European Heart Journal (2022) **43**, 1756–1758
https://doi.org/10.1093/eurheartj/ehab888

**EDITORIAL**

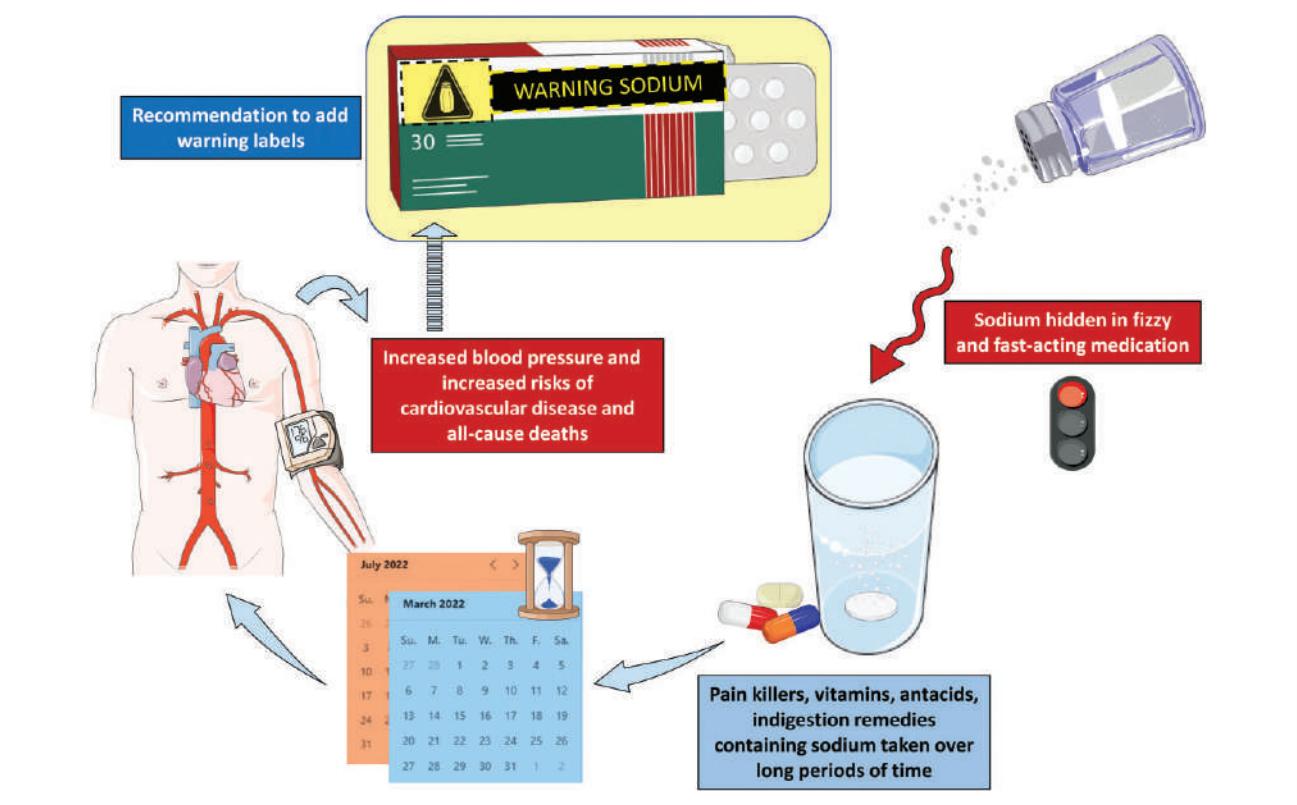
# The sodium hidden in medication: a tough pill to swallow

**Aletta E. Schutte** [1,2]* **and Bruce Neal** [2,3]

[1]School of Population Health, University of New South Wales, Sydney, Australia; [2]The George Institute for Global Health, Sydney, Australia; and [3]Department of Epidemiology and Biostatistics, Imperial College London, UK

