Evidence Based Analysis Project

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Completed in partial fulfillment of the requirements for

Nutr 485: Medical Nutrition Therapy I

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RESEARCH QUESTION

In healthy, adult individuals (ages 18 and older), does the consumption of plant protein reduce the risk of cardiovascular disease compared to the consumption of animal protein in healthy adult individuals?

The question was modified to look at healthy individuals instead of individuals at risk of cardiovascular disease. This was done in order to avoid as many confounding variables as possible from other health conditions the participants may have. This also gave us a wider pool of research to explore.

RESEARCH QUESTION TYPE

The research question was a prevention type of research question. It tries to determine whether the consumption of plant-based protein can help reduce the risk of cardiovascular disease compared to the consumption of animal protein.

RESEARCH DATABASE USED

For this research question, the databases PubMed, Cochrane, Science Direct, and ProQuest were used. Databases were selected from the David L. Rice Library database page because of their relevance to health professions and the food and nutrition program.

SEARCH PLAN AND RESULTS

Date of Literature Review: November 2021

Inclusion:

Human Research Subjects

Peer-Reviewed Articles

Adults aged 18 and older

Current health status of study participants: No current health issues such as CVD, renal failure, etc.

Study Design: Cohort, Case Control, Cross Sectional, or Observational

Year Range: 2010 - Present

Exclusion:

Animal Studies/ Non-human participants

Individuals less than 18 years of age

Non-Peer-Reviewed

Individuals with CVD, renal failure, or other conditions that could act as a confounding variable

Search Terms:

- Peer-Reviewed
- Plant Protein
- Animal Protein
- Cardiovascular Disease
- Adults
- Human Studies

Databases and Number of articles from database:

- 1- Cochrane
- 21- ProQuest
- 2 – PubMed
- 8 - Science Direct
- 26 Medline

Included articles (Does not include duplicate citations found on multiple databases):

Citations:

Akter S, Mizoue T, Nanri A, et al. Low carbohydrate diet and all cause and cause-specific mortality. *Clinical nutrition (Edinburgh, Scotland)*. 2021;40(4):2016-2024. doi:10.1016/j.clnu.2020.09.022
Aziz F, Bahadoran Z, Houshialsadat Z, Khalili-Moghadam S, Mirmiran P, and Shahrzad M K. Dietary acid load and risk of cardiovascular disease: a prospective population-based study. *BMC Cardiovascular Disorders.* 2021:21:432. https://doi.org/10.1186/s12872-021-02243-8.
Budhathoki S, Sawada N, Iwasaki M, et al. Association of Animal and Plant Protein Intake With All-Cause and Cause-Specific Mortality in a Japanese Cohort. *JAMA internal medicine*. 2019;179(11):1509-1518. doi:10.1001/jamainternmed.2019.2806
Chan R, Leung J, Woo J. High Protein Intake Is Associated with Lower Risk of All-Cause Mortality in Community-Dwelling Chinese Older Men and Women. *The journal of nutrition, health & aging*. 2019;23(10):987-996. doi:10.1007/s12603-019-1263-1
Chen Z, Glisic M, Song M, et al. Dietary protein intake and all-cause and cause-specific mortality: results from the Rotterdam Study and a meta-analysis of prospective cohort studies. *European journal of epidemiology*. 2020;35(5):411-429. doi:10.1007/s10654-020-00607-6
Huang J, Liao LM, Weinstein SJ, Sinha R, Graubard BI, Albanes D. Association Between Plant and Animal Protein Intake and Overall and Cause-Specific Mortality. *JAMA internal medicine*. 2020;180(9):1173-1184. doi:10.1001/jamainternmed.2020.2790
Larsson SC, Virtamo J, Wolk A. Dietary protein intake and risk of stroke in women. *Atherosclerosis*. 2012;224(1):247-251. doi:10.1016/j.atherosclerosis.2012.07.009

Naghshi S, Sadeghi O, Willett WC, Esmaillzadeh A. Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ*. 2020;370:m2412. Published 2020 Jul 22. doi:10.1136/bmj.m2412
Qi X-X, Shen P. Associations of dietary protein intake with all-cause, cardiovascular disease, and cancer mortality: A systematic review and meta-analysis of cohort studies. *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2020;30(7):1094-1105. doi:10.1016/j.numecd.2020.03.008
Sikand G, Severson T. Top 10 dietary strategies for Atherosclerotic Cardiovascular Risk Reduction. American Journal of Preventive Cardiology. 2020;4:100106. doi:10.1016/j.ajpc.2020.100106
Song M, Fung TT, Hu FB, et al. Association of Animal and Plant Protein Intake With All-Cause and Cause-Specific Mortality. *JAMA internal medicine*. 2016;176(10):1453-1463. doi:10.1001/jamainternmed.2016.4182
Sun Y, Liu B, Snetselaar LG, et al. Association of Major Dietary Protein Sources With All-Cause and Cause-Specific Mortality: Prospective Cohort Study. *Journal of the American Heart Association*. 2021;10(5):e015553. doi:10.1161/JAHA.119.015553
Tharrey M, Mariotti F, Mashchak A, Barbillon P, Delattre M, Fraser GE. Patterns of plant and animal protein intake are strongly associated with cardiovascular mortality: the Adventist health study-2 cohort. *Int J Epidemiol*. 2018 Oct 1;47(5):1603-1612. doi: 10.1093/ije/dyy030.

Excluded articles:

Citations:	**Reason/s Why Excluded:**
12th European Nutrition Conference (FENS), Berlin, Germany, October 20-23, 2015: Abstracts. *Ann Nutr Metab.* 2015;67:1-601. doi:http://dx.doi.org/10.1159/000440895.	Excluded because it consists of only abstracts that do not provide enough information.
Abstracts of the 48th EASD Annual Meeting of the European Association for the Study of Diabetes. *Diabetologia.* 2012;55:1-537. doi:http://dx.doi.org/10.1007/s00125-012-2688-9.	Excluded because it only consists of abstracts that do not provide enough information.
Babygirija R, Lamming DW. The regulation of healthspan and lifespan by dietary amino acids. Translational Medicine of Aging. 2021;5:17-30. doi:10.1016/j.tma.2021.05.001	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease.
Bel-serrat S, Mouratidou T, Huybrechts I, et al. The role of dietary fat on the association between dietary amino acids and serum lipid profile in European adolescents participating in the	Excluded because the article does not focus on cardiovascular disease.

HELENA Study. *Eur J Clin Nutr.* 2014;68(4):464-73. doi:http://dx.doi.org/10.1038/ejcn.2013.284.	
Bocanegra A, Macho-González A, Garcimartín A, Benedí J, Sánchez-Muniz FJ. Whole Alga, Algal Extracts, and Compounds as Ingredients of Functional Foods: Composition and Action Mechanism Relationships in the Prevention and Treatment of Type-2 Diabetes Mellitus. *International Journal of Molecular Sciences.* 2021;22(8):3816. doi:http://dx.doi.org/10.3390/ijms22083816.	Excluded because article focuses on the effect of dietary protein intake on insulin resistance in subjects with obesity.
Bols E, Smits L, Weijenberg M. Healthy Living: The European Congress of Epidemiology, 2015. *Eur J Epidemiol.* 2015;30(8):709-1001. doi:http://dx.doi.org/10.1007/s10654-015-0072-z.	Excluded because protein intake is not the focus of the article.
De Koning L, Fung TT, Liao X, et al. Low-carbohydrate diet scores and risk of type 2 diabetes in men. *The American journal of clinical nutrition*. 2011;93(4):844-850. doi:10.3945/ajcn.110.004333	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
Dong TS, Gupta A. Influence of early life, diet, and the environment on the microbiome. Clinical Gastroenterology and Hepatology. 2019;17(2):231-242. doi:10.1016/j.cgh.2018.08.067	Excluded because article examines the influence of environmental factors such as diet, early life adversity and stress in shaping and modifying the microbiome towards health and disease.
Gluba-Brzózka A, Franczyk B, Rysz J. Vegetarian Diet in Chronic Kidney Disease-A Friend or Foe. *Nutrients*. 2017;9(4). doi:10.3390/nu9040374	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
González-Salazar L,E., Pichardo-Ontiveros Edgar, Palacios-González Berenice, et al. Effect of the intake of dietary protein on insulin resistance in subjects with obesity: a randomized controlled clinical trial. *Eur J Nutr.* 2021;60(5):2435-2447. doi:http://dx.doi.org/10.1007/s00394-020-02428-5.	Excluded because article does not match the population in which we are interested in based on age.
Guasch-Ferré M, Satija A, Blondin SA, et al. Meta-Analysis of Randomized Controlled Trials of Red Meat Consumption in Comparison With Various Comparison Diets on Cardiovascular	Excluded because it focused on animal meat consumption

Risk Factors. *Circulation*. 2019;139(15):1828-1845. doi:10.1161/CIRCULATIONAHA.118.035225	
Hernández-Alonso P, Becerra-Tomás N, Papandreou C, et al. Plasma Metabolomics Profiles are Associated with the Amount and Source of Protein Intake: A Metabolomics Approach within the PREDIMED Study. *Molecular nutrition & food research*. 2020;64(12):e2000178. doi:10.1002/mnfr.202000178	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
Hooper L, Martin N, Jimoh OF, Kirk C, Foster E, Abdelhamid AS. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database of Systematic Reviews. 2020;8(CD011737). DOI: 10.1002/14651858.CD011737.pub3.	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
Hou W, Gao J, Jiang W, et al. Meal Timing of Subtypes of Macronutrients Consumption With Cardiovascular Diseases: NHANES, 2003 to 2016. *The Journal of clinical endocrinology and metabolism*. 2021;106(7):e2480-e2490. doi:10.1210/clinem/dgab288	Excluded because article does not examine relationship between protein intake and cardiovascular disease
Houston M. The role of nutrition and nutritional supplements in the treatment of dyslipidemia. *Clinical Lipidology.* 2014;9(3). doi:http://dx.doi.org/10.2217/clp.14.25.	Excluded because it focuses on nutritional supplements rather than protein intake.
Kitada M, Ogura Y, Monno I, Koya D. The impact of dietary protein intake on longevity and Metabolic Health. EBioMedicine. 2019;43:632-640. doi:10.1016/j.ebiom.2019.04.005	Excluded because article analyze the impact of protein intake as a critical role in longevity/metabolic health.
Larsen R, Eilertsen K-E, Elvevoll EO. Health benefits of marine foods and ingredients. Biotechnology Advances. 2011;29(5):508-518. doi:10.1016/j.biotechadv.2011.05.017	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease.
Lopez-Legarrea P, de la Iglesia R, Abete I, Navas-Carretero S, Martinez JA, Zulet MA. The protein type within a hypocaloric diet affects obesity-related inflammation: the RESMENA project. *Nutrition (Burbank, Los Angeles County, Calif)*. 2014;30(4):424-429. doi:10.1016/j.nut.2013.09.009	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
Meng S, Cui Z, Li M, et al. Associations between Dietary Animal and Plant Protein Intake and Cardiometabolic Risk Factors-A	Excluded because it does not directly examine the link between

