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Association between dietary acid load and risk of osteoporotic fractures in adults: a systematic review and meta-analysis of observational studies

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Abstract

Aim We aimed to systematically review and conduct a meta-analysis of the available evidence about the association between dietary acid load (DAL) and fractures in adults.

Method Relevant studies were searched through Web of Science, Scopus, PubMed, and Google Scholar until October 2024. The random-effect model was used to calculate the pooled Odd ratios (OR) and 95% confidence intervals (CIs). Publication bias was evaluated by statistical test of Egger. Subgroup analyses were conducted by study confounders. Moreover, the quality of studies was asessed using the Newcastle Ottawa Scale which is designed for observational studies.

Results Six studies were included in this review. According to the methodological heterogeneity between studies and their different charactristics, we performed the analysis based on random-effect model that indicated a marginally significant association between DAL and risk of fracture (N event = 5275, Pooled OR: 1.10; 95% CI: 0.99–1.21, $P = 0.073$) ($I^2 = 12.9\%$; $P = 0.321$). According to subgroup analysis, there was no significant association between DAL and risk of fracture in the cross-sectional effect sizes (N event = 337, OR:0.69; 95%CI:0.47–1.00). There was a significant association between DAL and a greater risk of fracture in cohort studies (N event = 4938, OR:1.12; 95%CI:1.03–1.22, $P = 0.006$). Also, high-quality studies (OR:1.12; 95%CI:1.03–1.22; $P = 0.006$) showed a significant association between DAL and fracture risk.

Conclusion DAL was marginally related to a higher risk of fracture. This finding is a trigger for bone health management with a healthy balanced dietary intake.

Keywords Dietary acid load, Fracture, Osteoporosis, Meta-analysis, Systematic review

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Introduction

Osteoporotic fracture and its related complications affect several million individuals globally and have become an important economic burden on public health systems [1, 2]. Because of the rising osteoporosis prevalence with age, the global aging of the population, and the changing habits and lifestyle, the prevalence of osteoporosis has increased significantly and will develop in the future [3, 4]. Hip fractures lead to an overall reduction in survival of about 15%, and the majority of excess deaths occur within the first 6 months following the fracture [5]. Around the world, 1 in 3 women over age 50 will experience osteoporosis fractures, as will 1 in 5 men aged over 50 [6–8]. Using the World Health Organization (WHO) definition of osteoporosis, the disease affects approximately 6.3% of men over the age of 50 and 21.2% of women over the same age range globally [9]. Thus, the prevalence and incidence of related fractures will also increase in the future. In 2010, about 158 million subjects were at high fracture risk, however, by 2040 it is estimated that these fractures will double because of demographic alters [10]. Demographic variables for possible associations with a fracture are age, race, sex, geographic region, urban or non-urban residence, and income [11]. Regardless of aging, the fracture is also affected by hormonal changes, comorbidities, medications, physical activity, alcohol consumption, smoking, lifestyle, and dietary factors [12, 13].

The acid-base equilibrium in the body is critical to bone health. One of the most important factors that affect this acid-base balance in the body is diet contents by providing acid precursors or base precursors [14, 15]. Such as fruits and vegetables (alkali-rich food groups) have lower dietary acid load (DAL) scores, and promote alkalinity, while meats, refined grains, and cheeses (high-phosphorus food groups) lead to acidity and have higher DAL [16]. Physiologically compounds such as potassium, magnesium, and calcium can be found in the bone matrix and act as a blood buffer. Consumption of foods such as meat, cheese, and salty foods causes the production of acid (hydrogen ions) in the blood [17, 18] that leads to the release of alkaline salts from the bone to maintain a balanced acid-base status, which causes an increase osteoclast activity, bone breakdown and finally the progression becomes osteoporosis [19]. Because of the sulfur and phosphate content of acid-generating potential foods (such as meats, fish, cheeses, grains, rice salted foods), these foods cause metabolic acidosis in the body, although this effect is balanced by alkali salts of organic acids such as bicarbonate provided by vegetable consumption [20–22].

Different researchers have reported an imbalance in the acid-base system due to changes in the structure and density of bone mass [23, 24]. The mechanisms for the negative effect of elevated metabolic acidosis on bone are: demineralization has been related to impaired osteoblastic function, raised bone resorption, activated mature osteoclasts, and increased calcium excretion. Thus, prolonged exposure to an acidic condition may induce calcium loss, causing the reduction of bone mineral density (BMD) and as a result increasing its fragility [23, 25, 26].

