



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

Journal:	<i>The Journal of Clinical Hypertension</i>
Manuscript ID	JCH-18-0138.R1
Wiley - Manuscript type:	Policy Statement from the World Hypertension League
Date Submitted by the Author:	n/a
Complete List of Authors:	<p>Lucko, Aaron; University of Calgary, Doktorchik, Chelsea; University of Calgary Cumming School of Medicine, Community Health Sciences</p> <p>Woodward, Mark; University of Oxford, The George Institute for Global Health; The George Institute for Global Health</p> <p>Cogswell, Mary; CDC/NCCDPHP, DHDSP</p> <p>Neal, Bruce; University of Sydney,</p> <p>Rabi, Doreen; University of Calgary Cumming School of Medicine, Departments of Medicine, Community Health and Cardiac Sciences</p> <p>Anderson, Cheryl; University of California San Diego, Department of Family Medicine and Public Health</p> <p>He, Feng; Barts and The London School of Medicine &amp; Dentistry, Wolfson Institute of Preventive Medicine</p> <p>MacGregor, Graham; Barts and The London School of Medicine &amp; Dentistry, Wolfson Institute of Preventive Medicine</p> <p>L'Abbé, Mary; University of Toronto, Faculty of Medicine</p> <p>Arcand, JoAnne; University of Ontario Institute of Technology, Faculty of Health Sciences</p> <p>Whelton, Paul; Tulane University School of Public, Epidemiology</p> <p>McLean, Rachael; University of Otago, Department of Preventive &amp; Social Medicine</p> <p>Campbell, Norm; University of Calgary, Medicine</p>
Keywords:	salt, Sodium, research methods, Diet/Nutrition/Hypertension, public health
Abstract:	<p>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</p>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

	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.

Aaron M Lucko BHSc<sup>1</sup>, Chelsea Doktorchik MSc<sup>2</sup>, Mark Woodward PhD<sup>3,4</sup>, Mary Cogswell DrPH, RN<sup>5</sup>, Bruce Neal MB ChB, MRCP, PhD, FRCP, FAHA<sup>6</sup>, Doreen Rabi MD MSc FRCPC<sup>7</sup>, Cheryl Anderson PhD, MPH, MS<sup>8</sup>, Feng J He PhD<sup>9</sup>, Graham A MacGregor FRCP<sup>9</sup>, Mary L'Abbe PhD<sup>10</sup>, JoAnne Arcand PhD, RD<sup>11</sup>, Paul K Whelton MB, MD, MSc<sup>12</sup>, Rachael McLean BA MB ChB MPH PhD<sup>13</sup>, Norm RC Campbell MD<sup>14</sup> for the TRUE Consortium

1 Department of Microbiology, Immunology, and Infectious Diseases, University of Calgary, Calgary, Alberta, Canada, T2N4Z6 Tel 1-403-968-6281, amlucko@ucalgary.ca

2. Department of Community Health Sciences, O'Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada, T2N4Z6 Tel: (403) 210-3875, email: ctadokto@ucalgary.ca

3. The George Institute for Global Health, University of Oxford, Le Gros Clark Building, South Parks Road, Oxford OX1 3QX, United Kingdom. Tel +44 7408 841174 mark.woodward@georgeinstitute.ox.ac.uk.

4. The George Institute for Global Health, Level 5, 1 King St, Newtown NSW 2042 Australia  
Tel +61 481 471 745 markw@georgeinstitute.org.au

4. Division for Heart Disease and Stroke Prevention, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 4770 Buford Highway, NE, Mailstop F-73, Atlanta, GA 30345, United States Tel +770-488-8053 mec0@cdc.gov

5. The George Institute for Global Health | AUSTRALIA, Level 5, 1 King St | Newtown NSW 2042 Australia  
Australia Tel +61 2 8052 4558 bneal@georgeinstitute.org.au

6. Departments of Medicine, Community Health and Cardiac Sciences University of Calgary, Calgary, Alberta, Canada, T2N4Z6 Tel 403-220-8867 Doreen.Rabi@albertahealthservices.ca

7. Department of Family Medicine and Public Health, University of California San Diego, MC 0725 La Jolla, CA 92093-0725, Tel +858-822-3699 c1anderson@ucsd.edu

8. Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ Tel 44 (0)20 7882 6266  
f.he@qmul.ac.uk, Tel +44 (0)20 7882 6217 g.macgregor@qmul.ac.uk

9. Faculty of Medicine, University of Toronto, FitzGerald Building, 150 College St, Rm 315  
Toronto ON Canada M5S 3E2, Tel 416-978-7235; Email: mary.labbe@utoronto.ca

10. Faculty of Health Sciences University of Ontario Institute of Technology 2000 Simcoe St. North, Science Building, Rm 3016 Oshawa Ontario, Canada L1H 7K4 Tel (647) 296-8426 JoAnne.Arcand@uoit.ca

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60
11. Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, U.S.A., Tel: (504) 988-6580, email: pkwhelton@gmail.com
12. Department of Preventive & Social Medicine, University of Otago, P.O. Box 56, Dunedin, New Zealand 9054 Phone +643 479 9428 rachael.mclean@otago.ac.nz
13. Department of Medicine, Physiology and Pharmacology and Community Health Sciences, O'Brien Institute for Public Health and Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada, T2N4Z6 Tel: (403) 210-7961, Fax: (403) 210-9837, email: ncampbel@ucalgary.ca

**Disclaimer:** The findings and conclusions expressed in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

**Conflicts of Interest:** FJH is a member of Consensus Action on Salt & Health (CASH) and World Action on Salt & Health (WASH). Both CASH and WASH are non-profit charitable organisations and FJH does not receive any financial support from CASH or WASH. GAM is Chairman of Blood Pressure UK (BPUK), Chairman of CASH, WASH and Action on Sugar (AoS). BPUK, CASH, WASH and AoS are non-profit charitable organisations. GAM does not receive any financial support from any of these organisations. NRCC was a paid consultant to the Novartis Foundation to support their program to improve hypertension control in cities of low to middle income countries which includes travel support for site visits and a contract to develop a survey (2016-2017). NRCC has provided paid consultative advice on accurate blood pressure assessment to Midway Corporation (2017) and is an unpaid member of World Action on Salt and Health (WASH). MW is a consultant to Amgen. RM has no conflicts of interest to declare.