Cross-Sectional Study in China Health and Nutrition Survey. *Nutrients*. 2021;13(2). doi:10.3390/nu13020336	protein intake and cardiovascular disease
Mottaghian M, Salehi P, Teymoori F, Mirmiran P, Hosseini-Esfahani F, Azizi F. Nutrient patterns and cardiometabolic risk factors among Iranian adults: Tehran lipid and glucose study. *BMC public health*. 2020;20(1):653. doi:10.1186/s12889-020-08767-6	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
Nagaoka S, Takeuchi A, Banno A. Plant-derived peptides improving lipid and glucose metabolism. Peptides. 2021;142:170577. doi:10.1016/j.peptides.2021.170577	Excluded because article focused only on physiological functions of plant protein-derived peptides for the improvement of lipid and glucose metabolism.
Nutritional Approach Targeting Gut Microbiota in NAFLD—To Date. *International Journal of Environmental Research and Public Health.* 2021;18(4):1616. doi:http://dx.doi.org/10.3390/ijerph18041616.	Excluded because article focuses on gut microbiome.
Padhi EMT, Ramdath DD. A review of the relationship between pulse consumption and reduction of cardiovascular disease risk factors. Journal of Functional Foods. 2017;38:635-643. doi:10.1016/j.jff.2017.03.043	Excluded because article only examines the relationship between plant protein and CVD, but not animal protein.
Petrisko M, Kloss R, Bradley P, et al. Biochemical, Anthropometric, and Physiological Responses to Carbohydrate-Restricted Diets Versus a Low-Fat Diet in Obese Adults: A Randomized Crossover Trial. *Journal of medicinal food*. 2020;23(3):206-214. doi:10.1089/jmf.2019.0266	Excluded because article examines the relationship between low and high carbohydrate diets paired with either plant or animal protein
Posters: T1 ADVANCES IN NUTRITION RESEARCH. *Ann Nutr Metab.* 2013;63:257-540. doi:http://dx.doi.org/10.1159/000178506.	Excluded because it is not able to provide enough information.
Posters: T2 NUTRITION THROUGH LIFE COURSE. *Ann Nutr Metab.* 2013;63:541-811. doi:http://dx.doi.org/10.1159/000354245.	Excluded because it does not provide an adequate amount of information.
Quek R, Bi X, Henry CJ. Impact of protein-rich meals on glycaemic response of rice. *Br J Nutr.* 2016;115(7):1194-1201. doi:http://dx.doi.org/10.1017/S0007114515005498.	Excluded because article focuses on glycemic response.
Richter CK, Skulas-Ray AC, Champagne CM, Kris-Etherton PM. Plant protein and animal proteins: do they differentially affect	Review journal

cardiovascular disease risk? *Advances in nutrition (Bethesda, Md)*. 2015;6(6):712-728. doi:10.3945/an.115.009654	
Rusu ME, Mocan A, Isabel CFRF, Popa D. Health Benefits of Nut Consumption in Middle-Aged and Elderly Population. *Antioxidants.* 2019;8(8):302. doi:http://dx.doi.org/10.3390/antiox8080302.	Excluded because article focuses on nut consumption.
Schwingshackl L, Hoffmann G. Comparison of High vs. Normal/Low Protein Diets on Renal Function in Subjects without Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *PLoS One.* 2014;9(5). doi:http://dx.doi.org/10.1371/journal.pone.0097656	Excluded because the level of protein intake rather than the type of protein is focused on.
Shang X, Scott D, Hodge A, et al. Dietary protein from different food sources, incident metabolic syndrome and changes in its components: An 11-year longitudinal study in healthy community-dwelling adults. *Clinical nutrition (Edinburgh, Scotland)*. 2017;36(6):1540-1548. doi:10.1016/j.clnu.2016.09.024	Excluded because it examines the relationship between protein intake and metabolic syndrome
The 11th NORDIC NUTRITION CONFERENCE NNC2016. *Food & Nutrition Research.* 2016;60(1). doi:http://dx.doi.org/10.3402/fnr.v60.31961.	Excluded because it lacks adequate data and information on protein intake.
Tielemans SMAJ, Kromhout D, Altorf-van der Kuil W, Geleijnse JM. Associations of plant and animal protein intake with 5-year changes in blood pressure: the Zutphen Elderly Study. *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2014;24(11):1228-1233. doi:10.1016/j.numecd.2014.05.013	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
Vanholder R, Steven VL, Glorieux G, Verbeke F, Castillo-Rodriguez E, Ortiz A. Deleting Death and Dialysis: Conservative Care of Cardio-Vascular Risk and Kidney Function Loss in Chronic Kidney Disease (CKD). *Toxins.* 2018;10(6). doi:http://dx.doi.org/10.3390/toxins10060237.	Excluded because article focuses on kidney related conditions rather than heart related functions.
Virtanen HEK, Voutilainen S, Koskinen TT, et al. Dietary proteins and protein sources and risk of death: the Kuopio Ischaemic Heart Disease Risk Factor Study. *The American journal of clinical nutrition*. 2019;109(5):1462-1471. doi:10.1093/ajcn/nqz025	Excluded because individuals in the study can have CVD, T2D, etc.
Visconti L, Benvenga S, Lacquaniti A, et al. Lipid disorders in patients with renal failure: Role in cardiovascular events and progression of chronic kidney disease. Journal of Clinical & Translational Endocrinology. 2016;6:8-14. doi:10.1016/j.jcte.2016.08.002	Excluded because article considers patients with renal failure.

Voortman T, Vitezova A, Bramer WM, et al. Effects of protein intake on blood pressure, insulin sensitivity and blood lipids in children: a systematic review. *Br J Nutr.* 2015;113(3):383-402. doi:http://dx.doi.org/10.1017/S0007114514003699.	Excluded because the study is focused on children rather than adults.
Xiao Y, Zhang Y, Wang M, Li X, Xia M, Ling W. Dietary protein and plasma total homocysteine, cysteine concentrations in coronary angiographic subjects. *Nutrition journal*. 2013;12(1):144. doi:10.1186/1475-2891-12-144	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
Yang JJ, Shu X-O, Herrington DM, et al. Circulating trimethylamine N-oxide in association with diet and cardiometabolic biomarkers: an international pooled analysis. *The American journal of clinical nutrition*. 2021;113(5):1145-1156. doi:10.1093/ajcn/nqaa430	Excluded because article does not examine link between plant-based/ animal-base protein intake and cardiovascular disease
Zhubi-Bakija F, Bajraktari G, Bytyçi I, et al. The impact of type of dietary protein, animal versus vegetable, in modifying cardiometabolic risk factors: A position paper from the International Lipid Expert Panel (ILEP). *Clinical nutrition (Edinburgh, Scotland)*. 2021;40(1):255-276. doi:10.1016/j.clnu.2020.05.017	Position paper

Number of Primary Articles: 48 articles

Number of Review Articles: 5 articles

Total Number of Articles: 53 articles

Hierarchy and Classification of Studies			
Primary Reports		Secondary Reports	
A	Randomized controlled trial (RCT)	M	Meta-analysis or Systematic review Decision analysis Cost-benefit analysis Cost-effectiveness study
B	Cohort study		

C	Nonrandomized trial with concurrent or historical controls Case-control study Study of sensitivity and specificity of a diagnostic test Time series	R	Narrative review (Review article) Consensus statement Consensus report
D	Cross-sectional study Trend Study Case series Case report Before and after study	X	Medical opinion

EVIDENCE ANALYSIS WORKSHEET

This article was obtained from ProQuest Health and Medical and Complete database out of 21 research results. The authors of the article "Dietary acid load and risk of cardiovascular disease: a prospective population-based study" are Parvin Mirmiran, Zeinab Houshialsadat, Zahra Bahadoran, Sajjad Khalili-Moghadam, Mohammad Karim Shahrzad and Fereidoun Azizi. All authors are contributing members to the Nutrition and Endocrine Research Center in Tehran, Iran. Tehran, Iran is the place in which the authors work and live making this study one that evaluates their direct market of patients and individuals around them. It was also an adult study that was specific to that demographic based on the relevance of CVD in older individuals. Living in an Asian country specifically Iran often puts limitations on the food sources consumed. The evaluation of the Western diet and the CVD related events as related to potential renal acid load and net endogenous acid production is of interest to these authors because it has a direct correlation to society today. Protein sources are significant to this case based upon their acid contributing factors.

Evidence Worksheet for Primary RESEARCH Article

Citation: *write in AMA format as found in JAND.*	Aziz F, Bahadoran Z, Houshialsadat Z, Khalili-Moghadam S, Mirmiran P, and Shahrzad M K. Dietary acid load and risk of cardiovascular disease: a prospective population-based study. *BMC Cardiovascular Disorders.* 2021:21:432. https://doi.org/10.1186/s12872-021-02243-8.
Study design: *Use algorithm – RCT, cohort, etc*	Prospective cohort
Study class: (A, B, C, D)	B

Research Quality Rating *This rating tells if the research design is good (+), bad (-), or neutral (Ø)* *This is determined by the quality criteria list. Delete the ratings that do not apply (i.e. if positive, delete minus/negative and neutral).*	**PLUS/POSITIVE (+)** *If most of the answers to the above validity questions are "Yes" including criteria 2, 3, 6, and 7 and at least one additional "yes," (the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*
Purpose/Population Studied/Practice Studied	
Research Purpose: *What is the research questing being investigated in the study?*	The inconsistencies in the cardiovascular effects of dietary acid load and the impact of dietary acidity on the acid-base homeostasis within the body.
Inclusion criteria: *requirements for study eligibility*	**70<x<19 years old, 4200<x<800 kcal/day, no history of CVD**
Exclusion criteria (conditions that make individual ineligible)	**Aged out of predefined limit (70<x<19 years old) and had misreported energy intake (4200<x<800 kcal/day) and CVD history at baseline (myocardial infarction, stroke, angina, coronary revascularization). Participants also excluded if they left the study within the follow-up period.**
Recruitment	This study was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS), a population-based study that aims to investigate noncommunicable diseases (NCDs) within a representative sample of Iranians from district 13 of Tehran. The TLGS was initiated in 1999 and includes repeated measurements at 3-year intervals. In total, 3678 men and women (aged ≥ 19) with complete demographic, anthropometric, biochemical, and dietary data, who have participated in the third TLGS examination (2006–2008), were recruited.
Blinding used: *some of the person involved are prevented from knowing certain information that might lead to conscious or unconscious bias on their part, invalidating the results*	a lab test was used to measure an outcome