In epidemiological studies, dietary acid-base load was calculated through various indices including net endogenous acid production (NEAP), potential renal acid load (PRAL), and renal net acid excretion (RNAE) [27]. Various observational studies have indicated reverse [28, 29] or no [30–32] associations between PRAL, NEAP, and BMD. Frassetto et al. reviewed various studies in this field and reported that those whose diets contain high net acid loads could potentially benefit the most from alkali therapies [33]. Findings of a review reported that no evidence that diet-derived acid load is deleterious for bone health [34]. A systematic review to evaluate causal relationships between DAL and osteoporosis involving 36 studies with bone health outcomes in healthy adults revealed that the causal association between DAL and osteoporotic bone disease is not supported and also no evidence that an alkaline diet is protective of bone health in vitro cell studies [35].

Hayhoe et al. disclosed an increased risk of fractures in the highest category of DAL compared with those in the lowest categorization [36] while Papageorgiou et al. failed to find any significant association [37]. Such evidence in this area raises the question of whether adherence to highly acidic diets might contribute to the loss of bone mass and increasing fractures or osteoporosis (especially in long-term adherence which show the importance of cohort studies). To the best of our knowledge, no study has summarized earlier observational studies on the association between DAL and fractures. Moreover, findings on the association between DAL and fracture are inconsistent. This inconsistency has been documented for studies with observational design that assessed the association of DAL and farcture risk [27, 38]. Therefore, in the present study, we systematically reviewed and conducted a meta-analysis of the available evidence about the association between DAL and fractures in adults.

Methods

The present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol [39].

Search strategy

Web of Science, PubMed, Google Scholar, and Scopus were searched to explore relevant documents published from inception to October 2024 by two independent

reviwers and the corresponding author reviewed it to resolve any discrepancy. Medical Subject Headings (MeSH) and non-MeSH terms were used in the search strategy: ("dietary acid-base load" OR "dietary acid load" OR "dietary acidity" OR "acid excretion" OR "net acid load" OR "net endogenous acid production" OR "potential renal acid load" OR PRAL OR "protein to potassium ratio" OR NEAP OR "protein/potassium ratio" OR "acidebase equilibrium" OR "acidebase imbalance" OR "acid-ash" OR "alkaline-ash" OR "acidebase" OR "acid load") AND ("fracture risk" OR "Osteoporotic Fractures" OR "Fractures Bone" OR "osteoporotic fractures" OR fractures OR fracture OR "risk of osteoporotic fractures" OR "risk of fractures"). Limitations of language and time of publication were not applied. In addition, to keep away from missing any relevant documents in the search process, we manually scanned the reference lists of related articles and reviews. Duplicate papers were removed after completing the search process.

Eligibility criteria

The inclusion criteria for the eligible studies were considered as follows: [1] observational studies [2], studies that assessed the general adult (≥18 years) population [3], studies that considered DAL as the main exposure [4], studies that considered fracture as the outcomes [5] articles that presented odds ratios (ORs), relative risk (RRs) or hazard ratios (HRs) with their 95% confidence intervals (CIs) for the association between DAL and fracture. Moreover, only English-language publications were included in the study. The PICO framework was defined as follows: adult subjects (Population); Highest DAL category (Intervention/ Exposure); Lowest DAL category (Comparison); Risk of fracture (Outcome).

Interventional studies, book chapters, conference abstracts, letters, gray literature as well as ecological and unpublished studies, articles with unusable information and abstracts, and those conducted on children and adolescents were excluded. Eligibility criteria assessment was performed by two independent researchers and the corresponding author reviewed it to resolve any discrepancy.

Data extraction

Two independent reviewers performed study data extractions. They independently extracted the following information from included articles by using an abstraction form: first author's last name, study design, date of publication (year), gender of participants, age range or mean age at study baseline, number of participants, incident cases, the methods that used for assessing dietary intakes, criteria for diagnosis of fracture, duration of follow-up for cohort studies, effect estimates (ORs and HRs) and the relevant 95%CI for fracture across categories of DAL scores, and confounders adjusted for in the multivariate analysis. Numerical estimates were extracted from graphs using by web plot digitizer. Any disagreement was resolved by consensus.

Assessment of study quality

The quality of studies was evaluated using the Newcastle Ottawa Scale (NOS) which is designed for observational studies [40] by by two independent researchers and the corresponding author reviewed it to resolve any discrepancy. It is based on 3 specific domains as follows: the selection of participants, comparability, and ascertainment of the outcome of interest. The NOS scores range from zero to nine. Papers with ≥7 stars were regarded as relatively high-quality documents [41].

