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Assessing the role of dietary acid load in the development of hypertensive disorders during pregnancy: uncovering the association through prospective cohort analysis

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Abstract

Background Hypertensive disorders of pregnancy (HDPs) are common complications encountered in pregnancy that affect between 5% and 15% of pregnancies worldwide. Some studies have associated adherence to a diet with a high acid load with an increased risk of HDPs. This study investigates the association between Dietary Acid Load (DAL) and the incidence of preeclampsia, chronic hypertension (HTN), and gestational hypertension (GHTN).

Methods Pregnant women aged 18 to 45 in the first trimester of pregnancy were selected and followed up until delivery. Diet was evaluated using a 168-question semi-quantitative food frequency questionnaire (FFQ). After calculating the DAL score, the inverse probability weight of the propensity scores, estimated from augmented generalized models, was used to obtain a causal risk ratio (RR) adjusted for potential confounders.

Results Out of 1,856 women, 92 (4.95%) developed preeclampsia. The potential renal acid load (PRAL) score ranged from − 16.14 to 0.58, while the net endogenous acid production (NEAP) score ranged from 34.61 to 50.15. Multivariable analysis revealed a significant association between PRAL and preeclampsia in the first (aRR: 1.87, 95% CI: 1.01, 3.49, $p=0.048$) and third (aRR: 2.01, 95% CI: 1.07, 3.81, $p=0.030$) quartiles compared to the reference group (Q2). No significant linear association was found in continuous analyses. For chronic HTN, significant associations were observed in the first (aRR: 2.56, 95% CI: 1.21, 5.42, $p=0.014$) and fourth (aRR: 4.79, 95% CI: 2.37, 9.71, $p<0.001$) PRAL quartiles, with similar findings for NEAP. Continuous analysis showed a significant linear association between both PRAL and NEAP scores and chronic HTN. Regarding GHTN, significant associations were found in the first (aRR: 1.48, 95% CI: 1.02, 2.16, $p=0.041$) and fourth (aRR: 1.88, 95% CI: 1.31, 2.70, $p=0.001$) PRAL quartiles, and in Q4 for NEAP (aRR: 1.56, 95% CI: 1.10, 2.21, $p=0.012$), with no significant linear association in continuous analysis.

Conclusion Extremes in DAL, as indicated by PRAL and NEAP, are associated with an increased risk of preeclampsia, chronic HTN, and GHTN, particularly in the highest and lowest quartiles. These findings highlight the potential impact of DAL on HDPs.

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Keywords Dietary acid load, Potential renal acid load, Net endogenous acid production, Preeclampsia

Background

Hypertensive disorders of pregnancy (HDPs) are common complications encountered in pregnancy that affect between 5% and 15% of pregnancies worldwide [1]. Despite advances in prenatal care, the etiology of these conditions remains complex and multifactorial, involving genetic, environmental, and lifestyle factors [2].

Besides non-modifiable risk factors, some studies have associated certain dietary patterns with HDPs. Dietary fiber, magnesium, potassium, calcium, and polyunsaturated fatty acids (PUFA) at the nutrient level, as well as fruits, vegetables, and the Mediterranean diet at the food level, have been shown to potentially attenuate the risk of HDPs [3, 4]. However, it is important to note that there are numerous studies with negative results as well, indicating the need for further research to clarify these associations [5–10]. Analyzing combinations of foods rather than single nutrients can inform more feasible clinical interventions and conclusions [5]. Diet not only provides calories and essential nutrients but also is the primary source of acid-base content through a combination of acid and base precursors [11, 12]. More than a ten-fold discrepancy in internal acid production amongst individuals can largely be attributed to dietary differences [13].

DAL encapsulates the balance between acid-forming and base-forming elements in dietary consumption. High-protein and phosphorus foods generally contribute to an accumulated acid load, while potassium-rich foods - typically fruits and vegetables - tend to tip the scale towards the alkaline range, thus reducing the DAL. DAL is mainly measured using two approaches in epidemiological studies: (1) NEAP which estimates the amount of acid produced endogenously, and (2) PRAL which calculates the acid load after food metabolization [12]. These considerations of dietary balance entered the scientific vernacular towards the latter part of the 20th century. The intriguing interplay between DAL and various health issues has been the centerpiece of multiple research studies. Predominant high DAL regimens have been shown to predispose populations to atherosclerosis [14], cardiovascular disease [15], metabolic disease [15], chronic kidney disease [16, 17], diabetes [18], insulin resistance [19], HTN [20], defective bone mineral density disorder [21], obesity [22], muscular mass loss [23], renal lithiasis [24], and non-alcoholic fatty liver disease [25]. One focal point has been its possible association with blood pressure disorders [20]. DAL is associated with hyperuricemia which is an independent risk factor for HTN and preeclampsia [26–28].

The conflicting trend on the impact of DAL on blood pressure has attracted researchers' attention [29]. While some studies have suggested an association between high DAL and increased risk of HTN in the general population, limited research has specifically addressed this association in pregnant women. Pregnancy induces significant physiological changes, including alterations in renal function and electrolyte balance, which may modify the impact of DAL on blood pressure [30, 31]. Moreover, the influence of DAL on HDPs may vary depending on other factors such as maternal age, body mass index (BMI), and pre-existing health conditions. Therefore, a comprehensive understanding of the association between DAL and HDPs requires a prospective cohort analysis that accounts for these potential confounders.

This study aims to fill this gap by examining the association between DAL and the risk of developing HDPs in a large, well-characterized cohort of pregnant women. By utilizing detailed dietary assessments and longitudinal follow-up, we aim to provide robust evidence on whether dietary acid load is a modifiable risk factor for HDPs. The findings from this study could have important implications for dietary recommendations and interventions aimed at reducing the burden of HDPs.

In this context, our study is designed to explore the potential role of DAL in the development of HDPs, using advanced statistical methods to account for confounding factors and assess the robustness of the observed associations. The results of this study will contribute to the growing body of evidence on the importance of dietary patterns in maternal health and may inform future guidelines on dietary management during pregnancy to prevent HDPs complications.

Methods

Study design and participants

The study named "Mothers and Their Children's Health" (MATCH), is a hospital-based longitudinal cohort involving pregnant women, accredited by Tehran University of Medical Science's Organizational Review boards (Approval Code: IR.TUMS.MEDICINE.REC.1398.576). This ongoing clinical research is guided by Arash Women's Hospital located in Tehran, Iran. Pregnant mothers in their first trimester, aged 18 to 45 years, were recruited from February 2020 to January 2023. The study's participant representation fairly reflects the Iranian female population during pregnancy. Comprehensive details of the methodology have been documented previously documented [32].

The study includes all pregnant women of Iranian nationality, aged 18 to 45, in their first trimester. Participants were enrolled from February 2020 to August 2021. Exclusion criteria include presence of metabolic

or chronic diseases, adherence to a special diet, use of specific food supplements (excluding pregnancy supplements like iron or folate), and any physical, mental, or cognitive impairments that impede participation or ability to provide informed consent.

