

1 **Sodium intake and blood pressure in children with clinical conditions: A**
2 **systematic review with meta-analysis**

3 **Short title: Sodium and blood pressure in children with clinical conditions**

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7

1 **Abstract**

2 Little is known on the effect of sodium intake on BP of children with clinical conditions. Our
3 objective was therefore to review systematically studies that have assessed the association between
4 sodium intake and BP in children with various clinical conditions. A systematic search of several
5 databases was conducted and supplemented by a manual search of bibliographies and unpublished
6 studies. Experimental and observational studies assessing the association between sodium intake
7 and BP and involving children or adolescents between 0 and 18 years of age with any clinical
8 condition were included. Out of the 6,861 records identified, 51 full-texts were reviewed, and 16
9 studies (10 experimental and 6 observational), involving overall 2,902 children and adolescents,
10 were included. Ten studies were conducted in children with elevated BP without identifiable cause,
11 two in children with familial hypertension, one in children with at least one cardiovascular risk
12 factor, one in children with chronic renal insufficiency, one in children with urolithiasis, and one
13 in premature infants. A positive association between sodium intake and BP was found in all studies,
14 except one. The meta-analysis of 6 studies among children with elevated BP without identifiable
15 cause revealed a difference of 6.3 mm Hg (95% CI 2.9-9.6) and 3.5 mm Hg (95% CI 1.2-5.7) in
16 systolic and diastolic BP, respectively, for every additional gram of sodium intake per day. In
17 conclusion, our results indicate that the BP response to salt is greater in children with clinical
18 conditions, mainly hypertension, than in those without associated clinical conditions.

19

1 **Introduction**

2 Hypertension is a major risk factor for cardiovascular disease and an important cause of morbidity
3 and mortality worldwide.¹⁻³ Because high sodium intake is a modifiable cause of elevated blood
4 pressure (BP) in adults,⁴⁻⁶ the World Health Organization recommends sodium intake reduction in
5 the population as a key strategy to reduce the burden of cardiovascular diseases.⁷ However, there
6 is a debate around this recommendation, as the sensitivity of BP to sodium intake has been shown
7 to vary between individuals, suggesting that sodium intake reduction should be targeted at
8 individuals with certain clinical conditions, instead of the whole population. For instance, it has
9 been shown that older adults with elevated BP, diabetes, or chronic kidney disease have a BP that
10 is more sensitive to a reduction in sodium intake than adults without these conditions.⁸⁻¹⁰

11 Much less is known about the association of sodium intake and BP among children, and especially
12 among those with clinical conditions. To this date, only three systematic reviews have been
13 conducted on the association between sodium intake and BP in children.¹¹⁻¹³ Two of these reviews
14 included experimental studies and showed that sodium reduction can significantly reduce BP in
15 children. Of note, these reviews did not separate studies between children with or without clinical
16 conditions.^{11,12} Hence, these reviews could not demonstrate if children with a clinical condition
17 have a different response to sodium intake compared to children without a clinical condition. More
18 recently, we have conducted a systematic review of both experimental and observational studies
19 assessing the association between salt intake and BP in children without clinical conditions.¹³
20 Eighteen studies of high quality showed that systolic and diastolic BP was reduced by
21 approximately 1 mmHg for a sodium reduction of 1 gram.¹³

1 To our knowledge, no systematic review examined the association between sodium intake and BP
2 in children with clinical conditions. Our objective was therefore to assess this association through
3 a systematic review of both experimental and observational studies.

4 **Methods**

5 Details of the research methods are given in the protocol of this systematic review registered in
6 PROSPERO (registration number CRD42016038245) and published.¹⁴ The first review included
7 studies with children without clinical conditions was recently published.¹³ The second review,
8 which is the subject of the current report, included only studies with children with a clinical
9 condition. Both reviews were conducted following the PRISMA guidelines.¹⁵

10 **Eligibility criteria**

11 Both reviews followed the same eligibility criteria, apart from the presence and absence of clinical
12 conditions respectively. We included randomized and non-randomized controlled and non-
13 controlled trials, quasi-experimental studies, case-control, cohort, and cross-sectional studies,
14 which had assessed the association between sodium intake and BP. Studies involving children or
15 adolescents between 0 and 18 years of age with any clinical condition were included. Experimental
16 studies assessing the acute or short-term effect of sodium intake (i.e. duration of 7 days or less) on
17 blood pressure were excluded.

