ABSTRACT
Background: Clinical trials assessing the effects of salt substitutes on blood pressure (BP) have reported mixed results.
Objectives: A meta-analysis of randomized controlled trials was conducted to evaluate the effect of salt substitutes on BP, including systolic BP (SBP) and diastolic BP (DBP).
Design: Studies were identified via systematic searches of the PubMed, Embase, Cochrane Library, Wanfang Data, and the China National Knowledge Infrastructure databases through December 2013. Random-effects models were used to estimate pooled mean differences in SBP and DBP.
Results: Six cohorts from 5 articles (1 trial enrolled 2 cohorts for independent intervention) consisting of 1974 participants were included. Pooled results showed that salt substitutes had a significant effect on SBP (mean difference: −4.9 mm Hg; 95% CI: −7.3, −2.5 mm Hg; P < 0.001) and DBP (mean difference: −1.5 mm Hg; 95% CI: −2.7, −0.3 mm Hg; P = 0.013). Significant heterogeneity was found for both SBP ($I^2 = 76.7\%$) and DBP ($I^2 = 65.8\%$). The sensitivity analysis indicated that the pooled effects of salt substitutes on SBP and DBP were robust to systematically dropping each trial. Furthermore, no evidence of significant publication bias from funnel plots or Egger’s tests ($P = 0.17$ and 0.22 for SBP and DBP, respectively) was found.
Conclusion: This meta-analysis showed that salt-substitution strategies are effective at lowering SBP and DBP, which supports a nutritional approach to preventing hypertension. Am J Clin Nutr 2014;100:1448–54.

Keywords blood pressure, hypertension, meta-analysis, salt substitutes, randomized controlled trial

INTRODUCTION
Hypertension is an important risk factor for cardiovascular disease (CVD) (1–4): ~60% of strokes (5) and half of ischemic heart disease cases (6) are attributable to elevated blood pressure (BP). Observational studies have supported a role of salt intake in the development of hypertension (7–13), and randomized controlled trials (RCTs) have confirmed that salt reduction can lower BP in both hypertensive and normotensive patients (14, 15). Given this strong scientific evidence, national and international guidelines now recommend population-based salt restriction for the prevention and treatment of hypertension (16–19). Indeed, the World Health Organization advocated for strategies to reduce dietary salt intake at the seminal United Nations Non-Communicable Disease Summit in the fall of 2011 (20, 21).

The UK salt-reduction program has achieved significant progress in reducing the salt content of many processed foods and 24-h urinary sodium concentrations via a food industry–level intervention (22). However, in contrast with developed countries such as the United Kingdom, the predominant source of dietary sodium in most developing countries is added salt from home cooking (23). Therefore, salt-reduction strategies that work in the developed world (22) may be inappropriate and ineffective in developing countries, and alternative strategies must be explored.

In the 1980s, a new potassium- and magnesium-enriched salt alternative was introduced that explicitly reduced the sodium content of foods (24, 25). Since then, many epidemiologic studies and clinical trials have explored the effects of these so-called salt substitutes on lowering BP (26–34). However, the results of these studies have been mixed, potentially as a result of differences in sample size and sample characteristics, study duration, and salt-substitute composition. The objective of this meta-analysis was to evaluate the effects of salt substitutes on BP.

MATERIALS AND METHODS
Eligibility and data extraction
PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (http://www.embase.com/home), and the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html) were searched for studies through December 2013 according to PRISMA guidelines for RCT meta-analysis (35). The following search terms were used: *salt substitute* or *salt substitution* or *low-sodium* or *low-salt*.

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4Abbreviations used: BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; RCT, randomized controlled trial; SBP, systolic blood pressure.

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sodium salt or mineral salt or smart salt or potassium-enriched salt or sodium reduced salt or sodium replacement, and blood pressure or hypertension. The Chinese databases Wanfang Data (http://www.wanfangdata.com.cn/) and China National Knowledge Infrastructure (http://www.cnki.net/) were also searched by using the terms salt substitute or low sodium salt and blood pressure in Chinese. The searches were completed by 2 authors (Y-GP and X-XW).

The inclusion criteria were as follows: 1) RCT that tested the effects of a salt substitute or a low sodium salt intervention versus a common salt (sodium chloride) control group; 2) blinding; 3) allocation concealment; 4) intervention duration ≥6 mo; and 5) reported BP, including both systolic BP (SBP) and diastolic BP (DBP), measured by using outpatient monitoring or home self-monitoring.

The following data were extracted from each study: name, year published, study design, study location, intervention duration, salt substitute ingredients, randomization method, blinding method, allocation concealment, statistical analysis approach, mean difference from baseline to the end of the intervention period in both SBP and DBP between the intervention and control groups, the corresponding SEs and 95% CIs, and, when reported, regardless of whether or not it was part of a predefined analysis of the main trial, hypertensive versus normotensive subgroup results. Data were extracted independently by 2 authors (Y-GP and X-XW), and discrepancies were discussed with a third author (J-HH).

