Nutrition, Metabolism & Cardiovascular Diseases (2019) 29, 665–675

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

SYSTEMATIC REVIEWS AND META-ANALYSES

Dietary acid load and risk of hypertension: A systematic review and dose-response meta-analysis of observational studies

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Received 5 August 2018; received in revised form 12 February 2019; accepted 15 March 2019
Handling Editor: P. Strazzullo
Available online 23 March 2019

KEYWORDS
Acid-base equilibrium;
Diet;
Hypertension;
Cardiovascular disease

Abstract *Background and aim:* Previous studies have assessed diet-induced mild metabolic acidosis in relation to blood pressure, however, data are conflicting. Current systematic review and dose-response meta-analysis aimed to summarize earlier findings from observational studies on the association between dietary acid load and hypertension.
Methods and results: We searched the online databases for relevant publications up to Feb 2019, using relevant keywords. Overall, 14 studies (3 prospective and 11 cross-sectional studies) that included 306,183 individuals and 62,264 cases of hypertension were included in the current meta-analysis. Combining effect sizes from both prospective and cross-sectional studies revealed no significant non-linear association between dietary acid load (based on net endogenous acid production (NEAP) method) and hypertension. However, stratified analysis based on study design showed a significant non-linear association between dietary acid load and hypertension in prospective studies (P = 0.006), but not cross-sectional ones. According to linear dose-response analysis, no significant association was found between dietary acid load (based on NEAP) and hypertension (combined effect size: 1.01, 95% CI: 0.97–1.06, P = 0.51). In terms of dietary acid load based on potential renal acid load (PRAL) method, no significant non-linear association was seen with hypertension (P = 0.52). However, in linear dose-response analysis, a-20 unit increase in PRAL values was associated with 3% increased risk of hypertension (combined effect size: 1.03, 95% CI: 1.00–1.06, P = 0.03).
Conclusion: We found a significant positive association between dietary acid load and hypertension. Further studies, particularly those with prospective nature, are needed to confirm our findings.

Abbreviation: NEAP, net endogenous acid production; PRAL, potential renal acid load; CVDs, cardiovascular diseases; OR, odds ratio; RR, relative risk; HR, hazard ratios; NOS, Newcastle Ottawa scale; FFQ, food frequency questionnaire; BMI, body mass index.

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https://doi.org/10.1016/j.numecd.2019.03.009

Introduction

Hypertension (HTN) is known as one of the most important causes of mortality in the world [1]. The prevalence of hypertension is increasing. It has been estimated that 29.2% of general population, around the world, will be affected in 2025 [2,3]. Hypertension is largely attributable to modifiable environmental factors, including diet. Among dietary factors, intake of meat, fruit, vegetables, dietary sodium, magnesium and potassium can affect risk of hypertension [4].

Recently, the association between acid-base homeostasis and risk of cardiovascular diseases (CVDs) has been studied [5,6]. Diet can change the body's acid-base balance by providing acid precursors (i.e. non-carbonic acids such as sulfuric acid) or base precursors (i.e. alkali salts from organic acids, such as citrate and bicarbonate) [7,8]. Sulphate- and phosphorus-containing foods including meat, fish, cheese, grain products, and rice contribute to acid load [7,9], whereas foods rich in bicarbonate, potassium, magnesium, and calcium such as fruit, legumes, vegetables, red wine, and potatoes contribute to alkali load [10]. Two major approaches were designed for measuring dietary acid load via dietary data: net endogenous acid production (NEAP) [8] and potential renal acid load (PRAL) [9]. In NEAP, dietary acid load is measured based on protein and potassium content of diet, while in PRAL, different contributing nutrients, ionic balances for calcium and magnesium, and dissociation of phosphate at pH 7.4 are considered. Higher NEAP and PRAL are associated with higher dietary acid load [8,9].

The association between dietary acid-base load and risk of hypertension has received considerable attention [11–24]. However, data in this association are conflicting. In Nurses' Health Study II, Zhang et al. reported an increased risk of hypertension for women in the highest category of NEAP compared with those in the lowest category [13]. In contrast, Chan et al. failed to find any significant association [11]. Despite several publications on the association between dietary acid load and hypertension, we are aware of no further study that summarized the findings from previous studies. In the current study, we aimed to systematically review the available evidence about the association between dietary acid load and hypertension in adults and to conduct a meta-analysis.

Material and methods

This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol for reporting systematic reviews and meta-analyses [25].

Search strategy

In the current study, we aimed to include observational studies with prospective, cross-sectional or case-control design that examined the association between dietary acid load and hypertension. Two independent investigators (AS and MP) conducted a systematic search in the online databases of PubMed, Institute for Scientific Information Web of Science, Scopus, ProQuest, Science Direct, and Embase for relevant publications up to Feb 2019. The following terms were used in our search strategy: "dietary acid load" OR "dietary acid-base load" OR "dietary acidity" OR "net acid load" OR "acid excretion" OR "potential renal acid load" OR PRAL OR "net endogenous acid production" OR NEAP OR "protein to potassium ratio" OR "protein/potassium ratio" AND "Blood Pressure" OR "Arterial Pressure" OR "Venous Pressure" OR "Hypotension" OR "Hypertension". We did not restrict our search on language of papers and time of publication. In addition, the reference lists of the related articles were screened to avoid missing any publication. When the search was completed, duplicate papers were removed.

