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META-ANALYSIS

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Dietary acid load, blood pressure, fasting blood sugar and biomarkers of insulin resistance among adults: Findings from an updated systematic review and meta-analysis

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Abstract

Objectives: There is no clear summarised report of the association between dietary acid load components including potential renal acid load (PRAL) and net-endogenous acid production (NEAP) with cardiometabolic risk factors. In the current meta-analysis, we aimed to systematically review and summarise the eligible observational studies evaluating the association between PRAL and NEAP with blood pressure and hypertension and markers of glucose haemostasis among adults.

Design and Setting: In a systematic search from PubMed, SCOPUS, Web of Sciences and Cochrane electronic databases up to May 2019, relevant studies were included in the literature review. Observational studies evaluating the association between PRAL and NEAP with the systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR), haemoglobin A_1C (HbA_1C), HOMA-β and quantitative insulin check index (QUICKI) and also prevalence or odds of hypertension, hyperglycaemia and diabetes were included.

Results: Total number of studies included in the 14 separate meta-analyses were as follows: Mean (SD) of SBP (PRAL, n = 12; NEAP, n = 6), mean (SD) of DBP (PRAL, n = 8; NEAP, n = 3), mean (SD) of FBS (PRAL, n = 12; NEAP, n = 5), mean (SD) of HbA_1C (PRAL, n = 6; NEAP, n = 4), mean (SD) of HOMA-IR (PRAL, n = 7), mean (SD) of insulin (PRAL, n = 7; NEAP, n = 2); OR of type 2 diabetes mellitus (T_2DM) (PRAL, n = 8; NEAP; n = 6), HTN prevalence (PRAL, n = 9; NEAP, n = 9), T_2DM prevalence (PRAL, n = 7; NEAP, n = 6). According to our results, being in the highest PRAL categories was associated with higher SBP (WMD = 0.98; CI: 0.51, 1.45; $P < .001$), DBP (WMD = 0.61; CI: 0.089, 1.135; $P = .022$), insulin (WMD = −0.235, CI: 0.070, 0.400; $P = .005$), higher odds of diabetes (OR = 1.19; CI: 1.092, 1.311; $P < .001$), higher prevalence of T_2DM (13% and 11% in highest vs lowest category). While, being in the highest category of NEAP was only associated with higher odds of diabetes (OR = 1.22; CI: 1.14, 1.31, $P < .001$). In subgroup analysis for finding the possible source of heterogeneity, the continent, dietary assessment tool, sample size and gender were the potent sources of heterogeneity. No association between PRAL and NEAP with HbA_1C, HOMA-IR was reported.

Conclusions: In the current meta-analysis, we found potent negative effects of high dietary acid load particularly higher PRAL scores cardiometabolic risk factors. Therefore, lower acidogenic food ingredients in the diets are suggested for the prevention of cardiovascular risk factors and diabetes.

1 | INTRODUCTION

Metabolic risk factors including raised blood pressure, hyperglycaemia and insulin resistance are the most important leading causes of numerous non-communicable diseases (NCDs) including cardiovascular disease (CVD), type 2 diabetes mellitus (T_2DM) and metabolic syndrome, killing more than 41 million people each year equivalent to 71% of deaths globally.[1] The diseases are a result of the combination of genetic, environmental and behavioural risk factors; diet is an important changeable risk factor and dietary modifications could substantially reduce the disease occurrence and mortality.[2] Acid-base balance is tightly regulated in human and even its minor changes would lead to deleterious effects including chronic kidney disease and its progression, impaired bone homoeostasis and insulin resistance.[3] Recently, the role of diet-related low-level metabolic acidosis in the pathogenesis of metabolic disorders including metabolic syndrome, diabetes and CVDs has been suggested by numerous researches highlighting the triggering effects of Western dietary pattern.[4-7] Several potential underlying mechanisms for the association between dietary acid load and metabolic disorders have also been suggested; it has been mentioned that the association of the higher dietary acid load with hypertension and insulin resistance is a result of excessive urinary execration of calcium and magnesium, increased cortisol and reduced urinary citrate excretions.[5,6] Reduced insulin sensitivity,[8] insulin secretion[9] and reduced insulin binding to its receptors because of impaired acid-base balance[10] are also several other possible suggested mechanisms. A diet rich in acidogenic foods including meat, fish, cheese and low in alkaline foods including fruits and vegetables are the potential cause of endogenous acid production and elevated dietary acid load.[11] In fact, diet is responsible for more than 10-fold difference in endogenous acid production in different individuals.[4] The diet-induced acid load is estimated according to potential renal acid load (PRAL) and net-endogenous acid production (NEAP) according to information about ingested protein, potassium, calcium, phosphorous and magnesium.[12] The PRAL calculation is based on the formula first suggested by Remer et al[13] as follows: PRAL (mEq/d) = 0.4888 × protein intake (g/d) + 0.0366 × phosphorus (mg/d) − 0.0205 × potassium (mg/d) − 0.0125 × calcium (mg/d) − 0.0263 × magnesium (mg/d). While NEAP is calculated based on the Frassetto et al suggested formula[14] as: Estimated NEAP (mEq/d) = (54.5 × protein intake [g/d] ÷ potassium intake [mEq/d]) − 10.2. These calculations are validated according to the estimated equivalents in the 24 hours urine measurement.[13,14] Numerous studies are available reporting the association between metabolic risk factors with dietary acid load as either PRAL or NEAP or both of them.[7,12,15-20] The results of these studies are inconsistence; several reported the positive association between metabolic risk factors[5,6,21] while others not.[4,22] According to our literature review, only one meta-analysis was carried out evaluating the association between dietary acid load and risk of T_2DM with literature review up to September 2017.[23] While no study is available summarising the association between dietary acid load components (eg PRAL or NEAP) with metabolic risk factors. Therefore, in the current meta-analysis we summarised the results of observational studies evaluated the association between PRAL of NEAP with systolic and diastolic blood pressure (SBP and DBP), serum glucose, insulin, HbA_1C, markers of insulin resistance including homoeostatic model assessment of insulin resistance (HOMA-IR), hypertension (HTN), hyperglycaemia, prevalence of diabetes, hypertension and odds of diabetes in an updated systematic review and meta-analysis.

Review criteria

The PubMed, SCOPUS, Web of Sciences and Cochrane electronic databases were systematically searched from their inception up to May 2019 identify all studies examining the associations between dietary acid load and its components with cardiometabolic risk factors including blood pressure, markers of glucose homoeostasis and risk of type 2 diabetes mellitus (T_2DM). Key terms for in search strategy are listed in the Material and Methods section.

Message for the clinic

- The current work evaluated the association between dietary acid load, blood pressure, fasting blood sugar and biomarkers of insulin resistance among adults in a systematic review and meta-analysis.
- Higher dietary acid load was associated with increased risk of cardiometabolic risk factors including blood pressure, blood glucose, insulin and higher risk of T_2DM.
- Dietary acid load could be assumed as a prognostic diet-related risk factor for cardiovascular and diabetes risk.

2 | METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used for writing this report.[24] The completed

PRISMA checklist is provided in the Supporting Information (Table S1). The 12-item PRISMA extension checklist was used to write the Abstract.[25]

2.1 | Search strategy

We performed a systematic search using PubMed, SCOPUS, Web of Sciences and Cochrane electronic databases to the studies evaluated the association between dietary acid load and hypertension and markers of glucose homoeostasis including fasting serum glucose, insulin, HOMA-IR, HOMA-β, HbA_1C, quantitative insulin check index (QUICKI) and hyperglycaemia up to May 2019. No language restriction was applied. Moreover, hand-searching from reference lists of all relevant papers, previous reviews and meta-analyses was performed to cover all relevant publications. Strategy of search was created using a combination of the MeSH (Medical Subject Headings) terms from the PubMed database and free text words were used. For each electronic database, search strategy was adopted. The PICO (patients, intervention, comparator and outcome) for studies' selection is presented in Table 1. The PICO is one of the most widely used models of formulating and structuring clinical questions in connection with evidence syntheses. The Cochrane Handbook for Systematic Reviews specifies using PICO as a model for developing a review question, thus ensuring that the relevant components of the question are well defined.[26,27] The protocol of the current study has been registered in PROSPERO with the identification number of CRD42019122272. Moreover, the study protocol has also been registered by the ethics committee of Tabriz University of Medical Sciences (Registration number: IR.TBZMED.VCR.REC.1398.140).

