The Association of Dietary Acid Load with Resting Metabolic Rate and Metabolic Components in Overweight and Obese Women: A Cross Sectional Study

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Research

Keywords: Dietary Acid Load, Resting metabolic rate, Component metabolic Overweight and obese

Posted Date: January 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-141018/v2>

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Abstract

Background: Several epidemiologic studies have reported that dietary acid load is associated with metabolic profiles; however, to our knowledge, the relationship of this dietary pattern with resting metabolic rate (RMR) among obese and overweight females remains unreported. Therefore, this study aimed to evaluate the association of dietary acid load RMR and metabolic components among overweight and obese adult women.

Methods: This cross-sectional study was conducted on 375 Iranian adults, aged 18–48 years. Dietary acid load indexes were calculated by using a validated 147-item semi-quantitative FFQ. Biochemical and anthropometric measures were assessed using standard methods. An impedance fat analyzer was used to obtain the body composition and an indirect calorimeter was used to assess the RMR.

Result: It was observed that after correction for potential confounders, DBP and NEAP and **PRAL** scores were inversely associated ($P < 0.05$). NEAP index was inversely associated with RMR ($\beta = -0.25$, 95% CI = -0.1.5 to 2.08, $P = 0.02$), and positively associated with WC ($\beta = 1.009$, 95% CI = -1.43 to 3.45, $P = 0.05$) and WHR ($\beta = 0.01$, 95% CI = -0.01 to 0.04, $P = 0.03$), such that subjects with higher scores in NEAP had lower RMR and higher WC and WHR. We also observed that DAL ($\beta = -0.02$, 95% CI = -0.08 to 0.03, $P = 0.08$) and PRAL ($\beta = -0.037$, 95% CI = -1.05 to 0.03 $P = 0.07$) were marginally associated with RMR.

Conclusion:

The results of the present study suggested that higher dietary acid load scores may be negatively associated with lower RMR, while directly associated with greater WC, WHR, DBP, and HOMA-IR.

Introduction

The prevalence of overweight and obesity are increasing globally, and concerning, it has been demonstrated that obesity is strongly related to several life-limiting disorders, including cardiovascular diseases, diabetes, various types of cancer, and stroke (1). Obesity is regarded as a multi-factorial disorder (2), which may be influenced by eating habits, low energy expenditure, and physical (in)activity (3).

The role of acid–base homeostasis in cardio-metabolic risk factors has recently been posited (4, 5). Generally, animal protein such as fish and meat, as well as grain products, are influential in a higher acid production in the body, while, conversely, vegetables, legumes, and fruits are known as alkaline foods (9, 10). It has been suggested that lower acid production is beneficial in human health (11). In recent years, dietary patterns have evolved towards a western-style diet, which is defined by a higher intake of animal products, fast foods, and other food types that result in higher production of acid in body (5, 12), and is not, generally, compensated for by fruits and vegetables, which can contribute to metabolic dysfunction.

Potential renal acid load (PRAL), net endogenous acid production (NEAP) (15), and dietary acid load (DAL) (16) indexes are commonly used to estimate dietary acid load in epidemiological studies. PRAL and DAL scores are, generally, better predictors of dietary acid load, as, in those formulas, calcium, phosphorus, and magnesium, as well as protein and potassium, are included; while NEAP is calculated, simply, by the ratio of protein and potassium (7, 9). Accordingly, a negative PRAL value demonstrates a base (or alkaline)-forming potential, while a positive value indicates an acid-forming potential (13).

Previous studies have mainly focused on the association of acid/base imbalance on kidney stones, nephropathy, and bone health (17, 18), whilst the Nurses' Health Study II reported a positive association between hypertension and acid/base imbalance (19). Metabolic acidosis, which can be influenced by dietary factors (20–22), may adversely affect blood pressure (23–25) through an increase in cortisol production (20), increasing calcium excretion (26, 27) or decreasing citrate excretion (28). Higher production of cortisol, as the result of metabolic acidosis (20, 22), may also have an adverse influence on the other cardio-metabolic risk factors, including hypertension, hypocholesteremia, obesity, and insulin resistance (IR) (29, 30). Indeed, several studies have illustrated that resting metabolic rate (RMR) can be reduced in type 2 diabetes with IR (31).

It has been posited that individuals with low RMR are at higher risk of developing obesity-related disorders, since a larger portion of their energy intake from their daily food is stored as fat, even with the similar calorie intake (32). Accordingly, studies have indicated that obese subjects with higher RMR have an overall better metabolic profile, with lower fasting plasma glucose and 2-hour post-load glucose levels, than obese individuals with lower RMR (33–35).

To the authors' knowledge, no study has examined the association between measures of dietary acid–base load and RMR and other metabolic components. Thus, in the present study, we assessed the relationship between three markers of dietary acid load and metabolic components and RMR in overweight and obese women.

Material And Methods

Study population

In the current study, a cohort of 375, women aged 18 to 48, with a body mass index (BMI) ≥ 25 kg/m², were recruited from Health Centers and Nutrition Clinics in Tehran, Iran between July 2017 and April 2019. The Medical Research Ethics Committee of Tehran University of Medical Sciences approved the study with the following identification IR.TUMS.VCR.REC.1395.1597. All participants expressed their willingness to participate in the study by providing informed written consent. The overall exclusion criteria were as follows: any history of acute and chronic disease including hypertension, diabetes mellitus, cardiovascular disease, and impaired renal and liver function, as well as regular use of medicine (other than birth control medication), pregnant or lactating, intake of alcohol, smoking, and menopause. In addition, participants who had been following any arbitrary special dietary regimen, as well as those with chronic disease(s) affecting their diet, or if their daily energy intake was < 800 kcal or > 4200 kcal (36), were excluded.

Dietary assessment

Dietary intake was assessed using a validated semi quantitative food frequency questionnaire (FFQ) with 147- food items(37). All FFQs were completed by a trained dietitian, who asked participants to designate their intake frequency for each food item consumed during the past year, on a daily, weekly, or monthly basis. Finally, we converted portion sizes of foods to grams by using household measures (38). NUTRITIONIST-IV (version 7.0; N Squared Computing, Salem, OR, USA) was used to assess nutrient and energy intakes.

Assessment of dietary acid load

Dietary acid-base load was evaluated via 3 indexes: PRAL, NEAP, and DAL which were calculated by using nutrients derived from the FFQ with the following formulas:

1) PRAL (mEq/d) = $0.4888 \times \text{dietary protein (g/d)} + 0.0366 \times \text{dietary phosphorus (mg/d)} - 0.0205 \times \text{dietary potassium (mg/d)} - 0.0125 \times \text{calcium (mg/d)} - 0.0263 \times \text{magnesium (mg/d)}$ (8)

2) NEAP = $54.5 \times \text{dietary protein (g/d)} / \text{dietary potassium (mg/d)} - 10.2$ (14)

3) DAL (mEq/ day) = PRAL + (body surface area (m²) × 41 (mEq / day)/1.73 m²) (39)

Body surface area (BSA) was calculated using the Du Bois formula: $0.007184 \times \text{height } 0.725 \times \text{weight } 0.425$ (16, 40). We adjusted both PRAL and NEAP for total energy intake, employing the residual method. Higher values of PRAL, DAL, and NEAP were considered to represent a higher acidic dietary acid-base load. Medians of diet dependent acid load scores were used in statistical analysis.

Anthropometric assessments

Weight was determined on a digital scale, where participants wore light indoor clothing, without shoes, and was recorded to the nearest 100 g. Height was measured to the nearest 0.5 cm while participants were in the normal standing position, without shoes. Waist circumference (WC) and hip circumference were measured to the nearest 0.5cm, according to standard procedures. Subsequently, waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), and BMI were calculated according to standard formulae. Overweight and obesity were defined as $25 \leq \text{BMI} \leq 29.9 \text{ kg/m}^2$ and $\text{BMI} \geq 30 \text{ kg/m}^2$, respectively. Neck circumference (NC) was measured below the laryngeal prominence and perpendicular to the long axis of the neck, and the minimal circumference was recorded to the nearest 0.1 cm(41)

Assessment of other variables

A demographic questionnaire to discern information on age, marital status, education, and economic status was collected by researchers.

Blood pressure assessment

Blood pressure measurements were taken using a standard mercury sphygmomanometer; where the participant sat for 10–15 min before two consecutive measurements were taken.

Physical activity

The Short form of the International Physical Activity Questionnaire (IPAQ) (42) was applied to evaluate physical activity and according to the frequency and time of common activities of daily life over the past year. Physical activity levels were expressed as metabolic equivalent hours per week (METs h/week)(43).

