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Sodium, chloride and cardiovascular mortality – Open access data is worth its salt

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The pernicious role of increased sodium intake in cardiovascular disease, particularly in hypertension and heart failure, is well appreciated. Hyponatremia has also long been recognized as a negative prognostic factor following decompensated heart failure[1] and more recently has also been shown to be predictive of increased mortality in the general population[2]. Interestingly, sodium's constant traveling companion chloride has historically been viewed more as an anodyne escort, and therefore has largely been exempt from rigorous study. However, chloride is the major anion in the extracelullar water space with homeostatic significance in maintaining proper body water distribution, osmotic pressure, and normal electrolyte balance. Perturbations in chloride have been observed with overhydration, congestive heart failure, as well as renal, endocrine and metabolic disorders. Emphasizing chloride's putative potential as a prognostic variable, several heart failure studies have now demonstrated a strong association between hypochloraemia and adverse outcomes, independently of hyponatremia[3, 4]. The next logical question is whether hypochloraemia is predictive of adverse outcomes in a more general population.

In this issue of the Journal, He and colleagues[5] examine and answer this question. Their study population consisted of 16,483 participants from the Unites States nationally representative National Health and Nutrition Examination Survey (NHANES). This is a program of studies designed to assess the health and nutritional status of American adults and children sponsored by the Centers for Disease Control and Prevention. This unique data source includes in-home personal interviews exploring demographic, socioeconomic, dietary, and health-related questions. In addition, physical examination results performed in mobile examination centers, as well as laboratory measurements of serum electrolytes, creatinine, protein, and lipids are available. NHANES used a multistage probability sampling design with oversampling of some subgroups to increase both reliability and precision for these groups. Ultimately this sample is meant to be reflective of the entire US population. The baseline data including blood samples come from surveys conducted between 1988 and 1994. The NHANES data set also includes information of the long-term mortality status of participants, ascertained through probabilistic record matching with the National Death Index, a centralized database of all U.S. This valuable data source of well phenotyped individuals with validated mortality data is available online for public download. Details on how to obtain the data are available in a supplemental file to the current publication.

Using this data, He and colleagues[5] assessed the long-term associations of serum sodium and chloride, as continuous variables, and cardiovascular mortality using weighted Cox proportional hazards models. Although they do not describe the actual process for their model selection, their choice of potential confounders seems intuitively appropriate. Specifically, the models were adjusted for multiple potential confounders including age, gender, race-ethnicity, education, income, smoking, body mass index, heart failure, myocardial infarction, stroke, diabetes, hypertension, hypercholesterolemia, estimated glomerular filtration rate category, malignancy, and diuretic use. Moreover, they have included several interaction terms and investigated possible non-linear associations with restrictive cubic splines and appropriately verified the assumptions underlying the models. Of course, as with all observational studies, possible unmeasured and residual confounding may influence any observed relationships and

such additional uncertainty is not contained by the 95% confidence intervals [CI], which capture only the sampling uncertainty.

Given the relatively large number of events, He and colleagues[5] have been able to provide reasonably precise estimates for the relationships between the independent predictors and cardiovascular mortality. In the fully-adjusted model, they observed an association of low serum sodium and cardiovascular mortality risk (HR, 1.10 per 2.4 mmol/L decrease; 95% CI, 1.02-1.18) but no association with serum chloride (HR, 1.04 per 3.3 mmol/L decrease; 95% CI, 0.97-1.12; p=0.278). The inverse association between mortality and sodium was present even after excluding the small minority of the sample with heart failure where, as mentioned above, this relationship has already been established. The authors report possible interactions between serum sodium and a history of malignancy, and between serum chloride and history of diabetes but the small magnitude of these interactions and the possibility of type 1 errors calls into question both the clinical and statistical significance of these observations. While a previous study of a general population had reported a statistically significant inverse association between chloride and mortality, He and colleagues[5] correctly point out that with 10 times more events their results are likely more robust.

Interestingly, He and colleagues[5] do not mention another study using the same NHANES dataset, but with a shorter follow-up time, that also found a similar association between hyponatremia with mortality[2]. Nevertheless, the present study is clinically important for 1) providing a replication of these earlier results with an extended follow-up time and 2) for its additional investigation into the relationship between chloride levels and mortality. Previous studies[6, 7] have suggested that NHANES sodium observations are applicable to a Canadian population suggesting good generalizability of these results to a Canadian context.

Apart from the clinical importance of the current study, it also serves to demonstrate the benefits that arise from open data and secondary data analyses. There exist many online resources that allow access to literally thousands of datasets, tools, and applications related to health and health care. For example, the US government site (https://www.healthdata.gov), offers completely open access to over 1900 health related datasets with a stated goal “to making high value health data more accessible to entrepreneurs, researchers, and policy makers in the hopes of better health outcomes for all”. NHLBI also offers data access to many of their sponsored trials, including for example, the recently added Surgical Treatment for Ischemic Heart Failure (STICH) dataset (https://biolincc.nhlbi.nih.gov/studies/stich/?q=STICH). Access to these clinical datasets does require submission of a brief protocol and agreement to protect the confidentiality of the data. However, this online process that nominally seeks to control quality is not onerous for individual researchers seeking data access. Other governments, including Canada (https://open.canada.ca/data/en/dataset?q=health) and the United Kingdom (https://data.gov.uk/data/search?theme-primary=Health) also have made their health data available.

The useful exploitation of these large and diverse data sets revolves around the triad of exploration, prediction, and inference, the central three axes or tenets of data science. Of

course, asking appropriate questions and sensibly interpreting the data can only be accomplished by the integration of these inferential and computational tools with clinical expertise. As demonstrated in He and colleagues' article[5], open data combined with data science techniques are able to provide new research findings in a cost-efficient manner by maximizing the use of existing resources. It is consequently easy to understand the movement by several peer reviewed funding agencies to encourage researchers to allow open access to publicly funded research data. In an era of limited funding, this new road map will likely be of increasing interest for clinical researchers.

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