STATE OF THE ART REVIEW

Compared With Usual Sodium Intake, Low- and Excessive-Sodium Diets Are Associated With Increased Mortality: A Meta-Analysis

Niels Graudal,¹ Gesche Jürgens,² Bo Baslund,¹ and Michael H. Alderman³

BACKGROUND

The effect of sodium intake on population health remains controversial. The objective was to investigate the incidence of all-cause mortality (ACM) and cardiovascular disease events (CVDEs) in populations exposed to dietary intakes of low sodium (<115 mmol), usual sodium (low usual sodium: 115–165 mmol; high usual sodium: 166–215 mmol), and high sodium (>215 mmol).

METHODS

The relationship between individual measures of dietary sodium intake vs. outcome in cohort studies and randomized controlled trials (RCTs) measured as hazard ratios (HRs) were integrated in meta-analyses.

RESULTS

No RCTs in healthy population samples were identified. Data from 23 cohort studies and 2 follow-up studies of RCTs (n = 274,683) showed that the risks of ACM and CVDEs were decreased in usual sodium vs. low sodium intake (ACM: HR = 0.91, 95% confidence interval (CI) = 0.82–0.99; CVDEs: HR = 0.90, 95% CI = 0.82–0.99) and

Population-wide opportunities to reduce the burden of cardiovascular disease (CVD) would be beneficial. To that end, sodium reduction is recommended based upon the hypothesis that sodium restriction, by lowering blood pressure, would prevent heart attacks and strokes.¹ To reach this goal, the Institute of Medicine (IOM) in 2004 defined a tolerable upper sodium intake level (UL) of 2,300 mg/day and an adequate intake level (AI) of 1,200-1,500 mg/day.¹ However, these definitions were inconsistent with IOM's own definition of AI,² which is "the approximate intake found in apparently healthy populations.^{2,3} Because the mean intake of sodium in populations ranges between approximately 2,700 mg and 4,900 mg,^{4,5} conventional estimates of AI and UL³ would have been similar to these values. The fragility of the 2004 UL of sodium intake (2,300 mg/day) has been highlighted by the 2013 IOM report based on studies that directly link sodium intake to morbidity and mortality,⁶

increased in high sodium vs. usual sodium intake (ACM: HR = 1.16, 95% CI = 1.03–1.30; CVDEs: HR = 1.12, 95% CI = 1.02–1.24). In population representative samples adjusted for multiple confounders, the HR for ACM was consistently decreased in usual sodium vs. low sodium intake (HR = 0.86; 95% CI = 0.81–0.92), but not increased in high sodium vs. usual sodium intake (HR = 1.04; 95% CI = 0.91–1.18). Within the usual sodium intake range, the number of events was stable (high usual sodium vs. low usual sodium: HR = 0.98; 95% CI = 0.92–1.03).

CONCLUSIONS

Both low sodium intakes and high sodium intakes are associated with increased mortality, consistent with a U-shaped association between sodium intake and health outcomes.

Keywords: blood pressure; cardiovascular disease; diet; hypertension; meta-analysis; mortality; salt; sodium chloride; stroke.

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which concludes that the population-based health outcome evidence is not sufficient to define a UL for sodium. An AI was also not defined.

Sodium reduction, moreover, produces several physiological effects,^{7,8} some of which may adversely influence health outcomes.^{9,10} The objective of this meta-analysis was to examine the association of sodium intake to mortality with the goal of identifying a range where the risks of inadequacy and of excess are minimal.^{2,3} We therefore intended to investigate the association between sodium intake and health outcomes (all-cause mortality (ACM) and cardiovascular disease (CVD) events) in population samples from prospective cohort studies and randomized controlled trials (RCTs) with a low, a usual, and a high sodium intake. The data are reported according to the statements by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.¹¹

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METHODS

Criteria for considering studies

Types of studies. Cohort studies with an individual measure of dietary sodium intake and RCTs allocating patients to low, usual, or high sodium diets with a follow-up period including outcome data on ACM and/or cardio-vascular morbidity/mortality were included if published in peer-reviewed journals.