Inclusion criteria

In the current meta-analysis, studies with the following criteria were eligible for inclusion: 1) all studies evaluating dietary acid load in relation to hypertension, 2) those with prospective, case-control or cross-sectional design, 3) studies that presented estimates of odds ratios (ORs), relative risk (RRs) or hazard ratios (HRs) as well as corresponding 95% confidence intervals (CIs) for the association between dietary acid load and hypertension. If >1 studies had been done on the same population, only the one with more complete findings or with the greatest number of cases (for prospective studies) was included. In case of disagreements, the principal investigator (OS) was consulted.

Excluded studies

Letters, comments, short communication, reviews, meta-analyses, ecologic studies, and animal studies were excluded during screening of publications. In our initial search, we found 283 articles. We excluded 252 papers after reviewing the title and abstract. After assessing the full texts of remaining articles, the other 16 articles were excluded due to the following reasons: 1) studies that evaluated the association between dietary acid load and risk of CVDs except hypertension (n = 13), 2) studies that were done on pregnant women assessing preeclampsia in relation to dietary acid load (n = 1) [26], 3) those that were done on patients with renal transplant (n = 1) [27] and 4) studies that presented mean ± SE for blood pressure across categories of dietary acid load scores (n = 1) [28]. Among 15 studies remaining, 2 cross-sectional studies were done on the same population [19,29]. We only included one with the larger sample size to avoid double-counting data [19]. Finally, 14 articles including 3 prospective [11–13] and 11 cross-sectional [14–23] studies were included in the current systematic review and meta-analysis (Fig. 1), 11 studies for NEAP [11–19,24] and 10 studies for PRAL [12,15–19,21–24].

Data extraction

Data extraction was conducted independently by two investigators (AS and MP) using a standardized data collection form. Any disagreement was resolved by consensus. The presence of participants across categories of dietary acid load scores was considered as the key exposure variable. All prospective studies had categorized participants based on the baseline values of dietary acid load. Outcome of interest in the current study was hypertension. Any reported ORs, RRs or HRs and related CIs for hypertension across categories of dietary acid load scores were extracted. The following information were also extracted from each study: first author, year of publication, country of origin, age range (at study baseline for prospective studies), sample size, number of cases with hypertension, duration of follow-up (for prospective studies), methods used for assessing dietary intakes and measuring blood pressure, criteria for diagnosis of hypertension, and statistical adjustment for confounding variables (Table 1). Among screened studies, six prospective studies did not present any estimate for the association between dietary acid load and hypertension, however, they contained required data at baseline for calculating OR for hypertension across categories of dietary acid load scores [15,16,18–21]. Therefore, we included these papers as cross-sectional studies and calculated OR and related 95% CI of hypertension across categories of dietary acid load scores.

Assessment of study quality

The quality of prospective studies was examined using a version of the Newcastle Ottawa Scale (NOS) designed for nonrandomized studies [30]. This scale assigns a maximum of 9 points to each study: 4 for selection and assessment of exposure, 2 for comparability, and 3 for assessment of outcome. To assess the quality of cross-sectional studies, we used another type of NOS designed for mentioned studies [30]. The maximum score of this version was 10 points: five for selection, two for comparability, and three for outcome assessment. When a study got 6 scores or more, it was considered to be high-quality publication (or low risk of bias). Any discrepancies were resolved by consultant with principal investigator (OS). Findings from quality assessment of included studies are shown in Supplemental Table 1.

Statistical analysis

In the current meta-analysis, we did only dose-response analysis and we could not combine effect sizes reported

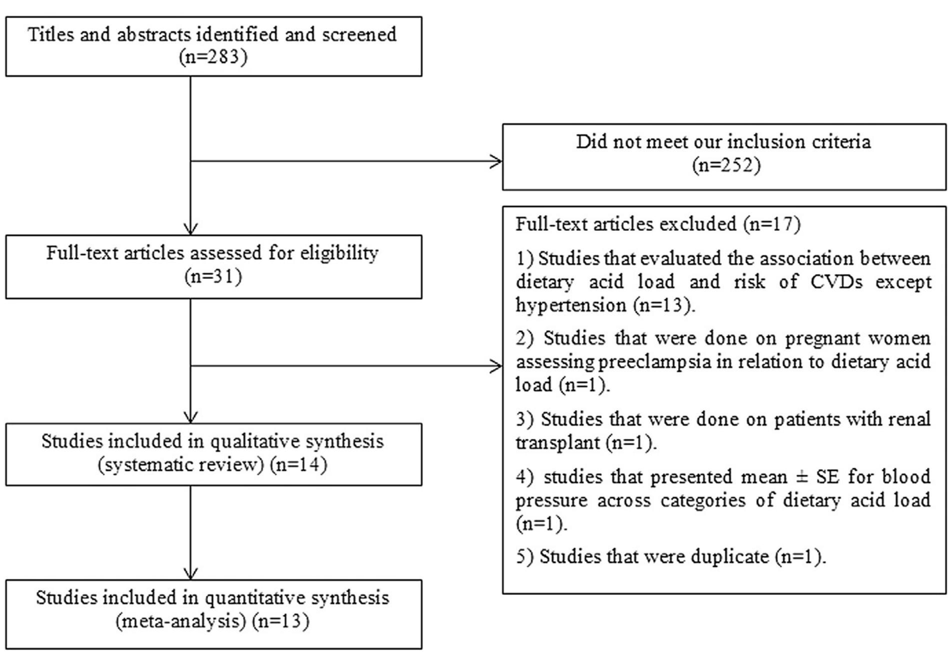

Figure 1 Flow diagram of study selection.

