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Low carbohydrate–high protein diet and mortality in a cohort of Swedish women

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Abstract. Lagiou P, Sandin S, Weiderpass E, Lagiou A, Mucci L, Trichopoulos D, Adami H-O (University of Athens Medical School, Goudi, Athens, Greece; Karolinska Institutet, Stockholm, Sweden; The Cancer Registry of Norway, Montebello, Oslo, Norway; Athens Technological Institute (TEI), Akadimia Platonos, Greece; Harvard School of Public Health, Boston, MA, USA; Harvard Medical School, Boston, MA, USA). Low carbohydrate–high protein diet and mortality in a cohort of Swedish women. *J Intern Med* 2007; **261:** 366–374.

Objective. The long-term health consequences of diets used for weight control are not established. We have evaluated the association of the frequently recommended low carbohydrate diets – usually characterized by concomitant increase in protein intake – with long-term mortality.

Design. The Women's Lifestyle and Health cohort study initiated in Sweden during 1991–1992, with a 12-year almost complete follow up.

Setting. The Uppsala Health Care Region.

Subjects. 42 237 women, 30–49 years old at baseline, volunteers from a random sample, who completed an extensive questionnaire and were traced through linkages to national registries until 2003.

Main Outcome Measures. We evaluated the association of mortality with: decreasing carbohydrate intake (in deciles); increasing protein intake (in deciles) and an additive combination of these variables (low carbohydrate–high protein score from 2 to 20), in Cox models controlling for energy intake, saturated fat intake and several nondietary covariates.

Results. Decreasing carbohydrate or increasing protein intake by one decile were associated with increase in total mortality by 6% (95% CI: 0–12%) and 2% (95% CI: −1 to 5%), respectively. For cardiovascular mortality, amongst women 40–49 years old at enrolment, the corresponding increases were, respectively, 13% (95% CI: −4 to 32%) and 16% (95% CI: 5–29%), with the additive score being even more predictive.

Conclusions. A diet characterized by low carbohydrate and high protein intake was associated with increased total and particularly cardiovascular mortality amongst women. Vigilance with respect to long-term adherence to such weight control regimes is advisable.

Keywords: Carbohydrate, cardiovascular mortality, diet, mortality, protein, weight control.

Introduction

Reduced energy intake has long been known to increase longevity in animals [1] and is likely to be beneficial for most persons in economically developed societies. Moreover, increased energy expenditure has been found to reduce mortality in humans [2, 3]. Beyond that, after controlling for energy intake and

expenditure, qualitative aspects of diet have also been associated with a range of chronic diseases, plant foods generally considered as beneficial and saturated fats of animal origin generally considered as unfavourable [4, 5]. Dietary patterns associated with reduced mortality are often characterized by high consumption of carbohydrates, mainly complex ones, and low consumption of proteins, mainly those of animal origin [6, 7]. During the last decades, however, several weight control diets have been introduced and popularized, with a focus on reduction of carbohydrates and increase of protein intake [8].

Low carbohydrate–high protein diets may have short-term effects on weight control [8–11], but concerns have been expressed on several grounds [12–16]. Although such diets may be acceptable if high protein is mainly of plant origin and the reduction of carbohydrates refers mainly to simple and refined ones [17], these qualifications may not be perceived as important by the general public, as they are rarely emphasized. Moreover, given the frequently life-long battle against overweight, diets perceived as contributing to better weight control may be adhered to for long periods. Yet, the long-term health effects of low carbohydrate–high protein diets have not been extensively evaluated.

The optimal study for assessing the health effects of a low carbohydrate diet would be a high compliance randomized trial lasting several years and comparing this diet with a usual or a 'healthy' diet. Such a study, however, appears to be unrealistic. Two observational studies have been recently published. In one of them, undertaken in a cohort of female USA nurses, no association between coronary heart disease and diets lower in carbohydrate and higher in protein and fat was found [18]. In another cohort study from the general population of men and women in Greece, low carbohydrate–high protein diets were significantly associated with increased total mortality and particularly cardiovascular mortality [19]. We set out to examine whether low carbohydrate–high protein diets are associated with increased mortality in a general population cohort of relatively young women in Sweden. The relevance of the study group is high, as low carbohydrate weight control diets are particularly used by women.