Types of participants. Because the dietary recommendations are universal, the definition of a participant was not restricted. Healthy and diseased persons, irrespective of race, sex, and age were included.

Types of exposures. Approximately 90% of the world's populations have a mean usual sodium intake within a range of approximately 115–215 mmol (±2 SD).⁴ According to the IOM definitions, the lower level (approximately 115 mmol) would be the AI below which there could be an increased risk of inadequacy and the upper level (approximately 215 mmol) would be the limit above which there could be an increased risk of side effects.³ Accordingly, participants from individual studies were organized in sodium exposure groups: (i) low sodium (mean daily sodium intake <115 mmol; 2,645 mg Na; 6,613 mg NaCl); (ii) usual sodium (mean daily sodium intake of 115–215 mmol); and (iii) high sodium (mean daily sodium intake >215 mmol; 4,945 mg Na; 12,363 mg NaCl). The usual sodium group was further subdivided into low usual sodium (115-165 mmol) and high usual sodium (166-215 mmol). The exposures were determined by means of 24-hour urine secretions, spot urine secretions, or dietary anamnesis (dietary recalls, food frequency questionnaires).

The experimental exposures were defined to be the low sodium group and the high sodium group, which were compared with the usual sodium group (the comparator). Any study that included groups with a mean sodium intake within at least 2 of the defined intervals were included. If a study included >1 percentile/group within 1 of the 3 groups, low sodium, usual sodium, or high sodium, all of the percentiles/ groups were included in the particular group. Studies reporting the outcome as a hazard ratio (HR) per unit of sodium (SD; mmol or gram) were classified as a usual sodium vs. low sodium study if the mean sodium intake in the whole population was ≤ 215 mmol and as a high sodium vs. usual sodium study if the mean sodium intake was ≥ 215 mmol.

Data from studies that had analyzed data in at least 2 percentiles (e.g., 2 quartiles or 2–3 quintiles) within the usual range (115–215 mmol) were included in a comparison of high usual sodium vs. low usual sodium in addition to studies that reported HRs per unit of sodium to investigate the possible significance of sodium intake within the usual range of sodium intake.

Types of outcome measure. Hypothetically sodium reduction works through a decrease in blood pressure, which might lead to a decrease in CVD events/mortality and especially stroke events/mortality and heart disease (HD) events/ mortality (from coronary heart disease and/or cardiac failure). These hypothetical effects do not take possible side effects of

sodium reduction into account. Relatively, the CVD effects would therefore only be important if they are also reflected in ACM. Furthermore, outcomes based on CVD diagnoses from death certificates may be inaccurate¹² in contrast with ACM, which can be assumed to be 100% accurate. Consequently, we defined the following outcomes: (i) ACM (primary outcome); (ii) CVD outcome, combined data of mortality and event; (iii) stroke outcome, combined data of mortality and event; (iv) HD outcome, combined data of mortality and event; (v) composite outcome: the outcome (ACM, CVD, stroke, or HD) with the largest incidence of events.

Criteria for exclusion. Observational studies in which participants at the time of inclusion had been advised to be on a low sodium diet were excluded because the sodium intake would less likely represent the habitual sodium intake (bias by indication), and studies in which the sodium exposure was combined with an additional exposure, for instance potassium intake or weight reduction, were excluded because the additional exposure could be a confounder.

Search methods for identification of studies

Electronic search. An independent search was performed by M.H. Alderman as described previously.¹⁰ N. Graudal performed the systematic electronic search in PUBMED described in the Supplementary Appendix. G. Jürgens performed a control search in EMBASE.

Search of other resources. We searched reference lists of relevant retrieved articles. Furthermore, we contacted authors of potentially relevant articles with insufficiently published data.

Data collection and analysis

Selection of studies. All headlines and relevant abstracts of the identified studies were read, and relevant articles were retrieved as full articles for further review. Multiple reports of the same study were identified and linked.

