



## The Perils of Sodium

# Sodium intake and blood pressure in children and adolescents: a systematic review and meta-analysis of experimental and observational studies

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### Abstract

**Background:** High sodium intake is a cause of elevated blood pressure in adults. In children and adolescents, less evidence is available and findings are equivocal. We systematically reviewed the evidence from experimental and observational studies on the association between sodium intake and blood pressure in children and adolescents.

**Methods:** A systematic search of the Medline, Embase, CINAHL and CENTRAL databases up to March 2017 was conducted and supplemented by a manual search of bibliographies and unpublished studies. Experimental and observational studies involving children or adolescents between 0 and 18 years of age were included. Random-effects meta-analyses were performed by pooling data across all studies, separately for experimental and observational studies, and restricting to studies with sodium intake and blood pressure measurement methods of high quality. Subgroup meta-analyses, sensitivity analyses and meta-regressions were conducted to investigate sources of heterogeneity and confounding. The dose–response relationship was also investigated.

**Results:** Of the 6572 publications identified, 85 studies (14 experimental; 71 observational, including 60 cross-sectional, 6 cohort and 5 case–control studies) with 58 531 participants were included. In experimental studies, sodium reduction interventions decreased systolic blood pressure by 0.6 mm Hg [95% confidence interval (CI): 0.5, 0.8] and diastolic blood pressure by 1.2 mm Hg (95% CI: 0.4, 1.9). The meta-analysis of 18 experimental and observational studies (including 3406 participants) with sodium intake and blood pressure measurement methods of high quality showed that, for every

additional gram of sodium intake per day, systolic blood pressure increased by 0.8 mm Hg (95% CI: 0.4, 1.3) and diastolic blood pressure by 0.7 mm Hg (95% CI: 0.0, 1.4). The association was stronger among children with overweight and with low potassium intake. A quasi-linear relationship was found between sodium intake and blood pressure.

**Conclusions:** Sodium intake is positively associated with blood pressure in children and adolescents, with consistent findings in experimental and observational studies. Since blood pressure tracks across the life course, our findings support the reduction of sodium intake during childhood and adolescence to lower blood pressure and prevent the development of hypertension.

**Key words:** blood pressure, sodium, salt, children, adolescents, systematic review, meta-analysis

### Key Messages

- Evidence on the association between sodium intake and blood pressure in children and adolescents is limited and equivocal. To our knowledge, this is the first systematic review and meta-analysis to assess the association between sodium intake and blood pressure in children including both experimental and observational studies.
- Out of the 85 studies identified, 14 were experimental and 71 observational. Only 18 had sodium intake and blood pressure measurement methods of high quality.
- Our results show that, for each addition gram of sodium consumed per day, systolic and diastolic blood pressures increase by approximately 1 mm Hg.
- This suggests that sodium consumption should be limited starting in childhood to prevent the development of hypertension over the life course and its associated consequences.

## Introduction

Hypertension is a strong modifiable risk factor for cardiovascular disease and an important cause of morbidity and mortality worldwide.<sup>1–3</sup> There is growing evidence that elevated blood pressure has its roots in childhood and that blood pressure tracks from early life to adulthood.<sup>4–6</sup> Moreover, elevated blood pressure during childhood and adolescence has been associated with markers of target organ damage, such as left ventricular hypertrophy and thickening of the carotid artery vessel wall.<sup>7–9</sup> Therefore, prevention of elevated blood pressure early in life, i.e. during childhood and adolescence, also called primordial prevention, could help prevent lifelong hypertension and its associated consequences.<sup>4,10–12</sup>

High sodium intake is a cause of elevated blood pressure in adults.<sup>13–15</sup> Among children and adolescents, less evidence is available and findings are equivocal; some studies have found a positive association between sodium intake and blood pressure in children,<sup>16–21</sup> whereas others have not.<sup>22–26</sup> Meta-analyses of experimental studies have concluded that the reduction of sodium intake can lower blood pressure in children.<sup>27,28</sup> However, external validity of these meta-analyses is limited, notably because the

sodium reduction in the trials included was often larger than what can be achieved in real-life settings, follow-up was short and the study participants were not sampled from the general population. Including observational studies allows assessing the association across usual levels of sodium intake in real-life settings, over longer periods of time and using population-based designs.

We therefore aimed to systematically review the evidence from both experimental and observational studies to assess the association between sodium intake and blood pressure in children and adolescents. This is the first review on this topic that systematically included both experimental and observational studies, with a strong emphasis on the assessment of study quality, and that investigated the dose–response relationship in children and adolescents.

## Methods

### Protocol development and reporting

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42016038245)

and published.<sup>29</sup> The writing of this paper adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>30</sup>

### Search strategy

A systematic search of the Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Central Register of Controlled Trials (CENTRAL) databases was conducted between the start date of each database and 9 March 2017. Three concepts were identified (i.e. children, sodium and blood pressure) and were used to define the search terms, related terms and medical subject headings and to build the full search strategies for each database (detailed search strategies are available in the open access published protocol).<sup>29</sup> To identify additional studies, a manual search of the bibliographies of retrieved articles, other reviews on the same topic, Web of Science, Google Scholar and trial registries was conducted.<sup>29</sup>

### Eligibility criteria

Studies were eligible if they involved children or adolescents between 0 and 18 years of age in whom the association between sodium intake and blood pressure had been assessed. Randomized-controlled trials, non-randomized trials, non-controlled trials, crossover trials, cohort studies, case-control studies and cross-sectional studies were included. Ecological studies, case series, case reports, reviews, meta-analyses, policy papers, comments, congress proceedings and animal studies were not included. Articles in English, French, German or Spanish were included. Experimental studies assessing the acute effect of sodium intake (i.e. duration of 7 days or less) on blood pressure were excluded. Studies including children who were hospitalized or with any clinical conditions were excluded.

