Percentage of ingested sodium excreted in 24-hour urine collections: a systematic review and meta-analysis.

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Abstract:	24 hr. urine sodium excretion is generally regarded as the 'gold' standard for assessing dietary sodium in population and epidemiological studies. This review examines the percentage of dietary sodium that is excreted in a 24 hr. urine collection. We systematically searched for all studies where a known and constant amount of dietary sodium was ingested for a minimum of 3 days and where sodium excretion in 24 hr. urine collections was measured. Studies with 'healthy' adult participants, or participants with health risks such as hypertension, were considered. 5264 unique studies were identified in the search; 392 underwent a full-text review and 35 studies were included. The pooled estimate for the percentage dietary sodium excreted in urine was 92.8% (95% confidence interval 90.7, 95.0) with little to no differences in subgroup analyses. There was high heterogeneity between studies, indicating that caution is required in

interpreting the average percentage excretion, however, lack of study methodological rigor is likely to have contributed to the high heterogeneity. Although the generally high variability in sodium intake indicates that results from a single 24 hr. urine collection should not be used to assess an individual's usual long-term sodium intake, this meta-analysis suggests that it is an appropriate method for assessing average dietary sodium in a healthy population or people with chronic stable health risks.

Percentage of ingested sodium excreted in 24-hour urine collections: a systematic review and meta-analysis.

Short title: Urine excretion of ingested sodium.

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Abstract: 218

24 hr. urine sodium excretion is generally regarded as the 'gold' standard for assessing dietary sodium in

population and epidemiological studies. This review examines the percentage of dietary sodium that is

excreted in a 24 hr. urine collection. We systematically searched for all studies where a known and constant

amount of dietary sodium was ingested for a minimum of 3 days and where sodium excretion in 24 hr. urine

collections was measured. Studies with 'healthy' adult participants, or participants with health risks such as

hypertension, were considered. 5264 unique studies were identified in the search; 392 underwent a full-text

review and 35 studies were included. The pooled estimate for the percentage dietary sodium excreted in urine

was 92.8% (95% confidence interval 90.7, 95.0) with little to no differences in subgroup analyses. There was

high heterogeneity between studies, indicating that caution is required in interpreting the average percentage

excretion, however, lack of study methodological rigor is likely to have contributed to the high heterogeneity.

Although the generally high variability in sodium intake indicates that results from a single 24 hr. urine

collection should not be used to assess an individual's usual long-term sodium intake, this meta-analysis

suggests that it is an appropriate method for assessing average dietary sodium in a healthy population or

people with chronic stable health risks.

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Introduction

High dietary sodium is estimated to be the leading dietary risk for death and disability according to the Global Burden of Disease Study [1,2]. The health risk associated with dietary sodium is largely related to a direct relationship between increasing dietary sodium and increasing blood pressure. Notably, increased blood pressure is a leading global risk factor for death and disability causing approximately 50% of cardiovascular disease[1]. In both observational and interventional studies, 24 hr. urine sodium excretion is often used as the 'gold standard' to estimate dietary sodium. Although it is generally stated that approximately 90% of dietary sodium is excreted in 24 hr. urine collections[4], to our knowledge, there has been no systematic review of the percentage of ingested sodium excreted in the urine. Previous studies in healthy people have reported that 24 hr. urine sodium excretion accounts for 61-107% of ingested sodium[5]. We have conducted a systematic review of studies that examined the percentage of sodium excreted in 24 hr. urine collections in study participants ingesting known quantities of sodium. Accurately defining the percentage of dietary sodium excreted in urine is important to assess the validity of using urine excretion studies as the best evidence for assessing relationships between dietary sodium and health.

This systematic review was conducted with the support of the TRUE consortium[6]. The TRUE consortium formed because of concerns that low quality research was causing controversy about the health impact of dietary sodium[7]. Specifically, studies that inadequately assess dietary sodium may be susceptible to drawing false conclusions between sodium intake and health outcomes. The TRUE consortium will provide recommendations about minimum and desirable standards for the conduct of research and also conduct systematic reviews of outcome studies that meet the minimum standards as part of a process to ensure clinical and population recommendations for dietary sodium are based on reliable, reproducible research.

Methods

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Selection Criteria

To establish the percentage of ingested sodium that is excreted in urine, we included only studies that rigorously assessed the amount of sodium ingested and the amount of sodium excreted in 24 hr. urine collections, in individuals on a prescribed intake of dietary sodium. To ensure adherence to prescribed dietary sodium, eligible studies had to either provide meals with known content of sodium to participants or record the weight of food ingested and the food samples be subsequently analyzed for sodium content. To be included, studies had to have adult participants and ensure adherence to a constant quantity of dietary sodium for a minimum of three days, to ensure participants were at a 'steady state' of urine sodium excretion relative to ingested sodium. Additionally, studies were excluded if the participants had any acute or major chronic illnesses (e.g. heart failure), or acute change in physical activity or heat exposure or ingestion of drugs (e.g. furosemide) that may have altered sodium absorption, metabolism, or excretion. Studies involving participants with stable chronic health risks such as hypertension were included.

Search Strategy

Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform were searched to identify potential studies. Search terms were developed with a librarian and tailored for each database (see Appendix A). The search terms for each database were developed to capture studies that evaluated our surrogate measure (24h urine sodium excretion) and our reference standard (sodium/salt, dietary consumption). The WHO Clinical Trials database used a broader set of terms because of restrictions caused by the search engine user interface. No language or date restrictions were applied. All searches were performed on October 3, 2016. All studies identified were initially screened using a title-abstract review, followed by a full-text review. Disagreements for article inclusion were resolved through consensus between two reviewers (AL and CD).