Data extraction and management. Two authors (N. Graudal/G. Jürgens or N. Graudal/B. Baslund) independently recorded data relevant to the population characteristics, study design, exposure, outcome, and possible effect modifiers. The type of extracted data is given in the Supplementary Appendix.

Assessment of confounding. Potential sources of bias are reviewed in the Supplementary Appendix. We recorded (i) whether the included studies were performed after elimination of patients with risk factors, which could give rise to biased risk estimates due to intentional dietary changes and (ii) had adjusted for confounders that could bias the risk estimate of the outcome measure. We used the recorded confounders in subanalyses.

Risk of bias in randomized trials. The Cochrane Collaboration's tool for assessing risk of bias¹³ (Supplementary

Appendix) was used in supplementary analyses and to assess the risk of bias in the randomized trials.

Summary measure. The summary measure was defined as an HR comparing 2 sodium intake groups.

Unit of analysis issues. If an observational study presented unadjusted HR and adjusted HR on ≥ 1 levels, the maximally adjusted HR was included in the analysis. If a group of patients was included in 2, 3, or 4 HRs, the 95% confidence interval (CI) of the HRs was increased with a factor corresponding to a reduction of the number of included patients per HR to avoid counting included participants more than once in the same analysis. Data from randomized trials were included unadjusted because the randomization procedure was assumed to have eliminated confounding.

Assessment of heterogeneity. Statistical heterogeneity across trials was estimated by the I^2 test.¹³

Data synthesis. For each observational study, each outcome was expressed as an HR (95% CI), either directly obtained from the study or estimated as explained in the Supplementary Appendix and entered in the meta-analysis model. Summary estimates were computed using the inverse variance method (Supplementary Appendix).^{13,14}

Supplementary analyses. In the supplementary analyses, we excluded populations at risk (hypertension, heart disease, diabetes, renal insufficiency, and overweight) and studies that did not include multiple adjustments. Outcomes reported both as mortality and event were analyzed separately. Separate analyses were performed on data obtained in populations in which the sodium intake was estimated by means of urine analyses. Causes of heterogeneity were explored. To explore blood pressure as a mediator, the significance of inclusion and exclusion of blood pressure in multiple adjustments was investigated.

RESULTS

Results of search

The search including a flow chart is described in the Supplementary Appendix. Studies excluded because of exclusion criteria are described in the Supplementary Appendix. Dr Merlin Thomas (personal communication) on behalf of the FinnDiane Study group provided HRs for the middle 2 sodium intake quartiles vs. the low quartile and the high quartile (Supplementary Appendix),¹⁵ and Dr Hannah Gardener, Dr Ralph Sacco, and Dr Mitchell Elkind (personal communication) provided data on ACM from the NOMAS study (Supplementary Appendix).¹⁶

Description of studies

A total of 25 different studies were included, of which 23 were prospective cohort studies described in 26 articles.¹⁵⁻⁴⁰ Because only 2 assessable RCTs (3 articles)⁴¹⁻⁴³ were identified, the separate investigation of RCTs was cancelled.

Further details are given in the Supplementary Appendix. An appendix with a detailed description of each HR (95% CI) from each study can be requested from the corresponding author.

Individual study characteristics are shown in Supplementary Tables S1–S3. Four articles analyzed 2 datasets (NHANES I^{21,22} and NHANES III^{29,30}). The first published study of each of the 2 datasets^{21,29} was included in the main analysis but was eliminated from the meta-analysis and exchanged with the second published reanalysis^{22,30} in a supplementary metaanalysis. The different interpretations of the 2 datasets were not included in the same analysis but could be included separately in subanalyses depending on the publication of different outcomes and subgroup results. Reference 23 supplies reference 22 with heart disease data.