Data collection

All eligible pregnant women were followed from the first trimester until delivery through face-to-face visits and phone calls. Ten trained interviewers collected data using ten structured questionnaires in four distinct visits: weeks 6–12, weeks 24–26, weeks 32–34, and 12–72 h post-delivery. Baseline data were collected before the 12th week of gestation, providing information on maternal demographics, lifestyle, medical and reproductive history, obstetric history, social history, sleep patterns and maternal nutritional status the year prior to pregnancy. Additionally, paternal demographics, social history, lifestyle, and family history were collected. Blood samples, anthropometric measurements, and dietary patterns, were only collected at the first prenatal visit. A second survey was conducted at 24 weeks of gestation (±14 days), focusing on maternal physical activity and maternal family history details. The third survey occurred at 32 weeks of gestation (±14 days) and included information on sleep disorders in early pregnancy. The final data collection point, completed 12–72 h after delivery, included birth outcome data such as gestational age, birth weight, size, delivery type, and any intrapartum or postpartum maternal and neonatal complications. All underlying past medical conditions were identified using participants' medical records and relevant documentation. This included a thorough review of their medical notes and any available diagnostic reports. By utilizing these valuable sources, we ensured a comprehensive assessment of the participants' medical histories. Maternal height, waist circumference, and hip circumference were measured only at the first visit, while maternal weight was measured at all four visits. Each measurement was taken twice, and the mean value was recorded. If the second measurement deviated by more than 1.5% from the first, a third measurement was taken, and the midpoint was recorded. Weight was measured using a digital scale (Seca 813) with a maximum capacity of 150 kg and an accuracy of 50 g. Participants were asked to remove their shoes, extra clothing, and empty their pockets before weighing. Infants were weighed without clothing using a baby scale (Seca 376), accurate to 10 g. Height was measured in the standing position without shoes, using a height scale (Seca 206) with an accuracy of one millimeter. Measurements were taken twice during two separate visits, and the average was recorded. If the second measurement differed by more than 1.5% from the first, a third measurement was taken, and the midpoint was recorded. During follow-ups, interviewers maintained regular contact with mothers via phone, email, or text message, and were notified if a participant gave birth at another hospital.

Food frequency questionnaire and dietary acid load estimation

This questionnaire was designed based on the structure of the Willet questionnaire and adjusted for Iranian food items. During the initial appointment, participants' dietary consumption was assessed using a structured 168-item FFQ. Conducted through interview, the FFQ enquired about the types/brands of foods eaten, cooking methods, consumption frequency, and quantities of food and beverages consumed over the year before pregnancy. Esfahani et al. confirmed the reproducibility and relative validity of the FFQ in the Tehran Lipid and Glucose Study (TLGS) in Iran [33]. The FFQ covers various items including legumes, meat types, oils, and rice, focusing primarily on individual food items except for composite dishes like pizza; salads, soups, and stews are also included. Respondents indicated how often they consumed these foods, with options ranging from daily (e.g., bread, rice), weekly or monthly (e.g., meat, fish), annually (e.g., organ meats), or never. Portion sizes were measured in standard servings (e.g., a slice of bread, a medium-sized apple, or a glass of milk) or household terms (e.g., a tablespoon of beans, a chicken thigh, a chicken breast, or a medium or full plate of cooked rice). Daily consumption of each food was calculated by multiplying frequency by portion size. Portion sizes were converted to grams per week per food item. Average consumption frequencies were input into Nutritionist 4 software (First Databank Inc., Hearst Corp., San Bruno, CA, USA) by two expert nutritionists, which calculated micro/macronutrients. PRAL and NEAP were subsequently determined based on a method developed by Remer et al. [11], and quartiles of the scores were used for statistical analysis:

1. PRAL (mEq/day) = (0.49×protein [g/day]) + (0.037×phosphorus [mg/day]) – (0.021 × potassium [mg/day]) – (0.026 × magnesium [mg/day]) – (0.013 × calcium [mg/day])
2. NEAP (mEq/day) = (54.5 × protein [g/day] / potassium [mEq/day]) – 10.2.

Methods for assessment of hypertensive disorders

HDPs during pregnancy were assessed following the criteria established by the American College of Obstetricians and Gynecologists (ACOG). These disorders include GHTN, preeclampsia, and chronic HTN.

GHTN was defined as new-onset HTN (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg) occurring after 20 weeks of gestation

in a previously normotensive woman, without significant proteinuria.

Various professional organizations have proposed multiple definitions for diagnosing preeclampsia, as detailed in scholarly literature. This has led to the creation of numerous guidelines by professional bodies globally for diagnosing and treating preeclampsia. For this research, the World Health Organization's (WHO) classification for HDPs was selected. This classification provides a consensus definition deemed suitable for research purposes. According to the WHO, preeclampsia is characterized by new-onset HTN after the 20th week of gestation in previously normotensive pregnant women, accompanied by proteinuria (protein > 300 mg/day in urine).

Chronic HTN was defined as HTN (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) diagnosed before pregnancy or before 20 weeks of gestation, or that persisted beyond 12 weeks postpartum.

Blood pressure and proteinuria assessment

In our study, blood pressure and proteinuria were assessed following rigorous protocols guided by the WHO classification for HDPs. This approach was selected due to its comprehensive and widely accepted criteria, ensuring the reliability of our findings.

Blood pressure was measured using a regularly calibrated aneroid sphygmomanometer (Seca b10) in a controlled environment. To ensure accuracy, measurements were taken in a calm setting with a suitable temperature. Participants were seated in an upright position, with their back supported and the right arm placed on a table at heart level to ensure consistency in readings. Excess clothing that might constrict arm blood flow was removed. Before the measurement, participants were instructed to relax for 3–5 min to stabilize their cardiovascular state. They were also asked to avoid intense physical activity, heavy meals, coffee, alcohol, stimulant drugs or drinks, and tobacco for at least 30 min prior to the assessment. This pre-measurement protocol aimed to minimize any external factors that could influence blood pressure readings. Blood pressure was measured twice, with a five-minute interval between the measurements, and the average of these two readings was recorded as the participant's blood pressure, providing a reliable and consistent measure.

Proteinuria was assessed by measuring the protein concentration in a 24-hour urine collection, with a threshold of > 300 mg/day indicating a positive diagnosis. This approach aligns with WHO guidelines, which emphasize the importance of accurate protein measurement in diagnosing preeclampsia. This methodology, based on WHO guidelines, ensures that the assessment of both blood pressure and proteinuria is conducted with precision and in accordance with globally recognized standards.

Sample size

We sorted and categorized the participants into quartiles 1–4 (Q1 had the least acidic diet, whereas Q4 had the most acidic diet) according to the PRAL and NEAP score. The required sample size is determined by considering cumulative incidence (Risk) of HDPs into quartiles 1–4. It was assumed that a total sample of 347 women (1735 women per group), which included a 10% dropout factor would provide 80% power to detect a 60% difference (RR = 1.6) in the proportion of HDPs between the quartiles.

Statistical analysis

Baseline characteristics were delineated as mean values with standard deviation (± SD) and analyzed using one-way analysis of variance (ANOVA) and independent sample t-tests. Categorical variables were denoted as frequencies and percentages, with the Chi-square test applied for comparative analysis. For estimating participants' propensity scores for DAL, we employed a generalized boosted model (GBM) to achieve covariate equilibrium between the quartiles of PRAL and NEAP. The 'TWANG' package, which incorporates nonparametric machine learning through GBMs with 10,000 regression trees, was used to generate the propensity scores. Directed acyclic graphs (DAGs) were utilized via dagitty.net to identify the minimal sufficient set of covariates (Fig. 1). The key confounders identified included age, BMI, alcohol consumption, current smoking, passive smoking, physical activity, and a history of preeclampsia in prior pregnancies. These variables were chosen based on their potential to confound the association between DAL and preeclampsia and were included in the propensity score model to balance the covariates across the PRAL and NEAP quartiles. The propensity scores were then used to perform inverse probability weighting (IPW), ensuring that the exposed groups (i.e., different quartiles of PRAL and NEAP) were comparable with respect to the identified covariates. This method allowed us to estimate the average treatment effect by creating a pseudo-population in which the distribution of measured baseline covariates was independent of the treatment assignment. The association between DAL and the incidence of HDPs was quantified using risk ratios (RRs) along with their 95% confidence intervals (CI), estimated through IPW. This approach enabled us to account for the potential confounding effects of the covariates and to provide a more accurate estimate of the association between DAL and HDPs. Data handling and statistical evaluations were conducted using Stata version 17 (StataCorp LP, College Station, TX, USA) and R version 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria).