### Study selection

All articles retrieved were examined by two independent reviewers, with Covidence (version 2013).<sup>31</sup> Each reviewer independently assessed eligibility by first screening the titles and abstracts and subsequently reviewing the full texts. Any disagreement on the exclusion or inclusion of an article between the two reviewers was resolved by discussion or, when necessary, by a third reviewer.

### Data extraction and quality assessment

The information extracted consisted of study identification information, study and population characteristics, sodium intake, sodium intake measurement method, description

of intervention (for experimental studies), systolic and diastolic blood pressure, blood pressure measurement method, effect sizes (i.e. correlations, standardized and unstandardized regression coefficients, and odds ratios) with corresponding standard errors, and potential confounding and effect modification factors.<sup>29</sup> If multiple publications were found to originate from one single study, the results of that study were collated into one.

The quality of each study was judged based on four criteria (method for sodium intake measurement, method for blood pressure measurement, external validity and reporting; see details in [Supplementary Table 1](#), available as [Supplementary data](#) at *IJE* online) along three levels (low, high or unclear quality). Measurement of sodium intake was judged as high-quality when assessed by 24-hour urine collection controlled for completeness or using duplicates of foods measured for their sodium content. Measurement of blood pressure was judged as high-quality when measured multiple times, by a trained professional, using standardized procedures and, for the oscillometric method, using a clinically validated device. In addition, the quality of experimental studies was assessed according to the Cochrane collaboration's risk-of-bias tool<sup>32</sup> and the quality of cohort, case-control and cross-sectional studies according to the Newcastle-Ottawa scales.<sup>33</sup>

The two reviewers independently extracted data from each study in duplicate using a standardized form in Microsoft Office Excel version 2007. Any disagreements on the data extracted or on the quality assessment were resolved by discussion between the two reviewers or, when necessary, by a third reviewer. Corresponding authors were contacted by e-mail (maximum of three e-mail attempts) to obtain any essential missing information.

### Statistical analysis

Data transformations and imputations were done according to the study protocol,<sup>29</sup> the *Cochrane Handbook for Systematic Reviews*<sup>32</sup> and following the recommendations of Borenstein *et al.*<sup>34</sup> Salt intakes in g were transformed to sodium intakes in g by multiplying by 0.4 and sodium intakes in mmol were transformed to sodium intakes in g by multiplying by 0.023. The following imputations were done: when the mean sodium intake or age was missing, the midpoint between the lowest and highest values was used; for the dose-response analysis, when the highest or lowest values of the upper or lower sodium-intake categories were not provided, they were imputed assuming that the sodium-intake range was the same as the adjacent sodium category;<sup>35</sup> if standard errors were not available, they were calculated from standard deviations, confidence

intervals (CIs),  $p$ -values,  $t$ -values, approximated using the Taylor series expansion or imputed as the weighted mean of all standard errors of all studies included in the systematic review. For experimental studies, the effect size was defined as the net difference between the intervention and control groups in the mean change in blood pressure from the baseline to the end of the intervention.<sup>27</sup> To analyse experimental and observational studies together, the unstandardized regression coefficients, which assessed the change or difference in blood pressure for every additional gram in sodium intake, was used as the effect size. For experimental studies, the regression coefficient was estimated by dividing the net change in blood pressure by the net change in sodium intake. If the reported effect sizes could not be transformed to unstandardized regression coefficients, they were analysed and reported separately.

Effect estimates were pooled using the DerSimonian-Laird random-effects model.<sup>32</sup> Distinct meta-analyses were done: (i) for all studies together, (ii) separately for experimental and observational studies and (iii) restricting to studies with high-quality sodium intake and blood pressure measurements. One study<sup>36</sup> was excluded from the analyses because the estimates of the association between sodium intake and systolic or diastolic blood pressure were adjusted for diastolic and systolic blood pressure, respectively, and such adjustment can be considered as over-adjustment.

The dose-response relationship between sodium intake and blood pressure was explored. First, the studies that investigated the dose-response relationship between sodium intake and blood pressure were reviewed and their results were plotted. Second, the dose-response relationship was modelled using all studies with high-quality sodium intake and blood pressure measurements. The mean blood pressure values and their standard error at a given value of sodium intake were extracted for each study and used as individual data points. For some studies, several blood pressure estimates at different levels of sodium intake were available and were included. The analysis excluded data points from children with elevated blood pressure and was restricted to sodium intakes between the 10th and 90th percentiles, in order to avoid a small number of influential points at the extreme ends of sodium intakes.<sup>37</sup> Data were pooled using random-effects meta-analysis methods and modelled using restricted cubic splines with three knots at the 33rd, 50th and 67th percentiles of the sodium intake, with adjustment for age.<sup>38</sup>

The heterogeneity was assessed by the  $I^2$  and  $\tau^2$  statistics.<sup>32</sup> Sources of heterogeneity and confounding were explored using subgroup meta-analyses, sensitivity analyses and meta-regressions.<sup>32</sup> Outlying and highly influential

studies were identified using leave-one-out analyses<sup>39</sup> and Baujat plots.<sup>40</sup> Publication bias was evaluated by the visual inspection of enhanced funnel plots and Egger's test.<sup>32,41</sup> All statistical analyses were conducted with R (version 3.3.1) and R Analytic Flow (version 3.0.6).