Data Extraction

Studies identified as suitable through the full text review were subject to data extraction for the

following variables: 1) health status; 2) sex; 3) study design; 4) sample size; 5) the duration of dietary

intervention; 6) prescribed daily sodium intake; 7) 24 hr. urine sodium excretion; 8) prescribed potassium

intake or excretion; and 9) study environment ('controlled study' (conducted in a research facility) vs.

'uncontrolled' study (conducted in free living subjects). Cochrane Collaboration tool for assessing risk of bias

was used to score biases and quality of each study[8]. Cochrane's tool contains measures that identify

selection, performance, detection, attrition, and reporting bias.

Statistical Analysis

The percentage of daily sodium intake excreted in 24-hour urine samples was calculated by dividing

sodium excreted in mg by daily sodium intake in mg and multiplying by 100. Once the percentage of daily

sodium excreted was calculated, the standard error of the amount of excreted urine was used to calculate the

95% confidence interval (CI) for the percentage of daily sodium excreted. To calculate the 95% CI, the mean

sodium excreted was added or subtracted (for the upper and lower ranges of confidence) to the z value of

1.96, multiplied by the standard error divided by the daily sodium intake. Studies that did not provide

standard errors were excluded from the meta-analysis as it was not possible to calculate the confidence

intervals (n=2), but these studies were included in the descriptive analysis [9,10].

A meta-analysis was performed on all percentages of sodium excretion provided in each study (n = 35).

A random effects model with inverse-variance weighting was used, as we expected that each of the study

point estimate(s) would differ based on varying study conditions and characteristics (e.g., age of participants

across studies differed). Heterogeneity was assessed using the I^2 statistic. Sub-group analysis was performed

on the following variables: potassium intake (calculated as either having a potassium intake above or below

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the sample mean of 77.6 mmol/day (n=22) and also calculated as a continuous variable, study environment ('controlled' (study conducted in a research facility) vs. 'uncontrolled' (study conducted in free living subjects outside of a research facility)), sex (male, female), sodium intake range, health status, dietary sodium changes (low to high, high to low, and no direction), length of steady state (3, 4-5 and 7 or more days), and study rigor. An additional subgroup analysis was conducted on those studies with sodium intake <1000 mg/day, and length of steady state. A random effects meta-regression was also performed on all subgroup analyses to obtain p values for the differences between subgroups. Sodium intake levels were as previously defined by Campbell et al., based on the paleolithic diets human evolved on, long term physiologic studies and the World Health Organization dietary recommendations, where low daily sodium intake was defined as < 100 mg, normal-physiological intake as 100 to <1000 mg, recommended intake as 1000 mg to < 2000 mg, high intake as ≥ 2000 mg to 4000 mg, very high intake as > 4000 to 6000 mg, and extremely high intake as >6000 mg[11]. Study rigor was considered high if dietary intake was assessed with a known unbiased reference measure (denominator) and the 24-h urine collections were high quality. Known unbiased reference measures for sodium intake include 1) controlled feeding studies or 2) direct observation[12]. Controlled feeding studies provide meals and carefully monitor the amount of food consumed[13]. High quality 24-hour urine collections were arbitrarily defined as including provision of explicit instructions for collection, an assessment of completion of 24-h urine collection (e.g., creatinine criteria, PABA recovery) and at least 80% of urine specimens meeting completion criteria[14]. Age was not assessed as a subgroup as there was inconsistent reporting of age across studies.

Studies that may have potentially influenced the final estimates and heterogeneity (i.e., high risk of bias, studies that did not assess completeness of 24 hr. urine collections or that included incomplete 24 hr. urine samples, and studies with larger changes in sodium intake over a shorter period in time where steady state sodium excretion may not have been achieved) were removed as part of the sensitivity analysis to assess whether the findings were robust.

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In most cases, studies assessed sodium excretion as a secondary rather than primary objective. Therefore, we did not consider publication bias.

Results

Study Characteristics

The search of the five electronic databases retrieved 6754 articles (Figure 1). After removing duplicate studies in the literature searches, 5264 unique studies were identified for the title/abstract search. The title and abstract search identified 392 (95% consensus between two reviewers) relevant articles which then underwent a full-text review. Of those, 359 were excluded because they did not meet the inclusion criteria for sodium intake and 24 hr. urine excretion measurements. Two more articles were excluded from the meta-analysis because the data they provided did not allow a confidence interval to be calculated[9,10]. Two studies were also removed because they included participants or used methodologies that may have affected sodium steady state[15,16]. These two articles were still included during data extraction, but not in the meta-analysis. Six additional studies were found from the reference lists of review articles that were identified during the literature search. A final 35 articles were included in the meta-analysis (Appendix B).

All studies included in the analysis were prospective and were either randomized controlled parallel group trials (n = 10) or randomized crossover trials (n = 25). Participants in each study ranged from 18 to 80 years of age and were considered to be either healthy (n=22) or have chronic health risks such as hypertension (n = 13). The studies used different schedules for urine sample collection, different methods for assessing completeness of 24 hr. urine collections and for ensuring dietary adherence. Only two of the studies [17,18] included had a primary objective of assessing the quantity of ingested sodium excreted in urine.

Percentage of Total Sodium Excreted

Figure 2 provides a forest plot for the pooled percentage of dietary sodium excretion in each study. The pooled estimate for the percentage of sodium excreted in urine for all studies included in the meta-analysis was 92.8% (95% CI 90.7, 95.0, heterogeneity 95.1%, p < 0.001).