Correspondence: to Dr Norm Campbell, GE -86, Libin Cardiovascular Institute of Alberta, University of Calgary, 3280 Hospital Drive NW, Calgary Alberta, Canada T2N 4Z6

## 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.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

**Introduction**

High dietary sodium is estimated to be the leading dietary risk for death and disability according to the Global Burden of Disease Study<sup>[1,2]</sup>. 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<sup>[1]</sup>. 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<sup>[4]</sup>, 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<sup>[5]</sup>. 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<sup>[6]</sup>. The TRUE consortium formed because of concerns that low quality research was causing controversy about the health impact of dietary sodium<sup>[7]</sup>. 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.

55

56

57

58

59

60

**Methods**

## 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).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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<sup>[8]</sup>. 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<sup>[9,10]</sup>.

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<sup>2</sup> statistic. Sub-group analysis was performed on the following variables: potassium intake (calculated as either having a potassium intake above or below



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  $\geq 2000$  mg to 4000 mg, very high intake as > 4000 to 6000 mg, and extremely high intake as >6000 mg<sup>[11]</sup>. 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<sup>[12]</sup>. Controlled feeding studies provide meals and carefully monitor the amount of food consumed<sup>[13]</sup>. 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<sup>[14]</sup>. 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.

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<sup>[9,10]</sup>. Two studies were also removed because they included participants or used methodologies that may have affected sodium steady state<sup>[15,16]</sup>. 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<sup>[17,18]</sup> 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.

**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 <sup>[11]</sup>. 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).

**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, 133.6, 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 ( $p = 0.742$ ).

**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<sup>[18]</sup>, a high risk of bias<sup>[19-21]</sup>, and for having a change in sodium intake of over 4600 mg/day<sup>[21-27]</sup>. 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<sup>[23]</sup> 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<sup>[15,16]</sup>. The other two studies did not include variance data for urine sodium excretion and so could not be used in the analysis<sup>[9,10]</sup>. The studies

1 ranged between 8 and 105 participants, with two studies being male only<sup>[15,16]</sup>. Two studies measured urine  
2 sodium while on a stable diet for 5 days or more, two measured urine sodium at either 3 or 4 days of a stable  
3 diet. Two of the studies assessed hypertensive patients<sup>[9,10]</sup>. Allsopp et al. had three sodium intake levels of  
4 1525, 4004, and 8013 mg/day during acute heat exposure and urine sodium excretion ranged from 38.14 to  
5 72.13%<sup>[15]</sup>. Armstrong et al. had 1081 and 5490 mg/day sodium intake levels during acute heat exposure and a  
6 sodium excretion range of 47.96 to 59.82%<sup>[16]</sup>. Mueller et al. and Parfrey et al. both had two levels of sodium  
7 intake of 1012 and 4048 mg/day and 230 and 8050 mg/day, respectively, and respective sodium excretion  
8 values ranging between 100.1 to 115.5% and 69.71 to 220%<sup>[9,10]</sup>.  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21

## 22 Discussion

23  
24 The overall pooled estimate from this meta-analysis indicates that on average 92.8% of 24 hr. dietary  
25 sodium was excreted in 24 hr. urine collections. This meta-analysis only included studies where participants  
26 had a constant amount of sodium in their diets for a minimum of 3 days. Where participants ate their usual  
27 diets, in other studies that included careful assessment of dietary sodium and collection of 24 hr. urines,  
28 similar percentages of dietary sodium were excreted in urine<sup>[2, 3]</sup>. For example, Holbrook reported 86% of  
29 sodium ingested was excreted in 24 hr. urine while on a usual dietary pattern during a year-long study that  
30 included 4 separate weeks of rigorous assessment of dietary sodium intake and urine excretion [2] and  
31 Schachter reported 98% of sodium was excreted in 24 hr. urines in a 3 day study<sup>[3]</sup>. When there is a  
32 substantive sustained change in dietary sodium, it can take 3 or more days before a new steady state urine  
33 excretion of sodium is achieved<sup>[4-7]</sup>. Therefore, in the absence of large recent changes in dietary sodium, this  
34 meta-analysis indicates quantitating 24 hr. urine sodium is a close (93%) estimate of average 24 hr. dietary  
35 sodium in a study population. However, most people vary their sodium intake meal to meal, day to day and  
36 often season to season<sup>[8, 9]</sup>. Further, a very carefully conducted physiological study found half weekly and  
37 weekly cyclic variation in sodium excretion when people were on a constant sodium diet<sup>[17]</sup>. Hence, there is  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1 no scientific rationale to expect a single 24 hr. urine sodium to reflect an individual’s usual long -term sodium  
2 intake. Several studies support the need for multiple 24 hr. urine collections, timed to account for usual daily  
3 variation of dietary intake and long-term cyclic changes in sodium excretion to accurately assess an  
4 individual’s usual sodium intake<sup>[6, 9]</sup>.  
5  
6  
7  
8  
9

10 The average 24 hr. urine sodium included large variations in the percentage of sodium excreted  
11 between studies leading to high heterogeneity. For example, the average excretion of ingested sodium varied  
12 from 76% to 122% (figure 2). The heterogeneity indicates caution should be exercised when interpreting the  
13 average result. It is likely that inaccuracies in quantitating sodium in the diet and in collecting 24 hr. urine  
14 accounts of some of the observed heterogeneity in the percentage of dietary sodium excreted. The studies  
15 were selected based on criteria that implied rigorous collection of 24 hr. urines and assessment of the amount  
16 of dietary sodium that was consumed. However, we noted, there was a general lack of quality assurance to  
17 ensure the accuracy of and adherence to dietary sodium and criteria to assess and exclude incomplete 24 hr.  
18 urine collections. The limitations of dietary assessment of sodium intake have been well documented and  
19 include difficulty accurately measuring discretionary salt and portion size, and inaccuracies in food  
20 composition databases<sup>[33]</sup>. In at least one study that reported measuring the sodium content in the foods  
21 provided, there was some variance from the amount of sodium the study intended to provide<sup>[10]</sup>. Further,  
22 most studies did not observe the diets being consumed and hence there is no certainty that additional sodium  
23 was not added to the foods or that more or less food was consumed than reported. In addition, it is likely that  
24 there was variation in the completeness of collecting 24 hr. urine samples within individuals and between  
25 studies. Incomplete 24 hr. urine collections are common in research studies and will lead to underestimates of  
26 the amount of sodium excreted<sup>[11]</sup>. Less commonly, excess urine is collected and can result in over estimates  
27 of sodium excretion. We noted wide variation in indirect methods used to exclude incomplete urine  
28 collections. The different methods for excluding incomplete urine collections can result in large differences in  
29 estimated dietary sodium<sup>[36]</sup>. Nevertheless, when we examined the 3 studies that most carefully assessed  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1 dietary sodium and completeness of urine collections, the average excretion was close to that in the overall  
2 meta-analysis (89.4% vs 92.8% of ingested sodium excreted in 24 hr. urine)<sup>[12-14]</sup>.  
3  
4

