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Dietary acid load and mortality from all causes, CVD and cancer: results from the Golestan Cohort Study

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Abstract

Given the limited studies and controversial results on association between dietary acid load and mortality from CVD and cancers, we aimed to investigate this association in a large population cohort study in Middle East, with a wide range of dietary acid load. The study was conducted on the platform of the Golestan Cohort Study (GCS), which enrolled 50 045 participants in 2004–2008. Dietary intake was assessed using a validated FFQ. Dietary potential renal acid load (PRAL) score was calculated from nutrient intake. Death and its causes were identified and confirmed by two or three physicians. Cox proportional hazards regression was used to estimate hazard ratio (HR) and 95 % CI for total and cause-specific mortalities. Then, the associations were modelled using restricted cubic splines. PRAL range was −57·36 to +53·81 mEq/d for men and −76·70 to +49·08 for women. During 555 142 person-years of follow-up, we documented 6830 deaths, including 3070 cardiovascular deaths, 1502 cancer deaths and 2258 deaths from other causes. For overall deaths, in final model after adjustment for confounders, participants in the first and fifth quintiles of PRAL had a higher risk of mortality compared with the second quintile of PRAL (HR: 1·08; 95 % CI1·01, 1·16 and HR: 1·07; 95 % CI 1·01, 1·15, respectively); $P_{\text{for trend}} < 0{\cdot}05$). Participants in the first and fifth quintiles of PRAL had a 12 % higher risk of CVD mortality compared with the Q2 of PRAL (HR: 1·12; 95 % CI 1·01–1·25 and HR: 1·12; 95 % CI 1·01, 1·26, respectively; $P_{\text{for trend}} < 0{\cdot}05$). We found that all-cause and CVD mortality rates were higher in the lowest and highest PRAL values, in an approximately U-shaped relation (*P*-values for the overall association and the non-linear association of energy-adjusted PRAL with total mortality were < 0·001 and < 0·001, and with CVD mortality were 0·008 and 0·003, respectively). Our results highlight unfavourable associations of high acidity and alkalinity of diet with the increased total and CVD mortality risk. It may be important to consider a balanced acid–base diet as a protective strategy to prevent pre-mature death, especially from CVD.

Key words: **Mortality: Cardiovascular: Cancer: Cohort: GCS**

Abbreviations: HR, hazard ratio; PRAL, potential renal acid load.

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The leading causes of death worldwide are non-communicable disorders such as CVD and cancers[1]. The most modifiable risk factor for these diseases is dietary intake[1]. Although there are several studies investigating the association between dietary food groups, nutrients and dietary patterns with risk of non-communicable disorders[2–8], there are very few studies evaluating the relationship between dietary acid load and risk of overall, CVD or cancer mortality.

It is well known that body acid–base balance can be affected by dietary composition[9–12]. Diet-dependent acid–base load can be calculated based on Remer and colleague's equation that estimated potential renal acid load (PRAL) using dietary intake of five nutrients (protein, P, K, Ca and Mg)[6,13].

In a prospective cohort study, biochemical markers of acidosis such as urine pH, serum bicarbonate or serum anion gap have been related to incident diabetes[14] and kidney disease progression[15]. Two studies have evaluated the association between dietary acid load and mortality; one of them has reported that higher metabolic acid load is associated with an increased risk of all-cause and cardiovascular mortality in Japanese adults[16], while the other one found a modest U-shaped association between dietary acid load and risk of all-cause and cardiovascular mortality in Swedish adults[17].

Given the lack of large-scale studies evaluating the association between dietary acid load and chronic disease risk in the Middle East region, with its special dietary pattern, we aimed to evaluate the possible association between dietary acid load and mortality from all causes, CVD and cancer in a large cohort study in this region.

Materials and methods

The design of the Golestan Cohort Study (GCS) and its follow-up have been previously described in detail[18,19]. Briefly, between 2004 and 2008, the GCS enrolled 50 045 adults, aged between 40 and 87 years, from Gonbad city and 326 rural villages in north-eastern Iran. After excluding those participants with extremely low or high energy intakes (< 2092 or > 20920 kJ/d), prevalent cancers at baseline, missing or incomplete information on the FFQ and/or the general lifestyle questionnaire, and those with an unreasonable BMI (< 15 or > 50 kg/m^2), 48 691 participants were included in this analysis.