Statistical analysis

OR for the cross-sectional study and HRs for cohort studies and their 95% CI were considered as the effect size in the included studies. We considered HR/OR for the highest vs. lowest DAL ranked group by tertiles [38], quartiles [30, 42], and quintiles [36, 43]. Only one study [37] was not ranked by equal subjects and classified by PRAL (acidic, neutral, and alkaline), therefore effect size was obtained by the acidic vs. alkaline group. Pooled ORs with 95% CIs were computed for fracture using a random-effect model to justify the heterogeneity between the included studies. Cochran's Q test and I^2 were used to assess statistical heterogeneity. In this study, between-study heterogeneity was determined as I^2 values of >50% [44]. We assessed publication bias by the statistical test of Egger. Subgroup analyses also were performed using by random-effect model to discern possible sources of heterogeneity, stratified by study design (cross-sectional or cohort), gender (male, female, or both), DAL assessment method (PRAL vs. NEAP or RNAE), sample size (<10000 vs. >10000 participants), study quality (fair vs. high), follow-up years (<10 vs. >10y), health condition (healthy vs. postmenopausal women and individuals with high CVD/ obesity risk) and dietary intake assessment (FFQ vs. food record). Sensitivity analysis was utilized to analyze the extent to which inferences might depend on a particular study. Statistical analyses were conducted using Stata, version 14 (Stata Corp, College Station, TX). P-values were recognized as significant at the level of <0.05 and marginally significant at the level of <0.1.

Results

Findings from the systematic review

Totally 237 articles were acquired in the initial search from all databases and reference list searches. After the exclusion of duplicate documents (118 papers) and papers that did not meet inclusion criteria (81 articles), 38 documents were assessed by full-text. Finally, 6 publications [5 cohorts and 1 cross-sectional study] were

included in the present systematic review and meta-analysis. The flow diagram of the study is indicated in Fig. 1.

Characteristics of included publications are presented in Table 1. Eligible articles were published from 2007 to 2020. In total, 77,845 subjects with the age range of 39 to 82 years were included. Follow-up periods for cohort studies were 6.1 to 17.9 years. One study was conducted among women [42], while others were conducted among both genders. All studies were conducted in European countries.

Dietary assessment in 4 studies was examined using by food frequency questionnaire [30, 38, 42, 43], and two