5 Other factors besides variation in dietary sodium and incomplete 24 hr. urine collections, have been  
6 reported to impact estimates of sodium excretion including health status, circadian variation, hydration status,  
7 excessive sweating, hormonal changes, and other dietary factors that may have not been reported in the  
8 studies<sup>[15-17]</sup>. Long-term cyclic variation in sodium excretion has also been reported, which could further  
9 complicate measurements taken during short-term studies<sup>[13]</sup>. Diets varied between and within studies, with  
10 some studies identifying relationships between dietary calcium, alcohol, potassium, and sodium excretion<sup>[18-</sup>  
11 21]. We did not confirm an impact of different levels of stable potassium intake on the percentage of dietary  
12 sodium excreted but this does not exclude an effect of changes in potassium intake. Studies should account  
13 potential confounding factors when reporting average sodium excretion and interpreting single 24 hr. urine  
14 excretions.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28

29 There was also variation in the mean percentage excretion of dietary sodium in the subgroup analysis  
30 comparing normal-physiological sodium intake to the high intake group. Studies included in the normal  
31 physiological sodium intake group (100 to < 1000 mg/day) often had >100% percentage of ingested sodium  
32 excreted. The >100% sodium excretion found in some studies may reflect a lack of adherence to the lower  
33 dietary sodium, or cyclic variations in sodium excretion. It is also possible that, due to a large recent reduction  
34 of sodium intake as part of some trials, the participants had not yet achieved a steady state of sodium  
35 excretion relative to intake. In our subgroup analysis examining the length of steady state at lower sodium  
36 intake levels, it was unclear if longer durations are needed to reach steady-state. Previous studies examining  
37 less substantive changes in intake of sodium indicate approximately 3 days are required to reach a steady  
38 state for the study groups average sodium excretion<sup>[4-6]</sup>. In our sub group meta-analyses, of all levels of  
39 dietary sodium, steady state diets longer than 3 days did not alter the percentage of dietary sodium excreted.  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

17 **Conclusion**

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

39 **Acknowledgements**

42 The authors would like to acknowledge the contributions of Ms. Helen Robertson in developing the search  
43 terms used in this project, as well as Ms. Jane Liang, Drs. Tyler Williamson, and Paul Ronksley for their  
44 consultation on the statistical analysis. Member organizations of the TRUE consortium include the American  
45 Heart Association, British and Irish Hypertension Society, Chinese Regional Office of the World Hypertension  
46 League, Hypertension Canada, International Council of Cardiovascular Prevention and Rehabilitation,  
47 International Society of Hypertension, International Society of Nephrology, Journal of Clinical Hypertension,  
48 Pan American Health Organization/World Health Organization Technical Advisory Group on Cardiovascular

1 Diseases Prevention Through Population Wide Dietary Salt Reduction, World Hypertension League, World  
2  
3 Stroke Organization.  
4  
5  
6  
7  
8  
9

## 10 References

- 11  
12 1. Global, regional, and national comparative risk assessment of 79 behavioral, environmental and  
13 occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global  
14 Burden of Disease Study 2015. *Lancet* 2016. 388(10053): p. 1659-1724.  
15  
16  
17  
18  
19
- 20 2. Campbell NRC, Lackland DT, Niebylski ML, Orias M, Redburn K, Nilsson P, et al. 2016 Dietary Salt Fact  
21 Sheet and Call to Action: The World Hypertension League, International Society of Hypertension, and  
22 the International Council of Cardiovascular Prevention and Rehabilitation. *J Clin Hypertens*  
23  
24 2016;18(11):1082–5.  
25  
26  
27  
28
- 29 3. Campbell NR, Khalsa T, Lackland DT, Niebylski M, Nilsson P, Redburn K, et al. High Blood Pressure  
30 2016 : Why Prevention and Control Are Urgent and Important . The World Hypertension League,  
31 International Society of Hypertension , World Stroke Organization , International Diabetes Foundation ,  
32 International Council of Cardiovascular Prevention and Rehabilitation. *J Clin Hypertens*  
33  
34 2016;18(8):714–7.  
35  
36  
37  
38  
39  
40
- 41 4. World Health Organization. Salt Reduction: Fact Sheet [updated June 2016; cited February 2017].  
42 Available from: <http://www.who.int/mediacentre/factsheets/fs393/en/>.  
43  
44  
45  
46
- 47 5. Cogswell M, Maalouf J, Elliott P, Loria CM, Patel S, Bowman B. Use of Urine Biomarkers to Assess  
48 Sodium Intake: Challenges and Opportunities. *Annu Rev Nutri* 2015;35:349-87.  
49  
50
- 51 6. TRUE Consortium (inTernational consoRtium for qUality resEarch on dietary sodium/salt),  
52  
53 *Recommended standards for assessing blood pressure in human research where blood pressure or*  
54  
55 *hypertension is a major focus. J Clin Hypertens*, 2017. 19(2): p. 108-113.  
56  
57  
58  
59  
60