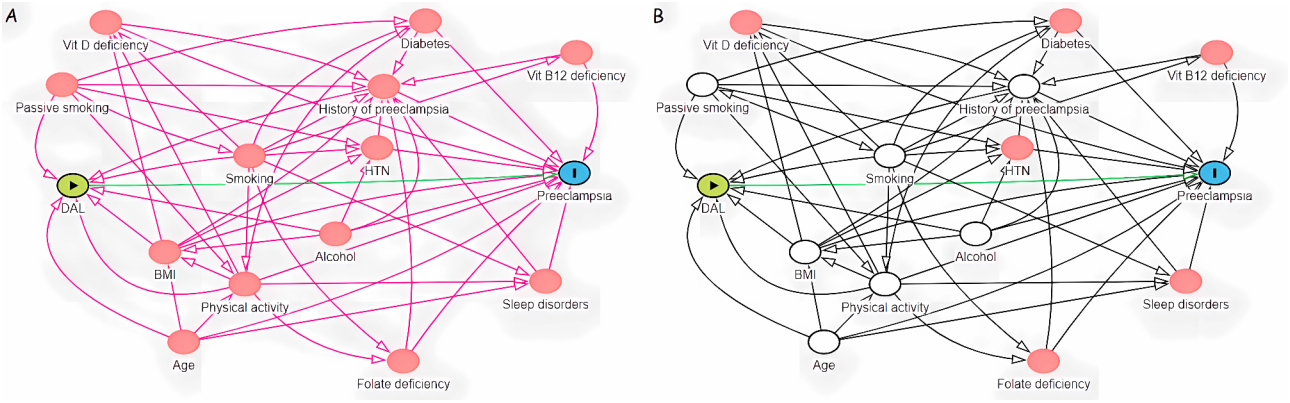

Fig. 1 Directed acyclic graphs, **A**: Unadjusted, **B**: Adjusted

Results

The flow chart in Fig. 1 illustrates the number of pregnant women examined at each time point, as well as the number of lost-to-follow-ups and the reasons for dropouts. Over the period from 1 February 2020 to January 2023, a total of 3,285 women underwent screening. Subsequently, 1,182 participants were excluded for the following reasons: (1) planned to deliver elsewhere (n=486, 41.11%); (2) gestational age>12 weeks (n=328, 27.74%); (3) multiple pregnancies (n=125, 10.57%); (4) presence of metabolic or chronic diseases (n=114, 9.64%); (5) following a special diet (n=32; 2.71%); and (6) declined participation (n=97, 8.20%). Finally, 2,103 women met the initial eligibility criteria for participation, and 1,856 of them completed the study, while 247 (11.74%) had incomplete follow-up data (Fig. 2). At baseline, the average age was 32.9±6.1 years, and the average BMI was 25.9±8.3 kg/m^2. Among all participants, 149 (7.5%) were employed and 845 participants (45.5%) had an academic education.

Characteristics of the study participants

In our study, we identified 109 women (5.88% of the cohort) with chronic hypertension and 249 women (13.42% of the cohort) with gestational hypertension. Throughout the follow-up period, 92 women (4.95% of the cohort) developed preeclampsia. These findings underscore the prevalence of hypertensive disorders within our study population, which were subsequently considered in our analysis to evaluate the association between dietary acid load (DAL) and hypertensive outcomes during pregnancy. Table 1 display the demographic and clinical characteristics of women with and without preeclampsia. Participants diagnosed with preeclampsia were generally older (averaging 35.1±6.3 years) and had a higher body weight (averaging 71.9±12.1 kg) compared to those without preeclampsia, who averaged 32.8±5.9 years in age and 65.4±12.5 kg in weight, these differences were statistically significant (p<0.001). Additionally, a higher non-significant proportion of women with preeclampsia had pre-existing HTN (8.7% compared to 5.7%; p=0.238), and had a family history of HTN (51.1% compared to 47.4%; p=0.069).

Table 2 outlines the baseline demographic and clinical characteristics of women grouped by PRAL quartiles. The average PRAL index was 2.82 mmol/100 g, with a standard deviation of 2.56, ranging from a minimum of -16.14 to a maximum of 0.58. Women with higher PRAL scores, indicating a diet more inclined toward acidity, had higher pre-pregnancy weight, waist/hip ratio, pre-existing diabetes, and HTN, and a higher calorie intake. There was no significant difference in maternal age, reproductive history, sleep disorders, body mass index, existing HTN, existing diabetes, or smoking patterns among the different PRAL quartiles.

Table 3 details the baseline demographics and clinical characteristics of the participants, segmented by NEAP quartiles. On average, the NEAP score was recorded at 2.82 mmol/100 g, with a standard deviation of 2.56, spanning from a low of 34.61 to a high of 50.15 mmol/100 g. Participants with higher NEAP scores, reflecting an endogenous shift towards acid production, tended to exhibit increased pre-pregnancy weights, waist-to-hip ratios, prevalence of pre-existing diabetes, and pre-existing HTN, along with a higher daily caloric intake. However, no significant differences were observed in terms of maternal age, reproductive background, sleep disorders, body mass index, current HTN, diabetes, or smoking habits when compared across NEAP score quartiles.

Association between dietary acid load and preeclampsia

Tables 4 and 5 displays the crude and adjusted RRs that measure the link between DAL and preeclampsia. Regarding PRAL quartiles, the unadjusted analysis did not exhibit any significant association with preeclampsia incidence. After adjusting for potential confounders such as age, BMI, alcohol consumption, current smoking, passive smoking, physical activity, and history

