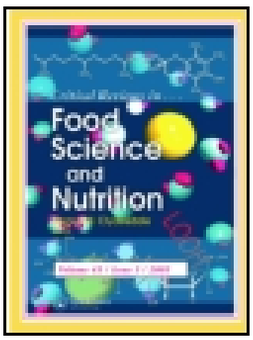

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Sodium status and the metabolic syndrome: A systematic review and meta-analysis of observational studies

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ABSTRACT

The prevalence of metabolic syndrome (MetS) has been greatly increased, worldwide. In recent years, investigators have proposed that sodium might contribute to the development of metabolic syndrome; however, the published data were conflicting. The present systematic review aimed to summarize the evidence from observational studies in this regard. We conducted a systematic search for relevant observational studies investigating the association between sodium status and MetS, published until June 2017 in electronic databases including PubMed, EMBASE, Scopus and Google Scholar. Summary effects were derived using random effects model. After screening the records, seventeen publications with 66,274 participants were eligible to be included in the systematic review and meta-analysis. The analysis revealed that subjects with MetS have significantly higher levels of sodium compared to healthy controls (Hedges' g = 0.21, 95% CI: 0.12, 0.29, I^2 = 68.6). Subgroup analyses revealed that the difference was significant when the sodium status was assessed using urinary sodium levels. The random effects meta-regression analysis also revealed that body sodium level increases with the number of MetS components. Furthermore, participants with highest dietary/urinary or serum sodium levels had 37% higher chance of developing MetS when compared with participants with the lowest sodium levels (OR = 1.37 95%CI: 1.31, 1.42, I^2 = 86.9). The current meta-analysis revealed that higher sodium input into the body is directly associated with the likelihood of MetS. Prospective cohort studies and well-designed randomized clinical trials considering the effect of sodium restricted diets on the risk of MetS as an outcome are necessary to represent the causal association.

KEYWORDS

Metabolic syndrome; sodium status; salt intake; systematic review; meta-analysis

Introduction

In parallel with nutrition transition, the incidence of non-communicable diseases had a growing trend, worldwide (World Health Organization, 2013). Non-communicable diseases such as diabetes, obesity, and hypertension are estimated to account for about two-thirds of years lived with disability in low-income and middle-income countries (World Health Organization, 2013). A cluster of risk factors for non-communicable diseases including glucose intolerance, dyslipidemia, abdominal obesity and high blood pressure are recognized as metabolic syndrome (MetS) (Grundy et al., 2005). The MetS is known to be a risk factor for fatty liver, gallbladder cholesterol stones, polycystic ovarian syndrome and cardiovascular diseases (CVDs)(Grundy et al., 2005).

As one of important modifiable lifestyle factors suggested for MetS, diet has considerably attracted the attention of investigators (Yamaoka and Tango, 2012). High intake of dietary sodium in recent years, as a consequence of changes in dietary pattern, has been mentioned as a global health problem (Brown et al., 2009). High salt intake has been attributed to the greater incidence of stroke and total CVDs (Strazzullo et al., 2009). A meta-analysis of high-quality randomized controlled trials reported that a reduction in sodium intake decreases blood pressure and has no adverse effect on blood lipids, in healthy adults (He and MacGregor, 2002). A 30% reduction in mean population intake of salt/sodium was set as a target of world health organization (WHO) for the prevention and control of non-communicable diseases to be achieved by 2025(World Health Organization, 2013).

Sodium which is often consumed as salt in our diet is an essential nutrient that plays important roles in the maintenance of the extracellular fluid volume, acid-base balance, and generation of the membrane potential of cells (Holbrook et al., 1984). The guideline provided by the institute of medicine has suggested 1500 mg/day as an acceptable sodium intake for middle-aged and older adults (Electrolytes and Water, 2005). However, the mean sodium intake is greater than 2300 mg/day in the

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most adult populations (Brown et al., 2009). The results of a survey conducted from 1975 to 2003 in the United State showed that the mean amount of salt intake was 8537.5 mg/day (Bernstein and Willett, 2010). In Japan, the average salt intake is estimated to be nearly twice more than the recommended daily allowance(Brown et al., 2009). It should be noted that various societies have different sources of sodium intake. Although, in western countries, 75% of sodium intake is from processed foods (Mattes and Donnelly, 1991), in Asian communities including China and Japan, a high proportion of sodium intake comes from salt added when cooking foods (Zhai and Yang, 2006).

In addition to the well-known effect of excessive salt intake on blood pressure (Blaustein et al., 2012), it is supposed that this mineral contributes to insulin and glucose homeostasis (Ogihara et al., 2003). A study revealed that high sodium intake incriminates the risk of type 2 diabetes, independently of obesity, hypertension, and sedentary lifestyle (Hu et al., 2005). The findings from several observational studies have also indicated a direct association between fractional excretion of sodium and insulin resistance (Strazzullo et al., 2006). The literature also revealed that salt sensitivity –blood pressure response to fluctuation in dietary sodium- is more frequent in people with insulin resistance compared to healthy subjects (Giner et al., 2001). A number of studies (Garg et al., 2011; Gomi et al., 1998) but not all (Patel et al., 2015) showed that salt restriction by activation of the renin-angiotensin-aldosterone pathway and sympathetic nervous system exacerbates the insulin sensitivity and plasma insulin response to oral glucose. On the other hand, obesity especially central obesity, which is one of the most frequent components of MetS, has been contributed to impaired renal tubular sodium reabsorption (Mathieu et al., 2009).