1 7. Campbell NRC, Appel LJ, Cappuccio FP, Correa-rotter R, Hankey G, Lackland, et al. A Call for Quality  
2 Research on Salt Intake and Health : From the World Hypertension League and Supporting  
3 Organizations. *J Clin Hypertens* 2014;16(7):469–71.  
4  
5  
6  
7 8. Higgins J, Altman D, Gotzsche P, Juni P, Moher D, Oxman A. The Cochrane Collaboration’s Tool for  
8 Assessing Risk of Bias in Randomized Trials. *BMJ* 2011;343:1-9.  
9  
10  
11 9. Mueller PW, Hall WD, Caudill SP, MacNeil ML, Arepally A. An in-depth examination of the excretion of  
12 albumin and other sensitive markers of renal damage in mild hypertension. *Am J Hypertens* 1985;8(11),  
13 1072-1082.  
14  
15  
16  
17 10. Parfrey PS, Markandu ND, Roulston JE, Jones BE, Jones JC, MacGregor GA. Relation between arterial  
18 pressure, dietary sodium intake, and renin system in essential hypertension. *BR Med J (Clin Res Ed)*  
19 1981;283(6284), 94-97.  
20  
21  
22  
23 11. Campbell NC, Correa-Rotter R, Cappuccio F, Webster J, Lackland D, Neal B, Macgregor G. Proposed  
24 Nomenclature for Salt Intake and for Reductions in Dietary Salt. *J Clin Hypertens*. 2015;17(4):247-51.  
25  
26  
27  
28 12. Thompson FE, Kirkpatrick SI, Subar AF, Reedy J, Schap TE, Wilson MM, et al. The National Cancer  
29 Institute’s Dietary Assessment Primer: A Resource for Diet Research. *J Acad Nutr Diet*  
30 2015;115(12):1986–95.  
31  
32  
33  
34 13. Lampe JW, Huang Y, Neuhouser ML, Tinker LF, Song X, Schoeller DA, et al. Dietary biomarker  
35 evaluation in a controlled feeding study in women from the Women’s Health Initiative cohort. *Am J Clin*  
36 *Nutr* 2017;105:466–75.  
37  
38  
39  
40 14. John KA, Cogswell ME, Campbell NR, Nowson CA, Diet DN. Accuracy and Usefulness of Select Methods  
41 for Assessing Complete Collection of 24-Hour Urine : A Systematic Review. *J Clin Hypertens*  
42 2015;18(5):456–467.  
43  
44  
45  
46 15. Allsopp AJ, Sutherland R, Wood P, Wootton SA. The effect of sodium balance on sweat sodium  
47 secretion and plasma aldosterone concentration. *Eur J Appl Physiol* 1998;78(6), 516-521.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

16. Armstrong LE, Costill DL, Fink WJ. Effects of dietary sodium on body and muscle potassium content during heat acclimation. *Eur J Appl Physiol* 1985;54(4), 391-397.
17. Birukov A, Rakova N, Lerchl K, Olde Engberink RHG, Johannes B, Wabel P, et al. Ultra-long-term human salt balance studies reveal interrelations between sodium, potassium, and chloride intake and excretion. *Am J Clin Nutr* 2016;104(1):49-57.
18. Sanchez-Castillo CP, Branch WJ, James WPT. A test of the validity of the lithium-marker technique for monitoring dietary sources of salt in man. *Clin Sci* 1987;72(1):87-94.
19. Breslau NA, Pak CY. Lack of effect of salt intake on urinary uric acid excretion. *J Urol* 1983;129(3):531-2.
20. Buckley M, Markandu N, Sagnella G, MacGregor G. Brain and atrial natriuretic peptides: a dual peptide system of potential importance in sodium balance and blood pressure regulation in patients with essential hypertension. *J Hypertens* 1994;12:809-13.
21. Shore AC, Markandu ND, MacGregor GA. A randomized crossover study to compare the blood pressure response to sodium loading with and without chloride in patients with essential hypertension. *J Hypertens* 1988;6(8):613-7.
22. Chan TY, Critchley JA, Ho CS, Chan JC, Tomlinson B. Urinary dopamine and noradrenaline outputs during oral salt loading in healthy Chinese subjects with a family history of hypertension. *J Autom Pharmacol* 1996;16(1):1-6.
23. Heer M, Drummer C, Baisch F, Gerzer R. Long-term elevations of dietary sodium produce parallel increases in the renal excretion of urodilatin and sodium. *Pflugers Arch* 1993;425(5-6):390-4.
24. Herrin JR, Rubright WC, Squier CA, Lawton WJ, Osborn MO, Stumbo PJ, et al. Local and systemic effects of orally applied sodium salts. *J Am Dent Assoc* 1986;113(4):607-11.
25. Manitius J, Kliz J, Krupa-Wojciechowska B. The effect of dietary sodium loading on the kinetics of sodium excretion and blood pressure regulation in essential hypertensive men. *Cor Vasa* 1985;27(1):29-35.

1 26. McKnight JA, Roberts G, Sheridan B, Atkinson AB. The effect of low and high sodium diets on plasma  
2 atrial natriuretic factor, the renin-aldosterone system and blood pressure in subjects with essential  
3 hypertension. *Clin Endocrinol* 1994;40(1):73-7.  
4  
5  
6  
7 27. Sakhaee K, Harvey JA, Padalino PK, Whitson P, Pak CY. The potential role of salt abuse on the risk for  
8 kidney stone formation. *J Urol* 1993;150(2 Pt 1):310-2.  
9  
10  
11 28. Holbrook JT, Douglas LW, Smith JC, Patterson Y, Bodner JE, Kelsay JL. Sodium and potassium intake and  
12 balance in adults consuming self-selected diets1 2. *Am J Clin Nutr* 1984;40(4):786-93.  
13  
14  
15 29. Schachter J, Harper PH, Radin ME, Caggiula AW, McDonald RH, Diven WF. Comparison of sodium and  
16 potassium intake with excretion. *Hypertens* 1980;2(5):695-9.  
17  
18  
19 30. Sagnella GA, Markandu ND, Singer DRJ, Macgregor GA. Kinetics of Renal Sodium Excretion During  
20 Changes in Dietary Sodium Intake in Man - An Exponential Process? *Clin Exp Hypertens*  
21 1990;12(2):171-8.  
22  
23  
24 31. Weaver C, Martin B, McCabe G, McCabe L, Woodward M, Anderson CAM, et al. Individual variation in  
25 urinary sodium excretion among adolescent girls on a fixed intake. *J Hypertens* 2016;34(7):1290-7.  
26  
27  
28 32. Cogswell ME, Elliott P, Wang C, Rhodes DG, Pfeiffer CM, Loria CM. Assessing U . S . Sodium Intake  
29 through Dietary Data and Urine Biomarkers. *Adv Nutr* 2013;4:560-2.  
30  
31  
32 33. Rhodes DG, Murayi T, Clemens JC, Baer DJ, Sebastian RS, Moshfegh AJ. The USDA Automated Multiple-Pass  
33 Method accurately assesses population sodium intakes. *Am J Clin Nutr* 2013;97(5):958-64.  
34  
35  
36 34. Luft FC, Fineberg NS, Sloan RS. Estimating dietary sodium intake in individuals receiving a randomly  
37 fluctuating intake. *Hypertens* 1982. 4(6): 805-8.  
38  
39  
40 35. John KA, Cogswell ME, Campbell NR, Nowson CA, Legetic B, Hennis AJM, et al. Accuracy and Usefulness  
41 of Select Methods for Assessing Complete Collection of 24-Hour Urine: A Systematic Review. *J Clin*  
42 *Hypertens* 2016;18(5):456-67.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