Description of study protocol *What happened in the study?*	• **The study protocol was complied with the 1975 Ethical Guidelines of the Helsinki Declaration and was approved by the Ethics Research Council of the Research Institute for Endocrine Science, Shahid Beheshti University of Medical Sciences.** • **Trained interviewers collected demographic information using pretested and standardized questionaries.** • **Weight was record to the nearest 100g, height was also measured to the nearest 0.5cm, standing.** • **Body Mass index was calculated by the division of weight in kg by the square of height in m.** • **Waist circumference measurement was taken to the nearest 0.1 cm, midway between the lower border of the ribs and the iliac crest.** • **Systolic and diastolic blood pressures were measured twice on the right arm. The frequency and duration of physical activity was assessed by a Modifiable Activity Questionnaire.** • **Baseline and follow-up blood samples were taken from all participants following a 12-14h fasting.** • **Triglyceride level was assayed by enzymatic colorimetric method with glycerol phosphate oxidase.** • **Fasting serum glucose was determined using enzymatic colorimetric analysis and glucose oxidase.** • **High-density lipoprotein cholesterol measurement was obtained after precipitation of the apolipoprotein-B-containing lipoprotein with phosphotungstic acid.** • **Demographic, dietary, anthropometric, and biochemical data were obtained from all participants at baseline.** • **Trained interviewers used a 168-item semi-quantitative Food Frequency Questionnaire at the first examination to assess participants' dietary intake over the past year.** • **The reliability, comparative validity and, stability of the questionnaire was previously evaluated in a random sample and proven to be reasonable.** • **The participant's consumption frequency of each food item was recorded on a daily, weekly, or monthly basis, and the household-measured portion sizes were converted to grams.** • **Dietary acid-base loaf was assessed by two indexes of PRAL and NEAP.** • **Participant's consumption frequency of each food item was recorded on a daily, weekly, or monthly basis and the household-measured portion sizes were converted to grams** • **The energy and nutrient content analysis of raw food and beverages was based on the USDA food composition table**
Intervention: *Describe interventions, regimens, risk factors, or procedures studied.*	**None**

Statistical analysis: *List tests, significance level set a priori (a=0.05); include intent to treat analysis if applicable; note if there is Power analysis.*	• **P-values less than or equal to 0.05 were statistically significant** • **Mean (SD) values of the baseline characteristics of participants without CVD were compared by independent t-test** • **Chi-square test to compare frequencies between two groups** • **Dietary intake of participants was compared across tertials of PRAL and NEAP using analysis of variance test.** • **Univariate analysis was conducted for each potential cofounder, and variables with PE < 0.2 were included in the multivariable model** • **Total dietary energy** • **Total dietary fat** • **Cox proportional hazards regression models were used to evaluate the hazard ratios and the 95% confidence intervals of dietary acid load and CVD events** • **Model 1 was adjusted for sex, age, and smoking status** • **Model 2 was further adjusted for energy intake (kcal/d) and total fat intake (g/d)** • **The median value of each dietary tertial was used to assess the overall HR trends in the Cox proportional hazard regression model**
Timing of measurements: *when outcomes were measured; usually baseline and one or more later times*	• **Person-year was considered as the underlying time metric** • **Time to event was defined as the time to the onset of an event, or time to the end of the follow-up**
Dependent variables: *outcomes that are measured or registered; variable who change or different states the researcher wants to understand, explain, or predict*	Occurrence of CVD related events
Independent variable (intervention or procedure; this variable can be manipulated; a variable whose effect upon the dependent variable one is trying to understand)	The PRAL and NEAP
Control Variables *Examples: 1) multivariate logistic regression controlled for age, BMI, albumin; 2) usual care; 3) isocaloric diet, etc.*	None
Initial n (e.g. 731 (298 males, 433 females))	12,523

<table>
<tr><td>Record number that entered study - not the number screened.</td><td></td></tr>
<tr><td>Final n (attrition)
Number of subjects that completed study</td><td>2,369</td></tr>
<tr><td>Age usually mean or range</td><td>38.4 ± 12.7</td></tr>
<tr><td>Ethnicity (if given)</td><td>Asian</td></tr>
<tr><td>Other relevant demographics: demographics describe the population (students, athletes, etc)</td><td>Men and Women</td></tr>
<tr><td>Anthropometrics: e.g. were groups same or different on important physical measures (BMI, fitness level)</td><td>• Body mass index (26.6 ± 4.8)</td></tr>
<tr><td>Location: Where did the study take place? City or country</td><td>Tehran, Iran</td></tr>
<tr><td>Summary of Results: Abstract results including quantitative data and statistics. Include statistical significance: P-values, confidence intervals (CI), relative risk (RR), odds ratios (OR), likelihood ratio, number needed to treat, power analysis if available).</td><td>Use a table to summarize when possible. Change number of columns and rows as needed on sample table. Fill in the variables and groups, DO NOT cut or copy directly from the text
<table>
<tr><th>Dependent Variable</th><th>Group 1 (n=xx)</th><th>Group 2 (n=xx)</th><th>P-Value</th></tr>
<tr><td>PRAL (mEq/day)</td><td></td><td></td><td></td></tr>
<tr><td>Model 1</td><td>0.73</td><td>0.79</td><td>0.346</td></tr>
<tr><td>Model 2</td><td>0.75</td><td>0.80</td><td>0.367</td></tr>
<tr><td>NEAP (mEq/day)</td><td></td><td></td><td></td></tr>
<tr><td>Model 1</td><td>0.72</td><td>0.76</td><td>0.986</td></tr>
<tr><td>Model 2</td><td>0.73</td><td>0.76</td><td>0.988</td></tr>
</table>
Other Findings:

Report on all the dependent variables you listed in the section above.</td></tr>
<tr><td colspan="2">Author's Conclusions</td></tr>
<tr><td>Author conclusion: paraphrase that stated by study author in body of the report or abstract</td><td>The results did not show significant associations between dietary acid load and the risk of CVD. Larger-scale and longer follow-up durations are needed to assess the risk of CVD and dietary acid load considering CVD prevalence, high treatment costs and burden. Lower NEAP score was related to lower consumption of animal meat, cheese, grains and rice, and higher intake of dietary fiber, calcium, potassium, magnesium, potato, and fruit and vegetables. The risk of CVD events was reduced significantly in the NEAP crude model (HRs=0.50; CI 0.32-0.96; P trend = 0.032).</td></tr>
</table>

Reviewer comments: *Note strengths and limitations of study; identify concerns that affect study validity and generalizability – your comment should be italicized*	*You do not have to write anything here, but if you do, remember to italicize.* *IF YOU RATE A PAPER AS NEUTRAL OR MINUS/NEGATIVE, YOU SHOULD PROVIDE AN EXPLANATION OF WHY (LIMITATIONS OF STUDY).*

RELEVANCE QUESTIONS					
Citation: *write it in AMA format as found in JADA (copy and paste from page 1 of worksheet)* Aziz F, Bahadoran Z, Houshialsadat Z, Khalili-Moghadam S, Mirmiran P, and Shahrzad M K. Dietary acid load and risk of cardiovascular disease: a prospective population-based study. *BMC Cardiovascular Disorders.* 2021:21:432. https://doi.org/10.1186/s12872-021-02243-8.	?	YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/ population group? (Not Applicable for some epidemiological studies)	1				X
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
1. **Was the <u>research question</u> clearly stated?** *This is usually stated at the introduction and just before methods section.*	?	YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified? *This is often called the treatment and explained in the methods section.*	1.1			X	
1.2 Was the outcome(s) dependent variables (s)) clearly indicated? *These are sometimes called the endpoints; the results section reports the outcomes, but this information should be in the methods section, too.*	1.2	X			

	1.3 Were the target population and setting specified? *The target population is group for whom findings may be applicable; look for this in the introduction and in the methods section*	1.3	X			
2.	**Was the <u>selection</u> of study subject/patients free from bias?**	?	YES	NO	UNCLEAR	NA
	2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? *The authors should give several points about the inclusion/exclusion criteria such as the age range of the subjects, disease condition (like hyperlipidemia) required for inclusion. Exclusion criteria should be listed, too, although some are understood. For example if the ages for inclusion are 18 to 70, the authors will probably not specifically note that children and people over age 70 were excluded. Most of the time, however, subjects may be excluded for certain characteristics such as being pregnant or having some disease (like CHD).*	2.1	X			
	2.2 Were the criteria applied equally to all study groups?	2.2	X			
	2.3 Were health, demographics, and other characteristics of subjects described? *There is usually a Table 1summring demographics and characteristics at baseline. Groups are not different if the P-Value is > 0.05. If there has been a previous paper describing the study population, that paper may be referenced and you would need to go back to the original publication to see that Table 1.*	2.3	X			
	2.4 Were the subjects/patients in a representative sample of the relevant population? *The abstractor may have to apply a bit of clinical judgment here. Authors try to be brief and may only sat that the patients come from the same clinic from people who met the inclusion criteria.*	2.4	X			
3.	**Were <u>study groups comparable?</u>** *There is usually a Table 1 summarizing demographics and characteristics at baseline. Groups are <u>not</u> different if the P-Value is > 0.05.*	?	YES	NO	UNCLEAR	NA

3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) *In a strong study, the authors may tell how the subjects were assigned to a group (e.g. randomized block design; or assigned by computer-generated random numbers)/ Look for instances that show bias; for example I once read a study where patients were randomized to receive liquid energy supplements; however, if someone disliked their supplement, they were allowed to change groups – this is not unbiased!*	3.1				X
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? *See Table 1 for this – there should be no significant differences across study groups in an intervention study.*	3.2	X			
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.) *Most RCTs use a concurrent control group. Occasionally an intervention study will use a prior study as a control group; that is an example of a historical control. That is not as strong a research design as use of concurrent control group. A crossover study where the subject acts as her/her own control is use of concurrent control.*	3.3				X
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? *The groups in cohort or cross-sectional study should not be different from each other; if they are, a strong study will utilize statistical techniques such as multivariate analyses to remove the variance due to the group differences. Look for this information in the statistics and results sections.*	3.4	X			
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies. *Subjects are generally matched for age, gender, etc. Look for this in the statistical description and results sections.*	3.5				X

	3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold Standard")? *Example: comparing body fat analysis method with underwater weighing (gold standard). In studies trying to determine the best equation (like Mifflin – St. Jero or Harris-Benedict) to predict energy needs, a gold standard measure of REE (Indirect Calorimetry) is used.*	3.6				X
4.	**Was method handling <u>withdrawals</u> described?**	?	YES	NO	UNCLEAR	NA
	4.1 Were follow up method described and the same for all groups?	4.1	X			
	4.2 Was the number characteristics of withdrawal (I.e. dropouts, lost to follow up attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.) *This should be found in the results section. If there is attrition > 20%, it is important to note that on the worksheet (as a note in the results section or in the reviewer comments at the very bottom)*	4.2	X			
	4.3 Were all enrolled subjects/patients (in the original sample) accounted for? *This information is often presented in a figure with # recruited, # enrolled (this is the initial N), # remaining at the end of study period (final N). Sometimes the reason that subjects withdrew or were dropped is given in the figure or in the text (results section).*	4.3	X			
	4.4 Were reasons for withdrawals similar across groups? *If there is a large attrition from one group and not others, you would want to look for a reason why; the answer to this question would then be no.*	4.4	X			
	4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study? The test under study should be compared to reference test all the time. An example of this might be using a DEXA machine to measure percent body fat only if a subject's BMI was > 35 but bioimedance analyzer indicated body fat < 30%.	4.5		X		
5.	**Was <u>blinding</u> used to prevent introduction of bias?**	?	YES	NO	UNCLEAR	NA