1 **Search strategy**

2 A systematic search of the MEDLINE, EMBASE, CINAHL and CENTRAL databases was
3 conducted in March 2017 and supplemented by a manual search of the bibliographies of the
4 included studies, Google Scholar, Web of Science and unpublished studies in trial registries.¹⁴

5 **Data collection process**

6 Study selection, quality assessment, and data extraction were performed in duplicate by two
7 independent reviewers. Disagreements were resolved by discussion and, if necessary, by a third
8 reviewer. The study selection was conducted using Covidence.¹⁶ The quality of experimental
9 studies was evaluated with the Cochrane's risk of bias tool¹⁷ and the observational studies with the
10 Newcastle-Ottawa Scale.¹⁸ Sodium intake measurement was considered of high quality when
11 assessed by 24-hour urine collection controlled for completeness or using duplicates of foods
12 measured for their sodium content. BP measurement was considered of high quality when
13 measured multiple times, by trained professional, using standardized procedures, and, for the
14 oscillometric method, using a clinically validated device. Data extraction was performed in Excel.

15 **Data analysis**

16 The reported effect sizes were transformed to unstandardized regression coefficients, i.e., the
17 change or difference in BP for every additional gram in sodium intake. If standard errors (SE) were
18 not available, they were calculated from standard deviations, confidence intervals (CI), p-values,
19 t-values, approximated using the Taylor expansion or imputed as the weighted mean of all standard
20 errors of all studies included in the systematic review.^{14,17}

1 Random effects meta-analyses were performed when there was a sufficient number of studies
2 involving the same condition. If a study reported separately several groups, they were first pooled
3 into one estimate using a fixed effect meta-analysis, before being pooled with other studies.
4 Heterogeneity was assessed with the I^2 statistic.¹⁷ The findings of the studies who could not be
5 meta-analyzed were summarized narratively. The statistical analyses were performed with R
6 (version 3.3.1) and R Analytic Flow (version 3.0.6).

7 **Results**

8 **Figure 1** shows the study selection process. After screening and reviewing, 16 studies (10
9 experimental studies and 6 observational studies, from 18 articles) involving overall 2,902 children
10 and adolescents with various clinical conditions were included.

11 The characteristics of each study are shown in **Table 1**. The majority of the studies (n=10) were
12 conducted in children with elevated BP without identifiable cause.¹⁹⁻²⁹ Only one of these studies
13 specifically excluded children under anti-hypertensive treatment.²⁰ Two studies were conducted
14 among children with familial hypertension,^{30,31} one among children with cardiovascular risk
15 factors,^{32,33} one among children with chronic renal insufficiency,³⁴ one among children with
16 urolithiasis,³⁵ and one among premature infants.^{36,37}

17 Assessment of study quality are reported in **Figure 2** and **Additional Figures A1 and A2**. Overall,
18 the overall quality of the studies was relatively low. Eight studies (50%) had a measurement of
19 sodium intake of high quality, four (25%) had a BP measurement of high quality, and three (19%)
20 had measurements of both sodium intake and BP of high quality.

1 **Elevated blood pressure**

2 The association between sodium intake and BP in children with elevated BP without identifiable
3 cause was assessed in 10 studies. Eight of these studies were experimental and two were
4 observational. Data from six studies, including 381 children, could be pooled together.^{20,23,25,26,29}
5 The meta-analysis of these studies showed a positive and substantial association between sodium
6 intake and systolic and diastolic BP (**Figure 3**), i.e., a difference of 6.3 mmHg (95% CI: 2.9-9.6)
7 of systolic BP and of 3.5 mmHg (95% CI: 1.2-5.7) of diastolic BP for a difference of 1 gram of
8 sodium intake. There were no statistically significant differences in effect estimates between the
9 experimental and observational studies (p=0.26 for systolic BP and p=0.77 for diastolic BP).

