Dietary Acid Load and Mortality from All Causes, Cardiovascular Disease, 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 cardiovascular disease (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 food frequency questionnaire (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 HRs and 95% CIs for total and cause specific mortalities. Then, the associations were modeled 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 5th quintiles of PRAL had a higher risk of mortality compared to the second quintile of PRAL (HR: 1.08; 95% CI: 1.01-1.16 and HR: 1.07; 95% CI: 1.01-1.15, respectively); P for trend <0.05). Participants in the first and 5th quintiles of PRAL had a 12% higher risk of CVD mortality compared to 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 for trend <0.05). 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 unfavorable 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 premature death, especially from CVD.

Keywords: Mortality; cardiovascular; cancer; cohort; GCS
INTRODUCTION

The leading causes of death worldwide are non-communicable disorders such as cardiovascular diseases (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, Phosphorus (P), Potassium (K), Calcium(Ca) and Magnesium (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, cardiovascular disease, 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 northeastern Iran. After excluding those participants with extremely low or high energy intakes (<500 or >5000 kcal/day), prevalent cancers at baseline, missing or incomplete information on the food frequency questionnaire (FFQ) and/or the general lifestyle questionnaire, and those with an
unreasonable body mass index (BMI) (<15 or >50 kg/m²), 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 World Health Organization International Agency for Research on Cancer (IARC). All participants provided written informed consent before enrollment.

Dietary intakes were assessed using a valid and reliable food frequency questionnaire [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 was collected for each food item at the 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 behaviors were collected using a structured lifestyle questionnaire. Anthropometric variables were measured by an expert dietitian who also filled out the FFQs.

The potential renal acid load (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 × phosphorus intake (mg/d) - 0.021 × potassium intake (mg/d) - 0.013 × calcium intake (mg/d) - 0.026 × magnesium 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, COPD, renal failure, diabetes and dietary fat, carbohydrate and fiber 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 cardiovascular disorders (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 Chi-square test for qualitative variables. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), 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, body mass index (BMI), physical activity score (low, moderate, or high), the daily intake of total fat, carbohydrate, and total fiber, and past medical history of any cardiovascular diseases (including ischemic heart disease, CVA, MI, or hypertension), diabetes, COPD, or past medical history of renal failure. For all models, the second quintile was used as the reference category.

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 5 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 zero 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 potential renal acid load (PRAL) are shown in Table 1. The mean ±SD 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 COPD (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 (Supplementary file). Table 2 also indicate HRs 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 to the Q2 reference quintile of PRAL (HR: 1.08; 95% CI:1.01-1.16 and HR: 1.07; 95% CI: 1.01-1.15, respectively; P for trend <0.05). Participants in Q1 and Q5 of PRAL also had a 12% higher risk of CVD mortality compared to 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 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 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 potassium could have a
detrimental effect on blood vessels and vasodilation [34 35]. Also, in the 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 cardiovascular
disorders 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 unfavorable 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 cardiovascular disease, 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 cause by cancer and cardiovascular disease [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 cardiovascular disease 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 can not 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 5 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 unfavorable 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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Conflict of interest
None

Authorship
The authors’ responsibilities were as follows—CCA, PB, SMD, PJB, PP, FK, and RM: designed the research; EH, HE, AH, HP, AE, and RM: conducted the research; EH, HE, and MS: analyzed data; EH, HE, AS, and AH: wrote the manuscript; CCA, PB, SMD, PJB, PP, AE, SGS, MS, AP, and FK: critically revised the manuscript for important intellectual content; and AH and RM: had primary responsibility for final content. All authors read and approved the final manuscript.
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Figure 1. Dose-response relation between PRAL and all-cause and cause-specific mortality using restricted cubic spline models.
Table1. Characteristics of participants according to quintiles of energy-adjusted Dietary Potential Renal Acid Load (PRAL)