Subgroup Analyses (Figure 3)

Studies conducted at different levels of potassium intake: Several studies reported levels for potassium intake, or potassium excretion. Studies that reported potassium intake exhibited a mean potassium intake or excretion of <77.6 mmol/day (n = 10) yielded a pooled estimate of 90.1% (95% CI 84.9, 95.3, heterogeneity 93.7, p < 0.001) for percentage of ingested sodium that was excreted in urine. The pooled estimate of sodium excretion for studies with potassium intake or excretion >77.6 mmol/day (n = 12) was 106.6% (95% CI 100.7, 112.6, heterogeneity 95.1%, p < 0.001). Dietary potassium (as a continuous variable) was not significantly related to the percentage of sodium excreted (p = 0.257).

Studies conducted in controlled research facilities vs. studies conducted in free-living participants: Studies that took place in controlled research facilities (e.g., metabolic wards, sealed chambers, hospitals; n = 7) demonstrated a percentage excretion of ingested sodium of 83.6% (95% CI 80.5, 86.7, heterogeneity 72.3%, p < 0.001). In comparison, participants in studies that were conducted in uncontrolled environments (n = 28) excreted 100.6% (95% CI 97.6, 103.7, heterogeneity 96.8%, p < 0.001) of ingested sodium intake. The percentage of sodium excreted did not differ between the study environments (controlled vs uncontrolled, p = 0.056). Studies with controlled environments did not appear to have any systematic differences in methodology (e.g. low dietary sodium, short dietary periods, etc.) compared to studies with uncontrolled environments.

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Males vs Females: In studies that reported sex- specific data, sex-specific estimates of urine sodium excretion were calculated. In studies that reported data in males only (n = 16), the pooled estimate of ingested sodium that was excreted in 24 hr. urines was 97.4% (95% CI 94.2, 100.6, heterogeneity 95.6% p < 0.001). Only three studies reported data in female participants; the percentage of dietary sodium excreted in urine was 93.2% (95% CI 86.1, 100.2, heterogeneity 79.1% p < 0.001). The percentage of sodium excreted by males and females were not significantly different (p = 0.481).

Studies conducted at different levels of sodium intake: Many studies reported sodium excretion, with differing levels of sodium intake [11]. Sodium intakes were categorized according to standardized nomenclature in the following ranges: low (<100 mg sodium/day, n = 0), normal-physiologic (100-<1000 mg sodium/day, n = 17), recommended (1000 -<2000 mg sodium/day, n = 6), high ($\geq$ 2000 – 4000 mg sodium /day, n = 13), very high ($\geq$4000-6000 mg sodium /day, n = 11), and extremely high (>6000 mg sodium/day, n = 10). Within the normal-physiologic range of sodium intake (100 to <1000mg/day), mean urine sodium excretion was 140.6% (95% CI 123.1, 158.1, heterogeneity 96.3%, p < 0.001). Studies that fell into the recommended (1000 to <2000 mg/day) and high ranges of sodium intake (2000-4000 mg/day) reported pooled estimates of sodium excretion of 104.5% (95% CI 88.9, 120.1, heterogeneity 95.2%, p < 0.001) and 90.1% (95% CI 85.7, 94.4, heterogeneity 97.9%, p < 0.001), respectively. Studies with very high intake (sodium >4000 to 6000 mg/day) reported pooled estimates of sodium excretion of 98.8% (95% CI 92.0, 105.5, heterogeneity 88.4%, p < 0.001) and the studies with extremely high levels of sodium intake (sodium > 6000 mg/day) had a pooled estimate of 86.4% (95% CI 81.2, 91.6, heterogeneity 94.7%, p < 0.001). The percentage sodium excreted was not different for recommended, very high, and extremely high compared to high sodium intake (p = 0.093, p = 0.284, p = 0.641 respectively). However, normal-physiological sodium intake had a higher percentage excretion of sodium compared with high levels of sodium intake (p <0.001).

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Healthy participants vs. those with chronic health risks: Studies assessing healthy populations (n = 25) had a pooled 24-hour excretion of ingested sodium estimate of 93.7% (95% CI 90.5, 96.8, heterogeneity 97.1%, p < 0.001). Comparatively, in the studies with participants who had chronic health risks, such as diabetes and hypertension (n = 9), the pooled estimate of urine sodium excretion was 109.7% (95% CI 102.8, 116.7, heterogeneity 96.2%, p < 0.001). The presence of health risks did not significantly affect the percentage of sodium excreted (p = 0.073).

Studies with changes in dietary sodium protocols: Studies that had dietary protocols that changed from low sodium intake to high sodium intake (n = 13) had a pooled estimate of 100.5% (95% CI 94.4, 106.7, heterogeneity 95.5%, p < 0.001) sodium excretion compared to studies with no directionality to dietary changes (n = 22) with a pooled estimate of 97.2% (95% CI 93.9, 100.4, heterogeneity 97.0%, p < 0.001). There were no significant differences in percentage of urine sodium excretion between the diets that increased sodium intake and those with no change in sodium intake (p = 0.745). There were no studies that had dietary protocols that changed from high to low sodium intake.