TABLE 1 The PICO criteria used for the present systematic review

PICO criteria	Description
Participants	General adult population
Exposure (interventions)	Highest category of dietary acid load represented by higher scores of PRAL or NEAP
Comparisons	Lowest category of dietary acid load represented by lower scores of PRAL or NEAP
Outcome	SBP, DBP, FBS, insulin, HOMA-IR, HOMA-β, HbA_1C, QUICKI and prevalence or odds of hypertension, hyperglycemia, diabetes
Study design	Observational studies with the design of cross-sectional, case control or cohort

Abbreviations: DBP, diastolic blood pressure; FBS, fasting blood sugar; HbA_1C, haemoglobin A_1C; HOMA-IR, homeostatic model assessment of insulin resistance; NEAP, net-endogenous acid production; PICO, patients, intervention, comparator and outcome; PRAL, potential renal acid load; QUICKI, quantitative insulin check index; SBP, systolic blood pressure.

2.2 | Selection and characteristics of the included studies

Our search obtained 658 potentially relevant articles from PubMed, SCOPUS, Web of Sciences and Cochrane electronic databases. Accordingly, 156 manuscripts were remained for full text screening after removing duplicates and excluded according to title and abstract reading. Totally, 124 manuscripts were excluded because of their irrelevant subject, inappropriate design, reviews including meta-analysis or systematic reviews, conferences and seminars, not relevant age groups, not evaluating the studied parameters or the target association between them or have a design other than observational designs. Accordingly 32 manuscripts were included in the systematic review. Figure 1 presents the flowchart of the study while and Table S2 represents the details of excluded studies after screening.

2.3 | Inclusion criteria

In the current systematic review and meta-analysis, observational studies with the design of cross-sectional, case-control or cohort evaluating the association between dietary acid load and hypertension, systolic and diastolic blood pressure, serum or plasma glucose, insulin, HbA_1C, HOMA-IR, HOMA-β, QUICKI were included. According to our set of parameters, we conducted 14 meta-analyses. Meta-analysis included the studies evaluated the odds ratio (OR), relative risk (RR), prevalence or mean ± SD of target variable in the highest vs lowest dietary acid load categories. For the search purpose, we used MESH (Medical Subject Heading) and non-MESH keywords including the following: ('dietary acid load' OR 'dietary acid-based load') AND ('glucose' OR 'fasting serum glucose' OR 'fasting blood glucose' OR 'fasting blood sugar' OR 'blood sugar' OR 'insulin' OR 'insulin resistance' OR 'homeostatic model assessment of insulin resistance' OR 'HOMA-IR' OR 'quantitative insulin check sensitivity' OR 'QUICKI' OR 'insulin sensitivity' OR 'hypertension' OR 'systolic blood pressure' OR 'diastolic blood pressure' OR 'cardiovascular risk factors' OR 'cardiometabolic risk factors' OR 'HbA_1C' OR 'glycosylated hemoglobin' OR 'hyperglycemia' OR 'obesity' OR 'BMI' OR 'lipid profile' (Table S3). The reviewed literatures were inserted into the EndNote software (version X8, for Windows, Thomson Reuters). Consequently retrieved citations were merged, duplications were eliminated and the review process has been facilitated. Titles and abstracts of all articles had been evaluated independently by two reviewers (MAF and PD). Articles not meeting the eligibility criteria were excluded. Moreover, the reference lists of relevant review article were also evaluated to be included as additional studies. Full-texts of relevant articles were retrieved if meet the eligibility criteria, and were re-evaluated. Any disagreements were discussed and resolved by consensus.

2.4 | Quality assessment

The methodological quality assessment of the included papers was performed by a nine-star Newcastle-Ottawa scale (NOS) for

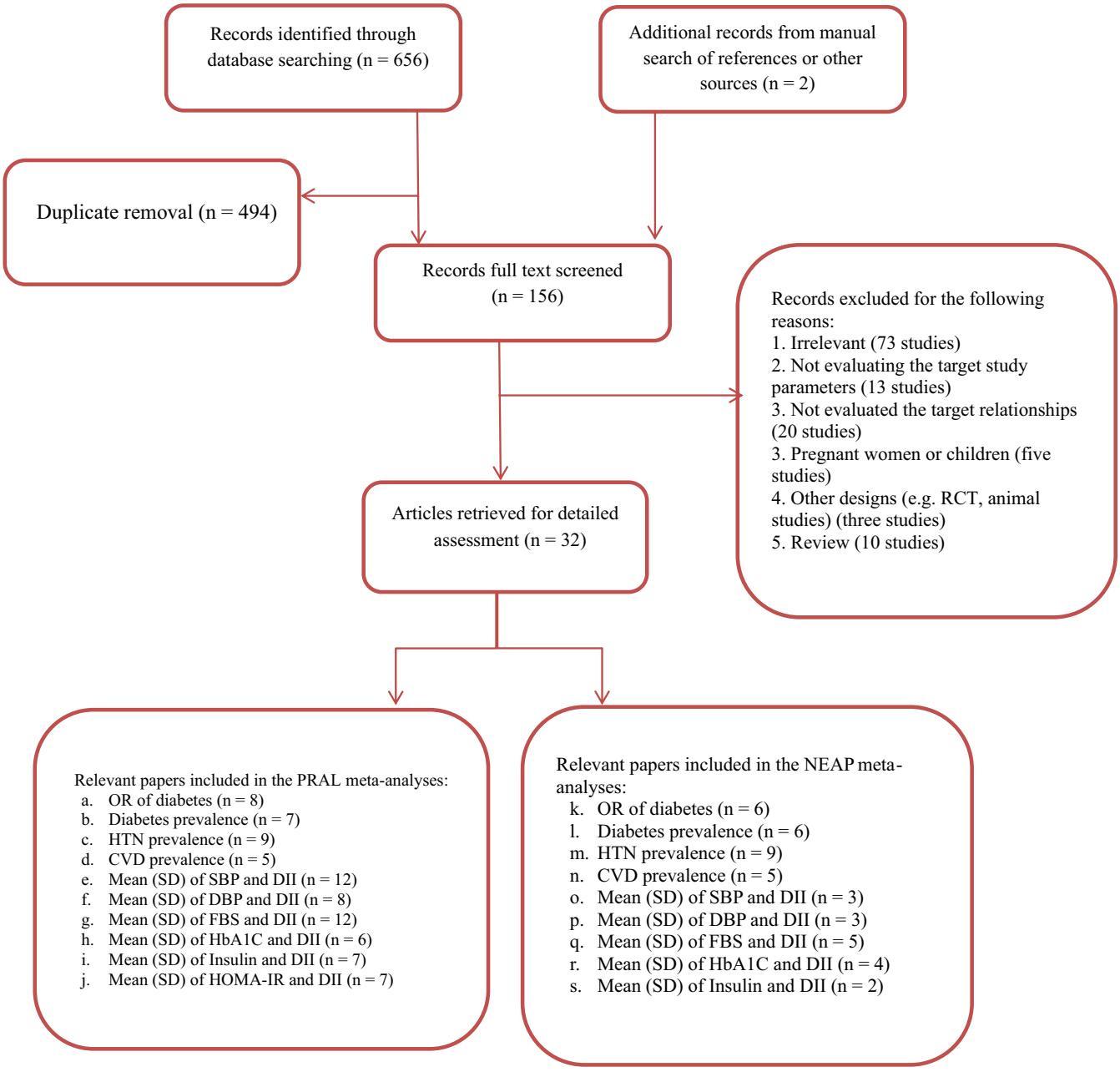

FIGURE 1 Flow diagram of study screening and selection process

quality assessment of the cross-sectional, case-control and cohort studies. The 9-point NOS scale has scoring ranges from 0 to 9 and is categorised into selection, comparability and ascertaining of outcome. Studies with equal or more than 8 stars were categorised as high quality.[28] Moreover, the Agency for Healthcare Research and Quality (AHRQ) checklist was used to assess the quality of cross-sectional studies.[29] There were no quality criteria for inclusion of the studies in the current meta-analysis. The items were scored '1' if the answer was 'Yes', and '0' if the answer was 'No' or 'Unclear'. The final quality assessments scores were as follows: low quality = 0-3; moderate quality = 4-7; high quality ≥8. The details of quality scoring for all of the included studies are provided in Tables S4 and S5 for cohort and cross-sectional studies, respectively.

