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A methodological look at the controversy about the influence of salt intake on cardiovascular risk

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Cardiovascular diseases are a major cause of premature death and disability. They represent an extraordinarily strong financial burden upon health-care systems in "developed" countries. Elevated blood pressure is a major cause of cardiovascular disease. There is much evidence that cardiovascular risk increases from normal blood pressure (i.e., from 115/75 mmHg upwards) [1]. Overwhelming evidence shows that reducing salt intake from 9–12 g/day to 5–6 g/day lowers blood pressure [2]. Blood pressure is a surrogate endpoint, but may be related to a reduction of morbidity and mortality due to cardiovascular causes. Thus, intensive support and encouragement to cut down on the intake of salt in foods might reduce cardiovascular risk. Such a primary prevention strategy might significantly reduce social and health-care costs. The meta-analysis published simultaneously by Taylor et al. [3, 4] in the *Cochrane Database of Systematic Reviews* and the *American Journal of Hypertension* deals with this important issue. Specifically, it assesses the long-term effects of interventions aimed at reducing dietary salt upon morbidity and mortality due to cardiovascular causes. They found 7 studies (involving 6,489 participants) that met the inclusion criteria. Three of the seven studies focused on normotensive subjects; two on hypertensives; one in a mixed population of normotensives and hypertensives; and one in subjects with heart failure ($n = 232$). Despite the large number of collated cardiovascular events (665 deaths in 6,250 participants), the meta-analyses fails to show significant differences in intervention groups compared with controls. There is only limited evidence that dietary advice to reduce salt intake may increase the prevalence of deaths in people with heart failure [relative risk at the end of the trial: 2.59; 95 % confidence interval (CI), 1.04–6.44; 21 deaths]. The authors conclude that there is insufficient power to exclude the clinically important effects of reduced dietary salt on mortality or cardiovascular morbidity in normotensive or hypertensive populations. Moreover, they state that further evidences from randomized controlled trials would be needed to confirm if the restriction of dietary sodium is harmful for people with heart failure.

In a recent comment, two preventive-medicine experts, Dr. He and Professor MacGregor [5], criticize the meta-analysis published by Taylor et al. [3, 4]. In their opinion, meta-analysis "reflects poorly on the reputation of the Cochrane Library and the authors". The two experts make statements regarding the fact that one trial in heart failure did not have to be included in the meta-analysis; they claimed that the trial was clinically heterogeneous. Indeed, patients who had been included in that trial were severely depleted of salt and water due to aggressive diuretic therapy. Moreover, the experts re-analyzed the data by combining together the results for hypertensive and normotensive subjects. Their results show a significant reduction in cardiovascular events by 20 % (pooled relative risk: 0.80; 95 % CI, 0.64–0.99). The meta-analysis was undertaken using the fixed-effect model because the heterogeneity among studies did not reach the standard probability value for significance. However, this could be the case of "not practicing what you preach". Despite accepting statistical homogeneity according to Cochrane's Q test ($p = 0.36$) and the low value of the I^2 index (only 6 % diversity among trials was detected), pooling data from two populations (hypertensives and normotensives)

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can be considered inappropriate or an artifact to more readily demonstrable risk differences by increasing the size of the pooled sample. We believe that conclusions about the influence of salt intake upon cardiovascular risk in hypertensives and normotensives must be supported by meta-analyses in different subgroups. Nevertheless, if data from these two populations must be pooled together, then the random-effect model is appropriate because clinical heterogeneity should be assumed. We re-analyzed the data using the random-effect model (Fig. 1). In this case, differences were not statistically significant (pooled relative risk: 0.80; 95 % CI, 0.63–1.03; $p = 0.0578$). Thus, what is heterogeneity and how should one evaluate it? The literature has highlighted heterogeneity as an important construct since the origins of evidence-based medicine in the early 1990s [6]. Heterogeneity can be defined as "any kind of variability among studies in a systematic review" [7]. Heterogeneity can be associated with any of the classic four factors (population, intervention, comparator and outcomes), even if the timing of the measurement of outcomes as well as the health-care setting must also be considered. Clinical heterogeneity is present if patient-level factors—most common variables related to patient characteristics, location and severity of disease, comorbidities, and accompanying treatment—influence or modify the magnitude of the treatment effect. Heterogeneity is also related to statistical and methodological aspects. In particular, statistical heterogeneity can be defined as the variability in the observed treatment effects beyond what would be expected by random error (chance). It is assessed by testing the null hypothesis that the studies have a common treatment effect given a chosen P value. Statistical heterogeneity may signal clinical heterogeneity, methodological heterogeneity, or chance. If statistical heterogeneity is detected, one cannot be sure whether to attribute it to clinical heterogeneity, methodological heterogeneity, chance, or a combination of the three variables [8]. If significant statistical heterogeneity is not detected by different methods (i.e., Cochrane's Q test, I^2 index, meta-regression), clinical heterogeneity can be present. Thus, an overall test of heterogeneity may be not significant, but a dimension of the study populations may vary significantly among studies, and influence the study findings. Such an analysis of population variation may also dictate: the choice of the statistical model in meta-analyses (random or fixed-effect models); employment of sensitivity analyses to determine the degree and impact of the variation on the pooled estimate; subgrouping of studies to estimate separate pooled estimates; a decision to forego any meta-analysis that pools data inferentially across studies [9]. Unfortunately, this is true in our case: hypertensives and normotensives are different populations. Thus, the findings