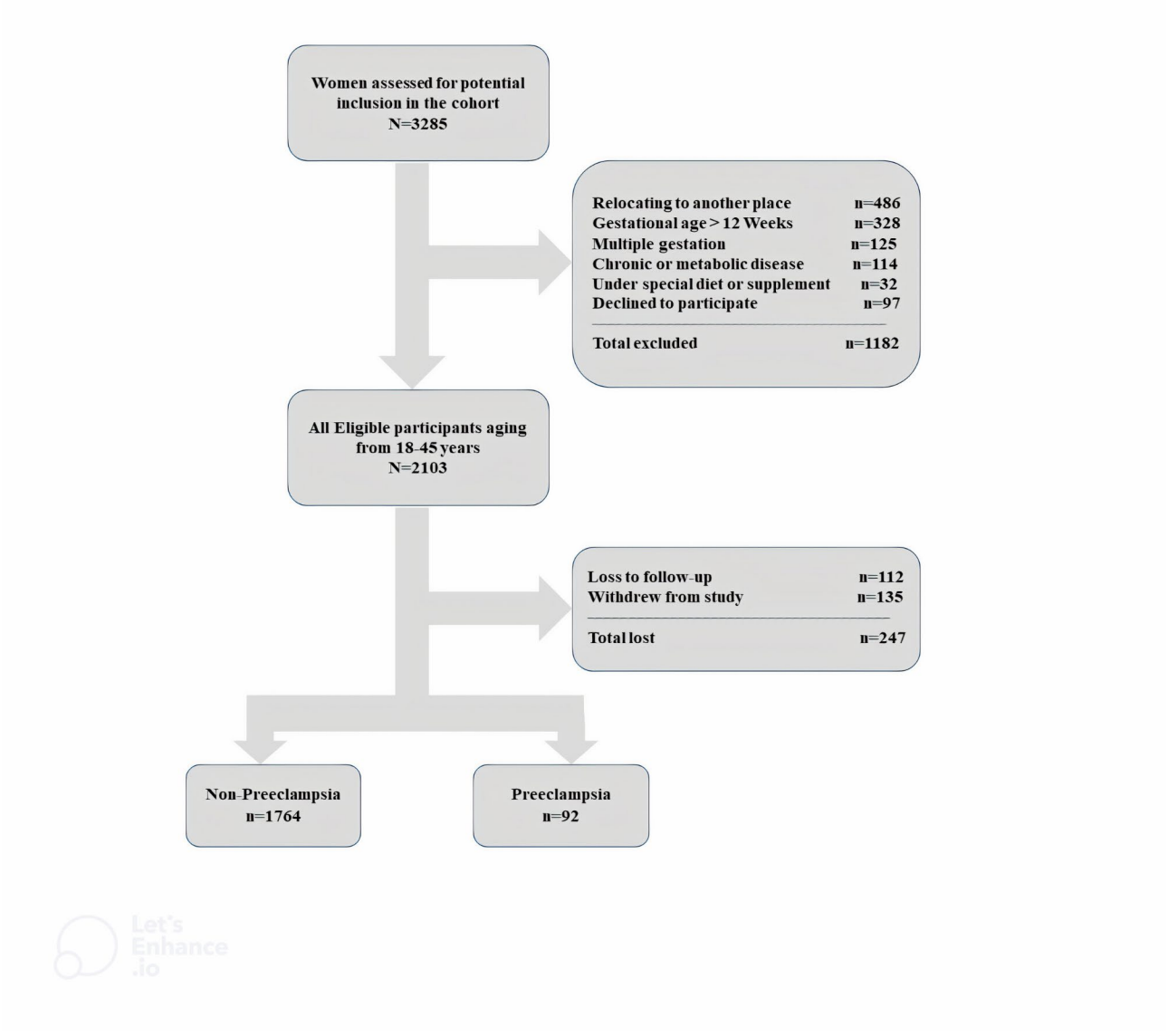

Fig. 2 Demonstrates the study participant flow, reflecting recruitment, enrollment, and the quantities of women diagnosed with or without preeclampsia. It also presents the reasons for exclusions, along with the corresponding numbers

of preeclampsia in prior pregnancies, the multivariable analysis demonstrated a higher risk of preeclampsia for patients in the first (aRR: 1.87, 95% CI: 1.01, 3.49, $p=0.048$) and third (aRR: 2.01, 95% CI: 1.07, 3.81, $p=0.030$) quartiles of PRAL score compared to the reference group (second quartile). However, the continuous analysis did not indicate any linear association between PRAL and preeclampsia incidence (aRR: 0.99, 95% CI: 0.98, 1.01, $p=0.931$) (Table 4). As shown in Table 5, the unadjusted analysis suggested no significant association between NEAP and preeclampsia. This lack of significance persisted even after adjusting for the aforementioned confounders.

Association between dietary acid load and gestational hypertension and chronic hypertension

Table 6 presents the crude and adjusted RRs for the association between DAL and the incidence of chronic HTN. When examining PRAL quartiles, a significant association was observed in the first (Q1) and fourth (Q4) quartiles compared to the reference group (Q2). Specifically, after adjusting for confounders, participants in Q1 and Q4 had a higher risk of developing chronic HTN (aRR: 2.56, 95% CI: 1.21, 5.42, $p=0.014$ for Q1; aRR: 4.79, 95% CI: 2.37, 9.71, $p<0.001$ for Q4). In contrast, the third quartile (Q3) did not show a significant association with chronic HTN (aRR: 1.65, 95% CI: 0.73, 3.73, $p=0.223$).

Similarly, for NEAP, significant associations were found in Q4 compared to the reference group (Q2). After

Table 1 Baseline characteristics of non-pregnant women according to prospective development of preeclampsia ($n=1,856$)

	PE incidence ($n=92$)	No PE ($n=1,764$)	*p*-value
Age (year)[a]	35.1 ± 6.3	32.8 ± 5.9	< 0.001
Employment [b]			
Housewife	83 (90.2)	1,634 (92.6)	0.391
Employed	9 (9.8)	130 (7.4)	
Education status [b]			
Junior high school or lower	30 (32.6)	421 (23.8)	0.176
Senior high school	35 (38.1)	808 (46.1)	
Undergraduate college or higher	27 (29.3)	529 (30.1)	
Pre-pregnancy BMI (kg/m^2)[a]	28.1 ± 4.3	25.8 ± 8.4	0.014
Pre-pregnancy weight [a]	71.9 ± 12.1	65.4 ± 12.5	< 0.001
Gravidity [a]	1.1 ± 1.1	1.1 ± 1.1	0.528
Parity [a]	0.7 ± 0.8	0.8 ± 0.8	0.672
Live birth [a]	0.7 ± 0.8	0.7 ± 0.7	0.884
Smoking [b]			
Current smoker	13 (14.1)	355 (20.1)	0.379
Before smoker	3 (3.3)	88 (4.9)	
Passive smoker	4 (4.3)	89 (5.1)	
Non-smoker	72 (78.3)	1,232 (69.9)	
Waist circumference (cm) [a]	102.2 ± 10.7	96.6 ± 12.8	< 0.001
Hip circumference (cm) [a]	112.1 ± 8.4	106.31 ± 10.1	< 0.001
Waist/Hip ratio [a]	0.9 ± 0.1	0.9 ± 0.1	0.440
Pre-existing HTN [b]	8 (8.7)	101 (5.7)	0.238
Pre-existing DM [b]	14 (15.2)	175 (9.9)	0.104
Pre-existing GDM [b]	6 (6.5)	115 (6.5)	0.999
Family history of HTN [b]	47 (51.1)	731 (47.4)	0.069
Dietary caloric intake (kcal/day) [b]			
≤ 2300	38 (41.3)	755 (42.8)	0.777
> 2300	54 (58.7)	1,009 (57.2)	

PE: preeclampsia, BMI: body mass index, DM: diabetes mellitus, GDM: gestational diabetes mellitus, HTN: hypertension

[a] Values given as mean ± SD (standard deviation) and analyzed by independent t-test

[b] Values given as numbers (percentage) and analyzed by Chi-squared test or Fisher's exact test

Missing data: age, $n=10$ (0.5%); occupation, $n=1$ (0.1%); education, $n=7$ (0.4%); smoking, $n=11$ (0.6%); history of GDM, $n=1$ (0.1%); family history of diabetes, $n=3$ (0.2%); parity, $n=56$ (3%); BMI, $n=28$ (1.5%); dietary caloric intake, $n=4$ (0.2%); physical activity, $n=83$ (4.5%)

adjustment, the risk of chronic HTN was significantly higher in Q4 (aRR: 3.63, 95% CI: 1.99, 6.61, $p<0.001$), but no significant association was observed in Q3 (aRR: 0.96, 95% CI: 0.45, 2.05, $p=0.930$). The continuous analysis revealed a significant linear association between both PRAL and NEAP scores and the risk of chronic HTN (PRAL aRR: 1.02, 95% CI: 1.01, 1.03, $p=0.022$; NEAP aRR: 1.02, 95% CI: 1.01, 1.03, $p<0.001$).

These findings indicate that higher and lower extremes of DAL, as reflected by PRAL and NEAP scores, are associated with an increased risk of chronic HTN, with significant associations evident in the highest and lowest quartiles compared to the middle quartiles.

Association between dietary acid load and gestational hypertension

Table 7 presents the crude and adjusted RRs for the association between DAL and the incidence of GHTN. When examining PRAL quartiles, a significant association was found in the first (Q1) and fourth (Q4) quartiles compared to the reference group (Q2). Specifically, after adjusting for confounders, participants in Q1 and Q4 had a higher risk of developing GHTN (aRR: 1.48, 95% CI: 1.02, 2.16, $p=0.041$ for Q1; aRR: 1.88, 95% CI: 1.31, 2.70, $p=0.001$ for Q4). In contrast, the third quartile (Q3) did not show a significant association with GHTN (aRR: 1.43, 95% CI: 0.98, 2.10, $p=0.066$).