5.1 In intervention study, were subjects, clinicians/practitioners and investigators blinded to treatment group, **<u>as appropriate</u>**? *The key term is as appropriate. For example, in the Lim et al 2008 study, the investigators studies the effect of MNT on lipid levels in hypercholesterolemia patients. It was an RCT, but obviously, the subjects and practitioners knew who was getting MNT and who was not. Therefore, you would not answer question 5.1 NO. It was appropriate for the dietitians and patients to know they were receiving MNT.*	5.1				X
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) *Answer yes, if a lab test was used to measure an outcome. A method of blinding a diet study is to have separate people analyzing the data (not the same ones who were collecting the data).*	5.2			X	
5.3 in cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? *Answer yes, if a lab test was used to measure an outcome. A method of blinding a diet study is to have separate people analyzing the data (not the same ones who were collecting the data).*	5.3	X			
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status? *Establish who is a case and who is a control at the beginning of the study.*	5.4				X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5				X
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	?	YES	NO	UNCLEAR	NA
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	X			
6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	X			
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? *Use clinical judgment (e.g. 12 weeks is long enough for a dietary intervention to make a difference in lab values for cholesterol; however, 12 days would not be long enough)*	6.3			X	

6.4 was the amount of exposure and, if relevant, subject/patient compliance measured? *How long did the treatment last? Did the patient follow directions?*	6.4		X		
6.5 Were co-interventions (e.g., ancillary treatments other therapies) described? *(e.g. were patients on lipid-lowering meds at the same time as the diet therapy)*	6.5		X		
6.6 Were extra or unplanned treatments described? *The text may not describe any unplanned treatments. If yes, it would likely be in the discussion section. It is likely there were no unplanned treatments, so a "no" answer is not a problem overall.*	6.6		X		
6.7 Was the information for 6.4, 6.5, 6.6, and 6.7 assessed the same way for all groups? *For a study to be valid and unbiased, it is important that this be yes.*	6.7	X			
6.8 In diagnostic study, were details of test administration and replication sufficient? *Usually answer n/a for diet study.*	6.8				X
7. Were <u>outcomes</u> clearly defined and the measurement valid and reliable?	?	YES	NO	UNCLEAR	NA
7.1 Were primary and secondary endpoints described and relevant to the question? *Primary endpoint – main result measured at the end of a study to see if the treatment worked. The primary endpoint is decided at the beginning of the study.* *Secondary endpoint – not as important as the main results not usually analyzed if the primary endpoint is not statistically significant.*	7.1	X			
7.2 Were nutrition measured appropriate to question and outcomes of concern? *Clinical judgment required: weight loss, changes in energy intake are relevant to MNT; Sometimes there are not nutrition measures and you should answer N/A.*	7.2	X			
7.3 Was the period of follow-up long enough for important outcome(s) to occur? *Clinical judgment required; was there enough time?*	7.3	X			
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? *Check that surveys were validated.*	7.4	X			

7.5 Was the measurement of effect an appropriate level of precision? *Precision is reproducibility or repeatability.*	7.5	X			
7.6 Were other factors accounted for (measured) that could affect outcomes? *Other factors are sometimes covered in the discussion of the strengths/limitations of the study.*	7.6			X	
7.7 Were the measurements conducted consistently across groups?	7.7	X			
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	?	YES	NO	UNCLEAR	NA
8.1 Were statistical analyses adequately described and the results reported appropriately? *There should be a discussion of the statistics in the methods section.*	8.1	X			
8.2 Were correct statistical test used and assumptions of test not violated? *You will get better at this the more papers you abstract. EAL abstractors are expected to have some statistical and research training (minimum of master's degree).*	8.2	X			
8.3 Were statistics reported with levels of significance and/or confidence intervals? *(P-value) and/or confidence intervals (mean ± CI)*	8.3	X			
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? Intent to treat – analysis is based on the original treatment intent, not the treatment ultimately administered (i.e. does not matter if treatment was for 2, 6, 8 or all the weeks in the study). The analyses are done using all the subjects in the study, not just the ones who completed it. This is done in order to avoid effects of dropout that can be a threat to randomization. *Intent-to-treat analysis of outcomes applies to any intervention study.* If the intent to treat analysis was done, it would be mentioned in the statistical section. If all subjects who began the trial completed it, intent-to-treat analysis was done.	8.4		X		
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)? *Multivariate analyses are used to adjust or control for other variables (age, sex, smoking, etc.). Assumes data is valid and reduces a larger number of*	8.5	X			

variables to a smaller number. Just answer yes or not that multivariate analyses were used.					
8.6 Was clinical significance as well as statistical significance reported? *Example: Lim, et al 2008 reported that after 12 weeks of MNT, total cholesterol was reduced from 229.2±158 to 181.3±16.3 (P<0.001); This includes; statistical significance (P-value) and clinical significance (compare to standard of < 200 mg/do for normal cholesterol). A problem can occur when only statistical significance is reported. Reducing cholesterol from 300 to 250 might be statistically significant, but clinically is still abnormal.*	8.6	X			
8.7 If negative findings, was a power calculation reported to address type 2 error? *Type II (B error is a false negative that happens when the investigators fail to reject the null hypothesis when the null hypothesis is false. Look for the authors to say something like "a sample size of n=xx is needs to provide 80% power."*	8.7		X		
9. Are <u>conclusions</u> supported by results with biases and limitation taken into consideration?	?	YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings? *Answer yes or no.*	9.1	X			
9.2 Are biases and study limitations identified and discussed? *There will be in the discussion of finding section that follows the results.*	9.2	X			
10. Is bias due to study's <u>funding or sponsorship unlikely?</u> *Be careful here – if <u>bias</u> is <u>unlikely</u>, answer YES*	?	YES	NO	UNCLEAR	NA
10.1 Where sources of funding and investigators' affiliations described? • *Look just under the abstract, or* • *The funding may be acknowledged at the end of the paper* • *Just because the work was funded by industry does not mean the study was biased*	10.1	X			

10.2 Was there no apparent conflict of interest? *If an investigator is testing a piece of equipment, progress or drug that he/she developed, it could be a conflict of interest.*	10.2	X			

SYMBOL
MINUS/NEGATIVE (-) *If most (six or more) of the answer to the above validity questions are "no" the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.*
NEUTRAL (Ø) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (Ø) symbol on the Evidence Quality Worksheet.*
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" including criteria 2, 3, 6, and 7 and at least one additional "yes", (the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*

EVIDENCE ANALYSIS (Quality Criteria) SUMMARY TABLE

RELEVANCE QUESTIONS			
		Sarah	Emily
Citation: *write it in AMA format as found in JADA (copy and paste from page 1 of worksheet)*	?		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/ population group? (Not Applicable for some epidemiological studies)	1	N/A	NA
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes	YES
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes	YES
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	N/A	YES
If the answers to all of the above relevance questions are "yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.			
VALIDITY QUESTIONS			

1. **Was the <u>research question</u> clearly stated? This is usually stated at the introduction and just before methods section.**	?		YES
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified? *This is often called the treatment and explained in the methods section.*	1.1	Yes	UNCLEAR
1.2 Was the outcome(s) dependent variables (s)) clearly indicated? *These are sometimes called the endpoints; the results section reports the outcomes, but this information should be in the methods section, too.*	1.2	Yes	YES
1.3 Were the target population and setting specified? *The target population is group for whom findings may be applicable; look for this in the introduction and in the methods section*	1.3	Yes	YES
2. **Was the <u>selection</u> of study subject/patients free from bias?**	?		YES
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? *The authors should give several points about the inclusion/exclusion criteria such as the age range of the subjects, disease condition (like hyperlipidemia) required for inclusion. Exclusion criteria should be listed, too, although some are understood. For example if the ages for inclusion are 18 to 70, the authors will probably not specifically note that children and people over age 70 were excluded. Most of the time, however, subjects may be excluded for certain characteristics such as being pregnant or having some disease (like CHD).*	2.1	Yes	YES
2.2 Were the criteria applied equally to all study groups?	2.2	Yes	YES
2.3 Were health, demographics, and other characteristics of subjects described? *There is usually a Table 1summring demographics and characteristics at baseline. Groups are not different if the P-*	2.3	Yes	YES

Value is > 0.05. If there has been a previous paper describing the study population, that paper may be referenced and you would need to go back to the original publication to see that Table 1.			
2.4 Were the subjects/patients in a representative sample of the relevant population? *The abstractor may have to apply a bit of clinical judgment here. Authors try to be brief and may only sat that the patients come from the same clinic from people who met the inclusion criteria.*	2.4	Yes	YES
3. **Were <u>study groups comparable?</u>** *There is usually a Table 1 summarizing demographics and characteristics at baseline. Groups are <u>not</u> different if the P-Value is > 0.05.*	?		YES
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) *In a strong study, the authors may tell how the subjects were assigned to a group (e.g. randomized block design; or assigned by computer-generated random numbers)/ Look for instances that show bias; for example I once read a study where patients were randomized to receive liquid energy supplements; however, if someone disliked their supplement, they were allowed to change groups – this is not unbiased!*	3.1	N/A	NA
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? *See Table 1 for this – there should be no significant differences across study groups in an intervention study.*	3.2	N/A	YES
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.) *Most RCTs use a concurrent control group. Occasionally an intervention study will use a prior study as a control group; that is an example of a historical control. That is not as strong a research design as use of concurrent control group. A crossover study where the subject acts as her/her own control is use of concurrent control.*	3.3	N/A	NA

3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? *The groups in cohort or cross-sectional study should not be different from each other; if they are, a strong study will utilize statistical techniques such as multivariate analyses to remove the variance due to the group differences. Look for this information in the statistics and results sections.*	3.4	Unclear	YES
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies. *Subjects are generally matched for age, gender, etc. Look for this in the statistical description and results sections.*	3.5	N/A	NA
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold Standard")? *Example: comparing body fat analysis method with underwater weighing (gold standard). In studies trying to determine the best equation (like Mifflin – St. Jero or Harris-Benedict) to predict energy needs, a gold standard measure of REE (Indirect Calorimetry) is used.*	3.6	N/A	NA
4. **Was method handling <u>withdrawals</u> described?**	?		NO
4.1 Were follow up method described and the same for all groups?	4.1	N/A	YES
4.2 Was the number characteristics of withdrawal (I.e. dropouts, lost to follow up attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.) *This should be found in the results section. If there is attrition > 20%, it is important to note that on the worksheet (as a note in the results section or in the reviewer comments at the very bottom)*	4.2	No	YES
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	N/A	YES