2.5 | Data collection and extraction

Data were collected according to a standard data extraction form gathering the information about the authors name, publication year, geographical area, study design, participants age range, mean age and number of case and control group, dietary assessment tool, setting, gender, sample size, information about the adjustment for possible confounders, the main findings and estimates of associations.

2.6 | Data synthesis and analysis

In the current meta-analysis, three meta-analysis approaches were used: the association between odds of diabetes and dietary acid load was analysed by estimating the ORs and 95% confidence intervals (CIs) by calculating the Ln of ORs and its standard error of mean (s.e.) as the effect size of the meta-analysis. Pooled OR (and 95% CI) was estimated using a weighted random effect model (the DerSimonian-Laird approach). The comparison of the continuous variables including SBP, DBP, FBS, insulin, HOMA-IR, HbA_1C, QUICKI, HOMA-β between highest vs lowest category of dietary acid load as the reference group was performed by measuring the unstandardised mean differences as the effect size calculated by pooled estimate of weighted mean difference (WMD) with 95% CI, and the fixed effects and random effects models. The prevalence of diabetes and HTN in highest vs lowest dietary acid load categories was performed by re-calculating the proportions of interest from the relevant numerator and denominator. The overall proportions of interest were derived using meta-analysis techniques by metaprop command in the STATA and presented along with 95% CIs calculated using a normal approximation. Cochran's Q test and I-squared test were used to identify between-study heterogeneity; I^2 <25%, no heterogeneity; I^2 = 25%-50%, moderate heterogeneity; I^2 >50% large heterogeneity.[30] The heterogeneity was considered significant if either the Q statistic had $P < .1$ or I^2 >50%. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or a number of publications. Subgroup analysis was performed to identify possible sources of heterogeneity, if required. Begg's Funnel plots were assessed to evaluate the publication bias followed by the Egger's regression asymmetry test and Begg's adjusted rank correlation for formal statistical assessment of Funnel plot asymmetry. The data were analysed using STATA version 13 (STATA Corp), and *P*-values less than .05 were considered as statistically significant.

3 | RESULTS

3.1 | Description of the studies reported the dietary acid load as PRAL and NEAP with blood pressure and hypertension associations

Table 2 presents the summary of systematically reviewed studies evaluated the association between dietary acid load (eg PRAL or NEAP), blood pressure and hypertension prevalence. Totally, 20 studies reported the association between HTN, blood pressure and PRAL or NEAP among the systematically reviewed literature.[4,5,7,12,15,18,19,22,31-42] In the study by Akter et al[18] evaluating the association between dietary acid load and prevalence of HTN in the Furukawa Nutrition and Health Study the odds of HTN in subjects in the highest tertile of PRAL and NEAP was 31% and 40% more than individuals in lowest tertile (PRAL; OR: 1.31; CI: 1.01-1.70; NEAP OR: 1.40; CI: 1.08-1.82) among 2028 working Japanese population. Several other studies also reported similar results of higher prevalence of HTN[12,34,41] or higher SBP and DBP values in highest vs lowest PRAL or NEAP groupings.[12,18,39,40] Only one study reported inverse association between HTN prevalence among NEAP quartiles[4] and several other studies found no difference.[7,15,19,22,31-33,35-38,42] In the data analysis of Rotterdam study by Engberink et al,[33] SBP in the highest tertile of PRAL was significantly higher than the lowest. While, no significant difference in the mean values of DBP was observed. In the study by Kiefte-de Jong[34] higher prevalence of HTN in highest vs lowest quintile of NEAP among NHS, NHS- II and HPFS cohorts was reported.

3.2 | Description of the studies reported the dietary acid load as PRAL and NEAP with insulin resistance, markers of glycaemic status and risk of diabetes associations

The summary of the studies' characteristics evaluated the association between PRAL, NEAP and markers of glucose homoeostasis, insulin resistance and the prevalence of T_2DM are also presented in Table 2. The association between dietary acid load and glycaemic markers, insulin resistance and the prevalence of diabetes or the odds of diabetes has been reported in 22 studies.[4,6,7,12,15,17-22,31-35,37-42] In the study by Akter et al PRAL and NEAP scores were positively associated with HOMA-IR values (*P*-trend: .045 and .03, respectively). NEAP was also positively associated with HOMA-β values (*P*-trend: .03). No association between PRAL, NEAP and FBS or HbA_1C was reported.[6] Similar results indicating higher HOMA-IR and HbA_1C values,[18,32] higher insulin concentrations[17] and higher odds of insulin resistance[39] in top categories of PRAL or NEAP vs lowest categories has also been reported in four other studies. In the study by Akter,[6] no association between PRAL, NEAP and FBS or HbA_1C was reported. Similar findings were also observed in several other studies.[7,12,17,22,31,35,37,39,40,42] Akter et al[6] reported that men in the highest quartiles of PRAL had 61% higher odds of developing diabetes compared with the lowest quartile; while no association was observed among women. Moreover, no association was reported among NEAP scores and odds of T_2DM. Similarly, in the study by Fagherazzi,[15] hazard ratio (HR) for the incidence of T_2DM according to the PRAL and NEAP categories in the E3N-EPIC cohort study was OR: 1.56; CI: 1.29, 1.90 and OR: 1.57; CI :1.30, 1.89, respectively ($P < .001$). In a population-based study by Gæde et al[17] in Denmark, women in the fifth quintile of PRAL were more likely to develop diabetes after 15 years follow-up (OR = 1.10; CI: 0.98, 1.25; $P = .02$). While no association among men was reported. Similar findings of the higher prevalence of diabetes or higher odds of diabetes were reported in two other studies.[37,41] In the study by Kiefte-de Jong,[34] the odds of T_2DM in highest quintile of NEAP and PRAL were higher compared with the lowest in NHS and NHS II cohorts while in the HPFS study these associations were not significant. Other reports found no associations between odds or prevalence of T_2DM and PRAL or NEAP

TABLE 2 Characteristics of studies included in the systematic review owing to report the association between dietary acid load, hypertension, blood pressure, markers of glucose homoeostasis and risk of diabetes

First author/ country	Year	Study design	Sex	Age range	Sample size/ population	Number of cases/ controls	Dietary assessment/ index	Results	Adjusted variables	Quality
Akter[5]/Japan	2015	Cross-sectional	Both	18-70 y	2028/ working population	676/676	BDHQ/PRAL, NEAP	The odds of developing HTN in highest vs lowest tertile of PRAL and NEAP were significant (PRAL OR: 1.31; CI: 1.01-1.70) (NEAP OR: 1.40; CI: 1.08-1.82)	Age, sex, work-related PA, leisure-time PA, smoking, alcohol consumption, night or rotating shift work, parental history of diabetes, BMI	8
Akter[6]/Japan	2016	Cross-sectional	Both	19-69 y	1732	433/433	DHQ/PRAL, NEAP	PRAL and NEAP were positively associated with HOMA-IR score (*P*-trend: .045 and .03 respectively). NEAP was also positively associated with HOMA-β score (*P*-trend: .03). No association between PRAL, NEAP and FBS or HbA_1C was reported.	Age, sex, PA, smoking, alcohol, shift work, FHD, BMI	8
Akter[21]/Japan	2016	Cross-sectional	Men	45-75 y	27 808	6952/6952	147-item FFQ/ PRAL,NEAP	The men in the highest quartiles of PRAL had 61% higher odds of developing diabetes compared with the lowest. NEAP was not associated with odds of T_2DM. OR: 1.61 (CI = 1.16, 2.24) *P* = .05	Age, BMI, HTN, smoking, alcohol, PA, FHD, energy, food groups intake	9
Akter[21]/Japan	2016	Cross-sectional	Women	45-75 y	36 851	9213/9213	147-item FFQ/NEAP	No significant association between dietary acid load and odds of T_2DM was observed. NEAP was not associated with odds of T_2DM. OR: 1.08 (CI = 0.72, 1.62) *P* = .7	Age, BMI, HTN, smoking, alcohol, PA, FHD, energy, food groups intake	9
Akter[2]/Japan	2017	Cross-sectional	Both	45-75 y	92 478	23 120/ 23 118	147-item FFQ/NEAP	Being at the highest PRAL quartile was associated with higher history of dyslipidemia (*P* < .001)	Age, sex, public health center area, BMI, smoking, alcohol use, PA, history of HTN, diabetes, dyslipidemia, occupation, and energy intake.	9
Amodu[4]/USA	2013	Cross-sectional	Both	≥20 y	13 274	2490/2477	24HR/NEAP	The prevalence of HTN and T_2DM in lowest quartile of NEAP was significantly higher than the highest (*P* < .001).	Age, sex, eGFR, race/ethnicity, BMI, poverty, education, smoking status, diuretic use, T_2DM, HTN, CVD, Alb–Cr ratio, albumin, CRP	6
Bahadoran[31]/Iran	2015	Cross-sectional	Both	19-70 y	5620	1405/1405	147-item FFQ/PRAL	No significant difference in the SBP, DBP, FBS and the prevalence of HTN and hyperglycaemia between quartiles was reported.	Age, sex, and energy intake;	6
Banerjee[32]/USA	2018	Cross-sectional	Both	21-84 y	3257	1074/1075	FFQ	HOMA-IR in the highest tertile was significantly higher. No significant difference in the prevalence of T_2DM and HTN was reported.	Age, sex, T_2DM, education, income, religion, BMI, insulin resistance, smoking, HTN, CVD, energy intake	6
Engberink[33]/ Netherland	2012	Cross-sectional baseline data	Both	≥55 y	2241/ general population	747/747	FFQ	SBP in the highest tertile of PRAL was significantly higher. No significant difference in the prevalence of T_2DM and the mean values of DBP was observed.	Age, sex, BMI, smoking, education, intakes of energy, alcohol, fibre,	7

