Mediterranean and carbohydrate-restricted diets and mortality among elderly men: a cohort study in Sweden[1–3]

Per Sjögren, Wulf Becker, Eva Warensjö, Erika Olsson, Liisa Byberg, Inga-Britt Gustafsson, Brita Karlström, and Tommy Cederholm

ABSTRACT

Background: Comparative studies on dietary patterns and long-term mortality are sparse.

Objective: The objective was to examine the relations between 10-y mortality and adherence to the World Health Organization dietary guidelines [Healthy Diet Indicator (HDI)], a Mediterranean-like diet, and a carbohydrate-restricted (CR) diet in elderly Swedish men.

Design: Dietary habits were determined by 7-d dietary records in a population-based longitudinal study of 924 Swedish men (age: 71 ± 1 y). The HDI score (−1 to 8 points), the Mediterranean Diet Score (MDS; 0–8 points), and the CR score (2–20 points) were calculated for each participant. Nonadequate reporters of energy intake were identified (n = 413). Mortality was registered during a median follow-up of 10.2 y. Cox proportional hazards regression, with multivariable adjustments, was used to determine the effects of adherence to each dietary pattern.

Results: Two hundred fifteen and 88 subjects died of all-cause and cardiovascular disease, respectively. In all individuals, risk relations to mortality for each SD increment in the scores were observed for only MDS, with an adjusted hazard ratio (HR) of 0.83 (95% CI: 0.70, 0.99). Among adequate dietary reporters (n = 511), adjusted HRs for each SD increment in scores were enhanced for MDS (ie, 0.71; 95% CI: 0.55, 0.92) for all-cause mortality and 0.63 (95% CI: 0.42, 0.96) for cardiovascular mortality. Corresponding HRs for CR diet score were 1.19 (95% CI: 0.97, 1.45) for all-cause mortality and 1.44 (95% CI: 1.03, 2.02) for cardiovascular mortality.

Conclusion: Adherence to a Mediterranean-like dietary pattern reduced mortality, whereas adherence to a CR dietary pattern appeared to increase mortality in elderly Swedish men, especially when only adequate dietary reporters were considered. *Am J Clin Nutr* 2010;92:967–74.

INTRODUCTION

Dietary guidelines are similar in most Western countries, resting on a platform built during decades of research and compiled to promote health and improve longevity in the population (1, 2). Despite the fact that adaptations toward the official dietary recommendations have occurred in most populations, epidemics of obesity and concurrent insulin resistance have evolved. There are several plausible explanations for this—eg, a more sedentary lifestyle, larger portion sizes, and easier food access. Still, the current guidelines have not been effective in preventing the obesity epidemic. Partly as a consequence of these shortcomings, alternative diets have gained in popularity. For example, diets low in carbohydrates have proved to be efficient in weight reduction studies (3–5), but the long-term safety of low-carbohydrate diets remains controversial. Adverse long-term health effects have been described for carbohydrate-restricted (CR) diets in a couple of studies (6, 7), but not all (8). Concurrently, evidence on the beneficial effects of a Mediterranean-like dietary pattern is accumulating (9). Although not extensively investigated, a couple of studies indicate beneficial effects from a Mediterranean diet also in Nordic populations (10–12).

Much of the previous research on diet and health has been focused on risk relations for individual nutrients. Due to the complexity of food and food intake, risk relations might be different when dietary patterns are considered. The dietary pattern approach is capable of capturing complex interactions between dietary components and health beyond the sum of each nutrient. This notion is supported by the results in the study by Trichopoulou et al (13) in which a Mediterranean dietary pattern was strongly related to survival, whereas the individual components were not.

Direct comparisons between dietary patterns and their relations to mortality within the same cohort are rare. Furthermore, the application of stringent criteria to circumvent the problem with systematic errors in dietary recalls is not often considered. The objective of this study was to assess the adherence to the World Health Organization (WHO)dietary guidelines, a Mediterranean-like diet, and a CR diet and investigate the relationships to total mortality and mortality due to cardiovascular disease (CVD) in a population-based study of elderly Swedish

[1] From the Department of Public Health and Caring Sciences, Section of Clinical Nutrition and Metabolism (PS, WB, EW, EO, BK, and TC), the Orthopedics Section, Department of Surgical Sciences (LB), and the Uppsala Clinical Research Centre (LB), Uppsala University, Uppsala, Sweden; the School of Hospitality, Culinary Arts, and Meal Sciences, Örebro University, Örebro, Sweden (I-BG); and the Swedish National Food Administration, Uppsala, Sweden (WB).

[2] Supported by Uppsala University, the Uppsala City Council Research Fund, and the Swedish Research Council.

[3] Address correspondence to P Sjögren, Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala Science Park, S-75185 Uppsala, Sweden. E-mail: per.sjogren@pubcare.uu.se.

Received February 8, 2010. Accepted for publication July 28, 2010.

First published online September 8, 2010; doi: 10.3945/ajcn.2010.29345.

men. Particular attention was given to the often encountered systematic error in dietary recalls.

SUBJECTS AND METHODS

This study is based on the Uppsala Longitudinal Study of Adult Men cohort (http://www.pubcare.uu.se/ULSAM/). All men born from 1920 to 1924 and living in Uppsala were, at the age of 50 y (1970–1974), invited to participate in the study, and 82% (n = 2322) agreed to participate. The cohort was reinvestigated 10 and 20 y later. At the latter reinvestigation—ie, in the beginning of the 1990s—detailed dietary habits were assessed for the first time, when 73% (n = 1221) of available men agreed to participate. This occasion, when participants were 70 y of age, is the baseline for the present study. The study was approved by the ethics committee at Uppsala University, and all participants gave informed consent to participate.

