended levels have had little impact on activation of the RAS, newer biomedical research indicates that an activated RAS is mainly a risk at high sodium, not low sodium, intake. Finally, antihypertensive drugs that stimulate the RAS, including diuretics that act to reduce body sodium, have a similar cardiovascular benefit to those antihypertensive drugs that reduce the RAS in management of hypertension.

O’Donnell et al. also use a personal nomenclature to support their position that high levels of sodium intake are reasonable. They claim that a sodium intake of 2300 mg/day is ‘very low’, although it is 3-fold higher than would be in a diet that did not have any added sodium and that humans evolved on. An international health and sodium expert group supported by the World Hypertension League, World Action on Salt and Health and the Australian Division of World Action on Salt & Health have recommended a standardized nomenclature that would classify O’Donnell’s ‘moderate’ intake classification as ‘high’ to ‘very high’ and O’Donnell’s ‘very low’ intake as ‘high’ to ‘recommended’. The standardized nomenclature was based on diets that do not have added sodium and on current World Health Organization recommended sodium intakes.

Supporting the observation of Trinquart et al., others have noted that a large volume of studies on dietary sodium find an adverse impact of lowering dietary sodium or no impact, see CIHR HSF Chair in Hypertension Prevention and Control [http://www.hypertensiontalk.com/science-of-salt-weekly/], accessed 31 July 2016. However when quality filters are applied to exclude low-quality research, the studies nearly all support the health benefits of lowering dietary sodium. For example, in systematic reviews of the literature conducted between June 2013 and May 2015, there were 564 studies reviewed with 14 studies meeting quality criteria, all of which supported health benefits from reducing dietary sodium. There has been a widely supported call to develop minimum standards for the conduct of research on dietary sodium to address this problem. The World Health Organization and other groups have previously used various quality standards which have not been adopted by dissenting scientists.

O’Donnell’s commentary also advocated that individuals with publicly stated positions on dietary sodium not be involved in dietary sodium recommendation processes. The World Heart Federation, with Dr Yusuf as President, appointed a committee to review the evidence on dietary sodium and to make recommendations on intake levels. Apart from appointing Dr O’Donnell to the committee, who has a dissenting opinion on dietary sodium, the co-chair is a former consultant to the sodium industry and a past paid court witness for tobacco companies, see University of California [https://industrydocuments.library.ucsf.edu/tobacco/], accessed 31 March 2016, and Integrity in Science [http://www.cspinet.org/integrity/], accessed 31 March 2016, search site under ‘sodium’. Further, many scientists including myself have become advocates for sodium reduction following involvement in comprehensive systematic reviews of the evidence. In fact, Consensus Action on Salt and also Health and World Action on Salt and Health formed following the UK review on dietary sodium by panel members.

O’Donnell et al. confuse the concept of ‘no evidence of effect’ with that of ‘evidence of no effect’. They call for randomized controlled trials showing that a moderate reduction in sodium intake reduces cardiovascular outcomes before reducing dietary sodium. They claim that it is the usual standard for most strategies recommended for cardiovascular prevention. However, there are no randomized definitive ‘hard-outcome’ clinical trials to back up many public health policies such as increasing physical activity, preventing diabetes without drugs or reducing air pollution (just to mention a few). Furthermore, many considerations suggest that it would not be feasible to perform large-outcome clinical trials on many of these topics. In public health, incomplete evidence is the rule, not the exception. Yet, public health policies are implemented almost invariably based on the appraisal of the best available evidence. O’Donnell et al. claim that prospective studies report higher risk of cardiovascular events at low vs moderate intake of dietary sodium, but this is only true of reviews that incorporate lower-quality studies. Although not definitive, a meta-analysis of randomized controlled trials was consistent with decreasing dietary sodium reducing total cardiovascular events, as was the World Health Organization (WHO) sponsored meta-analysis of cohort studies that used criteria to exclude low-quality research. I am a strong proponent for more definitive high-quality clinical trials on dietary sodium, but I recognize the difficulties in conducting such trials and, like the mainstream scientific and public health communities, I support the need to act on the best available evidence for public benefit.
I encourage the journal to invite reviews on the research methodology for assessing dietary sodium and on the impact of conflicts of interest on dietary research. I also encourage Trinquart et al. to further investigate their findings by applying quality filters as were used in the WHO review and more recently updated.49 Further, I encourage an independent comprehensive systematic investigation of commercial conflicts of interest, low-quality science and the scientific conduct of those who oppose dietary sodium reduction. This letter is not a comprehensive review but represents some of my experiences which I believe indicate potentially serious non-scientific issues generating controversy on a major public health topic. Finally, there is no role for low-quality research, which has a strong potential to produce misleading findings. I encourage dissenting researchers to use well-established rigorous research methodologies.

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References