Studies with longer dietary periods before sampling: Studies with stable dietary sodium intervention periods of 3 days before urine sampling (n = 5) had a pooled estimate of 114.4% (95 CI 95.1, 33.6, heterogeneity 96.4% p < 0.001). Studies that had stable dietary sodium intervention periods of 4 or 5 days before sampling (n = 9) had a pooled estimate of 109.9% (95% CI 101.5, 118.3, heterogeneity 95.4%, p < 0.001) excretion, while studies with 7 days or more days of stable dietary sodium intervention before sampling (n = 21) had pooled estimates of 93.9% (95% CI 90.8, 96.9, heterogeneity 97.1%, p < 0.001). The length of dietary intervention did not significantly affect the percentage of sodium excreted (p = 0.742).

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Studies that met more rigorous criteria for diet provision and completion of 24-h urine: Studies that had

high quality dietary assessment methods and 24-hr. urine sodium excretion measures (n = 3) reported a

pooled estimate of 91.8% (95% CI 89.1, 94.5, heterogeneity 79.8%, p = 0.001), while studies that did not meet

the criteria for high quality diets and 24-hr. urine sodium excretion measures (n = 32) reported a pooled

estimate of 100.3% (95% CI 96.4, 104.3, heterogeneity 96.9%, p < 0.001).

Assessment of low sodium intake and length of steady state: Studies categorized as having low sodium intake

were separately analyzed with meta-regression to assess the interaction between the length of steady state

and sodium excretion (Figure 4). The length of steady state did not affect the percentage of sodium excreted

(p = 0.134).

Sensitivity analyses: Ten separate studies were sequentially removed from the overall pooled analysis, as well

as each of the subgroups, to attempt to identify potential sources of heterogeneity and statistical outliers.

Studies were removed for not excluding incomplete urine samples[18], a high risk of bias[19-21], and for having a

change in sodium intake of over 4600 mg/day[21-27]. The heterogeneity of the overall pooled estimate did not

change by more than 4.5% when each of the studies was removed from the pool. The sensitivity analysis was

also applied to each of the subgroups, where the largest change in heterogeneity was from 95.1% to 76.3%

when one study[23] was removed (based on a very large change in sodium intake in the high potassium intake

subgroup). All other subgroup's heterogeneity changed by less than 18% during the sensitivity analysis.

Excluded studies: Four studies were separated prior to the analysis, but still included data that could be useful

when interpreting the conclusions of this analysis. Two of these studies did not meet methodological criteria

due to an intervention exposing the participants acutely to a hot environment [15,16]. The other two studies did

not include variance data for urine sodium excretion and so could not be used in the analysis[9,10]. The studies

ranged between 8 and 105 participants, with two studies being male only[15,16]. Two studies measured urine

sodium while on a stable diet for 5 days or more, two measured urine sodium at either 3 or 4 days of a stable

diet. Two of the studies assessed hypertensive patients[9,10]. Allsopp et al. had three sodium intake levels of

1525, 4004, and 8013 mg/day during acute heat exposure and urine sodium excretion ranged from 38.14 to

72.13%[15]. Armstrong et al. had 1081 and 5490 mg/day sodium intake levels during acute heat exposure and a

sodium excretion range of 47.96 to 59.82%[16]. Mueller et al. and Parfrey et al. both had two levels of sodium

intake of 1012 and 4048 mg/day and 230 and 8050 mg/day, respectively, and respective sodium excretion

values ranging between 100.1 to 115.5% and 69.71 to 220%[9,10].

Discussion

The overall pooled estimate from this meta-analysis indicates that on average 92.8% of 24 hr. dietary

sodium was excreted in 24 hr. urine collections. This meta-analysis only included studies where participants

had a constant amount of sodium in their diets for a minimum of 3 days. Where participants ate their usual

diets, in other studies that included careful assessment of dietary sodium and collection of 24 hr. urines,

similar percentages of dietary sodium were excreted in urine [2, 3]. For example, Holbrook reported 86% of

sodium ingested was excreted in 24 hr. urine while on a usual dietary pattern during a year-long study that

included 4 separate weeks of rigorous assessment of dietary sodium intake and urine excretion [2] and

Schachter reported 98% of sodium was excreted in 24 hr. urines in a 3 day study[3]. When there is a

substantive sustained change in dietary sodium, it can take 3 or more days before a new steady state urine

excretion of sodium is achieved[4-7]. Therefore, in the absence of large recent changes in dietary sodium, this

meta-analysis indicates quantitating 24 hr. urine sodium is a close (93%) estimate of average 24 hr. dietary

sodium in a study population. However, most people vary their sodium intake meal to meal, day to day and

often season to season[8, 9]. Further, a very carefully conducted physiological study found half weekly and

weekly cyclic variation in sodium excretion when people were on a constant sodium diet [17]. Hence, there is

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no scientific rationale to expect a single 24 hr. urine sodium to reflect an individual's usual long -term sodium

intake. Several studies support the need for multiple 24 hr. urine collections, timed to account for usual daily

variation of dietary intake <mark>and long-term cyclic changes in sodium excretion</mark> to accurately assess an

individual's usual sodium intake[6, 9].