In an observational study, which assesses the effects of the composition of diet controlling for energy intake, it is all but impossible to distinguish the effects of specific energy-generating nutrients, as a decrease in the intake of one is unavoidably linked to an increase in the intake of one or several of the others [20]. We have therefore opted for substituting carbohydrates with protein in the analysis for the following reasons: increased protein intake is the option preferred in the popular low carbohydrate diets [8]; a higher intake of saturated fat is generally undesirable and, thus, unlikely; an increase of unsaturated lipids of plant origin has been difficult in all but the Mediterranean countries; and proteins and carbohydrates are isocaloric.

Methods

Subject recruitment

The source population for this study was women 30–49 years old, residing in the Uppsala Health Care Region in Sweden during 1991–1992. These women were randomly selected from four age strata, namely 30–34, 35–39, 40–44 and 45–49 years of age and were invited by mail to participate in the Swedish component of the Scandinavian Women's Lifestyle and Health Cohort [21]. Women were asked to fill in a questionnaire and return it in a prepaid envelope. Altogether 49 261 questionnaires were returned. The study was approved by the Swedish Data Inspection Board and the regional Ethical Committee.

Questionnaire and dietary assessment

The self-administered questionnaire recorded information on lifestyle variables (including detailed smoking and alcoholic drinking habits), anthropometry and history of diagnoses of major diseases. Women were also asked to rate their overall level of physical activity (i.e. activities in the house, occupational and recreational physical activity) on a 5-point scale with examples attached to levels 1, 3 and 5. A validated

food frequency questionnaire [22] was used to assess the frequency of consumption and quantity of about 80 food items and beverages, focusing on the 6-month period prior to the woman's enrolment in the study. Eleven food groups were formed (measured in g day^{-1}), namely vegetables, legumes, fruits and nuts, dairy products, cereals, meat and meat products, fish and seafood, potatoes, eggs, sugars and sweets, and nonalcoholic beverages (measured in mL day^{-1}). Food consumption was translated into macronutrient and energy intakes on the basis of the Swedish National Food Administration database [23].

We used residuals from the regressions of, alternatively, protein and carbohydrate intake on total energy intake to estimate the energy-adjusted intakes of protein and carbohydrates for each woman [24]. Women were then assigned a score from 1 (very low protein intake) to 10 (very high protein intake), according to their decile of energy-adjusted total protein intake. An inverse score, from 1 (very high carbohydrate intake) to 10 (very low carbohydrate intake) was also assigned according to the woman's decile of energy-adjusted total carbohydrate intake. The scores were studied both separately and after being added creating a composite additive score simultaneously assessing the position of each subject in terms of protein and carbohydrate intake. Thus, a woman with a score of 2 is one with very high consumption of carbohydrates and very low consumption of proteins, whereas a woman with a score of 20 is one with very low consumption of carbohydrates and very high consumption of proteins.

Follow up

Linkages with the Swedish nationwide health registers, by means of the unique per individual Swedish national registration number, were used for the follow up of the cohort with respect to death and emigration. Information on dates of death for women who died during the follow-up period until 31 December 2003 was retrieved from the Register of Total Population. Additional information on cause of death, updated till 31 December 2002, was derived from the Swedish Cause of Death Register. Dates of emigration for women who moved out of Sweden were provided by the Register of Total Population. The date of return of the questionnaire during 1991–1992 was defined as the start of follow up. Observation time was calculated from date of entry into the cohort until the occurrence of death, or censoring. For overall mortality, censoring was on account of emigration or end of the observation period, whilst for cardiovascular or cancer mortality, it was also on account of death from any cause other than the one under study.

Statistical analysis

Of the original 49 261 Swedish women, the following were sequentially excluded: those who had emigrated without re-immigration prior to start of study (16 women), those who had not filled in the dietary questionnaire (583 women), those with prevalent cancer (excluding nonmelanoma skin cancer), coronary heart disease or diabetes at enrolment (1418 women), and those with missing information on any of the covariates studied (4403 women), as well as those with energy intake outside the first (1847 kJ day^{-1}) and 99th (12 474 kJ day^{-1}) centiles (604 women). Thus, a total of 42 237 women were available for the analysis.