The study was approved by the Institutional Review Boards of the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences, the US National Cancer Institute (NCI), and the WHO International Agency for Research on Cancer (IARC). All participants provided written informed consent before enrolment.

Dietary intakes were assessed using a valid and reliable FFQ[20]. The details of dietary intake measurement and the calculation of nutrients are described previously[21]. Data on typical portion size, consumption frequency and servings consumed each time were collected for each food item at beginning of the study. Consumption frequency of each food item was questioned on a daily, weekly or monthly basis and converted into daily intakes; portion sizes were then changed into grams using household measures. All participants were interviewed by trained physicians and/or technicians, and information on demographics and baseline lifestyle behaviours were collected using a structured lifestyle questionnaire. Anthropometric variables were measured by an expert dietitian who also filled out the FFQ.

The PRAL score was calculated according to the established algorithms[22], and nutrients were energy-adjusted before being introduced into the following equation: PRAL (mEq/d) = 0·49 × protein intake (g/d) + 0·037 × P intake (mg/d) − 0·021 × K intake (mg/d) − 0·013 × Ca intake (mg/d) − 0·026 × Mg intake (mg/d). A negative PRAL score value indicates a base (alkaline) forming potential, while a positive score indicates an acid-forming potential. Other potential confounders assessed in this cohort study were age, sex, opium and alcohol consumption, smoking status, wealth score, physical activity, BMI, history of CVD, chronic obstructive pulmonary disease, renal failure, diabetes and dietary fat, carbohydrate and fibre intake. Details of the follow-up procedures of this cohort study have been described previously[18,21,23].

During the follow-up period, investigators called participants annually asking about vital status and the occurrence of any significant disease. The primary endpoint was death from any cause. Any reported death was confirmed by a physician visit and a completed validated verbal autopsy questionnaire[24]. Moreover, two internists independently reviewed all the verbal autopsy information and medical records and ascertained the cause of death. When there was a discrepancy between the causes of death diagnosis of the two internists, all data were reviewed by a third more experienced internist and the final diagnosis was made. In the current analysis, the leading causes of death among the participants were CVD, cancers, respiratory diseases, infectious diseases and other causes.

The primary outcome of this study was the association between dietary acid load and total mortality. Secondary outcomes were the associations between dietary acid load and specific causes of death and the associations between dietary acid load and demographic and lifestyle risk factors for death, history of chronic diseases, and dietary intake of PRAL components.

Statistical analysis

Baseline characteristics were compared according to quintiles of energy-adjusted PRAL using the one way ANOVA or the Kruskal–Wallis test for quantitative variables and the χ^2 test for qualitative variables.

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95 CI, and the proportionality assumption was verified using Aalen plots. First, the age- and sex-adjusted model (model I) was conducted, and then the full model (model II) was further adjusted for smoking status (never, former or current), opiate use (never, ever), drinking alcohol (never, ever), wealth score, BMI, physical activity score (low, moderate or high), the daily intake of total fat, carbohydrate, and total fibre, and past medical history of any CVD (including ischemic heart disease, Cerebrovascular accident (CVA), myocardial infarction (MI) or hypertension), diabetes, chronic obstructive pulmonary disease, or past medical history of renal failure. For all models, the second quintile was used as the reference category.

Table 1. Characteristics of participants according to quintiles of energy-adjusted dietary potential renal acid load (PRAL)

