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ORIGINAL ARTICLE

Low-carbohydrate–high-protein diet and long-term survival in a general population cohort

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Objective: We have evaluated the effects on mortality of habitual low carbohydrate–high-protein diets that are thought to contribute to weight control.
Design: Cohort investigation.
Setting: Adult Greek population.
Subjects methods: Follow-up was performed from 1993 to 2003 in the context of the Greek component of the European Prospective Investigation into Cancer and nutrition. Participants were 22 944 healthy adults, whose diet was assessed through a validated questionnaire. Participants were distributed by increasing deciles according to protein intake or carbohydrate intake, as well as by an additive score generated by increasing decile intake of protein and decreasing decile intake of carbohydrates. Proportional hazards regression was used to assess the relation between high protein, high carbohydrate and the low carbohydrate–high protein score on the one hand and mortality on the other.
Results: During 113 230 persons years of follow-up, there were 455 deaths. In models with energy adjustment, higher intake of carbohydrates was associated with significant reduction of total mortality, whereas higher intake of protein was associated with nonsignificant increase of total mortality (per decile, mortality ratios 0.94 with 95% CI 0.89 –0.99, and 1.02 with 95% CI 0.98 – 1.07 respectively). Even more predictive of higher mortality were high values of the additive low carbohydrate–high protein score (per 5 units, mortality ratio 1.22 with 95% CI 1.09 –to 1.36). Positive associations of this score were noted with respect to both cardiovascular and cancer mortality.
Conclusion: Prolonged consumption of diets low in carbohydrates and high in protein is associated with an increase in total mortality.
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Keywords: diet; survival; protein intake; carbohydrate intake; cohort study

Introduction

Weight control is desirable for both medical and aesthetic reasons and diets conducive to weight reduction or weight control have become popular. Many of these diets emphasize reduction of carbohydrate intake and thereby encourage high protein intake, given that, in Western countries, high-fat diets are also generally avoided (Astrup *et al.*, 2004). There is evidence that low carbohydrate-high protein (LC/HP) diets do indeed lead to better weight control or even weight loss in the short term (Foster *et al.*, 2003; Samaha *et al.*, 2003; Willett, 2004; Truby *et al.*, 2006). In contrast, according to a randomized trial that examined for a year the effectiveness of four popular diets (Atkins, Zone, Weight Watchers, Ornish), the amount of weight loss and the changes in biochemical parameters were not significantly different among diets and were only evident among committed dieters (Dansinger *et al.*, 2005). Recently, however, concerns have been expressed about the health effects of low-carbohydrate and/or high-protein diets (Chen *et al.*, 2006; Stanton and Crowe, 2006; Steffen and Nettleton, 2006), even though, little documented information exists about the long-term health consequences of LC/HP diets. It is, thus, of considerable interest, to examine whether prolonged consumption of LC/HP diets is compatible with long-term

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health. We have examined mortality of individuals, healthy at enrolment, who participate in a population-based cohort study (the Greek component of the European Prospective Investigation into Cancer and nutrition study (EPIC)) according to their carbohydrate and protein intake, as well as by their position in a simple scale that covers the range from maximal consumption of carbohydrates/minimal consumption of proteins to minimal consumption of carbohydrates/maximal consumption of proteins.

Subjects and methods

Recruitment and approval

The initial study sample consisted of 28 572 volunteers, women and men 20–86 years old recruited between 1993 and 1999 from all regions of Greece, in order to participate in the Greek component of the EPIC (Trichopoulou *et al*., 2003). EPIC is a multicountry, prospective cohort study, conducted in 22 research centers across 10 European countries and coordinated by the International Agency for Research on Cancer. The aims of EPIC are the elucidation of the role of biological, dietary, lifestyle and environmental factors in the etiology of chronic diseases (Riboli *et al*., 2002). Cancer studies are jointly published by the EPIC consortium, whereas investigations with different objectives, like the present one, are also undertaken by individual countries. All procedures have been in accordance with the Helsinki declaration for human rights, all participants have provided written informed consent before enrolment, and the study protocol have been approved by the ethics committees at the International Agency for Research on Cancer and the University of Athens Medical School.