The participating women and the deaths that occurred amongst them were distributed by non-nutritional covariates, and age- and multivariate- adjusted mortality ratios were calculated. Hazard ratios for overall mortality and mortality from cancer, as well as cardiovascular diseases, were estimated through Cox proportional hazards regression using, alternatively, the high protein score, the low carbohydrate score and the composite additive score as the principal exposure variables. To accommodate secular trends the models were stratified by 1-year birth cohorts with attained age as time scale. In a stratified Cox model the baseline hazard is allowed to vary across strata. The models were adjusted for the following variables as reported at enrolment: height (cm, continuously), body mass index (BMI; <25, 25–29.99 and ≥30 kg m^2, categorically), smoking status (never smokers, former smokers of <10 cigarettes, former smokers of 10–14 cigarettes, former smokers of

15–19 cigarettes, former smokers of 20 or more cigarettes, current smokers of <10 cigarettes, current smokers of 10–14 cigarettes, current smokers of 15–19 cigarettes, current smokers of 20 or more cigarettes, categorically), physical activity [from 1 (low) to 5 (high), categorically], education (0–10, 11–13 and 14 or more years in school, categorically), energy intake (per 1000 kJ day^{-1}, continuously), saturated lipid intake (per 10 g, continuously) and alcohol intake (<5, 5–25 or >25 g day^{-1}, categorically). Unsaturated lipids should not be and were not controlled for in these models to avoid overdetermination generated by inclusion of all energy-generating nutrients as well as total energy intake in the same models. Fine control for tobacco smoking was necessary because of the powerful influence of smoking on mortality and the possibility that smoking may be associated with some dietary intakes. All analyses were conducted for all women, as well as separately for women <40 years old at enrolment and for women 40 years or older at enrolment, the rationale being that genetic and early life factors are likely to have a stronger influence amongst younger than amongst older adults.

Statistical analyses were performed using the statistical software R version 2.0.2 (http://www.r-project.org). The Cox proportional hazards assumption was checked by graphs of scaled Schoenfeldt residuals versus time [25]. None of the model covariates showed a deviation from the proportional hazards assumption and no evidence of collinearity was detected.

Results

Overall, the 42 237 women were followed up for an average of about 12 years and have generated a total of 507 325 person-years, with 592 deaths. Table 1 presents the distribution of participating women and the deaths that occurred amongst them by non-nutritional covariates, as well as age-adjusted and multivariate mortality ratios. The observed mortality patterns are generally in accordance with those expected on the basis of the scientific literature, in that mortality increases with age, BMI, smoking and heavy alcohol drinking and declines markedly with education and physical activity.

In this cohort of women, median intake of energy was 6396 kJ day^{-1} with 10th and 90th centiles 4246 and 9060 kJ day^{-1}, respectively. Percentage of energy intake from carbohydrates ranged from 72.0% (10th centile) to 32.4% (90th centile) and for proteins from 10.4% (10th centile) to 23.0% (90th centile). The additive score was significantly correlated positively with protein intake (Spearman $r = +0.35$), inversely with carbohydrate intake (Spearman $r = -0.28$), positively with lipid intake (for saturated lipids Spearman $r = +0.26$; for unsaturated lipids Spearman $r = +0.16$), but, importantly, it was not correlated with energy intake (Spearman $r = -0.006$).

In Table 2, the women are distributed by age at enrolment (≤39 or 40–49 years) and deaths by cause, as well as by the additive low carbohydrate–high protein score. The data in this table are not directly interpretable because confounding and time-to-event are not accounted for. Nevertheless, the data suggest that, amongst women who were 40–49 years at enrolment, total, as well as cardiovascular mortality increase with increasing score.

In Table 3, multivariate mortality rate ratios for death from any cause, cancer or cardiovascular diseases, per 1 unit increase in the low carbohydrate score or the high protein score, as well as per 2 units increase in the additive score (the range of which is twice that of the range of the component scores) are presented. Because the range of the additive score is from 2 to 20 points and 5-point differences are quite common (Table 2), the regression coefficients for a 2 units increase is shown in Table 3 can be transformed, for a more realistic representation into those corresponding to 5 units increment. The additive low carbohydrate–high protein score is positively associated with overall mortality, a 5 units increment corresponding to an increase in mortality by 11% [95% confidence interval (CI): 0–23%]. This increase in overall mortality is mostly accounted for by an increase of 37% in cardiovascular mortality (95% CI: 2–84%). The increase in cardiovascular mortality was evident amongst women who were 40–49 years old at enrolment and whose attained age at the end of the 12-year

Table 1 Distributions of 42 237 women by non-nutritional variables and corresponding mortality ratios