This information is often presented in a figure with # recruited, # enrolled (this is the initial N), # remaining at the end of study period (final N). Sometimes the reason that subjects withdrew or were dropped is given in the figure or in the text (results section).			
4.4 Were reasons for withdrawals similar across groups? *If there is a large attrition from one group and not others, you would want to look for a reason why; the answer to this question would then be no.*	4.4	N/A	YES
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study? The test under study should be compared to reference test all the time. An example of this might be using a DEXA machine to measure percent body fat only if a subject's BMI was > 35 but bioimedance analyzer indicated body fat < 30%.	4.5	N/A	NO
5. Was <u>blinding</u> used to prevent introduction of bias?	?		NO
5.1 In intervention study, were subjects, clinicians/practitioners and investigators blinded to treatment group, **<u>as appropriate</u>**? *The key term is as appropriate. For example, in the Lim et al 2008 study, the investigators studies the effect of MNT on lipid levels in hypercholesterolemia patients. It was an RCT, but obviously, the subjects and practitioners knew who was getting MNT and who was not. Therefore, you would not answer question 5.1 NO. It was appropriate for the dietitians and patients to know they were receiving MNT.*	5.1	N/A	NA
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) *Answer yes, if a lab test was used to measure an outcome. A method of blinding a diet study is to have separate people analyzing the data (not the same ones who were collecting the data).*	5.2	N/A	UNCLEAR
5.3 in cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? *Answer yes, if a lab test was used to measure an outcome. A method of blinding a diet study is to have separate people*	5.3	N/A	YES

analyzing the data (not the same ones who were collecting the data).			
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status? *Establish who is a case and who is a control at the beginning of the study.*	5.4	N/A	NA
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A	NA
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	?		YES
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A	YES
6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	Yes	YES
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? *Use clinical judgment (e.g. 12 weeks is long enough for a dietary intervention to make a difference in lab values for cholesterol; however, 12 days would not be long enough)*	6.3	No	UNCLEAR
6.4 was the amount of exposure and, if relevant, subject/patient compliance measured? *How long did the treatment last? Did the patient follow directions?*	6.4	N/A	NO
6.5 Were co-interventions (e.g., ancillary treatments other therapies) described? *(e.g. were patients on lipid-lowering meds at the same time as the diet therapy)*	6.5	No	NO
6.6 Were extra or unplanned treatments described? *The text may not describe any unplanned treatments. If yes, it would likely be in the discussion section. It is likely there were no unplanned treatments, so a "no" answer is not a problem overall.*	6.6	No	NO
6.7 Was the information for 6.4, 6.5, 6.6, and 6.7 assessed the same way for all groups?	6.7	Unclear	YES

For a study to be valid and unbiased, it is important that this be yes.			
6.8 In diagnostic study, were details of test administration and replication sufficient? *Usually answer n/a for diet study.*	6.8	N/A	NA
7. Were <u>outcomes</u> clearly defined and the measurement valid and reliable?	?		YES
7.1 Were primary and secondary endpoints described and relevant to the question? *Primary endpoint – main result measured at the end of a study to see if the treatment worked. The primary endpoint is decided at the beginning of the study.* *Secondary endpoint – not as important as the main results not usually analyzed if the primary endpoint is not statistically significant.*	7.1	Yes	YES
7.2 Were nutrition measured appropriate to question and outcomes of concern? *Clinical judgment required: weight loss, changes in energy intake are relevant to MNT; Sometimes there are not nutrition measures and you should answer N/A.*	7.2	Yes	YES
7.3 Was the period of follow-up long enough for important outcome(s) to occur? *Clinical judgment required; was there enough time?*	7.3	Yes	YES
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? *Check that surveys were validated.*	7.4	Yes	YES
7.5 Was the measurement of effect an appropriate level of precision? Precision is reproducibility or repeatability.	7.5	N/A	YES
7.6 Were other factors accounted for (measured) that could affect outcomes? Other factors are sometimes covered in the discussion of the strengths/limitations of the study.	7.6	Yes	UNCLEAR

7.7 Were the measurements conducted consistently across groups?	7.7	Unclear	YES
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	?		YES
8.1 Were statistical analyses adequately described and the results reported appropriately? There should be a discussion of the statistics in the methods section.	8.1	Yes	YES
8.2 Were correct statistical test used and assumptions of test not violated? You will get better at this the more papers you abstract. EAL abstractors are expected to have some statistical and research training (minimum of master's degree).	8.2	Yes	YES
8.3 Were statistics reported with levels of significance and/or confidence intervals? (P-value) and/or confidence intervals (mean *± CI)*	8.3	Yes	YES
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? Intent to treat – analysis is based on the original treatment intent, not the treatment ultimately administered (i.e. does not matter if treatment was for 2, 6, 8 or all the weeks in the study). The analyses are done using all the subjects in the study, not just the ones who completed it. This is done in order to avoid effects of dropout that can be a threat to randomization. *Intent-to-treat analysis of outcomes applies to any intervention study.* If the intent to treat analysis was done, it would be mentioned in the statistical section. If all subjects who began the trial completed it, intent-to-treat analysis was done.	8.4	N/A	NO
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)? Multivariate analyses are used to adjust or control for other variables (age, sex, smoking, etc.). Assumes data is valid and reduces a larger number of variables to a smaller number. Just answer yes or not that multivariate analyses were used.	8.5	Yes	YES
8.6 Was clinical significance as well as statistical significance reported?	8.6	No	YES

Example: Lim, et al 2008 reported that after 12 weeks of MNT, total cholesterol was reduced from 229.2*±158 to 181.3±16.3 (P<0.001); This includes; statistical significance (P-value) and clinical significance (compare to standard of < 200 mg/do for normal cholesterol). A problem can occur when only statistical significance is reported. Reducing cholesterol from 300 to 250 might be statistically significant, but clinically is still abnormal.*			
8.7 If negative findings, was a power calculation reported to address type 2 error? Type II (B error is a false negative that happens when the investigators fail to reject the null hypothesis when the null hypothesis is false. Look for the authors to say something like "a sample size of n=xx is needs to provide 80% power."	8.7	Unclear	NO
9. Are <u>conclusions</u> supported by results with biases and limitation taken into consideration?	?		YES
9.1 Is there a discussion of findings? Answer yes or no.	9.1	Yes	YES
9.2 Are biases and study limitations identified and discussed? There will be in the discussion of finding section that follows the results.	9.2	Yes	YES
10. Is bias due to study's <u>funding or sponsorship unlikely?</u> *Be careful here – if <u>bias</u> is <u>unlikely</u>, answer YES*	?		YES
10.1 Where sources of funding and investigators' affiliations described? · *Look just under the abstract, or* · *The funding may be acknowledged at the end of the paper* · *Just because the work was funded by industry does not mean the study was biased*	10.1	Yes	YES
10.2 Was there no apparent conflict of interest?	10.2	Yes	YES

If an investigator is testing a piece of equipment, progress, or drug that he/she developed, it could be a conflict of interest.			

SYMBOL
MINUS/NEGATIVE (-) **If most (six or more) of the answer to the above validity questions are "no" the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.**
NEUTRAL (Ø) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (Ø) symbol on the Evidence Quality Worksheet.*
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" including criteria 2, 3, 6, and 7 and at least one additional "yes", (the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*

RELEVANCE QUESTIONS.	**Sebastian**	**Megan**
1. Will the answer if true, have a direct bearing on the health of patients?	Yes	yes
2. Is the outcome or topic something that patients/clients/population groups would care about?	Yes	yes
3. Is the problem addressed in the review one that is relevant to dietetics practice?	Yes	yes
4. Will the information, if true, require a change in practice?	No	no
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
VALIDITY QUESTIONS		
1. Was the question for the review clearly focused and appropriate?	yes	yes
2. Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described?	yes	yes

3. Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	no	yes
4. Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	yes	yes
5. Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	yes	no
6. Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	yes	yes
7. Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	no	yes
8. Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	no	yes
9. Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	yes	yes
10. Was bias due to the review's funding or sponsorship unlikely?	no	yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the review should be designated with a minus (-) symbol on the Evidence Quality Worksheet.*		
NEUTRAL (Æ) *If the answer to any of the first four validity questions (1-4) is "No," but other criteria indicate strengths, the review should be designated with a neutral* (Æ) *symbol on the Evidence Worksheet.*		

PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (must include criteria 1, 2, 3, and 4), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*	

OVERVIEW TABLE

Author, Year, Study Design, Class Rating	Study Purpose	Key Demographics of Study Population	Intervention	Outcomes	Author's Conclusions	Reviewer's Comments
Aziz F, Bahadoran Z, Houshialsadat Z, Khalili-Moghadam S, Mirmiran P, and Shahrzad M K., 2021, Prospective Cohort, B.	The purpose of this study was to examine inconsistencies in the cardiovascular effects of dietary acid load. Along with the impact of dietary acidity on the acid-base homeostasis within the body. Which can lead to the occurrence of CVD or CVD related events.	Asian ethnicities, specifically from Tehran, Iran. Age 38.4 ± 12.7 including males and females.	The intervention consisted of follow up interview by trained professionals.	BMI of participant was 26.6 ± 4.8 kg/m2 at baseline. 79 participants experience CVD events and angiographic proven CVD, definite MI, unstable angina, and stoke were the common outcomes related to CVD. Participants with CVD events were older. Diabetes and	Aziz et al. 2021 concluded that the results did not show significant associations between dietary acid load and the risk of CVD. Larger-scale and longer follow-up durations are needed to assess the risk of CVD and dietary acid load considering CVD prevalence, high treatment	Based on the research a lower NEAL and PRAL score were beneficial in the prevention of CVD related events. The lower the NEAL and PRAL levels the less acid is produced in the body reducing the strain put on the heart. Animal protein sources create and acidic environment while plant proteins produce and alkaline

				hypertension were most prevalent among incident cases compared to the entire cohort. A higher percentage of those with CVD related events were smokers. Patients in the lowest tertials of dietary intake had a potential renal acid load (PRAL) had higher intakes of total dietary fiber, calcium, potassium, magnesium, potato, fruits, and vegetables, and lower consumption of animal meat, cheese, grains and rice. Similarly, lower net	costs and burden. Lower NEAP score was related to lower consumption of animal meat, cheese, grains and rice, and higher intake of dietary fiber, calcium, potassium, magnesium, potato, and fruit and vegetables. The risk of CVD events was reduced significantly in the NEAP crude model (HRs=0.50; CI 0.32-0.96; *P trend = 0.032).*	environment that works to neutralize the acidity and reduce the risk of CVD related events. The study should have excluded factors such as smoking and follow up interviews should have taken place over a longer period of time.

				endogenous acid production (NEAP) score was related to lower consumption of animal meat, cheese, grains and rice and higher intake of dietary fiber, calcium, potassium, magnesium, potato, and fruits and vegetables.		
Sikand, Geeta and Severson, Tracy, 2020, systematic review, M.	Implementation of current nutrition recommendations from the American Heart Association (AHA), American College of Cardiology (ACC) and the National Lipid Association (NLA) can markedly benefit the primary and secondary prevention of atherosclerotic	Not available because the authors responded to each strategy based on different studies, which we do not have information on how they were collected. However, one of the strategies "6) implement ACC/AHA/NLA nutrition and lifestyle recommendat	N/A	Vegetarians and vegans, compared to omnivores, have lower BMI, LDL-C, glucose, hsCRP and TMAO levels, along with a lower incidence of mortality (CVD and overall).	Adults should eat a heart-healthy diet which emphasizes plant-based foods such as vegetables, fruits, legumes, nuts, whole grains, and lean protein foods and fish. Limit foods high in	The authors established that all the strategies implemented generate a significant benefit in patients. Although some nutraceuticals have been shown to significantly improve the efficacy of standard pharmacological treatments, more

	c cardiovascular disease.	ions for optimizing triglyceride levels" discusses the benefits of plant protein over animal protein, which is relevant to the solution of our PICO question.		"flexitarian" diets, primarily plant-based diets with limited intake of animal products also confer cardiovascular benefits.	saturated fats and dietary cholesterol and reduce sodium (salt). Avoid trans-fat, processed meats, refined carbohydrates and sugar-sweetened foods and beverages.	research is needed as no outcome studies are available proving that nutraceuticals can prevent CVD morbidity or mortality.
Sina Naghshi, Omid Sadeghi, Walter C Willett, and Ahmad Esmaillzadeh, 2020, systematic review and meta-analysis, M	A systematic review and dose-response meta-analysis of prospective cohort studies to summarize the association between intake of dietary protein and risk of mortality from all causes, cardiovascular disease, and cancer.	Age range between 19 and 101 years, men, and women, and 18 different countries	N/A	The association between consumption of animal protein and cardiovascular disease mortality was examined in eight papers, which included 290 542 participants and 13 667 deaths. No significant association was found (pooled effect size comparing the highest	Naghshi et al. 2020 concluded that having a high intake of total proteins is associated with a lower risk of mortality from all causes. When looking at the intake of plant protein compared to animal protein, the intake of plant protein was associated with a lower risk	*The problem is they are observational studies. And that could contribute some problems.*

				and lowest intakes was 1.02, 95% confidence interval 0.94 to 1.11, P=0.56), with no significant heterogeneity among the studies (I^2=31.7%, P=0.16; fig 3). For plant protein consumption, however, which was examined in 10 articles with a total of 425 781 participants and 14 021 deaths, an inverse association was found with cardiovascular disease (pooled effect size comparing the highest and lowest intakes was 0.88, 0.80 to 0.96,	of all-cause mortality and death related to cardiovascular disease.	