Participants and follow-up

Dietary records (*see* below) were completed at a single occasion by 1138 subjects. Sixty-seven subjects with self-reported type 2 diabetes and 136 with a history of ischemic heart disease were excluded, because their conditions may have induced dietary changes. A further 26 men with weight loss >10% over the 10 y before the baseline examination were excluded. This weight loss indicated serious illness as shown by an unadjusted increase in mortality [hazard ratio (HR): 4.21; 95% CI: 2.67, 6.64] in this subgroup compared with remaining individuals. After additional exclusions for extreme values of reported energy intake (<3200 or >18,000 kJ/d, n = 4), 924 subjects were eligible for the present investigation. A subpopulation of adequate dietary reporters was identified, as described below.

Follow-up was from the examination date for the baseline examination in 1991–1995 and to 31 December 2003, with a maximum of 12.4 y of follow-up and a mean of 10.1 y. The Swedish National Registry recording for cause of death was used to define endpoints. The register includes all Swedish citizens, which minimizes loss to follow-up. The endpoints were defined a priori as cardiovascular mortality—ie, *International Classification of Diseases, ninth revision* (ICD-9), codes 390–459, ICD-10 (10th revision) codes I00–I99, to comply with current European guidelines (14)—and total mortality (for additional information on ICD codes, *see* http://www.who.int/classification/icd/en).

Baseline examinations

All investigations were performed under standardized conditions as described (15, 16). The investigation included a medical questionnaire and interview, blood sampling, as well as anthropometric measurements and blood pressure. Fasting blood samples were drawn and circulating lipoproteins, triacylglycerol, cholesterol, glucose, and insulin were determined as previously described (17). High-sensitivity ELISA was used to quantify C-reactive protein (CRP) (R&D Systems, Minneapolis, MN). Insulin sensitivity was estimated with the euglycemic clamp technique as described (18), and the insulin sensitivity index was calculated as glucose disposal rate (mg glucose infused · min^{-1} · kg body $weight^{-1}$) divided by the mean plasma insulin concentration × 100 (mU/L) during the last 60 min of the 2-h clamp. Type 2 diabetes was diagnosed if glucose values at 120 min plus one more time during 30–90 min of an oral-glucose-tolerance test were ≥11.1 mmol/L. The metabolic syndrome was defined according to the criteria from the National Cholesterol Education Program (Adult Treatment Panel III) (19). Information on lipid-lowering and blood pressure–lowering treatments, smoking, physical activity, and occupational status was collected from the questionnaire. Smoking was defined as current smokers. Regular physical activity was defined as the reporting of regular or athletic leisure-time exercise habits according to 4 physical activity categories (sedentary, moderate, regular, and athletic) (20). Three conventional social classes (based on occupational status) were used and classified according to the Central Bureau of Statistics (21).

Dietary recall and identification of dietary nonadequate reporters

Dietary habits were determined with an optically readable form of a 7-d dietary record that was based on a validated precoded menu book (22), which was prepared and previously used by the Swedish National Food Administration (NFA) (23). The participants were given oral instructions by a dietitian on how to perform the dietary registration, and the amounts consumed were reported in household measurements or specified as portion sizes. The daily intake of energy and selected nutrients was calculated by using a database from the Swedish NFA containing about 1500 food items, drinks, and recipes. Dietary habits were not reassessed during follow-up.

In the whole study group, participants with extreme values of reported energy intake were excluded. However, more stringent criteria to identify nonadequate reporters of energy intake were also applied, according to the Goldberg cutoff (24), taking the level of physical activity and calculated basal metabolic rate into consideration. In this procedure, an acceptable range of energy intake is identified for each subject in relation to estimated energy expenditure—ie, producing a 95% CI for energy intake that is required for weight maintenance. Subjects with reported energy intake outside the 95% CI were regarded as nonadequate reporters. Two subjects reported energy intake exceeding their calculated need, and 411 subjects reported lower energy intake than their expected need and were thus classified as nonadequate reporters. With this strategy, a subpopulation of adequate reporters was created (n = 511).

Assessment of dietary patterns

Dietary patterns were defined according to previously published dietary scores, as shown in **Table 1**. Depending on the definitions, dietary variables were energy adjusted before scoring either by dividing the nutrient value with total energy intake (nutrient density) or by using the residuals from the regression of nutrients to total energy intake (residual method), as described (25). Dietary pattern scoring was performed in the 2 populations—ie, all and adequate reporters—separately.