<table>
<thead>
<tr>
<th>PRAL range (mEq/d)</th>
<th>PRAL</th>
<th>Q1 (n=9,739)</th>
<th>Q2 (n=9,738)</th>
<th>Q3 (n=9,739)</th>
<th>Q4 (n=9,738)</th>
<th>Q5 (n=9,737)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n=20,727 (43%))</strong></td>
<td>-57.36 to -1.32</td>
<td>-1.32 to +1.68</td>
<td>+1.68 to +4.13</td>
<td>+4.13 to +7.06</td>
<td>+7.06 to +53.81</td>
<td></td>
</tr>
<tr>
<td><strong>Women (n=27,964 (57%))</strong></td>
<td>-76.70 to -2.09</td>
<td>-2.08 to +1.16</td>
<td>+1.16 to +3.77</td>
<td>+3.77 to +6.85</td>
<td>+6.85 to +49.08</td>
<td></td>
</tr>
<tr>
<td>Age ** (y)</td>
<td>52.53 ± 8.79</td>
<td>51.71 ± 8.71</td>
<td>51.40 ± 8.67</td>
<td>51.49 ± 8.73</td>
<td>52.97 ± 9.39</td>
<td></td>
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<tr>
<td>BMI ** (kg.m^2)</td>
<td>26.15 ± 5.52</td>
<td>26.59 ± 5.46</td>
<td>26.80 ± 5.37</td>
<td>26.91 ± 5.38</td>
<td>26.96 ± 5.44</td>
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<tr>
<td>Smoking status **, %</td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>78.75</td>
<td>82.87</td>
<td>83.41</td>
<td>84.34</td>
<td>84.00</td>
<td></td>
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<tr>
<td>Current</td>
<td>17.65</td>
<td>14.06</td>
<td>13.15</td>
<td>12.45</td>
<td>12.10</td>
<td></td>
</tr>
<tr>
<td>former</td>
<td>3.60</td>
<td>3.07</td>
<td>3.44</td>
<td>3.21</td>
<td>3.90</td>
<td></td>
</tr>
<tr>
<td>History of diabetes **, %</td>
<td>7.24</td>
<td>5.50</td>
<td>5.67</td>
<td>6.17</td>
<td>10.07</td>
<td></td>
</tr>
<tr>
<td>History of renal failure*, %</td>
<td>0.23</td>
<td>0.11</td>
<td>0.15</td>
<td>0.17</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>History of COPD*, %</td>
<td>6.52</td>
<td>6.04</td>
<td>5.44</td>
<td>5.60</td>
<td>6.22</td>
<td></td>
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<tr>
<td>Physical activity**, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1st tertile</td>
<td>36.50</td>
<td>33.91</td>
<td>33.69</td>
<td>34.83</td>
<td>37.87</td>
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</tr>
<tr>
<td>2nd tertile</td>
<td>31.60</td>
<td>31.80</td>
<td>32.05</td>
<td>31.30</td>
<td>31.32</td>
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<tr>
<td>3rd tertile</td>
<td>31.89</td>
<td>34.28</td>
<td>34.26</td>
<td>33.88</td>
<td>30.81</td>
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<tr>
<td>Wealth score** (×10^2)</td>
<td>-0.53 ± 22.35</td>
<td>-0.08 ± 21.42</td>
<td>0.66 ± 20.79</td>
<td>0.79 ± 20.66</td>
<td>0.84 ± 20.85</td>
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</tr>
<tr>
<td>Energy intake (kcal/d)</td>
<td>2029.53 ± 618.88</td>
<td>2188.17 ± 556.64</td>
<td>2213.08 ± 552.89</td>
<td>2230.09 ± 566.09</td>
<td>2190.23 ± 616.29</td>
<td></td>
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<tr>
<td>Total dietary fat**, (g/d)</td>
<td>70.86 ± 23.24</td>
<td>76.29 ± 23.87</td>
<td>77.07 ± 23.35</td>
<td>77.61 ± 22.50</td>
<td>77.69 ± 25.65</td>
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<tr>
<td>Total carbohydrate intake**, (g/d)</td>
<td>301.59 ± 106.31</td>
<td>319.52 ± 91.86</td>
<td>318.63 ± 89.71</td>
<td>315.36 ± 91.47</td>
<td>287.93 ± 93.25</td>
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<tr>
<td>PRAL components</td>
<td></td>
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<tr>
<td>Protein intake (g/d)</td>
<td>60.86± 20.47</td>
<td>70.07± 18.60</td>
<td>74.92± 19.13</td>
<td>80.59 ± 20.60</td>
<td>95.33± 34.58</td>
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<tr>
<td>Phosphorus intake (mg/d)</td>
<td>1151.68± 388.34</td>
<td>1290.79± 352.24</td>
<td>1352.28± 362.26</td>
<td>1403.99± 379.33</td>
<td>1460.02± 439.63</td>
<td></td>
</tr>
<tr>
<td>Calcium intake (mg/d)</td>
<td>646.30± 282.04</td>
<td>698.98± 255.06</td>
<td>726.45± 262.53</td>
<td>740.63± 261.78</td>
<td>720.37± 272.67</td>
<td></td>
</tr>
<tr>
<td>Potassium intake (mg/d)</td>
<td>3058.91± 992.34</td>
<td>2919.29± 758.90</td>
<td>2823.25± 720.93</td>
<td>2746.79± 712.91</td>
<td>2622.35 ± 758.43</td>
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<tr>
<td>Magnesium intake (mg/d)</td>
<td>420.33 ± 147.15</td>
<td>453.76± 129.39</td>
<td>464.26± 130.86</td>
<td>468.49± 136.07</td>
<td>449.94± 142.74</td>
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</tr>
</tbody>
</table>