## Results

### Study characteristics

A total of 6572 publications were identified. After screening of titles and abstracts, 254 full texts were assessed for eligibility and 96 publications (83 articles, 11 abstracts and 2 theses) were included in the review (Figure 1). The included publications consisted of 85 distinct studies, among which 14 were experimental and 71 observational. There were 7 randomized-controlled trials,<sup>42-48</sup> 1 non-randomized-controlled trial,<sup>49</sup> 3 randomized crossover trials,<sup>26,50,51</sup> 1 non-randomized crossover trial,<sup>21,51</sup> 2 non-controlled trials,<sup>52-54</sup> 6 cohort studies,<sup>19,36,55-59</sup> 5 case-control studies<sup>60-64</sup> and 60 cross-sectional studies.<sup>16-18,20,25,65-124</sup> Details on the characteristics of each study are presented in the [Supplementary Tables 2 and 3](#), available as [Supplementary data](#) at *IJE* online.

The quality of the studies varied greatly: 32% ( $n=27$ ) were judged to have a high-quality measurement of sodium intake, 56% ( $n=48$ ) high-quality measurement of blood pressure, 49% ( $n=42$ ) high external validity and 24% ( $n=20$ ) high-quality reporting. However, only five studies<sup>19,45,66,76,123</sup> were judged as high-quality for all of these four criteria. For experimental studies, the most common risk of bias was the lack of blinding of participants and staff to the intervention. For observational studies, the most common lowest quality item was the measurement of sodium intake. Details of the other quality and risk-of-bias assessments are reported in [Supplementary Figures 1-5](#), available as [Supplementary data](#) at *IJE* online.

Data from 58 531 participants (3094 in experimental studies and 55 437 in observational studies) were available. The mean age of the participants was 11.5 years (range: 0.0-18.9 years) and the mean sodium intake was 3.0 g per day (range: 0.1-7.9 g) [which corresponds to a salt intake of 7.5 g per day (range: 0.3-19.8 g)]. Among all the different estimates of effect size reported, 60 were positive and statistically significant, 8 were negative and statistically significant and 219 were not statistically significant. Moreover, among the studies in which the degree of statistical significance was not reported, 84 estimates of effect sizes were reported to be positive and 38 negative. Thirteen observational studies did not provide enough quantitative information to be included in the meta-analyses.

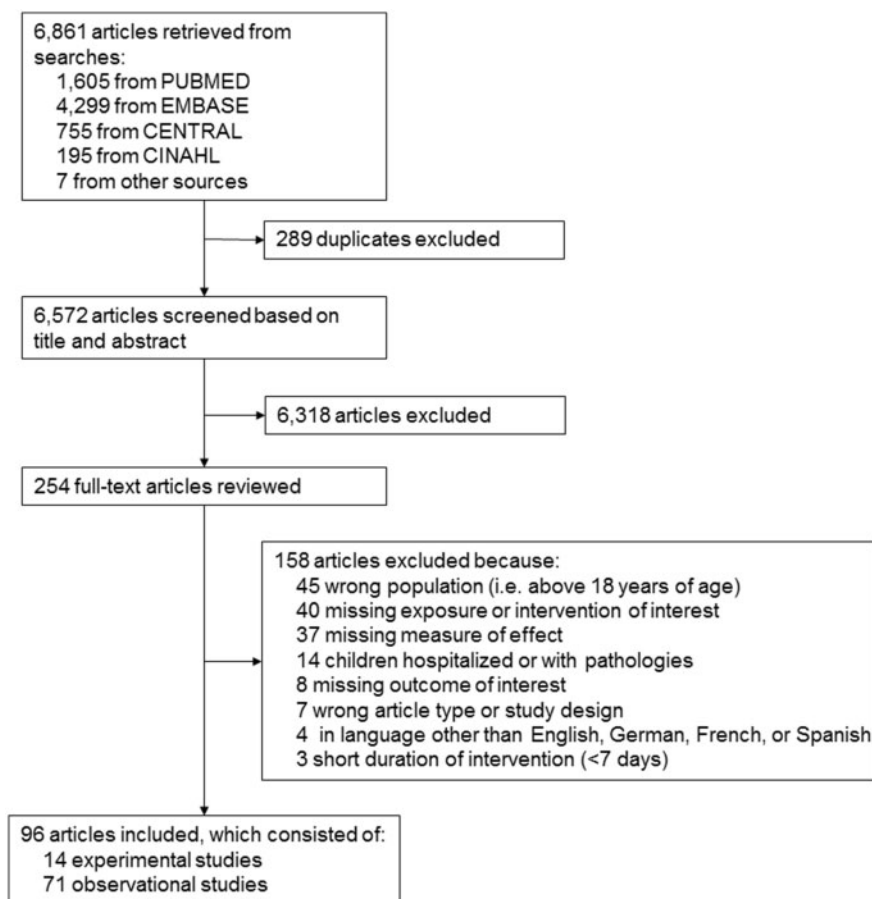


Figure 1. Flow chart of the study selection process.