36. Wielgosz A, Robinson C, Mao Y, Jiang Y, Campbell NRC, Muthuri S, et al. The Impact of Using Different Methods to Assess Completeness of 24-Hour Urine Collection on Estimating Dietary Sodium. *J Clin Hypertens* 2016;18(6):581–4.
37. Dahl, W.J., S.J. Whiting, and A.M. Stephen, *Dietary lentils and calcium balance in adult men. Nutr Res* 1995. 15(11): 1587-1598.
38. Armanini D, Bordin L, Andrisani A, Ambrosini G, Dona G, Sabbadin C. Considerations for the Assessment of Salt Intake by Urinary Sodium Excretion in Hypertensive Patients. *J Clin Hypertens* 2016;18(11):1143–5.
39. Baldo, M.P., S.L. Rodrigues, and J.G. Mill, *High salt intake as a multifaceted cardiovascular disease: new support from cellular and molecular evidence. Heart Fail Rev* 2015. 20(4): 461-474.
40. Titze, J., D.N. Muller, and F.C. Luft, *Taking another "look" at sodium. Can J Cardiol* 2014. 30(5): 473-475.
41. Sterns, R.H., *Disorders of plasma sodium--causes, consequences, and correction. N Engl J Med* 2015. 372(1): 55-65.
42. Panel on Dietary Reference Intakes for, E., Water, and I. Standing Committee on the Scientific Evaluation of Dietary Reference, *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride and Sulfate. Scientific Evaluation of Dietary Reference* 2004: 1-640.
43. Kojima S, Kawano Y, Abe H, Sanai T, Yoshida K, Imanishi M, et al. Acute effects of alcohol ingestion on blood pressure and erythrocyte sodium concentration. *J Hypertens* 1993;11:185–90.
44. Vaughan LA, Manore MM, Russo ME, Swart A, Carroll SS, Felicetta J V. Blood pressure responses of mild hypertensive caucasian males to a metabolic diet with moderate sodium and two levels of dietary calcium. *Nutr Res* 1997;17(2):215–29
45. Akita S, Sacks FM, Svetkey LP, Conlin PR, Kimura G, Group DA-STCR. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet on the pressure-natriuresis relationship. *Hypertension* 2003;42(1):8-13.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

46. Evans CE, Chughtai AY, Blumsohn A, Giles M, Eastell R. The effect of dietary sodium on calcium metabolism in premenopausal and postmenopausal women. *Eur J Clin Nutr* 1997;51(6):394-9.

47. Feng W, Cai Q, Yuan W, Liu Y, Bardeesi AS, Wang J, et al. Low Response of Renin-Angiotensin System to Sodium Intake Intervention in Chinese Hypertensive Patients. *Medicine* 2016;95(6):e2602.

48. Gijsbers L, Dower JI, Mensink M, Siebelink E, Bakker SJ, Geleijnse JM. Effects of sodium and potassium supplementation on blood pressure and arterial stiffness: a fully controlled dietary intervention study. *J Hum Hypertens* 2015;29(10):592-8.

49. Gill JR, Jr., Gullner G, Lake CR, Lakatua DJ, Lan G. Plasma and urinary catecholamines in salt-sensitive idiopathic hypertension. *Hypertension* 1988;11(4):312-9.

50. Imafuku T, Ogawa Z, Itoh H, Suzuki H, Saruta T. Na<sup>+</sup>, K<sup>(+)</sup>-ATPase inhibitory activity of fractionated urine during changes in dietary sodium intake in man. *Endocrinol Jpn* 1990;37(1):39-46.

51. Kawano Y, Abe H, Kojima S, Takishita S, Matsuoka H. Effects of repeated alcohol intake on blood pressure and sodium balance in Japanese males with hypertension. *Hypertens Res* 2004;27(3):167-72.

52. Keane P, Burgess E, Watanabe M, Wong T. Plasma sodium-potassium ATPase inhibition activity in low- and normal-renin hypertension. *Am J Hypertens* 1991;4(1 Pt 1):9-13.

53. Lawton W, Sinkey C, Fitz A, Mark AL. Dietary Salt Produces Abnormal Renal Vasoconstrictor Responses to Upright Posture in Borderline Hypertensive Subjects. *Hypertension* 1988;11(6):529–36.

54. Luft FC, Fineberg NS, Sloan RS, Hunt JN. The effect of dietary sodium and protein on urine volume and water intake. *J Lab Clin Med* 1983;101(4):605-10.

55. Ogihara T, Hara H, Shima J, Iinuma K, Kumahara Y. Changes in the plasma hANP level during long-term salt loading in patient with essential hypertension. *Clin Exp Hypertens* 1988;10(1):105-17.

56. Overlack A, Ruppert M, Kolloch R, Gobel B, Kraft K, Diehl J, et al. Divergent Hemodynamic and Hormonal Responses to Varying Salt Intake in Normotensive Subjects. *Hypertension* 1993;22(3):331–9.