10 The four other studies are summarized narratively here. Two studies (n=80, n=210) aimed reducing
11 sodium intake in children with elevated BP through educational interventions over long periods,
12 i.e., 1 and 3 years.^{21,27} However, the difference in sodium intake at the end of the intervention
13 between the control and intervention groups was negligible, i.e., -0.17 g sodium/day and -0.03 g
14 sodium/day, respectively, and the effect of sodium on BP could therefore not be further
15 investigated. In another study (n=100) conducted in a group of children with normal and elevated
16 BP, sodium intake was reduced through an intervention combining education and provision of low
17 sodium bread, and was not associated with a change in BP.²² The change in sodium intake in
18 children with elevated BP was not reported and therefore could not be included in our meta-
19 analysis. Finally, an observational study (n=278) among children with different levels of BP found
20 “a general tendency [...] toward positive association in the high BP stratum” between sodium
21 intake and BP, but did not report any figures.¹⁹

22 **Familial hypertension**

1 In a population-based study conducted in the 1970s in the United States,³⁰ over 20,000 men aged
2 35-58 years of age were screened for essential hypertension. The children (n=154) of the men
3 diagnosed with essential hypertension were invited to have an assessment of BP and sodium
4 excretion. The association between sodium excretion and BP was positive with a difference of 0.9
5 mmHg (SE: 0.3) systolic BP and 0.4 mmHg (SE: 0.2) diastolic BP for 1 g difference in sodium
6 intake respectively. However, upon adjustment for age and body anthropometry, the associations
7 were reduced for both systolic BP and diastolic BP, and no longer reached statistical significance.

8 In a sub-analysis of a study conducted in 1980s in the Netherlands in children (n=750) of mothers
9 with a diastolic BP equal or above 90 mmHg,³¹ a significant positive association was found
10 between BP and sodium intake with a difference of 1.5 mmHg (SE: 0.3) systolic BP and of 0.7
11 mmHg (SE: 0.3) diastolic BP for a 1 g difference in sodium intake.

12 **Children with at least one cardiovascular risk factor**

13 In a non-controlled trial conducted in the 2000s in Croatia,^{32,33} 17 adolescents with at least one
14 cardiovascular risk factor (i.e. family history of cardiovascular disease, elevated BP, or obesity)
15 were given a 2-hour individual education session with dietary recommendations, notably to reduce
16 sodium intake. The effect of the session on sodium intake and BP was assessed after two months.
17 For a reduction of 1 gram of sodium, the decrease in systolic BP and diastolic BP was 8.9 mmHg
18 (SE: 0.5) and 2.7 mmHg (SE: 0.5), respectively. Data were not analyzed separately for family
19 history of cardiovascular disease, elevated BP, or obesity.

20 **Chronic renal insufficiency**

1 In a cross-sectional study including 118 children with chronic renal insufficiency between 18
2 months and 10 years of age, nutritional intake was assessed in detail.³⁴ Sixteen children were
3 hypertensive and six took anti-hypertensive medication. In multi-variate analysis, sodium intake
4 was associated with systolic BP with a difference of 1.0 mm Hg (SE: 1.7, p=0.571) systolic BP and
5 of 0.9 mm Hg (SE: 1.8, p=0.608) diastolic BP for a 1 g difference in sodium intake.

6 **Urolithiasis**

7 One case-control study³⁵ compared children (n=124) below 18 years of age with urolithiasis (so
8 called stone formers, n=71) and children with non-glomerular hematuria (non-stone formers,
9 n=53). The stone formers had higher systolic and diastolic BP (systolic BP: 109.4 vs 103.0 mm
10 Hg, p=0.01 and diastolic BP: 65.0 vs 61.4 mm Hg, p=0.02) and higher 24-h sodium excretion (2.8
11 vs 2.4 g). In stone formers, systolic BP was associated positively with 24-h urine sodium with a
12 difference of 3.6 mmHg (SE: 1.1, p=0.001) for a 1 g difference in sodium intake. Upon adjustment
13 for age, sex, and BMI z-score, the association remained statistically significant. The association
14 with diastolic BP was not reported.