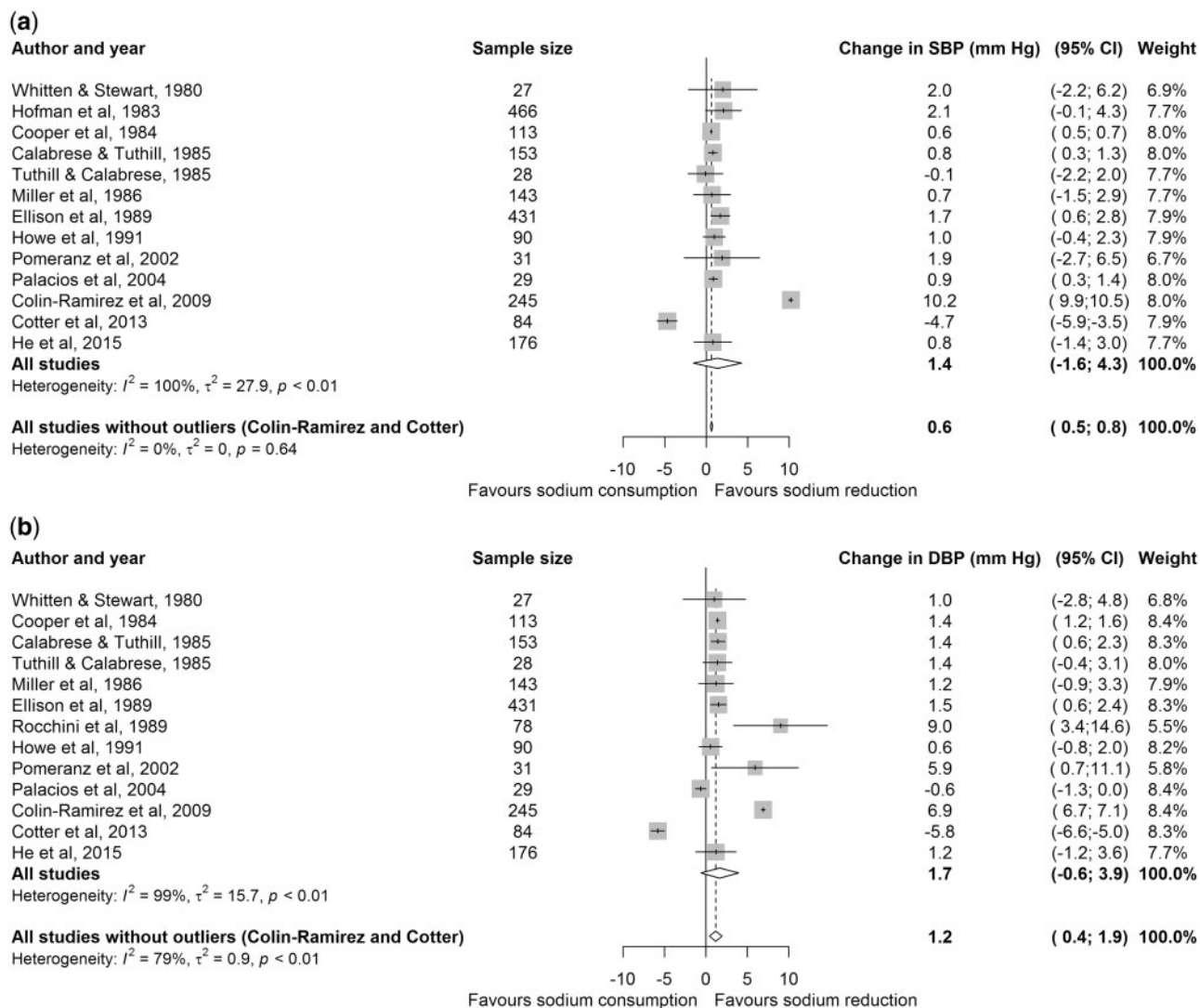
### Effect of sodium-reduction interventions

In the 14 experimental studies included, the mean duration of intervention was 16 weeks (range 2–52 weeks). The mean net reduction in sodium intake from the interventions was 1.2 g (range: 0.2–4.3 g). One study<sup>47</sup> did not provide information on the net change in sodium intake. The types of interventions differed largely between studies, such as education of children or parents to reduce sodium intake,<sup>43–45,50,52</sup> information for employees of school canteens to reduce the use of salt for cooking,<sup>21</sup> provision of meals or water with reduced salt content<sup>26,42,46,47,49,50,53,125</sup> or provision of salt capsules.<sup>48,53</sup> Pooling data from these studies, interventions aimed at decreasing sodium intake reduced systolic blood pressure by 1.4 mm Hg (95% CI: –1.6, 4.3) and diastolic blood pressure by 1.7 mm Hg (95% CI: –0.6, 3.9) (Figure 2). However, the heterogeneity between the trials was very high ( $I^2 = 100\%$  and  $99\%$  for systolic and diastolic blood pressure). Estimates from two studies were found to be outliers and highly influential<sup>43,44</sup> (see details in Supplementary Figure 6, available as Supplementary data at *IJE* online). Upon removal of these two studies,

heterogeneity was substantially reduced ( $I^2 = 0\%$  and  $79\%$ , respectively) and the confidence intervals around the effect estimates became narrower for both systolic (0.6 mm Hg, 95% CI: 0.5, 0.8) and diastolic (1.2 mm Hg, 95% CI: 0.4, 1.9) blood pressure (Figure 2).

### Association between sodium intake and blood pressure

Pooling data from experimental and observational studies, a difference of 1 g of sodium per day resulted in a difference of 0.6 mm Hg (95% CI: 0.4, 0.8) in systolic blood pressure and of 0.2 mm Hg (95% CI: –0.2, 0.6) in diastolic blood pressure (Table 1). Since only five studies were judged of high quality for all four criteria, the subgroup analyses were done with studies of high quality for the two most important of the four criteria, i.e. the quality of sodium intake and blood pressure measurement methods. When restricting the analysis to studies with sodium intake and blood pressure measurement methods of high quality (18 studies, including 3406 participants), the difference in blood pressure for each gram of sodium per day was larger,



**Figure 2.** Net change (in mm Hg) in systolic (a) and diastolic blood pressure (b) in experimental studies, with and without outliers. Leave-one-out analyses and Baujat plots indicated that there were two outlying and highly influential studies (i.e. Colin-Ramirez *et al.*, 2009<sup>43</sup> and Cotter *et al.*, 2013<sup>44</sup>) for systolic and diastolic blood pressure. SBP, systolic blood pressure; CI, confidence interval; DBP, diastolic blood pressure.

i.e. 0.8 mmHg (95% CI: 0.4, 1.3) for systolic blood pressure and 0.7 mmHg (95% CI: 0.0, 1.4) for diastolic blood pressure (Figure 3). The heterogeneity between the studies was high ( $I^2 = 99\%$ ). Subgroup analyses indicated that there were no statistically significant differences between the experimental and observational studies ( $p = 0.692$  and  $0.939$ , respectively; Table 1 and Figure 3).