				P=0.003; fig 3). No significant heterogeneity was found between studies (I^2=63.7%, P=0.001).		
Tharrey et al., 2018, Longitudinal Cohort Study, B	The purpose of this study is" to examine the associations between patterns of protein intake and cardiovascular mortality in the Adventist Health Study-2." Patterns of protein intake specifically looked at various types of plant and animal proteins.	Key demographics include members of the Seventh-day Adventist church ages 30 and older from the United States and Canada. Participants were primarily Caucasian and Black/African American. 96,387 participants completed the survey and 2,736 participants were included in this analysis	The intervention is the FFQs that were looked at to determine plant and animal protein consumption	"There were 2276 cardiovascular deaths during a mean follow-up time of 9.4 years. The HRs for cardiovascular mortality were 1.61 [98.75% confidence interval (CI), 1.12 2.32; *P*-trend < 0.001] for the 'Meat' protein factor and 0.60 (98.75% CI, 0.42 0.86; *P*-trend < 0.001) for the 'Nuts & Seeds' protein factor	"Associations between the 'Meat' and 'Nuts & Seeds' protein factors and cardiovascular outcomes were strong and could not be ascribed to other associated nutrients considered to be important for cardiovascular health"	This study is very strong in several areas such as its large sample size and the long period in between baseline measures and follow up. There are some weaknesses of the study. Because of the long period in between baseline and follow up, diets could have changed, and we only get the snapshot from the period of data collection. Additionally, the plant proteins

				(highest vs lowest quintile of factor scores). No significant associations were found for the 'Grains', 'Processed Foods' and 'Legumes, Fruits & Vegetables' protein factors."		were broken into subcategories, but meats were not. Would a lean cut of meat have a different impact compared with a less lean cut of meat. The author also notes the importance of phytochemicals as a potentially important confounding factor that was not taken into consideration. Being an epidemiological cohort study, there are limitations to the data and conclusions drawn from it, but it provides a framework and has potentially raised other important questions.

BRIEF SUMMARY STATEMENT

Aziz et al. 2021 established that the risk of cardiovascular disease events is reduced significantly in the net endogenous acid production (NEAP) crude model. A low NEAP score was related to lower consumption of animal meat, cheese, grains and rice, and higher intake of dietary fiber, calcium, potassium, magnesium, potato, and fruit and vegetable. Meaning the lower the dietary acid the less likely an individual is to develop a cardiovascular event.

Naghshi et al. 2020 concluded that having a high intake of total proteins is associated with a lower risk of mortality from all causes. When looking at the intake of plant protein compared to animal protein, the intake of plant protein was associated with a lower risk of all-cause mortality and death related to cardiovascular disease.

Sikand et al. 2020 determined that vegetarians typically have a higher intake of fiber, carbohydrate, potassium, magnesium, folate, n-6 fatty acids, non-heme iron and vitamin C than non-vegetarians. As a result, studies have shown that vegetarians and vegans, compared to omnivores, have lower BMI, LDL-C, glucose, hsCRP and TMAO levels, along with a lower incidence of mortality (CVD and overall).

Tharrey et al. 2018 found that "'Meat' and 'Nuts & Seeds' protein factors and cardiovascular outcomes were strong and could not be ascribed to other associated nutrients considered to be important for cardiovascular health". Those who consumed nuts and seeds had a significantly lower incidence of death than those who consumed animal meat.

CONCLUSION STATEMENT

Currently, there is evidence to answer the question posed at the beginning of the research. Based on our studies, we can conclude that there is a positive relationship between plant proteins and cardiovascular disease. An increased consumption of plant protein is related to a lower incidence of cardiovascular-related mortality.

GRADE FOR THE CONCLUSION STATEMENT

Grade II: Fair – the evidence consists of results from studies of strong design answering the question addressed, but there is uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the questions addressed, nut the results have been confirmed in separate studies and are consistent with minor exceptions at most.

EVALUATION

Upon completion of this assignment, my confidence has increased in my ability to perform the following activities:

Write and develop a nutrition-related research question in PICO format.

Classify, grade, and analyze research and research studies.

Complete an evidence analysis worksheet and project with a peer group.

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RESEARCH

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Dietary acid load and risk of cardiovascular disease: a prospective population-based study

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Abstract

Background and aim: Considering the inconsistencies in the cardiovascular effects of dietary acid load and the impact of dietary acidity on the acid–base homeostasis within the body, we aimed to assess the association of dietary acid load and the risk of cardiovascular disease (CVD) in a prospective community-based study.

Materials and methods: Participants (n = 2369) free of CVD at baseline (2006–2008) were included from the Tehran Lipid and Glucose Study (TLGS) and followed up for a mean of 6.7 ± 1.4 years. Dietary intakes of the participants were assessed using a semi-quantitative food frequency questionnaire (FFQ). The dietary acid load was evaluated by Potential Renal Acid Load (PRAL) and Net Endogenous Acid Production (NEAP) scores. Both scores have used the macronutrient and micronutrient data of the Food Frequency Questionnaires. Multivariate Cox proportional hazard regression models were used to estimate the 6-years incident risk of CVDs across tertiles of PRAL and NEAP scores.

Results: Mean age and body mass index of participants were 38.5 ± 13.3 years and 26.6 ± 4.8 kg/m^2 at baseline. Within 6.7 ± 1.4 years of follow-up, 79 cases of cardiovascular events were reported. NEAP was significantly associated with the incidence of CVDs (HRs = 0.50, CI 0.32–0.96; *P* for trend = 0.032); however, after adjusting for potential confounders, no significant associations were observed between PRAL and NEAP scores and the risk of CVDs.

Conclusions: This study failed to obtain independent associations between dietary acid load and the incidence of CVDs among an Asian population.

Keywords: Diet, Dietary acid load, Potential renal acid load, Net endogenous acid production, Cardiovascular disease

Introduction

The acid–base balance within the body can be influenced by eating patterns and the acid load of the diet [1]. Animal-based food products raise the acidifying potentials of diets [2, 3] and negatively manipulate the metabolic and physiologic status [4]. The acidic dietary patterns have become prevalent within the global dietary transition [5], which may be a risk factor for the development of metabolic and cardiovascular diseases (CVDs).

Potential Renal Acid Load (PRAL) [6] and Net Endogenous Acid Production (NEAP) [7] are common and valid indicators of dietary acid load and overall nutritional quality of a diet [6, 7]. The PRAL score is comprised of dietary magnesium, potassium, phosphorus, calcium, and protein [7], and NEAP formula is based on dietary intake of protein and potassium [8]. Both scores are associated with the prevalence of type 2 diabetes [9, 10] and hypertension [11–14]. PRAL alone is linked to the incidence of insulin resistance [15, 16], metabolic syndrome [17], and progression of chronic kidney disease [18, 19].

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Observational and epidemiological studies have reported inconsistent results on dietary acid load, and CVD outcomes [12, 14, 20, 21]. PRAL and CVD mortality were positively associated among Swedish individuals [22] and inversely related among the Japanese population [23]. In contrast, no significant association was detected between dietary acid load and CVD incidence among the Polish [24] and Dutch [12] populations. Meanwhile, the majority of the findings confirm the detrimental impacts of acidic dietary patterns on health [14, 17], which is mostly related to the increased tissue metabolic acidosis [25], changes in the glycemic [16, 26, 27] and lipid profiles [28] and, increased blood pressure [12, 13, 29].

Inadequate and inconsistent results bring unclear findings and challenge the documentation of standard global dietary guidelines. Here, we aimed to evaluate whether dietary acid load, defined as PRAL and NEAP scores, could be a predictor of CVD risk in the framework of a population-based study among an Asian population.

Methods

Study population

This study was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS), a population-based study that aims to investigate non-communicable diseases (NCDs) within a representative sample of Iranians from district 13 of Tehran. The TLGS was initiated in 1999 and includes repeated measurements at 3-year intervals [30]. In total, 3678 men and women (aged ≥ 19) with complete demographic, anthropometric, biochemical, and dietary data, who have participated in the third TLGS examination (2006–2008), were recruited. Participants were excluded if they aged out of the predefined limit ($70 < x < 19$ years old; $n = 626$), and had misreported energy intake ($4200 < x < 800$ kcal/day; $n = 579$) and CVD history at baseline (myocardial infarction (MI), stroke, angina, coronary revascularization; $n = 90$). Participants were also excluded if they left the study within the follow-up period ($n = 14$). Finally, 2369 adults (1030 men and 1339 women) were included in the analyses (Fig. 1) [30, 31].

All participants have provided written consents at baseline. The study protocol complied with the 1975 Ethical Guidelines of the Helsinki Declaration and was approved by the Ethics Research Council of the Research Institute for Endocrine Science, Shahid Beheshti University of Medical Sciences.

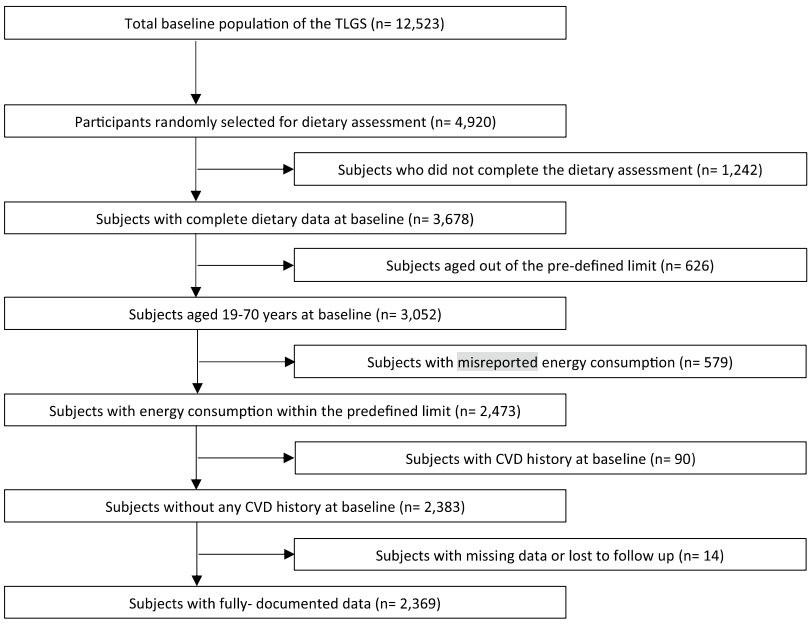

Fig. 1 Flowchart of the study population

Demographic and anthropometric measurements

Trained interviewers have collected demographic information using pretested and standardized questionnaires [31]. Weight was recorded to the nearest 100 g by digital scales, while participants had light clothing. Height was measured to the nearest 0.5 cm, standing without shoes, using a drop-down tape-meter. Body mass index (BMI) was calculated by the division of weight (kg) by the square of height (m^2). Waist circumference measurement was taken to the nearest 0.1 cm, midway between the lower border of the ribs and the iliac crest, while participants were minimally dressed by a soft measuring tape. Systolic (SBP) and diastolic blood pressures (DBP) were measured twice on the right arm using a standardized mercury sphygmomanometer; the mean of the two measurements was considered as the final blood pressure of the participants [31]. The frequency and duration of physical activity (expressed as metabolic equivalent hours per week; MET-h/wk) was assessed by a Modifiable Activity Questionnaire (MAQ) [32].