Measurement of biochemical parameters

Blood samples were collected after 10-12 hours fasting, and collected into tubes containing 0.1% Ethylenediaminetetraacetic acid (EDTA). Then, they were centrifuged for 10 min at 3000 rpm, aliquoted into 1 ml tubes, and stored at – 70°C until analysis. Samples were analyzed by using an autoanalyzer (Selectra 2; Vital Scientific, Spankeren, Netherlands).

The GOD/PAP (glucose oxidase phenol 4-Aminoantipyrine Peroxidase) method was used for the measurements of fasting blood sugar (FBS) and triglyceride (TG) levels, and cholesterol levels were evaluated using the cholesterol oxidase Phenol 4-Aminoantipyrine Peroxidase (CHOD-PAP) method. Total cholesterol (TC) levels and direct high-density lipoprotein (HDL) were evaluated by the Immunoinhibition assay. Aspartate aminotransferase (AST) and Serum alanine aminotransferase (ALT) were specified by the International Federation of Clinical Chemistry and Laboratory Medicine method. Serum high-sensitivity C-reactive protein (hs- CRP) was determined using a high-sensitivity immunoturbidimetric assay (Hitachi 902 analyser; Hitachi Ltd., Tokyo, Japan).

We used the homeostasis model assessment method to compute insulin resistance based on the following Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) formula: $\text{fasting serum insulin (mIU/L)} \times \text{FBS (mmol/l)} / 22.5$.

Resting metabolic rate assessment

RMR measurement was performed by professional nutritionists using a standard protocol (33), and was measured by indirect calorimetry (spirometer METALYZERR 3B-R3, Cortex Biophysik GmbH, Leipzig, Germany). Based on the manufacturer's instructions, prior to each test, gas exchange and ventilation were calibrated. Fitmate is a desktop device designed for providing accurate RMR for all fields dealing with obesity and malnutrition with a mask to cover the nose and mouth. The device is designed to measure oxygen consumption and energy expenditure during rest and exercise. It uses a turbine flow meter to measure ventilation and a galvanic fuel cell oxygen sensor for analyzing the proportion of oxygen in expiration gases. Moreover, it uses a patent-pending sampling method that allows the analyzer to monitor the performance of a metabolic cart in a standard mixing chamber. RMR was calculated using information such as oxygen consumption, a fixed respiratory quotient of 0.85, and estimated quantity of urinary nitrogen using a modified Weir equation below.

Weir equation: $\text{RMR} = (\text{O}_2 \text{ consumed [liter]} \times 3.941 + \text{produced CO}_2 \text{ [liter]} \times 1.11) \times 1440 \text{ min/d.}$

The RMR was evaluated in the morning, after a night's sleep and following 10 to 12 hours of overnight fasting. Participants were asked to avoid vigorous exercise and alcohol or caffeine consumption for a day before RMR assessment. The RMR was measured for 30 min in a quiet room and participants in fixed, comfortable position. The respiratory exchange ratio and oxygen uptake (VO_2) were investigated within the average 30 min of the resting period. However, the first 5 minutes were not included, and only the last 15 minutes were used to calculate RMR. Predictive RMR was determined using the Harris-Benedict equation, which considers age, weight, and height for individuals.

Complete body composition analysis

Body composition of subjects was evaluated via Body Composition Analyzer BC-418MA- In Body (United Kingdom), in accordance with manufacturer guidelines. To avoid possible discrepancies in the measured values, participants were asked not to exercise vigorously, to not use any electrical devices, and not consume excessive fluid or food before evaluating their body composition.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of the data. Continuous variables were represented by mean $\pm$ Standard Deviations (SDs) and mean $\pm$ standard Errors (SEs), and categorical information was represented by percentage and number. To avoid classification errors, we calculated the energy-adjusted PRAL, NEAP, and DAL using the residual method, and then based on the median, dichotomized participants into low or high dietary acid load. Baseline characteristics of participants were compared by independent samples t test between the median of PRAL, NEAP, and DAL score and chi square(χ^2) tests for categorical variables. Also, we adjusted variables for confounders, such as age, energy intake, BMI, physical activity, and economic status, in addition further adjustment for free fat mass (FFM), using Analysis of covariance (ANCOVA). General linear regression (GLM) was used to assess the association of PRAL, NEAP, and DAL score with body composition, biochemical variables and RMR per kg. Results in crude and adjusted models were presented as beta(β) and 95% confidence intervals (CIs). Data were analyzed using IBM SPSS version 25.0 (SPSS, Chicago, IL, USA) and p-values less than 0.05 were considered, *a priori*, to represent statistical significance.

Result

Study Population Characteristics

The mean of quantitative variables including; age, BMI, RMR, RMR normal, RMR per kg, and RMR per BSA of the participants in our study were; 36.67 years (SD = 9.1), 30.98 kg/m² (SD = 3.9), 1574.96 kg/day (SD = 259.71), 1720.38 kg/day (SD = 152.36), 19.59 kg/day (SD = 3.09), and 850.21 kg/day (SD = 113.89), respectively. 45.5% of participants had middle economic status and 70.8% of them were married. The percentages of participants distribution in low and high acid load scores based on PRAL and NEAP were; 36.1% and 63.9% s, and based on DAL, 34.9% and 65.1%.

Association between quantitative and qualitative variables among PRAL, NEAP, and DAL medians

The differences between the medians of PRAL, NEAP, and DAL and some quantitative and qualitative variables are shown in Table 1. After adjustment, physical activity was higher in high intake of PRAL, NEAP, DAL and also about age in high intake of NEAP ($P < 0.05$). FFM was higher in high intake of PRAL and DAL ($P < 0.05$) and normal RMR was higher in low intake of NEAP ($P = 0.04$).

Table 1
Study participant characteristics between High and Low acid load scores

Variables	PRAL		P-value	P-value†	NEAP		P-value	P-value†	DAL		P-value	P-value†	
	Low	High			Low	High			Low	High			
	(<-19.98)	(>-19.98)			(<-9.03)	(>-9.03)			(<-18.52)	(>-18.52)			
Age (years)	35.77 ± 8.78	37.17 ± 9.25	0.14	0.29	35.44 ± 8.78	37.36 ± 9.22	0.04	0.11	35.58 ± 8.71	37.24 ± 9.26	0.08	0.29	
Physical activity (MET-minutes/week)	854.07 ± 919.3	1560.98 ± 2782.47	0.006	0.02	88.83 ± 944.30	1538.56 ± 2789.83	0.01	0.04	863.00 ± 930.01	1530.74 ± 2745.44	0.006	0.03	
Anthropometric variables													
Weight(kg)	79.64 ± 10.36	80.64 ± 11.43	0.13	0.30	79.60 ± 10.46	80.66 ± 11.37	0.36	0.78	79.64 ± 10.36	80.64 ± 11.43	0.38	0.56	
Height(cm)	161.49 ± 6.08	161.06 ± 5.74	0.38	0.02	161.53 ± 6.10	161.04 ± 5.74	0.42	0.21	161.43 ± 6.04	161.10 ± 5.78	0.97	0.03	
HC(cm)	105.66 ± 6.05	105.65 ± 9.16	0.99	0.83	105.65 ± 6.10	105.66 ± 9.14	0.98	0.56	105.35 ± 5.71	105.82 ± 9.2	0.87	0.79	
BMI (kg/m²)	Crude	30.70 ± 3.89	31.14 ± 3.90	0.28	0.22	30.66 ± 3.86	30.16 ± 3.91	0.22	0.30	30.64 ± 3.84	31.17 ± 3.92	0.19	0.26
	Model 1	30.84 ± 0.31	30.29 ± 0.32			30.88 ± 0.31	30.33 ± 0.32			30.79 ± 0.31	30.28 ± 0.31		
Body composition													
BFM(kg)	Crude	34.30 ± 8.40	34.98 ± 8.95	0.45	0.13	34.14 ± 8.46	35.08 ± 9.87	0.30	0.56	33.55 ± 7.44	35.37 ± 9.33	0.04	0.03
	Model 1	33.79 ± 0.26	33.63 ± 0.27			34.23 ± 0.45	33.19 ± 32.97			33.78 ± 0.26	33.26 ± 0.27		
FFM(kg)	Crude	46.51 ± 5.49	46.53 ± 5.85	0.98	0.01	46.65 ± 5.61	46.45 ± 5.78	0.74	0.47	46.17 ± 5.21	45.71 ± 5.96	0.37	0.03
	Model 1	46.12 ± 0.46	47.02 ± 0.47			46.33 ± 0.45	46.81 ± 0.47			46.10 ± 0.46	47.04 ± 0.47		
Deviation from normal RMR	Crude	-7.65 ± 13.09	-9.24 ± 12.1	0.27	0.06	-7.57 ± 12.03	-9.32 ± 12.03	0.23	0.04	-7.72 ± 13.09	-9.14 ± 0.96	0.33	0.13
	Model1 ^{II}	-7.40 ± 1.18	-9.14 ± 1.23			-7.37 ± 1.12	-10.09 ± 1.15			-7.49 ± 1.12	-9.98 ± 1.17		
Qualitative variables													
Economic status			0.42	0.31			0.46	0.69			0.34	0.43	
Low level		34(38.6)	54(61.4)			32(36.4)	56(63.6)			33(37.5)	55(62.5)		
Moderate level		72(39.1)	112(60.9)			72(39.1)	112(60.9)			70(38)	114(62)		
High level		35(31.8)	75(68.2)			35(31.8)	75(68.2)			33(30)	77(70)		
Education level											0.73	0.48	
Illiterate		25(1)	3(75)	0.84	0.48	1(25)	3(75)	0.74	0.68	1(25)	3(75)		
Under diploma		17(34.7)	32(65.3)			16(32.7)	33(67.3)			16(32.7)	33(67.3)		
Diploma		54(35.3)	99 (64.7)			54(35.3)	99(64.7)			51(33.3)	102(66.7)		
Master and higher		73(38.6)	116(61.4)			74(39.2)	115(60.8)			72(38.1)	117(61.9)		
Marital status			0.40	0.69			0.10	0.17			0.29	0.69	
Single		35(32.1)	74(67.9)			33(30.3)	76(69.7)			34(31.2)	75(68.8)		
Married		110(38.5)	176(61.5)			112(39.2)	174(60.8)			106(37.1)	180(62.9)		