Similarly, for NEAP, significant associations were observed in Q4 compared to the reference group (Q2). After adjustment, the risk of GHTN was significantly higher in Q4 (aRR: 1.56, 95% CI: 1.10, 2.21, $p=0.012$), but no significant associations were found in Q3 (aRR: 1.14, 95% CI: 0.78, 1.65, $p=0.500$). The continuous analysis did not reveal any significant linear association between both PRAL and NEAP scores and the risk of GHTN (PRAL aRR: 1.00, 95% CI: 0.99, 1.01, $p=0.183$; NEAP aRR: 1.00, 95% CI: 0.99, 1.01, $p=0.881$). These findings indicate that extremes in DAL, as reflected by PRAL and NEAP scores,

Table 2 Baseline characteristics of participants by quartiles of the potential renal acid load (PRAL) score ($n = 1,856$)

Pre-pregnancy characteristic	PRAL score quartiles (mEq/day)				*p*
	Quartile 1 < −16.14 (*n* = 465)	Quartile 2 −16.15 to −6.89 (*n* = 466)	Quartile 3 −6.90 to 0.57 (*n* = 460)	Quartile 4 ≥ 0.58 (*n* = 465)	
Age (year)[a]	33.2 ± 6.1	32.7 ± 6.1	33.1 ± 5.8	32.8 ± 5.9	0.598
Employment [b]					
Housewife	431 (92.7)	438 (94.1)	420 (91.3)	428 (92.0)	0.456
Employed	34 (7.3)	28 (6.0)	40 (8.7)	37 (8.0)	
Education status [b]					
Junior high school or lower	114 (24.6)	110 (23.7)	115 (25.0)	112 (24.3)	0.941
Senior high school	217 (46.8)	218 (46.9)	206 (44.8)	202 (43.8)	
Undergraduate college or higher	133 (28.7)	137 (29.5)	139 (30.2)	147 (31.9)	
Pre-pregnancy BMI (kg/m^2)[a]	26.2 ± 9.0	25.4 ± 7.7	25.8 ± 10.3	26.2 ± 5.4	0.361
Pre-pregnancy weight [a]	66.4 ± 12.8	64.8 ± 12.8	65.1 ± 11.9	66.8 ± 12.8	0.039
Gravidity [a]	1.1 ± 1.1	1.1 ± 1.1	1.1 ± 1.1	1.1 ± 1.1	0.564
Parity [a]	0.7 ± 0.8	0.8 ± 0.7	0.8 ± 0.8	0.8 ± 0.8	0.819
Live birth [a]	0.7 ± 0.7	0.7 ± 0.7	0.7 ± 0.7	0.8 ± 0.8	0.856
Smoking [b]					
Current smoker	82 (17.6)	87 (18.7)	107 (23.3)	92 (19.8)	0.321
Before smoker	28 (6.1)	22 (4.7)	24 (5.2)	17 (3.7)	
Passive smoker	26 (5.6)	28 (6.1)	20 (4.3)	19 (4.1)	
Non-smoker	329 (70.8)	329 (70.6)	309 (67.2)	337 (72.5)	
Waist circumference (cm) [a]	97.2 ± 12.4	97.3 ± 13.2	97.1 ± 13.4	96.3 ± 12.2	0.598
Hip circumference (cm) [a]	107.6 ± 9.7	106.8 ± 10.3	106.9 ± 10.2	107.7 ± 10.5	0.590
Waist/Hip ratio [a]	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.028
Pre-existing hypertension [b]	27 (5.8)	12 (2.5)	18 (3.9)	52 (11.2)	< 0.001
Pre-existing diabetes [b]	49 (10.5)	34 (7.3)	46 (10.0)	60 (13.0)	0.041
Pre-existing GDM [b]	28 (6.0)	34 (7.3)	32 (7.0)	27 (5.8)	0.757
History of preeclampsia in prior pregnancies [b]	26 (5.6)	13 (2.8)	12 (2.6)	15 (3.2)	0.051
Dietary caloric intake (kcal/day) [b]					
≤ 2300	132 (28.4)	202 (43.3)	253 (55.0)	206 (44.3)	< 0.001
> 2300	333 (71.6)	264 (56.7)	207 (45.0)	259 (55.70)	
Physical activity (MET-h/week) [c]	2719 (3365, 3987)	3130 (3554, 4135)	2817 (3236, 3777)	2596 (3123, 3689)	0.796

PRAL: potential renal acid load, BMI: body mass index, GDM: gestational diabetes mellitus, MET: metabolic equivalent of task

[a] Values given as mean ± SD (standard deviation) and analyzed by independent t-test

[b] Values given as numbers (percentage) and analyzed by Chi-squared test or Fisher's exact test

[c] Values given as median ± IQR (inter quartile range) and analyzed by independent t-test

NEAP: net endogenous acid production, BMI: body mass index, GDM: gestational diabetes mellitus, MET: metabolic equivalent of task

are associated with an increased risk of GHTN, with significant associations observed in the highest and lowest quartiles, but no significant association was found when DAL was analyzed as a continuous variable.

Discussion

In this prospective cohort study, we explored the association between DAL and HDPs, including preeclampsia, chronic HTN, and GHTN. Our findings provide novel insights into the complex association between DAL and these adverse pregnancy outcomes, particularly emphasizing the significance of both high and low extremes of DAL in the risk of developing these conditions.

The association between DAL and preeclampsia, a major concern during pregnancy, yielded significant results. Our study demonstrated a notable statistical and clinical association between the dietary PRAL scale and the incidence of preeclampsia. Specifically, the probability of developing preeclampsia was 87% higher in the first quartile and 101% higher in the third quartile of PRAL compared to pregnant women in the second quartile. Additionally, the risk of developing preeclampsia in the third quartile of PRAL was 14% higher than in the first quartile, indicating that both higher and lower DALs may increase the risk of preeclampsia. However, our study did not reveal a consistent association for the fourth quartile of PRAL. Several factors, such as physiological changes during pregnancy, potential imprecision in DAL assessment, and limited statistical power due to the low incidence of preeclampsia, may account for this

Table 3 Baseline characteristics of participants by quartiles of the net endogenous acid production. (NEAP) score ($n=1,856$)

Pre-pregnancy characteristic	NEAP score quartiles (mEq/day)[a]				*p*
	Quartile 1 < 34.61 ($n=464$)	Quartile 2 34.62 to 41.79 ($n=463$)	Quartile 3 41.80 to 50.14 ($n=465$)	Quartile 4 ≥ 50.15 ($n=464$)	
Age (year) [a]	33.14 ± 6	32.59 ± 6.05	33.0 ± 5.92	33.05 ± 6.03	0.515
Employment [b]					
Housewife	430 (92.7)	423 (91.4)	432 (92.9)	432 (93.1)	0.743
Employed	34 (7.3)	40 (8.6)	33 (7.1)	32 (6.9)	
Education status [b]					
Junior high school or lower	113 (24.4)	109 (23.6)	103 (22.2)	126 (27.3)	0.560
Senior high school	214 (46.1)	214 (46.4)	222 (47.9)	193 (41.8)	
Undergraduate college or higher	137 (29.5)	138 (29.9)	138 (29.8)	143 (31.0)	
Pre-pregnancy BMI (kg/m^2)[a]	25.7 ± 7.5	25.7 ± 9.3	26.1 ± 10.4	26.37 ± 5.1	0.520
Pre-pregnancy weight [a]	65.4 ± 12.8	64.8 ± 12.6	65.6 ± 12.2	67.3 ± 12.5	0.023
Gravidity [a]	1.1 ± 1.1	1.0 ± 1.1	1.2 ± 1.1	1.1 ± 1.1	0.358
Parity [a]	0.8 ± 0.8	0.7 ± 0.7	0.8 ± 0.8	0.8 ± 0.8	0.083
Live birth [a]	0.7 ± 0.8	0.7 ± 0.7	0.8 ± 0.8	0.8 ± 0.8	0.122
Smoking [b]					
Current smoker	84 (18.1)	100 (21.6)	91 (19.6)	93 (20.0)	0.740
Before smoker	27 (5.8)	24 (5.2)	21 (4.5)	19 (4.1)	
Passive smoker	25 (5.4)	28 (6)	20 (4.3)	20 (4.3)	
Non-smoker	328 (70.7)	311 (67.2)	333 (71.6)	332 (71.6)	
Waist circumference (cm) [a]	96.2 ± 12.5	98.1 ± 13.0	96.9 ± 13.1	96.5 ± 12.6	0.134
Hip circumference (cm) [a]	106.8 ± 9.9	107.2 ± 10.2	107.3 ± 10.1	107.6 ± 10.5	0.821
Waist/ Hip ratio [a]	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.005
Pre-existing hypertension [b]	23(4.9)	16 (3.4)	15 (3.2)	55 (11.8)	< 0.001
Pre-existing diabetes [b]	47 (10.1)	39 (8.5)	40 (8.6)	63 (13.7)	0.031
Pre-existing GDM [b]	23 (5)	31 (6.7)	38 (8.2)	29 (6.3)	0.259
History of preeclampsia in prior pregnancies [b]	21 (4.5)	16 (3.5)	12 (2.6)	17 (3.7)	0.459
Dietary caloric intake (kcal/day) [b]					
≤ 2300	195 (42)	174 (37.6)	222 (47.7)	202 (43.5)	0.019
> 2300	269 (58)	289 (62.4)	243 (52.3)	262 (56.5)	
Physical activity (MET-h/week) [c]	2865 (3407, 4023)	2920 (1408, 4917)	2692 (1326, 5097)	2994 (1611, 4818)	0.796