	PRAL														
	Q1(*n* 9739)			Q2 (*n* 9738)			Q3 (*n* 9739)			Q4 (*n* 9738)			Q5(*n* 9737)		
	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD
PRAL range (mEq/d)															
Men (*n* 20 727 (43 %))		−57·36 to −1·32			−1·32 to +1·68			+1·68 to +4·13			+4·13 to +7·06			+7·06 to +53·81	
Women (*n* 27 964 (57 %))		−76·70 to −2·09			−2·08 to +1·16			+1·16 to +3·77			+3·77 to +6·85			+6·85 to +49·08	
Age** (years)		52·53	8·79		51·71	8·71		51·40	8·67		51·49	8·73		52·97	9·39
BMI** (kg.m^2)		26·15	5·52		26·59	5·46		26·80	5·37		26·91	5·38		26·96	5·44
Smoking status**, %															
Never	78·75			82·87			83·41			84·34			84·00		
Current	17·65			14·06			13·15			12·45			12·10		
Former	3·60			3·07			3·44			3·21			3·90		
Opium ever used**, %	24·10			17·01			14·40			14·43			14·55		
Alcohol ever used**, %	4·77			3·31			3·18			3·07			3·15		
History of CVD**, %	23·15			21·15			21·25			21·73			28·14		
History of diabetes**, %	7·24			5·50			5·67			6·17			10·07		
History of renal failure*, %	0·23			0·11			0·15			0·17			0·31		
History of COPD*, %	6·52			6·04			5·44			5·60			6·22		
Physical activity**, %															
1st tertile	36·50			33·91			33·69			34·83			37·87		
2st tertile	31·60			31·80			32·05			31·30			31·32		
3st tertile	31·89			34·28			34·26			33·88			30·81		
Wealth score** (×10^2)		−0·53	22·35		−0·08	21·42		0·66	20·79		0·79	20·66		0·84	20·85
Energy intake (kJ/d)		8489·3	2585·7		9154·6	2326·3		9259·2	2309·5		9330·3	2368·1		9162·9	2577·3
Total dietary fat** (g/d)		70·86	23·24		76·29	23·87		77·07	23·35		77·61	22·50		77·69	25·65
Total carbohydrate intake** (g/d)		301·59	106·31		319·52	91·86		318·63	89·71		315·36	91·47		287·93	93·25
PRAL components															
Protein intake (g/d)		60·86	20·47		70·07	18·60		74·92	19·13		80·59	20·60		95·33	34·58
P intake (mg/d)		1151·68	388·34		1290·79	352·24		1352·28	362·26		1403·99	379·33		1460·02	439·63
Ca intake (mg/d)		646·30	282·04		698·98	255·06		726·45	262·53		740·63	261·78		720·37	272·67
K intake (mg/d)		3058·91	992·34		2919·29	758·90		2823·25	720·93		2746·79	712·91		2622·35	758·43
Mg intake (mg/d)		420·33	147·15		453·76	129·39		464·26	130·86		468·49	136·07		449·94	142·74
Food intakes															
Total dietary fibre (g/d)		21·79	8·26		23·25	6·88		23·5	6·79		23·47	7		21·73	7·33
Nuts intake (g/d)		3·11	6·1		3·04	5·44		3·03	7·58		2·71	5·04		2·31	5·19
Fish intake (g/d)		6·08	10·78		6·59	11·42		7·28	11·68		8·67	13·9		11·73	21·63
Egg intake (g/d)		9·25	11·71		10·76	12·76		11·28	12·89		12·22	14·41		11·91	16·43
White meat intake(g/d)		33·02	27·76		42·65	30·49		51·21	33·14		65·52	38·36		122·65	101·37
Red meat intake (g/d)		14·55	14·09		16·01	14·86		15·82	15·65		15·82	16·74		15·16	28·07
Dairy product intake (g/d)		186·62	143·39		192·21	135·22		198·67	140·71		201·85	139·93		196·8	146·3
Vegetable intake (g/d)		217·83	106·71		199·29	83·78		184·7	76·5		171·41	71·11		151·59	75·47
Fruits intake (g/d)		200·37	192·03		164·18	125·5		143·94	103·9		132·91	95·24		117·25	90·81
Total grain intake (g/d)		348·25	146·48		419·26	137·36		444·52	144·25		458·18	153·61		433·31	165

COPD, chronic obstructive pulmonary disease.
Values are means ± SD for continuous variables and percentages for categorical variables.
* Statistically significant ($P < 0·05$).
** Statistically significant ($P < 0·001$).

Table 2. HR for total and cause-specific mortality, according to the energy-adjusted PRAL quintiles†