Variables	PRAL		P-value	P-value†	NEAP		P-value	P-value†	DAL		P-value	P-value†
	Low	High			Low	High			Low	High		
	(<-19.98)	(>-19.98)			(<-9.03)	(>-9.03)			(<-18.52)	(>-18.52)		
HC, Hip circumference; BMI, body mass index, BFM, body fat mass; FFM, fat free mass; PRAL, potential renal acid load; DAL, dietary acid load NEAP, net endogenous acid production												
Values are mean ±SD for crude model and mean± SE for adjusted model and qualitative variables are presented as n (%)												
All variables adjusted with age, energy intake, physical activity, BMI, economic status												
Model1 : further adjustment for fat free mass												
Crude P-value obtained from independent sample T test												
† adjust P-value obtained from analysis of covariance												

Association between some dietary intake components among PRAL, NEAP, and DAL medians

Dietary intakes of the participants across PRAL, NEAP, and DAL medians are shown in Table 2. After adjustment for confounders, cereals consumption was higher in high intake of all three scores (PRAL, NEAP, DAL) and fruits consumption was higher in low intake of all three scores (P < 0.001); vegetables consumption was higher in low PRAL and DAL scores, and fat intake was higher in high PRAL, NEAP, and DAL scores. However, nuts and carbohydrate consumption was higher in low PRAL, NEAP, and DAL scores (P < 0.05); whilst, participants with high PRAL and low NEAP scores consumed higher amounts of total fiber and calcium, respectively (P = 0.05). Magnesium, folate, potassium, and vitamins C, A, B6 were consumed in higher amounts in low PRAL, NEAP, and DAL scores (P < 0.05), whilst sodium and B12 consumption was higher in participants with high NEAP and DAL scores (P ≤ 0.05).

Table 2
Dietary intakes of study population between high and low acid load Scores

Variables	PRAL		P- value [†]	NEAP		P- value [†]	DAL		P- value [†]
	Low (<-19.98)	High (>19.98)		Low (<-9.03)	High (>9.03)		Low (<-18.52)	High (>18.52)	
Food groups									
Cereal(g/d)	1258.95 ± 16.39	1357.70 ± 16.87	< 0.001	1256.23 ± 16.23	1361.47 ± 16.89	< 0.001	1258.95 ± 16.39	1357.70 ± 16.87	< 0.001
Fruits(g/d)	1676.69 ± 22.31	652.15 ± 23.89	< 0.001	1668.69 ± 22.42	1395.42 ± 23.28	< 0.001	1677.69 ± 22.31	1390.6 ± 22.78	< 0.001
Vegetables(g/d)	497.74 ± 2012	294.69 ± 19.59	< 0.001	305.59 ± 19.84	487 ± 20.55	< 0.001	1215.59 ± 19.79	1013 ± 20.15	< 0.001
Legumes(g/d)	263.40 ± 3.78	261.41 ± 3.88	0.52	264.23 ± 3.57	260.49 ± 3.70	0.47	263.30 ± 3.60	261.52 ± 3.68	0.73
Nuts(g/d)	144.98 ± 1.37	138.81 ± 1.41	0.002	144.09 ± 1.38	139.72 ± 1.43	0.03	145.30 ± 11.18	138.53 ± 18.59	0.002
Dairy(g/d)	1272.09 ± 21.60	1234.64 ± 21.32	0.26	1272.09 ± 20.66	1244.64 ± 21.37	0.36	1260.49 ± 20.90	1257.09 ± 22.02	0.97
Eggs(g/d)	19.77 ± 1.28	23.94 ± 1.31	0.02	19.11 ± 1.26	24.68 ± 19.11	0.003	19.92 ± 1.29	23.74 ± 1.31	0.04
Meat [†] (g/d)	350.42.39 ± 4.53	366.12 ± 4.66	0.01	349.40 ± 4.66	367.36 ± 4.66	0.007	351.43 ± 4.57	364.95 ± 4.66	0.04
Energy and macronutrients									
Energy (kcal)	2515.59 ± 66.65	2703.51.45	0.02	2530.33 ± 66.75	2694.62 ± 51.52	0.05	2491.56 ± 67.66	2713.20 ± 50.81	0.009
Carbohydrates(g/d)	370.85 ± 42.57	330.47 ± 46.58	< 0.001	369.86 ± 3.81	331.67 ± 3.96	< 0.001	370.77 ± 3.83	331.37 ± 3.91	< 0.001
Fat (g/d)	99.93 ± 0.51	112.69 ± 0.39	< 0.001	100.55 ± 1.71	112.12 ± 1.77	< 0.001	99.86 ± 0.53	112.65 ± 0.39	< 0.001
protein (g/d)	92.00 ± 0.21	93.28 ± 0.16	0.56	91.40 ± 0.21	93.94 ± 0.16	0.25	92.00 ± 0.21	93.28 ± 0.16	0.13
Total fiber(g/d)	44.32 ± 1.35	49.40 ± 1.04	0.05	43.83 ± 1.22	47.13 ± 1.23	0.06	44.100 ± 1.25	46.76 ± 1.22	0.13
MUFA(g/d)	33.98 ± 0.71	30.87 ± 0.55	< 0.001	33.72 ± 0.72	29.20 ± 0.73	< 0.001	33.25 ± 0.75	29.82 ± 0.73	0.001
PUFA(g/d)	30.87 ± 0.55	21.87 ± 0.62	0.002	21.58 ± 0.64	18.60 ± 0.64	0.001	21.18 ± 0.66	19.09 ± 0.64	0.02
SFA(g/d)	27.51 ± 0.47	29.97 ± 0.61	< 0.001	29.69 ± 0.63	26.87 ± 0.64	0.002	30.09 ± 0.64	26.60 ± 0.63	< 0.001
Micronutrients and caffeine									
Iron (mg/d)	18.88 ± 1.52	31.30 ± 1.17	0.09	18.60 ± 0.24	18.82 ± 0.25	0.53	18.48 ± 0.25	18.93 ± 0.24	0.20
Zinc (mg/d)	12.70 ± 0.21	13.84 ± 0.16	0.08	12.74 ± 0.19	13.11 ± 0.19	0.17	12.71 ± 0.19	13.13 ± 0.19	0.13
Calcium (mg/d)	1151.11 ± 32.71	1339.63 ± 25.29	0.19	1234.98 ± 25.38	1205.600 ± 25.66	0.05	1153.14 ± 26.10	1185.86 ± 25.44	0.37
Magnesium(mg/d)	504.41 ± 6.14	428 ± 7.96	< 0.001	490.45 ± 6.84	428.44 ± 6.77	< 0.001	489.47 ± 6.75	427.19 ± 6.93	< 0.001
Potassium (mEq/d)	4931.33 ± 63.14	2499.4 ± 209.9	< 0.001	4993.33 ± 67.53	3690.11 ± 66.79	< 0.001	4959.74 ± 67.68	3677.52 ± 69.43	< 0.001
Sodium (mg/d)	4347.68 ± 108.48	4852.55	0.18	4360.44 ± 98.48	4679.05 ± 102.48	0.02	4353.21 ± 9.16	4681.28 ± 101.69	0.02
Phosphor (mg/d)	1633.98 ± 25.98	1700.7 ± 20.07	0.68	1624.61 ± 25.42	1658.69 ± 25.70	0.35	1637.81 ± 26.04	1644.95 ± 25.38	0.84
Vitamin C(mg/d)	216.63 ± 6.19	141.18 ± 8.01	< 0.001	250.43v8.38	145.16 ± 8.29	< 0.001	250.17 ± 8.2	141.57 ± 8.43	< 0.001
Vitamin E(mg/d)	18.38 ± 0.68	16.23 ± 0.52	0.24	18.36 ± 0.73	16.51 ± 0.74	0.08	17.85 ± 0.75	17.05 ± 0.74	0.45
Vitamin A (mg/d)	887.79 ± 30.03	673.3 ± 29.70	< 0.001	888.46 ± 29.94	672.71 ± 29.61	< 0.001	879.99 ± 29.67	673.67 ± 29.67	< 0.001
Thiamin (mg/d)	2.18 ± 0.04	2.12 ± 0.03	0.001	2.00 ± 0.03	2.18 ± 0.2	< 0.001	2.22 ± 0.02	2.17 ± 0.03	< 0.001