Table 1 Risk of hypertension across categories of dietary acid load based on included prospective and cross-sectional studies.

Authors (year)	Design	Country	Age range (y)	Sample size	Cases	Follow-up (y)	Exposure	Exposure assessment	Hypertension assessment and diagnosis	Comparison	OR, RR or HR (95%CI)	Adjustment[a]
Kucharska et al., 2018	cross-sectional	Poland	>20	M: 2760	1392		PRAL NEAP	Dietary recall	Mercury sphygmomanometers, SBP ≥ 140, DBP ≥ 90	T3 vs. T1 (>9.7 vs. <-8.0) T3 vs. T1 (>57.4 vs. <38.5)	OR: 1.19 (0.99−1.42) OR: 1.12 (0.94−1.35)	
				F: 3409	1988		PRAL NEAP			T3 vs. T1 (>0.28 vs. <-13.9) T3 vs. T1 (>42.0 vs. <27.4)	OR: 1.01 (0.85−1.19) OR: 0.83 (0.70−0.98)	
Han et al., 2016	cross-sectional	Korea	40−79	F/M: 11,601	4286		PRAL	Dietary recall	Mercury sphygmomanometers, SBP ≥ 140, DBP ≥ 90	T3 vs. T1 (>4.15 vs. <-12.35)	OR: 1.19 (1.09−1.31)	
Akter et al., 2015	cross-sectional	Japan	18−70	F/M: 2028	504		PRAL NEAP	Diet history questionnaire	Automated sphygmomanometers, SBP ≥ 140, DBP ≥ 90	T3 vs. T1 (≥12.35 vs. <4.01) T3 vs. T1 (≥57.95 vs. <47.1)	OR: 1.23 (0.87−1.72) OR: 1.28 (0.91−1.81)	1,2,3,4,5,6,7, 8,9,10,16
Akter et al., 2017	cross-sectional	Japan	40−69	F/M: 92,478	15,442		PRAL NEAP	FFQ	Medical records	Q4 vs. Q1 (≥14.16 vs.<-2.34) Q4 vs. Q1 (≥58 vs.< 38.8)	HR: 1.01 (0.95−1.05) HR: 1.01 (0.95−1.05)	2
Chan et al., 2015	Prospective	China	≥65	F/M: 795	310	4	NEAP	FFQ	Mercury sphygmomanometer, SBP ≥ 140, DBP ≥ 90	Q4 vs. Q1 (≥62.6 vs.<35.25)	OR: 1.32 (0.72−2.43)	1,2,3,5,6,9,11, 12,13,14,15,16
Engberink et al., 2012	Prospective	Netherlands	≥55	F/M: 2241	1113	6	PRAL NEAP	FFQ	Sphygmomanometer, SBP ≥ 140, DBP ≥ 90	T3 vs. T1 (≥5.8 vs. <-7.06) T3 vs. T1 (≥39.8 vs. <35.4)	HR: 1.02 (0.88−1.18) HR: 0.94 (0.81−1.10)	1,2,3,5,6,9,11,12
Zhang et al., 2009	Prospective	USA	31−41	F: 87,293	15,385	14	NEAP	FFQ	Medical records	D10 vs. D1 (≥69.85 vs. <38.95)	RR: 1.23 (1.08−1.41)	1,2,4,5,6,8,9,13, 14,15,16,17,18,19
Banerjee et al., 2014	cross-sectional	USA	20−70	F/M: 12,293	4119		NEAP	Dietary recall	Self-reported, SBP ≥ 140, DBP ≥ 90 or use of antihypertensive medications	Q5 vs. Q1 (≥75.65 vs. <37.35)	OR: 0.79 (0.70−0.89)	
Fagherazzi et al., 2014	cross-sectional	French	40−65	F: 66,485	8758		PRAL NEAP	Diet history questionnaire	Self-reported, or use of antihypertensive medications	Q4 vs. Q1 (≥7.00 vs.<-14) Q4 vs. Q1 (≥52.85 vs.< 36.1)	HR: 0.94 (0.88−1.01) HR: 0.94 (0.88−1.01)	
Luis et al., 2015	cross-sectional	Sweden	>70	M: 673	368		PRAL	7-d dietary record	Sphygmomanometer, SBP ≥ 130, DBP ≥ 80 or use of antihypertensive medications	T3 vs. T1 (≥7.55 vs. <-0.6)	OR: 1.13 (0.78−1.64)	
Rebholz et al., 2015	cross-sectional	USA	45−64	F/M: 15,055	5152		PRAL NEAP	FFQ	Sphygmomanometer, SBP ≥ 140, DBP ≥ 90	Q4 vs. Q1 (≥12.2 vs.<- −3.2) Q4 vs. Q1 (≥60.4 vs.< 39.25)	HR: 1.29 (1.17−1.42) HR: 1.29 (1.17−1.42)	