The association between sodium status and MetS has been considerably controversial (Choi et al., 2014; Kim et al., 2012, Rodrigues et al., 2009). Several observational studies (Hoffmann and Cubeddu, 2009; Raisanen et al., 2012; Rhee et al., 2014) addressed that the sodium intake is positively associated with MetS while other studies could not replicate this result (Choi, Kim and Chung, 2014; Kim et al., 2012; Rodrigues et al., 2009). Moreover, there is no general consensus about the effects of sodium intake on components of the MetS, including anthropometric measurements and lipid profile (Baudrand et al., 2014; Chen et al., 2009; Hoffmann and Cubeddu, 2009). Given these conflicting results regarding the association between sodium and MetS, we aimed to systematically review the published epidemiologic evidence from observational studies on the association between sodium status and MetS.

Methods

The review protocol and reporting of the data were conducted according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000) and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009). The purpose followed in this review was to determine whether there was a relationship between prevalence of MetS and salt intake in adults. The study protocol was registered in the international prospective register of systematic reviews database (http://www.crd.york.ac.uk/PROSPERO, registration no: CRD42016048984).

Search strategy: We conducted a systematic search for observational studies considered sodium status and MetS, published until June 2017 and indexed in electronic databases including PubMed, EMBASE, and Scopus. No language restriction was applied.

The search was done by SS and RKM combining the following MeSH or non-MeSH keywords: 1) "Sodium", "salt", "salty" and 2)"insulin resistance", "insulin resistance syndrome", "syndrome x", "cardio-metabolic syndrome", "metabolic syndrome", "ravens' syndrome", "metabolic syndrome x", "Diabetes", "T2DM", "glucose tolerance", "NIDDM", "impaired glucose", "impaired fasting glucose", "prediabetes", "dysglycemia", "Diabetes Mellitus", "Diabetes Mellitus, type 2", "Hemoglobin A, Glycosylated", "Hyperglycemia", "Glucose Tolerance Test", "Glucose Intolerance", "hyperglycemia", "fasting blood glucose", "FBS", "HBA1C", "GTT", "fasting plasma glucose", "hyperinsulinemia", "insulin sensitivity", "Insulin Resistance", "Metabolic syndrome", "metabolic syndrome x", "metabolic syndrome", "cardio-metabolic syndrome". In addition, we checked the references of retrieved relevant article to reinforce these search.

Study selection: The inclusion criteria were a) original studies with observational design; b) considered sodium status as urinary or blood sodium levels or dietary sodium/ salt intake; c) the outcome of interest was MetS based on different criteria including adult treatment panel III (NCEP ATPIII) (Expert Panel on Detection, 2001) or the harmonized definition (Alberti et al., 2009) and international diabetes foundation (IDF) (Alberti et al., 2006); d) conducted in adult participants without endocrine disorders such as dysfunction of adrenal gland and hypo/hyperthyroid disorders, kidney failure, kidney stone, pregnancy and lactation; and e) included subjects were not following any specific dietary pattern. Titles and abstracts of studies were reviewed independently by two investigators (SS, RKM) based on the inclusion criteria. Apparent disagreements about the inclusion of abstracts were discussed with the third author (ASA).

Data extraction: Two investigators (SS, RKM) extracted the data (the first author's full name, year of publication, country, gender, age, the criteria used to define MetS, method used to assess sodium status, mean sodium intake and sample size) from relevant articles. Finally, the extracted data were compared and discrepancies between investigators were discussed to reach a consensus and to ensure the accuracy of data. If a study didn't report sufficient information for data extraction, we contacted the corresponding author by e-mail at least two times, one week apart.

Quality assessment: A modified version of Newcastle-Ottawa scale (Herzog et al., 2013) adapted for cross-sectional studies was used to assess the quality of related articles by a single investigator to examine the quality of the eligible studies. The quality assessment results were also checked by the second investigator. This scale consisted of three domains: selection (population representativeness) with Maximum 5 stars, comparability for controlling confounding factors in design or analysis with Maximum 2 stars and ascertainment of outcome with Maximum 3 stars. We decided to assign the highest quality to the top 33.3 percent of the possible scores (7–10), and the other studies in the mid 33.3 percent of the possible scores (3–6)

were categorized as medium quality and those in the first 33.3 percent of quality scores (0–2) were defined as low quality.

Statistical Analysis: Included studies compared the means and their corresponding standard deviation (SD) of urinary, serum or dietary sodium levels in cases with MetS and healthy controls which were used to calculate bias corrected standardized mean difference (hedges' g) as effect size to be included in the meta-analysis. Furthermore, a number of studies reported mean serum, urinary or dietary sodium intake based on the number of MetS components; therefore, we tried to calculate bias corrected standardized mean difference (Hedges' g) between participants with one, two, three, four and more components of MetS vs. healthy participants who were free of all MetS components to see if there is an increasing trend of mean difference in sodium status exists by increasing the number of MetS components. In addition, the ORs and their 95% confidence intervals (CIs) for comparing the MetS prevalence between groups with highest and lowest sodium status were also used to calculate log OR and its corresponding standard error (SE) to be used as effect size for a separate meta-analysis (Egger et al., 2001). We calculated OR and its 95% CI, if a study reported the number of participants with and without MetS based on sodium status strata. Overall effects were derived using Dersimonian and Liard random effects model, which takes the variability between true study effects into account (Egger, Smith, and Altman, 2001). Subgroup analysis was incorporated to investigate the possible sources of heterogeneity. Statistical heterogeneity was assessed using Cochran's Q test and I-squared (I^2) (Higgins and Thompson, 2002). We conducted a meta-regression analysis to explore the association between the number of MetS components and the variation in mean difference in sodium status. Sensitivity analysis was conducted by pulling the studies from meta-analyses one by one. We also evaluated the publication bias using Begg's funnel plots (Egger et al., 1997) and the asymmetry tests (Egger's and Begg's test). If publication bias was observed, the trim-and-fill method was applied to further evaluate if the correction of bias significantly change the meta-analysis result (Peters et al., 2007). All statistical analyses were done using STATA version 11.2 (STATA Corp, College Station, TX). P values lower than 0.05 were considered as statistically significant.