**Food intakes**

| Total dietary fiber (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 |

PRAL, Dietary Potential Renal Acid Load; CVD, Cardiovascular disease; COPD, Chronic Obstructive Pulmonary Disease; BMI, Body mass index;

* Statistically significant (P<0.05), ** statistically significant (P<0.001).

Values are means ± SDs for continuous variables and percentages for categorical variables.
Table 2. Hazard ratios for total and cause-specific mortality, according to the energy-adjusted PRAL quintiles

<table>
<thead>
<tr>
<th>PRAL</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of person-years</td>
<td>111457</td>
<td>112539</td>
<td>112144</td>
<td>110934</td>
</tr>
<tr>
<td></td>
<td>No. of overall deaths</td>
<td>1696</td>
<td>1396</td>
<td>1338</td>
<td>1359</td>
</tr>
<tr>
<td>Model I</td>
<td>1.17 (1.09-1.26) **</td>
<td>ref</td>
<td>0.99 (0.92-1.07)</td>
<td>1.01 (0.94-1.09)</td>
<td>1.14 (1.06-1.22) **</td>
</tr>
<tr>
<td>Model II</td>
<td>1.08 (1.01-1.16) *</td>
<td>ref</td>
<td>1.01 (0.94-1.09)</td>
<td>1.03 (0.95-1.11)</td>
<td>1.07 (1.01-1.15) *</td>
</tr>
<tr>
<td>No. of CVD deaths</td>
<td>675</td>
<td>537</td>
<td>565</td>
<td>559</td>
<td>734</td>
</tr>
<tr>
<td>Model I</td>
<td>1.21 (1.08-1.36) **</td>
<td>ref</td>
<td>1.09 (0.97-1.23)</td>
<td>1.07 (0.95-1.21)</td>
<td>1.25 (1.11-1.39) **</td>
</tr>
<tr>
<td>Model II</td>
<td>1.12 (1.01-1.25) *</td>
<td>ref</td>
<td>1.10 (0.98-1.24)</td>
<td>1.07 (0.95-1.20)</td>
<td>1.12 (1.01-1.26) *</td>
</tr>
<tr>
<td>No. of cancer deaths</td>
<td>340</td>
<td>299</td>
<td>275</td>
<td>262</td>
<td>326</td>
</tr>
<tr>
<td>Model I</td>
<td>1.11 (0.95-1.29)</td>
<td>ref</td>
<td>0.95 (0.80-1.11)</td>
<td>0.90 (0.76-1.06)</td>
<td>1.02 (0.87-1.19)</td>
</tr>
<tr>
<td>Model II</td>
<td>1.07 (0.91-1.25)</td>
<td>ref</td>
<td>0.97 (0.82-1.15)</td>
<td>0.93 (0.79-1.10)</td>
<td>1.04 (0.89-1.22)</td>
</tr>
<tr>
<td>No. of deaths from other causes deaths</td>
<td>519</td>
<td>428</td>
<td>395</td>
<td>423</td>
<td>493</td>
</tr>
<tr>
<td>Model I</td>
<td>1.18 (1.03-1.34)</td>
<td>ref</td>
<td>0.96 (0.83-1.10)</td>
<td>1.02 (0.89-1.17)</td>
<td>1.07 (0.94-1.22)</td>
</tr>
<tr>
<td>Model II</td>
<td>1.07 (0.94-1.22)</td>
<td>ref</td>
<td>0.99 (0.86-1.13)</td>
<td>1.06 (0.93-1.22)</td>
<td>1.02 (0.89-1.16)</td>
</tr>
</tbody>
</table>

PRAL, Dietary Potential Renal Acid Load; CVD, Cardiovascular disease.

* Statistically significant (P<0.05), ** Statistically significant (P<0.001).

*a Cox proportional hazards regression models for estimating HRs and 95% CIs.

b Model 1: adjusted for age and gender.

c 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 fiber intake.