Krupp et al., 2018	cross-sectional	Germany	18–79	F/M: 6765	2167	PRAL	FFQ	Sphygmomanometer, SBP ≥ 140, DBP ≥ 90	Q5 vs. Q1 (≥9.3 vs.<-23.7)	HR: 1.45 (1.18–1.78)	1,3,5,6,9,10,21,22,23,24,25,26
Ko et al., 2017	cross-sectional	Korea	≥18	F/M: 1369	623	NEAP	FFQ	Medical records	Q4 vs. Q1 (≥60.6 vs.<33.3)	OR: 1.15 (0.85–1.56)	
Xu et al., 2014	cross-sectional	Sweden	70–71	M: 911	657	PRAL	7-d dietary record	Sphygmomanometer, SBP ≥ 140, DBP ≥ 90 or use of antihypertensive medications	T3 vs. T1 (≥21.1 vs. <4.0)	OR: 1.18 (0.82–1.67)	2
						NEAP			T3 vs. T1 (≥39.45 vs. <33.35)	OR: 1.18 (0.82–1.67)	

Abbreviation: OR: odds ratio, RR: relative risk, HR: hazard ratio, Q: quartile or quintile, FFQ: food frequency questionnaire, NEAP: net endogenous acid production, PRAL: Potential renal acid load.

[a] Adjustment: Age (1), calorie intake (2), Sex (3), physical activity (4), smoking (5), Alcohol (6), shift work (7), history of hypertension (8), BMI (9), eGFR (10), education (11), fiber intake (12), calcium intake (13), magnesium intake (14), potassium intake (15), sodium intake (16), oral contraceptive (17), folate intake (18), protein intake (19), size of blood pressure cuff (20), fasting duration (21), natrium excretion (22), use of diuretics (23) use of beta-blocker (24), serum glucose (25), total cholesterol (26).

for the highest versus lowest category of dietary acid load scores, because included studies applied different cut-offs to categorize participants according to these scores.

A method suggested by Greenland and Longnecker [31] and Orsini et al. [32] was used to compute the trend from the corrected log OR/RR/HR estimates and their CIs across categories of dietary acid load scores. In this method, the distribution of cases and the OR/RR/HR with the variance estimates for ≥3 quantitative categories of exposure were required. We considered the midpoint of dietary acid load scores (including NEAP and PRAL) in each category as the corresponding OR/RR/HR estimate. For studies that reported the scores of dietary acid load as range, we estimated the midpoint in each category by calculating the mean of the lower and upper bound. When the highest and lowest categories were open-ended, the length of these open-ended intervals was assumed to be the same as that of the adjacent intervals. A two-stage random-effects dose-response meta-analysis was applied to examine a probable non-linear association between dietary acid load scores and hypertension. This was done through modeling of dietary acid load scores and restricted cubic splines with three knots at fixed percentiles of 10, 50 and 90% of the distribution [33]. Based on Orsini method, we calculated restricted cubic spline model using generalized least-squares trend estimation method which takes into account the correlation within each set of reported OR/RR/HR [32]. Then, all the study-specific estimates were combined by use of the restricted maximum likelihood method in a multivariate random-effects meta-analysis [34]. A probability value for non-linearity was estimated using null hypothesis testing in which the coefficient of the second spline was considered equal to 0. A linear dose-response association of a-40 unit increment in NEAP values or a-20 unit increment in PRAL values with hypertension was investigated using the two-stage generalized least-squares trend estimation method [31,32,35]. First, study-specific slope lines were estimated and then, these lines were combined to obtain an overall average slope [32]. Study-specific slope lines were combined using a random-effects model. To assess between-study heterogeneity, Cochran's Q test and I^2 were used. In the current study, between-study heterogeneity was defined as I^2 values of >50% [36]. In addition to the main analyses, we assessed publication bias by visual inspection of funnel plots as well as formal statistical test of Begg. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study. Statistical analyses were done using Stata, version 11.2 (Stata Corp, College Station, TX). P-values were considered significant at the level of <0.05.

Results

Study characteristics

Characteristics of 14 studies [11–24], included in the current systematic review and meta-analysis, are summarized in Table 1. Among them, 3 were prospective [11–13] and 11 were cross-sectional (n = 5) [14,17,22–24] or prospective assessing cross-sectionally (n = 6) [15,16,18–21]. Of the 14 studies published between 2009 and 2018, 3 were conducted in the United States [13,14,18], 6 in Europe [12,15,16,21,23,24] and 5 [11,17,19,20,22] in Asia. Out of 14 studies, 2 were done on male subjects [16,21], 2 on female [13,15] subjects and 10 on either sex [11,12,14,17–20,22–24]. The number of participants in these studies varied from 673 to 92,478 with an age range between 18 years and more. In total, 306,183 apparently healthy individuals with 62,264 cases of hypertension were included in the current systematic review. Among prospective studies, mean duration of follow-up varied from 4 to 14 years.