Healthy Diet Indicator

The Healthy Diet Indicator (HDI) is based on dietary guidelines from the WHO and includes mainly nutrient-based but also some food-based targets (26, 27). If a person's intake matched the preset (and desirable) range for included food components,

TABLE 1
Composition of diet-quality scores[1]

	Cutoff scoring	Points
HDI[2]		
SFAs	0–12% of energy	1
PUFAs	5–10% of energy	1
Protein	10–20% of energy	1
Total carbohydrates	50–70% of energy	1
Sucrose	>10% of energy	−1
Fiber	≥3 g/MJ	1
Fruit and vegetables	>400 g/d	1
Cholesterol	0–300 mg/d	1
Fish	≥35 g/d	1
Range	—	−1 to 8
MDS[3]		
PUFAs/SFAs	>Median	1
Vegetables and legumes	>Median	1
Fruit	>Median	1
Cereals and potatoes	>Median	1
Fish	>Median	1
Meat and meat products	<Median	1
Milk and milk products	<Median	1
Alcohol	Moderate	1
Range	—	0–8
CR diet		
Carbohydrate intake	Lowest to highest decile	10 to 1
Protein intake	Lowest to highest decile	1 to 10
Range	—	2–20

[1] Before scoring, variables were energy adjusted, either as nutrient densities (% of energy) or with use of the residual method (in g/d). HDI, Healthy Diet Indicator; SFAs, saturated fatty acids; PUFAs, polyunsaturated fatty acids; MDS, Mediterranean Diet Score; CR, carbohydrate restricted.

[2] Because dietary habits in older Swedish men are traditionally rich in SFA, the upper border of acceptable intakes of SFA was set to 12% of energy. The modified ranges used for acceptable intakes of PUFAs (5–10% of energy), protein (10–20% of energy), and fiber (≥3 g/MJ) were set to match the Swedish national guidelines. Due to a very low intake, nuts and seeds were excluded, and leguminous plants were pooled with vegetables in our score. Total carbohydrates replaced complex carbohydrates, and a negative score (−1) was introduced for sucrose when >10% of energy (to compensate for a high intake of simple carbohydrates). A regular intake of fish was added to the score with cutoff set to 35 g/d, corresponding to an intake of 2 meals of fish/wk.

[3] Compared with the original score, PUFAs replaced monounsaturated fatty acids when estimating dietary fat quality, because the consumption of olive oil in the present population was very low at the time of the investigation, and in a traditional Swedish diet saturated and monounsaturated fats have similar food origins and are therefore strongly correlated. In addition, because of their very low intake, nuts and seeds were excluded, and dietary leguminous plants were pooled with vegetables in our score. The reported intake of potatoes was added to cereals, because potato consumption was the predominant source of carbohydrates in this population. Moderate alcohol consumption was defined as a residual adjusted intake of 10–50 g/d and with no biochemical signs of alcohol abuse (ie, aspartate aminotransferase:alanine aminotransferase ratio < 2).

variables were coded as 1; otherwise, they were coded 0. The HDI was modified (*see* Table 1 footnote) to match the dietary guidelines advocated by the Swedish NFA (28), which are based on the Nordic Nutrition Recommendations from 2004 (29). The modified HDI score could take a value from −1 to 8 points, and individuals were categorized according to the adherence to HDI in low-adherent (≤1 point), medium-adherent (2–4 points), and high-adherent (≥5 points) individuals. For all dietary scores, the cutoffs were chosen to be able to compare extreme groups of comparable and reasonable sizes, and cutoffs are similar to those applied in previous studies (6, 13, 27).

Mediterranean-like diet

The Mediterranean Diet Score (MDS) (13) was applied with slight modifications (*see* Table 1 footnote). The MDS is a population-dependent quality score using dietary intake medians as cutoffs for food components typical of a Mediterranean diet. Compared with the HDI, the MDS is based more on food categories but also includes alcohol and fatty acids. An intake on the favorable side of the median was coded 1; otherwise it was coded 0. The population medians (interquartile range) in energy-adjusted grams per day for each MDS component in the whole study sample and in adequate reporters were 67 (38–104) g and 75 (44–116) g for vegetables and legumes, 106 (43–169) g and 124 (61–184) g for fruit, 352 (294–429) g and 405 (340–489) g for cereals, 25 (14–38) g and 27 (15–41) g for fish, 91 (70–117) g and 98 (77–125) g for meat and meat products, 356 (252–478) g and 417 (314–555) g for milk and milk products, and 4.2 (1.0–9.4) g and 4.6 (1.2–10.4) g for alcohol, respectively. The corresponding medians for the polyunsaturated fatty acid (PUFA) to saturated fatty acid (SFA) ratio were 0.34 (0.28–0.40) and 0.33 (0.28–0.40). Thus, the modified MDS could take a value from 0 to 8 points, and individuals were categorized as low-adherent (≤2 points), medium-adherent (3–5 points), and high-adherent (≥6 points) individuals.

CR diet

The CR diet score applied in our study distinguishes individuals according to their intake of energy-adjusted carbohydrates and proteins, as previously described (6, 7). The cohort was divided into deciles according to the carbohydrate and protein intakes, respectively, and the individuals were assigned a score from 1 to 10 due to decile participation. Increases in carbohydrate intake yielded a descending score (10 points to the lowest intake) and, inversely, increases in protein intake resulted in an ascending score (10 points to the highest intake). Consequently, the CR score could take a value from 2 to 20 points. Subjects were categorized as low-adherent (2–6 points), medium-adherent (7–15 points), and high-adherent (16–20 points) individuals.