(Continues)

TABLE 2 Continued

First author/ country	Year	Study design	Sex	Age range	Sample size/ population	Number of cases/ controls	Dietary assessment/ index	Results	Adjusted variables	Quality
Fagherazzi[15]/ France	2014	Cohort- baseline data for HTN Follow-up data for HR of diabetes incidence	Women	40-65 y	66 485/ general population	16 621/ 16 622	208-item DHQ	HR for the association between PRAL and NEAP with incident T_2DM were (OR: 1.56; CI: 1.29, 1.90) and (OR: 1.57; CI: 1.30, 1.89) respectively ($P < .001$). The prevalence of HTN was not significantly different at baseline.	Age, education, smoking, PA, HTN, HCL, T_2DM, alcohol intake, intake of omega 3 FA, CHO, energy, coffee, sugar, ASB, fruits, vegetable, processed meat, dietary patterns, BMI	8
Gæde[17]/Denmark	2018	Cohort- follow-up data for HR of diabetes incidence	Men	50-64 y	25 808/ general population	5162/5162	192-Item FFQ/PRAL	The HR for incidence of diabetes according to PRAL score quintiles was not significantly different between highest vs lowest.	BMI, fat, energy, PA CHO intake, smoking,	8
Gæde[17]/Denmark	2018	Cohort- follow-up data for HR of diabetes incidence	Women	50-64 y	28 843/ general population	5769/5769	192-Item FFQ/PRAL	Women in the fifth quintile of PRAL were more likely to develop diabetes after 15 years follow-up (OR = 1.10; CI: 0.98, 1.25; $P = .02$)	BMI, fat, energy, PA, CHO intake, smoking,	8
Gæde[17]/Denmark	2018	Cross- sectional (Inter 99)	Men	30-60 y	2842/ general population	569/569	FFQ/PRAL	Insulin and HOMA-IR were significantly higher in top quintile vs lowest. Glucose, HbA_1C not different.	Age, BMI, smoking, PA, fat, energy, carbohydrate intake	8
Gæde[17]/Denmark	2018	Cross- sectional (Inter 99)	Women	30-60 y	2790/ general population	558/558	FFQ/PRAL	Significantly higher insulin and lower HBA_1C in highest quintile vs lowest quintile. No significant difference in glucose, HOMA-IR	Age, BMI, smoking, PA, fat, energy, CHO intake	8
Haghighatdoost[18]/ Iran	2015	Cross- sectional	Both	Mena age 66.8	547/general population	274/273	FFQ/PRAL	FBS was significantly lower and HbA_1C, SBP significantly higher in highest vs lowest PRAL categories.	Intake of protein, fat, cholesterol, fibre, whole refined grains, fruit, meat, potassium, phosphorus, beans, nuts, vegetable, BMI	7
Han[12]/Korea	2016	Cross- sectional	Both	40-79 y	11 601/ general population	4202/3859	24HR/PRAL	SBP, DBP and the prevalence of HTN and in highest tertile was significantly higher than the lowest. FSG, insulin, HOMA-IR were not different.	Age, sex, PA, family history of cardio and cerebro-vascular disease, T_2DM, HTN, LDL, eGFR, urine pH	7
Ikizler[19]/USA	2016	Cross- sectional	Both	Mean age 60.8	63/general population	21/21	3-day prospective FD/NEAP	FBS, insulin, SBP, DBP were none significantly higher in highest vs lowest NEAP tertile.	Age, race, sex, BMI, eGFR, use of diuretics	8
Iwase[7]/Japan	2015	Cross- sectional	Both	Mean aged 65.7 ± 9.3	149/general population	74/75	DHQ/PRAL	No significant difference in SBP, HbA_1C was observed.	Age, sex, serum uric acid and creatinine, total energy intake, CHO and sodium intake.	8

(Continues)

TABLE 2 Continued

First author/ country	Year	Study design	Sex	Age range	Sample size/ population	Number of cases/ controls	Dietary assessment/ index	Results	Adjusted variables	Quality
Iwase[7]/Japan	2015	Cross-sectional	Both	Mean aged 65.7 ± 9.3	149/general population	74/75	DHQ/NEAP	No significant difference in SBP, HbA_1C was observed.	Age, sex, serum uric acid and creatinine, total energy, CHO and sodium intake.	8
Jia[20]/Sweden	2015	Cross-sectional	Both	≥70 y	861/general population	215/215	7-day FR/NEAP	No significant difference in the prevalence of diabetes between NEAP quartiles was observed.	Sex, BMI, PA, energy intake, alcohol intake, smoking, eGFR education.	7
Kiefte-de Jong[34]/ USA	2017	Cohort-NHS-median follow-up data	Both	30-55 y	121 700/ general population	14 974/ 11 449	FFQ/NEAP, PRAL	Higher prevalence of HTN in highest vs lowest quintile of NEAP was reported. The odds of T_2DM in highest quintile of NEAP and PRAL were higher compared with the lowest.	Age, energy intake, BMI, FHD, menopausal status, HTN and HCL, smoking, alcohol intake, PA, glycaemic load, AHEI index, western dietary pattern	9
Kiefte-de Jong[34]/ USA	2017	Cohort-NHS2-median follow-up data	Women	25-42 y	116 430/ general population	13 878/ 18 030	FFQ/NEAP, PRAL	Higher prevalence of HTN in highest vs lowest quintile of NEAP was reported. The odds of T_2DM in highest quintile of NEAP and PRAL were higher compared with the lowest.	Age, energy intake, BMI, FHD, menopausal status, HTN and HCL, smoking, alcohol intake, PA, glycaemic load, AHEI index, western dietary pattern	9
Kiefte-de Jong[34]/ USA	2017	Cohort-HPFS-median follow-up data	Men	40-75 y	51 529/ general population	7472/6428	FFQ/NEAP, PRAL	Higher prevalence of HTN in highest vs lowest quintile of NEAP was reported. The odds of T_2DM in highest quintile of NEAP and PRAL were non-significantly higher than the lowest.	Age, energy intake, BMI, FHD, HTN menopausal status, HCL, smoking, alcohol intake, PA, glycaemic load, AHEI index, western dietary pattern	9
Ko[35]/Korea	2017	Cross-sectional	Both	≥65 y	1369/ general population	342/343	FFQ/eNEAP	No significant difference in FBS, SBP, DBP, the prevalence of diabetes and HTN between lowest and highest e-NEAP quartiles was reported.	Age, sex, Dietary caloric and sodium; BMI, smoking, education, PA; HTN, T_2DM, HLP, CVD	7
Krupp[36]/Germany	2018	Cross-sectional	Both	18-79 y	7115/ general population	1358/1356	FFQ/PRAL	No significant difference between SBP and DBP was observed. The prevalence of HTN was lower in fifth quintile compared with the first.	Age, sex, BMI, BP, fasting duration, eGFR, FBS, TC, smoking, natrium excretion, alcohol use, diuretics, beta-blockers	8
Kucharska[37]/ Poland	2018	Cross-sectional	Men	≥20 y	2760/ general population	920/920	24HR/NEAP	No significant difference in the prevalence of HTN and the SBP and DBP values between NEAP tertiles was reported.	Age, WC	5
Kucharska[37]/ Poland	2018	Cross-sectional	Women	≥20 y	3409/ general population	1136/1137	24HR/NEAP	No significant difference in FBS, the prevalence of HTN, diabetes between PRAL tertiles was observed.	Age, WC	5
Kucharska[37]/ Poland	2018	Cross-sectional	Men	≥20 y	2760/ general population	920/920	24HR/PRAL	No significant difference in FBS, the prevalence of HTN, diabetes between NEAP tertiles was observed.	Age, WC	5
Kucharska[37]/ Poland	2018	Cross-sectional	Women	≥20 y	3409/ general population	1136/1137	24HR/PRAL	No significant difference in FBS, the prevalence of HTN, between PRAL tertiles was observed. The prevalence of T_2DM in highest tertile of PRAL was higher.	Age, WC	5