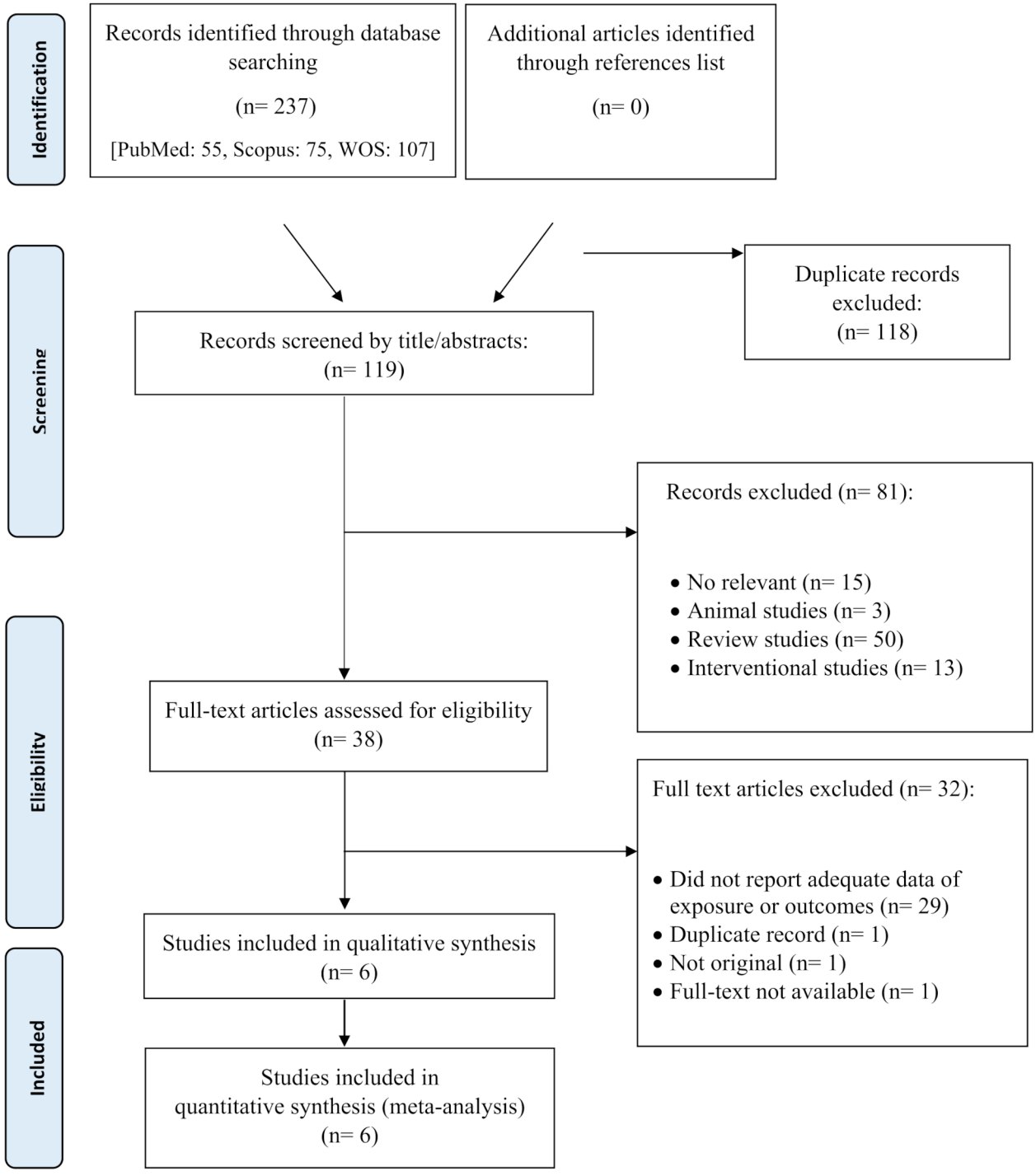

Fig. 1 Flowchart of the number of studies identified and selected for the meta-analysis

Table 1 Characteristics of included studies

Author (Year)	Country	Design	Follow-up (Year)	Age (Year)	Gender	Sample size (*N*)	Fracture incident	DAL method	Health condition	OR (95%CI)	Adjustment	Dietary intake assessment	Fracture site	Fracture measurement method	Quality assessment
Garcia-gavilan et al. (2020)	Spain	Cohort	8.9	55–80	Both	870	114	NEAP/PRAL	High CVD risk or overweight/obese with M.S	NEAP: 1.02 (0.48–2.14) PRAL: 1.04 (0.53–2.28)	eGFR [mL/(min · 1.73 m2)], the prevalence of diabetes (yes/no), the prevalence of HTN (yes/no), the prevalence of previous fractures (yes/no), use of insulin (yes/no), use of estrogen drugs (yes/no), use of calcium and/or vitamin D supplementation (yes/no), total yearly mean CHO intake (gr/d), total yearly mean fatty acid intake (gr/d), total yearly mean fiber intake (gr/d), total yearly mean vitamin D intake (mcg/d), total yearly mean energy intake (kcal/d), PA	FFQ	Femur, lumbar spine, femur neck, trochanter, femoral diaphysis	Medical records/fracture with score > 5	8

Table 1 (continued)

Author (Year)	Country	Design	Follow-up (Year)	Age (Year)	Gender	Sample size (*N*)	Fracture incident	DAL method	Health condition	OR (95%CI)	Adjustment	Dietary intake assessment	Fracture site	Fracture measurement method	Quality assessment
Papageorgiou et al. (2020)	Switzerland	Cohort	6.1	65	Both	Male: 177 Female: 676	Male: 5 Female: 87	PRAL	Healthy men/ postmenopausal women	PRAL: Women: 1.17 (0.88–1.56) Men: 0.88 (0.28–2.79)	Age, BMI, smoking status, PA, family history of osteoporosis, steroid use. (Moreover, menopausal, HRT status in women)	3 day Food record	Hip, radius, spine	CT	7
Hayhoe et al. (2020)	10 European countries	Cohort	17.9	39–79	Both	Male: 13,927 Female: 11,511	Male: 610 Female: 1583	PRAL	Healthy	PRAL: Male: 1.33 (1.03–1.72) Women: 1.20 (1.02–1.41)	Age, BMI, smoking status, PA, family history of osteoporosis, steroid use. (Moreover, menopausal, HRT status in women, and steroid use in women)	7 day Food record	Total, hip, wrist, spine	Contact ultrasound bone analyzer	9
Jia et al. (2015)	Sweden	Cohort	9.2	70	Both	861	131	NEAP/PRAL	Healthy	NEAP: 1.03 (0.57–1.85) PRAL: 0.93 (0.55–1.55)	energy intake, sex, BMI, lifestyle factors, alcohol intake, smoking, PA, education, eGFR	7 day FFQ	Neck down/ lumbar spine, femoral neck, total hip	ICD/DEXA	9

Table 1 (continued)