The average 24 hr. urine sodium included large variations in the percentage of sodium excreted

between studies leading to high heterogeneity. For example, the average excretion of ingested sodium varied

from 76% to 122% (figure 2). The heterogeneity indicates caution should be exercised when interpreting the

average result. It is likely that inaccuracies in quantitating sodium in the diet and in collecting 24 hr. urine

accounts of some of the observed heterogeneity in the percentage of dietary sodium excreted. The studies

were selected based on criteria that implied rigorous collection of 24 hr. urines and assessment of the amount

of dietary sodium that was consumed. However, we noted, there was a general lack of quality assurance to

ensure the accuracy of and adherence to dietary sodium and criteria to assess and exclude incomplete 24 hr.

urine collections. The limitations of dietary assessment of sodium intake have been well documented and

include difficulty accurately measuring discretionary salt and portion size, and inaccuracies in food

composition databases[33]. In at least one study that reported measuring the sodium content in the foods

provided, there was some variance from the amount of sodium the study intended to provide[10]. Further,

most studies did not observe the diets being consumed and hence there is no certainty that additional sodium

was not added to the foods or that more or less food was consumed than reported. In addition, it is likely that

there was variation in the completeness of collecting 24 hr. urine samples within individuals and between

studies. Incomplete 24 hr. urine collections are common in research studies and will lead to underestimates of

the amount of sodium excreted[11]. Less commonly, excess urine is collected and can result in over estimates

of sodium excretion. We noted wide variation in indirect methods used to exclude incomplete urine

collections. The different methods for excluding incomplete urine collections can result in large differences in

estimated dietary sodium[36]. Nevertheless, when we examined the 3 studies that most carefully assessed

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dietary sodium and completeness of urine collections, the average excretion was close to that in the overall meta-analysis (89.4% vs 92.8% of ingested sodium excreted in 24 hr. urine)[12-14].

Other factors besides variation in dietary sodium and incomplete 24 hr. urine collections, have been reported to impact estimates of sodium excretion including health status, circadian variation, hydration status, excessive sweating, hormonal changes, and other dietary factors that may have not been reported in the studies[15-17]. Long-term cyclic variation in sodium excretion has also been reported, which could further complicate measurements taken during short-term studies[13]. Diets varied between and within studies, with some studies identifying relationships between dietary calcium, alcohol, potassium, and sodium excretion[18-21]. We did not confirm an impact of different levels of stable potassium intake on the percentage of dietary sodium excreted but this does not exclude an effect of changes in potassium intake. Studies should account potential confounding factors when reporting average sodium excretion and interpreting single 24 hr. urine excretions.

There was also variation in the mean percentage excretion of dietary sodium in the subgroup analysis comparing normal-physiological sodium intake to the high intake group. Studies included in the normal physiological sodium intake group (100 to < 1000 mg/day) often had >100% percentage of ingested sodium excreted. The >100% sodium excretion found in some studies may reflect a lack of adherence to the lower dietary sodium, or cyclic variations in sodium excretion. It is also possible that, due to a large recent reduction of sodium intake as part of some trials, the participants had not yet achieved a steady state of sodium excretion relative to intake. In our subgroup analysis examining the length of steady state at lower sodium intake levels, it was unclear if longer durations are needed to reach steady-state. Previous studies examining less substantive changes in intake of sodium indicate approximately 3 days are required to reach a steady state for the study groups average sodium excretion[4-6]. In our sub group meta-analyses, of all levels of dietary sodium, steady state diets longer than 3 days did not alter the percentage of dietary sodium excreted.

An important limitation of this study is the generalizability of findings. The focus on strict dietary protocols to ensure metabolic steady state may not represent participants who do have varying dietary protocols (e.g. substantive short-term change in sodium intake). Likewise, individuals with acute health problems, rigorous physical activity, short term exposure to high temperature, drug therapies that impact sodium excretion, or chronic kidney disease, may excrete different percentages of sodium[9, 19]. Therefore, 24 hr. urine sodium measurements during acute dietary transition, acute changes in physical activity, large temperature changes or illness may not be able to accurately define sodium intake level.

Conclusion

The current meta-analysis found that approximately 93% of dietary sodium is excreted in urine. The primary and subgroup analyses had substantive heterogeneity which may in part be explained by a general lack of quality control in assessing dietary intake of sodium and the completeness of 24 hr. urine collections. Nevertheless, the average percentage excretion of each subgroup analysis was close to 93% providing strong support for using 24h urine collections to assess average dietary sodium intake (while accounting for the loss of approximately 7% of dietary sodium). It is noteworthy though that diet usually changes meal to meal and day to day therefore to determine a person's usual salt intake, multiple 24 hr. urines are required.

Diseases Prevention Through Population Wide Dietary Salt Reduction, World Hypertension League, World Stroke Organization.

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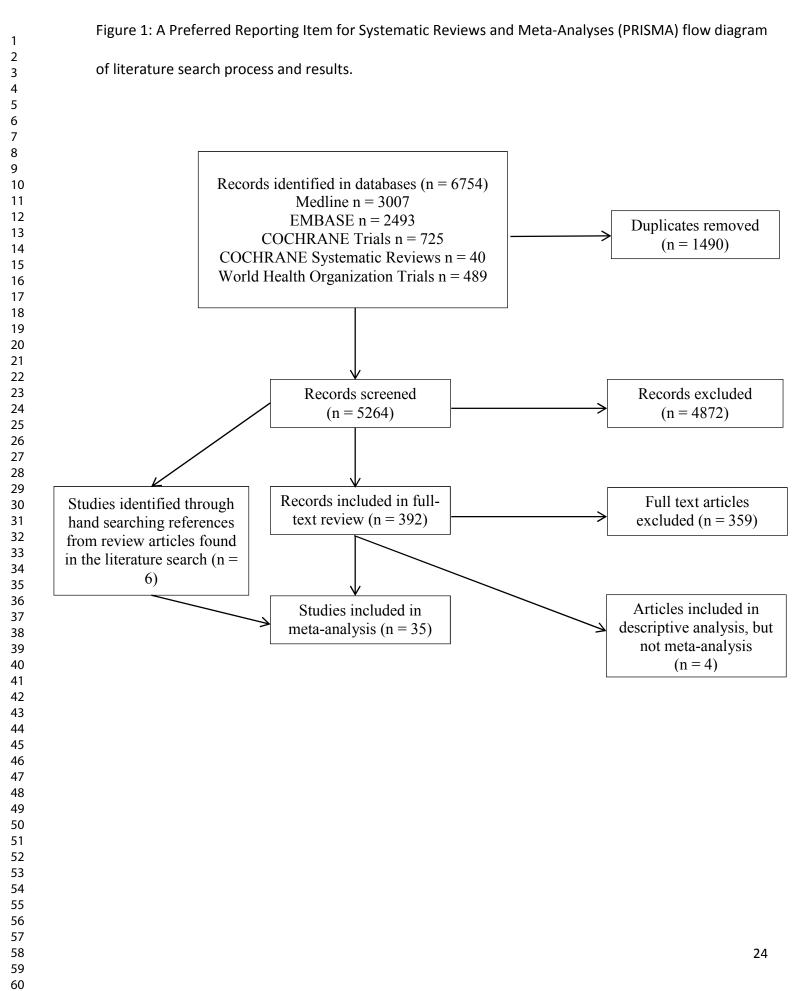
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Figure 1: A Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