Results

Included studies: As described in Figure 1, 44,456 records were obtained by electronic and hand search of which 31,425 records remained after duplicate references were removed. We excluded 31,141 studies after screening titles/abstracts; therefore, 287 studies were remained to be carefully checked by reading their full-text. Of the remaining, 269 articles were excluded because of the following reasons: case report (n = 1), cell line or animal studies (n = 2), studies conducted in patients with diabetes insipidus (n = 6), conducted in children (n = 3), clinical trial in design (n = 48), did not consider sodium status as the exposure (n = 101), MetS relevant outcome was not available (n = 84), review or commentary (n = 20) and study protocol (n = 4). In total, 18 articles were eligible to be addressed in the qualitative systematic review (Baudrand et al., 2014; Cheng et al., 2017; Choi, Kim, and Chung, 2014; Ge et al., 2015;

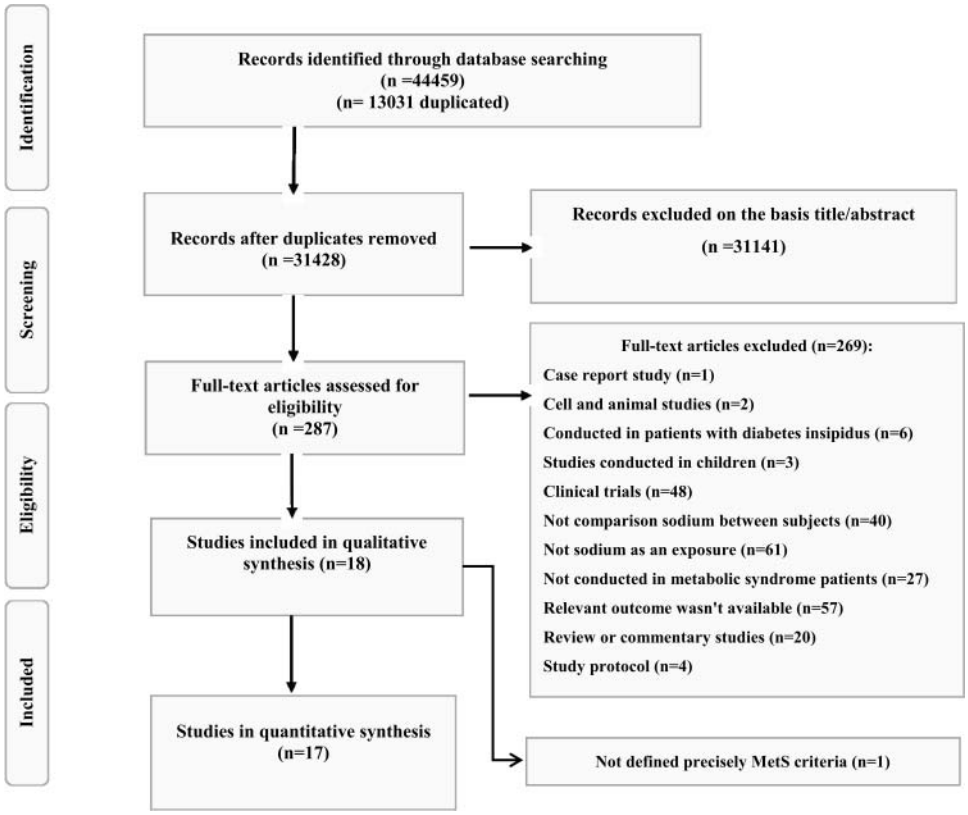

Figure 1. Flow diagram for study selection procedure.

Hernández et al., 2012; Hoffmann and Cubeddu, 2009; Kim et al., 2012; Kimura et al., 2016; Oh et al., 2015; Ohta et al., 2007; Pavlov et al., 2012; Raisanen et al., 2012; Rhee et al., 2014; Rodrigues et al., 2009; Sulibursk a et al., 2011; Teramoto et al., 2011; Unal et al., 2014; Won et al., 2016). One study was not included in the meta-analysis because it did not mention the diagnosis criteria for insulin resistance and also did not consider the waist circumference in defining the MetS (Sulibursk a et al., 2011). Therefore, in meta-analysis we used data from 17 publications with 66,274 participants. All eligible studies were cross-sectional regarding their design.