Subgroup analyses and meta-regressions showed that the association between sodium intake and blood pressure was stronger among overweight children and among children with a low-potassium intake (Table 1 and Supplementary Table 4, available as Supplementary data at *IJE* online). The relationship with age was not clear. Indeed, the association tended to be stronger among infants (i.e. 0–1 year of age) and older children (i.e. 12–18 years of age) than in children aged 2–11 years old. However, there

was a very large uncertainty around the estimate for infants. When analyses were restricted to studies with high quality of sodium intake and blood pressure measurement methods, the associations remained similar (Supplementary Table 5, available as Supplementary data at *IJE* online). Further sensitivity analyses showed that the positive association between sodium intake and blood pressure was still observed when excluding either studies with small sample sizes ( $n < 200$ ), studies providing only unadjusted estimates (i.e. studies not adjusting for any confounders), studies for which effect estimates were transformed or studies with sodium intake and blood pressure measurement methods of low quality (Table 1 and Supplementary Tables 4 and 6, available as Supplementary data at *IJE* online). Funnel plots and Egger's test did not show evidence of asymmetry whatever the study type, which is compatible with the absence

**Table 1.** Subgroup meta-analyses of regression coefficients of the association between sodium intake and systolic and, respectively, diastolic blood pressure (in mm Hg/g sodium per day). *n*, number of studies; CI, confidence interval; *p*, *p*-value for test for the difference between sub-groups

	Systolic blood pressure				Diastolic blood pressure			
	<i>n</i>	Estimate (95% CI)	<i>I</i> <sup>2</sup>	<i>p</i>	<i>n</i>	Estimate (95% CI)	<i>I</i> <sup>2</sup>	<i>p</i>
All	61	0.6 (0.4, 0.8)	99.2%	–	51	0.2 (–0.2, 0.6)	99.4%	–
<b>Study type</b>								
Experimental	12	1.0 (–2.5, 4.6)	99.8%	0.692	12	0.0 (–3.7, 3.8)	99.8%	0.939
Observational	49	0.3 (0.2, 0.5)	97.6%		39	0.2 (–0.1, 0.5)	98.3%	
<b>Quality<sup>a</sup></b>								
High	17	0.8 (0.4, 1.3)	99.0%	0.653	17	0.7 (0.0, 1.4)	99.2%	0.183
Low	44	0.7 (0.3, 1.1)	99.2%		34	0.0 (–0.7, 0.7)	99.5%	
<b>Age</b>								
0–1 year	4	3.5 (–1.8, 8.7)	99.5%	0.031	2	0.2 (–1.4, 1.9)	85.4%	0.198
6–11 years	31	0.1 (–0.2, 0.5)	99.5%		22	0.5 (0.1, 0.8)	94.0%	
12–18 years	26	0.5 (0.3, 0.7)	90.8%		27	0.0 (–0.6, 0.6)	99.7%	
<b>Weight status</b>								
Normal	6	0.4 (–0.4, 1.2)	92.4%	<0.001	6	–0.2 (–0.3, 0.0)	0.0%	<0.001
Normal and overweight	50	1.1 (0.9, 1.3)	98.4%		39	0.7 (0.4, 0.9)	97.7%	
Overweight	5	1.5 (–0.3, 3.4)	98.5%		5	1.1 (–0.3, 2.6)	95.7%	
<b>Potassium intake<sup>b</sup></b>								
High intake	13	0.6 (0.1, 1.0)	99.1%	0.004	12	0.3 (–0.3, 0.8)	99.1%	0.307
Low intake	12	1.6 (1.0, 2.2)	99.2%		9	1.1 (–0.4, 2.6)	98.7%	
<b>Sex</b>								
Boys	32	0.7 (0.3, 1.2)	85.2%	0.629	26	0.2 (–0.3, 0.6)	88.8%	0.167
Girls	28	0.9 (0.6, 1.1)	98.4%		25	1.2 (0.6, 1.8)	99.4%	

<sup>a</sup>Quality of sodium intake and blood pressure measurements.

<sup>b</sup>Above or below median potassium intake, i.e. 1.6 g per day.