Variables	PRAL		P-value [†]	NEAP		P-value [†]	DAL		P-value [†]
	Low (<19.98)	High (>19.98)		Low (<9.03)	High (>9.03)		Low (<18.52)	High (>18.52)	
Riboflavin (mg/d)	2.18 ± 0.04	2.33 ± 0.03	0.44	2.17 ± 0.04	2.25 ± 0.04	0.23	2.19 ± 0.04	2.22 ± 0.04	0.64
Niacin (mg/d)	38.59 ± 0.52	39.54 ± 0.40	0.94	38.33 ± 0.50	40.21 ± 0.51	0.01	38.67 ± 0.52	39.83 ± 0.51	0.14
Vitamin B6(mg/d)	2.04 ± 0.03	2.29 ± 0.02	< 0.001	2.07 ± 0.03	2.27 ± 0.03	< 0.001	2.04 ± 0.03	2.29 ± 0.03	< 0.001
Folate (mcg/d)	648.23 ± 9.10	612.54 ± 7.03	0.008	643.00 ± 8.98	617.42 ± 8.99	0.06	648.71 ± 9.06	612.39 ± 8.83	0.01
Vitamin B12(mcg/d)	13.50 ± 0.18	14.00 ± 0.14	0.06	13.50 ± 0.18	14.01 ± 0.18	0.05	13.52 ± 0.18	13.98 ± 0.17	0.09
Caffeine (mg/d)	162.93 ± 16.07	315.66 ± 53.44	0.008	161.72 ± 13.52	205.25 ± 14.10	0.02	163.14 ± 13.67	203.03 ± 14.02	0.04
MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; PRAL, potential renal acid load; DAL, dietary acid load NEAP, net endogenous acid production Values are mean ±SE. Nutrients and food groups were adjusted for age, BMI, physical activity and total energy intake* *: Meat alternatives included meat, poultry and sea foods* † adjust P-value obtained from analysis of covariance*									

Investigation of body composition, biochemical variables, and RMR among PRAL, NEAP, and DAL medians

We made three models for investigation of body composition, blood parameters and type of RMR; crude model, model 1, and model 2 (Table 3). In the crude model, WC and WHR were higher in of the high DAL group ($P \leq 0.05$), and WHtR was incomparable across all three scores ($P = 0.05$). In model 1, we considered age, BMI, physical activity, and total energy intake as confounders, and in model 2, other variables, in addition to the aforementioned, were considered as confounders. In model 2: WC was higher in high DAL group ($P \leq 0.05$); NC and WHR were higher in high DAL and NEAP scores, respectively ($P < 0.05$); WHtR was higher in high NEAP scores, whereas FBS and HOMA-IR were inversely higher with low NEAP ($P < 0.05$); TG was higher in high NEAP, and HDL was higher in low PRAL ($P < 0.05$); hs-CRP was higher in high PRAL and NEAP ($P \leq 0.05$) and DBP was higher in low PRAL and DAL ($P < 0.05$). To investigate RMR types and RQ, we made two models; a crude model and model 1, which was adjusted for age, BMI, physical activity, and total energy intake (Table 3). In the crude model, RMR per kg was higher in low PRAL, NEAP, and DAL scores ($P < 0.05$) and RMR of carbohydrate was higher in low NEAP ($P = 0.03$). In model 1: RMR per kg was higher in low PRAL and NEAP ($P < 0.05$), but RMR of carbohydrate was higher in low DAL ($P = 0.05$); whilst RQ lost was no longer significant after adjustment in the Model 1.

Table 3
Body composition, blood parameters and all type of RMRs between high and low acid load scores

Variables		PRAL		P-value	P-value [†]	NEAP		P-value	P-value [†]	DAL		P-value	P-value [†]
		Low	High			Low	High			Low	High		
		(<-19.98)	(>19.98)			(<-9.03)	(>9.03)			(<-18.52)	(>18.52)		
Body composition													
WC(cm)	Crude	98.98 ± 9.49	99.27 ± 9.40	0.77	-	98.90 ± 9.44	99.31 ± 9.43	0.67	-	98.61 ± 9.22	99.47 ± 9.53	0.05	-
	Model 1	99.39 ± 0.73	95.78 ± 0.83	-	0.002	99.05 ± 0.74	96.16 ± 0.84	-	0.01	99.39 ± 0.73	95.78 ± 0.83	-	0.00
	Model 2	98.44 ± 1.03	96.98 ± 1.25	-	0.46	97.46 ± 1.00	99.23 ± 1.2	-	0.02	98.37 ± 1.02	98.06 ± 1.23	-	0.48
NC(cm)	Crude	38.14 ± 9.83	36.87 ± 2.35	0.21	-	37.20 ± 3.48	37.94 ± 10.14	0.46	-	38.05 ± 10.05	37.02 ± 2.40	0.31	-
	Model 1	38.32 ± 0.82	36.63 ± 0.93	-	0.18	37.19 ± 0.82	38.07 ± 0.94	-	0.48	38.32 ± 0.82	36.63 ± 0.93	-	0.18
	Model 2	36.03 ± 1.10	38.97 ± 1.32	-	0.61	35.63 ± 1.04	40.09 ± 1.28	-	0.02	38.06 ± 1.08	38.94 ± 1.30	-	0.59
WHR	Crude	0.93 ± 0.53	1.29 ± 5.69	0.45	-	0.93 ± 0.05	1.029 ± 5.69	0.45	-	0.93 ± 0.05	1.28 ± 5.63	0.04	-
	Model 1	0.93 ± 0.00	0.91 ± 0.00	-	0.001	0.93 ± 0.00	0.91 ± 0.00	-	0.004	0.93 ± 0.00	0.91 ± 0.00	-	0.00
	Model 2	0.93 ± 0.00	0.92 ± 0.00	-	0.44	0.92 ± 0.00	0.94 ± 0.00	-	0.02	0.93 ± 0.00	0.92 ± 0.00	-	0.48
WHtR	Crude	0.61 ± 0.06	0.61 ± 0.05	0.52	-	0.61 ± 0.05	0.61 ± 0.05	0.40	-	0.61 ± 0.05	0.61 ± 0.56	0.05	-
	Model 1	0.61 ± 0.00	0.59 ± 0.00	-	0.01	0.61 ± 0.00	0.59 ± 0.00	-	0.03	0.61 ± 0.00	0.59 ± 0.00	-	0.01
	Model2	0.609 ± 0.00	0.605 ± 0.00	-	0.81	0.604 ± 0.00	0.640 ± 0.00	-	0.02	0.608 ± 0.00	0.609 ± 0.00	-	0.93
Biochemical variables													
FBS (mg/dL)	Crude	88.12 ± 0.90	87.25 ± 0.88	0.49	-	87.98 ± 0.90	87.37 ± 0.89	0.63	-	88.06 ± 0.95	87.35 ± 9.94	0.59	-
	Model 1	87.48 ± 0.96	86.73 ± 0.92	-	0.85	87.26 ± 0.92	87.91 ± 0.93	-	0.62	87.36 ± 0.97	87.36 ± 0.94	-	0.73
	Model2	87.46 ± 1.25	89.34 ± 1.23	-	0.02	87.12 ± 0.16	88.13 ± 0.15	-	0.12	87.64 ± 0.22	89.52 ± 0.18	-	0.08
Insulin (mIU/ ml)	Crude	1.22 ± 0.02	1.20 ± 0.02	0.40	-	1.20 ± 0.02	1.20 ± 0.02	0.80	-	1.22 ± 0.02	1.20 ± 0.02	0.44	-
	Model 1	1.22 ± 0.02	1.20 ± 0.02	-	0.63	1.21 ± 0.02	1.21 ± 0.02	-	0.87	1.22 ± 0.02	1.20 ± 0.02	-	0.61
	Model 2	1.23 ± 0.03	1.20 ± 0.03	-	0.53	1.21 ± 0.02	1.22 ± 0.03	-	0.76	1.23 ± 0.03	1.20 ± 0.03	-	0.85
HOMA-IR	Crude	5.80 ± 0.12	5.85 ± 0.11	0.78	-	5.74 ± 0.11	5.91 ± 0.11	0.31	-	5.77 ± 0.11	5.95 ± 0.11	0.25	-
	Model 1	5.76 ± 0.12	5.92 ± 0.12	-	0.35	5.74 ± 0.12	5.88 ± 0.12	-	0.45	5.75 ± 0.12	5.94 ± 0.11	-	0.26
	Model 2	5.79 ± 0.16	5.91 ± 0.16	-	0.05	5.69 ± 0.15	6.01 ± 0.16	-	0.01	5.75 ± 0.16	5.85 ± 0.16	-	0.12
Total cholesterol (mg/dL)	Crude	183.35 ± 35.90	187.04 ± 35.69	0.41	-	182.97 ± 36.02	187.45 ± 35.53	0.31	-	187.81 ± 36.04	182.31 ± 35.36	0.22	-
	Model 1	182.38 ± 3.54	182.11 ± 3.40	-	0.95	182.11 ± 3.47	182.38 ± 3.45	-	0.95	180.27 ± 3.74	183.03 ± 3.63	-	0.60
	Model 2	184.79 ± 4.91	177.81 ± 4.91	-	0.40	183.95 ± 4.71	178.59 ± 4.79	-	0.50	179.12 ± 5.05	184.74 ± 4.89	-	0.51
TG(mg/dL)	Crude	119.95 ± 61.94	116.42 ± 56.15	0.63	-	120.57 ± 61.93	115.80 ± 56.03	0.52	-	118.64 ± 61.40	117.64 ± 56.88	0.89	-