	PRAL								
	Q1		Q2	Q3		Q4		Q5	
	HR	95 % CI	HR	HR	95 % CI	HR	95 % CI	HR	95 % CI
No. of person-years	111 457		112 539	112 144		110 934		108 068	
No. of overall deaths	1696		1396	1338		1359		1698	
Model I	1·17	1·09, 1·26**	ref	0·99	0·92, 1·07	1·01	0·94, 1·09	1·14	1·06, 1·22**
Model II	1·08	1·01, 1·16*	ref	1·01	0·94, 1·09	1·03	0·95, 1·11	1·07	1·01, 1·15*
No. of CVD deaths	675		537	565		559		734	
Model I	1·21	1·08, 1·36**	ref	1·09	0·97, 1·23	1·07	0·95, 1·21	1·25	1·11, 1·39**
Model II	1·12	1·01, 1·25*	ref	1·10	0·98, 1·24	1·07	0·95, 1·20	1·12	1·01, 1·26*
No. of cancer deaths	340		299	275		262		326	
Model I	1·11	0·95, 1·29	ref	0·95	0·80, 1·11	0·90	0·76, 1·06	1·02	0·87, 1·19
Model II	1·07	0·91, 1·25	ref	0·97	0·82, 1·15	0·93	0·79, 1·10	1·04	0·89, 1·22
No. of deaths from other causes deaths	519		428	395		423		493	
Model I	1·18	1·03, 1·34*	ref	0·96	0·83, 1·10	1·02	0·89, 1·17	1·07	0·94, 1·22
Model II	1·07	0·94, 1·22	ref	0·99	0·86, 1·13	1·06	0·93, 1·22	1·02	0·89, 1·16

HR, hazard ratios; PRAL, potential renal acid load; COPD, chronic obstructive pulmonary disease.
* Statistically significant ($P < 0·05$).
** Statistically significant ($P < 0·001$).
† Cox proportional hazards regression models for estimating HR and 95 % CI.
Model 1: adjusted for age and sex.
Model 2: additionally adjusted for BMI, smoking, alcohol use, opium use, wealth score, physical activity, history of CVD, COPD, renal failure, diabetes and dietary fat, carbohydrate and fibre intake.

Dose–response relationships between PRAL and all-cause and cause-specific mortality were investigated using restricted cubic spline models. The restricted cubic spline was conducted with five knots according to the percentiles of the distribution of PRAL. Overall and nonlinear associations were assessed by setting the coefficients of the first and second spline transformations equal to 0, respectively. PRAL of 0 was considered as reference.

All statistical analyses were performed using STATA version 12.0 statistical software (STATA Corporation).

Results

Baseline characteristics of the participants according to the quintiles of energy-adjusted dietary PRAL are shown in Table 1. The mean and standard deviation age of participants at baseline was 52·03 ± 8·9 years, and 43 % of the participants were male. The total PRAL range was −57·36 to +53·81 mEq/d for men and −76·70 to +49·08 mEq/d for women. Age, BMI, smoking status, opium and alcohol usage, history of CVD and diabetes, physical activity, wealth score, total fat and carbohydrate intake ($P < 0·001$), and history of renal failure and chronic obstructive pulmonary disease ($P < 0·05$) were different among quintiles of PRAL.

As shown in Table 2, during 555 142 person-years of follow-up, we documented 6830 deaths, including 3070 cardiovascular deaths, 1502 cancer deaths and 2258 deaths from other causes. Table 2 also indicates HR for the associations between PRAL quintiles and risk of total and cause-specific mortality. For overall deaths in final model, after adjustment for confounders, participants in Q1 and Q5 of PRAL had higher risks of mortality compared with the Q2 reference quintile of PRAL (HR: 1·08; 95 % CI1·01, 1·16 and HR: 1·07; 95 % CI 1·01, 1·15, respectively; $P_{\text{for trend}} < 0·05$). Participants in Q1 and Q5 of PRAL also had a 12 % higher risk of CVD mortality compared with the Q2 of PRAL (HR: 1·12; 95 % CI 1·01, 1·25 and HR: 1·12; 95 % CI 1·01, 1·26, respectively; $P_{\text{for trend}} < 0·05$). Fully adjusted models did not show any association between PRAL quintiles and cancer or other causes of death.

Figure 1 shows the dose–response relationships between energy-adjusted PRAL values and all-cause and cause-specific mortality. We found that all-cause and CVD mortality rates were higher in participants with the lowest and highest PRAL values, in an approximately U-shaped relation (*P*-values for the overall association and the non-linear association of energy-adjusted PRAL with total mortality were < 0·001 and < 0·001, and with CVD mortality were 0·008 and 0·003, respectively).

Discussion

The results of this large population-based cohort study demonstrated that both the highest and lowest dietary acid load scores were significantly associated with increased risk of total and CVD mortality. In the dose–response model, a U-shaped relationship between PRAL and both total and CVD mortality was observed. This relationship indicates both higher diet acidity and diet alkalinity were associated with higher mortality.