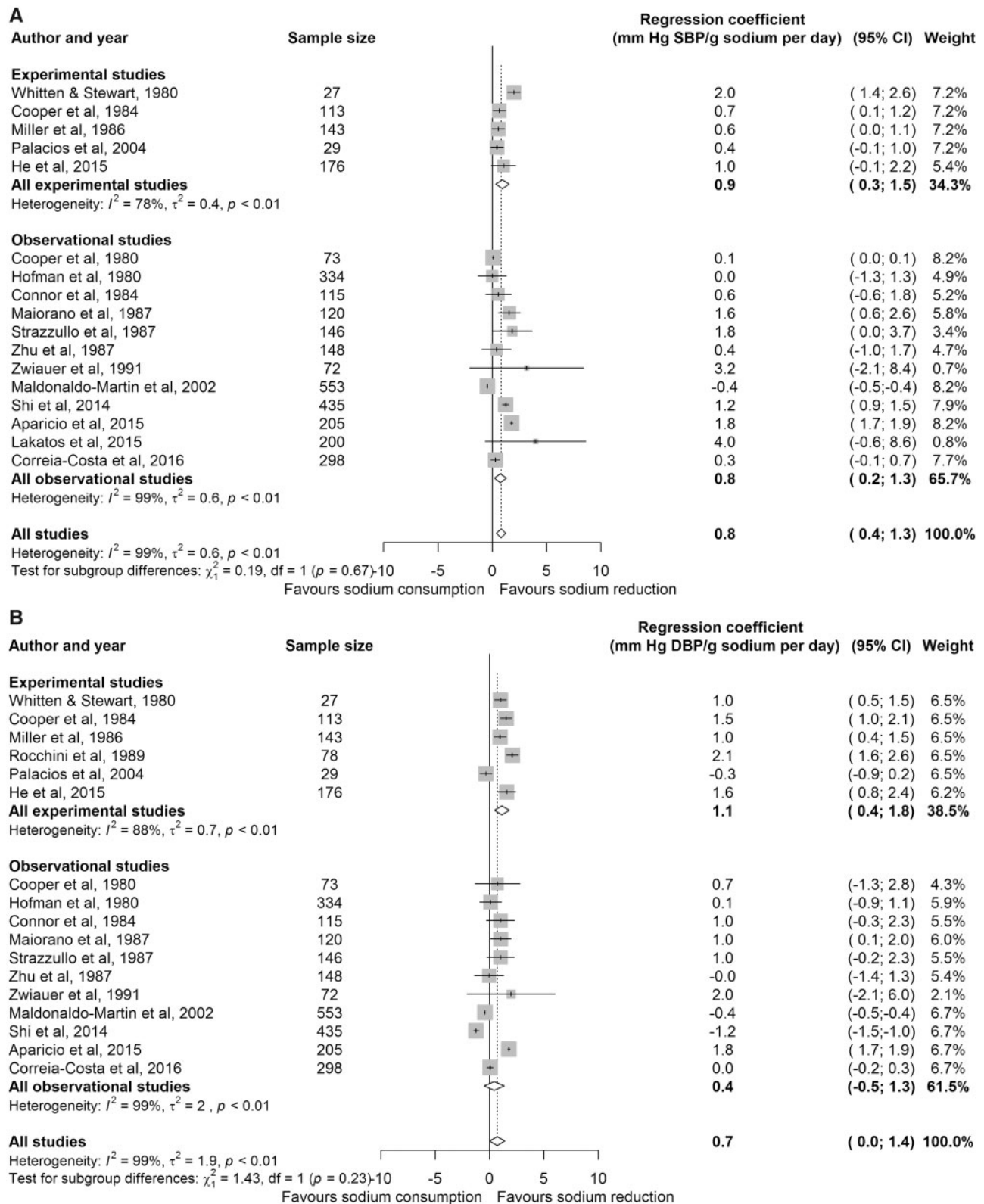
of publication bias (Supplementary Figure 7, available as Supplementary data at *IJE* online).

Six studies reported odds ratios (ORs) for the association between sodium intake categories (highest/lowest) and high blood pressure. A meta-analysis of these studies showed that children with the highest intakes of sodium had a higher odds of having high blood pressure than children with the lowest sodium intakes (2.00 OR, 95% CI: 1.38, 2.62; Supplementary Figure 8, available as Supplementary data at *IJE* online). The odds ratios were higher for unadjusted ratios (2.80 OR, 95% CI: 0.98, 4.61; Supplementary Figure 8, available as Supplementary data at *IJE* online) than for adjusted ORs (1.66 OR, 95% CI: 1.12, 2.20; Supplementary Figure 8, available as Supplementary data at *IJE* online). In 12 studies, sodium intake was compared between children with normal and with high blood pressure, respectively, without further details on the level of blood pressure. Their meta-analysis showed that children with high blood pressure had a slightly higher sodium intake than children with a normal blood pressure (0.15 g per day, 95% CI: 0.02, 0.27; Supplementary Figure 9, available as Supplementary data at *IJE* online).

### Dose–response relationship

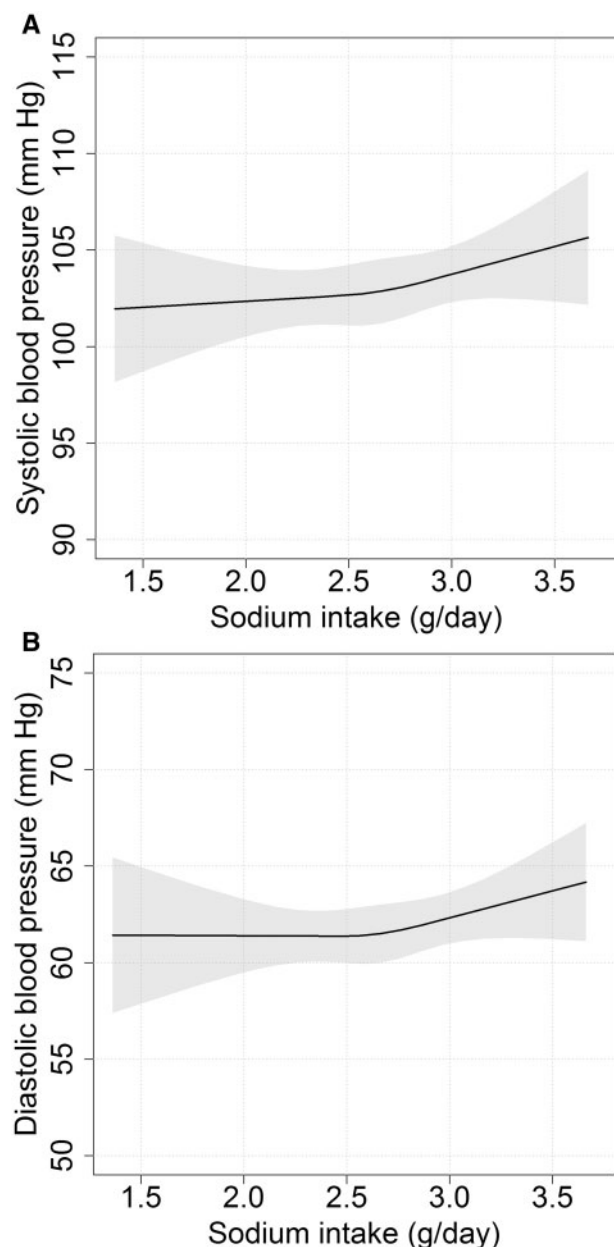
Seven studies<sup>17,71,74,88,103,114,124</sup> investigated the dose–response between sodium intake and blood pressure (Supplementary Figure 10, available as Supplementary data at *IJE* online). Systolic blood pressure tended to increase with sodium intake: three studies showed a linear trend, two a u-shaped trend and two no specific trend. On the other hand, for diastolic blood pressure, no clear tendency was observed: three studies showed a u-shaped trend and three studies no specific trend. Only one<sup>71</sup> out of these seven studies had a high quality of sodium intake and blood pressure measurement methods. Therefore, these data were not pooled across studies.