[a] Values given as mean ± SD (standard deviation) and analyzed by independent t-test

[b] Values given as numbers (percentage) and analyzed by Chi-squared test or Fisher's exact test

[c] Values given as median ± IQR (inter quartile range) and analyzed by independent t-test

NEAP: net endogenous acid production, BMI: body mass index, GDM: gestational diabetes mellitus, MET: metabolic equivalent of task

Table 4 Risk ratio (95% CIs) for associations between the potential renal acid load (PRAL) at baseline and incidence of preeclampsia ($n=1,856$)

Quartile of the potential renal acid load (PRAL)	PE cases *n* (% pregnancies)	Model 1	*p*	Model 2	*p*
		cRR (95% CI)		aRR (95% CI)	
Quartile 1 ($n=465$)	27 (5.81)	1.80 (0.97, 3.34)	0.062	1.87 (1.01, 3.49)	0.048
Quartile 2 ($n=466$)	15 (3.22)	1 (reference)		1 (reference)	
Quartile 3 ($n=460$)	27 (5.87)	1.82 (0.98, 3.38)	0.057	2.01 (1.07, 3.81)	0.030
Quartile 4 ($n=465$)	23 (4.95)	1.53 (0.83, 2.90)	0.187	1.62 (0.84, 3.13)	0.147
Continuous [a]	92 (4.96)	0.99 (0.98, 1.01)	0.733	0.99 (0.98, 1.01)	0.931

Model 1 was a univariable model; model 2 was a multivariable model to account for potential confounding, the impact of the dietary acid load on preeclampsia was estimated using a propensity score approach. We used an inverse probability weighting estimator to estimate the average exposure effect. The propensity score was estimated using a gradient-boosting algorithm. The following variables were included in the propensity score model: body mass index (kg/m2), smoking, age, alcohol, physical activity, passive smoking and history of preeclampsia in prior pregnancies. Minimal sufficient adjustment sets were selected based on the directed acyclic graph (presented in Fig. 1)

[a] 1 SD increase in score

cRR: crude risk ratio, aRR: adjusted risk ratio, PE: preeclampsia

Table 5 Risk ratio (95% CIs) for associations between NEAP at baseline and incidence of preeclampsia ($n=1,856$)

Quartile of the net endogenous acid production (NEAP)	PE cases *n* (% pregnancies)	Model 1	*p*	Model 2	*p*
		cRR (95% CI)		aRR (95% CI)	
Quartile 1 ($n=465$)	27 (5.82)	1.41 (0.79, 2.51)	0.232	1.42 (0.80, 2.53)	0.224
Quartile 2 ($n=465$)	19 (4.10)	1 (reference)		1 (reference)	
Quartile 3 ($n=465$)	20 (4.30)	1.04 (0.56, 1.93)	0.881	1.03 (0.54, 1.95)	0.911
Quartile 4 ($n=465$)	26 (5.60)	1.36 (0.76, 2.43)	0.291	1.34 (0.74, 2.43)	0.322
Continuous [a]	369 (19.87)	0.99 (0.98, 1.01)	0.733	0.99 (0.97, 1.01)	0.154

Model 1 was a univariate model; model 2 was a multivariate model to account for potential confounding, the impact of dietary acid load on preeclampsia was estimated using a propensity score approach. We used inverse probability weighting estimator to estimate the average treatment effect. Propensity score was estimated using gradient boosting algorithm. The following variables were included in the propensity score model: body mass index (kg/m2), age, smoking, passive smoking, alcohol, physical activity and history of preeclampsia in prior pregnancies. Minimal sufficient adjustment sets selected based on directed acyclic graph (presented in Fig. 1)

[a] each 1 SD increase in score

cRR: crude risk ratio, aRR: adjusted risk ratio, PE: preeclampsia

Table 6 Risk ratio (95% CIs) for associations between the dietary acid load at baseline and incidence of chronic hypertension ($n=1,856$)

	Chronic HTN cases *n* (% pregnancies)	Model 1	*p*	Model 2	*p*
		cRR (95% CI)		aRR (95% CI)	
Quartile of the potential renal acid load (PRAL)					
Quartile 1 ($n=465$)	27 (5.81)	2.25 (1.15, 4.39)	0.017	2.56 (1.21, 5.42)	0.014
Quartile 2 ($n=466$)	12 (2.58)	1 (reference)		1 (reference)	
Quartile 3 ($n=460$)	18 (3.91)	1.51 (0.73, 3.12)	0.255	1.65 (0.73, 3.73)	0.223
Quartile 4 ($n=465$)	52 (11.21)	4.35 (2.35, 8.05)	<0.001	4.79 (2.37, 9.71)	<0.001
Continuous [a]	109 (5.88)	1.02 (1.01, 1.03)	0.015	1.02 (1.01, 1.03)	0.022
Quartile of the net endogenous acid production (NEAP)					
Quartile 1 ($n=465$)	23 (4.96)	1.43 (0.76, 2.68)	0.258	1.60 (0.81, 3.12)	0.169
Quartile 2 ($n=466$)	16 (3.46)	1 (reference)		1 (reference)	
Quartile 3 ($n=460$)	15 (3.23)	0.93 (0.46, 1.86)	0.846	0.96 (0.45, 2.05)	0.930
Quartile 4 ($n=465$)	55 (11.88)	3.43 (1.99, 5.91)	<0.001	3.63 (1.99, 6.61)	<0.001
Continuous [a]	109 (5.88)	1.02 (1.01, 1.03)	<0.001	1.02 (1.01, 1.03)	<0.001

Model 1 was a univariable model; model 2 was a multivariable model to account for potential confounding, the impact of the dietary acid load on preeclampsia was estimated using a propensity score approach. We used an inverse probability weighting estimator to estimate the average exposure effect. The propensity score was estimated using a gradient-boosting algorithm. The following variables were included in the propensity score model: body mass index (kg/m2), smoking, age, alcohol, physical activity, and passive smoking. Minimal sufficient adjustment sets were selected based on the directed acyclic graph (presented in Fig. 1)

[a] 1 SD increase in score

cRR: crude risk ratio, aRR: adjusted risk ratio, HTN: hypertension

inconsistency. Moreover, while the crude and multivariable analysis of the NEAP scale did not indicate a significant association with preeclampsia, the continuous analysis of PRAL did not reveal a significant linear association either, suggesting that the association between DAL and preeclampsia may be non-linear and influenced by specific dietary thresholds rather than a gradual increase in risk across the spectrum of PRAL scores.