Statistical analysis

All analyses were performed with use of the STATA statistical package (Intercooled STATA 10.0 for Windows; Stata Corp, College Station, TX), and significance was set at 0.05. Group comparisons (*see* supplemental material under "Supplemental data" in the online issue) were performed with unpaired *t* tests and analysis of variance if data were normally distributed and with Kruskal-Wallis and Mann-Whitney *U* tests if distributions were skewed. Differences in proportions were calculated with chi-square tests. Cox proportional hazards regression analysis was used to calculate HRs with 2-tailed 95% CIs for overall and cardiovascular mortality by adherence to the respective dietary scores—ie, by level of adherence (groups)—and by each SD increment. Proportional hazard assumptions were confirmed by Schoenfeldt's test. Cox analyses were performed separately in the large study sample (including subjects assessed as nonadequate dietary reporters) as well as in the subpopulation of adequate dietary reporters. The independent contribution to mortality from adherence to the various diet scores was tested by adjusting with population-specific covariates that showed a group difference (for any of the dietary scores) with a *P* value < 0.20 (*see* Supplemental Tables 1 and 2 under "Supplemental data" in the online issue). Body mass index, insulin sensitivity index, and waist circumference were different between groups, but due to strong colinearity only the latter was used in the adjustment models. In both populations, model 1 included energy intake (continuous), smoking (yes or no), and social class (low, middle, high). Model 2 applied in the whole study group included, apart from the variables in model 1, the presence of type 2 diabetes, the metabolic syndrome, lipid-lowering treatment, blood pressure–lowering treatment, and waist circumference (continuous), diastolic blood pressure (continuous), fasting insulin (continuous), and CRP (categorized as normal, <3 mg/L; slightly elevated, 3–10 mg/L; and elevated, >10 mg/L). Model 2 applied in the subpopulation of adequate reporters included, apart from the variables in model 1, waist circumference (continuous), fasting glucose and insulin (continuous), and CRP (categorized as above). Subjects with missing data for covariates were not included in the adjusted models. Information on lipid-lowering treatment was missing in 13 subjects, waist circumference in 15 subjects (*n* = 5 in adequate reporters), fasting insulin in 29 subjects (*n* = 14 in adequate reporters), and CRP in 30 subjects (*n* = 20 in adequate reporters).

RESULTS

Baseline characteristics

Compared with dietary nonadequate reporters, adequate reporters had a lower frequency of the metabolic syndrome, higher HDL cholesterol, and lower body mass index, waist circumference, glucose, insulin, and CRP concentrations (data not shown). The apparently healthier state of adequate reporters is further shown in Supplemental Tables 1 and 2 under "Supplemental data" in the online issue, which presents baseline characteristics in relation to adherence to each diet score in the whole study group and adequate reporters, respectively. In addition, these data indicate that clinical characteristics in relation to dietary adherence groups differed between the whole study group and adequate reporters. Thus, modulators of long-term risk may not be identical, and population-specific covariates were identified and applied in the subsequent risk analyses for CVD and total mortality.

The CR diet was a moderate, low-carbohydrate diet with a mean (±SD) carbohydrate intake of 43 ± 3% energy in the high-adherent group of adequate reporters. For the 7 participants belonging to the lowest decile for carbohydrate intake and the highest decile for protein intake, equivalent to 20 p in the CR score, the mean energy-adjusted intake of carbohydrates and proteins was 40 ± 2% energy and 18 ± 2% energy, respectively. The corresponding values for the 12 participants simultaneously belonging to the deciles with the highest intake of carbohydrates and the lowest protein intake—ie, CR score equivalent to 2 points—were 60 ± 8% energy and 12 ± 1% energy, respectively.

Mortality and dietary patterns

During the follow-up period of (median) 10.1 y (8846 person-years at risk), 215 died (23%): 88 (10%) deaths were due to CVD. In the subpopulation of adequate reporters, the corresponding numbers were 10.2 y (4954 person-years at risk) and 107 deaths (21%), 41 (8%) of which were due to CVD.

HRs for mortality for each SD increment in the dietary scores and for degree of adherence (low, medium, high) for each dietary pattern with use of the whole study group, including nonadequate dietary reporters, are shown in **Table 2**. By this approach, no consistent relations to total or CVD mortality were found for either the HDI score or CR score. In contrast, each SD increment in the MDS showed a reduced HR for total mortality by 18% in the confounder-adjusted model and by 17% in the fully adjusted model. With use of low-adherent individuals as a reference group, HR for total mortality was reduced in MDS high-adherent individuals by 45% in the confounder-adjusted model and by 44% in the fully adjusted model.

Next, similar calculations were performed after exclusion of nonadequate dietary reporters. As shown in **Table 3**, a somewhat different picture emerged. There was still no significant relation between mortality and HDI score, neither when evaluated as a continuous variable nor when grouping into low, medium, and high adherence to the HDI dietary pattern. The potential

TABLE 2
Hazard ratios for the whole study group for total and cardiovascular mortality associated with a continuous increment in scores and with subjects grouped according to their adherence to each diet score[1]