Author (Year)	Country	Design	Follow-up (Year)	Age (Year)	Gender	Sample size (*N*)	Fracture incident	DAL method	Health condition	OR (95%CI)	Adjustment	Dietary intake assessment	Fracture site	Fracture measurement method	Quality assessment
Dargent-molina et al. (2008)	France	Cohort	15	40–65	Female	36,217	2408	RNAE	Postmenopausal women	RNAE: 1.05 (0.93–1.19)	BMI, PA, parity, maternal history of hip fracture, HT use, smoking status, alcohol intake	208-item dietary questionnaire	NR	Self - report	9
Welch et al. (2007)	UK	Cross-sectional	NA	42–82	Both	Male: 6018 Female: 7588	Male: 95 Female: 242	PRAL	Healthy	PRAL: Women: 0.59 (0.36–0.97) Men: 0.82 (0.46–1.55)	Age, BMI, PA, previously diagnosed osteoporosis, calcium, protein intake, smoking status (and HRT status in women)	FFQ	Hip, wrist, vertebral (spinal)	Contact ultrasound bone analyzer	6

DAL: dietary acid load; OR; odd ratio; CI: confidence interval; RNAE: renal net acid excretion; BMI: body mass index; PA: physical activity; HT: hormonal therapy; NR: not reported; NEAP: net endogenous acid production; PRAL: potential renal acid load; CVD: cardiovascular disease; M.S: metabolic syndrome; HTN: hypertension; CHO: carbohydrate; eGFR: estimated glomerular filtration rate; FFQ: food frequency questionnaire; HRT: hormone replacement therapy; UK: United Kingdom; NA: not applicable; CT: computed tomography; ICD/ DEXA: international classification of diseases/Dual-energy X-ray absorptiometry

other studies used food records [36, 37]. To assess DAL, 5 studies had used PRAL [30, 36–38, 43], 2 had used NEAP [30, 38] and one had used RNAE [42]. Fractures in most studies were controlled for BMI, physical activity, and smoking. The NOS score of the included studies ranged between 6 and 9 (Supplemental Table 1).

Findings from the meta-analysis

Six studies examined the association between DAL and fracture. These studies included a total of 77,845 participants, among them 5275 fracture cases were found. According to the methodological heterogeneity between studies and their different charactristics, we performed the analysis based on random-effect model that indicated a marginally significant association between DAL and risk of fracture (Pooled OR: 1.10; 95% CI: 0.99–1.21, $P=0.073$) ($I^2=12.9\%$; $P=0.321$). Figure 2.

Subgroup analysis was applied to investigate between-study heterogeneity and test the robustness of the results. These analyses were accomplished based on study design, follow-up years, gender, type of assessed DAL, dietary assessment method, health condition of participants, and quality and sample size of the included studies. Table 2 indicates the findings of different subgroups based on random-effect model analysis.

DAL was associated with an increased risk of fracture in cohort studies (pooled HR: 1.12; 95%CI: 1.03–1.22; $P=0.006$), however, there was a marginally significant inverse association between DAL and fracture event for the pooled effect sizes of cross-sectional studies ($P=0.052$). DAL was not associated with fracture event in those studies that assessed PRAL for DAL (pooled effect sizes: 1.09; 95%CI: 0.93–1.28; $P=0.296$) (I^2: 32.5%; $P_{heterogeneity}$: 0.169). This non-significant association was observed for other DAL method assessment. High-quality studies (pooled effect sizes: 1.12; 95%CI: 1.03–1.22; $P=0.006$) (I^2: 0%; $P_{heterogeneity}$: 0.808) and studies with more than 10,000 participants or more than 10 years follow-up (pooled effect sizes: 1.15; 95%CI: 1.01–1.32; $P=0.031$) (I^2: 44.1%; $P_{heterogeneity}$: 0.167) showed a significant association between DAL and fracture risk. Studies that used food record for dietary assessment indicated a significant positive association between DAL and fracture risk (pooled effect sizes: 1.22; 95%CI: 1.08–1.38) ($P=0.001$).

According to Egger test ($P=0.291$), there was no significant publication bias or for DAL and fracture. Sensitivity