Our investigation into chronic HTN revealed a clearer association with DAL. Both extremes of PRAL and NEAP were significantly associated with an increased risk of chronic HTN. Participants in the lowest and highest PRAL quartiles, as well as the highest NEAP quartile, exhibited a markedly higher risk of developing chronic HTN compared to those in the second quartile. Moreover, a significant linear association was observed in the continuous analysis for both PRAL and NEAP, reinforcing the robustness of our findings and suggesting a direct impact of DAL on chronic HTN risk.

Similarly, the analysis of DAL in relation to GHTN also demonstrated significant associations in the extreme quartiles of PRAL and NEAP, with higher risks observed in the lowest and highest quartiles compared to the reference group. Interestingly, as with preeclampsia, the continuous analysis did not reveal a significant linear association between DAL and GHTN, further highlighting the possibility of a threshold effect in the association between DAL and HDPs outcomes.

These findings collectively indicate that the association between DAL and HDPs is complex and likely influenced by specific dietary patterns that create either high or low acid loads. The increased risk observed at both extremes of DAL underscores the importance of maintaining a balanced diet during pregnancy, as both excessive and insufficient acid-producing foods may contribute to adverse

Table 7 Risk ratio (95% CIs) for associations between the dietary acid load at baseline and incidence of gestational hypertension ($n = 1,856$)

	GHTN cases *n* (% pregnancies)	Model 1	*p*	Model 2	*p*
		cRR (95% CI)		aRR (95% CI)	
Quartile of the potential renal acid load (PRAL)					
Quartile 1 ($n = 465$)	62 (13.33)	1.32 (0.92, 1.88)	0.125	1.48 (1.02, 2.16)	0.041
Quartile 2 ($n = 466$)	47 (10.09)	1 (reference)		1 (reference)	
Quartile 3 ($n = 460$)	59 (12.83)	1.27 (0.88, 1.82)	0.192	1.43 (0.98, 2.10)	0.066
Quartile 4 ($n = 465$)	81 (17.42)	1.72 (1.23, 2.41)	0.001	1.88 (1.31, 2.70)	0.001
Continuous [a]	249 (13.42)	1.00 (0.99, 1.01)	0.163	1.00 (0.99, 1.01)	0.183
Quartile of the net endogenous acid production (NEAP)					
Quartile 1 ($n = 465$)	63 (13.58)	1.21 (0.86, 1.70)	0.280	1.30 (0.91, 1.86)	0.154
Quartile 2 ($n = 466$)	52 (11.23)	1 (reference)		1 (reference)	
Quartile 3 ($n = 460$)	58 (12.47)	1.11 (0.78, 1.58)	0.559	1.14 (0.78, 1.65)	0.500
Quartile 4 ($n = 465$)	76 (16.38)	1.49 (1.05, 2.03)	0.024	1.56 (1.10, 2.21)	0.012
Continuous [a]	249 (13.42)	1.00 (0.99, 1.01)	0.942	1.00 (0.99, 1.01)	0.881

Model 1 was a univariable model; model 2 was a multivariable model to account for potential confounding, the impact of the dietary acid load on preeclampsia was estimated using a propensity score approach. We used an inverse probability weighting estimator to estimate the average exposure effect. The propensity score was estimated using a gradient-boosting algorithm. The following variables were included in the propensity score model: body mass index (kg/m2), smoking, age, alcohol, physical activity, and passive smoking. Minimal sufficient adjustment sets were selected based on the directed acyclic graph (presented in Fig. 1)

[a] 1 SD increase in score

cRR: crude risk ratio, aRR: adjusted risk ratio, GHTN: gestational hypertension

HDPs outcomes. Further research is needed to elucidate the underlying mechanisms driving these associations and to establish clear dietary guidelines for pregnant women to mitigate the risk of HDPs. Overall, our findings suggest that it may be beneficial for pregnant women to follow a standardized dietary regimen with consistent levels of DAL, avoiding both extremes, to reduce the likelihood of developing these conditions.

Numerous studies have been carried out over the past decades to examine the association between prenatal and pre-pregnancy dietary habits and negative outcomes in pregnancy and neonatal health. The results of these investigations, however, have varied and lacked consistency. This research marks one of the initial attempts to assess the association between DAL and the development of HDPs. The impacts of maternal DAL on pregnancy-related complications are not yet fully understood. While prior studies in non-pregnant populations have yielded inconsistent results regarding the impact of DAL on HTN risk, this investigation contributes novel insights. Hajianfar et al. suggested that high dietary PRAL and NEAP both have a protective effect against the odds of developing preeclampsia while being associated with pregnancy-related complications such as intrauterine growth restriction and a significant increase in SBP and DBP. This protective effect was associated with glutamine, a non-essential amino acid [34]. This theory contains several inaccuracies and unfounded conclusions. First, the association between glutamine intake and preeclampsia risk is not supported by strong evidence. While glutamine plays various roles in the body, the claim that adequate glutamine consumption diminishes the risk of muscle degradation and inflammatory reactions in pregnant women is not well-substantiated. Second, the argument oversimplifies the complex etiology of preeclampsia, which involves multifactorial and often poorly understood mechanisms. Third, although previous evidence has linked HDPs, particularly preeclampsia, with IUGR, this study indicates that a high DAL regimen heightened the risk of IUGR while simultaneously reducing the likelihood of developing preeclampsia. Furthermore, smoker were excluded from the study without providing a clear rationale for the exclusion. Tielemans et al. reported a null association between dietary PRAL, NEAP, vegetable or animal protein/potassium ratio, and the risk of developing HDPs. Based on this study, a higher vegetable protein/potassium ratio can alleviate DBP due to less sulfur content in vegetable proteins [35]. In this study, participants provided their medical histories through self-reporting without any accompanying documentation, raising concerns about the accuracy of the data. Two notable limitations of the aforementioned studies are the use of odds ratios to compare NEAP and PRAL quartiles, acknowledging that in non-rare outcomes, the odds ratio can exaggerate and magnify the findings. Also, a lack of exclusion for women adhering to specific dietary regimens or taking supplements. Additionally, the statistical analysis did not incorporate a causal approach.

Delving into the literature, some meta-analyses have demonstrated dietary PRAL association with hypertensive disorders in non-pregnant populations. For instance, Parohan et al. reported a 20-unit increase in dietary PRAL values was associated with a 3% increase in the risk

of HTN [36]. Studies that did not find a significant association tended to be of lower quality compared to those that found a positive association [36]. Out of the nine studies in Parohan et al.'s meta-analysis that found a non-significant or inverse association between NEAP and HTN, six included fewer than 10,000 participants without any control for energy intake and BMI [36]. On the other hand, among the two studies that found a positive association, both had a sample size of 10,000 individuals or more, and one controlled for energy intake and BMI [36]. Daneshzad et al. indicated the association between high DAL with 1.74 and 0.75 mmHg increase in SBP and DBP, respectively [37]. Chen et al.'s meta-analysis showed a strong association between dietary PRAL and NEAP with essential HTN, reporting that higher dietary PRAL had a positive impact on increasing SBP and DBP, and a higher NEAP increased the odds of developing HTN by about 35% [38]. Additionally, Dehghan et al. demonstrated that despite NEAP, the highest dietary PRAL category was associated with a 0.98 mmHg increase in SBP and 0.61 mmHg in DBP [39].