Data on diet

An interviewer-administered, food frequency questionnaire including approximately 150 foods and beverages commonly consumed in Greece was used to assess dietary intake (Gnardellis *et al*., 1995). The interview focused on the year before enrolment to accommodate seasonal variation, but is likely to adequately reflect the diet during several years preceding enrolment (Willett *et al*., 1988; Goldbohm *et al*., 1995). The questionnaire was validated, during the pilot phase of the Greek EPIC study (Gnardellis *et al*., 1995). Nutrient intakes were calculated with the use of a food composition database that has been modified to accommodate the special characteristics of the Greek diet (Trichopoulou and Georga, 2004).

Lifestyle variables

The frequency and duration of participation in occupational and leisure time physical activities were recorded in the questionnaire (Trichopoulou *et al*., 2000) and allowed the calculation of a metabolic equivalent index (MET value) to each activity (Ainsworth *et al*., 1993) and eventually an overall MET-hour sum, which indicates the amount of energy per kilogram of body weight expended during an average day by each participant (Trichopoulou *et al*., 2003). Standard interviewing and measuring procedures were used to assess sociodemographic, lifestyle and anthropometric characteristics, such as age, years of schooling (as an indicator of socio-economic status), tobacco smoking and body mass index (BMI).

Study participants and follow-up

From the original cohort of 28 572 study participants, 844 (3%) were excluded because information was missing for one or more of the dietary, anthropometric or lifestyle variables. From the remaining 27 728, an additional 1397 (5%) have not been followed up till December 2003. These study participants were residents of remote areas of Greece and the active follow-up used in the Greek EPIC cohort had not yet covered them. From the remaining 26 331 volunteers, 3387 (13%) were excluded, because at enrolment had coronary artery disease, diabetes mellitus, cancer or a combination of these diseases. Thus, in the main study, 22 944 participants were eventually evaluated.

The 22 944 participants were followed up till December 2003 for a total of 113 230 person- years, during which 455 deaths have occurred. The mean duration of follow-up was 4.9 years (59 months), with a range of 1 month (for a participant who died shortly after enrolment) to 125 months. The date and cause of death for all participants who died were obtained from death certificates and other official sources, and deaths were classified on the basis of the International Classification of Diseases, 10th Revision (World Health Organization, 1992).

As indicated, the study participants that were followed up were, at enrolment, free from coronary artery disease, diabetes mellitus or cancer. In order, however, to examine whether findings in the main study group are also applicable to persons who, at enrolment, have diseases generally considered to be related to obesity, mainly diabetes mellitus and coronary artery disease, we have undertaken a similar analysis, as outlined below, to two additional groups. Firstly, a group of 1302 Greek-EPIC study participants who reported at enrolment, a previous diagnosis of coronary artery disease with or without diabetes, but no cancer (Trichopoulou *et al*., 2005a), and, secondly, a group of 1013 Greek-EPIC study participants who, at enrolment, had clinical diabetes mellitus without coexistent prevalent cancer or cardiovascular disease (Trichopoulou *et al*., 2006). There was no overlapping between the main study cohort and any of the two additionally analysed groups of patients.

Statistical analysis

All analyses were performed using the STATA statistical package (INTERCOOLED STATA 7.0 for Windows 98/95/NT;

Stata Corp, College Station, TX, USA). Distributions of study participants at enrolment by non-nutritional variables, as well as saturated and unsaturated lipids, carbohydrates, protein and total energy intake, were examined separately for men and women. Subsequently, all study participants were classified by deciles of, alternatively, absolute and energy adjusted carbohydrate and protein intake. Energy adjustment was performed through the residuals method (Willett and Stampfer, 1998). Further on, for each participant, ascending decile of protein intake and descending decile of carbohydrate intake were added to create an additive LC/HP using, alternatively, absolute and energy-adjusted carbohydrate and protein values. Thus, a subject with LC/HP score 2 is one with very high consumption of carbohydrates and very low consumption of protein, whereas a subject with score 20 is one with very low consumption of carbohydrates and very high consumption of protein. A matrix depicting Spearman's correlation coefficients among principal groups of energy generating nutrients, energy intake and the LC/HP score (from, alternatively, absolute and energy-adjusted values) was generated. For the main analysis, the data were modeled through proportional hazards regression assessing the hazard of death (or death from specific causes) in relation to increasing deciles of carbohydrate and protein intake, as well as the LC/HP score (from absolute or energy-adjusted carbohydrate and protein values). All the recorded likely predictors of mortality, which could act as confounding variables, namely gender, age at enrolment, years of schooling as an indicator of socioeconomic status, smoking habits, body mass index (BMI), physical activity, ethanol intake, total energy intake and, saturated or unsaturated lipids, were controlled for, as detailed in the tables. In the Cox models, the assumption of proportionality was met, there was no collinearity among the variables used and no time-dependent covariates were used.