Variables		PRAL		P-value	P-value [†]	NEAP		P-value	P-value [†]	DAL		P-value	P-value [†]
		Low	High			Low	High			Low	High		
		(<-19.98)	(>19.98)			(<-9.03)	(>9.03)			(<-18.52)	(>18.52)		
	Model 1	109.06 ± 5.91	120.89 ± 6.14	-	0.17	108.31 ± 5.99	121.27 ± 6.02	-	0.13	110.98 ± 6.02	119.81 ± 6.20	-	0.31
	Model 2	105.22 ± 3.30	120.02 ± 3.30	-	0.07	97.60 ± 8.16	132.02 ± 8.03	-	0.01	105.88 ± 8.21	125.70 ± 8.49	-	0.17
	Crude	47.77 ± 9.77	45.51 ± 11.68	0.04	-	47.65 ± 9.57	45.59 ± 11.88	0.13	-	47.76 ± 9.86	45.58 ± 11.57	0.10	-
HDL (mg/dL)	Model 1	47.42 ± 1.11	45.85 ± 1.07	-	0.31	47.41 ± 1.09	45.81 ± 1.08	-	0.31	47.63 ± 1.11	45.58 ± 1.08	-	0.19
	Model 2	48.32 ± 1.53	44.78 ± 1.53	-	0.09	47.91 ± 1.48	45.16 ± 1.50	-	0.28	48.80 ± 1.56	44.39 ± 1.51	-	0.06
	Crude	94.51 ± 24.56	95.96 ± 23.82	0.84	-	95.54 ± 23.16	95.07 ± 23.16	0.87	-	94.51 ± 24.56	95.96 ± 23.82	0.63	-
LDL (mg/dL)	Model1	93.28 ± 2.42	93.38 ± 2.33	-	0.97	93.49 ± 2.37	93.17 ± 2.36	-	0.92	93.67 ± 2.45	94.32 ± 2.38	-	0.85
	Model2	96.86 ± 3.27	89.95 ± 3.27	-	0.21	96.84 ± 3.17	89.89 ± 3.22	-	0.20	92.89 ± 3.40	95.89 ± 3.40	-	0.53
	Crude	18.29 ± 10.57	20.57 ± 16.17	0.19	-	19.00 ± 12.19	19.94 ± 15.23	0.58	-	18.11 ± 10.67	20.66 ± 15.96	0.14	-
ALT (μKat/L)	Model 1	17.42 ± 0.78	18.16 ± 0.75	-	0.35	18.89 ± 1.38	18.79 ± 1.38	-	0.96	17.91 ± 1.27	18.70 ± 1.24	-	0.66
	Model 2	17.27 ± 1.72	19.12 ± 1.72	-	0.53	18.79 ± 1.66	17.58 ± 1.69	-	0.67	16.59 ± 1.73	19.78 ± 1.67	-	0.27
	Crude	17.38 ± 5.70	18.66 ± 9.19	0.18	-	17.79 ± 6.80	18.30 ± 8.56	0.60	-	17.35 ± 5.80	18.65 ± 9.05	0.18	-
AST (μKat/L)	Model 1	17.42 ± 0.78	18.16 ± 0.75	-	0.50	17.95 ± 0.77	17.66 ± 0.77	-	0.79	17.34 ± 0.69	18.91 ± 1.27	-	0.84
	Model 2	17.02 ± 0.98	19.12 ± 1.72	-	0.59	18.11 ± 0.94	16.82 ± 0.96	-	0.42	16.87 ± 0.97	18.00 ± 0.94	-	0.49
	Crude	4.82 ± 4.93	4.94 ± 4.32	0.13	-	4.09 ± 4.89	4.69 ± 4.36	0.27	-	4.72 ± 4.95	4.04 ± 4.33	0.2	-
Hs-CRP(mg/l)	Model 1	4.03 ± 0.48	4.50 ± 0.46	-	0.49	4.10 ± 0.47	4.40 ± 0.47	-	0.67	4.68 ± 0.47	3.91 ± 0.47	-	0.26
	Model 2	3.92 ± 0.68	4.63 ± 0.68	-	0.01	3.22 ± 0.66	4.91 ± 0.67	-	0.05	4.31 ± 0.68	4.81 ± 0.66	-	0.07
	Crude	111.73 ± 12.27	111.75 ± 14.86	0.98	-	111.88 ± 12.02	111.58 ± 15.06	0.85	-	111.23 ± 12.11	112.18 ± 14.89	0.55	-
SBP (mmHg)	Model 1	112.06 ± 1.18	110.00 ± 1.23	-	0.23	112.40 ± 1.17	109.60 ± 1.23	-	0.10	112.82 ± 1.39	109.67 ± 1.35	-	0.11
	Model 2	112.94 ± 2.00	111.34 ± 2.00	-	0.29	111.677 ± 1.93	112.57 ± 1.96	-	0.35	112.08 ± 109.27	111.27 ± 1.91	-	0.25
	Crude	76.65 ± 1.40	77.58 ± 1.21	0.09	-	76.93 ± 1.40	77.69 ± 1.12	0.11	-	77.96 ± 1.51	79.82 ± 11.77	0.09	-
DBP (mmHg)	Model1	76.78 ± 0.86	77.21 ± 0.01	-	0.06	76.45 ± 0.02	77.02 ± 0.07	-	0.08	76.32 ± 0.07	79.10 ± 0.05	-	0.06
	Model2	76.14 ± 1.02	78.13 ± 1.01	-	0.01	77.45 ± 1.02	78.22 ± 1.02	-	0.22	75 ± 1.00	80.12 ± 1.03	-	0.04
	Crude	1586.91 ± 258.69	1563.79 ± 261.01	0.44	-	1589.74 ± 259.87	1561.14 ± 259.64	0.34	-	1577.17 ± 253.52	1573.00 ± 265.86	0.89	-
RMR (kcal/day)	Model 1[‡]	1581.80 ± 18.12	1546.69 ± 18.59	-	0.28	1574.00 ± 18.41	1549.90 ± 19.09	-	0.18	1574.66 ± 18.46	1538.09 ± 19.15	-	0.17
	Crude	1717.32 ± 138.37	1723.25 ± 164.77	0.73	-	1718.41 ± 138.86	1722.23 ± 164.41	0.82	-	1707.98 ± 126.95	1731.36 ± 171.41	0.18	-
	Model 1[‡]	1721.87 ± 8.11	1707.86 ± 8.32	-	0.83	1706.09 ± 6.32	1710.58 ± 6.55	-	0.80	1705.78 ± 6.43	1702.61 ± 6.67	-	0.73
RMR normal (kcal/day)	Crude	1717.32 ± 138.37	1723.25 ± 164.77	0.73	-	1718.41 ± 138.86	1722.23 ± 164.41	0.82	-	1707.98 ± 126.95	1731.36 ± 171.41	0.18	-
	Model 1[‡]	1721.87 ± 8.11	1707.86 ± 8.32	-	0.83	1706.09 ± 6.32	1710.58 ± 6.55	-	0.80	1705.78 ± 6.43	1702.61 ± 6.67	-	0.73