Table 1 describes the characteristics of studies included in the systematic review. The studies were published between 2007 and 2017. All studies had recruited both men and women and eleven studies were conducted in Asia (Cheng et al., 2017; Choi, Kim, and Chung, 2014; Ge et al., 2015; Kim et al., 2012; Kimura et al., 2016; Oh et al., 2015; Ohta et al., 2007; Rhee et al., 2014; Teramoto et al., 2011; Unal et al., 2014; Won et al., 2016), three in Latin America(Baudrand et al., 2014; Hoffmann and Cubeddu, 2009; Rodrigues et al., 2009) and four in Europe (Hernández et al., 2012; Pavlov et al., 2012; Raisanen et al., 2012; Sulibursk a et al., 2011). Two studies were published in a non-English language (Hernández et al., 2012; Pavlov et al., 2012). Twelve studies used NCEP ATP III criteria or the harmonized definition for defining MetS (Baudrand et al., 2014; Cheng etal., 2017; Choi, Kim and Chung, 2014; Ge et al., 2015; Hernández et al., 2012; Hoffmann and Cubeddu, 2009; Kimura et al., 2016; Oh et al., 2015; Pavlov et al., 2012; Rodrigues et al., 2009; Unal et al., 2014; Won et al., 2016), four studies used IDF criteria (Kim et al., 2012; Ohta et al., 2007; Raisanen et al., 2012; Rhee et al., 2014) and one study incorporated the criteria established by the Japanese Society of Internal Medicine to define MetS (Teramoto et al., 2011). One study did not precisely mention the definition for MetS (Sulibursk a et al., 2011). Eleven studies used urine collection to assess the sodium status (Baudrand et al., 2014; Ge et al., 2015; Hernández et al., 2012; Hoffmann and Cubeddu, 2009; Oh et al., 2015; Ohta et al., 2007; Pavlov et al., 2012; Rhee et al., 2014; Rodrigues et al., 2009; Unal et al., 2014; Won et al., 2016), one defined sodium intake as a sodium dietary score, on the basis of Arakawa formula (Arakawa et al., 2009) which defines a 10-point increase in sodium dietary score according to an increased sodium intake of 3 gr (Teramoto et al., 2011), two studies assessed sodium intake using food record (Raisanen et al., 2012) and two studies used 24-hour food recall (Cheng et al., 2017; Kim et al., 2012) and daily sodium intake was adjusted for total energy intake in three studies (Cheng et al., 2017; Kim et al., 2012; Raisanen et al., 2012) and three studies used serum sodium as a biochemical marker of daily sodium intake (Choi, Kim, and Chung, 2014; Kimura et al., 2016; Sulibursk a et al., 2011).

Quality assessment of included studies: The result of quality assessment based on the modified Newcastle-Ottawa scale is reported in Table 2. In brief, sixteen included studies achieved relatively high scores (Baudrand et al., 2014; Cheng et al., 2017; Choi, Kim, and Chung, 2014; Ge et al., 2015; Hernández et al., 2012; Hoffmann and Cubeddu, 2009; Kim et al., 2012; Kimura et al., 2016; Oh et al., 2015; Ohta et al., 2007; Raisanen et al., 2012; Rhee et al., 2014; Rodrigues et al., 2009; Sulibursk a et al., 2011; Unal et al., 2014; Won et al., 2016) (7 or more) except two studies conducted by Teramoto et al (Teramoto et al., 2011) (5 out of 10) and Pavlov et al (Pavlov et al., 2012) (6 out of 10) which were moderate in quality.

Meta-analysis

Comparison of mean sodium status in subjects with Mets and healthy controls: Twelve studies on 16,007 subjects with 4,378 prevalent cases of MetS were included in the meta-analysis to compare the mean sodium status between the subject with and without MetS (Choi, Kim, and Chung, 2014; Ge et al., 2015; Hernández et al., 2012; Hoffmann and Cubeddu, 2009; Kim et al., 2012; Kimura et al., 2016; Oh et al., 2015; Pavlov et al., 2012; Raisanen et al., 2012; Rhee et al., 2014; Rodrigues et al., 2009; Unal et al., 2014). Figure 2 represents that subjects with MetS had higher levels of sodium status compared to those without MetS (Hedges' g = 0.21, 95% CI: 0.12, 0.29) with moderate heterogeneity between studies (Cochrane Q test, $P_{heterogeneity} < 0.001$, $I^2 = 68.6\%$). The positive association between sodium status and MetS was only limited to urinary sodium excretion (Hedges' g = 0.27, 95% CI: 0.19, 0.35) with no evidence of heterogeneity between studies (Cochrane Q test, $P_{heterogeneity} = 0.251$, $I^2 = 21.7\%$) (Ge et al., 2015; Hernández et al., 2012; Hoffmann and Cubeddu, 2009; Oh et al., 2015; Pavlov et al., 2012; Rhee et al., 2014; Rodrigues et al., 2009; Unal et al., 2014) (Supplementary online materials, Table 1).

Sensitivity analysis revealed that removal of each study at a time did not substantially change the overall effect. There was a slight asymmetry in the Begg's funnel plot (Supplementary online materials, Figure 1) and this was also confirmed by Egger's regression test (Begg's test, P = 0.161 and Egger's test, P = 0.011); Using trim and fill analysis two studies were added to make the funnel plot symmetrical, however the summary effect was not changed (Hedges' g = 0.188, 95% CI: 0.105–0.271).

Sodium status based on the number of MetS components: We had also six articles with 28,960 individuals which reported sodium status based on the number of MetS components (Cheng et al., 2017; Hernández et al., 2012; Hoffmann and Cubeddu, 2009; Rhee et al., 2014; Rodrigues et al., 2009; Won et al., 2016). Therefore we tried to compare the sodium status of participants with 1, 2, 3 and ≥4 components of MetS with those free of MetS components in separate analyses, to see if the sodium status increases with the number of MetS components. Our analysis revealed that those with one MetS components had greater amount of body sodium in comparison to those without MetS components (Hedges' g = 0.11, 95%CI = 0.01, 0.21). The body sodium status was significantly higher when people with two MetS components were compared with those less than one MetS components (Hedges' g = 0.19, 95%CI: 0.09, 0.29), as well as for three (Hedges' g = 0.24, 95%CI: 0.11, 0.36) and four components (Hedges' g = 0.22, 95%CI: 0.11, 0.33) (Figure 3). The heterogeneity was high between studies when comparing sodium status between subjects with 1, 2 or 4 MetS components and participants without

Table 1. Characteristic of observational studies that evaluated the effect of the association of sodium status and prevalence of MetS.