The confounders adjusted for in most of the cohort studies were sex, age, body mass index, smoking, alcohol, diabetes, CVD, blood pressure, hypertension, use of diuretics, intake of total energy, potassium, cholesterol, and education. One of the 23 cohort studies published separate data for men and women,¹⁹ and 2 corrected for sex and age only.^{17,20} All other studies were multi-adjusted (Supplementary Table S2).

Usual sodium intake vs. low sodium intake

The 4 specific outcomes (ACM, CVD, stroke, and HD) are shown in Figure 1 and Supplementary Figures S1–S3. The risk of ACM (Figure 1) and CVD (Supplementary Figure S1) is significantly lower in the US group than in the low sodium group, whereas stroke (Supplementary Figure S2) and HD (Supplementary Figure S3) did not differ between the 2 groups.

High usual sodium intake vs. low usual sodium intake

To obtain data from as many studies as possible within the usual range (115–215 mmol) different outcomes were integrated in 1 analysis (Figure 2). The analysis showed that there was no significant difference between the high usual sodium group (166–215 mmol) and the low usual sodium group (115–165 mmol) (HR = 0.98; 95% CI = 0.92–1.03; P = 0.39). Analysis of the most frequent outcome (ACM) did not change the result (HR = 0.93; 95% CI = 0.86–1.01; P = 0.09).

High sodium intake vs. usual sodium intake

The four specific outcomes (ACM, CVD, stroke, and HD) are shown in Figure 3 and Supplementary Figures S4–S6. The risks of all 4 outcomes (ACM: HR = 1.16, 95% CI = 1.03–1.30; CVD: HR = 1.12, 95% CI = 1.02–1.24; stroke: HR = 1.18, 95% CI = 1.05–1.33; HD: HR = 1.17, 95% CI = 1.08–1.27) were significantly lower in the usual sodium group than in the high sodium group.

Supplementary analyses

Eliminating the first analyses of the NHANES I and III studies^{21,29} from the meta-analysis and exchanging them with

Charles .	T I	14/ - 1 - I - I	Hazard ra	zard ratio, Hazard ratio,	
Study	Iotal	weight	random (95	% CI) rand	om (95% CI)
Lennie ³⁵ mild heart failure	134	1.3%	0.44 (0.20 – 0.	97)	-
Alderman,19 M	1,900	5.4%	0.70 (0.52 – 0.	94) —	-
Ekinci ³⁶	620	6.0%	0.72 (0.55 – 0.	94) —	
Cohen ²⁶ (NH II)	7,154	9.2%	0.78 (0.67 - 0.	91) 🗕	
Stolarz-Skrypek ³⁷	2,454	5.8%	0.82 (0.62 - 1.	08)	-
Tunstall-Pedoe, ²⁰ M	3,453	6.5%	0.82 (0.64 - 1.	05)	-
Cohen ²⁹ (NH III)	6,525	9.9%	0.83 (0.73 – 0.	94) 🗕	
Thomas ¹⁵	2,105	1.7%	0.87 (0.45 - 1.	68)	
Alderman ²¹ (NH I)	11,346	10.7%	0.88 (0.80 - 0.	97) 👎	+
Gardener ¹⁶	2,099	8.2%	0.89 (0.74 - 1.	07) -	-
Tuomilehto, ²⁴ F	1,263	2.8%	0.91 (0.56 - 1.	48)	
O'Donnel ³⁸	23,327	10.9%	0.92 (0.84 - 1.	01) 1	•
Tunstall-Pedoe, ²⁰ F	4,700	5.4%	0.93 (0.69 - 1.	25) -	-
Yang, ³⁰ NW (NH III)	4,000	0.0%	0.93 (0.73 - 1.	18)	
He, ²² NW (NH I)	6,797	0.0%	0.98 (0.88 - 1.	09)	
Geleijnse ²⁷	1,578	6.2%	1.12 (0.86 - 1.	46) -	
Taylor ⁴¹ (Appel 43)	291	2.8%	1.14 (0.70 - 1.	86) —	+ -
Alderman, ¹⁹ F	1,037	3.1%	1.17 (0.74 - 1.	85) —	
He, ²² OW (NH I)	2,688	0.0%	1.32 (1.16 – 1.	50)	
Yang, ³⁰ OW (NH III)	5,200	0.0%	1.44 (1.06 – 1.	96)	
Lennie ³⁵ severe heart failure	163	1.1%	2.54 (1.10 - 5.	87)	
Costa ⁴¹	372	1.8%	2.86 (1.50 - 5.	44)	
Arcand ³⁴	123	1.0%	3.54 (1.46 - 8.	58)	
Total (95% CI)	70,644	100.0%	0.91 (0.82 – 0	.99)	
Heterogeneity: $\tau^2 = 0.02$; χ^2	= 46.41, df = 1	$8 (P = 0.0003); I^{2}$	$^{2} = 61\%$		+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
Test for overall effect: $Z = 2.0$	7 (P = 0.04)		Fav	ors	Favors
	นรเ	usual sodium low sodium			