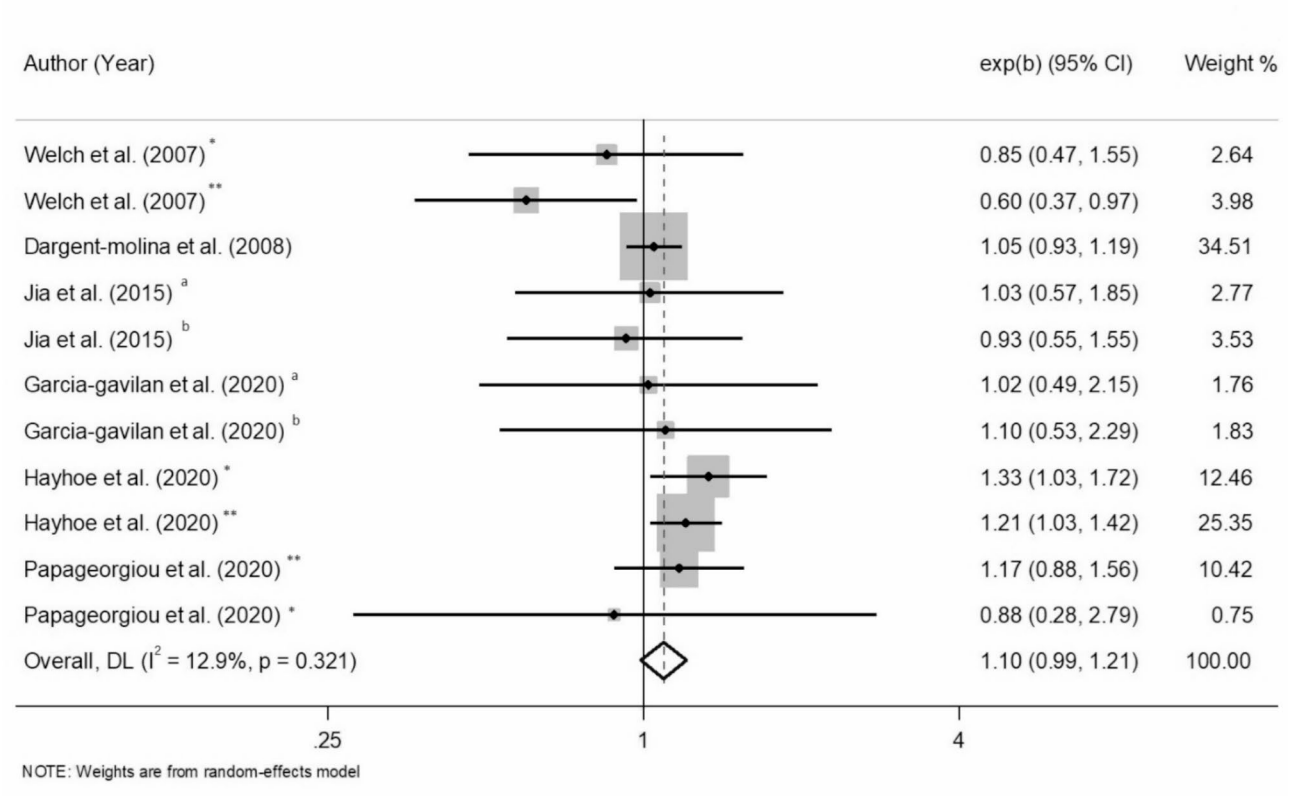

Fig. 2 Forest plot for the association of DAL and fracture risk (random-effect model). * shows the effect sizes which have been reported among male participants. ** shows the effect sizes which have been reported among female participants. [a] shows the effect sizes that have been reported for the association between fractures and DAL which was assessed by NEAP. [b] shows the effect sizes that have been reported for the association between fractures and DAL which was assessed by PRAL

Table 2 Subgroup analysis based on random-effects models for the association between DAL and risk of fracture

Subgroup	Reported Effect sizes in 6 studies	Effect sizes (95% CI)	I^2 (%)	*P* Heterogeneity	*P* Within
Overall	11	1.10 (0.99, 1.21)	12.9	0.321	0.073
Design					
Cross-sectional	2	0.69 (0.47, 1.00)	0	0.370	0.052
Cohort	9	1.12 (1.03, 1.22)	0	0.808	0.006
DAL Method					
PRAL	8	1.09 (0.93, 1.28)	32.5	0.169	0.296
NEAP	2	1.03 (0.65, 1.63)	0	0.987	0.910
RNAE	1	1.05 (0.93, 1.19)	-	-	0.438
Gender					
Both	4	1.00 (0.74, 1.37)	0	0.984	0.980
Male	3	1.21 (0.93, 1.56)	5.9	0.346	0.157
Female	4	1.06 (0.89, 1.27)	62.4	0.047	0.511
Study quality					
Fair	2	0.69 (0.47, 1.00)	0	0.370	0.052
High	9	1.12 (1.03, 1.22)	0	0.808	0.006
Sample size (n)					
< 10,000	8	0.97 (0.81, 1.17)	0	0.557	0.788
> 10,000	3	1.15 (1.01, 1.31)	44.1	0.167	0.031
Follow-up (year)					
< 10	6	1.08 (0.88, 1.33)	0	0.978	0.450
> 10	3	1.15 (1.01, 1.32)	44.1	0.167	0.031
Health condition					
Healthy	7	1.04 (0.85, 1.28)	42.4	0.107	0.678
Postmenopausal women	2	1.07 (0.95, 1.20)	0	0.496	0.255
CVD risk/obesity	2	1.06 (0.63, 1.79)	0	0.884	0.818
Diet assessment					
FFQ	7	1.01 (0.90, 1.12)	0	0.505	0.891
Food record	4	1.22 (1.08, 1.38)	0	0.834	0.001

DAL: dietary acid load; CI: confidence intervals; PRAL: potential renal acid load; NEAP: net endogenous acid production; RNAE: renal net acid excretion; CVD: cardiovascular disease; FFQ: food frequency questionnaire

analysis showed that the exclusion of any effect size from the analysis did not exchange the pooled effect sizes (Supplemental Fig. 1).