In the recent two decades, the relationship between diet-induced acidosis and some chronic diseases such as diabetes[14], hypertension[25], insulin resistance[26] and osteoporosis[27] have been investigated[28]; however, we found only two studies evaluating the association between dietary acid load and mortality from CVD and other specific causes of death. In a Swedish population, Xu et al. found that high diet acidity as well as diet alkalinity may increase the risk of mortality (a U-shaped relationship) (4), which is in line with our study results. Conversely, Akter et al.[29] found that only a high dietary acid load was related to a higher risk of total and CVD mortality in a Japanese population. It appears that this different finding may have been due to different PRAL score ranges in the

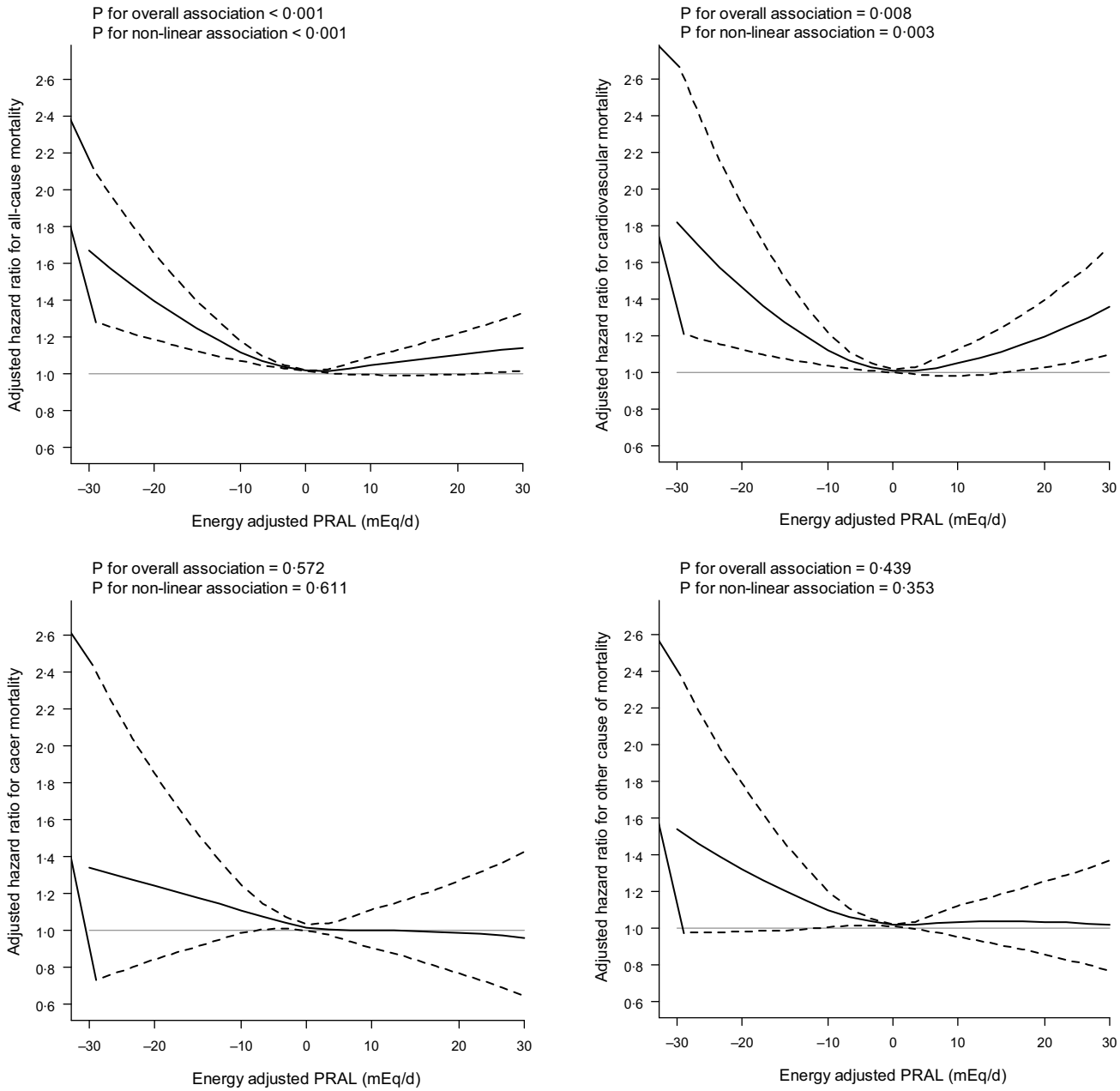

Fig. 1. Dose–response relation between PRAL and all-cause and cause-specific mortality using restricted cubic spline models. PRAL, potential renal acid load.