(Continues)

TABLE 2 Continued

First author/ country	Year	Study design	Sex	Age range	Sample size/ population	Number of cases/ controls	Dietary assessment/ index	Results	Adjusted variables	Quality
Luis[38]/Sweden	2014	Cross-sectional	Both	70-71 y	673/general population	224/224	7d-FR/PRAL	No significant difference in SBP, DBP, the prevalence of HTN, T_2DM, between tertiles of PRAL was observed.	Age, BMI, smoking status, sodium, alcohol, energy intake, PA, HLP, education, CVD, T_2DM, eGFR, SBP, the nighttime/daytime SBP ratio	8
Moghadam[39]/Iran	2016	Cross-sectional	Both	22-80 y	925/general population	224	FFQ/PRAL	SBP and DBP were significantly higher in highest vs lowest quartile of PRAL. No significant difference in fbs, insulin, HOMA-IR, HOMA-β, insulin resistance at baseline between quartiles of PRAL was reported.	Age	6
Moghadam[39]/Iran	2016	Cohort	Both	22-80 y	925/general population	224	FFQ/PRAL, NEAP	Significantly higher odds of insulin resistance in the highest vs lowest PRAL and NEAP quartiles after 3 y follow-up. No significant difference in SBP, DBP, FBG, insulin, HOMA-IR, HOMA-β, insulin resistance after 3 y follow-up between quartiles of PRAL was reported.	Age, sex, BMI,PA, dietary energy, fat, CHO, SFA, fibre	8
Murakami[40]/Japan	2008	Cross-sectional	Both	18-22 y	1136/ general population	227/227	DHQ/PRAL	Significantly higher values of SBP, DBP between different quartiles of PRAL. No difference in FBS, HbA_1C was observed.	Residential block, residential area size, survey year, PA, smoking, BMI, WC.	7
Rebholz[41]/USA	2015	Cross-sectional	Both	45-64 y	15 055	3011/3011	FFQ/NEAP, PRAL	Significantly higher prevalence of T_2DM (13.8% vs 10%) and HTN (37.7% vs 31.9%) in highest vs lowest PRAL quartile.	Age, sex, race-center, caloric intake, diabetes, HTN, obese, smoking, education, PA, baseline eGFR	8
van-den Berg[22]/ Denmark	2012	Cross-sectional	Both	≥18 y	707/renal transplant patients	236/236	FFQ/NEAP	No difference in the SBP, DBP, HbA_1C and the prevalence of T_2DM or HTN between tertiles of NEAP was reported.	Age, BSA, sex medications, eGFR, time since transplantation, smoking	7
Xu[42]/Sweden	2016	Cross-sectional	Both	70-71 y	911	304/303	7-d FR/PRAL	No significant difference in the FBS, insulin, the prevalence of T_2DM, HTN between PRAL tertiles was observed. The PRAL or NEAP were not associated with odds of T_2DM incidence.	Age, BMI, smoking status, PA, education, glucose disposal rate, CVD, HTN, HLP, energy-adjusted fibre, MUFA, PUFA, SFA, CHO intake, eGFR, UAER	8

Abbreviations: 24 HR, 24-hour dietary recall questionnaire; AHEI, alternative healthy eating index; ASB, artificially sweetened beverages; BDHQ, brief validated self-administered diet history questionnaire; BMI, body mass index; BSA, body surface area; CHO, carbohydrate; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; FD, food diary; FHD, family history of diabetes; HbA_1C, haemoglobin A_1C; HCL, hypercholesterolaemia; HLP, hyperlipidaemia; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; HTN, hypertension; MUFA, monounsaturated fatty acid; NEAP, net-endogenous acid production; PA, physical activity; PRAL, potential renal acid load; PUFA, polyunsaturated fatty acid; SBP, systolic blood pressure; SFA, saturated fatty acid; T_2DM, type 2 diabetes mellitus; UAER, urinary albumin excretion; WC, waist circumference.

scores.[20-22,32-34,37,42] Inverse associations of the higher prevalence of T_2DM in the lowest categories of NEAP in the study by Amodu et al,[4] lower HbA_1C concentrations in the higher quintile of PRAL in a cross-sectional analysis of Inter99 cohort of Gæde et al study[17] and lower FBS concentrations in the higher category of PRAL[18] should also be mentioned.

3.3 | Findings from meta-analysis of mean SBP and DBP across different dietary acid load categories

All of the studies included in the current meta-analysis had cross-sectional design while only two studies were cohort. In the cross-sectional and even in the cohort studies, the baseline data (data before follow-up) were included in the meta-analysis. Therefore, the design of the included studies could not be a source of bias in the current analysis. Although, for more assurance, we also performed subgroup analysis according to all of possible confounders including design, country, sample size, gender, dietary assessment tool and study quality score. Totally, in the meta-analysis of the mean difference of SBP in different PRAL categories 12 studies were included; the Forest plot is presented in Figure 2. Accordingly, higher dietary acid load was associated with 0.97 mm Hg increase in SBP (WMD = 0.98; CI: 0.51, 1.45; $P < .001$) with the moderate heterogeneity (Heterogeneity chi-squared = 20.73 [$df = 11$]; $P = .036$; $I^2 = 49.6\%$; $Tau^2 = 0.225$). In the meta-analysis of NEAP and SBP including six studies (Figure 2), however, no significant association was observed (WMD = 0.495; CI = −0.29, 1.28; $P = .22$) and no evidence of heterogeneity was also present (Heterogeneity chi-squared = 3.13 [$df = 5$]; $P = .68$; $I^2 = 0.0\%$; $Tau^2 = 0.00$). For the meta-analysis of the association between dietary acid load identified as PRAL and DBP (Figure 3), totally, eight studies were included and higher PRAL categories were associated with significant increase equal to 0.61 mm Hg in DBP values (WMD = 0.61; CI: 0.089, 1.135; $P = .022$) with a partially high level of heterogeneity (Heterogeneity chi-squared = 28.77 [$df = 7$]; $P < .001$; $I^2 = 75.7\%$; $Tau^2 = 0.31$). Accordingly, in the meta-analysis of NEAP and DBP associations (Figure 3), no evidence of association was observed (WMD = 0.03; CI = −1.07, 1.13; $P = .95$) and no heterogeneity was reported (Heterogeneity chi-squared = 0.1 [$df = 2$]; $P = .95$; $I^2 = 0.0\%$; $Tau^2 = 0.00$). The results of the subgroup analysis of the PRAL-DBP associations (Table S6) showed that subgrouping according to country, dietary assessment tool and gender significantly reduced the amount of heterogeneity and therefore, these parameters could be considered as the possible sources of heterogeneity. Study quality was not a source of heterogeneity.