Figure 1. All-cause mortality, usual sodium vs. low sodium. Exchanging the first NHANES analyses^{21,29} with the reanalyses:^{22,20} (hazard ratio = 0.99; 95% confidence interval = 0.88–1.11; *P* = 0.84). Cl, confidence interval; F, female; M, male; NH, NHANES, NW, normal weight; OW, overweight.

the reanalyses of the NHANES I and III studies^{22,30} yielded results that were no longer significant for the usual sodium group vs. the low sodium group (Figure 1; Supplementary Figure S1) but were significant for the high sodium group vs. the low sodium group (Figure 3; Supplementary Figure S4). The results for the high usual sodium group vs. the low usual sodium group did not change (Figure 2).

The results of analyses of multiple adjusted population representative samples after exclusion of subgroups at risk and studies without adjustment for multiple confounders generally confirm the main analyses (Table 1). The results shown in Figures 1–3 and Supplementary Figures S1–S6 were consistent in 5 studies investigating both outcomes (Supplementary Table S4).

Stroke. A separate analysis excluding a study not providing data for high and usual sodium intake¹⁸ did not change the result (HR = 1.18; 95% CI = 1.05–1.33) (Supplementary Figure S5). The risk of stroke was only significant in Japanese populations (HR = 1.21, 95% CI = 1.12–1.30, P = 0.00001; $I^2 = 49\%$, P = 0.10, fixed effect). Whites on a high sodium diet did not have an increased risk of stroke (HR = 1.00, 95% CI = 0.94–1.07, P = 0.94; $I^2 = 53\%$, P = 0.08, fixed effect).

CVD and HD mortality and events. Subanalyses on CVD and HD mortality and events confirmed the main analysis (Supplementary Table S5).

Significance of sodium intake estimation method. Sensitivity analyses that only included studies in which the salt intake was based on urine analysis confirmed the main analyses (Supplementary Table S6).

Blood pressure as mediator. Only 2 studies made an analysis with and without blood pressure as a confounder.^{27,30} Only 1 of the studies reported the data,²⁷ but both reported no difference between the analyses.

Heterogeneity. Causes of heterogeneity were explored as described in the Supplementary Appendix. All analyses (Figures 1–3; Supplementary Figures S1–S6) except 2 (Supplementary Figures S2 and S6) were statistically heterogeneous. However, after excluding participants at risk (hypertension, heart failure, diabetes, chronic renal failure, overweight), statistical evidence of heterogeneity disappeared, except for in 2 analyses (Supplementary Figures S1 and S5) in which heterogeneity disappeared after exclusion of Japanese populations.

DISCUSSION

As we previously emphasized, there was a lack of RCTs, with only 2 assessable follow-up studies of RCTs identified.^{42,43} Consequently the results of this meta-analysis were

Figure 2. Composite outcome (most frequent events combined), high usual sodium vs. low usual sodium. Exchanging the first NHANES analyses^{21,29} with the reanalyses:^{22,30} (hazard ratio = 1.01; 95% confidence interval = 0.95–1.07; P = 0.79). ACM, all-cause mortality; CVD, cardiovascular disease; F, female; M, male; NH, NHANES; S, stroke.