Of the 14 included studies, 11 assessed dietary acid load based on NEAP [11–19,24] and 10 based on PRAL [12,15–19,21–24]. Dietary intakes had been assessed using food frequency questionnaire (FFQ) in 7 studies [11–13,18,19,23], by dietary recall in 3 studies [14,22,24], by dietary record in 2 studies [16,21] and using dietary history questionnaire in 2 studies [15,17]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by using sphygmomanometer in 9 studies [11,12,16–18,21–24], were obtained from medical records in 3 studies [13,19,20] and assessed self-reported in 2 studies [14,15]. Hypertension was defined as a SBP ≥140 mm Hg and a DBP ≥90 mm Hg in 7 studies [11,12,17,18,22–24], as a SBP ≥130 mm Hg and a DBP ≥80 mm Hg along with antihypertensive drugs use in one study [21], based on a SBP ≥140 mm Hg and a DBP ≥90 mm Hg along with antihypertensive drugs use in 2 studies [14,16], according to only antihypertensive drugs use in one study [15] and using information obtained from medical records in 3 studies [13,19,20]. Participants had been categorized based on the values of dietary acid load (baseline values in prospective studies) in all studies. Among 14 included studies, 6 had assessed the risk of hypertension across tertiles [12,16,17,21,22,24], 4 across quartiles [15,18,19], 2 across quintiles [14,23] and remaining one across deciles of dietary acid load scores [14]. In all studies, participants in the lowest category of dietary acid load scores were considered as the reference category. Seven from fourteen included studies had presented adjusted ORs, RRs, or HRs and 95% CIs for the association between dietary acid load and hypertension [11,12,16,17,19,23]. In addition, out of 14 studies, five presented energy-adjusted estimates [11,12,16,17,19] and five reported BMI-adjusted ones [11,12,17,23]. Based on the NOS, all included studies were of high quality (Supplemental Table 1).

Findings from the systematic review

Among 11 studies that assessed the association between dietary acid load (based on NEAP) and hypertension [11–19,24], 2 had shown a significant positive association [13,18], 2 had reported a significant inverse association [14,24] and remaining 7 studies failed to find any significant association [11,12,15,16,19,20]. Out of 10 studies considering dietary acid load based on PRAL as the main exposure [12,15–19,21–24], 3 revealed a significant positive association with hypertension [18,22,23] and others did not find any significant relationship [12,15–19,21–24].

Findings from the dose-response analysis

Overall, out of 14 studies included in the systematic review, 13 were included in dose-response analysis. Study of Krupp et al. was excluded due to lack of required data for dose-response analysis [23]. In six studies that did not report OR for the association between dietary acid load and hypertension [15,16,18–21], we could calculate ORs and related 95% CIs using presented data in those studies. In total, 13 studies that included 299,421 individuals and 60,097 cases of hypertension were included in the current dose-response meta-analysis.

Dietary acid load based on NEAP and hypertension

Overall, 11 studies (3 prospective [11–13] and 8 cross-sectional studies [14–19,24]) with total sample size of 287,144 participants and 55,443 cases of hypertension were included in the dose-response analysis for the association between dietary acid load based on NEAP and hypertension. We found no significant non-linear association between dietary acid load and hypertension ($P = 0.86$) (Fig. 2A). When we did stratified analysis based on study design, a significant positive non-linear relation was seen in prospective studies ($P = 0.006$) (Fig. 2B), but not in cross-sectional ones ($P = 0.93$) (Fig. 2C). Findings from linear dose-response analyses revealed no significant association between dietary acid load and hypertension based an increase of 40 units in NEAP values (combined effect size: 1.01, 95% CI: 0.97–1.06, $P = 0.51$) (Fig. 3). However, between-study heterogeneity was significant (I^2: 78.0, $P < 0.001$) When we did study design-stratified analysis, no alteration in this association was seen either in prospective or cross-sectional studies (Supplemental Fig. 1).

Dietary acid load based on PRAL and hypertension

In total, one prospective [12] and eight cross-sectional [15,16,18,19,21,22,24] studies with total population of 197,668 participants and 39,660 cases of hypertension were included in dose-response analysis on the association between dietary acid load (based on PRAL) and hypertension. No significant non-linear relation was found in this regard ($P = 0.52$) (Fig. 2D). Such finding was also observed after excluding one prospective study and keeping only cross-sectional studies ($P = 0.59$) (Fig. 2E). With regard to linear dose-response meta-analysis, a significant positive association was seen between dietary acid load (based on PRAL) and hypertension; such that a-20 unit increase in PRAL values was associated with 3% greater risk of hypertension (combined effect size: 1.03, 95% CI: 1.00–1.06, $P = 0.03$) (Fig. 4). Between-study heterogeneity was not significant in this regard (I^2: 44.3, $P = 0.06$). When we did this analysis on cross-sectional