The following study attributes were considered when assessing study quality: randomization approach [random number table (0 points) or computerized (1 point)], blinding method [single blinded (0 points) or double blinded (1 point)], allocation concealment [enveloped (0 points) or central randomized system (1 point)], statistical analysis approach [per protocol (0 points) or intent-to-treat (1 point)], and salt substitute composition [not reported (0 points) or reported (1 point)]. We considered studies with >4 points as “high quality.”

Statistical analysis

The main outcome of the meta-analysis was the mean difference in BP (mm Hg SBP and DBP) between the intervention and control groups from baseline to the end of the intervention period. For studies that did not report the mean difference in BP between the groups, we computed it by using the reduction in BP reported independently for each group. For studies that reported 95% CIs rather than SEs, the SEs were calculated according to the 95% CI formula. The following cutoffs were used to evaluate heterogeneity: $I^2 = 0–25\%$, no heterogeneity; $I^2 = 25–50\%$, moderate heterogeneity; $I^2 = 50–75\%$, large heterogeneity; and $I^2 = 75–100\%$, extreme heterogeneity (36). Pooled mean differences were estimated by using fixed-effects models when there was no heterogeneity or moderate heterogeneity ($I^2 < 50\%$) and random-effects models when there was moderate, large, or extreme heterogeneity ($I^2 \geq 50\%$).

For the subgroup analysis, the participants were divided into hypertensive and normotensive subgroups. The criteria for hypertension were SBP $\geq 140$ mm Hg or DBP $\geq 90$ mm Hg. Participants in studies that were conducted only in hypertensive patients were included in the hypertensive subgroup. An additional subgroup analysis was conducted by dividing results according to study sample size (≥300 versus <300 participants). Separate random-effects models were used to estimate the pooled mean differences in the various subgroups.

Publication bias was evaluated by using the Egger’s test (significance considered for $P < 0.10$) and by visually inspecting a funnel plot. A sensitivity analysis exploring the effect of a single study on the pooled results was conducted by omitting one study at a time. A meta-analysis was applied by using the meta procedure in STATA 11.0 (Stata Corp).

RESULTS

A summary of the search procedure is presented in Figure 1. A total of 645 articles were identified from PubMed, Embase, and the Cochrane Library, and 156 articles were identified from Wanfang Data and the China National Knowledge Infrastructure. Of these, 108 duplicates and 670 irrelevant articles were excluded. The full text of the remaining 23 articles was reviewed, and an additional 18 articles were excluded because they did not meet the study design criteria (e.g., quasiexperimental studies without randomization, editorials and reviews, RCTs that included interventions other than salt substitutes or control groups other than common salt, studies with intervention durations <6 mo, and studies that did not report on BP). Therefore, 6 cohorts from 5 articles (1 trial enrolled 2 cohorts for independent intervention) consisting of 1974 participants were included in this meta-analysis (Table 1).
### TABLE 1
Characteristics of 5 randomized controlled trials (6 cohorts) included in the meta-analysis