Study	Total	Weight	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Yang, ³⁰ NW	2,667	0.0%	0.86 (0.51 - 1.45)	
Cohen ²⁹ (NH III)	6,525	15.5%	0.94 (0.79 – 1.12)	
Tunstall-Pedoe, ²⁰ M	4,604	12.7%	0.96 (0.77 – 1.20)	
Tuomiletho, ²⁴ M, NW	659	7.9%	0.98 (0.70 - 1.37)	
Stolarz-Skrzypek ³⁷	2,454	6.5%	1.13 (0.77 – 1.66)	
Tunstall-Pedoe, ²⁰ F	3,525	7.3%	1.14 (0.80 - 1.62)	
O'Donnel ³⁸	25,408	21.5%	1.20 (1.11 - 1.30)	
Gardener ¹⁶	2,337	10.0%	1.32 (1.00 - 1.74)	
Thomas ¹⁵	2,105	7.5%	1.43 (1.01 – 2.02)	
Tuomilehto, ²⁴ M, OW	514	11.0%	1.56 (1.21 – 2.01)	
Yang, ³⁰ OW	3,467	0.0%	2.07 (1.35 - 3.17)	
Total (95% CI)	48131	100.0%	1.16 (1.03 – 1.30)	•
Heterogeneity: $\tau^2 = 0.01$; χ Test for overall effect: $Z = 2$	2 ² = 17.61, df = 8 2.46 (<i>P</i> = 0.01)	$(P = 0.02); I^2 =$	55% 0.5 Favors high sc	0.7 1 1.5 2 Favors odium usual sodium

Figure 3. All-cause mortality, high sodium vs. usual sodium. Exchanging the first NHANES analysis²⁹ with the reanalysis³⁰ (hazard ratio = 1.22; 95% confidence interval = 1.08-1.39; P = 0.002). F, female; M, male; NH, NHANES; NW, normal weight; OW, overweight.

primarily based on observational studies. The main finding is that, compared with the usual sodium intake throughout the world,^{4,5} those consuming more or less sodium were at increased risk of both ACM and CVD. Furthermore, there was no difference in outcomes between the higher and lower sodium intake groups within the usual range of sodium intake. These findings are consistent with the previously hypothesized J/U–shaped relation of sodium intake to health outcomes^{9,10} and confirmed the finding of the J/U shape in 2 of the cohort studies included in this meta-analysis.^{15,38} Finally, the J/U shape is in accordance with the generally accepted relationship between a low level of nutrient

Table 1. Lifed sizes in meta-analyses of population representative samples adjusted for multiple comound	Table 1.	Effect sizes in meta-analy	yses of population	representative samples ad	ljusted for multipl	le confounders
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	LS vs. US				HS vs. US					
Outcome	References	No. at risk	HR	95% CI	P value	References	No. at risk	HR	95% CI	P value
ACM ^{21,29}	16,21,24,26,27,29,37	32,419	0.86	0.81–0.92	0.0001	16,24,29,37	11,975	1.04	0.91–1.18	0.58
ACM ^{22,30}	16,22,24,26,27,30,37	25,345	0.91	0.85–0.98	0.01	16,24,30,37	8,117	1.12	0.94–1.34	0.20
CVD ^{21,29}	16,21,24,26,27,28,29,37	67,657	0.93	0.82- 1.05	0.23	16,24,28,29,33,37	134,139	1.07	0.9–1.27	0.48
CVD ^{22,30}	16,22,24,26,27,28,30,37	60,583	1.01	0.92, 1.09	0.90	16,24,28,30,33,37	132,456	1.14	1.06-1.22	0.0003
Stroke	16,22,24,26,27,28,37	56,582	1.05	0.93–1.18	0.45	16,24,25,28,31,33,37	186,091	1.21	1.04–1.41	0.02
Heart disease	16,22,24,26,27,28,30,37	65,772	0.96	0.88–1.06	0.44	16,24,28,37	130,455	1.10	0.97–1.24	0.15