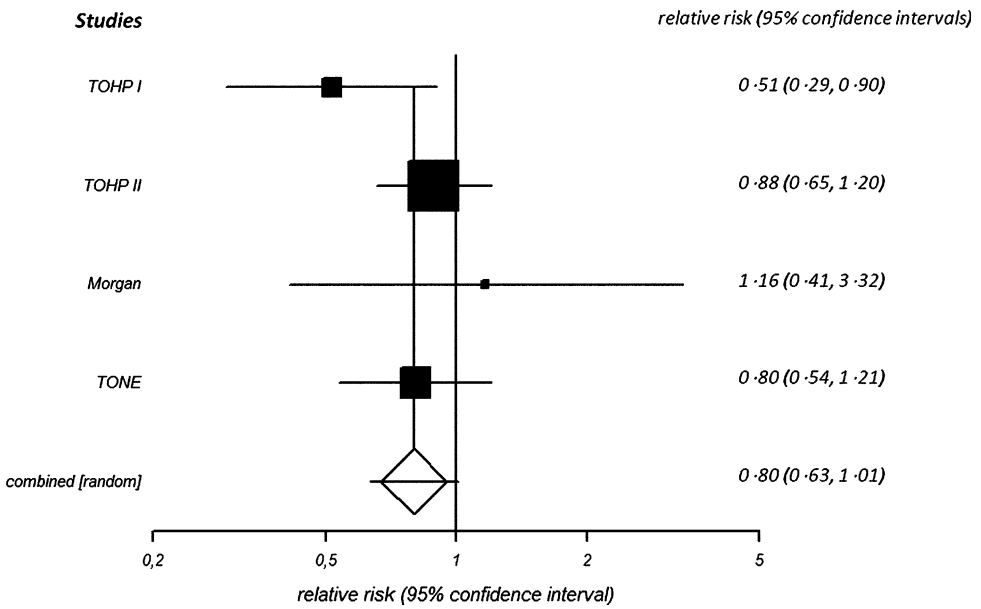

Fig. 1 Forrest plot of outcome trials of salt reduction at longest follow-up combining hypertensive and normotensive individuals: relative risk of cardiovascular disease (CVD) events. Duration of follow-up ranged from 7 months to 11.5 years. We used a random-effect model by combining data from normotensive and hypertensive subjects. Pooled relative risk = 0.798115 (95 % CI = 0.632276–1.007452). Chi-squared test (test relative risk differs from 1) = 3.600484 (degree of freedom = 1) $p = 0.0578$. Egger: bias = –0.37627 (95 % CI = −7.437157 to 6.684616), $p = 0.84$. *TOHP I* Trial of hypertension prevention, phase 1. *TOHP II* Trial of hypertension prevention, phase 2. *TONE* Trial of nonpharmacologic interventions in the elderly. *Data for individual trials taken from the meta-analysis from Taylor et al

from the main analysis should be confirmed across subgroups because the magnitude of the effect can differ greatly across different populations.

In conclusion, we believe that the conclusions reached by Taylor et al. in their Cochrane systematic review are quite balanced and based upon the facts. Moreover, a relevant "take home" message is that statistical computation cannot substitute for clinical reasoning and methodological issues. The controversy between salt intake and cardiovascular risk remains open, and further studies are needed to draw strong conclusions.

Conflict of interest None.

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