	Total mortality		CVD mortality	
	Model 1[2]	Model 2[3]	Model 1[2]	Model 2[3]
HDI: continuous (SD increment)	0.96 (0.78, 1.19)	0.96 (0.77, 1.19)	0.99 (0.72, 1.37)	1.07 (0.77, 1.49)
Grouped as				
Low (−1 to 1 points)	Ref	Ref	Ref	Ref
Medium (2–4 points)	0.80 (0.53, 1.21)	0.76 (0.49, 1.17)	0.50 (0.28, 0.90)	0.53 (0.28, 1.00)
High (5–8 points)	0.95 (0.53, 1.70)	0.95 (0.51, 1.75)	1.03 (0.48, 2.21)	1.25 (0.55, 2.80)
P for trend[4]	0.76	0.76	0.88	0.67
MDS: continuous (SD increment)	0.82 (0.69, 0.97)	0.83 (0.70, 0.99)	0.86 (0.66, 1.12)	0.93 (0.70, 1.22)
Grouped as				
Low (0–2 points)	Ref	Ref	Ref	Ref
Medium (3–5 points)	0.74 (0.54, 1.01)	0.73 (0.52, 1.00)	0.75 (0.46, 1.23)	0.82 (0.49, 1.38)
High (6–8 points)	0.55 (0.33, 0.92)	0.56 (0.33, 0.96)	0.55 (0.24, 1.23)	0.60 (0.26, 1.38)
P for trend[4]	0.013	0.018	0.12	0.22
CR diet score: continuous (SD increment)	1.11 (0.97, 1.27)	1.11 (0.96, 1.28)	1.13 (0.91, 1.40)	1.07 (0.86, 1.34)
Grouped as				
Low (2–6 points)	Ref	Ref	Ref	Ref
Medium (7–15 points)	1.32 (0.88, 1.98)	1.28 (0.84, 1.95)	1.53 (0.78, 2.99)	1.39 (0.71, 2.75)
High (16–20 points)	1.25 (0.76, 2.06)	1.22 (0.73, 2.05)	1.28 (0.56, 2.93)	1.06 (0.45, 2.50)
P for trend[4]	0.41	0.47	0.61	0.94

[1] Risk estimates are presented as hazard ratios (95% CIs) derived by Cox proportional hazards regression analyses. CVD, cardiovascular disease; HDI, Healthy Diet Indicator; MDS, Mediterranean Diet Score; CR, carbohydrate restricted; Ref, reference.
[2] Adjusted for energy intake, smoking, and social class; $n = 904$.
[3] Adjusted as for model 1 plus type 2 diabetes, the metabolic syndrome, lipid-lowering treatment, blood pressure–lowering treatment, waist circumference, diastolic blood pressure, insulin, and C-reactive protein; $n = 871$.
[4] In low-, medium-, and high-adherent groups.

protective effects from the Mediterranean-like diet (MDS) emerged more clearly. Each SD increment in the score was related to a 29% risk reduction in total mortality and a 37% risk reduction in CVD mortality in the fully adjusted model. With low-adherent individuals as a reference group, high adherence to the Mediterranean-like diet was associated with a 74% reduction in total mortality and an 81% reduction in CVD mortality in the fully adjusted model. In contrast, each SD increment in the CR diet score was associated with a nonsignificant 19% increased risk in total mortality ($P = 0.09$) and a 44% increased risk in CVD mortality ($P = 0.03$) in the fully adjusted model. With low-adherent individuals as a reference group, high-adherent individuals to the CR diet had a nonsignificant doubled risk of total mortality in both confounder- and fully adjusted models ($P = 0.05$ and $P = 0.06$, respectively). In turn, high-adherent individuals to the CR diet had a 5-fold increased risk of CVD mortality in the confounder-adjusted model ($P = 0.04$), which became nonsignificant after additional adjustments for potential intermediates ($P = 0.08$).

Unadjusted survival curves in low-, medium-, and high-adherent individuals of each diet score, as shown among the adequate reporters, are presented in **Figure 1**, A, B, and C.

DISCUSSION

In this population-based study of elderly men, health effects from the adherence to predefined dietary patterns are described. The current data contribute 3 important findings. First, in line with previous reports, a Mediterranean-like diet was found to be beneficial, with a 17% reduction in 10-y total mortality for each SD increment in the 0–8-point score. Second, when adequate dietary reporters were considered, the protective effects from a Mediterranean-like diet was enhanced, showing a 29% risk reduction in total mortality and a 37% risk reduction in CVD mortality for each SD increment in the score (fully adjusted). Moreover, a moderately CR diet was associated with increased mortality after adjustments for potential confounders, with a nonsignificant 20% increased risk in total mortality and a significant 50% increased risk in CVD mortality for each SD increment in the 2–20-point score. Third, the identification of dietary nonadequate reporters affected the subsequent risk analyses, underscoring the importance of considering misreporting in dietary studies.

Recently, CR diets have been proposed as alternative steps to combat the global obesity epidemic that has emerged during the latter decades. Indeed, such diets have strong short-term weight-reducing effects (30), but longer term studies, ≤2 y, indicate no difference between weight-reducing regimes (3, 4). Advocates of CR diets usually recommend increased fat intake with no restrictions on saturated fat. Current consensus is that saturated fat intake should be limited to reduce cardiovascular risk (1, 2). Thus, concerns have been raised about the long-term safety of CR diets. Only a few previous studies have investigated the long-term health effects of a high-protein CR diet. Such a diet, defined as in the present study, was associated with increased mortality in a general Greek population (7) and with increased CVD mortality in 30- to 49-y-old Swedish women (6). However, in the Nurses' Health Study, no relations to coronary heart disease were

The American Journal of Clinical Nutrition

TABLE 3

Hazard ratios for adequate dietary reporters for total and cardiovascular mortality associated with a continuous increment in the scores and with subjects grouped according to the adherence to each diet score[1]