Discussion

The current meta-analysis on observational studies disclosed that high DAL was marginally associated with a higher risk of fracture. It seems this marginally significant result was obtained from cohort studies. Based on subgroup analysis, high-quality studies and studies with more than 10,000 participants as well as studies that follows more than 10 years showed a positive significant association between DAL and risk of fracture.

Evidence indicates that dietary imbalance of acid- and alkali-producing foods may lead to chronic systemic acidosis due to an imbalance of CO_2 and HCO_3^- and cause metabolic disorders such as osteoporosis in older adults [45]. The glomerular filtration rate (GFR) decreases by 50% from age of 20–80 years, therefore, the daily produced acid should be justified to preserve the neutral body pH [46]. On the other hand, impaired renal function was associated with fracture risk [47] and disturbances in bone metabolism [48]. Moreover, metabolic acidosis could enhance the release of calcium from the bone matrix, thus making bones susceptible to fracturing by increasing osteoclastic resorption [21]. A prospective study reported that urinary citrate as a dependent biomarker on both diet and acid-base balance was inversely associated with fracture risk, while urinary PRAL was significantly associated with fracture risk in women but not in men [49]. Also, the impact of metabolic acidosis on bone health can include decreased insulin sensitivity and disruption of glucose balance, ultimately resulting in inflammation and oxidative stress [21, 50]. Therefore, insulin resistance and inflammation are believed to be possible factors contributing to the link between acidity and bone health [51, 52].

Therefore, dietary management in adults or older adults is needed to decline the acidity of the body and prevent metabolic disorders. Diets that consist of high amounts of vegetables and fruits showed lower rates of bone loss. Vegetables and fruits tend to promote systemic

alkalinity and cause a lower PRAL due to increasing bicarbonate. In contrast, some foods that are rich in Sulphur-containing amino acids (methionine and cysteine) such as grains, meats, and cheeses generate hydrogen ions and increase acidity which is the opposite effect in comparison to bicarbonate [21]. Five servings/day of vegetables and fruits was associated with a lower risk of hip fracture in a large study of both genders in Sweden, compared to no consumption of vegetables and fruits [53]. Moreover, in a previous study, the Mediterranean dietary pattern as a diet that contains high amounts of vegetables and fruits was associated with a 20% lower risk of hip fracture [54]. The Framingham Heart Study presented that greater intakes of fruits, vegetables, magnesium, and potassium were associated with higher BMD in men [55]. Potassium not only impacts acid-base balance but also acts as a surrogate measure of bicarbonate and leads to maintaining calcium hemostasis through urinary calcium excretion [56].

As mentioned, bone can be affected by DAL regarding that bone is involved by a buffering system for alkali components such as potassium and calcium and acid components such as protein sources [57]. Therefore, DAL might influence the risk of fracture by influencing bone mass density (BMD) [31]. It may be hypothesized that there is a non-linear association between DAL and bone; for example, one mechanism is related to dietary proteins that have both catabolic and anabolic effects on bone, catabolic due to the acidity property of proteins and anabolic for the amino acids as the important substrates of building bone matrix [58]. Also, a previous review demonstrated that high NEAP score were associated with a lower spinal and femoral BMD [59]. Consistent with a nonlinear relationship, García-Gavilán et al. found a U-shaped association between DAL and fracture [38]. In a prospective cohort study on 4672 individuals aged 45 years and over, they found no significant association between DAL and BMD [31]. However, they found inconsistent results which showed the probable detrimental effect of DAL on bone health by influencing the trabecular integrity without necessarily altering BMD [31]. Also, Jonge et al. results did not support that high DAL is associated with low BMD, however, their included population had a low median of DAL with a small variance [31] in comparison to other studies [60, 61]. According to cross-sectional analysis of the Geneva Retirees Cohort [37], BMD, bone microstructure and strength were not different or were slightly better in women or men with an acidic diet compared to those with alkaline/neutral diets. Findings from Wynn et al. revealed that lower NEAP was significantly associated with higher broadband ultrasound attenuation, however, the small sample size must be considered in interpretation [62]. Our results revealed that high DAL was not significantly associated with a greater risk of freacture in all methots including PRAL and NEAP/RAE. Our finding may be derived for a few numbers of included effect sizes in these scores. Moreover, for NEAP method does not take into account various nutrients and the absorption rate of included nutrients in its formula [62]. Since we observed no significant association between NEAP and fractures based on subgroup analysis, according to a previous study [62] estimation of NEAP from 24-h urine collection may be more useful for future.