Japanese dietary intakes. PRAL score ranges in the Japanese population were narrower than ours and were only in the bottom and ascending parts of our U-shaped association diagram. Thus, they could not assess the association of diet alkalinity and mortality.

An important aspect of the association of diet acid load and mortality is that higher acid levels in blood predispose to various metabolic complications like mineral excretions, insulin resistance, increase in blood pressure and higher cortisol secretion[30]. A higher acid load may result in a lower affinity of insulin to bind to its receptor, causing insulin resistance[31], and insulin resistance appears to be associated with greater risk of CVD and all-cause mortality[32,33]. Moreover, previous studies have documented that a diet low in K could have a detrimental effect on blood vessels and vasodilation[34,35]. Also, in the National Health and Nutrition Examination survey (NHANES) III study, untreated or uncontrolled hypertension increased the risk of all-cause and CVD-specific mortality[36]. Furthermore, hypercortisolism is associated with metabolic and CVD which can increase mortality risk[37,38]. As previously documented, a diet rich in acidogenic foods (such as meat and fish) but low in alkaline foods (such as fruits and vegetables) can influence the acid–base balance of the body[38], and in turn, could result in the aforementioned metabolic disorders which probably affect CVD risk factors and mortality.

The mechanism for a positive association between diet acidity and risk of mortality is not yet fully known. Some potential mechanisms may mediate the unfavourable impact of major determinants of diet acid load on overall health, such as higher intake of animal sources protein and lower consumption of fruits and vegetables, which are also risk factors for overall mortality and CVD mortality[39]. Dietary meat consumption or high intake of protein from animal sources may increase the risk of CVD, according to previous reports[40,41]. Sinha et al. in their large prospective study demonstrated that consumption of red, white and processed meat was associated with higher risk of total mortality, including death caused by cancer and CVD[42]. On the other hand, higher intake of phytochemicals in fruits and vegetables has been previously proposed as an important component of a healthy dietary pattern to reduce CVD risk[43,44]. Moreover, results of other prospective cohort studies documented that nut, fruit and vegetable intake was significantly associated with a lower risk of all-cause mortality and cardiovascular mortality[45,46].

On the other hand, metabolic alkalosis is also associated with an increase in mortality, so that the mortality rate at arterial pH of 7·55 is 45 % and at pH of greater than 7·65 it reaches to 80 %[47]. However, it is not clear whether diet can increase blood pH despite the body's precise compensatory regulatory mechanisms. No study has been done on the health effects of alkaline diet and therefore available evidence cannot explain the exact mechanism to justify the negative effects observed in the present study. Although higher intake of fruits and vegetables as the main food with alkaline load is associated with a reduced risk of mortality, but this effect reaches a plateau in the intake of more than five servings of fruits and vegetables[48]. On the other hand, as the diet becomes more alkaline, the intake of some food items like fruits simple sugars, including glucose and fructose, artificially sweetened beverages, nectars, and margarine, increase, and excessive consumption of these may justify an increased risk of metabolic disorders and the mortality rate is in this pH range[49,50].

Our study has several strengths. First, it was a population-based prospective study in a large cohort. Second, we assessed the diet with a locally validated FFQ[20]. Third, this study took place in the understudied Middle East region, with its special dietary intakes such as high intake of rice and low intake of meats and dairy products. Finally, the dietary intakes in this population included enough variety to cause a wide range of diet acid loads, which could be compared with the mortality outcomes. However, some limitations also need to be considered. We collected the FFQ data only once, at the cohort baseline. And although we adjusted the analysis for a number of important risk factors and potential confounders, there may have been residual confounding from unmeasured or residual variables. Selection of participants (28 % did not agree to participate) and dietary changes are other limitations.

In conclusion, our results highlight unfavourable associations of both high acidity and high alkalinity of diet with increased total mortality and CVD mortality risk. It may be important to consider a balanced acid–base diet as a protective strategy to prevent premature death, especially from CVD; however, additional research should be done to confirm these results.

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There are no conflicts of interest.

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