15 **Prematurity**

16 One randomized-controlled trial was conducted among premature children born between 1982 and
17 1985 in the United Kingdom.^{36,37} Some 347 premature infants without any major congenital
18 anomalies and with a low birthweight (<1850 g) were assigned to pre-term formula (high sodium,
19 0.5 g sodium/L), standard term formula (low sodium, 0.2 g sodium/L), or banked breastmilk (low
20 sodium, 0.2 g sodium/L). Further, in each group, the feeds could be complemented with expressed
21 breastmilk (0.3 g sodium/L). Infants received the assigned diets until they reached 2,000 g or were

1 discharged. The infants were followed-up at 18 months and at 15 years of age. This study found
2 no differences in BP between groups at 18 months of age. However, differences in BP were found
3 at 15 years of age between breastmilk and the pre-term and term formulas (BP breastmilk - BP pre-
4 term formula: 2.7 mmHg for systolic BP ($p=0.075$) and 3.1 mmHg for diastolic BP ($p=0.016$); BP
5 breastmilk - BP term formula: 4.2 mmHg for systolic BP (p -value not reported) and 2.9 mmHg for
6 diastolic BP (p -value not reported)). This study suggests that, compared to formula, breastmilk
7 during infancy in premature infants could lower BP later in life, possibly due to factors other than
8 the amount of sodium provided. However, a relatively low-sodium (standard term) formula was
9 not associated with a lower BP compared to relatively high-sodium (preterm) formula.

10 **Discussion**

11 In this systematic review, 16 studies, involving overall 2,902 children and adolescents, with various
12 clinical conditions were identified. Ten studies were conducted in children with elevated BP
13 without identifiable cause, two studies in children with familial hypertension, one study in children
14 with one or more cardiovascular risk factors, one study in children with renal insufficiency, one
15 study in children with urolithiasis, and one study in premature infants. A positive association
16 between sodium intake and BP was found in all studies ($n=16$), except one.²² Sodium intake was
17 strongly associated with BP in children and adolescents with elevated BP without identifiable
18 cause. A positive association was found in children with other selected clinical conditions, however
19 with a lower level of evidence. Since BP tracks across the life course, our findings support the
20 reduction of sodium intake among children with elevated BP to lower BP and, ultimately, to
21 prevent the development of hypertension later in life.

1 The meta-analyses of studies with children with elevated BP showed a stronger association
2 between sodium intake and BP than in another systematic review and meta-analysis with only
3 healthy children (see **Table 2**).¹³ Similarly, in adults, the association between sodium intake and
4 BP has been shown to be higher in hypertensives, than in normotensives.^{10,12,38} The greater
5 sensitivity of BP to sodium intake in children and adults with elevated BP suggests that reducing
6 sodium intake at all ages can have a substantial effect on the level of BP. It may also indicate that
7 salt sensitivity could track from childhood to adulthood, similarly to the tracking on BP.^{39,40}

8 Our review indicates that evidence linking sodium intake and BP is very limited among children
9 with conditions other than elevated BP, notably familial hypertension, prematurity, and chronic
10 renal failure. Of note, we could not identify studies conducted among children with diabetes, while
11 diabetes in adults has been shown to increase BP sensitivity to sodium intake.⁴¹

12 High sodium intakes are one of the causes of progression of renal insufficiency.⁴² Patients with
13 renal insufficiency should therefore reduce sodium intake. Several studies in adults with chronic
14 renal disease have shown the high sensitivity of BP to sodium intake.⁴² In the study by Trachtman
15 et al³⁴, a positive yet non-statistically significant association was found between sodium intake and
16 BP in children with chronic renal insufficiency. Some of the children included in this study took
17 anti-hypertensive medication, which could have partly masked the association between sodium
18 intake and BP. Nevertheless, because of the equivocal and limited evidence in children with chronic
19 kidney disease, further studies are needed to estimate the effect of sodium reduction on BP in this
20 population.