57. Roos JC, Koomans HA, Delawi IMK. Renal sodium handling in normal humans subjected to low, normal, and extremely high sodium supplies. *Am J Physiol - Ren Physiol* 1985;249(6):941–7.
58. Sagnella GA, Markandu ND, Buckley MG, Miller MA, Singer DR, MacGregor GA. Hormonal responses to gradual changes in dietary sodium intake in humans. *Am J Physiol* 1989;256(6 Pt 2):R1171-5.
59. Schwartz GL, Turner ST, Sing CF. Twenty-four-Hour Blood Pressure Profiles in Normotensive Sons of Hypertensive Parents. *Hypertension* 1992;20:834–41.
60. Sharma AM, Arntz H, Kribben A, Schattenfroh S, Distler A. Klinische schrift Dietary Sodium Restriction : Adverse Effect on Plasma Lipids. *Klin Wochenschr* 1990;68:664–8.
61. Shore AC, Markandu ND, Sagnella GA, Singer DR, Forsling ML, Buckley MG, et al. Endocrine and renal response to water loading and water restriction in normal man. *Clin Sci* 1988; 75(2):171-7.
62. Sowers JR, Zemel MB, Zemel P, Beck FW, Walsh MF, Zawada ET. Salt sensitivity in blacks. Salt intake and natriuretic substances. *Hypertension* 1988;12(5):485-90.
63. van Buren M, Rabelink AJ, Bijlsma JA, Koomans HA. Natriuretic and kaliuretic response to potassium load: Modulation by sodium intake. *Nephrol Dial Transplant* 1993;8(6):495-500.
64. van Buren M, Rabelink TJ, van Rijn HJ, Koomans HA. Effects of acute NaCl, KCl and KHCO<sub>3</sub> loads on renal electrolyte excretion in humans. *Clin Sci* 1992; 83(5):567-74.
65. Yamakawa H, Suzuki H, Nakamura M, Ohno Y, Saruta T. Disturbed calcium metabolism in offspring of hypertensive parents. *Hypertension* 1992;19(6):528-34.

Figure 1: A Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of literature search process and results.

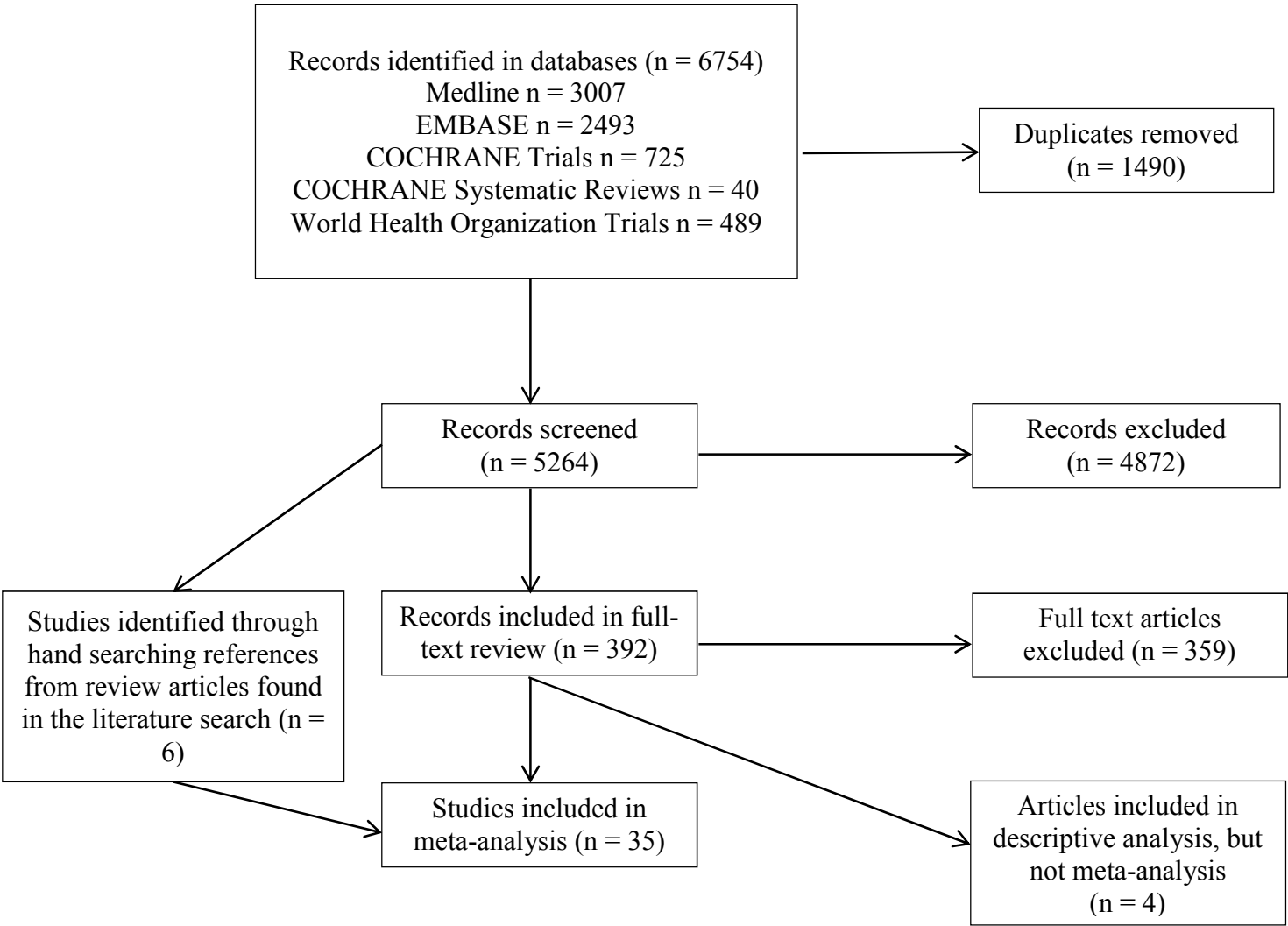


Figure 2: Forest plot for pooled percentage of dietary sodium excretion in each study.