Biochemical measurements

Baseline and follow-up blood samples were taken from all participants following a 12–14 h fasting. Triglyceride (TG) level was assayed by enzymatic colorimetric method with glycerol phosphate oxidase. Fasting serum glucose (FSG) was determined using enzymatic colorimetric analysis and glucose oxidase. High-density lipoprotein cholesterol (HDL-C) measurement was obtained after precipitation of the apolipoprotein-B-containing lipoproteins with phosphotungstic acid. The Pars Azmoon kits (Pars Azmoon Inc., Tehran, Iran) and Selectra 2 auto-analyzers (Vital Scientific, Spankeren, Netherlands) were used to perform the analyses.

Dietary assessment

Demographic, dietary, anthropometric, and biochemical data were obtained from all participants at baseline (2006–2008). Trained interviewers used a 168-item semi-quantitative Food Frequency Questionnaire (FFQ) at the first examination to assess participants' dietary intake over the past year. The reliability, comparative validity and, stability of the questionnaire were previously evaluated in a random sample and proven to be reasonable [33].

The participant's consumption frequency of each food item was recorded on a daily, weekly, or monthly basis [31], and the household-measured portion sizes were converted to grams. The energy and nutrient content analysis of raw food and beverages was based on the US Department of Agriculture Food Composition Table (USDA FCT). Since the Iranian Food Composition Table has limited nutritional data, it was only used for the traditional items not listed within the USDA FCT [34].

Dietary acid load calculation

In this study, the dietary acid–base load was assessed by two indexes of PRAL and NEAP, using the following formula [7, 8]:

$$\begin{aligned}\text{PRAL (mEq/d)} = &\left[\text{protein}(\text{g/d}) \times 0.49\right] \\ &+ \left[\text{phosphorus}(\text{mg/d}) \times 0.037\right] - \left[\text{potassium}(\text{mg/d}) \times 0.021\right] \\ &- \left[\text{calcium}\ (\text{mg/d}) \times 0.013\right] - \left[\text{magnesium}\ (\text{mg/d}) \times 0.026\right]\end{aligned}$$

$$\text{NEAP(mEq/d)} = \left[54.5 \times \text{protein}(\text{g/d})/\text{potassium}\ (\text{mEq/d})\right] - 10.2$$

Dietary PRAL is a validated proxy for renal net acid excretion [1, 8], and the NEAP score is defined as the total nonvolatile acid load that results from endogenous acid production and gastrointestinal absorption [35]. A diet with acidifying potentials has higher PRAL and NEAP scores [4, 29]. There is a large variation in dietary acid load within the countries. The mean score of PRAL ranged from − 23.0 mEq/day in France [26] to − 22.0 mEq/day in Iran [18], − 21.8 mEq/day in Korea [14], − 14.6 mEq/day in Netherland [12], 10.4 mEq/day in Japan [11], and 22.1 mEq/day in China [37]. Likewise, mean dietary NEAP score ranged from 86.8 mEq/day in China [36], to 32.6 mEq/day among American children [6], and 31.5 mEq/day in France [26]. Both PRAL and NEAP were calculated using residual energy-adjusted nutrient intake data from the FFQs.

Definition of terms

Diabetes was defined as FSG over 126 mg/dL, 2-h serum glucose above 200 mg/dL or use of anti-diabetic medications [37]. Hypertension was explained as SBP above 140 mm Hg, DBP higher or equal to 90 mm Hg, or concurrent use of antihypertensive medications [33].

Definition of outcomes

Details of the collection of CVD-related data have been described elsewhere [31]. The CVD terminology was

primarily defined as CHD-related events, stroke (a new neurological deficit that took ≥ 24 h), or CVD death (definite fatal stroke, definite fatal CHD, and definite fatal MI) [38]. CHD-related outcomes were including definite or probable MI, and angiographic-approved CHD [39].

In the current study, participants were followed up annually by telephone calls, and a trained nurse or a physician collected the required information on possible medical events. Further information was extracted from the medical records. The collected data were reviewed by an adjudication committee, which included a physician, an internist, an epidemiologist, a cardiologist, an endocrinologist, and associate external experts as needed. The final diagnosis was reported by a predefined coding protocol [40].

Statistical analysis

In this study, IBM SPSS (SPSS Inc., Chicago, IL, USA, version 20.0) was used to perform the analyses, and *P*-values ≤ 0.05 were statistically significant. Mean (SD) values of the baseline characteristics of participants with and without CVD were compared by independent t-test. The chi-square test was used to compare frequencies (%) between two groups. Dietary intake of participants were compared across tertiles of PRAL and NEAP using analysis of variance (ANOVA) test. A univariate analysis was conducted for each potential confounder, and variables with $P_E < 0.2$ were included in the multivariable model; total dietary energy, and total dietary fat were included in the final model and the physical activity was eliminated. Cox proportional hazards regression models were used to evaluate the hazard ratios (HRs) and the 95% confidence intervals (CIs) of dietary acid load and CVD events, and person-year was considered as the underlying time metric. Time to event was defined as the time to the onset of an event, or time to the end of follow-up.

Three Cox proportional hazards regression models were identified across tertiles of PRAL and NEAP; model 1 was adjusted for sex, age and smoking status, and model 2 was further adjusted for energy intake (kcal/d) and total fat intake (g/d). The median value of each dietary tertile was used to assess the overall HR trends in the Cox proportional hazard regression model.

Results

Mean age and BMI of participants were 38.5 ± 12.7 years and 26.6 ± 4.8 kg/m^2 at baseline, respectively, and 43.5% were men. During an average follow-up period of 6.7 ± 1.4 years, 79 participants experienced CVD events (3.3%), and angiographic proven CVD, definite MI, unstable angina, and stroke were the most common outcomes.

Table 1 represents the distribution of major CVD risk factors and biochemical variables for participants with and without CVD events. Participants with CVD events were older ($P = 0.001$). Diabetes (13.2 *vs.* 3.7%, $P = 0.001$) and hypertension (42.1 *vs.* 9.4%, $P = 0.001$) were more prevalent among incident cases compared to the rest of the cohort. Also, a higher percentage of subjects with CVD events were current smokers (20.2 *vs.* 11.7%, $P = 0.02$).

Dietary intakes of participants across tertiles of PRAL and NEAP are reported in Table 2. Mean

Table 1 Baseline characteristics of the participants: Tehran Lipid and Glucose Study (TLGS)

	Participants with CVD outcomes (n = 79)	Participants without CVD outcomes (n = 2290)
Age (year)*	58.4 ± 9.7	37.4 ± 12.8
Male (%)*	68.4	42.6
Smoking (%)	20.2	11.7
Body mass index (m^2/kg)	28.4 ± 4.4	26.5 ± 4.8
Waist circumference (cm)*	97.4 ± 9.9	87.9 ± 13.3
Serum creatinine (μmol/L)*	102 ± 24.1	91.8 ± 13.1
Systolic blood pressure (mm Hg)*	109 ± 14.8	109 ± 14.8
Diastolic blood pressure (mm Hg)*	79.9 ± 11.2	72.4 ± 10.3
Fasting blood glucose (mg/dL)*	104 ± 37.5	88.3 ± 16.1
Serum triglycerides (mg/dL)*	188 ± 102	132 ± 77.4
HDL-C (mg/dL)*	39.4 ± 7.6	43.3 ± 10.3
Diabetes (%)*	13.2	3.7
Hypertension (%)*	42.1	9.4

Independent *t* test was used for continuous variables, chi-square test was used for dichotomous variables.

Data are mean ± SD, unless stated otherwise

**P* value ≥ 0.001

Table 2 Dietary intake of participants across tertiles of PRAL and NEAP: Tehran Lipid and Glucose Study (TLGS)

	PRAL (mEq/day)			NEAP (mEq/day)		
	< − 16.7 (n = 789)	− 16.7 to − 2.45 (n = 790)	> − 2.45 (n = 790)	< 30.6 (n = 789)	30.6 to 39.3 (n = 794)	> 39.3 (n = 786)
	− 31.6 ± 13.0	− 9.49 ± 4.07	7.76 ± 8.6	24.9 ± 4.11	34.6 ± 2.47	48.3 ± 7.75
Nutrient intake						
Energy intake (kcal)	2371 ± 23.7	2150 ± 25.1	2260 ± 27.4*	2196 ± 23.8	2269 ± 24.9	2316 ± 27.8*
Protein (% of energy)	13.4 ± 0.08	13.3 ± 0.08	14.1 ± 0.08*	13.11 ± 0.08	13.6 ± 0.08	14.2 ± 0.08*
Carbohydrate (% of energy)	58.7 ± 0.25	56.8 ± 0.25	56.1 ± 0.25*	58.8 ± 0.25	56.6 ± 0.25	56.3 ± 0.25**
Fat (% of energy)	31.3 ± 0.25	32.2 ± 0.25	31.2 ± 0.25**	31.6 ± 0.25	32.1 ± 0.25	31.0 ± 0.25*
Fiber (gr/d)	40.4 ± 0.59	35.9 ± 0.59	34.1 ± 0.58*	39.7 ± 0.59	35.6 ± 0.59	35.4 ± 0.59*
Calcium (mg/d)	1362 ± 14.5	1229 ± 14.4	1087 ± 14.4*	1364 ± 14.3	1247 ± 14.2	1067 ± 14.3*
Potassium (mg/d)	4476 ± 29.0	3655 ± 29.0	2936 ± 28.9*	4480 ± 28.8	3659 ± 28.7	2925 ± 28.8*
Magnesium (mg/d)	397 ± 2.83	366 ± 2.82	346 ± 2.81*	398 ± 2.81	366 ± 2.80	345 ± 2.81*
phosphorus (mg/d)	1448 ± 10.8	1438 ± 10.7	1445 ± 10.7*	1445 ± 10.7	1462 ± 10.7	1424 ± 10.7*
Food intake						
Meat (gr/d)	47.5 ± 1.46	50.9 ± 1.46	63.2 ± 1.45*	42.5 ± 1.43	52.1 ± 1.42	67.1 ± 1.43*
Grains (gr/d)	319 ± 5.91	389 ± 5.91	486 ± 5.88*	323 ± 5.92	387 ± 5.90	485 ± 5.93*
egg (gr/d)	14.4 ± 0.44	13.8 ± 0.44	15.9 ± 0.44*	14.1 ± 0.44	14.1 ± 0.44	15.1 ± 0.44*
cheese (gr/d)	19.0 ± 0.72	18.9 ± 0.72	20.3 ± 0.72*	18.5 ± 0.72	19.1 ± 0.71	20.6 ± 0.72*
Fish (gr/d)	6.27 ± 0.74	7.84 ± 0.74	6.46 ± 0.74*	6.53 ± 0.74	6.07 ± 0.74	7.97 ± 0.75*
Rice (gr/d)	202 ± 5.85	248 ± 5.85	307 ± 5.79*	208 ± 5.84	248 ± 5.82	302 ± 5.85*
Coffee (ml/w)	59.4 ± 77.6	58.8 ± 68.3	57.1 ± 65.2**	55.3 ± 73.3	61.6 ± 70.6	58.4 ± 70.5**
Fruit and vegetable (gr/d)	732 ± 8.61	497 ± 8.61	303 ± 8.57*	734 ± 8.60	490 ± 8.56	307 ± 8.61*
Potato (gr/d)	19.9 ± 0.69	17.0 ± 0.69	14.2 ± 0.69*	18.9 ± 0.69	17.9 ± 0.69	14.4 ± 0.70*
Legumes (gr/d)	17.1 ± 0.76	15.8 ± 0.77	14.9 ± 0.76*	16.1 ± 0.76	16.1 ± 0.76	15.5 ± 0.76*