However, the dose–response was modelled using the data from all studies with a high quality of sodium intake and blood pressure measurements. Systolic and diastolic blood pressure slightly increased quasi-linearly with increasing amount of sodium intake, with a steeper slope for systolic than for diastolic blood pressure and for sodium intakes above approximately 2.5 g per day (Figure 4). Wide CIs were, however, found around the dose–response curve.



**Figure 3.** Forest plot of the regression coefficients of the association between sodium intake and systolic (a), respectively, diastolic (b), blood pressure (in mm Hg/g sodium per day) of experimental and observational studies with a high quality of sodium intake and blood pressure measurements. SBP, systolic blood pressure; CI, confidence interval; DBP, diastolic blood pressure.





**Figure 4.** Dose–response relationship between sodium intake (g per day) and systolic (a) and diastolic (b) blood pressure (mm Hg) for studies with a high quality of sodium intake and blood pressure measurements. The line was modelled with random-effects meta-analyses, using restricted cubic splines with three knots at percentiles 33, 50 and 67, over sodium intake range between percentiles 10 and 90, and controlled for age. The graph presents the line for the mean age, i.e. 11.5 years of age. Confidence intervals are represented in grey.

## Discussion

### Main findings

In this systematic review and meta-analysis of 85 studies including 58 531 children and adolescents, sodium intake was associated positively with blood pressure in children. Experimental and observational studies with sodium intake and blood pressure measurement methods of high

quality consistently showed that sodium intake was associated with systolic and diastolic blood pressure. The association between sodium intake and blood pressure tended to be stronger among overweight children and among children with a low potassium intake. Our exploratory dose–response analysis showed a quasi-linear increase in systolic and diastolic blood pressure increase across the usual range of daily intake of sodium.

### Strengths and limitations

A major strength of our study is the inclusion of evidence from both experimental and observational studies. Experimental studies provide evidence of a causal relationship between sodium intake and blood pressure among children. One caveat to this causal interpretation is that the interventions to decrease sodium intake differed between studies and could have been associated with several other complex changes in the diet that may have directly affected blood pressure levels. Including observational studies enhanced the external validity of our findings<sup>126</sup> and allowed us to assess the association across groups of children with different characteristics (i.e. age, weight status and potassium intake). Moreover, we excluded studies with children with a clinical condition. Due to all of the above-mentioned issues, our results may be more easily generalizable to the general population than previous meta-analyses.<sup>4,127</sup>

The main limitations of this systematic review are that several studies included were of low quality, especially for sodium intake measurement methods, and that there was high between-study heterogeneity, limiting our confidence in the effect estimates.<sup>128</sup> Moreover, 60 out of the 85 studies included had a cross-sectional design. It is standard to assume that cross-sectional studies are not ideal to assess a causal effect. In our case, there is no reason to believe that the level of blood pressure influences sodium intake. Indeed, whereas, among older adults, a low-sodium diet may be adopted in case of high blood pressure, which would bias the cross-sectional association, by contrast, changing sodium intake as a result of elevated blood pressure is unlikely to occur in children. Of note, our estimates of the strength of the association with blood pressure are certainly underestimated, due to regression dilution bias as a result of measurement error in sodium intake,<sup>129–131</sup> as well as due to the intra-individual variability of urinary sodium excretion at constant sodium intake.<sup>132,133</sup> The included studies varied on several aspects, such as their design, quality, measurement methods and adjustment strategy. Subgroup meta-analyses, meta-regressions and sensitivity analyses could explain only a small part of the heterogeneity. To increase our confidence in the overall

estimates, we conducted separate analyses restricted to studies with a high quality of sodium intake and blood pressure measurement methods, and we found consistent estimates. Another limitation is that the whole body of evidence may not have been included in this review, despite efforts to cover as much of the literature as possible. There is growing evidence that many studies, notably in the field of nutritional epidemiology, are never published.<sup>134</sup> This may lead to publication bias, as studies showing a positive association between sodium intake and blood pressure are more easily published than studies not showing a positive association. Nevertheless, the funnel plots and Egger's tests did not suggest major publication bias. An additional limitation is that our dose–response analysis was not done at the individual level, i.e. mean sodium intakes and blood pressures of aggregated groups were analysed. Therefore, the results of the dose–response analysis may be subject to ecological fallacy.<sup>135</sup> For instance, energy intake could be associated with an increase in sodium intake and an increase in blood pressure, and confound the association found at the aggregated levels. Of note, the dose–response analysis was adjusted for age—a major potential confounder—but was not adjusted for other confounders (e.g. energy intake, potassium intake). Moreover, the CIs of the dose–response curve were large and would have been even wider if robust estimation had been used.