*Online publish-ahead-of-print 25 February 2022*

**This editorial refers to 'Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension', by C. Zeng *et al.*, https://doi.org/10.1093/eurheartj/ehac059.**




**Graphical Abstract** Sodium hidden in medication warrants warning labels by drug companies.

For many years, epidemiological and clinical trial evidence inferring serious harmful effects of excess dietary sodium consumption on human health has accumulated.[1–4] In the 2017 report of the Global Burden of Disease study, excess intake of sodium was among the leading dietary risks and was estimated to cause 3 million deaths [95% confidence interval (CI) 1–5 million] and 82 million disability-adjusted life years (95% CI 34–118 million) around the world every year.[5]

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +61 450315918. Email: a.schutte@unsw.edu.au

© The Author(s) 2022. Published by Oxford University Press on behalf of European Society of Cardiology. All rights reserved.
For permissions, please e-mail: journals.permissions@oup.com

Downloaded from https://academic.oup.com/eurheartj/article/43/18/1756/6535540 by guest on 09 May 2022

Sodium balance in humans involves a complex interplay between kidney sodium transport, sodium storage in the skin, systemic adaptation of the vascular system, and neurohormonal signalling. Despite decades of research, the finer physiological details of sodium management still require further unravelling and understanding.[6] Nevertheless, the adverse consequences of excess sodium intake are now clear. Excessive sodium consumption is causally related to elevated blood pressure and an increased prevalence of hypertension.[7] A recent Cochrane review showed that a large dietary sodium reduction of 3160 mg per day (from 11.5 to 3.8 g of salt per day) reduced systolic blood pressure by 1.1 mmHg in non-hypertensive individuals and produced a more pronounced 5.7 mmHg reduction in people with hypertension.[1]

Although the effect of dietary sodium on cardiovascular risk has been debated, high quality prospective studies using gold standard multiple 24-h urine samples to assess exposure to dietary sodium have reported consistent positive dose–response relationships of sodium with cardiovascular risk.[4] In addition, a large, cluster randomized trial showed that persons who received a potassium-containing salt substitute with 25% less sodium chloride not only had lower blood pressure but also had lower rates of stroke, major cardiovascular events, and all-cause deaths.[3]

Based on this evidence, multiple national and international blood pressure guidelines, as well as the World Health Organization, recommend that daily sodium intake should not exceed 2000 mg (~1 teaspoon of salt). In turn, many governnment and non-governmental organizations, and cardiac and hypertension societies advocate strongly for actions to reduce population sodium intake. Numerous governments have implemented interventions targeting public education, front-of-pack labelling on foods, promotion of salt substitutes, improved food procurement policies, and industry reformulation of packaged and restaurant foods.[8]

The study by Zeng and colleagues[9] in this issue of the *European Heart Journal* adds further to the case for dietary sodium reduction. Using an electronic medical record database with records of ~17 million patients cared for by general practitioners in the UK, the authors carried out a highly innovative investigation of the effects of supplementing dietary sodium. The analyses compared the risks of incident cardiovascular disease and all-cause deaths among persons who initiated sodium-containing paracetamol (also called acetaminophen) with the corresponding risks among initiators of the same paracetamol formulations without sodium. The study included individuals with ($n = 151\,398$) and without hypertension ($n = 147\,299$), which is important because there are known greater effects of sodium on blood pressure in persons with hypertension compared with those without. The findings were highly consistent across the two cohorts, with use of sodium-containing paracetamol associated with increased proportional risks of cardiovascular disease and all-cause deaths irrespective of hypertension status. The hazard ratio (HR) was 1.59 (95% CI 1.32–1.92) in those with hypertension and 1.45 (95% CI 1.18–1.79) in those without hypertension. There were also consistently increased risks across different cardiovascular outcomes including myocardial infarction, stroke, and heart failure, that were also obsered in both those with and those without hypertension.