21 A rise in the frequency of urinary stones has been reported worldwide and could be due to the
22 increases in sodium intake.⁴³⁻⁴⁵ High sodium intake can increase urinary calcium excretion, which

1 can in turn increase the formation of calcium stones.⁴⁵ Patients with urinary stone diseases are
2 therefore encouraged to limit sodium intake.⁴³⁻⁴⁵ The study by Nikolis et al³⁵ suggests that the
3 association between sodium intake and systolic BP could be higher in children with urolithiasis
4 than in healthy children.¹³ This finding supports the reduction of sodium intake in children with
5 urolithiasis not only to prevent the formation of stones, but also to reduce BP during childhood and
6 prevent hypertension later in life. Of note, urinary stones are uncommon in children and many
7 children with stones have either an underlying abnormality of the urinary tract or a metabolic
8 disease and often a reduced renal function.

9 Numerous studies have shown that children born prematurely or with low birth weight have
10 relatively high BP later in life.⁴⁶ A study, in which the duration of the intervention was of only 7
11 days and which was therefore excluded from this review, compared the salt sensitivity of children
12 born preterm and at term.⁴⁷ This study found that children with low birth weight and small for
13 gestational age were more likely to be salt sensitive. Salt sensitivity was inversely correlated with
14 kidney length, which was smaller in low birth weight children. The Barker and the Brenner
15 hypotheses both support that fetal and perinatal exposures can have long-term effects on the
16 development of hypertension and coronary heart diseases.^{48,49} The study by Lucas et al showed that
17 breastmilk could reduce BP later in life among preterm infants compared to formula, irrespective
18 of sodium content. This study suggests not only that the first months of life may be a key time
19 window for the development of high BP later in life^{36,37}, but also that nutrients other than sodium
20 and present in breastmilk could have an effect on BP.

21 To our knowledge, this is the first systematic review on the association between sodium intake and
22 BP in children with clinical conditions. The major strengths of this study are the comprehensive

1 and systematic review of the literature and the assessment of the study quality. The limitations of
2 this review are that too few studies were identified to determine with confidence the association
3 for each condition and that the overall quality of the studies was low. We were only able to pool
4 results of some studies in children with elevated BP. There was nevertheless high heterogeneity
5 between these studies, limiting our confidence in the pooled estimates. Moreover, due to the limited
6 number of studies, we were not able to assess the presence of publication bias through an analysis
7 of funnel plots or Egger's test. We can however suspect that studies showing no association
8 between sodium intake and BP may not have been published. As a result, we may have
9 overestimated the association between sodium intake and BP. Moreover, due to the limited number
10 of studies for which data was poolable, we were not able to assess whether the association between
11 sodium intake and BP differs by age, sex, or weight. To overcome this limitation, we would need
12 to conduct individual data analyses. Interestingly, in our previous review of studies including
13 children without a clinical condition, we identified a large number of studies and we could show
14 that the association was stronger among overweight children and children having a low potassium
15 intake; no substantial difference was observed with age or sex.¹³

16 Our findings suggest that targeting salt reduction to children with elevated BP, with a condition
17 associated with elevated BP or at risk for elevated BP in the future (such as with familial history),
18 could be efficient as these children seem to be more salt sensitive than children with normal BP.
19 For example, clinicians who identify children with elevated BP could provide dietary counselling
20 to reduce salt intake in those children. This targeted high-risk approach could complement a
21 population-based approach to for example reduce sodium content of foods consumed by children.¹³

22 **Conclusions**

1 In conclusion, our systematic review suggests that sodium intake is positively associated with BP
2 in children and adolescents with clinical conditions, in particularly in those with elevated BP.
3 Consistent with findings in adults, the association between sodium intake and BP is stronger in
4 children with elevated BP than in healthy children. Our findings support therefore the reduction of
5 sodium intake in children with elevated BP to ultimately to prevent the development of
6 hypertension later in life.

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12 **Disclosures**

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14 **Authors' contributions**

15 ArC and MRL designed the research protocol. MRL conducted the databases and manual searches,
16 statistical analyses, and wrote the manuscript. MRL, CB, and AnC selected the studies, extracted
17 the data, and assessed the quality, and ArC resolved conflicts. ArC provided guidance for the
18 statistical analyses. ArC, CB, PB, AnC, GP, MiB, MuB, RT, and VS provided inputs to the

1 manuscript. ArC had primary responsibility for final content. All authors read and approved the
2 final manuscript.

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1 Tables

2 **Table 1.** Characteristics of the included studies. BP: blood pressure.