As body homeostasis is a balance of intricate mechanisms and varies from one individual to another, the impact of DAL could be modulated by multiple factors. Genetic predisposition, overall health status, lifestyle choices, and other complexities may substantially shape these outcomes. There are several proposed mechanisms through which metabolic acidosis might elevate blood pressure. The association between acid–base equilibrium and increased blood pressure could be due to the absorption impairment of blood pressure-lowering essential minerals (i.e. calcium and magnesium) induced by metabolic acidosis [40]. High DAL has been shown to increase calcium and magnesium urinary excretion while lowering intracellular potassium [40]. To compensate for the intracellular loss of potassium, through a flawed cycle, sodium is dragged into the cell which eventually triggers HTN [41, 42].

High DAL could trigger the renin-angiotensin-aldosterone system (RAAS), inducing the body to retain sodium and cause vasoconstriction, potentially contributing to the onset or worsening of HTN. This reaction is thought to be a way of compensating for acid-base disruptions. McCarty et al. proposed that high DAL could activate the renin-angiotensin hormone system through the glutaminase enzyme [43]. Moreover, Armin et al. in a randomized clinical trial design of a low dietary PRAL regimen on 80 type II diabetes patients demonstrated potential benefits for blood pressure regulation, indirectly indicating the involvement of the RAAS [44].

Endothelial dysfunction, oxidative stress, and inflammation are well-known common pathophysiologies of preeclampsia that can result from high DAL. Mazidi et al. indicated in a population of 4,864 participants aged 40–85 years, after adjustment for main clinical and anthropometrical confounders, high dietary PRAL could be associated with 31% higher odds of peripheral artery disease through endothelial dysfunction resulting from oxidative stress and inflammation [45]. Wu et al., in a cross-sectional setting of 3,042 breast cancer survivors, indicated the highest quartiles of DAL had a 30–33% increase in c-reactive protein (CRP), which is a marker of inflammation [46]. Varkaneh et al. designed a cross-sectional study of 185 type II diabetes mellitus patients to evaluate the association of high DAL with inflammatory biomarkers. Patients in the highest tertile had significantly higher tissue necrosis factor-α (TNF-α) levels [47]. On the other hand, Farhangi et al., in 454 patients undergoing coronary artery bypass surgery, found a null association for CRP while Jafari reported an inverse association between high DAL and TNF-α [48, 49]. In their study, Jafari et al. mentioned that they did not take into consideration the use of anti-inflammatory drugs or supplements, as well as the overall quality of the participants' diets [48].

A surge in DAL can result in heightened ammonia production in the proximal tubule of the kidney and a corresponding increase in acid removal. A decrease in functioning nephrons essentially due to ammonia harm in the kidneys - leads to a greater demand for acid removal per nephron [50]. This need triggers higher rates of ammonia production, significant increases in intramedullary ammonium levels, and boosts in hormones such as angiotensin II, aldosterone, and endothelin-1 which all play key roles in expediting acid excretion [50]. Moreover, metabolic acidosis resulting from high DAL could trigger inflammation and endothelial dysfunction which are key features associated with the onset of preeclampsia [51]. Additionally, another proposed pathophysiology of high DAL in the development of HDPs is via hyperuricemia. Esche et al. reported reduced urate transport through the proximal tubule in high quintiles of DAL leading to hyperuricemia [52]. Hyperuricemia and systemic metabolic acidosis boost serum cortisol levels, which induces vasoconstriction [53]. Moreover, hyperuricemia has been shown to induce local and systemic arterial stiffness, which plays a key role in the development of HTN [54]. The acid-base balance plays a crucial role in regulating the excretion of urinary citrate [55]. Metabolic acidosis induced by high DAL increases the reabsorption of citrate within the nephrons and subsequently reduces citrate excretion [52, 55]. This process might affect blood pressure in salt-sensitive individuals by influencing citrate levels. Additionally, metabolic acidosis may independently impact blood pressure through an elevated serum anion gap [56]. However, the exact underlying pathway for this effect remains unclear.

The strengths of our study lie in the casualty approach with consideration of potential confounders in a large, prospective, population-based design. Another strength of our analysis is that we utilized RRs to compare non-rare outcomes, such as preeclampsia, across different quartiles of DAL. However, limitations include the use of a somewhat imprecise FFQ for estimating DAL, the absence of information on kidney function, and direct blood/urine acidity measurement. Future research could explore urinary biomarkers, such as pH, nitrogen, and potassium, in addition to dietary assessments, to elucidate the potential influence of DAL on preeclampsia development during pregnancy.

Further investigations could prioritize mechanistic designs to evaluate urinary pH, urinary nitrogen, and urinary potassium levels as additional indicators of DAL, alongside dietary assessment. The inclusion of these biomarkers in research endeavors may offer enhanced evidence regarding the potential influence of DAL on the incidence of HTN during pregnancy. Further longitudinal cohort designs with larger sample sizes and a diverse population could provide better public clinical judgment.

One notable limitation of our study is the relatively high rate of loss to follow-up and participant withdrawal. Unfortunately, we do not have comprehensive data regarding whether the women who withdrew or were lost to follow-up developed preeclampsia. Additionally, we lack detailed information on baseline characteristics for these non-completers, which precludes us from assessing potential differences between those who completed the study and those who did not. This missing data could introduce bias, as it is unclear whether the reasons for dropout are related to the study outcomes or if they might have systematically differed in ways that could impact the study's findings. Future studies should aim to reduce loss to follow-up through enhanced participant retention strategies and ensure comprehensive data collection to allow for a more thorough analysis of the impact of attrition on study outcomes.

Conclusion

In this prospective cohort study, we investigated the association between DAL and HDPs during pregnancy, including preeclampsia, chronic HTN, and GHTN. Our findings reveal that both high and low extremes of DAL, as reflected by PRAL and NEAP scores, are associated with an increased risk of developing these conditions. Specifically, women with very high or very low PRAL scores had a significantly higher risk of preeclampsia, while extremes in both PRAL and NEAP were linked to a greater risk of chronic HTN and GHTN. These results highlight the complex association between DAL and HDPs during pregnancy, suggesting that both excessive and insufficient DALs can contribute to adverse outcomes. The lack of a significant linear association in some analyses further indicates that the impact of DAL may be influenced by specific dietary thresholds rather than a gradual increase in risk. Our study underscores the importance of maintaining a balanced dietary regimen during pregnancy to manage DAL and potentially reduce the risk of HDPs. Future research should focus on elucidating the mechanisms underlying these associations and developing evidence-based dietary guidelines for pregnant women to mitigate the risk of these serious health conditions.

Abbreviations

HDPs	Hypertensive disorders of pregnancy
FFQ	Food frequency questionnaires
DAL	Dietary Acid Load
PRAL	Potential renal acid load
NEAP	Net endogenous acid production
RR	Risk ratio
CI	Confidence interval
HTN	Hypertension
ESRD	End-stage renal disease
PUFA	Polyunsaturated fatty acids
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MATCH	Mothers and Their Children's Health
TLGS	Tehran Lipid and Glucose Study
WHO	World Health Organization
ANOVA	One-way analysis of variance
GBM	Generalized boosted model
DAGs	Directed acyclic graphs
BMI	Body mass index
GDM	Gestational diabetes mellitus
GBM	Generalized boosted model
IPW	Inverse probability weighting
RAAS	Renin-angiotensin-aldosterone system
CRP	C - reactive protein
TNF-α	Tumor necrosis factor-α

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Author contributions

M.S., F.S., R.P. and M.R. conceptualised the project. A.M-M., M.E., R.N., Z.B., and A.M. were involved in data gathering. M.S. and F.S. refining the analysis approach, undertook the statistical analysis and prepared the results. M.R. (guarantor) conducted the literature review and drafted the manuscript. All authors provided feedback on subsequent drafts of the manuscript. All authors have seen and approved the final version.

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Data availability

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval

for this study was provided by ethical committee of Tehran and Kermanshah University of Medical Sciences (Project numbers: IR.TUMS.MEDICINE.REC.1398.576 and IR.KUMS.REC.1399.655). All participants accepted to enroll in this study with written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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