The results are compelling. The effects were consistent across several different methodological approaches and in a series of sensitivity analyses. Effervescent and soluble forms of paracetamol is not the only example of a medication that can be delivered with very different levels of sodium content and, while there were smaller numbers of persons starting sodium-containing ibuprofen or sodium-containing ranitidine, the high-sodium versions were also associated with higher risks of both cardiovascular disease and mortality.

The quantity of sodium in the formulations studied by Zeng *et al.*[9] is an important strength of the anlayses, with effervescent and soluble formulations of paracetamol containing 390–440 mg of sodium per tablet. This equates to >3000 mg of additional sodium per day for a full dose paracetamol regimen, which is far above the daily recommended maximum sodium intake for an adult.[13] Large increments would also be anticipated for other types of effervescent medications, with a single 5 g sachet of effervescent antacids containing ~850 mg of sodium, fizzy vitamins ~280 mg of sodium per tablet, and urinary alkalinizers some 644 mg of sodium per dose.[12] The large doses of sodium studied in these analyses provided for a robust test of the effects on blood pressure and cardiovascular outcomes. There was also a dose–response relationship, with a greater number of sodium-containing paracetamol prescriptions associated with progressively greater risks of cardiovascular disease ($P = 0.034$) and mortality ($P < 0.001$) for both individuals with hypertension and those without. The clear association of sodium-containing paracetamol with incident hypertension (HR 1.37, 95% CI 1.22–1.54), which lies on the causal pathway between sodium consumption and disease risk, is another piece of evidence that supports the likely validity of the main findings.

At the same time, these findings should be interpreted in light of their potential limitations. This was not a randomized trial, but an observational study, and confounding cannot be excluded. Baseline imbalances between the intervention and control groups were relatively small, probably because both arms of the study included the same active compound. However, there were probably specific reasons why individuals received effervescent compared with standard formulation paracetamol, and these reasons may have been assoociated with the risk of the clinical outcomes studied. The authors report extensive efforts to control for potential confounding, and there were significant, and broadly constant, adverse effects associated with the sodium-containing forms of paracetamol across all analyses reported. The multiple approaches used for imputation of missing values—for missing data about paracetamol use, or to account for potential confounders—have different strengths and weaknesses, but none raised substantive concerns about the likely validity of the main conclusions.

The study had a short follow-up period of only 1 year. The effects of sodium on blood pressure, and of blood pressure on cardiovascular risk are, however, known to be rapid and to accrue fully within weeks or a few months. As such, it seems unlikely that the abbreviated follow-up period will have resulted in systematic over- or underestimation of the association between sodium-containing medications and risk.

The direct message from this study is clear—there are likely to be millions of people worldwide taking paracetamol on a daily basis in a 'fast-acting' effervescent or soluble formulation who are increasing their risks of cardiovascular disease and premature death.

Downloaded from https://academic.oup.com/eurheartj/article/43/18/1756/6535540 by guest on 09 May 2022

In the UK alone, in 2014 there were some 42 million paracetamol-containing medicines prescribed, with a further 200 million packs sold over the counter.[10] This equates to ~6300 tons of paracetamol sold each year in the UK with the figure for France close to 10 000 tons. Fortunately, only a small proportion of paracetamol formulations contain sodium but, with 'fast-acting' and 'fizzy' medications increasing in popularity, the adverse effects of medication-related sodium intake look set to rise rather than fall. There are also many more effervescent, dispersible, and soluble medications and vitamin pills that contain large quantities of hidden sodium. A study done in 2018 in France found that 27% of a general population sample who underwent medical check-ups had consumed 'fizzy' tablets in the past 30 days.[11] Nine in 10 of these were instances of self-medication, with paracetamol, aspirin, vitamins, and betaine accounting for 95% of tablets used.[11]