Variables		PRAL		P-value	P-value [†]	NEAP		P-value	P-value [†]	DAL		P-value	P-value
		Low	High			Low	High			Low	High		
		(<-19.98)	(>-19.98)			(<-9.03)	(>-9.03)			(<-18.52)	(>-18.52)		
RMR per kg(kcal/day)	Crude	19.89 ± 3.30	19.11 ± 2.88	0.01	-	19.93 ± 3.33	19.27 ± 2.83	0.04	-	19.97 ± 3.28	19.26 ± 2.89	0.01	-
	Model 1 [‡]	19.70 ± 0.28	19.50 ± 0.28	-	0.03	19.92 ± 0.26	19.48 ± 0.27	-	0.01	19.95 ± 0.27	19.47 ± 0.28	-	0.22
RMR per BSA (kcal/day)	Crude	857.7 ± 118.95	843.13 ± 108.86	0.27	-	858.67 ± 119.60	842.30 ± 108.07	0.21	-	856.74 ± 119.04	844.42 ± 109.18	0.35	-
	Model 1 [‡]	852.09 ± 9.97	842.60 ± 10.23	-	0.49	853.64 ± 10.23	843.86 ± 10.61	-	0.35	854.92 ± 10.26	841.45 ± 10.65	-	0.37
RMR carbohydrate (kcal/day)	Crude	204.18 ± 63.15	192.46 ± 61.93	0.10	-	206.07 ± 63.78	190.62 ± 60.93	0.03	-	203.12 ± 63.69	193.69 ± 61.66	0.19	-
	Model 1 [‡]	204.03 ± 5.31	191.77 ± 5.45	-	0.06	204.17 ± 5.46	191.55 ± 5.66	-	0.09	204.30 ± 5.49	188.66 ± 5.69	-	0.05
RMR protein(kcal/day)	Crude	17.74 ± 3.22	17.62 ± 2.92	0.72	-	17.76 ± 3.23	17.60 ± 2.91	0.19	-	17.63 ± 3.16	17.72 ± 34.75	0.79	-
	Model1 [‡]	17.66 ± 0.22	17.45 ± 0.22	-	0.69	17.65 ± 0.20	17.50 ± 0.21	-	0.35	17.56 ± 0.22	17.36 ± 0.23	-	0.56
RMR fat (kcal/day)	Crude	72.48 ± 25.56	75.33 ± 26.21	0.34	-	71.93 ± 25.16	75.85 ± 26.50	0.63	-	71.94 ± 25.39	75.73 ± 26.28	0.21	-
	Model 1 [‡]	71.99 ± 2.18	73.82 ± 2.24	-	0.32	71.12 ± 2.18	74.33 ± 2.26	-	0.42	71.14 ± 2.39	73.73 ± 2.28	-	0.29
RQ	Crude	0.85 ± 0.03	0.85 ± 0.04	0.19	-	0.85 ± 0.04	0.85 ± 0.04	0.05	-	0.85 ± 0.04	0.85 ± 0.04	0.20	-
	Model 1 [‡]	0.85 ± 0.00	0.85 ± 0.00	-	0.18	0.85 ± 0.00	0.85 ± 0.00	0.22	-	0.85 ± 0.00	0.85 ± 0.00	-	0.13
HC, Hip circumference; WC, Waist circumference; NC, neck circumference; WHtR, Waist to height ratio; WHR, Waist to hip ratio; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein- cholesterol; TG, Triglycerides; FBS, Fasting blood sugar; HOMA, Homeostatic model assessment, RMR, Resting metabolic rate, BSA, Body surface area; resting metabolic rate; PRAL, potential renal acid load; DAL, dietary acid load NEAP, net endogenous acid production, SBP, Systolic blood pressure; DBP, Diastolic blood pressure; AST, Aspartate Aminotransferase, ALT, Alanine Transferase, Hs-CRP, high-sensitivity C-reactive protein, RQ, respiratory quotient Values are mean ±SD for crude model and mean± SE for adjusted model· Model 1: Adjusted for: age, BMI, physical activity and total energy intake, Model 2: Additionally controlled for significant dietary intakes in Table 2. For PRAL, we controlled the effect cereal, fruits, vegetables, nuts, egg, meat, carbohydrate, total fat intake, phosphor, total fiber, MUFA PUFA, SFA, caffeine and some of micronutrients magnesium, potassium, vitamin C,A, B1, B6, B9 and B12, NEAP we controlled for calcium, sodium, B3 apart from iron. For Dal score we controlled for all confounder for NEAP apart from B12· Model1 [‡] : Adjusted for: age, BMI, physical activity and total energy intake and fat free mass Crude p-value for all variables obtained from independent sample T test· † adjust p-value obtained from analysis of covariance·													

Relationship of body composition, blood parameters, RMR per kg, and high-low acid load scores of PRAL, NEAP, and DAL

We made three models to investigate body composition, blood parameters, and RMR per kg: a crude model, model 1, and model 2 (Table 4). In the crude model, we found a negative association between NEAP and FBS (P = 0.03). In model 1, we considered age, BMI, physical activity, total energy intake, and economic status as confounders, and in model 2, other variables, in addition to the aforementioned, were considered as confounders. In model 2 we observed a positive association for PRAL with WHtR (P = 0.09) and for NEAP with WC (P = 0.05), WHR (P = 0.03), TG (P = 0.01), and HOMA-IR (P = 0.08). Hs-CRP was positively associated with PRAL, NEAP, and DAL scores (P ≤ 0.08) and insulin with PRAL and DAL (P ≤ 0.08). In this model, some variables became negatively related with all three scores including: PRAL with HOMA-IR (P = 0.04) and HDL (P = 0.09), DAL with FBS (P = 0.07), and HOMA-IR (P = 0.007), and all three scores with DBP (P < 0.05). To investigate RMR per kg, we made four models; crude model, and model 1 (as above), model 3, that adjusted to age, BMI, physical activity, total energy intake, and fat free mass, and a final model that adjusted for other confounders, in addition to those mentioned in model 3 (Table 4). In the crude model, a negative association between NEAP and RMR per kg was found (β= -0.66, 95% CI=-1.37 to -0.04, P = 0.05), and in the final model this association became stronger (β= -0.25, 95%CI= -0.1.5 to 2.08, P = 0.02), and a marginal negative association for PRAL (β= -0.03, 95% CI= -1.05 to 0.03, P = 0.07) and DAL (β= -0.02, 95% CI=-0.08 to 0.03, P = 0.08) was found.

Table 4
Association between body composition, blood parameters and all RMR per kg(kcal/d) between high and low acid load scores