3.4 | Findings from meta-analysis of mean FBS and HbA_1C across different dietary acid load categories

Totally the association between PRAL and NEAP with FBS was reported in 12 and 5 studies (Figure 4). No effects of dietary acid load measured by PRAL and NEAP on the serum FBS were identified (PRAL: WMD = 0.034, CI: −2.913, 2.981; $P = .98$ and for NEAP: WMD = 0.502; CI: −0.164, 1.168; $P = .139$). The heterogeneity was also high for the FBS-PRAL analysis (Heterogeneity chi-squared = 26.24 [$df = 1$]; $P < .001$; $I^2 = 98.6\%$; $Tau^2 = 26.23$); while no heterogeneity was observed for FBS-NEAP associations (Heterogeneity chi-squared = 2.93 [$df = 4$]; $P = .57$; $I^2 = 0.0\%$;

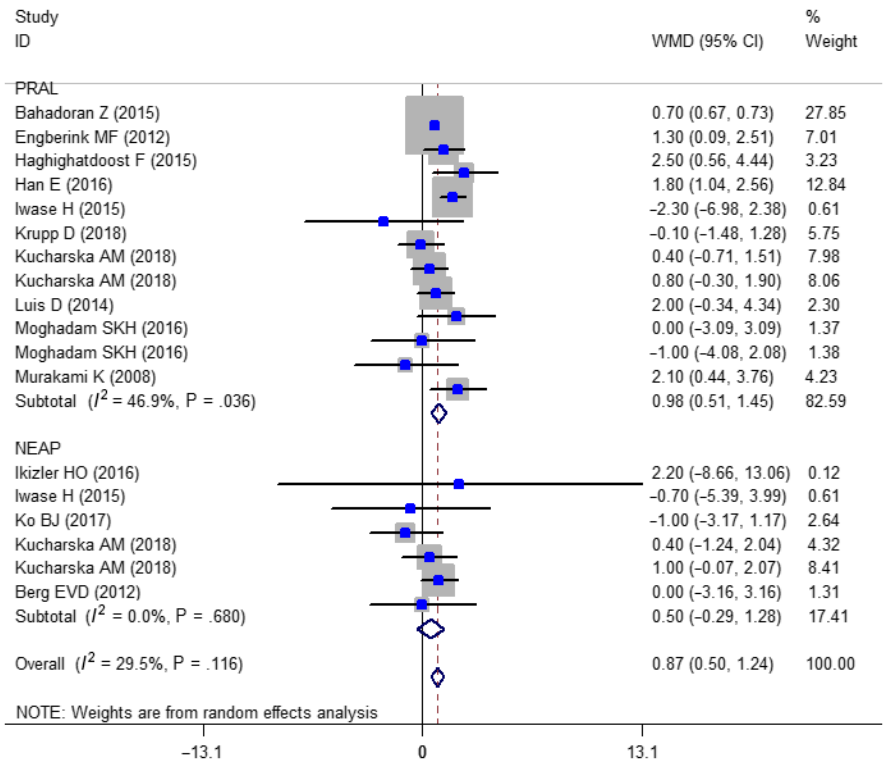

FIGURE 2 Forest plot illustrating weighted mean difference in systolic blood pressure (SBP) in highest vs lowest potential renal acid load (PRAL) and net-endogenous acid production (NEAP)

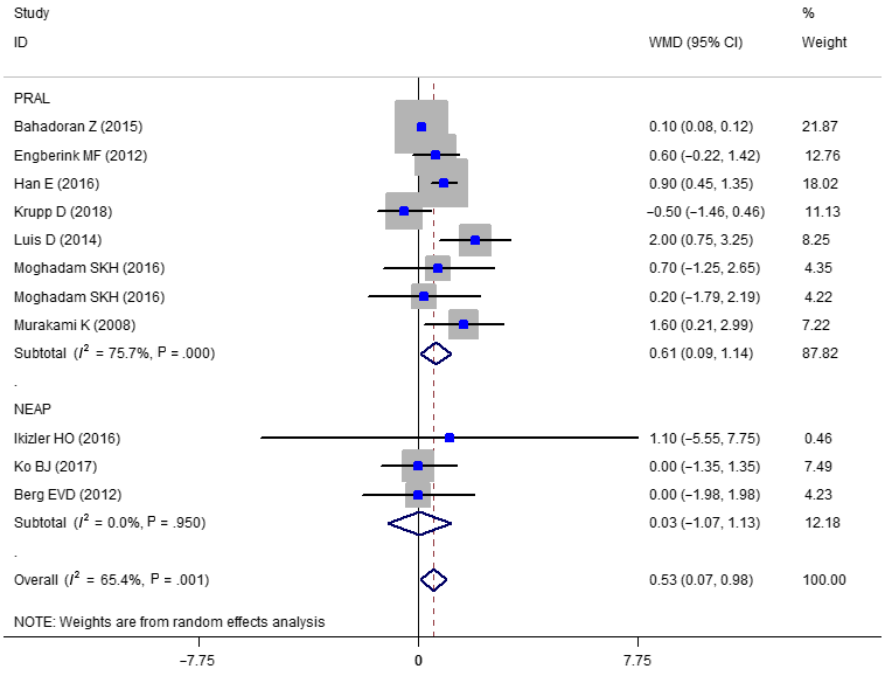

FIGURE 3 Forest plot illustrating weighted mean difference in diastolic blood pressure (DBP) in highest vs lowest potential renal acid load (PRAL) and net-endogenous acid production (NEAP)

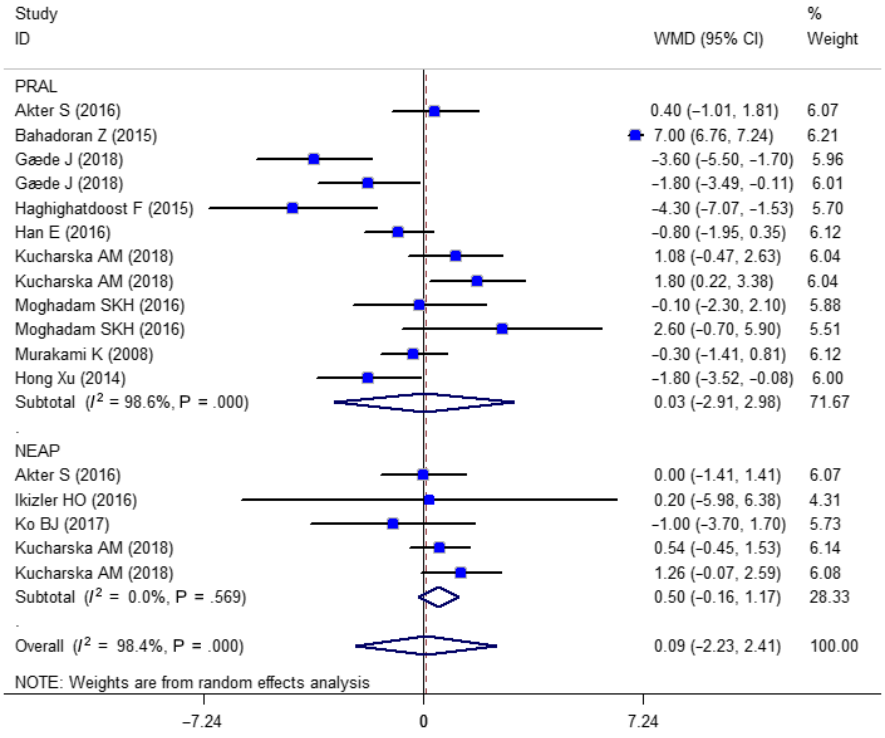

FIGURE 4 Forest plot illustrating weighted mean difference in fasting blood sugar (FBS) in highest vs lowest potential renal acid load (PRAL) and net-endogenous acid production (NEAP)

Tau^2 = 26.23). Sensitivity analysis showed no significant alterations in the obtained results. The subgroup analysis for finding the possible source of heterogeneity for the FBS-PRAL associations is presented in Table S7 and country and dietary assessment tool found to be the possible sources of heterogeneity. The Forest plot of the associations between PRAL and NEAP with serum HbA_1C are presented in Figure 5 presenting no significant effects of neither PRAL nor NEAP on the serum glycosylated haemoglobin (PRAL: WMD = −0.307, CI: −0.954, 0.341; P = .35 and for NEAP: WMD = −0.032; CI: −0.088, 0.024; P = .265) while again, the great heterogeneity was identified in the PRAL-HbA_1C analysis (Heterogeneity chi-squared = 2175.30 [df = 5]; P < .001; I^2 = 99.8%; Tau^2 = 0.649) but not in NEAP-HbA_1C meta-analysis (Heterogeneity chi-squared = 0.32 [df = 2]; P = .85; I^2 = 0.0%; Tau^2 = 0.00). Subgroup analysis for the association between HbA_1C and PRAL, presented in Table S8 revealed that subgrouping according to country, continent, dietary assessment tool and sample size are the possible sources of observed heterogeneity.