Author and year	Study type	Study design	Duration of follow-up	Country	Sex	Age range	Sample size	Condition	Quality of sodium intake measurement	Quality of BP measurement
Berenson et al, 1979	Observational	Cross-sectional study	Not applicable	United States	Boys and girls	7-15 years	278	Elevated BP	High	High
Couch et al, 2014	Experimental	Randomized controlled trial	6 months	United States	Boys and girls	Not reported	159	Elevated BP	Low	Unclear
Gillum et al, 1981	Experimental	Randomized controlled trial	1 year	United States	Boys and girls	6-9 years	80	Elevated BP	Low	Unclear
Howe et al,1985; Howe et al, 1986	Experimental	Non-randomized cross-over trial	3 weeks	Australia	Boys and girls	11-14 years	21	Elevated BP	Low	Low
Howe et al, 1991	Experimental	Randomized crossover trial	4 weeks	Australia	Boys and girls	11-14 years	100	Elevated BP	Low	Low
Johnson et al, 1991	Experimental	Non-randomized controlled trial	12 weeks	United States	Boys and girls	9-13 years	19	Elevated BP	High	Unclear
Maiorano et al, 1987	Observational	Cross-sectional study	Not applicable	Italy	Boys and girls	11-14 years	120	Elevated BP	High	High
Sinaiko et al, 1993	Experimental	Randomized controlled trial	3 years	United States	Boys and girls	10-14 years	210	Elevated BP	Unclear	High
Tochikubo et al, 1986 a	Experimental	Non-randomized non-controlled trial	10 weeks	Japan	Boys	15-18 years	41	Elevated BP	High	Unclear
Tochikubo et al, 1986 b	Experimental	Non-randomized non-controlled trial	6 months	Japan	Boys	15-18 years	111	Elevated BP	High	Unclear
Siervogel et al, 1980	Observational	Cross-sectional study	Not applicable	United States	Boys and girls	8-18 years	154	Familial hypertension	High	High

ten Berge-van der Schaaf & May, 1990	Observational	Cross-sectional study	Not applicable	Netherlands	Boys and girls	10-13 years	750	Familial hypertension	Unclear	Low
Kokanovic et al, 2011; Kokanovic et al, 2014	Experimental	Non-randomized non-controlled trial	2 months	Croatia	Boys and girls	Not reported	17	One or more cardiovascular risk	Low	Unclear
Trachtman et al, 1995	Observational	Cross-sectional study	Not applicable	United States	Boys and girls	1.5-10 years	118	Chronic renal insufficiency	Low	Unclear
Nikolis et al, 2017	Observational	Case-control study	Not applicable	United States	Boys and girls	3-17 years	124	Urolithiasis	High	Low
Lucas et al, 1988; Singhal et al, 2011	Experimental	Randomized controlled trial	18 months, 13-16 years	England	Boys and girls	0-18 months, 13-16 years	347	Prematurity	High	Unclear