Variables	Number	Number of deaths	Age-adjusted mortality ratios (95% CI)	Multivariate[a] mortality ratios (95% CI)
Age at enrolment (years)				
29–34	10 251	60	1.00	1.00
35–39	10 898	113	1.77 (1.29–2.42)	1.78 (1.30–2.43)
40–44	11 119	173	2.65 (1.98–3.56)	2.53 (1.88–3.40)
45–49	9969	226	3.87 (2.91–5.14)	3.48 (2.59–4.65)
P-value for trend			$<10^{-4}$	$<10^{-4}$
Education (years)				
0–10	12 537	265	1.00	1.00
11–13	16 418	183	0.67 (0.55–0.82)	0.73 (0.61–0.90)
>13	13 282	124	0.52 (0.42–0.65)	0.63 (0.50–0.78)
P-value for trend			$<10^{-4}$	$<10^{-4}$
Height (cm)				
<160	5239	90	1.00	1.00
160–164.9	11 920	159	0.78 (0.60–1.00)	0.82 (0.63–1.06)
165–169.9	13 538	186	0.82 (0.64–1.05)	0.88 (0.68–1.13)
≥170	11 540	137	0.73 (0.56–0.96)	0.81 (0.62–1.06)
P-value for trend			0.07	0.29
Body mass index (kg m^2)				
<25	30 663	366	1.00	1.00
25–29.9	9234	144	1.19 (0.98–1.45)	1.08 (0.88–1.31)
≥30	2340	62	2.01 (1.53–2.63)	1.66 (1.26–2.19)
P-value for trend			$<10^{-4}$	0.003
Physical activity				
1 (low)	1724	50	1.00	1.00
2	4496	81	0.63 (0.44–0.89)	0.75 (0.52–1.06)
3	25 183	338	0.46 (0.34–0.62)	0.56 (0.41–0.76)
4	7227	75	0.36 (0.25–0.52)	0.51 (0.35–0.73)
5 (high)	3607	28	0.29 (0.18–0.45)	0.39 (0.25–0.63)
P-value for trend			$<10^{-4}$	$<10^{-4}$
Smoking at enrolment				
Never smoker	17 427	160	1.00	1.00
Ex-smoker	12 476	158	1.35 (1.09–1.69)	1.34 (1.08–1.68)
Current smoker	12 334	254	2.32 (1.90–2.82)	2.07 (1.69–2.54)
P-value for trend			$<10^{-4}$	$<10^{-4}$
Alcohol intake (g day^{-1})				
<5	31 453	415	1.00 (0.83–1.21)	1.01 (0.84–1.23)
5–25	10 595	148	1.00	1.00
>25	189	9	3.29 (1.68–6.38)	2.59 (1.32–5.09)
P-value for trend			0.45	0.41
Total	42 237	572		

[a]Mutually adjusted for the variables in this table through Cox proportional hazards regression.

Table 2 Participants by age at enrolment, cause of death and value in a low carbohydrate–high protein additive score

Age at enrolment (years):	≤39				40–49			
		Number of deaths (‰)				Number of deaths (‰)		
Low carbohydrate–high protein additive score[a]	Number of women	All[b]	Cancer[c]	Cardiovascular[c]	Number of women	All[b]	Cancer[c]	Cardiovascular[c]
≤6	4131	27 (6.5)	10 (2.4)	3 (0.7)	3986	63 (15.8)	34 (8.5)	5 (1.3)
7–9	3972	34 (8.6)	11 (2.8)	6 (1.5)	4035	71 (17.6)	36 (8.9)	7 (1.7)
10–12	4815	48 (10.0)	26 (5.4)	3 (0.6)	4940	85 (17.2)	44 (8.9)	12 (2.4)
13–15	4085	33 (8.1)	17 (4.2)	5 (1.2)	4089	86 (21.0)	46 (11.2)	15 (3.7)
≥16	4146	37 (8.9)	14 (3.4)	2 (0.5)	4038	104 (25.8)	46 (11.4)	17 (4.2)
Total	21 149	179 (8.5)	78 (3.7)	19 (0.9)	21 088	409 (19.4)	206 (9.8)	56 (2.7)

[a]The low carbohydrate–high protein score is derived by summing the position of a woman in deciles of descending carbohydrate intake and deciles of ascending protein intake. The score ranges from 2 (very low protein and very high carbohydrate intake) to 20.
[b]Data on total deaths updated until December 2003.
[c]Data on deaths from cancer or cardiovascular diseases updated until December 2002.