	Total mortality		CVD mortality	
	Model 1[2]	Model 2[3]	Model 1[2]	Model 2[3]
HDI: continuous (SD increment)	0.85 (0.63, 1.15)	0.87 (0.64, 1.17)	0.93 (0.58, 1.49)	0.97 (0.60, 1.57)
Grouped as				
Low (−1 to 1 point)	Ref	Ref	Ref	Ref
Medium (2–4 points)	0.69 (0.42, 1.15)	0.69 (0.42, 1.15)	0.58 (0.26, 1.30)	0.61 (0.27, 1.38)
High (5–8 points)	0.97 (0.45, 2.11)	1.05 (0.48, 2.31)	1.31 (0.44, 3.92)	1.36 (0.44, 4.13)
P for trend[4]	0.59	0.68	0.89	0.85
MDS: continuous (SD increment)	0.69 (0.54, 0.89)	0.71 (0.55, 0.92)	0.61 (0.40, 0.91)	0.63 (0.42, 0.96)
Grouped as				
Low (0–2 points)	Ref	Ref	Ref	Ref
Medium (3–5 points)	0.61 (0.39, 0.94)	0.67 (0.43, 1.05)	0.44 (0.23, 0.87)	0.51 (0.25, 1.01)
High (6–8 points)	0.25 (0.10, 0.60)	0.26 (0.11, 0.65)	0.16 (0.04, 0.72)	0.19 (0.04, 0.86)
P for trend[4]	0.001	0.002	0.003	0.009
CR diet score: continuous (SD increment)	1.20 (0.99, 1.46)	1.19 (0.97, 1.45)	1.50 (1.09, 2.08)	1.44 (1.03, 2.02)
Grouped as				
Low (2–6 points)	Ref	Ref	Ref	Ref
Medium (7–15 points)	1.96 (1.04, 3.70)	2.02 (1.03, 3.96)	4.19 (1.00, 17.7)	3.40 (0.80, 14.5)
High (16–20 points)	2.05 (0.99, 4.23)	2.06 (0.97, 4.39)	5.01 (1.09, 22.9)	3.98 (0.86, 18.5)
P for trend[4]	0.068	0.091	0.039	0.098

[1] Risk estimates are presented as hazard ratios (95% CIs) derived by Cox proportional hazards regression analyses. CVD, cardiovascular disease; HDI, Healthy Diet Indicator; MDS, Mediterranean Diet Score; CR, carbohydrate restricted; Ref, reference.

[2] Adjusted for energy intake, smoking, and social class; $n = 503$.

[3] Adjusted as for model 1 plus waist circumference, fasting glucose and insulin, and C-reactive protein; $n = 494$.

[4] In low-, medium-, and high-adherent groups.

found for a CR diet score, which also included fat intake (8). A recent 2-y study showed that a CR, high-fat diet reduced body weight and improved serum lipids in overweight individuals (3). In that study, the ingested fats were mainly of unsaturated origin. In the present study, an inverse relation between the polyunsaturated:saturated fat ratio and CR adherence was observed (data not shown). However, the amount of carbohydrate intake in that study was similar to what was observed in individuals that adhered to the CR diet in the present study. It could be speculated that in a short-term perspective, low-carbohydrate diets may stimulate a dietary change in highly motivated subjects that results in negative energy balance and weight reduction. In the long run, the risk may be that the CR diet would induce harmful effects, because the diet is abundant in energy-dense foods, low in fruit and vegetables, and has a fat composition that might be unfavorable. From this point of view, data from the present prospective observational study and previous publications (6, 7) argue against the long-term safety of CR diets.

In this study, we further described survival benefits from the adherence to a Mediterranean-like diet. It is important to stress, however, that a high MDS score does not per se reflect a true Mediterranean diet, especially in a non-Mediterranean population. A number of previous studies have suggested that a Mediterranean diet may prevent overweight and obesity and reduce total and CVD mortality (9, 31). In a recent meta-analysis including 9 studies (9), the pooled relative risk estimate for overall 4–12-y mortality was 0.91, with a variation from 0.48 to 0.93. Although the health effect from a Mediterranean diet varies between populations (12), the magnitude of the beneficial effect detected in the currently presented population is comparatively high. It is uncertain whether this is a population-specific observation, an effect of the MDS-modifications performed, or can be explained by the use of 7-d dietary records in the present study.

Previous publications have detected significant risk reductions of ≈10–15% in total mortality from HDI adherence (27, 32). In the current study, no association between the WHO dietary guidelines and mortality was observed. However, the application of HDI with strict ranges and firm cutoffs for the composite components will be insensitive to capture the diversity of the diet. As a consequence, participants tend to cluster in the middle with subsequent loss of power. Considering the low number of individuals identified as highly adherent to HDI in our population, this likely contributes to the absent relationships between HDI and mortality in this study. One could speculate, though, that if HDI adherence was calculated with use of the same population-based technique as for MDS, HDI would also emerge as promoting health.

