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CORRESPONDENCE

Meta-analytic research of the dose-response relationship between salt intake and risk of heart failure

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There is a growing epidemic of heart failure (HF) worldwide. Hypertension and coronary heart disease (CHD) are major contributors to HF [1]. Increased salt intake is associated with a rise in blood pressure [2], and the risk of CHD-related mortality is well known [3]. The risk of HF is believed to be reduced with restricted salt intake. However, some data contradict this belief. We explored the dose-response relationship between salt intake and HF risk using a meta-analytic approach.

The study protocol was registered in the international prospective register of systematic reviews (PROSPERO) (ID: CRD42020163680). Using MEDLINE and EMBASE (from 1950 Jan. 1 to 2019 Sep. 30), we searched for cohort studies of HF risk related to salt intake. Studies had to assess salt intake using 24-h urine Na excretion (UNa) by collection of 24-h urine specimens or validated estimation from spot urine samples and show data on the number of participants at baseline and HF events for participants classified by UNa. A 1 g/day UNa corresponds to 2.5 g/day of salt intake [4]. Studies evaluating salt intake using dietary assessments (e.g., food frequency questionnaire or 24-h dietary recall) were excluded because self-reported salt intake has been critically underestimated compared with actual intake [5]. Since this research focuses on primary prevention of HF, we also excluded studies targeting patients with existing HF. Search keywords consisted of the following elements: UNa, HF, incidence, and cohort study (Supplementary Table 1). Of 351 studies retrieved, 6 were eligible (Supplementary Fig. 1). Supplementary Table 2 shows the characteristics of these 6 studies. One cohort study [6] combined participants with and without a past history of HF. We contacted the author and obtained data on the number of HF events in each UNa category after excluding participants with HF history. The numbers of participants and HF events were 477469 and 3562, respectively (Supplementary Fig. 1, Supplementary Table 2).

To standardize methods for categorizing participants into groups according to UNa, the referent group was defined wherein the mean, median or midpoint of UNa was between 3 and 4 g/day. Risk groups were defined by other values. We plotted the representative value of UNa against its corresponding relative risk (RR) for HF. A restricted cubic spline regression was applied to the semilogarithmic scatter plot, with the inverse of the standard deviation used as a statistical weight and UNa from 3 to 4 g/day as the referent. Supplementary Table 3 provides additional explanations of the statistical methods. All analyses were calculated by STATA 16 statistical software (STATA Corp., College Station, TX, USA). A two-sided $P < 0.05$ was considered statistically significant.

A reverse J-shaped association was observed between the UNa and natural logarithm of RR for HF (Fig. 1). Goodness of fit was borderline significant ($R = 0.48$, $P = 0.047$). The cubic regression model was significantly superior to the linear model ($P = 0.01$). In the UNa range <2 g/day, the HF risk (95% confidence interval (CI)) for 1 g/day UNa reduction (corresponding to 2.5 g/day salt intake) [4] was 1.49 (1.10–2.04). However, for UNa >8 g/day, HF risk for a 1 g/day increase in UNa was nonsignificant (RR (95% CI), 1.03 (0.90–1.19)). The World Health Organization (WHO) recommends a salt intake of ≤5 g/day (i.e., ≤2 g/day of UNa) for cardiovascular health [7]. The predicted RR (95% CI) of

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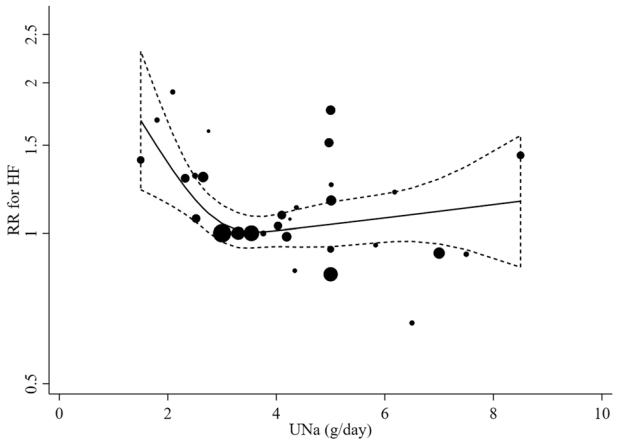

Fig. 1 Cubic regression curve explaining the relationship between 24-h urine Na excretion (UNa) and relative risk (RR) for incident HF in a semilogarithmic scatter plot. Knots in this curve are at 3.0 g/day and 4.0 g/day of UNa. The area of each black circle shows its statistical weight (inverse of the standard deviation). The RR for HF was adjusted for UNa in the reference group of each study

HF for 2 g/day UNa vs. 3-4 g/day UNa was 1.38 (1.15–1.66).

This meta-regression analysis indicated that low rather than high salt intake was associated with an elevated risk of HF. The risk was significant even at the level recommended by the WHO, suggesting that excessive restriction of salt intake is not recommended for the prevention of HF. A plausible explanation is that low salt intake activates the renin-angiotensin aldosterone system, which increases ventricular preload and postload. This was suggested by a previous meta-analysis showing that a sodium-restricted diet elevated plasma renin, aldosterone, and catecholamines [8]. Another explanation is that impaired Na excretion itself rather than low sodium intake was associated with increased HF risk, which is supported by the finding that renal sodium avidity is enhanced not only in HF patients but also in patients before clinical signs of HF due to intrinsic renal rearrangements such as a reduced number of nephrons, intrarenal hemodynamic alterations, and tubular hypertrophy [9]. This suggests that adherence to a salt-restricted diet is critical for such salt-sensitive patients, although they may represent a minority of patients, and this advice is opposite to suggesting that restricting salt intake is not recommended.

Several limitations can be addressed. First, the UNa covered by this research ranged from 1.5 g/day to 8.5 g/day. The HF risk for extremely low, and high salt intake could not be confirmed. Second, as indicated in Supplementary Table 2, the characteristics of the study population and incident rates of HF were heterogeneous among studies. Pooling studies with a wide spectrum of characteristics potentially leads to an imprecise conclusion. Third, spot urine sampling instead of 24-h urine collection to estimate UNa, used in all but one study (see Supplementary Table 2), is potentially inaccurate, although the formula (i.e., Kawasaki and Tanaka) revealed a high intraclass correlation coefficient between estimated and measured UNa [10]. Moreover, even if the UNa had been correctly estimated, a single measurement of spot urine might not be reliable because salt intake differs daily. Fourth, as with all observational studies and their meta-analyses, confounding and reverse causality could potentially explain at least a part of the observed risk associated with exposures. In fact, we had to calculate crude RRs instead of using adjusted RRs because it was impossible to standardize study-specific confounders. In addition, reverse causality could not be ruled out. For example, individuals had restricted salt intake because they possessed multiple risk factors for HF at baseline, and these risk factors contributed to HF during follow-up.

Despite these limitations, the current meta-analytic research indicates that low salt intake (<5 g/day), as recommended by general guidelines such as those from the WHO, may elevate the risk of HF. This suggests that the optimal level of salt intake should be reconsidered for preventing HF.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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