Moreover, protein is one of the other important contributors to DAL. In contrast to the overall finding of our study, a meta-analysis of 12 cohort studies found that total dietary protein can reduce just hip fracture risk, however, they concluded that evidence was insufficient to find that result was drawn by vegetable or animal protein. Moreover, they found no association between total, vegetable, or animal protein and all other fractures [63]. Dargent-Molina et al. found a trend of increasing fracture risk with high protein-high acid ash diets, however, they did not find any significant association between overall protein intake and risk of fracture [42]. Proteins may promote bone health by supplying substrate for collagen formation and raising insulin-like growth factor-1, a well-known bone growth factor [64]. Also, probably low-sulfate protein sources such as soy may be beneficial in osteoporosis-related outcomes through a reduction in DAL [65]. On the other hand, the methods that were used to assess dietary intake should be considered to discuss the results. Based on our findings, studies that evaluated the dietary intake by food record showed a positive meaningful association between DAL and fracture ($P_{between\ studies}$= 0.001), but there was no significant association in studies that assessed dietary intake by FFQ. Due to recall bias, FFQ is prone to measurement errors and subjects' memory or motivation to assess dietary intakes [31, 66].

In the present study, DAL was not associated with fracture risk in women or men. However, according to previous studies, it seems gender could be a confounder variable and must be considered in the discussion or future studies. Welch et al. found no association between PRAL and broadband ultrasound attenuation in men, however, bone density and broadband ultrasound attenuation decreased with age in women [43]. Age-related metabolic acidosis as a consequence of renal function dysfunction could be pathophysiologically involved in developing osteoporosis prevalence with aging [67]. Moreover, reduced production of circulating estrogen during and after menopause leads to bone loss and probably the effects of metabolic acidosis could interact with the effects of estrogen withdrawal in women [43].

To the author's knowledge, it is the first systematic review and meta-analysis that studied the association

between DAL and bone fractures. As associations between DAL and bone health and fractures have been studied extensively with conflicting results [31, 36, 37], a systematic review and meta-analysis seem to be beneficial to summarize results. Also, most of the included studies were prospective cohort studies with high quality and low heterogeneity. Moreover, different measures of DAL were considered as subgroup analyses. All included studies reported the adjusted effect sizes for physical activity which is an important confounder in the association of DAL and fracture/BMD. Several limitations should be considered for future studies. Although we have performed a comprehensive literature search, causality cannot be indicated due to the observational nature of the included studies and its suggest to assess the results of trials in the future. Moreover, all type of fractures were considered in this study and we did not find an overall estimation according to specific types of fracture. Regarding insufficient data, we did not perform subgroup analysis by biomarkers of DAL such as serum bicarbonate levels and urinary pH. The included studies except for Jia et al. [30] and Garcia-gavilan et al. [38] did not assess GFR, while it can be a confounder for the real relationship between DAL and bone fractures in different ages and health/disease conditions. Changes in acid-base intake can differ throughout seasons due to variations in fruit/vegetable intakes during summer or winter [30]; thus this can be considered a confounding variable in future studies.

Conclusion

In the present meta-analysis, we found a marginally significant association between DAL and bone fractures which were significantly highlighted in high-quality cohort studies. It seems the dietary balance of acidogenic ingredients of diet (e.g. dairy, meats, and animal proteins) with alkalinogenic ingredients (e.g. vegetables and fruits) is important for bone health and should be considered in dietary management for the prevention and improvement of osteoporosis among adults. Further original studies throughout the world; not just in European countries and also with more participants are needed to approve or reject our findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08495-1.

Supplementary Material 1

Supplementary Material 2

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The present study has been approved by the committee of the Non-Communicable Diseases Research Center of Alborz University of Medical Sciences (Grant Number: 103–4544).

Author contributions
AM and ED designed the study. MD and OA performed searching, screening, and extracting data processes and ED rechecked them. AM and VB wrote the first draft of the manuscript. ED performed the statistical analysis. ED edited whole the manuscript. All authors confirmed the last version of the paper.

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Data availability
Due to the nature of this research, data was a secondary database that was extracted from initial studies and gathered in an Excel file. The datasets generated and analyzed during the current study are not publicly available due to ethical reasons but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The present study has been approved by the committee of the Non-Communicable Diseases Research Center of Alborz University of Medical Sciences (Grant Number: 103–4544).

Consent for publication
Not applicable.

Conflict of interest
Atieh Mirzababaei, Mojtaba Daneshvar, Vahid Basirat, Omid Asbaghi, and Elnaz Daneshzad declare that they have no conflict of interest and all authors confirmed this issue.

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