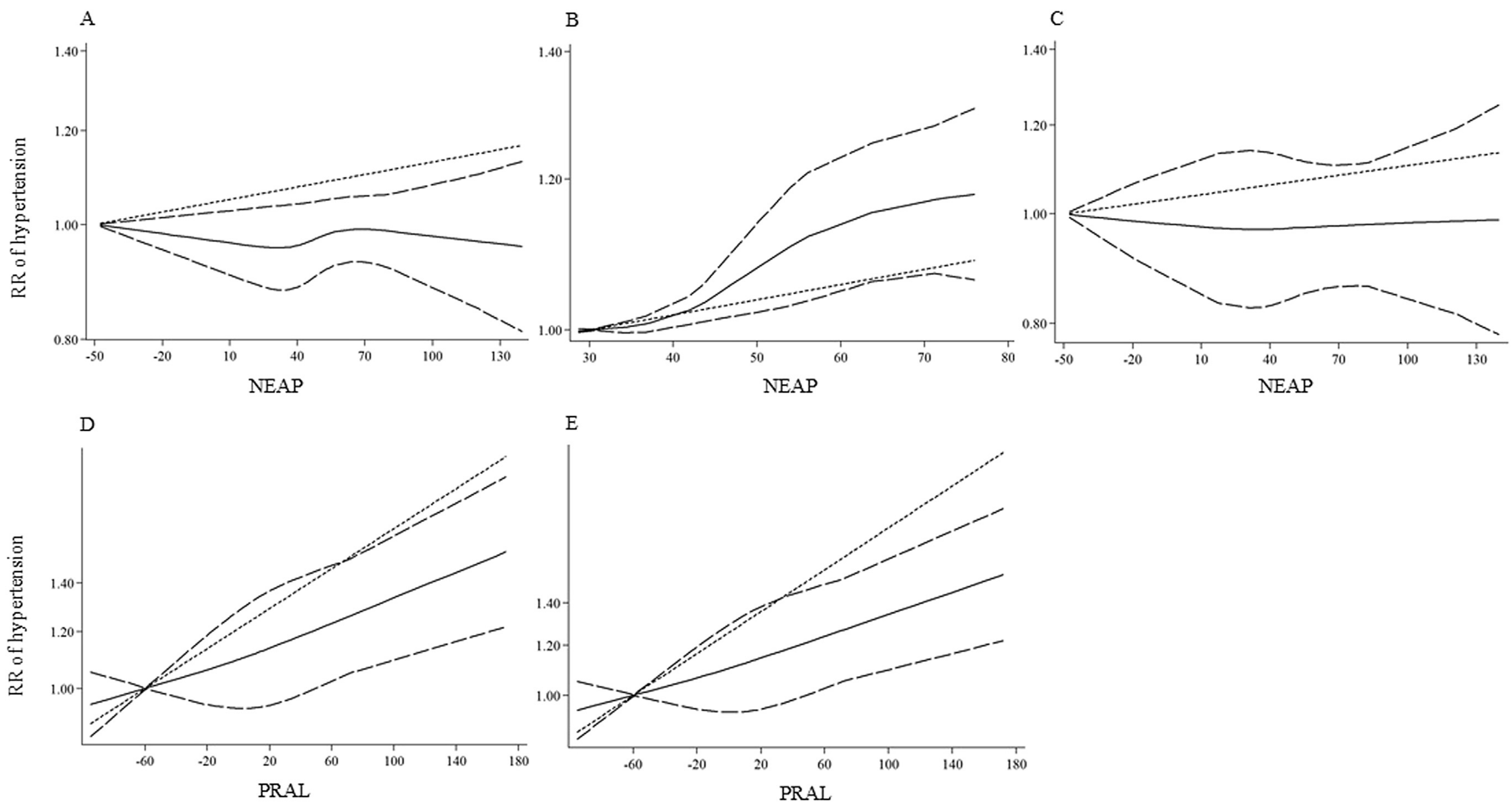

Figure 2 Non-linear dose-response association between dietary acid load and hypertension; A, D) by considering estimates from both prospective and cross-sectional studies; B) by considering estimates from only prospective studies; C, E) by considering estimates from only cross-sectional studies. NEAP: net endogenous acid production, PRAL: Potential renal acid load.