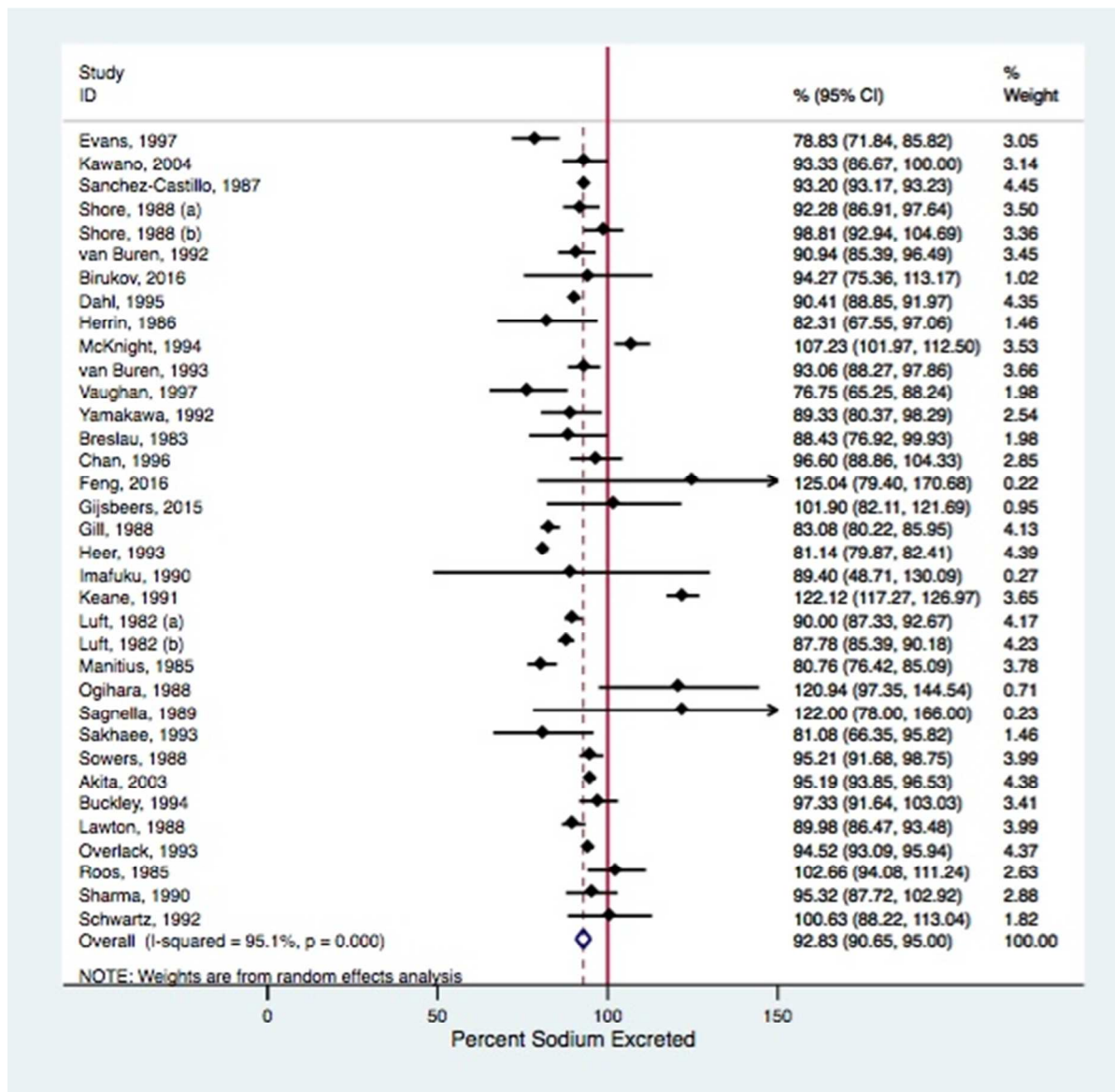
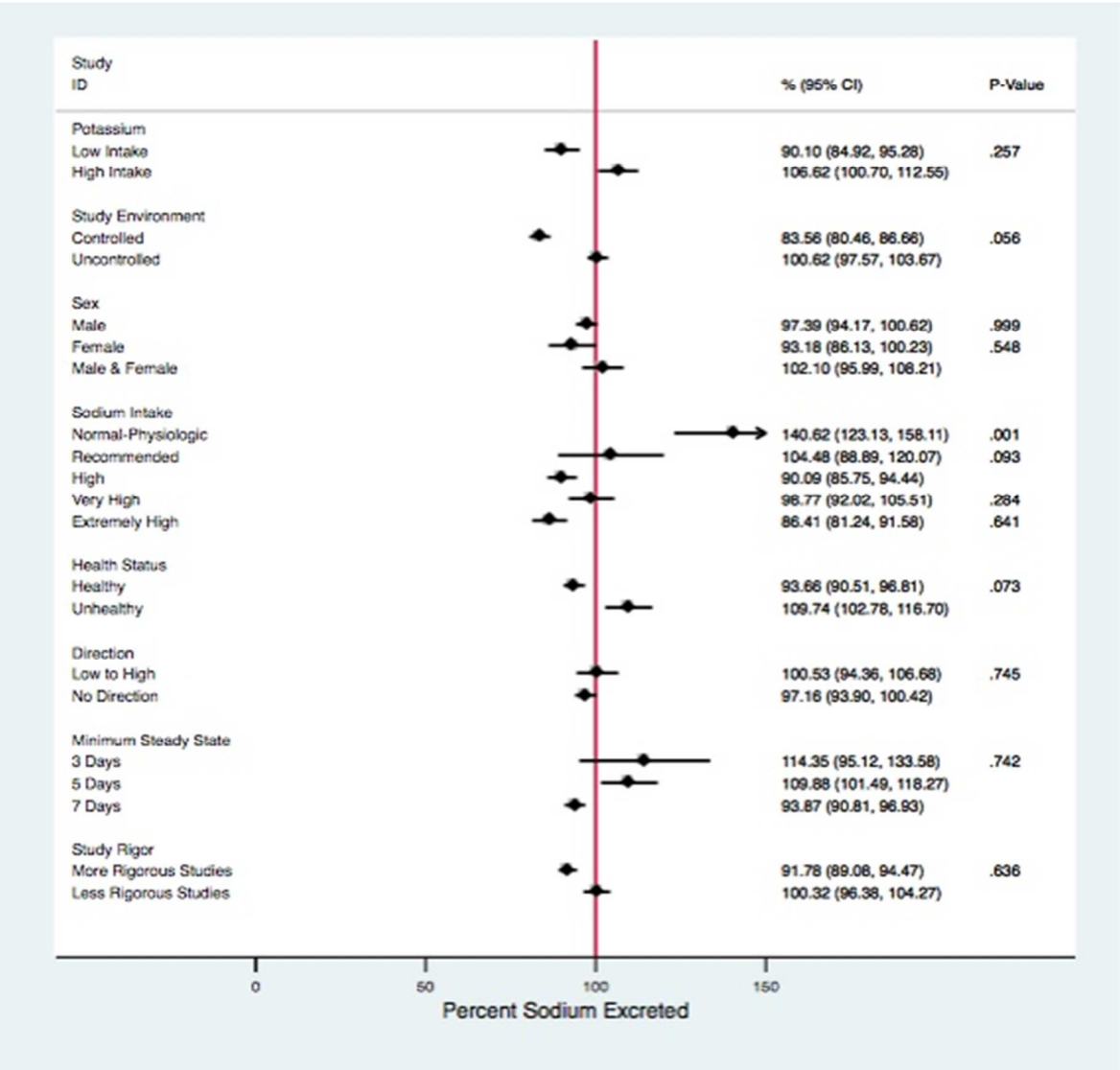