Table 3 Hazard ratios[a] for overall[b], cancer or cardiovascular mortality[c] per decreasing decile of carbohydrate intake, increasing decile of protein intake and their addition

	Hazard ratios[a] (95% CI)		
	Death from any cause	Deaths from cancer	Deaths from cardiovascular diseases
All women			
Lower carbohydrate (per decile)	**1.06 (1.00–1.12)**	1.04 (0.97–1.11)	1.10 (0.96–1.26)
Higher protein (per decile)	1.02 (0.99–1.05)	1.01 (0.96–1.05)	**1.10 (1.01–1.20)**
Sum of above (per 2 units)	**1.04 (1.00–1.08)**	1.02 (0.96–1.08)	**1.15 (1.01–1.28)**
Women ≤39 years old			
Lower carbohydrate (per decile)	1.09 (1.00–1.18)	1.05 (0.92–1.20)	1.08 (0.82–1.43)
Higher protein (per decile)	1.01 (0.96–1.07)	1.01 (0.94–1.10)	0.95 (0.81–1.12)
Sum of above (per 2 units)	1.04 (0.96–1.12)	1.04 (0.92–1.15)	0.98 (0.77–1.23)
Women 40–49 years old			
Lower carbohydrate (per decile)	1.05 (0.99–1.11)	1.04 (0.96–1.13)	1.13 (0.96–1.32)
Higher protein (per decile)	1.02 (0.99–1.06)	1.00 (0.95–1.05)	**1.16 (1.05–1.29)**
Sum of above (per 2 units)	**1.04 (1.00–1.10)**	1.02 (0.94–1.08)	**1.21 (1.04–1.39)**

[a]Hazard ratios per indicated increase in the corresponding score. Cox models, using attained age as time scale, stratifying for 1-year birth cohorts and adjusting for height (cm, continuously), body mass index (<25, 25–29.99 and ≥30 kg m^2, categorically), smoking status (never smokers, former smokers of <10 cigarettes, former smokers of 10–14 cigarettes, former smokers of 15–19 cigarettes, former smokers of 20 or more cigarettes, current smokers of <10 cigarettes, current smokers of 10–14 cigarettes, current smokers of 15–19 cigarettes, current smokers of 20 or more cigarettes, categorically), physical activity [from 1 (low) to 5 (high), categorically], education (0–10, 11–13 and 14 or more years in school, categorically), energy intake (per 1000 kJ day^{-1}, continuously), saturated lipid intake (per 10 g, continuously) and alcohol intake (<5, 5–25 or >25 g day^{-1}, categorically).
[b]Until the end of 2003.
[c]Until the end of 2002.

follow up was from 52 to 61 years (increase of 60%, with 95% CI: 13–115%). Increased protein intake and decreased carbohydrate intake appear to be equally unfavourable for cardiovascular mortality (Table 3).

Although there is no significant deviation from linearity for the statistically significant trend results shown in Table 3, we also evaluated the association of the additive low carbohydrate–high protein score

categories (as shown in Table 2) with overall and cardiovascular mortality amongst all women and cardiovascular mortality amongst women 40–49 years old at enrolment. Using additive score values ≤6 as baseline, the mortality ratios (and 95% CI) for successively increasing categories were: for total mortality amongst all women, 1.10 (0.82–1.47), 1.10 (0.83–1.46), 1.11 (0.83–1.50), 1.23 (0.91–1.67); for cardiovascular mortality amongst all women 1.65 (0.68–4.06), 1.61 (0.66–3.91), 2.30 (0.96–5.52), 2.38 (0.95–6.01); and for cardiovascular mortality amongst women 40–49 years old at enrolment, 1.45 (0.45–4.66), 2.18 (0.74–6.42), 3.06 (1.04–8.96), 3.86 (1.28–11.63). These trends are essentially monotonic.

Discussion

In a population-based prospective study, 42 237 Swedish women were followed up for an average of about 12 years, thus generating a total of 507 325 person-years. After fine controlling for all assessed mortality risk factors that could act as confounding variables, as well as for total energy and saturated fat intake, women with lower intake of total carbohydrates and higher intake of total proteins, in comparison to those with higher intake of total carbohydrates and lower intake of total proteins, had significantly higher total mortality and, in particular, cardiovascular mortality. These results followed an exposure-response pattern. The results were more pronounced for cardiovascular mortality amongst women who at enrolment were 40 years or older and, thus, at the end of the follow up had reached ages between 52 and 61 years.

The validity of our results can be assessed at three levels: the characteristics of the study base, the adequacy of the analytical strategy and the biological plausibility. With respect to the study base, the cohort was population-based, the dietary questionnaire used was validated, potential confounding variables were ascertained in detail, women with comorbidity at enrolment were excluded and nationwide data linkage in Sweden allowed complete follow up.

