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## Supplementary information

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# The impact of excessive salt intake on human health

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**Supplementary table 1 | Selected large observational studies that have evaluated the association between sodium intake and CVD or mortality**

| Study                               | Population (follow-up)                                                                                                     | Method for estimating Na intake*         | Outcomes                                                                                     | Confounders                                                                                                                                                                                            | Observation                                                                                                                                                                   | Refs           |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| PURE                                | General population aged 35–70 years; ~100,000 participants (~3.5 years)                                                    | Spot urine samples (Kawasaki formula)    | Composite of all-cause mortality and CVD (CV death, MI, stroke, HF) by questionnaire         | Age, sex, educational level, ethnicity, EtOH, DM, BMI, CVS Hx, smoking, lipids                                                                                                                         | J-shaped association with nadir at Na intake 4–6 g (~170–260 mmol; 10–13 g NaCl) per day                                                                                      | <sup>1,2</sup> |
| PURE, EPIDREAM, ONTARGET, TRANSCEND | General population and patients with HTN, median age 55 years; ~130,000 participants, 48% had HTN (~4.2 years)             | Spot urine samples (Kawasaki formula)    | Composite of CVD (death, MI, stroke, HF)                                                     | Age, sex, ethnicity, BMI, smoking, diabetes, education, EtOH, physical activity, CVD, treatment assignment**                                                                                           | Increased risk in all participants with Na intake <4 g (~170 mmol; 10 g NaCl) per day; increased risk in patients with HTN with Na intake >6 g (~255 mmol; 15 g NaCl) per day | <sup>3</sup>   |
| TOHP                                | “Pre-hypertensive”; ~2200 participants aged 30–54 years in USA with high-normal blood pressure (5–10 years)                | Median of five 24-hour urine collections | Incident CVD (CV death, MI, stroke, CABG, PCI) by questionnaire                              | Age, sex, ethnicity, treatment assignment ** (+/- education, weight, EtOH, smoking, exercise, K excretion, family history of CVD)                                                                      | Continuous positive association                                                                                                                                               | <sup>4</sup>   |
| UK Biobank                          | Healthy general population aged 40–69 years; ~350,000 participants in UK (~6 years)                                        | Spot urine samples (INTERSALT formula)   | Incident CVD (CAD, stroke, HF) and all-cause mortality by linkage to national health records | Age, sex, deprivation index, K excretion, blood pressure***, smoking status, EtOH, BMI, sedentary behaviour, ethnicity, body mass, family history of CVD, rheumatoid arthritis, AF, co-morbidity score | No association with CV disease in the main analysis; positive association when not adjusted for BMI; J-shaped association with all-cause mortality                            | <sup>5</sup>   |
|                                     |                                                                                                                            | Spot urine samples (Kawasaki formula)    |                                                                                              |                                                                                                                                                                                                        | No association even when not adjusted for blood pressure                                                                                                                      | <sup>6**</sup> |
|                                     |                                                                                                                            | Urine Na:K ratio                         |                                                                                              |                                                                                                                                                                                                        | Inverse association with stroke and CAD that tended to null when blood pressure was not included as a covariate                                                               | <sup>7**</sup> |
| 24-hour urine study meta-analysis   | Meta-analysis of six prospective cohorts of ~10,000 healthy adults (including the TOHP study also listed separately above) | At least two 24-hour urine collections   | Cardiovascular event (CABG, PCI, MI, stroke)                                                 | Age, sex, race, education, height, BMI, smoking, EtOH, physical activity, DM, cholesterol, family history, 24-hour urinary potassium excretion                                                         | Continuous positive association                                                                                                                                               | <sup>8</sup>   |

\* The use of spot urine samples to estimate sodium intake has been widely criticised (**Box 2**). \*\* Part of interventional trial but analysis restricted to observation in subjects not allocated to intervention in dietary sodium; \*\*\* Blood pressure was included as a covariate in the main analysis by two of the Biobank studies<sup>6,7</sup>, both of which conducted sensitivity analyses in which models were not adjusted for blood pressure. **Abbreviations:** CVD, cardiovascular disease; MI, myocardial infarction; HF, heart failure; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; EtOH, alcohol; DM, diabetes mellitus; BMI, body mass index; CVS, cardiovascular system; AF, atrial fibrillation; CAD, coronary artery disease.

## Supplementary table 2 | Summary of society guidelines on dietary salt restriction

| Guideline (date)           | Recommendation                                                                               | Benefits                                                                                                                        | Strength of recommendation                                        | Refs  |
|----------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|-------|
| <b>General population</b>  |                                                                                              |                                                                                                                                 |                                                                   |       |
| WHO (2012)                 | Restrict to <5 g NaCl (85 mmol) per day                                                      | Reduction in blood pressure (mean 3.4/1.5 mmHg); greater benefit in patients with hypertension                                  | Strong                                                            | 9     |
| NAS (2019)                 | Restrict if >5.85 g NaCl (100 mmol) per day; adequate intake is 3.8 g NaCl (65 mmol) per day | Reductions in blood pressure, risk of hypertension and incidence of composite CVD outcome                                       | Strong effects on blood pressure; weak-to-moderate effects on CVD | 10,11 |
| <b>Hypertension</b>        |                                                                                              |                                                                                                                                 |                                                                   |       |
| NICE (2019)                | Restrict (no threshold stated)                                                               | Reduction in blood pressure                                                                                                     | Strong                                                            | 12    |
| ESC (2018)                 | Restrict to <5 g NaCl per day                                                                | Reduction in blood pressure                                                                                                     | Strong                                                            | 13    |
| <b>Hypertension in CKD</b> |                                                                                              |                                                                                                                                 |                                                                   |       |
| KDIGO (2021)               | Restrict to <5 g NaCl per day                                                                | Reduction in blood pressure in patients with CKD; reduction in blood pressure and albuminuria in patients taking ACE inhibitors | Weak                                                              | 14    |
| <b>Heart failure</b>       |                                                                                              |                                                                                                                                 |                                                                   |       |
| ESC (2016)                 | Avoid excessive salt intake (>6 g NaCl (102 mmol) per day)                                   | Not stated                                                                                                                      | Ungraded                                                          | 15,16 |
| AHA (2013)                 | Restrict (no threshold stated) in symptomatic patients                                       | Not stated                                                                                                                      | Weak                                                              | 17    |
| <b>Cirrhosis</b>           |                                                                                              |                                                                                                                                 |                                                                   |       |
| EASL (2018)                | Restrict to 4.6–6.9 g NaCl (80–120 mmol) per day in patients with moderate ascites           | Resolution of ascites (not adequately quantified)                                                                               | Strong*                                                           | 18    |

Guidelines restricted to advice for the non-pregnant, adult population. \*Strength of recommendation graded as strong by EASL but the studies cited are small and do not report any benefit of sodium restriction relative to a control group so in our opinion the level of evidence is weak. For all of these guidelines, the strength of recommendations was assessed using GRADE criteria<sup>19</sup>. These take into account the balance between desirable and undesirable effects of an intervention, the quality of the evidence, the values and preferences of stakeholders and cost. **Abbreviations:** WHO, World Health Organisation; NAS, United States National Academies Dietary Reference Intakes for Sodium and Potassium; NICE, UK National Institute for Clinical Excellence; ESC, European Society of Cardiology; KDIGO, Kidney Disease Improving Global Outcomes; AHA, American Heart Association; EASL, European Association for the Study of the Liver; CKD, chronic kidney disease; ACE, angiotensin converting enzyme; CVD, cardiovascular disease.

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