Author (year)	Study location	subjects	sex	age	Criteria for Mets	Sodium assessment method	Results
Ohta et al. (2007) (Ohta, Tsuchihashi, Arakawa, Onaka, and Ueno, 2007)*	Japan	230	Both	64	IDF[1]	24-hour urine sodium	Subjects with Mets had higher sodium exertion compared to subjects without MetS
Hoffmann et al. (2009) (Hoffmann and Cubeddu, 2009)*	Venezuela	301	Both	44.9	ATP III	24-hour urine sodium	Higher urinary sodium excretion was associated with likelihood of MetS
Rodrigues et al. (2009) (Rodrigues, Baldo, de Sá Cunha, Andreão, Molina, Gonçalves, Dantas, and Mill, 2009)*"	Brazil	1655	Both	45	ATP III	12-hour urine sodium	higher sodium intake was not associated with MetS
Teramoto et al. (2011) (Teramoto, Kawamori, Miyazaki, and Teramukai, 2011)¥	Japan	9585	Both	64.9	Japanese Society ofInternal Medicine	Sodium intake scores	Higher sodium intake was associated with MetS only in men
Suliburska (2011) (Suliburska, Bogdanski, Pupek-Musialik, and Krejpcio, 2011)	Poland	80	Both	25–65	Not mentioned	Serum sodium	No association found between sodium status and MetS components
Hernández et al. (2012) (Hernández, Alfieri, Hoffmann, and Ramírez, 2012)*"	Spain	998	Both	48.8	ATP III	24-hour urine sodium	Participants with Mets had higher urinary sodium exertion compared to healthy participants
Kim et al. (2012) (Kim, Lim, Kim, Kim, and Shin, 2012)*	Korea	3757	Both	50.6	IDF	Sodium intake	Sodium intake was not different between participants with MetS and their healthy controls
Pavlov et al. (2012) (Pavlov, Alekseev, Agaverdiev, and Ishemgulov, 2012)*	Russia	165	Both	—	ATP III	24-hour urine sodium	Subjects without MetS had higher sodium exertion compared to subjects with MetS
Raisanen et al. (2012) (Raisanen, Silaste, Kesaniemi, and Ukkola, 2012) *	Finland	716	Both	40	IDF	Sodium intake	High sodium intake found to be a significant predictor of the MetS
Baudrand et al. (2014) (Baudrand, Campino, Carvajal, Olivieri, Guidi, Faccini, Vohringer, Cerda, Owen, Kalergis, and Fardella, 2014)¥	Chile	370	Both	50.1	Harmonized definition	24-hour urine sodium	High sodium intake was associated with MetS
Choi et al. (2014) (Choi, Kim, and Chung, 2014)*	Korea	456	Both	47.5	ATP III + cutoff point for abdominal obesity (≥90 cm for men and ≥85 cm for women)	Serum sodium	No differences in the serum sodium between participants with MetS compared to healthy subjects
Rhee et al. (2014) (Rhee, Kim, Kim, Chung, Bae, Nah, Kim, Lee, Lim, Byun, Park, Kang, Kim, and Kim, 2014)*"¥	Korea	463	Both	35–65	IDF	24-hour urine sodium	A significant relationship was addressed between the number of MetS component and 24-hour urine sodium excretion
Unal et al. (2014) (Unal, Kocyigit, Sipahioglu, Tokgoz, and Oymak, 2014)*	Turkey	76	Both	38	ATP III	24-hour urine sodium	Urinary sodium excretion was higher in patients with MetS compared to those without MetS
Ge et al. (2015) (Ge, Guo, Chen, Tang, Yan, Ren, Zhang, Lu, Dong, Xu, Cai, Liang, and Ma, 2015)*¥	China	1906	Both	18–69	Harmonized	24-hour urine sodium	for every 100 mmol/d increase in urinary sodium, the odds of the MetS was increased by 29%
Oh et al. (2015) (Oh, Han, Han, Koo, Kim, and Chin, 2015)¥	Korea	18146	Both	46.8	ATP III	12-hour urine sodium	Sodium intake was associated with MetS
Kimura (2016) (Kimura, Hashimoto, Tanaka, Asano, Yamazaki, Oda, Toda, Marunaka, Nakamura, and Fukui, 2016)	Japan	3875	Both	48.3	Harmonized	Serum sodium	The higher serum sodium was associated with an increased risk of the development of MetS.
Cheng (2016)"(Cheng, Wang, Wang, Du, Ouyang, and Zhang, 2017)	China	6034	Both	18–75	Harmonized	Sodium intake	Sodium intake was the high risk factors correlating with the increased number of MetS components in women.
Won (2016)"¥ (Won, Hong, Noh, and Kim, 2016)	Korea	17541	Both	45.2	ATP III	24-hour urine sodium	Urinary sodium have an independent association with the presence of MetS.

[1]IDF: International diabetes federation; ATPIII: Adult treatment panel III; MetS: Metabolic syndrome
*Compared mean sodium status between the subject with and without MetS
"Described sodium status based on the number of MetS components
¥Examined odds ratio for MetS in participants with highest sodium levels compared to those with lowest sodium levels

Table 2. Study quality and risk of bias assessment using the modified Newcastle-Ottawa scale (Herzog et al. 2013).