of literature search process and results.

Records identified in databases (n = 6754)
Medline n = 3007
EMBASE n = 2493
COCHRANE Trials n = 725
COCHRANE Systematic Reviews n = 40
World Health Organization Trials n = 489

Duplicates removed
(n = 1490)

Records screened
(n = 5264)

Records excluded
(n = 4872)

Studies identified through hand searching references from review articles found in the literature search (n = 6)

Records included in full-text review (n = 392)

Full text articles excluded (n = 359)

Studies included in meta-analysis (n = 35)

Articles included in descriptive analysis, but not meta-analysis
(n = 4)

Figure 2: Forest plot for pooled percentage of dietary sodium excretion in each study.

Study ID	% (95% CI)	% Weight
Evans, 1997	78.83 (71.84, 85.82)	3.05
Kawano, 2004	93.33 (86.67, 100.00)	3.14
Sanchez-Castillo, 1987	93.20 (93.17, 93.23)	4.45
Shore, 1988 (a)	92.28 (86.91, 97.64)	3.50
Shore, 1988 (b)	98.81 (92.94, 104.69)	3.36
van Buren, 1992	90.94 (85.39, 96.49)	3.45
Birukov, 2016	94.27 (75.36, 113.17)	1.02
Dahl, 1995	90.41 (88.85, 91.97)	4.35
Herrin, 1986	82.31 (67.55, 97.06)	1.46
McKnight, 1994	107.23 (101.97, 112.50)	3.53
van Buren, 1993	93.06 (88.27, 97.86)	3.66
Vaughan, 1997	76.75 (65.25, 88.24)	1.98
Yamakawa, 1992	89.33 (80.37, 98.29)	2.54
Breslau, 1983	88.43 (76.92, 99.93)	1.98
Chan, 1996	96.60 (88.86, 104.33)	2.85
Feng, 2016	125.04 (79.40, 170.68)	0.22
Gijsbeers, 2015	101.90 (82.11, 121.69)	0.95
Gill, 1988	83.08 (80.22, 85.95)	4.13
Heer, 1993	81.14 (79.87, 82.41)	4.39
Imafuku, 1990	89.40 (48.71, 130.09)	0.27
Keane, 1991	122.12 (117.27, 126.97)	3.65
Luft, 1982 (a)	90.00 (87.33, 92.67)	4.17
Luft, 1982 (b)	87.78 (85.39, 90.18)	4.23
Manitius, 1985	80.76 (76.42, 85.09)	3.78
Ogihara, 1988	120.94 (97.35, 144.54)	0.71
Sagnella, 1989	122.00 (78.00, 166.00)	0.23
Sakhaee, 1993	81.08 (66.35, 95.82)	1.46
Sowers, 1988	95.21 (91.68, 98.75)	3.99
Akita, 2003	95.19 (93.85, 96.53)	4.38
Buckley, 1994	97.33 (91.64, 103.03)	3.41
Lawton, 1988	89.98 (86.47, 93.48)	3.99
Overlack, 1993	94.52 (93.09, 95.94)	4.37
Roos, 1985	102.66 (94.08, 111.24)	2.63
Sharma, 1990	95.32 (87.72, 102.92)	2.88
Schwartz, 1992	100.63 (88.22, 113.04)	1.82
Overall (I-squared = 95.1%, p = 0.000)	92.83 (90.65, 95.00)	100.00

NOTE: Weights are from random effects analysis

Percent Sodium Excreted

Figure 3: Forest plot detailing the percentage excretion by each subgroup category.

P-values represent the test statistic for differences between each variable and sodium excretion. Potassium

intake and duration of steady state were meta-regressed as continuous variables, the rest were categorical.

Low potassium intake was defined as < 77.6 mmol/day and high potassium as greater than 77.6 mmol/day.

Controlled environments included studies where the participants were in a research facility (e.g. hospital

ward) and uncontrolled studies were those where the participants were 'free living'. The sodium intake meta-

regression was compared to high intake. Sodium intakes were categorized and included the following ranges:

normal-physiologic (100-<1000 mg sodium/day), recommended (1000 to <2000 mg sodium/day), high ($\geq$ 2000

– 4000 mg sodium /day), very high (>4000-6000 mg sodium /day), and extremely high (>6000 mg sodium/day).