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Country</th>
<th>Language</th>
<th>Randomization method</th>
<th>Blinding</th>
<th>Allocation concealment</th>
<th>Analysis method</th>
<th>Substitute salt</th>
<th>Control salt</th>
<th>Participants</th>
<th>Intervention duration</th>
<th>Completion rate</th>
<th>Sample size (intervention/control)</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al., 2013 (32)</td>
<td>China</td>
<td>English</td>
<td>Computer</td>
<td>Double blind</td>
<td>Coding</td>
<td>ITT</td>
<td>NaCl, 65%; KCl, 25%; MgSO₄, 10%</td>
<td>NaCl, 100%</td>
<td>Hypertensive and normotensive</td>
<td>2 y</td>
<td>81%</td>
<td>224/238</td>
<td>5</td>
</tr>
<tr>
<td>Zhou et al., 2009 (33)</td>
<td>China</td>
<td>English</td>
<td>Computer</td>
<td>Single blind</td>
<td>Envelope</td>
<td>ITT</td>
<td>NaCl, 65%; KCl, 30%; Ca²⁺, 5%; folic acid</td>
<td>NaCl, 100%</td>
<td>Hypertensive and normotensive, 50–80 y of age</td>
<td>6 mo</td>
<td>91%</td>
<td>119/129</td>
<td>4</td>
</tr>
<tr>
<td>CSSS, 2007 (31)</td>
<td>China</td>
<td>English</td>
<td>Central randomized system</td>
<td>Double blind</td>
<td>Central randomized system</td>
<td>ITT</td>
<td>NaCl, 65%; KCl, 25%; MgSO₄, 10%</td>
<td>NaCl, 100%</td>
<td>High risk level of CVD</td>
<td>1 y</td>
<td>96%</td>
<td>306/302</td>
<td>5</td>
</tr>
<tr>
<td>Hu, 2007 (34)¹</td>
<td>China</td>
<td>Chinese</td>
<td>Computer</td>
<td>Double blind</td>
<td>Coding</td>
<td>ITT</td>
<td>NaCl, 65%; KCl, 25%; MgSO₄, 10%</td>
<td>NaCl, 99.8%</td>
<td>Hypertensive, ≥18 y of age</td>
<td>1 y</td>
<td>94%</td>
<td>110/110</td>
<td>5</td>
</tr>
<tr>
<td>Hu, 2007 (34)¹</td>
<td>China</td>
<td>Chinese</td>
<td>Computer</td>
<td>Double blind</td>
<td>Coding</td>
<td>ITT</td>
<td>NaCl, 65%; KCl, 25%; MgSO₄, 10%</td>
<td>NaCl, 99.8%</td>
<td>Hypertensive and normotensive, ≥18 y of age</td>
<td>1 year</td>
<td>83%</td>
<td>171/165</td>
<td>5</td>
</tr>
<tr>
<td>Geleijinse et al., 1994 (27)</td>
<td>Netherlands</td>
<td>English</td>
<td>Random number table</td>
<td>Double blind</td>
<td>Coding</td>
<td>ITT</td>
<td>NaCl, 41%; KCl, 41%; Mg²⁺, 17%; trace minerals, 1%</td>
<td>NaCl, 100%</td>
<td>Hypertensive, 55–75 y of age</td>
<td>6 mo</td>
<td>99%</td>
<td>49/51</td>
<td>5</td>
</tr>
</tbody>
</table>

CSSS, China Salt Substitute Study; ITT, intent-to-treat.

¹The following study attributes were considered when study quality was assessed: randomization approach [random number table (0 points) or computerized (1 point)], blinding method [single blind (0 points) or double blind (1 point)], allocation concealment [enveloped (0 points) or central randomized system (1 point)], statistical analysis approach [per protocol (0 points) or ITT (1 point)], and salt-substitute composition [not reported (0 points) or reported (1 point)]. We regarded studies with ≥4 points as “high quality.”

²One trial with 2 independent cohorts.
Four of the trials were conducted in China (31–34), and 1 of these 4 studies included 2 cohorts (34). The remaining trial (27) was conducted in the Netherlands in the 1990s. Intervention durations ranged from 6 mo to 2 y. Three trials used the same salt substitutes, composed of 65% NaCl, 25% KCl, and 10% MgSO$_4$ (31, 32, 34). One trial used a salt substitute comprised mainly of 41% NaCl, 41% KCl, 17% magnesium salt, and several trace minerals (27). Another ingredient of salt substitute was 65% NaCl, 30% KCl, 5% calcium salt, and some folic acid (33). All trials used common salt in the control group. Three cohorts enrolled both hypertensive and normotensive participants (32–34), and one cohort enrolled participants at high risk of CVD (31). The remaining 2 cohorts enrolled only hypertensive participants (27, 34). The quality of all of the trials was high. Only one trial (33) used a single blinding method (participant). All trials used adequate allocation concealment and reported completion rates.

A summary of the reported effects of salt substitutes on SBP and DBP is listed in Table 2. Heterogeneity values for the outcomes of SBP and DBP were $I^2 = 76.7\%$ and $I^2 = 65.8\%$, respectively. Pooled results from the random-effects model showed that salt substitutes significantly reduced both SBP (mean difference: $-4.9$ mm Hg; 95% CI: $-7.3$, $-2.5$; $P < 0.001$) and DBP (mean difference: $-1.5$ mm Hg; 95% CI: $-2.7$, $-0.3$; $P = 0.013$) (Figure 2).

To further explore heterogeneity and evaluate differences between trials accounting for confounding, subgroup analyses were performed according to the participants’ hypertension status and study sample size (Table 3). The effect of salt substitutes on SBP and DBP was significant only in the hypertensive subgroup; the normotensive subgroup had substantially higher heterogeneity ($I^2 = 82\%$ for SBP in the normotensive subgroup compared with 52% in the hypertensive subgroup). Much less heterogeneity was observed in the sample size subgroups, and the mean differences were all significant.

In sensitivity analyses, the pooled effects of salt substitutes on SBP and DBP did not change after systematically dropping each trial. No evidence of publication bias was indicated from the funnel plots (Figure 3) or Egger’s tests ($P = 0.17$ and 0.22 for SBP and DBP, respectively).