	Selection				Outcome			
Author (year)	Representativeness of sample	Sample size	Ascertainment of exposure	Comparability	Assessment of the outcome	Statistical test	score	Quality of studies
Ohta et al. (2007) (Ohta, Tsuchihashi, Arakawa, Onaka and Ueno 2007)	**	*	**	*	**	*	9	High
Hoffmann et al. (2009) (Hoffmann and Cubeddu 2009)	**	*	**	**	**	*	10	High
Rodrigues et al. (2009) (Rodrigues, Baldo, de Sá Cunha, Andreão, Molina, Gonçalves, Dantas and Mill 2009)	**	*	**	*	**	*	9	High
Teramoto et al. (2011) (Teramoto, Kawamori, Miyazaki and Teramukai 2011)	*	*	*	—	*	*	5	Moderate
Suliburska et al. (2011) (Suliburska, Bogdanski, Pupek-Musialik and Krejpcio 2011)	—	*	**	*	**	*	7	High
Hernández et al. (2012) (Hernández, Alfieri, Hoffmann and Ramírez 2012)	*	*	**	*	**	*	8	High
Kim et al. (2012) (Kim, Lim, Kim, Kim and Shin 2012)	**	*	**	**	**	*	10	High
Pavlov et al. (2012) (Pavlov, Alekseev, Agaverdiev and Ishemgulov 2012)	—	—	**	*	**	*	6	Moderate
Raisanen et al. (2012) (Raisanen, Silaste, Kesaniemi and Ukkola 2012)	**	*	**	**	**	*	10	High
Baudrand et al. (2014) (Baudrand, Campino, Carvajal, Olivieri, Guidi, Faccini, Vohringer, Cerda, Owen, Kalergis and Fardella 2014)	**	*	**	**	**	*	10	High
Choi et al. (2014) (Choi, Kim and Chung 2014)	**	*	**	*	**	*	9	High
Rhee et al. (2014) (Rhee, Kim, Kim, Chung, Bae, Nah, Kim, Lee, Lim, Byun, Park, Kang, Kim and Kim 2014)	**	*	**	**	**	*	10	High
Unal et al. (2014) (Unal, Kocyigit, Sipahioglu, Tokgoz and Oymak 2014)	*	—	**	*	**	*	7	High
Ge et al. (2015) (Ge, Guo, Chen, Tang, Yan, Ren, Zhang, Lu, Dong, Xu, Cai, Liang and Ma 2015)	**	*	**	**	**	*	10	High
Oh et al. (2015) (Oh, Han, Han, Koo, Kim and Chin 2015)	**	*	**	**	**	*	10	High
Kimura et al. (2016) (Kimura, Hashimoto, Tanaka, Asano, Yamazaki, Oda, Toda, Marunaka, Nakamura and Fukui 2016)	**	*	**	*	**	*	9	High
Cheng et al. (2016) (Cheng, Wang, Wang, Du, Ouyang and Zhang 2017)	**	*	**	**	**	*	10	High
Won et al. (2016)(Won, Hong, Noh and Kim 2016)	**	*	**	**	**	*	10	High

MetS components. This heterogeneity disappeared in male participants when the studies were stratified by sex. However, the high heterogeneity remained in female subgroup. (Supplementary online materials, Table 2). Random-effects meta-regression analysis revealed that difference in sodium status increases as the number of components of MetS increases ($\beta = 0.061$,$P = 0.012$) (Supplementary online materials, Figure 2).

Sodium status and likelihood of MetS: The meta-analysis of seven studies (Baudrand et al., 2014; Ge et al., 2015; Kimura et al., 2016; Oh et al., 2015; Rhee et al., 2014; Teramoto et al., 2011; Won et al., 2016) with 51,886 participants which examined the association between sodium status and odds of MetS (Figure 4) suggested that subjects in the highest categories of sodium status had 37% greater chance of developing MetS (odds ratio (OR) = 1.37, 95%CI: 1.31,1.42). The heterogeneity between studies was high (Cochrane Q test, $P_{heterogeneity} < 0.001$, $I^2 = 86.9\%$). The increase in the risk of MetS appeared more evident when the sodium status was assessed by urinary exertion (OR = 1.41, 95%CI: 1.34, 1.47), however the heterogeneity remained significant (Cochrane Q test, $P_{heterogeneity} = 0.007$, $I^2 = 90.1\%$) (Baudrand et al., 2014; Ge et al., 2015; Oh et al., 2015; Rhee et al., 2014; Won et al., 2016). Sensitivity analysis revealed that the prevalence of MetS did not change with the exclusion of individual studies. We could observe a slight asymmetry in Begg's funnel plot (Supplementary online materials, Figure 3), however the publication bias was not shown to be significant using statistical asymmetry tests (Egger's test, P = 0.092 and Begg's test, P = 0.175). It should be noted that the power of asymmetry tests are limited when the number of included studies is lower than 10 (Sterne et al., 2000).

Discussion

Findings from the current systematic review indicated that subjects with MetS had statistically significant higher levels of

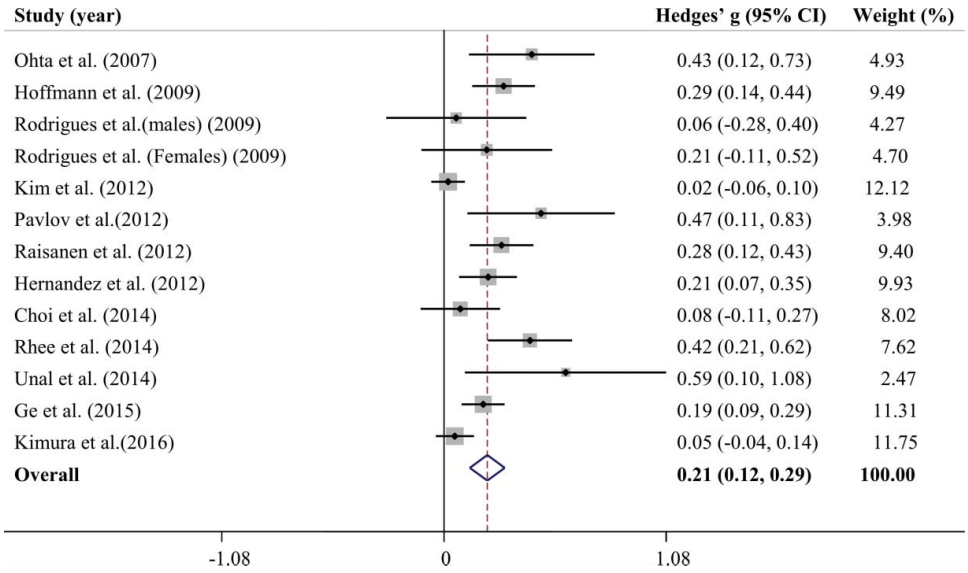

Figure 2. Forest plot demonstrating meta-analysis of studies examining sodium levels in patients with metabolic syndrome compared with healthy subjects. The analysis was done using random effects model.

sodium than subjects with the healthy metabolic profile. Moreover, the highest category of sodium status was associated with a 37% higher odds of MetS when compared to the lowest category. The meta-analysis also revealed that the difference in body sodium status increases with the number of MetS components when compared with healthy individuals. To the best of our knowledge this is the first meta-analysis to explore the potential association between sodium status and MetS.