The low to high 'direction' indicates sodium intake had been increased before the assessment of excretion

while no direction indicates there had been no change in sodium intake before the assessment. Steady state

refers to the duration of a constant sodium diet before assessment of excretion. Studies were considered to

have more rigor if dietary intake was assessed with a known unbiased reference measure (denominator) and

the 24-h urine collections were high quality.

Figure 4: Meta-regression plot of the percentage of sodium excreted to length of steady state, in those with

low sodium intake.

Appendix A – Search Terms

Medline

1   chlorides/ or potassium chloride/ or sodium chloride/ (110384)

2   Salts/ (12384)

3   (sodium or chloride* or salt or salts or Na).tw,kw. (532478)

4   1 or 2 or 3 (599066)

5   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 sodium).tw,kw. (31697)

6   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 salt).tw,kw. (9121)

7   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 Na).tw,kw. (2515)

8   5 or 6 or 7 (40141)

9   ((24-hr* or 24hr* or 24 hour* or 24hour*) adj5 urin*).tw,kw. (8801)

10   urine.fs. (200058)

11   analysis.fs. (1801499)

12   9 or 10 or 11 (1970407)

13   ((sodium or salt* or Na) adj5 (excret* or urin* or retention* or balanc* or storage or output*).tw,kw. (32656)

14   4 and 8 and 12 and 13 (3007)

Embase

1   chlorides/ or potassium chloride/ or sodium chloride/ (249573)

2   Salts/ (6748)

3   (sodium or chloride* or salt or salts or Na).tw,kw. (614270)

4   1 or 2 or 3 (785735)

5   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 sodium).tw,kw. (36202)

6   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 salt).tw,kw. (10987)

7   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 Na).tw,kw. (2900)

8   5 or 6 or 7 (46170)

9   ((24-hr* or 24hr* or 24 hour* or 24hour*) adj5 urin*).tw,kw. (13267)

10   Urine/ or urinary excretion/ (197722)

11   sodium retention/ (3580)

12   9 or 10 or 11 (208568)

13   ((sodium or salt* or Na) adj5 (excret* or urin* or retention* or balanc* or storage or output*)).tw,kw. (36117)

14   4 and 8 and 12 and 13 (2493)

Cochrane Trials

1   chlorides/ or potassium chloride/ or sodium chloride/ (2503)

2   Salts/ (54)

3   (sodium or chloride* or salt or salts or Na).tw,kw. (23655)

4   1 or 2 or 3 (25326)

5   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 sodium).tw,kw. (4038)

6   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 salt).tw,kw. (651)

7   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 Na).tw,kw. (137)

8   5 or 6 or 7 (4465)

29

9   ((24-hr* or 24hr* or 24 hour* or 24hour*) adj5 urin*).tw,kw. (1487)

10   Urine/ or urinary excretion/ (588)

11   Urin*.tw,kw. (32798)

12   sodium retention/ (0)

13   9 or 10 or 11 or 12 (32950)

14   ((sodium or salt* or Na) adj5 (excret* or urin* or retention* or balanc* or storage or output*).tw,kw.. (3100)

15   4 and 8 and 13 and 14 (725)

Cochrane Systematic

1   (sodium or chloride* or salt or salts).mp. (1264)

2   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 sodium).mp. (195)

3   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 salt).mp. (107)

4   ((dietar* or chloride* or intake* or food* or consumption or consume*) adj5 Na).mp. (6)

5   2 or 3 or 4 (268)

6   ((24-hr* or 24hr* or 24 hour* or 24hour*) adj5 urin*).mp. (111)

7   Urin*.mp. (1700)

8   ((sodium or salt* or Na) adj5 (excret* or urin* or retention* or balanc* or storage or output*)).mp. (131)

9   6 or 7 (1700)

10   1 and 5 and 8 and 9 (40)

WHO Clinical Trials Database

(Sodium or salt) or (diet* or food* or intake or consum*) -   Title

Or

(Sodium or salt) or (diet* or food* or intake or consum*) -   Condition

Or

(Sodium or salt) or (diet* or food* or intake or consum*) -   Intervention

(489)