Analysis of variance (ANOVA) was done and the first tertile was considered as the reference

PRAL potential renal acid load, *NEAP* net endogenous acid production

Data are presented as mean ± SE or percentage, unless stated otherwise

Adjusted for energy intake

**P* value < 0.001

***P* value < 0.05

dietary PRAL and NEAP were − 11.1 ± 18.6 mEq/day and 35.9 ± 10.9 mEq/day, respectively. Range of PRAL score across tertiles was < − 16.7 mEq/day, − 16.7 to − 2.45 mEq/day, and > − 2.45 mEq/day. Range of NEAP was < 30.6 mEq/day, 30.6–39.3 mEq/day, and > 39.3 mEq/day, in the first, second and third tertile, respectively. Participants in the lowest tertiles of PRAL had higher intakes of total dietary fiber, calcium, potassium, magnesium, potato, fruits and vegetables, and lower consumption of animal meat, cheese, grains and rice (*P* for all < 0.001). Similarly, lower NEAP score was related to lower consumptions of animal meat, cheese, grains and rice, and higher intakes of dietary fiber, calcium, potassium, magnesium, potato, and fruits and vegetables (*P* for all < 0.001).

The hazard ratio (95% CI) of CVD incidence across tertile categories of PRAL and NEAP are shown in Table 3. The risk of CVD events was reduced significantly in the NEAP crude model (HRs = 0.50; CI 0.32–0.96; *P* trend = 0. 032). No significant associations were observed for PRAL and NEAP scores and CVD incidence after adjusting for age, sex, and smoking status in the second model, and total energy and total fat intake in the third model.

Discussion

In this population-based cohort study, we assessed the potential associations between dietary acid load and CVD outcomes. After adjusting for potential confounders, no significant associations were observed for PRAL and NEAP and CVD incidence risk, which may be explained by the low number of CVD cases, relatively

Table 3 Hazard ratio (95% CI) of cardiovascular disease across tertiles of PRAL and NEAP: Tehran Lipid and Glucose Study (TLGS)

	T1	T2	T3	*P* trend
	< − 16.7 (n = 789)	− 16.7 to − 2.45 (n = 790)	> − 2.45 (n = 790)	
PRAL (mEq/day)				
Crude	1	0.67 (0.39–1.14)	0.65 (0.38–1.11)	0.094
Model 1	1	0.73 (0.43–1.24)	0.79 (0.46–1.36)	0.346
Model 2	1	0.75 (0.44–1.28)	0.80 (0.46–1.37)	0.367
	T1	T2	T3	*P* trend
	< 30.6 (n = 789)	30.6 to 39.3 (n = 794)	> 39.3 (n = 786)	
NEAP (mEq/day)				
Crude	1	0.63 (0.37–1.07)	0.50 (0.32–0.96)	0.032
Model 1	1	0.72 (0.42–1.21)	0.76 (0.44–1.33)	0.986
Model 2	1	0.73 (0.43–1.23)	0.76 (0.44–1.32)	0.988

Cox proportional hazard regression model was used to estimate hazard ratio (HR) and 95% confidence intervals (CI) for cardiovascular disease across tertiles of dietary acid load

PRAL, potential renal acid load; NEAP, net endogenous acid production

Model 1: adjusted for sex, age, smoking status

Model 2: adjusted for sex, age, smoking status, dietary energy intake (kcal/d), total fat intake (g/d)

short follow-up period, young study population, and potential changes in the dietary patterns of participants over time.

Our findings, however, were in line with the results of a large-scale study in Poland [21]. In contrast, a 2016 cross-sectional study on Korea National Health and Nutrition Examination data reported a positive association between the dietary acid load and incidence risk of CVD [14]. The higher dietary acid load has also elevated the risk of CVD mortality among Japanese individuals [23], increased 10-year mortality of patients with coronary artery bypass surgery in Iran [41] and, influenced the likelihood of chronic peripheral arterial disease among Americans [42]. Indeed, various populations differ in baseline characteristics and habitual dietary intakes, composing a dietary acid load spectrum [11, 21].

Previous publications have reported associations between the dietary acid load and CVD risk factors [11, 29, 43–46]. Dietary acidity induces low-grade acidosis that is linked to the development of metabolic complications, including diabetes [47], hypertension, and renal and bone complications [19, 48, 49]. PRAL and NEAP scores were both positively associated with serum TG levels [43]. PRAL was also independently associated with increased TG, SBP [44], and low-density lipoprotein cholesterol (LDL) [11] levels, and inversely related to fasting blood glucose [44]. In a 2018 systematic review and meta-analysis, a non-linear association was observed between NEAP and hypertension, and a 20-unit increase in PRAL value raised the risk of hypertension by 3% [45]. Furthermore, one study in South China highlighted the gender-dependent hypotensive properties of PRAL, which appeared insignificant in the context of NEAP [29]. A recent meta-analysis found positive associations between PRAL scores and SBP, DBP, insulin concentrations, and diabetes [50]. In contrast, no cross-sectional or longitudinal associations were observed between dietary acid load and various blood pressure indices in Swedish middle-aged men [51], metabolic syndrome risk factors [52], and risk of hypertension in older Dutch adults [12].

The mean dietary PRAL and NEAP in this study were − 11.1 ± 18.6 mEq/day and 35.9 ± 10.9 mEq/day, respectively, which confirms the dietary pattern of our population to be less acidic comparing to the Korean (PRAL: − 21.8 mEq/day) [14] and French (PRAL: − 23.0 mEq/day) [26] populations. Nevertheless, the dietary patterns of Chinese (PRAL: 22.1 mEq/day) [29] and Japanese (10.4 mEq/day) populations [11] appeared to be more alkalizing. This study was conducted on Iranian adults with transitional dietary patterns and an estimated animal-to-plant protein ratio of approximately 1.3–2.1.4 [53].

Participants with lower values of PRAL and NEAP scores had lower intakes of animal products and higher intakes of fruits and vegetables. It is generally confirmed that animal-based food items hold acidifying properties [3], whereas plant-food sources are more alkalizing [54]. Western dietary patterns, with an average 15–17% of energy from animal protein, are major acid suppliers to the body [2, 3]. On the contrary, the Dietary Approach to Stop Hypertension (DASH) pattern that is mainly comprised of plant foods and monounsaturated and polyunsaturated fats substantially

reduces the dietary acid load (NEAP; 31 mEq/day vs. 78 mEq/day) [55]. Inadequate consumption of low-potassium fruit and vegetables in large samples of American individuals had adverse effects on the dietary acid load [3]. The dietary potassium of vegetables can bind to organic anions and metabolize to bicarbonate, which is ultimately capable of reducing NEAP [46]. The total or partial replacement of low-nutrient and energy-dense food items with fruits and vegetables can reduce the overall NEAP regardless of the amount of protein required [56].

To date, mechanistic information linking dietary acid load and CVD outcomes is mostly attributed to the role of chronic metabolic acidosis and hypertension. High adherence to Western dietary patterns enhances metabolic acidosis, and in return, increases the production of cortisol, ammoniagenesis, and renal acid excretion [6, 57]. Together, this leads to the diagnosis of hypertension [6]. In addition, restrictions in the dietary intake of potassium can affect the vascular vasodilation and damage blood vessels, and result in intracellular potassium deficiencies and compensatory sodium gains into the cell for the maintenance of the tonicity and volume [57]. Other mediators of metabolic acidosis and hypertension are the reduced excretion of citrate, increased release of calcium and cortisol, and the quality and quantity of the dietary protein [48]. High dietary acid load and chronic metabolic acidosis are also closely linked to the reduced affinity of the insulin to its receptor, increased risk of insulin resistance, and subsequently, hyperglycemia [15–17]. CVD can be autonomously promoted from insulin resistance through various pathways, including coronary microcirculatory dysfunction [58] and increased arrhythmogenesis [59].

This study has a number of strengths, including the high follow-up rate in the framework of a prospective population-based design, and the use of a validated FFQ for the assessment of habitual dietary intakes. The use of dietary PRAL for the measurement of dietary acid–base balance is one of the main limitations of this study. Although PRAL and NEAP scores have been widely used in previous publications, they are measured indirectly from the FFQs and can be influenced by inaccurate dietary reports [6, 7]. Also, the variations in the dietary patterns over time, the actual nutrient composition of specific meals, the preparation methods, and the nutrients' absorption within the gastrointestinal tract are not considered by the PRAL and NEAP equations. Moreover, the low rate of CVD events in our population could have led to underestimations in CVD incidence. Lastly, the relatively short follow-up period with a relatively young population made it difficult to follow CVD endpoints.

Conclusion

Our results did not show any significant associations between dietary acid load and risk of CVDs within a representative sample of Iranians. The global growth in CVDs prevalence, the high treatment costs and burden of CVDs, and the critical role of diet in cardiovascular health call for investigations on dietary acid load and CVDs risk, with larger-scale samples and longer follow-up durations.

Abbreviations

BMI: Body mass index; CHD: Coronary heart disease; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; FFQ: Food frequency questionnaire; FSG: Fasting serum glucose; HDL-C: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; NCDs: Non-communicable diseases; NEAP: Net endogenous acid production; PRAL: Potential renal acid load; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; TLGS: Tehran lipid and glucose study.

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Authors' contributions

PM designed the study. SK and ZB analyzed the data from the TLGS population, SK and ZH wrote the manuscript, ZH corrected the manuscript, FA and MS revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The database used and/ or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

Ethics Approval and consent to participate

Written informed consents were obtained from all participants at baseline. The study protocol complied with the 1975 Ethical Guidelines of the Helsinki Declaration and was approved by the Ethics Research Council of the Research Institute for Endocrine Science, Shahid Beheshti University of Medical Sciences.

Consent for publication

Not Applicable.

Competing interest

There is no conflict of interest.

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