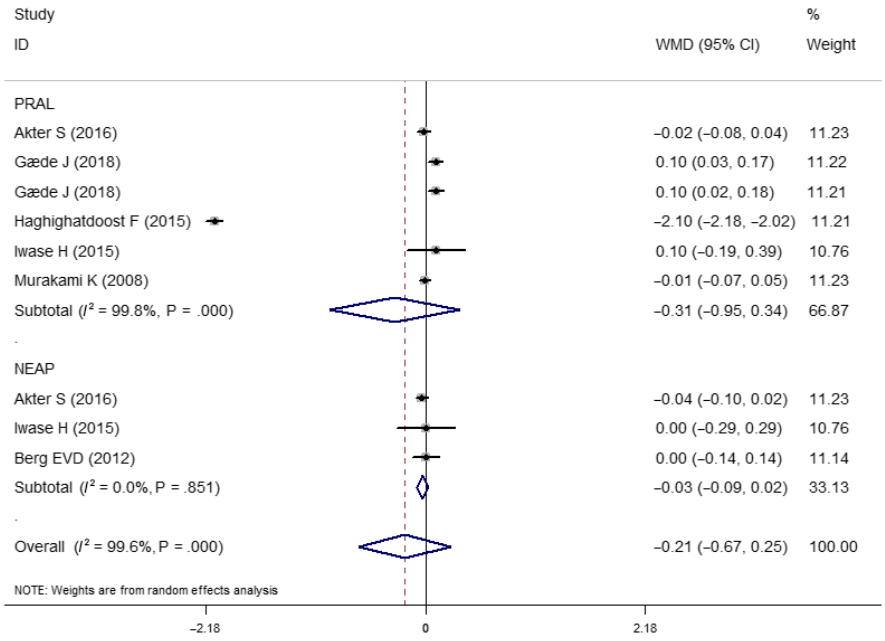

FIGURE 5 Forest plot illustrating weighted mean difference in haemoglobin A_1C (HbA_1C) in highest vs lowest potential renal acid load (PRAL) and net-endogenous acid production (NEAP)

3.5 | Findings from meta-analysis of mean insulin and HOMA-IR across different dietary acid load categories

The Forest plot of the effects of PRAL and NEAP on the serum insulin concentrations is presented in Figure 6. High dietary PRAL values, increases serum insulin concentrations by 0.23 μIU/mL (WMD = 0.235, CI: 0.070, 0.400; *P* = .005), while this effect was not observed for the NEAP (WMD = −0.318, CI: −0.039, 0.676; *P* = .081). A modest heterogeneity was identified in the PRAL-insulin analysis (Heterogeneity chi-squared = 14.09 [*df* = 6]; *P* = .029; I^2 = 57.4%; Tau^2 = 0.022) and not in NEAP-insulin meta-analysis (Heterogeneity chi-squared = 0.17 [*df* = 1]; *P* = .68; I^2 = 0.0%; Tau^2 = 0.00). According to subgroup analysis (Table S9), continent, dietary assessment tool, sample size and gender were the possible source of heterogeneity. In evaluating the association between HOMA-IR and dietary acid load, eight studies reported the association between PRAL and HOMA-IR while only one study reported the association as NEAP[6] therefore it was excluded from the analysis. According to the meta-analysis results summarised in Figure 7 as Forest plot, no evidence of the effects of PRAL on HOMA-IR was obtained (WMD = −0.053, CI: −0.007, 0.113; *P* = .085). The sensitivity analysis revealed no meaningful change in the results. Moreover, because of the high heterogeneity obtained (Heterogeneity chi-squared = 14 759.28 [*df* = 6]; *P* < .001; I^2 = 100.0%; Tau^2 = 0.005) the subgroup analysis was also performed and the results are presented in Table S10 and the results introduced no source of heterogeneity except for the possible effects of dietary assessment tool. Moreover, only two studies[6,39] reported the association of HOMA-β with PRAL which no significant association was observed (Data not shown). The information of QUICKI and hyperglycaemia was absent in almost all of the included studies. Therefore no analysis was done.

3.6 | Findings from meta-analysis of proportions of dietary acid load-hypertension, diabetes and odd's ratios of diabetes

Totally, nine studies reported the prevalence of HTN in the highest vs lowest category of PRAL. The Forest plot of the prevalence of HTN by subgroups highest vs lowest categories of PRAL is presented in Figure S1. Accordingly, the prevalence of HTN was 19% (CI: 0.19-0.20) in highest and lowest category of PRAL. No heterogeneity was observed in the meta-analysis. The Forest plot of the prevalence of HTN in different NEAP categories is reported in Figure S2 indicating 19% prevalence of HTN in lowest and highest NEAP categories with no evidence of heterogeneity. The Forest plot of the proportions of diabetes in lowest vs highest PRAL categories (Figure S3) presents the 13% (CI: 0.13, 0.14) prevalence of T_2DM in the highest vs 11% (CI: 0.10-0.12) in the lowest category of PRAL including seven studies with no evidence of heterogeneity. In the Forest plot of the T_2DM prevalence in different NEAP categories (Figure S4), 9% prevalence was reported both in highest and lowest category of NEAP with no evidence of heterogeneity. The Forest plot of the meta-analysis of odds of T_2DM in highest vs lowest PRAL or NEAP categories is identified in Figure S5. A positive association was observed between diabetes and PRAL (OR = 1.19; CI: 1.092, 1.311; *P* < .001) and NEAP (OR = 1.22; CI: 1.14, 1.31, *P* < .001) in random effect model. In other word, being in the highest category of PRAL and NEAP makes individuals 19% and 22% more likely to develop diabetes compared with the lowest category. A great between-study heterogeneity was also observed for the given results (for PRAL: Heterogeneity chi-squared = 22.55 [*df* = 7]; *P* = .002; I^2 = 69.0%; Tau^2 = 0.0104 and for NEAP: Heterogeneity chi-squared = 11.12 [*df* = 5]; *P* = .049; I^2 = 55.0%; Tau^2 = 0.0069). For finding the possible source of heterogeneity, the subgroup analysis based on the difference in included studies is performed (Tables S11

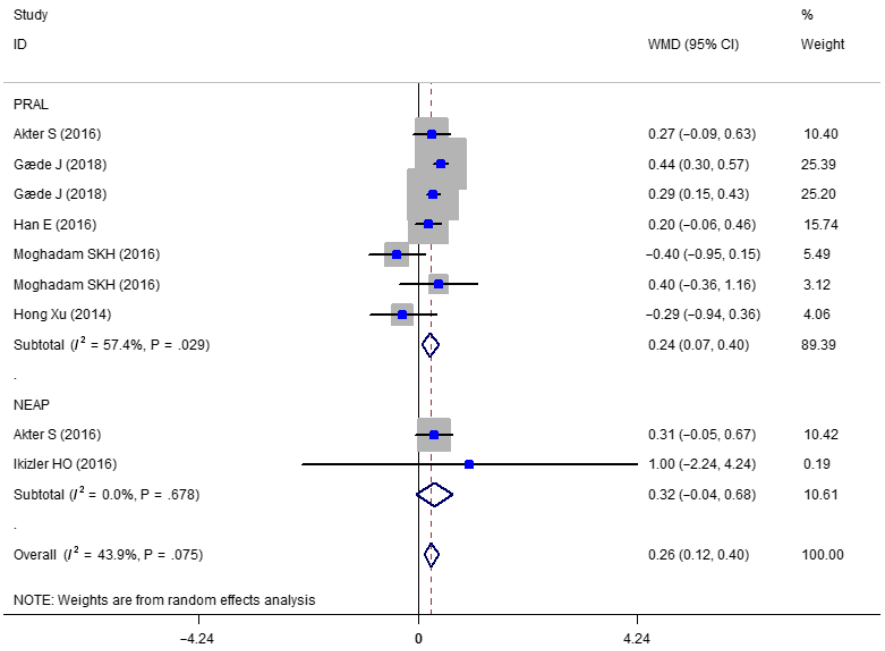

FIGURE 6 Forest plot illustrating weighted mean difference in Insulin in highest vs lowest potential renal acid load (PRAL) and net-endogenous acid production (NEAP)