There is also an important indirect conclusion from this study regarding the evidence for sodium-related harms. Large-scale supplementation of dietary sodium in a randomized trial studying cardiovascualr outcomes has never been done and would almost certainly be viewed as unethical. This type of analysis is as close as researchers are ever likely to come to doing that trial, and, while the current report is observational in nature, it provides strong evidence of harmful effects of adding large quantities of sodium to the diet. The present findings are highly aligned with previous similar papers, most notably a report done in 2013 by George and colleagues.[14] In an anlaysis of 1.3 million patients over a period of 7.2 years that included 61 000 patients with an incident cardiovascular event and matched controls, they reported odds ratios for cardiovascular events consistent with those reported here. There was also in the report an odds ratio of 7.18 (95% CI 6.74–7.65) for hypertension in individuals exposed to sodium-containing drugs.[14]

Zeng and colleagues conclude that it would be best if 'individuals avoid unnecessary excessive sodium intake through sodium-containing acetaminophen use'.[9] George and colleagues concluded almost a decade earlier that 'sodium-containing formulations should be prescribed with caution only if the perceived benefits outweigh these risks'.[14] The weight of the evidence makes ongoing inaction on sodium-containing medications untenable. The widespread use of effervescent medication in the general population,[11] and the enormous doses of sodium that can be consumed inadvertently by unsuspecting consumers requires urgent action. Particularly concerning is the observation in some surveys that up to 94% of uses of fizzy medications are self-medication using over-the-counter preparations.[10] There is an immediate need for protection of consumers against these risks. The most plausible and effective strategy is likely to be the mandatory labelling of all medications containing significant quantities of sodium with a front-of-pack warning label (*Graphical Abstract*). Information programmes that raise public and practitioner awareness of the hidden sodium in medications, and educate about the need to avoid effervescent, dispersible, and soluble medicines in all but essential circumstance should also be considered.

## Acknowledgements

The authors used Servier Medical Art for the development of the Graphical Abstract.

**Conflict of interest:** none declared.

## References

1. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database Syst Rev* 2020;(12):CD004022.
2. O'Donnell M, Mente A, Alderman MH, Brady AJB, Diaz R, Gupta R, *et al.* Salt and cardiovascular disease: insufficient evidence to recommend low sodium intake. *Eur Heart J* 2020;**41**:3363–3373.
3. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, *et al.* Effect of salt substitution on cardiovascular events and death. *N Engl J Med* 2021;**385**:1067–1077.
4. Ma Y, He FJ, Sun Q, Yuan C, Kieneker LM, Curhan GC, *et al.* 24-Hour urinary sodium and potassium excretion and cardiovascular risk. *N Engl J Med* 2021;doi: 10.1056/NEJMoa2109794.
5. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2019;**393**:1958–1972.
6. Ellison DH, Welling P. Insights into salt handling and blood pressure. *N Engl J Med* 2021;**385**:1981–1993.
7. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, *et al.* Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. *BMJ* 1996;**312**:1249–1253.
8. World Health Organization. *SHAKE the Salt Habit. The SHAKE Technical Package for Salt Reduction.* Geneva, Switzerland: WHO; 2016.
9. Zeng C, Rosenberg L, Li X, Djousse L, Wei J, Lei G, *et al.* Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension. *Eur Heart J* 2022;**43**:1743–1755.
10. Moore RA, Moore N. Paracetamol and pain: the kiloton problem. *Eur J Hosp Pharm* 2016;**23**:187–188.
11. Perrin G, Berdot S, Thomas F, Pannier B, Danchin N, Durieux P, *et al.* Evaluation of exposure to effervescent drugs in a large health check-up population in France: a cross-sectional study. *BMJ Open* 2018;**8**:e022368.
12. Saxelby C. *The hidden sources of sodium in medicines and additives.* https://foodwatch.com.au/blog/additives-and-labels/item/the-hidden-sources-of-sodium-in-medicines-and-additives.html (23 November 2021).
13. UK Medicines Information. *What is the sodium content of medicines?* https://www.sps.nhs.uk/articles/about-ukmi-medicines-qas/ (18 May 2018).
14. George J, Majeed W, Mackenzie IS, MacDonald TM, Wei L. Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study. *BMJ* 2013;**347**:f6954.

Downloaded from https://academic.oup.com/eurheartj/article/43/18/1756/6535540 by guest on 09 May 2022