Although several types of analyses were performed in order to assess the robustness of the findings, our primary objective was to evaluate the associations with mortality of the LC/HP score derived from energy-adjusted residuals, because absolute values of all energy-generating nutrients are, in general, strongly positively associated with total energy intake, rising concerns about collinearity in the statistical models. Moreover, after controlling for energy intake, it is impossible to evaluate the association of the intake of a particular energy-generating nutrient with any outcome, including mortality, because for given total energy intake a change in the quantity of a particular energy generating nutrient is unavoidably accompanied by undeterminable changes of intakes of one or more of the other energy-generating nutrients (Wacholder *et al.*, 1994). In contrast, the LC/HP score not only captures the essence of most low-carbohydrate diets (that tend to be high protein diets) (Astrup *et al.*, 2004), but also relies on opposite changes of two nutrients with equivalent energy values and tends to be unrelated to total energy intake.

Results

The characteristics of study participants at enrolment with respect to the studied non-nutritional and nutritional variables are shown in Table 1. In the EPIC cohort in general, and the Greek component in particular, there were by design more women than men, as the principal focus of the EPIC study was breast cancer. The table demonstrates the high prevalence of obesity in the Greek population, the high prevalence of smoking among men in Greece and the high intake of unsaturated lipids, mostly accounted by high olive oil consumption. With respect to the choice LC/HP score that relies on energy-adjusted components, at the high extreme of the distribution around 20% of energy intake was derived from proteins, whereas around 25% was derived from carbohydrates. At the low extreme of the distribution, around 10% of energy intake was derived from protein, whereas more than 50% was derived from carbohydrates.

In Table 2, Spearman's correlation coefficients among energy-generating nutrients, energy intake and the two alternative LC/HP scores are presented. The LC/HP scores were positively associated with intake of protein and lipids of any type and inversely associated with intake of carbohydrates. Energy intake was weakly positively associated with the LC/HP score (absolute values) and essentially uncorrelated with the LC/HP score (energy-adjusted components). In this population, the mean intake of protein was 76 g/day with standard error of the mean (s.e.m.) 0.16 g/day, the mean intake of carbohydrates was 208 g/day with s.e.m. 0.44 g/day, and the mean intake of lipids was 109 g/day (28% saturated, 15% polyunsaturated, 48% monounsaturated fatty acids and 9% other components of the lipid group) with s.e.m. 0.25 g/day.

In Table 3, adjusted mortality ratios from any cause during the follow-up period in relation to energy-generating nutrients, total energy intake and the two alternative LC/HP scores are shown. In all models, all non-nutritional potentially confounding variables were controlled for. As presented in previous publications (Trichopoulou *et al.*, 2003), the results with respect to non-nutritional variables were mostly in line with expectations, in showing that mortality was higher among men than among women, increased sharply with age, declined with increasing years of schooling, higher physical activity and alcohol intake and increased with smoking and total energy intake. Models 1 and 2 are non-isocaloric because total energy intake was not controlled for (inclusion in these models of total energy intake, as well as all energy generating nutrients would create collinearity problems). In model 1, increasing protein intake was significantly associated with total mortality, whereas increasing carbohydrate intake was associated with nonsignificant reduction of this mortality. In model 2, the LC/HP score (absolute values) was positively associated with mortality, although the association did not reach statistical significance ($P = 0.14$). Models 3 and 4 are, as they should be, isocaloric, because energy intake was controlled for. In model 3, mortality was significantly associated with reduction of energy-adjusted carbohydrate

Table 1 Distribution of the 22 944 study participants by selected variables. The Greek EPIC cohort