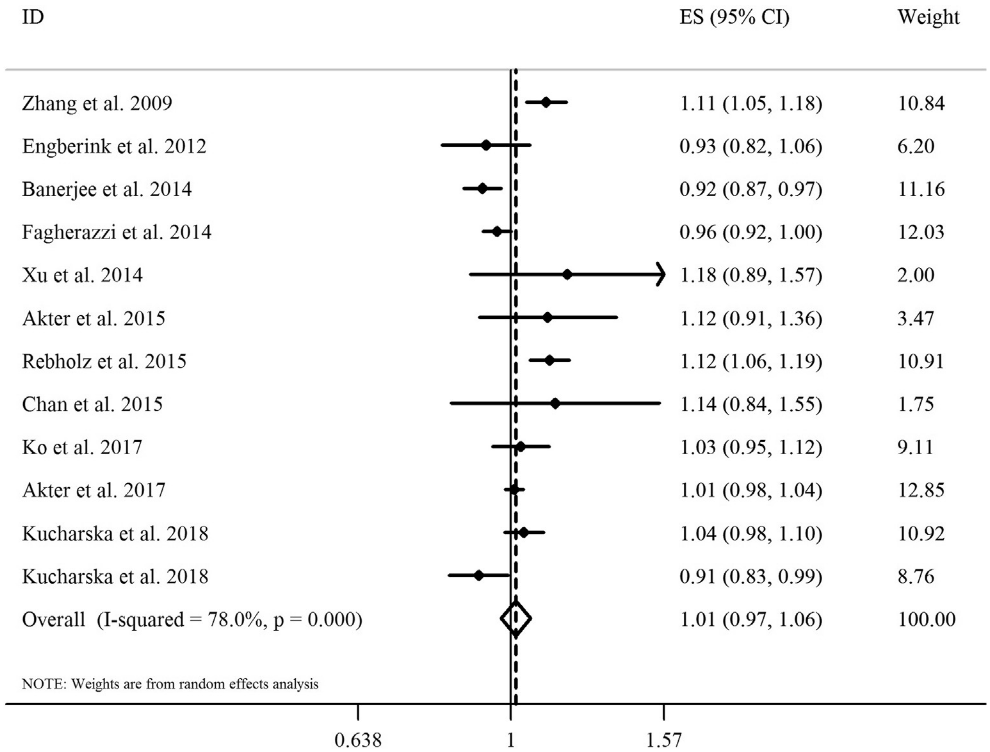

Figure 3 Forest plot for the linear dose-response association between dietary acid load (based on NEAP) and hypertension. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis. ES: effect size, CI: confidence interval, NEAP: net endogenous acid production.

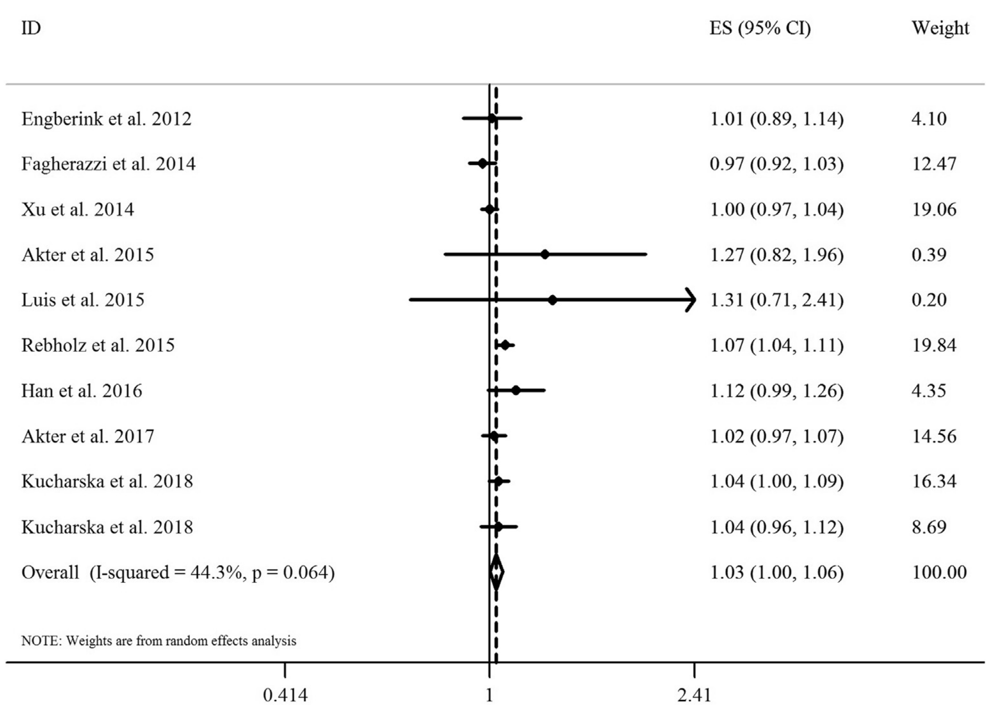

Figure 4 Forest plot for the linear dose-response association between dietary acid load (based on PRAL) and hypertension. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis. ES: effect size, CI: confidence interval, PRAL: Potential renal acid load.

studies and excluded one prospective study, we observed similar finding (combined effect size: 1.03, 95% CI: 1.00−1.06, P = 0.04) (Supplemental Fig. 2).

Publication bias and sensitivity analysis

On the basis of visual inspection of funnel plots, we found no evidence of publication bias in all relationships assessed in this meta-analysis (Supplemental Fig. 3). These findings were confirmed by formal test of Begg (P > 0.50). In addition, sensitivity analysis showed that pooled effect sizes, obtained for the association between dietary acid load and hypertension, did not depend on a particular study.

Discussion

In the current study, we found a significant non-linear association between dietary acid load (based on NEAP) and hypertension in prospective studies, but not cross-sectional ones. In terms of PRAL, a-20 unit increase in dietary acid load values was associated with 3% increased risk of hypertension. No other significant linear and non-linear association was observed between dietary acid load and hypertension.