Figure 3: Forest plot detailing the percentage excretion by each subgroup category.

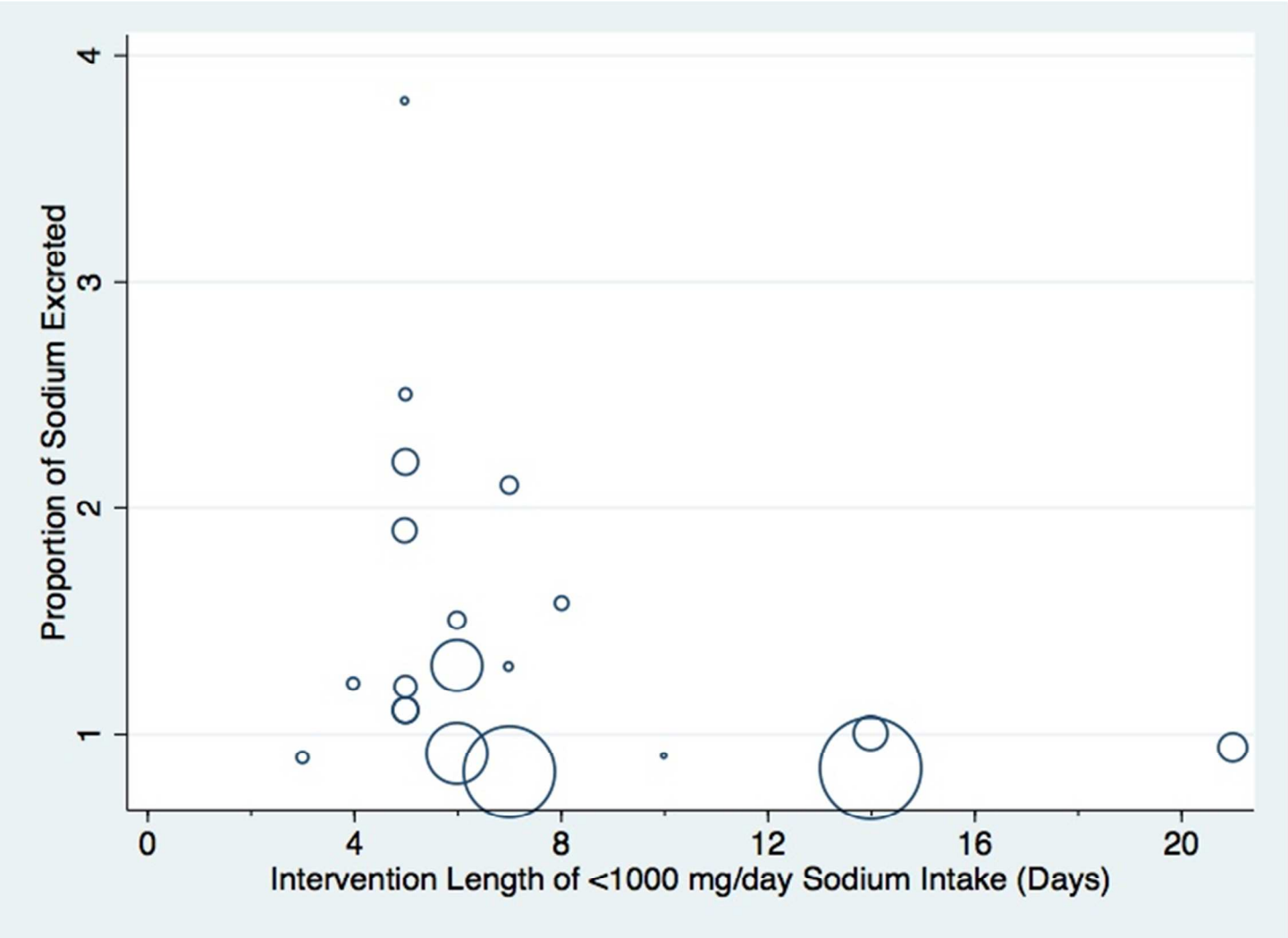


P-values represent the test statistic for differences between each variable and sodium excretion. Potassium intake and duration of steady state were meta-regressed as continuous variables, the rest were categorical. Low potassium intake was defined as < 77.6 mmol/day and high potassium as greater than 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-

1 regression was compared to high intake. Sodium intakes were categorized and included the following ranges:  
2  
3 normal-physiologic (100-<1000 mg sodium/day), recommended (1000 to <2000 mg sodium/day), high ( $\geq$  2000  
4  
5 – 4000 mg sodium /day), very high (>4000-6000 mg sodium /day), and extremely high (>6000 mg sodium/day).  
6

7 The low to high 'direction' indicates sodium intake had been increased before the assessment of excretion  
8  
9 while no direction indicates there had been no change in sodium intake before the assessment. Steady state  
10  
11 refers to the duration of a constant sodium diet before assessment of excretion. Studies were considered to  
12  
13 have more rigor if dietary intake was assessed with a known unbiased reference measure (denominator) and  
14  
15 the 24-h urine collections were high quality.  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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)

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..  
15 (3100)  
16 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
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