Variables	*Men*		*Women*	
	n	%	n	%
Age (yrs)				
<45	3249	34.9	4247	31.2
45–54	2355	25.3	3437	25.2
55–64	1888	20.3	3281	24.1
⩾65	1820	19.5	2667	19.6
Education (yrs)				
<6	1135	2.2	3121	22.9
6–11	3712	39.9	5608	41.1
12	1115	12.0	2194	16.1
⩾13	3350	36.0	2709	19.9
BMI (kg/m^2)				
<25	1858	20.0	3471	25.5
25–30	4905	52.7	5073	37.2
⩾30	2549	27.4	5088	37.3
Physical activity (METh/d)				
<30	1183	12.7	881	6.5
30–<35	3838	41.2	5572	40.9
35–<40	2339	25.1	5402	39.6
⩾40	1952	21.0	1777	13.0
Ethanol intake (g/d)				
<10	4396	47.2	12 408	91.0
10–<30	3077	33.0	1095	8.0
⩾30	1839	19.8	129	1.0
Smoking status				
Never	2331	25.0	9742	71.5
Past	2922	31.4	1090	8.0
Current	4059	43.6	2800	20.5
Protein (g/d)				
<50	539	5.8	2329	17.1
50–<70	2174	23.4	5294	38.8
70–<90	2982	32.0	4083	30.0
⩾90	3617	38.8	1926	14.1
Carbohydrates (g/d)				
<140	552	5.9	2218	16.3
140–<190	2178	23.4	5060	37.1
190–<240	2872	30.8	4014	29.5
⩾240	3710	39.8	2340	17.2
Saturated lipids (g/d)				
<20	1063	11.4	3106	22.8
20–<30	2673	28.7	5139	37.7
30–<40	2804	30.1	3427	25.1
⩾40	2772	29.8	1960	14.4
Unsaturated lipids (g/d)				
<40	362	3.9	1414	10.4
40–<60	2134	22.9	5122	37.6
60–<80	3299	35.4	4570	33.5
⩾80	3517	37.8	2526	18.5
Energy intake (kJ/d)				
<6000	428	4.6	2396	17.6
6000–7999	1783	19.2	4908	36.0
8000–9999	2650	28.5	3837	28.2
⩾10 000	4451	47.8	2491	18.3
Total	9312	100.0	13 632	100.0

intake and nonsignificantly with increasing protein intake. This model, however, does not specify the complementary changes that have to be introduced for the preservation of total energy intake, when carbohydrates and proteins change. Model 4 is the most appropriate as it is both isocaloric and changes in the LC/HP score are essentially unrelated to total energy intake. In this model, increasing LC/HP score was significantly associated with mortality ($P = 0.001$). It is worth noting that in all these models mortality tends to be inversely associated with intake of unsaturated lipids and positively, although not always significantly, with saturated lipids.

An increase in the LC/HP score (energy-adjusted components) by two units was associated with an increase in mortality by 8% (95% confidence interval (CI), 3–13%). Therefore, a realistic increase in the LC/HP score by five units (corresponding to, e.g., an increase of protein intake by about 15 g/day and a decrease of carbohydrate intake by about 50 g/day) was associated with a 22% increase in overall mortality (CI, 9–36%). We have further probed exposure-response by calculating mortality ratios according to categories of LC/HP score (energy-adjusted components), rather than assessing, as previously performed an underlying linear trend. We have used as referent the group of study participants with score ⩽6. The mortality ratio was 1.20 for score between 7 and 9 (CI, 0.89–1.62), whereas for score between 10 and 12 the ratio was 1.42 (CI, 1.06–1.89), for score between 13 and 15 the ratio was 1.56 (CI, 1.13–2.13) and for score ⩾16 the ratio was 1.71 (CI, 1.22–2.41). Thus, the categorical data are consistent with the trend data.

We have also evaluated the relation of the LC/HP score (energy-adjusted components) with mortality ratios by cause of death, but for each category of deaths the CI were too wide to allow specific inferences. The mortality ratios (and Cis) by 2-unit increase in the LC/HP score were: for 193 cardiovascular deaths 1.09 (1.01–1.17), for 175 cancer deaths 1.07 (0.99–1.15) and for 87 deaths from other causes (19 respiratory, 13 digestive, 24 other pathological, 31 injuries) 1.11 (1.00–1.23).

In complementary analyses, we have run models 1–4 among Greek EPIC participants who, at enrolment, had either coronary artery disease or diabetes mellitus, as indicated in the Subjects and methods section. For a two-unit increase in the LC/HP score (absolute values), the mortality ratios were: for coronary artery disease 1.18 (CI, 0.97–1.43) and for diabetes mellitus 1.27 (CI, 1.02–1.59). For a two-unit increase in the LC/HP score (energy -adjusted components), the corresponding ratios were 1.05 (CI, 0.96–1.14) and 1.06 (CI, 0.95–1.17). Thus, the results in the three study groups are consistent.