The underlying explanation for the relations between dietary patterns and mortality described in this study is not fully explained. Most important, our risk estimates were adjusted for potential confounders, which may have influenced diet-disease relations. Physical activity is a classical confounder in this context, but we did not adjust for physical activity due to a lack of difference between dietary pattern groups. However, additional adjustments for physical activity did not influence the risk estimates presented. Furthermore, risk relations were essentially unchanged after adjusting for potential intermediates, such as abdominal obesity, inflammation, and insulin resistance, suggesting the occurrence of unidentified risk mediators and residual confounding in the present investigation. Interestingly, a recent experimental study in mice

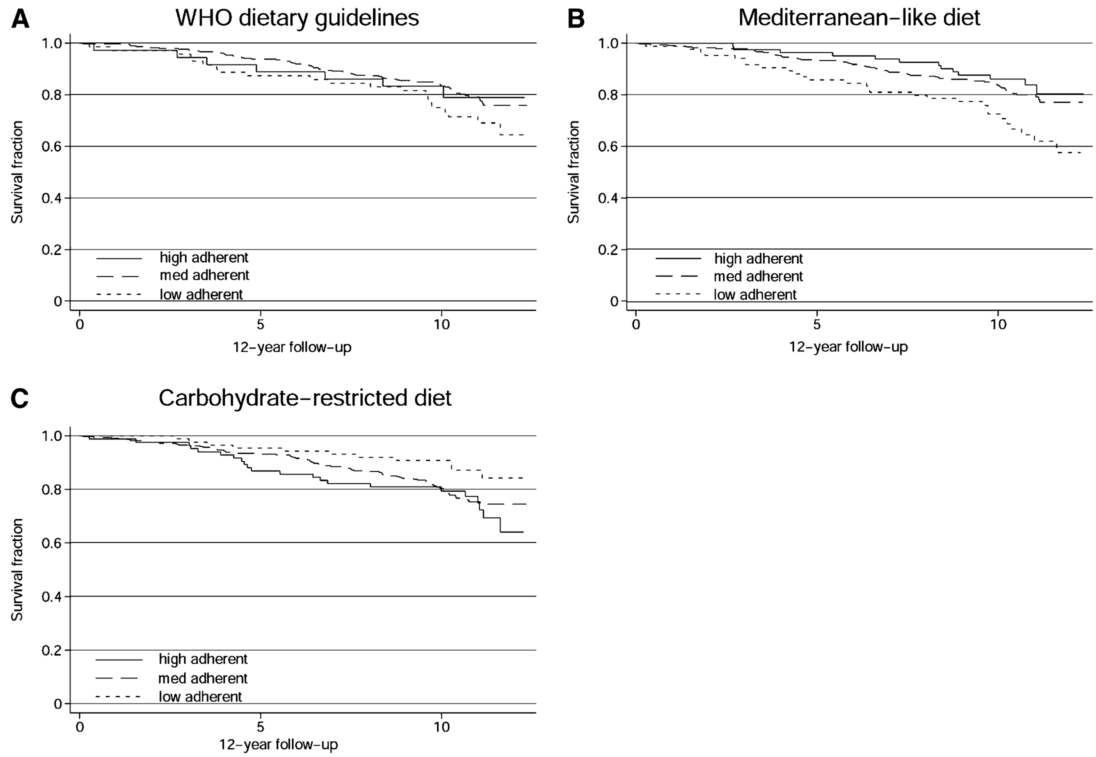

FIGURE 1. Kaplan-Meier survival curves for individuals considered adequate reporters of dietary intake, grouped as low-, medium-, or high-adherent individuals to the dietary patterns investigated. Crude hazard ratios (HRs) and 95% CIs were calculated from Cox proportional hazards regression analyses with the use of low-adherent individuals as the reference group for each dietary pattern. A: World Health Organization (WHO) dietary guidelines, according to the Healthy Diet Indicator: medium adherent (HR: 0.70; 95% CI: 0.43, 1.15), high adherent (HR: 0.97; 95% CI: 0.45, 2.07). B: Mediterranean-like diet, according to the Mediterranean Diet Score: medium adherent (HR: 0.68; 95% CI: 0.44, 1.04), high adherent (HR: 0.29; 95% CI: 0.12, 0.70. C: Carbohydrate-restricted (CR) diet, according to the CR diet score: medium adherent (HR: 1.92; 95% CI: 1.02, 3.62), high adherent (HR: 2.17; 95% CI: 1.05, 4.45).

showed a diet low in carbohydrates and high in protein to induce adverse vascular effects by reducing the number of bone marrow and peripheral blood endothelial progenitor cells (33). Adverse vascular effects from a low-carbohydrate diet were also indicated in a 6-wk study on obese subjects on an Atkins-style diet (34). These data on health effects from a low-carbohydrate diet may be of relevance for the increased risk of mortality associated with CR diet in the present study.

There are several limitations as well as advantages of this study. One limitation is that only elderly men were investigated, and the generalizability of our findings to women or other age groups is uncertain. The sample size was limited. However, the observation period of ≈10 y is fairly long and appropriate for a population that is 70 y old at baseline, as evidenced by a mortality rate of >20%. Another limitation is that close to one-half of the participants were not able to give an adequate dietary recall, as evidenced by a high degree of unacceptable reporting. This limitation is concurrent with many similar studies, as unacceptable reporting always is an important issue, especially in overweight subjects. A corresponding strength of the study is the endeavor to take this limitation into consideration. It is likely to think that the conclusions drawn from adequate dietary reporters are safer than those drawn from a population where nonadequate reporters are included. The size of the study group considered as adequate dietary reporters was small, which indicates that they may not have been representative for the whole group. Nevertheless, the individuals considered as adequate dietary reporters were healthier at baseline compared with the nonadequate reporters, indicating that the relations to mortality may have been underestimated rather than overestimated in this study. Further advantages of the study include its prospective nature, the population-based sample, the use of 7-d food records (instead of food-frequency questionnaires), and the use of scores previously applied in studies relating dietary patterns with mortality. In addition, official registry data on mortality and cause of death with high reliability and virtually no loss to follow-up were used.