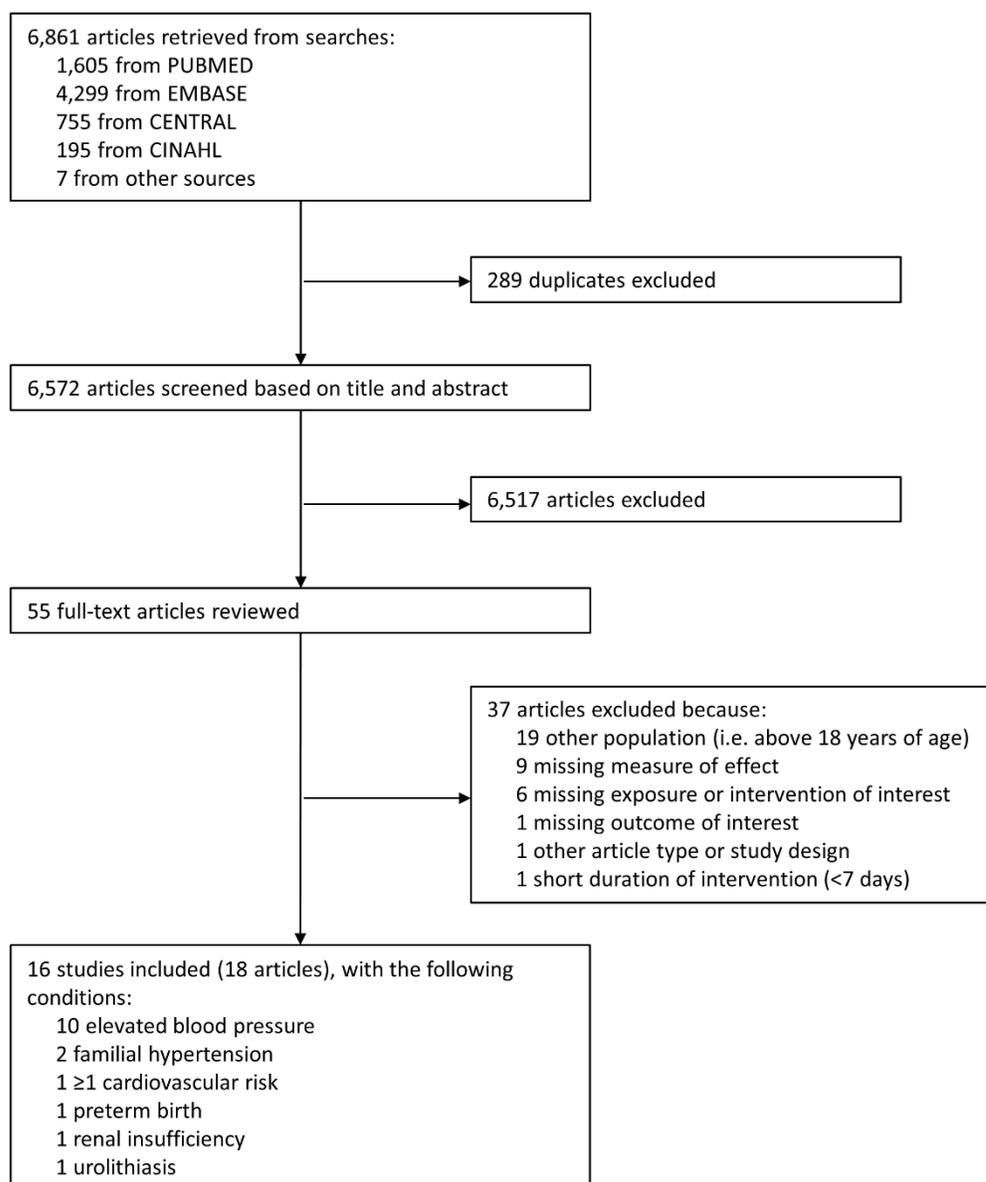
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1 **Table 2.** Comparison of the association between sodium intake and systolic and diastolic blood pressure (BP) in adults and children with
 2 normal and elevated BP. The number indicate the difference in systolic or diastolic BP that is expected for a reduction in one gram of
 3 sodium intake per day. CI: confidence interval.