### Comparison with other studies

In our study, sodium reduction in experimental studies decreased systolic and diastolic blood pressure in orders of magnitude similar to estimates from previous systematic reviews.<sup>27,28</sup> He and MacGregor<sup>27</sup> identified 10 experimental studies of children between 8 years and 16 years of age and estimated that sodium reduction could lower systolic blood pressure by 1.2 mmHg (95% CI: 0.6, 1.8) and diastolic blood pressure by 1.3 mmHg (95% CI: 0.7, 1.9). In a more recent systematic review of nine experimental studies of children between 2 years and 19 years of age, Aburto *et al.*<sup>28</sup> found that sodium intake reduction reduced systolic blood pressure by 0.8 mmHg (95% CI: 0.3, 1.4) and diastolic blood pressure by 0.9 mmHg (95% CI: 0.1, 1.2).

Meta-analyses of experimental trials in normotensive adults have found slightly larger effect sizes<sup>13,28</sup> than in children. He *et al.*<sup>13</sup> identified 12 trials in adults and found that sodium reduction decreased systolic blood pressure by 2.4 mmHg (95% CI: 1.3, 3.6) and diastolic blood pressure by 1.0 mmHg (95% CI: 0.2, 1.9). More recently, Aburto *et al.*<sup>28</sup> identified seven experimental studies and found that systolic blood pressure was reduced by 1.4 mmHg (95% CI: 0.0, 2.7) and diastolic blood pressure by 0.6 mmHg (95% CI: 0.1, 1.3). When analysing experimental and

observational studies together, we found that every additional gram of sodium intake per day was associated with an increase in systolic and diastolic blood pressure of 0.8 mmHg and 0.7 mmHg, respectively. These results are similar to those of a recent meta-analysis of individual data from 69 559 normotensive adults from four international prospective studies that showed that, for every gram of sodium intake, systolic and diastolic blood pressure increased by 1.2 mmHg and 0.5 mmHg, respectively.<sup>37</sup>

The association between sodium intake and blood pressure was modified by weight status and potassium intake and, although less clearly, by age. Whereas these subgroup analyses should be interpreted with great caution, they may provide some insights. Increased blood pressure sensitivity to salt is expected in obese children, possibly in relation to hyperinsulinemia, hyperaldosteronism and increased activity of the sympathetic nervous system.<sup>53</sup> Weight loss in adolescents has been shown to reduce their blood pressure sensitivity to sodium.<sup>53,136</sup> Efforts to reduce sodium intake in children could therefore particularly target overweight and obese children and adolescents, as they seem more sensitive to salt intake. We also observed a weaker association between sodium intake and blood pressure with increasing potassium intake. In fact, potassium intake has been shown to lower blood pressure: in children, one systematic review and meta-analysis found that increasing potassium intake decreased systolic and diastolic blood pressure by 0.3 mmHg and 0.9 mmHg, respectively.<sup>137</sup> The finding that the association tended to be stronger among infants suggests that the first months of life could be a key time window for the development of high blood pressure later in life. For instance, an experimental study<sup>138</sup> restricted sodium intake during the first 6 months of life and found lower systolic blood-pressure levels in children at 15 years of age. This could be explained by the fact that infants have a low capacity for sodium excretion, which gradually increases over the first 2 years of life.<sup>139</sup> However, there was a large uncertainty around the estimate for infants. The finding that the association is strengthened with age, after 1 year of age, is in continuity with the strengthening of the association with age observed in adults.<sup>140</sup>

### Future research

We recommend further research on the feasibility of long-term (greater than 1 year) reductions in sodium intake during childhood and adolescence, and its long-term effects on blood pressure and other outcomes in adulthood, with regular and high-quality measurements of sodium intake. Our dose–response meta-analysis is the first to have been conducted in children. We found a quasi-linear relationship

between sodium intake and blood pressure, with a steeper slope for systolic than for diastolic blood pressure and for sodium intakes above approximately 2.5 g per day. The few very large studies with individual data from adults found similar shapes between sodium intake and blood pressure.<sup>141–143</sup> However, there were large uncertainties around our dose–response analyses. To assess with greater confidence the dose–response relationship, a meta-analysis with data at the individual level and taking into consideration other individual characteristics that influence blood pressure and salt sensitivity<sup>136</sup> should be conducted. A randomized–controlled trial assessing the effect of different levels of sodium intake on blood pressure could be also highly informative. This would provide necessary evidence to help determine optimal sodium requirements in children.<sup>144</sup>

## Conclusions

In conclusion, sodium intake was associated positively with blood pressure in children. The strength of the association was relatively small, but of similar magnitude across study types. Similar effect sizes have been observed among adults. The effect size of about 1 mm Hg for a difference of 1 g of sodium is clinically modest, but can be considered as substantial from a public-health point of view. Indeed, a small shift in the distribution of blood pressure at the population level can have an important public-health impact. Childhood and adolescence are also key periods of an individual's life during which dietary habits are formed. Given that high blood pressure can cause vascular damage starting at a young age<sup>7,8</sup> and that it tracks from childhood to adulthood,<sup>5,6</sup> primordial prevention starting in childhood has the potential to reduce the burden of hypertension and its associated consequences.<sup>4</sup> Sodium intake should be limited during childhood to prevent hypertension over the life course.

## Supplementary Data

Supplementary data are available at *IJE* online.

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