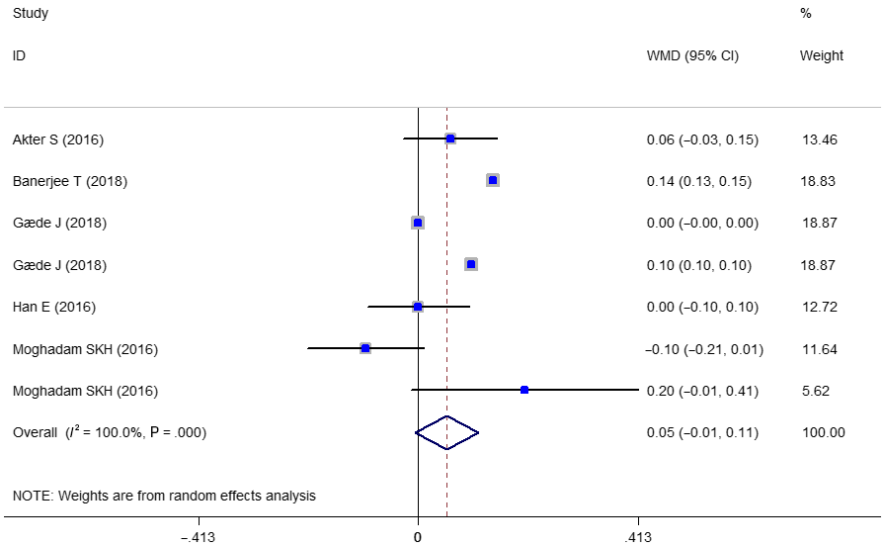

FIGURE 7 Forest plot illustrating weighted mean difference in homeostatic model assessment of insulin resistance (HOMA-IR) in highest vs lowest potential renal acid load (PRAL) and net-endogenous acid production (NEAP)

and S12). Accordingly, in the studies evaluating the dietary acid load by PRAL and odds of diabetes, country and the sample size could be considered as the source of heterogeneity. In NEAP evaluating studies country, design, sample size and gender difference could be a source of heterogeneity.

3.7 | Publication bias

The Funnel plots revealed moderate asymmetry (Figures S6 and S7). However, the Begg's and Egger's tests provided no evidence of substantial publication bias for all of the variables. Exceptionally, Egger's test for the FBS was significant as an evidence of possible publication bias. The provided values are as follows: DBP, Egger's test (P = .087) and Begg's test (P = 0.93); SBP, Egger's test (P = .72) and Begg's test (P = 0.54); FBS, Egger's test (P < .001) and Begg's test (P = .09); HOMA-IR, Egger's test (P = .87) and Begg's test (P = 0.38). Insulin, Egger's test (P = .17) and Begg's test (P = .99); HbA_1C, Egger's test (P = .87) and Begg's test (P = 0.09); OR diabetes, Egger's test (P = .33) and Begg's test (P = .11).

4 | DISCUSSION

In the current meta-analysis, we summarised the results of studies reporting the association between PRAL, NEAP and metabolic risk factors of glucose homoeostasis, blood pressure, the prevalence of diabetes, HTN and the odds of diabetes. Accordingly, being in the highest category of PRAL scores was associated with higher SBP, DBP, insulin concentrations and higher prevalence and risk of diabetes compared with lowest category. Whereas, being in the highest category of NEAP was only associated with higher odds

of diabetes. No association between markers of glucose homoeostasis including fasting blood glucose, HbA_1C and HOMA-IR with PRAL or NEAP was observed. Animal foods including meat, fish, egg, chicken, cheese and also cereals are rich in sulphur-containing amino acids, phosphorous and chloride are potentially acid formers; while vegetables and fruits high in malate, citrate and glutamate are potentially base formers therefore, animal-based foods and high contents in western diets are potentially considered as most important acid-producer diets and are associated with higher risk of insulin resistance, high blood pressure and diabetes as established in numerous works.[11] Accordingly, western dietary pattern with high dietary acid load content, is a potent inducer of metabolic disorders; several studies had revealed significant relationships between western dietary pattern and the increased risk of metabolic syndrome, hypertension and dyslipidemia. Accordingly, western dietary pattern with high content of red meat, eggs and refined grains is associated with increased risk of obesity and increased levels of blood sugar, systolic blood pressure, triglycerides, and reduced levels of HDL.[43-45] It has been suggested that PRAL is a more accurate measure of dietary acid load because it considers dietary intake of protein and numerous micronutrients, potassium, calcium phosphorus and magnesium and takes into account the absorption rate of the nutrients in the intestinal border, unlike the NEAP score, which only consider the dietary protein and potassium intake.[15] Therefore, this lead to PRAL be a good predictor of the effects of acidity on the body.[46] In subgroup analysis of men and women separately, the odds of diabetes among women were stronger than men in both PRAL and NEAP assessment. A possible explanation is the difference in sex-hormones affecting acid-base balance[47] and also possibly the higher sample size of women participants compared with men is a possible source of higher effect size among them. As mentioned in the results section, gender, dietary assessment tool and continent could be a source of heterogeneity among observed association. In the current meta-analysis, PRAL and NEAP calculations were based on self-reported data gathered by 24-hour recall method, 24-hour record method and food frequency questionnaire which might be potential sources of bias. Moreover, difference in the items of the FFQ might be a source of heterogeneity; as described previously, the FFQ items ranged from 63 to 168 items and the local foods in the FFQ could also affect the heterogeneity,[48] although, almost all of the included studies used validated and reliable FFQs. FFQ covers a wide range of dietary ingredients and is more accurate than 24-hour recall method reflecting usual dietary intake in a short period of time; it has been confirmed that FFQ could be more helpful in evaluating the diet-disease relationships.[49] Another source of heterogeneity, the continent, presents the possible role of geographical distribution, genetic background and cultural factors influencing the association between dietary acid load and metabolic risk factors.[50] In the current meta-analysis, higher PRAL scores were associated with both higher SBP and DBP concentrations although no difference in the odds of HTN in different PRAL or NEAP categories was reported. The possible underlying mechanisms are decline in renal function and reduced citrate excretion, increased calcium and cortisol secretion.[33] We did not observe any association between PRAL, NEAP and markers of glucose homoeostasis including FBS, HbA_1C and HOMA-IR values. Higher FBS concentrations in higher PRAL categories were reported in the Haghighatdoost et al study[18] although this association did not achieve significant threshold, while other studies reported no significant difference.[7,12,17,22,31,35,37,39,40,42] The current meta-analysis has several limitations and strengths; the current meta-analysis included the results of observational studies with the cross-sectional or cohort design which makes the causal inference impossible; although, the studies were large population-based studies with acceptable quality. However, our study, based on our knowledge, is the first meta-analysis evaluating the association between dietary acid load as both PRAL and NEAP scores with a wide range of metabolic risk factors including systolic and diastolic blood pressure, fasting serum glucose, HbA_1C, insulin, HOMA-IR and the prevalence of hypertension and diabetes. In conclusion, in the current meta-analysis, we found a potent role of high acid content of diet as a possible leading cause of metabolic abnormalities, high blood pressure, higher insulin concentrations and high prevalence of hypertension. We suggest interventional studies in this regard for better causal inference.

DISCLOSURE

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTION

MAF and PD designed the research; MAF conducted the research and performed statistical analysis; NAF and PD wrote the paper; both authors read and approved the final manuscript.

ETHICAL CONSIDERATIONS

The protocol of the current study has been registered in PROSPERO with the identification number of CRD42019122272. Moreover, the study protocol has also been registered by the ethics committee of Tabriz University of Medical Sciences (Registration number: IR.TBZMED.VCR.REC.1398.140).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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