ACM, all-cause mortality; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HS, high sodium; LS, low sodium; US, usual sodium.

intake and risk of inadequacy and a high level of nutrient intake and risk of adverse event.^{2,3}

The harmful effect associated with a high sodium intake (HR = 1.16) (Figure 3) was stronger than the harmful effect associated with a low sodium intake (HR = 0.91) (Figure 1). However, in population-representative samples adjusted for multiple confounders, the pattern was the opposite (HR = 1.04, not significant for high sodium vs. usual sodium; HR = 0.86, P < 0.00001 for usual sodium vs. low sodium) (Table 1). Furthermore, subanalyses showed symmetric ACM and CVD outcomes in studies measuring both outcomes in the low sodium and high sodium intervals (Supplementary Table S4).

In the meta-analyses, which included the reanalyses of NHANES I and III,^{22,30} there was no association of low sodium intake with ACM (Figure 1), but in the subanalysis of population-representative studies adjusted for multiple confounders, there was a significant association of low sodium intake, but not high sodium intake, with ACM, whereas the pattern for CVD was the opposite (Table 1). Consequently, a selective conclusion based on inclusion of the reanalyses of the NHANES studies^{22,30} would be that a low sodium intake is associated with ACM but not CVD, whereas a high sodium intake is associated with CVD but not ACM. In none of the supplementary meta-analyses was a low sodium intake associated with a beneficial effect on ACM or CVD.

Strengths of this analysis were the power of a substantial number of participants (n = 274,683) and the fact that most of the included studies adjusted the outcome for multiple assumed confounders (Supplementary Table S2). A reason for adjustment of blood pressure–related factors would be to decrease bias by indication. However, because blood pressure may be the mediator of the effect of salt, such adjustment could lead to overadjustment bias, which might underestimate the total effect. Only two studies^{27,30} analyzed data with and without blood pressure in the model, and they found no statistical differences between the two analyses. Consequently it appears that the inclusion of blood pressure–related factors had no impact on the outcome.

In general, heterogeneity disappeared after exclusion of subgroups at risk and studies without adjustment for multiple confounders. With a few exceptions (Supplementary Figures S1 and S5), the influence of race on the outcomes was weak, probably because all investigated groups were classified to be homogenous with respect to sodium exposure. The analysis seemed robust because supplementary analyses of population-representative samples adjusted for multiple confounders (Table 1) and studies stratifying for sodium intake estimation method (Supplementary Table S5) generally did not change the results of the analyses. The results of 2 follow-up studies of RCTs,⁴¹⁻⁴³ which reduced sodium intake from the mean usual population level (3.8 g) to a level close to the low usual level $(2.3 g_{3}^{43} 3.0 g^{42})$, were consistent with the meta-analysis of cohort studies of high usual intake vs. low usual intake (Figure 2). In another randomized study, Chang et al.44 also found no effect on ACM, but they did report a decline in CVD mortality when reducing sodium intake from a high level of 5.3 g to a usual level of 3.8 g. We excluded this trial from our analysis because a concomitant increase in potassium in the reduced sodium group confounded its interpretation.

Inaccurate measurement (measurement error) of the independent variable (sodium intake) was a limitation, which could bias the outcome toward zero (regression dilution bias) if the measurement error leads to random misclassification. This would underestimate the outcome effects. If the measurement error systematically misclassifies certain subgroups, the outcome effects could be directionally biased. One study³⁰ corrected the estimation of sodium intake (single 24-hour recall estimation) for regression dilution by means of a second 24-hour recall estimation obtained in a representative sample of 7.4% of the participants. This correction did not change the result on CVD but did increase ACM significantly and thus created an intuitively paradoxical inconsistency between the CVD mortality and ACM in conflict with the hypothetical causal pathway. Consequently, this correction may have created more bias than it eliminated. Thus, there is no convincing evidence that participants are systematically misclassified because of measurement error per se. Furthermore, systematic measurement error should not be a problem in the usual sodium intake range in which no association of salt intake with outcome was detected (Figure 2). A more plausible confounder could be that ill participants might accumulate in the low sodium intake interval because of dietary advice or poor appetite or in the high sodium intake interval because of high energy intake (overweight, diabetes), which could have contributed to increased mortality in the low and the high sodium groups (reverse causality). However, most studies took measures to adjust for such confounding by excluding patients with CVD and cancer from the analyses or adjusting for CVD, diabetes, and energy intake.