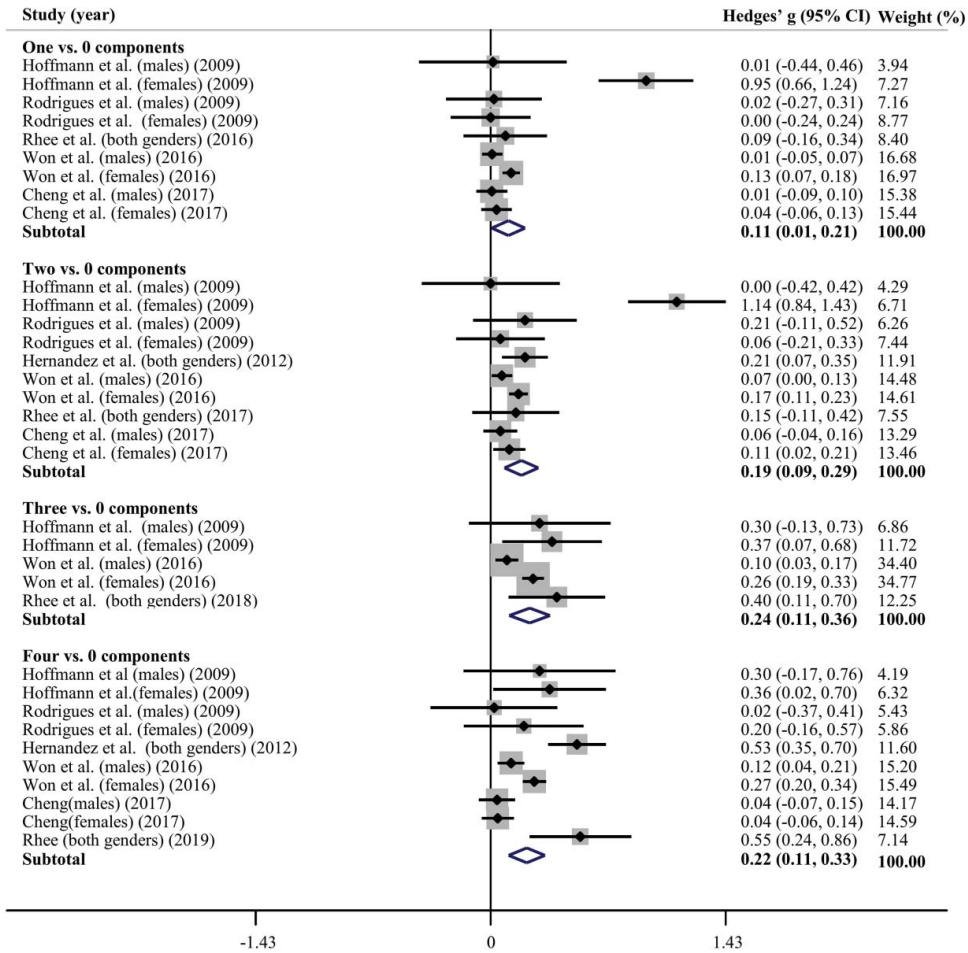

Figure 3. Meta-analysis describing the sodium status in subjects with one, two, three, and four and more components of metabolic syndrome compared to subjects without metabolic syndrome components. The analysis was conducted using random effects model.

Our findings are in line with most short-term clinical trials which found that high vs. low salt intake might lead to a decreased insulin sensitivity as a key component of MetS (Donovan et al., 1993; Facchini et al., 1999; Vedovato et al., 2004). It is proposed that high sodium intake significantly decrease the rate of glucose infusion and impairs insulin induced hepatic glycogen synthesis (Ogihara, Asano and Fujita, 2003). Reductions in a number of insulin receptors and insulin mRNA transcription after consuming a high salt diet have been reported in the kidney in an animal model (Ogihara, Asano and Fujita, 2003). Additionally, sodium loading diet activates brain Renin-Angiotensin-Aldosterone system (Lastra et al., 2010). Angiotensin II which is drived from angiotensinogen through the stimulation of oxidative stress pathway is able to induce insulin resistance (Fujita, 2007); consequently, angiotensin II leads to radical oxygen spices (ROS) up-regulation and ROS has been demonstrated to impair Insulin receptor substrate 1 (IRS-1) phosphorylation and a reduction in IRS-1 stimulated phosphoinositide 3-kinase- (PI3K-) activation (Ogihara et al., 2004). Another aspect of the link between MetS and sodium intake is the effect of insulin on tubular reabsorption of sodium (DeFronzo et al., 1975). The Na+-H+ exchanger type 3 (NHE3) which is an important factor in apical sodium entry activities in proximal tubules of the animal model is directly increased by insulin (Gesek and Schoolwerth, 1991). In proximal tubules, insulin also activates the basolateral electrogenic sodium bicarbonate cotransporter (NBCe1) which had an important role in sodium and bicarbonate exit from the proximal tubular cell (Ruiz et al., 1998). Furthermore, it is found that insulin has the ability to stimulate Na-K-ATPase in the proximal, distal and connecting tubule. It has been suggested that insulin induces a sodium transporter activity via a signaling which involves PI3K and 3-phosphoinositide-dependent protein kinase (PDK1) (Shiue et al., 2005).