**DISCUSSION**

This meta-analysis showed that salt substitutes are effective for achieving reductions in both SBP and DBP. This has important clinical implications for salt reduction in developing countries such as China, where salt substitutes are readily available and affordable (only ~50% more expensive than normal salt) (31). Replacing normal salt with salt substitutes can be a relatively low-cost complement to clinical therapy for hypertension and a low-cost intervention at the community level to prevent hypertension (37). An effective dietary intervention for BP reduction would be sustainable, would be achieved at a low cost, and may be of a magnitude comparable with that seen in large-scale trials of drug therapy (38).

High dietary salt intake is an important risk factor for hypertension, which in turn increases the risk of CVD (7–15). Many developed countries have achieved progress in dietary salt reduction. For example, the nationwide implementation of the UK salt-reduction program has achieved a significant 15% reduction in 24-h urinary sodium (from 9.5 to 8.1 g/d) over 7 y in
a nationally representative evaluation sample (22). Since the 1970s, the Finnish government has worked with the food industry to reduce the sodium content of foods by using a variety of substitutes, such as low-sodium, high-potassium, calcium, and magnesium salts (39, 40). This has resulted in a 33% reduction in the population average salt intake, a \( \textbf{10-mm Hg} \) decrease in the population average of both SBP and DBP, and a 75–80% decrease in both stroke and coronary artery disease mortality (39, 40). A similar salt-reduction strategy has also been implemented with the food industry in Japan and Australia and achieved successful results (41, 42).

Interventions to address dietary salt intake in China will need to take into account the fact that 75% of dietary salt intake comes from home cooking, in contrast with processed foods such as canned goods or bread in developed countries (23). Given that cooking is an important tradition in China, elimination of salt would be difficult and not culturally acceptable. The high completion rates in the trials included in this meta-analysis suggest that a salt-substitution strategy may be more acceptable and feasible in China (31–34). Of note, a large-scale cluster randomized trial was recently started in China and will test the effects of an intervention consisting of community health education and a food-supply strategy based on providing access to a salt substitute (43). In conjunction with this meta-analysis, results of this trial will inform national strategies to reduce population salt intake and prevent and treat hypertension in China.

A consistent, significant effect on SBP reduction (pooled mean difference: 4.91 mm Hg) was observed in all of the included studies, whereas the effect on DBP reduction was weaker (pooled mean difference: 1.52 mm Hg) (27, 31–34). As expected, heterogeneity, both in SBP and DBP, was reduced in the subgroup analysis. Of note, the reduction in BP levels by salt substitutes compared with common salt was 5.7 mm Hg for SBP and 2.4 mm Hg for DBP in hypertensive participants. Although the reduction in normotensive participants was not statistically significant, possibly because of the high heterogeneity seen in this subgroup, there was still a tendency toward lower BP levels in these participants.

Salt substitutes have been shown to reduce urinary sodium excretion and increase potassium excretion in a Chinese population (33) and a UK population (28). These results suggest that the reduction in BP that we observed in this meta-analysis was likely attributable to the salt substitutes. Whereas perception of saltiness was not the focus of this meta-analysis, it is important to note that, in one of the included studies (31), no change over time was observed between the salt-substitute group and the common-salt group in the perception of saltiness, liking, or overall acceptability of food.

None of the participants enrolled in the included trials had kidney disorders. Adverse effects of salt substitutes in patients with severe renal impairment have been reported (44, 45) and should be considered when applying salt-substitution strategies in large diverse populations.

All of the trials included in this meta-analysis were categorized as “high quality” according to an a priori point system.
However, several important limitations and gaps in the current literature were worth noting. The sample sizes of the included studies were small (all <350 per group), particularly for normotensive participants, and all but one of the studies was conducted in China, which limited the generalizability of these results. Other low- and middle-income countries that are not advanced in the nutrition transition and in which the primary source of dietary salt is cooking may also benefit from salt substitutes, and future research should evaluate the effectiveness of this salt-reduction strategy in these places. Furthermore, the utility of salt substitutes as a public health intervention, and thus their long-term effect and cost-effectiveness, are unknown. This is an important gap in our current knowledge that will need to be addressed before moving forward with policy recommendations. Nonetheless, our meta-analysis provides an important “first step” in the direction toward understanding the efficacy of salt substitutes relative to common salt over a relatively long period of time (6 mo to 2 y) in reducing both SBP and DBP.

In conclusion, results of our meta-analysis suggest that salt substitutes are effective at lowering SBP and DBP. Salt substitution may therefore be a viable dietary approach for population-level hypertension control. Given that high BP was recently ranked the number one risk factor for the global burden of disease (46), identifying culturally appropriate, economically sustainable interventions with long-term effectiveness is of utmost importance. Salt substitution shows promise, but more studies in large diverse samples are needed to demonstrate their utility at the population level.

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