The prevalence of hypertension is increasing at an alarming rate. Diet is an important factor affecting the risk of hypertension [37−39]. Recently, it has been shown that acid-base balance caused by dietary factors contributes to hypertension [13,22]. However, data in this regard are conflicting. Based on our findings, dietary acid load was positively associated with risk of hypertension. In line with our findings, Taylor et al. reported that several metabolic indicators of "subclinical" metabolic acidosis are associated with increased blood pressure. For example, individuals with hypocitraturia (<320 mg/day) had 2.5 times greater odds for having prevalent hypertension than those without hypocitraturia [40]. Low levels of citrate can result from systemic acidosis [13]. In a prospective study, every 1 mEq/L increase in the serum anion gap was related to a significant 0.48 mm Hg greater SBP independent of age, gender, BMI and renal function [41]. Such finding was also seen in another similar study [42]. In a cross-sectional study, mean of blood pressure was higher in individuals in the top quintile of PRAL compared with those in the bottom quintile [28]. In contrast, a prospective study revealed no significant association between dietary acid load and blood pressure among pregnant women [26]. Assessing pregnant women might be a reason for different findings observed in this study compared with previous studies.

Some studies included in the current meta-analysis showed no significant association between dietary acid load and hypertension [11−13,17−19,22,23]. It must be kept in mind that studies that found no significant association had mostly lower quality than those that found a positive relation. For example, out of 9 studies in our meta-analysis that reached no significant association [11,12,15,16,19,20] or inverse association between NEAP and hypertension [14,24], 6 had included <10,000 participants [11,12,16,17,20,24], 5 had not controlled for energy intake [14,15,20,24] and 6 had not controlled for BMI [14,15,19,20,24]. Alternatively, among 2 studies that found a positive association between NEAP and hypertension [13,18], both had a sample size of ≥10,000 individuals and one had controlled for energy intake and BMI [13].

In the current study, findings obtained for dietary acid load according to NEAP and PRAL approaches were different. Given the NEAP and PRAL have been used interchangeably; it is difficult to explain this discrepancy. It seems that different nutrients involved in calculation of NEAP and PRAL may be a reason for observed discrepancy [12]. In NEAP approach, protein and potassium content of foods are involved in calculating of dietary acid load, while PRAL is measured by taking into account the ionic balances for calcium and magnesium, and dissociation of phosphate at pH 7.4 [12]. Therefore, NEAP and PRAL may reveal different results about dietary acid load. Furthermore, compared with NEAP, PRAL considers intestinal absorption rates of contributing nutrients [12]. Moreover, study of Remer et al. showed that PRAL values were highly significantly correlated with net acid excretion in 24-h urine samples compared with NEAP [9].

Although not established, several plausible mechanisms have been proposed for the positive association between dietary acid load and hypertension. Mild metabolic acidosis, which can be caused by diet, stimulates the production of cortisol contributing to increase blood pressure [43−45]. In addition, metabolic acidosis is associated with increased calcium excretion [46,47]. Low levels of calcium have a role in increasing blood pressure [48]. Diet with high acid load contains low amount of potassium and magnesium that both are negatively associated with risk of hypertension [49−52].

Our present meta-analysis had some strengths. To the best of our knowledge, this was the first systematic review and dose-response meta-analysis that explored the association between dietary acid load and hypertension. The quality assessment indicated that all the studies included in this meta-analysis were of high quality, and the majority of studies had a large sample size. Despite these strengths, several limitations should be noticed when interpreting our findings. Some non-differential misclassification of participants in terms of dietary acid load may have occurred in included studies and also in the meta-analysis, which may have attenuated any true association between dietary acid load and hypertension. The majority of studies included in the current meta-analysis were cross-sectional which cannot provide a causal link between dietary acid load and hypertension. Because our meta-analysis was done on observational studies, we cannot rule out the possibility that residual confounding still may have affected the results in each study and also the pooled estimates in the meta-analyses. For example, out of all included studies, only two had controlled for renal function or chronic kidney disease on the association between dietary acid load and hypertension [17,23]. There is no significant correlation between net acid excretion and

NEAP/PRAL (a proxy for net acid excretion) in patients with chronic kidney disease. Therefore, lack of adjustment for this important confounder can adversely affect the estimates of each study and also the overall estimates in the meta-analyses.

Conclusion

We found a significant positive non-linear association between dietary acid load (based on NEAP) and hypertension in prospective studies. Moreover, dietary acid load based on PRAL was positively associated with hypertension; such that a-20 unit increase in PRAL values was associated with 3% increased risk of hypertension. Additional studies, particularly those with prospective design considering wide number of important confounders, are required to confirm our findings.

Funding statement

This study was supported jointly by Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran, and Gerash University of Medical Sciences, Gerash, Iran.

Conflicts of interest

Authors declared no personal or financial conflicts of interest.

Authors' contribution

AS, MN, AP, MK and OS contributed in conception, design, statistical analyses, data interpretation and manuscript drafting. VM and MP contributed in data analysis, data interpretation and manuscript drafting. All authors approved the final manuscript for submission.

Acknowledgment

The authors appreciate the financial and technical supports of Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran, and Gerash University of Medical Sciences, Gerash, Iran.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.03.009.

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