Association between body composition, blood parameters and air RMR per kg(kcal/d) between high and low acid load scores												
Variables		PRAL		P-value	P-value*	NEAP		P-value	P-value*	DAL		P-value
		β	CI (95%)			β	CI (95%)			β	CI (95%)	
Body composition												
WC(cm)	Crude	0.28	-1.66,2.22	0.77	-	-1.71	-4.12,0.69	0.16	-	-0.03	-0.08,0.1	0.19
	Model 1	-0.02	-0.04,0.004	-	0.10	-1.09	-3.39,1.21	-	0.35	-1.04	-3.40,1.31	-
	Model 2	0.04	-1.31,0.04	-	0.33	1.009	-1.43,3.45	-	0.05	-0.05	-0.13,0.02	-
NC(cm)	Crude	-1.26	-3.26,0.73	0.21		-1.12	-4.23,1.20	0.18	-	-1.20	-2.61,0.92	-
	Model 1	-0.03	-0.09,0.03	-	0.34	-1.35	-4.68,1.96	-	0.42	-1.49	-3.91,0.93	-
	Model 2	-0.17	-0.40,0.05	-	0.13	-5.95	-13.46,1.56	-	0.12	-0.14	-0.36,0.08	-
WHR	Crude	-1.07	-0.03,0.03	0.98	-	-0.13	-1.51,1.23	0.84	-	0.00	-0.032,0.03	0.99
	Model 1	0.00	1.001,0.000	-	0.034	-0.00	-0.02,0.00	-	0.17	-0.008	-0.02,0.00	-
	Model 2	0.001	-0.001,0.01	-	0.72	0.01	-0.01,0.04	-	0.03	0.001	-0.001,-0.00	-
WHtR	Crude	0.004	-0.008,0.01	0.24	-	-0.01	-0.02,0.003	0.11	-	0.001	0.00-0.004	0.29
	Model 1	0.00	0.001-0.00	-	0.09	-0.007	-0.02,0.007	-	0.29	-0.008	-0.02,0.00	-
	Model 2	0.00	-0.001,0.00	-	0.60	0.002	-0.01,0.01	-	0.72	0.001	-0.001,0.00	-
Biochemical variables												
FBS (mg/dL)	Crude	0.04	-0.02,0.1	0.19	-	2.84	0.29,5.38	0.02	-	0.03	-0.02,0.09	0.24
	Model 1	0.06	-0.004,0.12	-	0.05	2.89	0.27,5.51	-	0.03	0.06	-0.003,0.12	-
	Model 2	0.92	0.08,1.76	-	0.03	3.82	-1.96,9.60	-	0.01	0.93	0.10, 1.76	-
Insulin (mIU/ ml)	Crude	0.001	-0.001,0.002	0.41	-	0.02	-0.03,0.087	0.40	-	0.001	-0.001,0.002	0.58
	Model 1	0.001	-0.02,0.00	-	0.24	0.01	-0.05,0.04	-	0.51	0.01	-0.05,1.01	-
	Model 2	0.004	-0.01,0.00	-	0.07	0.01	0.00,0.16	-	0.09	0.001	-0.006,0.001	-
HOMA-IR	Crude	0.004	-0.004,0.01	0.28	-	0.21	-0.12,0.56	0.21	-	0.004	-0.004,0.01	0.29
	Model 1	0.007	-0.006,0.03	-	0.17	0.19	-0.14,0.52	-	0.26	0.007	-0.001,0.016	-
	Model 2	0.046	-0.06,0.15	-	0.02	0.13	-0.90,0.64	-	0.09	0.043	-0.06,0.15	-
Total cholesterol(mg/dL)	Crude	3.69	-5.13,12.51	0.41	-	2.47	-7.20,12.15	0.61	-	0.08	-0.13,0.31	0.44
	Model 1	0.003	-0.24,0.24	-	0.98	0.86	-8.89,10.61	-	0.17	0.56	-9.02,10.15	-
	Model 2	0.69	-1.51,0.13	-	0.10	2.086	-24.98,20.81	-	0.85	-0.59	-1.34,0.15	-
TG(mg/dL)	Crude	0.12	-0.24,0.50	0.50	-	6.18	-9.77,22.13	0.76	-	0.13	-0.23,0.49	0.48
	Model 1	0.004	-0.42,0.43	-	0.98	4.11	-12.93,21.16	-	0.04	-9.61	-26.48,7.25	-
	Model 2	-0.093	-1.58,1.40	-	0.90	26.96	-14.05,67.99	-	0.01	0.09	-1.23,1.42	-
HDL (mg/dL)	Crude	-2.26	-4.93,0.40	0.09	-	-1.67	-4.56,1.21	0.25	-	-0.029	-0.09,0.04	0.40
	Model 1	-0.03	-0.10,0.04	-	0.42	-1.34	-4.35,1.65	-	0.37	-1.060	-4.67,1.47	-
	Model 2	-0.02	-0.28,0.23	-	-0.20	-1.32	-8.48,5.82	-	0.71	-0.04	-0.28,0.19	-
LDL (mg/dL)	Crude	1.28	-0.62,3.19	0.18	-	-2.62	-9.07,3.82	0.42	-	0.009	-0.14,0.16	0.90
	Model 1	-0.01	-0.17,0.15	-	0.88	-1.67	-8.14,4.78	-	0.60	-0.01	-6.53,6.50	-
	Model 2	0.136	-7.00,0.42	-	0.63	-6.73	-22.25,8.78	-	0.39	0.08	-0.42,0.59	-
ALT (μKat/L)	Crude	2.27	-1.13,5.67	0.19	-	-1.34	-4.80,2.12	0.44	-	-0.01	-0.09,0.06	0.73
	Model 1	-0.03	-0.11,0.05	-	0.32	-1.01	-4.38,2.36	-	0.55	1.83	-1.88,5.55	-

Variables		PRAL		P-value	P-value*	NEAP		P-value	P-value*	DAL		P-value
		β	CI (95%)			β	CI (95%)			β	CI (95%)	
AST (μ Kat/L)	Model 2	-0.23	-0.52,0.05	-	0.11	-0.53	-8.56,7.48	-	0.89	-0.20	-0.49,0.07	-
	Crude	1.28	-0.62,3.19	0.18	-	-0.84	-2.80,1.11	0.39	-	-0.01	-0.05,0.03	0.61
	Model 1	-0.03	-0.08,0.01	-	-	-1.06	-2.94,0.81	-	0.26	1.83	-1.88,5.55	-
	Model 2	-0.09	-0.26,0.06	-	0.23	1.25	-3.27,5.77	-	0.58	-0.08	-0.24,0.07	-
Hs-CRP(mg/l)	Crude	-0.88	-2.05,0.27	0.13	-	-1.10	-2.35,0.13	0.08	-	-0.02	-0.05,0.00	0.13
	Model 1	0.01	-0.04,0.01	-	0.36	-0.94	-2.30,0.41	-	0.17	0.72	2.03,0.57	-
	Model 2	1.08	-0.22,1.10	-	0.06	2.76	-5.93,0.41	-	0.08	0.11	-0.21, 0.16	-
SBP (mmHg)	Crude	-0.02	-0.10,0.06	0.60	-	-1.46	-5.03,2.09	0.41	-	-0.02	-0.10,0.05	0.59
	Model 1	-0.05	-0.14,0.03	-	0.19	-2.00	-5.60,1.60	-	0.27	-0.05	-0.14,0.02	-
	Model 2	-0.11	-0.42,0.19	-	0.47	0.29	-7.75,8.35	-	0.94	-0.05	-0.33,0.23	-
DBP (mmHg)	Crude	-0.03	-0.09,0.01	0.17	-	-2.07	-4.56,0.41	0.10	-	-0.03	-0.09,0.01	0.18
	Model 1	0.04	-0.11,0.06	-	0.12	1.12	-4.71,1.22	-	0.09	0.01	-0.10,-0.11	-
	Model 2	0.33	-0.47,-1.15		0.04	0.64	-4.99,6.28	-	0.02	0.37	-0.42,1.18	-
RMR per kg (kcal/day)	Crude	-0.57	-1.27,0.13	0.11	-	-0.66	-1.37,0.04	0.05	-	-0.009	-0.02,0.00	0.34
	Model 1	-0.135	-0.96,0.69	-	0.74	-0.28	-1.109,0.53	-	0.08	-0.31	-1.13,0.50	-
	Model2#	-0.338	-1.118-0.442	-	0.39	-0.44	-1.21,-0.32	-	0.04	-0.33	-1.11,0.44	-
	Model3&	-0.037	-1.05,0.03	-	0.07	-0.25	-0.1.5,2.08	-	0.02	-0.02	-0.08,0.03	-

HC, Hip circumference; WC, Waist circumference; NC, neck circumference; WHtR, Waist to height ratio; WHR, Waist to hip ratio; HDL, high density lipoprotein– cholesterol; LDL, low density lipoprotein– cholesterol; Triglycerides; FBS, Fasting blood sugar; HOMA, Homeostatic model assessment, RMR, Resting metabolic rate, BSA, Body surface area; resting metabolic rate; PRAL, potential renal acid load; DAL, dietary acid load; NEAP, net endogenous acid production, SBP, Systolic blood pressure; DBP, Diastolic blood pressure; AST, Aspartate Aminotransferase, ALT, Alanine Transferase, Hs-CRP, high-sensitivity C-reactive protein, R, respiratory quotient

Values are mean $\pm$ SD for crude model and mean $\pm$ SE for adjusted model.

Model 1: Adjusted for: age, BMI, physical activity, total energy intake, economic status

Model 2: Additionally controlled for significant dietary intakes in Table 2. For PRAL, we controlled the effect cereal, fruits, vegetables, nuts, egg, meat, carbohydrate, total fat intake, phosphor, total fiber, MUFA, SFA, caffeine and some of micronutrients magnesium, potassium, vitamin C, B1, B6, B9 and B12, NEAP we controlled for calcium, sodium, B3 apart from iron. For Dal score we controlled for all confounder NEAP apart from B12.

Model2#: Adjusted for: age, BMI, physical activity and total energy intake and fat free mass

Model3&: Model2# confounder variables additionally controlled for significant dietary intakes in Table 2. For PRAL, we controlled the effect cereal, fruits, vegetables, nuts, egg, meat, carbohydrate, total fat intake, phosphor, total fiber, MUFA, PUFA, SFA, caffeine and some of micronutrients magnesium, potassium, vitamin C, B1, B6, B9 and B12, NEAP we controlled for calcium, sodium, B3 apart from iron. For Dal score we controlled for all confounder for NEAP apart from B12.

Crude p-value for all variables obtained from independent sample T test.