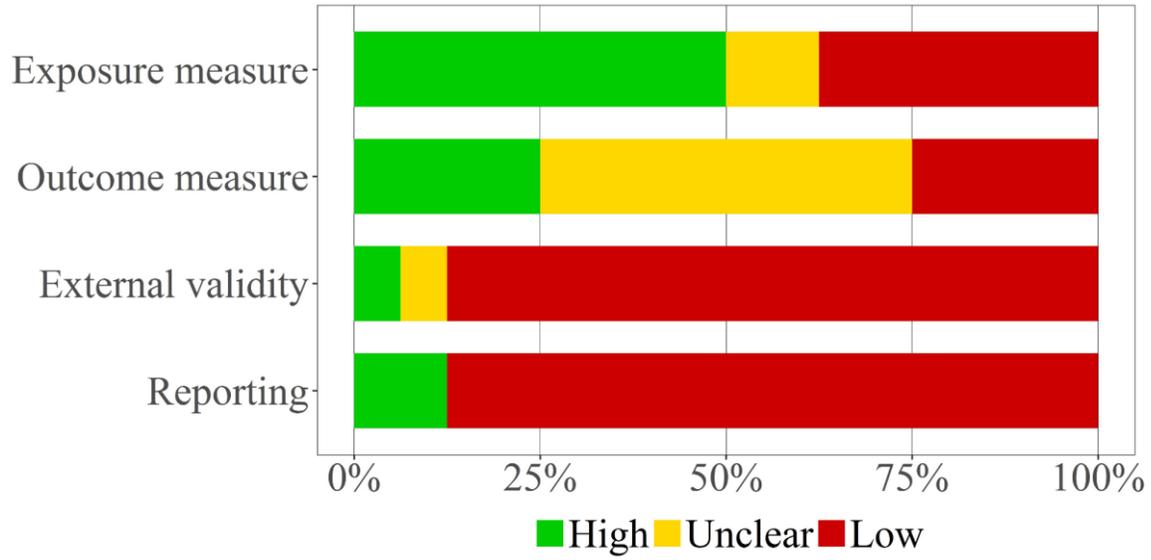
Population group	Systolic BP (95% CI) [mmHg/g sodium per day]	Diastolic BP (95% CI) [mmHg/g sodium per day]
Adults with normal BP ⁴	1.4 (0.7, 2.1)	0.6 (0.1, 1.1)
Adults with hypertension ⁴	3.1 (2.4, 3.8)	1.6 (1.2, 2.1)
Children without any clinical conditions ¹³	0.8 (0.4, 1.3)	0.7 (0.0, 1.4)
Children with elevated BP [this review]	6.3 (2.9, 9.6)	3.5 (1.2, 5.7)

4

1 **Figures**

2

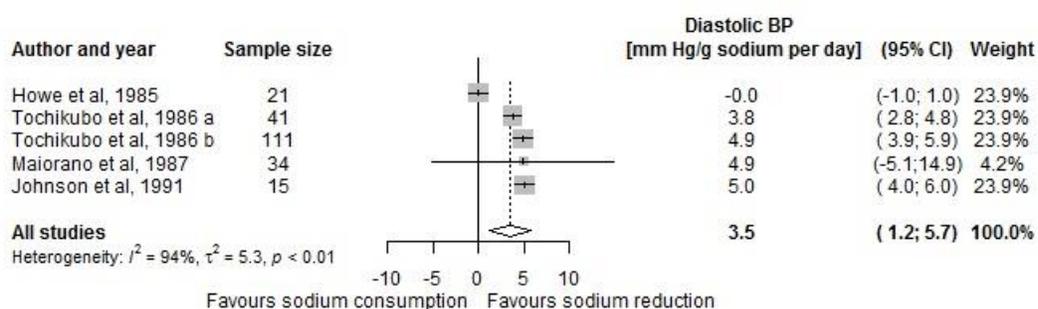
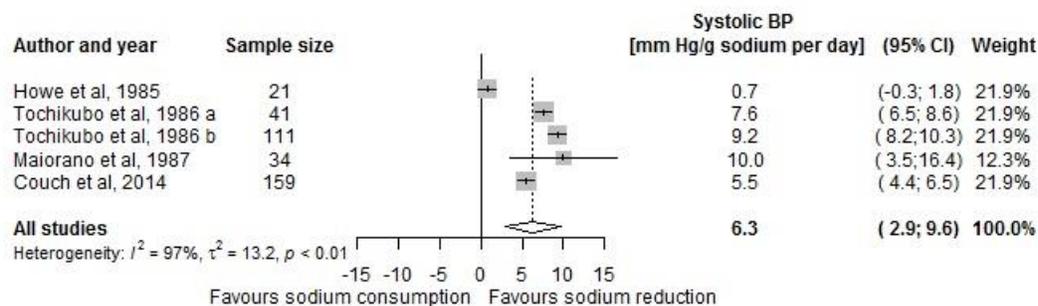
3 **Figure 1.** Flowchart of the study selection



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2 **Figure 2.** Quality assessment of all studies (n=16)

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- 3 **Figure 3.** Forest plot of the association between sodium intake and systolic (upper panel) and
 4 diastolic (lower panel) BP among studies including children with elevated BP. BP: blood pressure;
 5 CI: Confidence interval.