Discussion

In a large population-based study, we found that individuals with habitual diets low in carbohydrates and high in protein tend to have higher overall mortality, compared to

Table 2 Spearman correlation coefficients among the indicated nutritional variables in the 22 944 study participants[a]

	Protein	*Carbohydrates*	*Saturated lipids*	*Mono-unsaturated lipids*	*Poly-unsaturated lipids*	*Energy intake*	*Low carbohydrate-high protein score (absolute values)*	*Low carbohydrate-high protein score (energy-adjusted values)*
Protein	1.00							
Carbohydrates	0.78	1.00						
Saturated lipids	0.91	0.66	1.00					
Monounsaturated lipids	0.78	0.65	0.77	1.00				
Polyunsaturated lipids	0.65	0.56	0.64	0.48	1.00			
Energy intake	0.93	0.88	0.86	0.84	0.69	1.00		
Low carbohydrate-high protein score (absolute values)	0.32	−0.31	0.35	0.19	0.13	0.07	1.00	
Low carbohydrate-high protein score (energy-adjusted values)	0.28	−0.31	0.31	0.14	0.09	0.02	0.90	1.00

[a]Because the study sample is very large all correlation coefficients are significantly different from zero.
The Greek EPIC cohort.

Table 3 Adjusted mortality ratios from any cause (and 95% Confidence Intervals) by a decile increase of intake of total energy or specified energy generating nutrients or a 2-unit increase in low carbohydrate-high protein score (LC/HP)[a]

Increasing intake	*Model 1*	*Model 2*	*Model 3*	*Model 4*
Carbohydrates (per decile)	0.97 (0.92, 1.02)			
Energy-adjusted carbohydrates[b] (per decile)			0.94 (0.89, 0.99)	
Protein (per decile)	1.13 (1.03, 1.23)			
Energy-adjusted protein[b] (per decile)			1.02 (0.98, 1.07)	
Saturated lipids (per decile)	1.02 (0.94, 1.10)	1.08 (1.01, 1.14)		
Unsaturated lipids (per decile)	0.92 (0.86, 0.98)	0.94 (0.89, 0.99)		
Energy-adjusted unsaturated lipids[b] (per decile)			0.92 (0.87, 0.96)	0.93 (0.90, 0.97)
Total energy (per decile)			1.03 (0.99, 1.07)	1.03 (0.99, 1.07)
LC/HP[c] absolute values (per 2-units)		1.08 (0.97, 1.20)		
LC/HP[c] energy-adjusted components (per 2-units)				1.08 (1.03, 1.13)

[a]Controlling for sex (men, women; categorically), age (<45 years, 45–54 years, 55–64 years, ⩾65 years; categorically), years of schooling (<6, 6–11, 12, ⩾13; categorically), smoking (never, former and 1–10 cigs per day, 11–20 cigs per day, 21–30 cigs per day, 31–40 cigs per day, ⩾41 cigs per day; ordered), BMI (per quintile; ordered), physical activity (per quintile; ordered), ethanol intake (<10 g per day, 10–<30 g per day, ⩾30 g per day; categorically).
[b]Adjusted through the residuals method (Willett & Stampfer, 1998).
[c]The low carbohydrate-high protein score for each individual was derived by adding the decile position of this individual in the ascending scale of protein (or energy-adjusted protein) intake and the decile position of this individual in the descending scale of carbohydrate (or energy-adjusted carbohydrate) intake. A higher score implies higher protein and/or lower carbohydrate intake.
Participants healthy at enrolment; The Greek EPIC cohort.

individuals with habitual diets high in carbohydrates and low in protein. The mortality gradient is considerable, so that a modest 5-point difference in a 19-point low-carbohydrate–high-protein score with energy-adjusted components corresponds to increased mortality ratio of about 22% (CI, 9–36%). The increase in mortality was not concentrated to particular causes, but was significant only with respect to cardiovascular deaths. The results were adjusted for known or possible predictors of mortality.

There are several arguments in support of the validity of these results. The cohort design and the proportionally few losses to follow-up indicate that selection and information bias are unlikely to play a major role. Findings with respect to other variables were generally compatible with the collective evidence from the literature. Dietary information has been validated and previous results relying on a subset (in terms of person-time) of the present study (Trichopoulou *et al*., 2003) have been supported by large investigations based on multicenter cohorts (Knoops *et al*., 2004; Trichopoulou *et al*., 2005b). Finally, ascertainable comorbidity that could act as a confounding factor has been controlled for, by excluding persons who, at enrolment, had diagnosed (prevalent) cancer, coronary artery disease or diabetes mellitus. Nevertheless, among Greek-EPIC participants who, at enrolment, had obesity-related prevalent diseases, notably coronary artery disease and diabetes mellitus, the results with respect to LC/HP score (energy-adjusted components) were very similar to those in the main cohort, whereas the results with respect to the LC/HP score (absolute values) tended to be, if anything, more evident.