*P-value obtained from adjustment. All of p-values obtained from analysis of General linear model.

Definition of RMR per kg:

Discussion

The current study investigated the association of a diet with high acid load (characterized by a high DAL, a high PRAL or a high NEAP score) with anthropometric parameters, biochemical factors, and RMR among obese and overweight women. The principal findings of this study were that, after consideration of potential confounders, we observed a direct association between blood pressure (DBP) for two scores, and a direct relationship between hs-CRP and DAL, and TG and NEAP. In addition, a favorable relationship between HOMA-IR and PRAL, as well as DAL, was observed. Findings pertaining to HOMA-IR and DBP seem to be more reliable than other biochemical markers that were significantly related to only one of the dietary acid load indicators. Interestingly, the individuals with higher NEAP had lower RMR, while WC and WHR were higher in those subjects. We also observed that DAL and PRAL were marginally associated with RMR.

The load of acid production in body will be increased after higher intake of foods which are rich in animal protein, including meat, eggs, cheese, and grain. As highlighted in the present study, it was indicated that individuals with higher dietary acid load had higher intake of eggs and meat, as well as sodium, cereals, fat, and energy intake. These foods contain sulfur, amino acid, and phosphoric acid, and are strongly related with a higher production of hydrogen sulfate, which can increase the acid load in the body.

Diet acid load scores have been predicted and validated in people with kidney diseases (44), however, to date, studies have reported conflicting findings regarding the relationship of dietary acid load and cardio-metabolic risk factors (13, 19, 44–46). Indeed, several studies suggested that higher acid load has a negative association (19, 44, 45), while others refuted this association (13, 44). For instance, in an observational study on a cohort of 1136 females, it was suggested that PRAL was directly and independently associated with total cholesterol and HDL, although WC and BMI were substantially correlated with Pro:k (19).

The current study showed a significant association of NEAP and PRAL with DBP. Previous studies have reported that in metabolic acidosis related to diet, blood pressure was increased (23, 25). The Nurses' Health Study II, which was conducted on 1136 women aged 18 to 22, who had normal BMI, showed that a higher NEAP is connected with a greater risk of hypertension (44). However, this relationship is not universally supported; for instance, it has been reported that no association between blood pressure and dietary acid load was evident among participants that were higher than 55 years old (13). Confounding the equivocal reports, the mechanism underlying the proposed relationship have not been well defined, although several pathways have been suggested, such as reduction in elimination of citrate, higher production of cortisol, and higher excretion of calcium (20, 26, 28).

The association of glycemic profile and dietary acid load has been investigated in several studies. In the present study, we showed that subjects with higher dietary acid score had greater HOMA-IR. It was reported that all of metabolic acidosis markers, such as low serum bicarbonate, higher anion gap, and low urine pH are associated with insulin resistance (19, 47); indeed, in the Atherosclerosis Risk in Communities (ARIC) cohort, it was also confirmed that the risk of type 2 diabetes incidence was increased with higher levels of serum lactate (47). Thus, concomitant to the Nurses' health study, evidence suggests that higher plasma bicarbonate may be linked to an decreased odds of type 2 diabetes incidence (48). Sakhaee, et al (2002), in their prospective research, suggested that subjects with a lower urinary pH had greater prevalence of glucose intolerance and type 2 diabetes in comparison with normal counterparts (17). On the other hand, no significant association was found for Hemoglobin A1C (HbA1c) and serum glucose levels in young Japanese women (44). Several studies have reported that an acidogenic diet may contribute to insulin resistance by constantly inducing a chronic acidosis condition in body (49, 50). It is also proposed that insulin tendency to bind to its receptors is lessened in metabolic acidosis, which results in insulin resistance, albeit in animal studies (51). Moreover, insulin discharge is reduced whenever the body is faced with acid/base variations (52). Another possible mechanism may be related to the association of greater dietary acid load with higher discharge of magnesium, which decreases insulin sensitivity (53).

The associations of metabolic or urinary acidosis with biochemical parameters have been evaluated in several studies, yet, in spite of controversial results among such studies, we showed a positive association with dietary acid load and TG, WC, and WHR, and a negative relationship with RMR among the obese and overweight subjects in this study. The influence of an acidogenic diet on RMR can be the result of higher insulin resistance (50). In a cohort of 782 adults, it was reported that RMR and HOMA-IR were significantly related (54), thus, it can be inferred that higher acid load, by increasing the insulin resistance, may reduce RMR. This finding may be suggested as an effective impact of a diet with a lower acid load in women with higher than normal BMI. Kentaro Murakami et al. found an independent and positive association of total and HDL-cholesterol with PRAL, and also reported that BMI and waist circumference are independently associated with Pro:k (44). However, van den Berg et al (2012) did not report any meaningful correlation between urinary acidosis and TG, HDL, and HbA1c, however, lower levels of hs-CRP and cholesterol were seen in subjects with higher acidosis (5).

The association of the dietary acid load and metabolic factors has not been fully discerned, therefore, the underlying mechanisms of how an acidogenic diet influences metabolic outcomes have not been well explained. As mentioned above, animal protein in the diet may represent a cause of increasing acid load in body. In our study, the adverse effects of higher dietary acid score on TG, DBP, HOMA-IR and RMR was seen. The equivocal outcomes reported in studies can be explained by differences in target population, methodology, and specific dietary behaviors; the current study focused on overweight and obese women. In addition, the validation of dietary acid load measurement methods among obese and overweight subjects is important; it has been shown that higher protein intake is not the only cause of higher acid production (6). Indeed, in the present study, we also observed that higher consumption of cereals, sodium, fat, and energy intake is related to higher acid load (6). There are several limitations in this study that should be considered when interpreting the results. The present study was conducted on only one gender, so cannot be extrapolated to males. The number of participants were relatively low, moreover, based on the cross-sectional design of the study, we are not able to show any causal inference.

Conclusion

To date, no study has examined the relationship between dietary acid load and components of metabolic and RMR in obese and overweight females. Accordingly, we found that dietary acid load scores were significantly related to lower RMR and higher WC, WHR, DBP and HOMA-IR in overweight and obese women. Further studies are warranted to confirm the clinical consequences of dietary acid load in obesity.

Abbreviations

ARIC: Atherosclerosis Risk in Communities, **ALT:** Serum alanine aminotransferase, **ANCOVA:** Analysis of Covariance, **AST:** Aspartate aminotransferase, **B:** beta, **BIA:** Bioelectrical Impedance Analyzer, **BMI:** Body mass index, **BIA:** Bioelectrical impedance analysis, **BSA:** Body surface area, **BW:** body weight, **BFM:** body fat mass, **CHOD-PAP:** Phenol 4-Aminoantipyrine Peroxidase, **CIs:** con-fidence intervals, **CVD:** cardiovascular disease, **DAL:** dietary acid load, **DBP:** diastolic blood pressure, **EDTA:** Ethylenediaminetetraacetic acid, **FBS:** fasting blood sugar, **FFM:** Fat Free Mass, **GOD/PAP:** glucose oxidase phenol 4-Aminoantipyrine Peroxidase), **GLM:** General linear regression, **HbA1C:** Hemoglobin A1C, **HC:** hip circumferences, **HDL:** High density lipoprotein cholesterol,

HOMA-IR: Homeostatic model assessment insulin resistance, **hs-CRP:** Hypersensitive C - reactive protein, **IR:** insulin resistance, **IPAQ:** International Physical Activity Questionnaire, **LDL:** Low density lipoprotein cholesterol, **PRAL:** potential renal acidload, **NC:** Neck circumference , **NEAP:** net endogenous acid production , **RQ:** Respiratory quotient, **SDs:** Standard Deviations , **SEs:** standard Errors, **TC:** total cholesterol, **TG:** Triglyceride **WC:** Waist circumference ,**WHR:** waist and hip, **WHR:** waist-to-height ratio

Declarations

Ethics approval and consent to participate

The study protocol has approved by the ethics committee of Endocrinology and Metabolism Research Center of Tehran University of Medical Sciences (TUMS) with the following identification: IR.TUMS.VCR.REC.1395.1597.

Consent for publication

Each participant was completely informed about the study protocol and provided a written and informed consent form before taking part in the study.

Availability of data and materials

The data that support the findings of this study are available from Khadijeh Mirzaei but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Khadijeh Mirzaei.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by Tehran University of Medical Sciences (Grant number 95-04-161-33893).

Authors' contributions

The project was designed and implemented by AT and KhM. Data were analyzed and interpreted FSH, LS, AT and CC prepared the manuscript. KhM, supervised overall project. All authors read and approved the final manuscript.

Acknowledgments

We thank the school of Nutritional and Dietetics at Tehran University of medical sciences and participants in this investigation.

Authors' information (optional)

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