Concerning the analytical strategy, although it is not possible to completely separate the effects of individual macronutrients and those of total energy intake in observational epidemiological studies, the effect of substitution, in this instance between proteins and carbohydrates, can be estimated, controlling for total energy intake. Our analysis followed the substitution approach [20, 24], taking into account that energy generated by carbohydrates and proteins is equivalent and that a simple additive score reflecting the balance of intakes of these two energy-generating nutrients was uncorrelated with total energy intake. Controlling for saturated fat intake (but not simultaneously for other types of fats, to avoid overdetermination of the model) and as finely as possible for other potential confounders, particularly smoking, minimizes the potential for confounding bias.

The biomedical plausibility of our findings is considerable. Vegetables, fruits, cereals and legumes, which have been found in a number of studies to be core components of healthy dietary patterns [6, 7, 26], are important sources of carbohydrates and reduced intake of these food groups is likely to have adverse health effects. Increased meat consumption and high protein intake are also discouraged on account of empirical findings [5, 27–30], pathophysiological arguments [stemming from the positive association between protein intake and insulin like growth factor1 (IGF-1) blood levels] [31] and practical considerations (restriction of healthy foods) [32]. The fact that the impact of the additive low carbohydrate–high protein score is stronger amongst the older women in our study population with respect to cardiovascular diseases is compatible with a likely cumulative effect of diet over time and recent evidence pointing to a stronger association of diet with cardiovascular diseases than with cancer [33].

Amongst the weaknesses of the study are concerns about residual confounding and the long interval between exposure ascertainment and death outcomes. Residual confounding, however, is a general concern in observational studies, whereas in the present investigation important potential confounders, notably age and smoking, were finely controlled for. The long interval between exposure and outcome is a source of concern, because certain individuals may change their dietary habits during the intervening period. This,

however, is likely to generate nondifferential misclassification and, thus, have an attenuating impact on the evaluated association, except in unusual circumstances. Finally, we did not have blood cholesterol levels or blood pressure measurements at enrolment, two important risk factors for coronary heart disease, but even if such values were available, they would likely be intermediates in the association between diet and mortality and, thus, should have not been controlled for. Furthermore, as already indicated, persons with prevalent serious diseases at enrolment were excluded.

Low carbohydrate diets, recommended for weight control, typically contain <15% of energy intake from carbohydrates and about 30% of proteins [34, 35]. Amongst the studied women, carbohydrate intake at the low extreme of the distribution was higher and protein intake at the high extreme of the distribution was lower than the respective intakes advocated by many prescribed weight control diets. Nevertheless, it is reasonable to assume that any underlying trend between low carbohydrate–high protein intake and mortality, particularly cardiovascular mortality, would be monotonic, if not linear.

There are now three studies, including the present one, that have evaluated the long-term health effects of low carbohydrate–high protein diets. One of them relied on a cohort of the USA nurses and focused on incidence of coronary heart disease [18], whereas the two others were general population cohorts and focused on overall mortality, as well as coronary and cancer mortality. The American study found no association of low carbohydrate diets with incidence of coronary heart disease. In the Greek study [19], low carbohydrate–high protein diets were positively associated with cardiovascular mortality and, to a lesser extent, cancer mortality. Finally, in the present investigation, a positive association was evident with respect to cardiovascular, but not cancer mortality. It should be noted that in the Greek study, as well as in the present one, total mortality – for which misclassification is not an issue – was significantly positively associated with consumption of low carbohydrate–high protein diets. There are differences in the populations covered in the three studies. The Greek study covered both men and women and the women in the Swedish study tended to be younger than the American women at the end of follow up. These differences, as well as differences in the studied outcomes may have contributed to the apparent inconsistency in the results of the three studies. We believe, however, that a sample of the general population of young women and a focus on cardiovascular, as well as total mortality make the present study most appropriate for the study question. Clearly, evidence from additional prospective investigations is needed, before conclusive inferences can be drawn.

The results of the present investigation do not address questions concerning the potential short-term effects of low carbohydrate and/or high protein diets in the control of body weight or insulin resistance. Nor do they preclude the formulation of dietary regimes low in refined carbohydrates and high in plant proteins or unsaturated lipids that could have no adverse health effects or even be beneficial. They draw attention, however, to the potential for long-term adverse health effects of diets generally low in carbohydrates and generally high in protein, notably with respect to cardiovascular health.

Conflict of interest statement

None of the authors had any conflict of interest.

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