Salt-sensitive phenotype (blood pressure responders to sodium intake) was more common among patients with the MetS (Chen et al., 2009). Central obesity and insulin resistance as a key MetS features might result in sodium retention and extracellular fluid volume expansion, thereby increasing blood pressure response to sodium intake (Shimamoto et al., 1994). It is revealed that salt-sensitive phenotype significantly increased plasma insulin concentrations following a high salt diet, independent from blood pressure status (Sharma et al., 1991; Zavaroni et al., 1995). Recently published observational studies found a possible positive association between urinary sodium excretion/sodium intake and increase in abdominal obesity and body fat percentage, and development of obesity independent of total energy intake (Libuda et al., 2012; Murakami et al., 2015). High salt intake induces capacity to glucose conversion into lipids via increased lipogenic activity and leads to excessive fat accumulation (Fonseca−Alaniz et al., 2007). Obesity is proposed to be a cause of hypertension and accordingly leads to insulin resistance induced high blood pressure (Karaca et al., 2014).

In the present study, the positive association between sodium status and MetS prevalence was only observed when sodium status was assessed using urinary exertion levels. Dietary sodium intake assessment methods such as food records and 24-hour recall and food frequency questionnaires (FFQs) are tended to underestimate the mean of sodium intake (Micheli and Rosa, 2003) because of inaccurate or incomplete food composition tables, error in estimation of salt added in food preparation and at the table, variation in sodium concentration of water supplies and ignorance of salt added to manufacture foods(Elliott and Brown, 2007). As approximately more than 95% of dietary sodium excretes in the urine, 24-hour urinary exertion has known as a gold standard technique for measuring sodium intake (Ljungman et al., 1981). The 24-hour urine collection is regarded as an standard assessment method for sodium intake and has been used to evaluate dietary sodium intake in 32 countries in the INTERSALT study (Dyer et al., 1997).

The interpretation of finding from this study should be done considering some limitations. Included studies were cross-sectional in their design; therefore, causality cannot be inferred from the current analysis. Although the 24-hour urinary sample is regarded as the gold standard method for sodium intake evaluation, a single 24-hour urine sample is not sufficient to

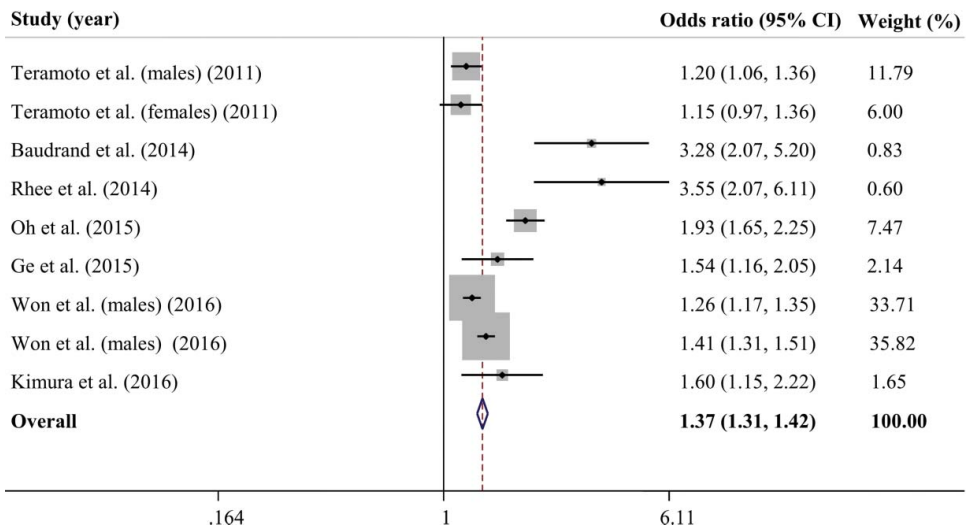

Figure 4. Forest plot summarizing the odds ratio for metabolic syndrome in participants with highest sodium levels compared to those with lowest sodium levels. The analysis was accomplished using random effects model.

estimate the long-term sodium intake because day-to-day intra-individual variation is large for sodium intakes, Liu et al. (LIU et al., 1979) and Joossens et al (Joossens et al., 1980) demonstrated that fourteen 24-hour urine collections might be needed to accurately estimate the long-term sodium intake. Hence, the greater the variance in the sodium measurement and the random error resulted from an imprecise measure of sodium status will lead to regression dilution and a weak association between sodium intake as an exposure and MetS as a result. The strengths of the present study include its comprehensive search strategy trying to encompass approximately all investigations studies the association between sodium status and MetS without language restriction. Moreover, we applied extensive analysis in exploring different aspects of the association between sodium status and MetS and considered the most important variables that could affect this finding. Further studies with prospective design are needed to establish potential causal relationship between sodium status and the MetS. Well-designed randomized trials with long follow-up period examining the sodium restriction diet on risk of MetS as an outcome might be of great intereset to elucidate such an association.

In conclusion, the current meta-analysis found that, high sodium status is positively associated with the prevalence of MetS. Future prospective studies are recommended to confirm this result.

Conflict of interest

Authors declare that they have no conflict of interest regarding the publication of the manuscript.

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Authors' contribution

SS, RKM and SSB conceived the study. ASA, SS and RKM carried out the literature search and data extraction. ASA and SS conducted the quality checking of included studies; Data analysis and interpretation were conducted by ASA, SS and RKM. All authors contributed to the study conception, design and drafting of the manuscript.

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