Appendix B – Study Characteristics

First author, year	Country	Population characteristics	Population health risks/status	Age range or average age (years)	Study Design	Sodium Intervention Duration	Washout Time Between Dietary Intervention Periods	Sample Size			Mean sodium ingested (mmol/day)	Met additional criteria for rigorous methodology
								Male	Female	Total		
Akita, 2003	USA	None stated	Hypertension	22	Randomized control trial	30 days	0 days	NA	NA	412	50 100 150	No
Birukov, 2016	Russia	Healthy male volunteers	None	34.3 +/- 5.2, 31.5 +/- 5	Control trial	105, and 205 days	NA	12	0	12	12, 9, 12, 6 grams per day (individual outputs not given for each sodium intake)	Yes
Breslau, 1983	USA	Normal volunteers	None	22-36	Randomized crossover trials	10 days	0 days	6	5	11	10 250	No
Buckley, 1994	UK	None stated	Hypertension	48.7 +/- 2.3	Randomized crossover	5 days	0 days	5	7	12	10 350	No
Buren, 1992	The Netherlands	Healthy subjects	None	none stated	Control trial	4 days	NA	NA	NA	21	100 150	No
Buren, 1993	The Netherlands	Healthy volunteers	None	18-22	Crossover trial	8 days	2-8 weeks	4	2	6	10 100 400	No
Chan, 1996	China	Male Chinese subjects	None	21-31	Crossover trial	5 days	0 days	7	0	7	20 220	No
Dahl, 1995	Canada	Male volunteers with no medications or GI problems	None	25.3 +/- 2.3	Randomized crossover trial	3 weeks	0 days	10	0	10	160 150	Yes
Evans, 1997	United Kingdom	Pre and postmenopausal women	None	22-70	Randomized control trial	1 week	0 days	0	22	22	50 300	No
Feng, 2016	China	newly diagnosed hypertensive patients	Hypertension	27-52	Control trial	10 days	NA	74	51	125	173.91	No
Gill, 1988	USA	Hypertensive patients, normotensive controls	Hypertension	20-75	Crossover trial	7 days	0 days	12	17	29	109	No
Gijsbeers, 2015	The Netherlands	Non-smoking men and women aged 40-80.	None	65.8	Randomized control trial	4 weeks	0 days	24	12	36	87 217.5	No
Heer, 1993	Germany	Non-smoking male patients	None	24 +/- 1	Crossover trial	8 days	0 days	6	0	6	220 440 660	No
Herrin, 1986	NA	Healthy volunteers	None	24-63	Randomized control trial	7 days	NA	NA	NA	5	65	No
Imafuku, 1990	Japan	Normotensive males	None	21-39	Crossover trial	3 and 4 days	0 days	7	0	7	34.9	No
Kawano, 2004	Japan	Japanese males with hypertension and drinking habits	Hypertension	54 +/- 2	Control trial	13 days	NA	14	0	14	120	No
Keane, 1991	Canada	Medical patients	None	42 +/- 2	Crossover trial	5 days	0 days	13	24	37	10 100	No
Lawton 1988	USA	None stated	Hypertension and normal subjects	24.8 +/- 1.1 and 24.3 +/- 0.6	Randomized crossover	6 days	3-4 weeks	22	0	22	8.5 380	No
Luft, 1982 A	USA	Black and white men and women	None	19-54	Randomized crossover trial	5 days	NA	22	21	43	150	No
Luft. 1982 B	USA	Black and white men	None	19-32	Randomized control trial	7 days	NA	24	0	24	10 200 400	No
Manitius, 1985	Poland	Men with benign hypertension	Hypertension	20-41	Crossover trial	5 days	0 days	12	0	12	80 280	No

First author, year	Country	Population characteristics	Population health risks/status	Age range or average age (years)	Study Design	Sodium Intervention Duration	Washout Time Between Dietary Intervention Periods	Sample Size			Mean sodium ingested (mmol/day)	Met additional criteria for rigorous methodology
								Male	Female	Total		
McKnight, 1994	United Kingdom	Hypertensive men	Hypertension	34-50	Crossover trial	6 days	0 days	8	0	8	12 250	No
Ogihara, 1988	Japan	Patients in an outpatient clinic	Hypertension	56 +/- 3	Crossover trial	5 days	0 days	4	6	10	33.9	No
Overlack, 1993	Germany	None stated	None	38 +/- 1.2	randomized crossover	7 days	0 days	98	65	163	20 300	No
Roos, 1985	The Netherlands	None stated	None	21-26	Crossover trial	5 days	2 days	5	3	8	20 200	No
Sagnella, 1989	United Kingdom	Young, normotensive subjects	None	19-21	Crossover trial	4 days	NA	4	2	6	10	No
Sakhaee, 1993	USA	Normal volunteers with no renal or heart disease.	None	29	Crossover trial	7 days	Unclear	6	8	14	50 300	No
Sanchez-Castillo, 1987	United Kingdom	Healthy male volunteers	None	NA	Control trial	34 days	NA	5	0	5	144	Yes
Schwartz, 1992	USA	Sons of hypertensive parents and sons of non-hypertensive patients	None	41 +/- 4 and 47 +/- 5	crossover trial	7 days	0 days	22	0	22	10 200	No
Sharma, 1990	Germany	None stated	None	20-31	randomized crossover	3 weeks	0 days	15	0	15	20 220	No
Shore, 1998 A	United Kingdom	Patients with no history of renal or heart disease	None	NA	Randomized crossover trial	5 days	0 days	NA	NA	6	10 122	No
Shore, 1988 B	United Kingdom	Healthy volunteers	None	18-24	Randomized crossover trial	12 days	3 days	8	1	9	150	No
Sowers, 1988	USA	Normotensive and hypertensive black adults	Hypertension	34 +/- 6 and 44 +/- 8	Crossover trial	14 days	0 days	NA	NA	25	40 180	No
Vaughan, 1997	USA	Free living caucasian males	Hypertension	50 +/- 10	Randomized control trial	6 weeks	NA	NA	NA	15	143.48	No
Yamakawa, 1992	Japan	Normotensive subjects with and without a family history of hypertension	None	20-22	Crossover trial	7 days	0 days	NA	NA	14	101.7	No
Allsopp, 1998	United Kingdom	None stated	None	18-40	Randomized control trial	8 days	0 days	25	0	25	348.4 66.3 174.1 348.4	No
Armstrong, 1985	USA	College aged males with no record of regular exercise	None	None stated	Randomized crossover trial	16 days	24 days	8	0	8	98 399	No
Mueller, 1995	USA	None stated	Some patients with hypertension.	None stated	Randomized crossover trial	3 and 4 days	0 days	NA	NA	30	176 44	No
Parfrey, 1981	United Kingdom	Patients with essential hypertension, normotensive controls	Hypertension	None stated	Crossover trial	5 days	0 days	45	60	105	10 350	No