Finally, the unbiased randomized studies with the most accurate repeated 24-hour urine measurements confirmed that sodium reduction did not significantly reduce ACM within the usual sodium intake range,^{41–43} although the studies were performed in risk groups.

The findings here lend support to those who have questioned the scientific basis for sodium reduction,45-48 which are based primarily on the assumed blood pressure effect obtained in selected intervention studies^{42,49} and a selected meta-analysis of intervention studies.⁵⁰ However, the blood pressure effect is proportional to the baseline blood pressure, and because the baseline blood pressure in these intervention studies^{42,49} and the meta-analysis⁵⁰ was much higher (approximately 130/85 mm Hg) than the mean blood pressure of the normotensive population (116/69 mm Hg) and the general population (122/71 mm Hg),⁵¹ the association of salt intake with blood pressure is overestimated. Furthermore, the meta-analysis downplays other surrogate markers (hormones, lipids), which previously have been shown to increase during sodium reduction^{7,8} and thus have the potential to adversely affect outcomes.

Sodium reduction also finds support in studies that inflate the small effect on blood pressure by means of computersimulated projected effects of dietary salt reductions on future CVD.⁵² This approach may be flawed for several reasons: (i) the assumption of a linear relationship between sodium reduction and blood pressure may be wrong because it is based on the above-mentioned selected studies with high baseline blood pressures;^{42,49,50} (ii) a blood pressure reduction due to an intervention cannot automatically be translated into decreased mortality as exemplified by betablockers, which decrease blood pressure but not mortality;⁵³ and (iii) potential harms were ignored in the model.

Recent meta-analyses of population studies^{54,55} have found increased stroke risk, but not increased ACM, associated with higher sodium intake. These studies are partly in agreement with ours, but they typically compared the highest intake percentiles with the lowest intake percentiles and did not use the information of the intermediate intake groups and thus did not specify that the increased stroke risk is limited to those with sodium intake well above the usual sodium intake. The conflation of high, usual, and low sodium intakes may obscure the possibility that the potential harm of sodium excess may be blood pressure driven, whereas the potential harm of a low sodium intake may be because of elevated renin-aldosterone activity, sympathetic nerve activation, and/or lipid abnormalities.^{7,8}

The 2013 IOM report concluded that subgroups should not be treated differently from the general population.⁶ Our finding that there was no difference in the trends of the outcomes between analyses including and excluding diseased populations supports this conclusion. The 2013 IOM report also concluded, "Science was insufficient and inadequate to establish whether reducing sodium intake below 2,300 mg/d either decreases or increases CVD risk in the general population."⁶

Our study extends the IOM report by identifying a specific range of sodium intake (2,645–4,945 mg) associated with the most favorable health outcomes, within which variation in sodium intake is not associated with variation in mortality. Moreover, this optimal range of intake, based upon available evidence, is coterminous with the current dietary intake of most of the world's population^{4,5} and is in accordance with the IOM rules for definition of an AI and UL of sodium.³ Finally, an increased mortality risk was found to be associated with intakes that violate this range. In none of the primary or supplementary analyses was a low sodium intake associated with beneficial effects on ACM or CVD. Thus, these data are consistent with the hypothesis that a U shape best describes the relationship of sodium intake to health outcomes.

SUPPLEMENTARY MATERIALS

Supplementary materials are available at *American Journal* of *Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

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