There are different types of weight control diets, according to macronutrient composition. Many are low in carbohydrates and high in protein, such as the Atkins diet (Volek and Westman, 2002; Astrup *et al*., 2004; Lara-Castro and Garvey, 2004). Very-low-carbohydrate diets typically contain less than 10% carbohydrates, 25–35% proteins and 55–65% lipids. For comparison, the average American diet contains 35% lipids (85 g/day), 50% carbohydrates (275 g/day) and 15% protein (83 g/day) (CDC, 2004). In Great Britain, the mean intake, as a percentage of total energy, is about 35% lipids, of about 48% carbohydrates and about 17% protein (Swan, 2004). In our study population, consumption of carbohydrates, even at the low extreme of the distribution, was higher than that advocated by the prescribed low-carbohydrate diets and few individuals consumed more than 20% of their energy from proteins. Nevertheless, it is unlikely that at the extremes of the low-carbohydrate–high-protein intake distribution there would be a reversal of the trend evident in our study population. Indeed, many of contemporary public health policies rely on extrapolations, so that if something is detrimental at a certain exposure level, its effect is likely to be more detrimental at a more extreme level. The biology that underlines the positive association of LC/HP diets with overall mortality is not clear. It appears that high protein intake may be as important as low-carbohydrate intake and the results of a recent study (Kelemen *et al*., 2005) point to the same direction. Moreover, the apparent detrimental effect of the LC/HP diet should not be unexpected, in view of the fact that dietary scores that have been reported to be associated with reduced mortality are to a large extent 'mirror idols' to the LC/HP diets (McCullough *et al*., 2002; Trichopoulou *et al*., 2003). In fact, the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association has stated that high protein diets are not recommended because they restrict healthful foods (St Jeor *et al*., 2001).

Wacholder *et al*. (1994) have pointed out that in studies assessing the effect of diet and in which energy intake has to be adjusted for (substitution models), it is very difficult to disentangle the effects of specific energy-generating nutrients, because an increase in the intake of one is unavoidably linked to a decrease in the intake of one or more of the others. In this context, the use of a score that is minimally related to energy intake (Table 2) is likely to minimize this problem, so that the impact on mortality of a change in macronutrient profile with respect to protein and carbohydrate intake can be reliably estimated.

Some limitations of the present study need to be considered. Foremost is the issue of residual confounding. We could not identify, however, any such factors. The question of generalizability is also relevant, because sources of carbohydrates, proteins and dietary lipids are different in various populations and these distinct sources may have different health implications. In the American population, intake of protein is similar to that in our study, whereas intake of carbohydrates is slightly higher than in Greece (Yang *et al*., 2003; Tsai *et al*., 2004). More striking are differences concerning lipid intake, because in the US and British populations saturated and monounsaturated lipids are taken in approximately the same quantities (Smith-Warner *et al*., 2001; Swan, 2004), whereas in the Greek population intake of monounsaturated lipids is considerably higher than that of saturated lipids. We could not, however, identify biological or empirical reasons for challenging the generalizability of our findings, because intake of unsaturated and saturated lipids has been controlled for in the various models. Thirdly, the participants in our study were not following, at least explicitly, versions of weight reduction diets, so that our results do not directly address the question of whether these diets are innocuous or not; weight reduction diets, however, frequently recommend more extreme increases of protein intake or carbohydrate reduction, in comparison to those captured in the present investigation. Lastly, nutrition supplements were not accounted for in our study. Such supplements, however, are infrequently used in Greece and, even when used, they generally concern micronutrients rather than energy-generating nutrients.

Our results should not be interpreted as indicating that short-term use of LC/HP diets are detrimental to health, as our data have evaluated the health consequences of long-term habitual dietary intakes. Also, our findings do not indicate that all forms of LC/HP diets have adverse long-term effects. Indeed, a high LC/HP score is not incompatible with high intake of protein of plant origin or complex carbohydrates, that is, nutrients that are generally considered as innocuous, if not beneficial, to health (World Cancer Research Fund, 1997).

In conclusion, we have found evidence that dietary patterns that indiscriminate focus on low intake of carbohydrates in general and high intake of proteins in general, and reflect diets that have been frequently recommended for weight reduction, may be associated with increased total mortality if they are pursued for extended periods.

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