The question of whether or not adherence to certain dietary patterns is advantageous is a major public health issue. CR diets have gained in popularity, but our observations indicate adverse effects from such a dietary pattern. Whether this is a true diet effect from reduced carbohydrate intake or increased fat intake cannot be surely deduced from this prospective cohort study, but the study adds further knowledge to the field. Conversely, beneficial effects were observed for dietary patterns reflecting Mediterranean habits. Our data indicate that a Mediterranean-like pattern with more focus on dietary food choices than nutrient composition have strong health-promoting effects, but whether this diet is superior to the official recommendations is undetermined and remains to be resolved.

We thank Bengt Vessby (Uppsala) and Mai-Lis Hellenius (Stockholm) for helpful comments on the interpretation of our findings, Björn Zethelius (Uppsala) and Magdalena Rosell (Stockholm) for valuable comments on the analytical procedure, and Lisa Stenroth and Lars Berglund at the Uppsala Clinical Research Centre, Uppsala University, for statistical consultancy.

The authors' responsibilities were as follows—PS, WB, and TC: responsible for the conception and design of the study and analysis and interpretation of data obtained; PS, EW, and LB: responsible for statistical analysis; EO, I-BG, and BK: responsible for data acquisition; and PS and TC: responsible for drafting the manuscript. All authors critically revised the draft and gave final approval of the version to be published. TC is the guarantor. None of the authors had a personal or financial conflict of interest.

REFERENCES

1. The Swedish National Food Administration and the Swedish National Institute of Public Health. Background material to the action plan for healthy dietary habits and increased physical activity. The Swedish National Institute of Public Health. Available from: http://www.slv.se/upload/nfa/documents/food_nutrition/Theactionplanforhealthdietaryhabitsandincreasephysicalactivity.pdf (cited 2 February 2010).
2. US Department of Agriculture and Department of Health and Human Services. Report of the dietary guidelines advisory committee on the dietary guidelines for Americans, 2005. Available from: http://www.health.gov/dietaryguidelines/dga2005/document/pdf/DGA2005.pdf (cited 4 February 2010).
3. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359:229–41.
4. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–73.
5. Buckland G, Bach A, Serra-Majem L. Obesity and the Mediterranean diet: a systematic review of observational and intervention studies. Obes Rev 2008;9:582–93.
6. Lagiou P, Sandin S, Weiderpass E, et al. Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. J Intern Med 2007;261:366–74.
7. Trichopoulou A, Psaltopoulou T, Orfanos P, Hsieh CC, Trichopoulos D. Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. Eur J Clin Nutr 2007;61:575–81.
8. Halton TL, Willett WC, Liu S, et al. Low-carbohydrate-diet score and the risk of coronary heart disease in women. N Engl J Med 2006;355:1991–2002.
9. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ 2008;337:a1344.
10. Lagiou P, Trichopoulos D, Sandin S, et al. Mediterranean dietary pattern and mortality among young women: a cohort study in Sweden. Br J Nutr 2006;96:384–92.
11. Osler M, Schroll M. Diet and mortality in a cohort of elderly people in a north European community. Int J Epidemiol 1997;26:155–9.
12. Trichopoulou A, Orfanos P, Norat T, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. BMJ 2005;330:991.
13. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599–608.
14. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003;24:1601–10.
15. Byberg L, Siegbahn A, Berglund L, McKeigue P, Reneland R, Lithell H. Plasminogen activator inhibitor-1 activity is independently related to both insulin sensitivity and serum triglycerides in 70-year-old men. Arterioscler Thromb Vasc Biol 1998;18:258–64.
16. Vessby B, Tengblad S, Lithell H. Insulin sensitivity is related to the fatty acid composition of serum lipids and skeletal muscle phospholipids in 70-year-old men. Diabetologia 1994;37:1044–50.
17. Skarfors ET, Selinus KI, Lithell HO. Risk factors for developing non-insulin dependent diabetes: a 10 year follow up of men in Uppsala. BMJ 1991;303:755–60.
18. Zethelius B, Lithell H, Hales CN, Berne C. Insulin sensitivity, proinsulin and insulin as predictors of coronary heart disease: a population-based 10-year, follow-up study in 70-year old men using the euglycaemic insulin clamp. Diabetologia 2005;48:862–7.
19. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–52.
20. Byberg L, Zethelius B, McKeigue PM, Lithell HO. Changes in physical activity are associated with changes in metabolic cardiovascular risk factors. Diabetologia 2001;44:2134–9.
21. Andersen R, Smedby B, Andersson D. Medical care use in Sweden and the United States. A comparative analysis of systems and behaviour. Center for Health Administration Studies. Research Series 1970;27:151–5. Available from: http://www.chas.uchicago.edu/documents/Publications/RS/RS27.PDF (cited 18 August 2010).
22. Nydahl M, Gustafsson IB, Mohsen R, Becker W. Comparison between optical readable and open-ended weighed food records. Food Nutr Res 2009:53.
23. Becker W. [Food habits and intake in Sweden 1989] (in Swedish). Uppsala, Sweden: The Swedish National Food Administration, 1994.
24. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations. Int J Obes Relat Metab Disord 2000;24:1119–30.
25. Willett W. Nutritional epidemiology. New York, NY: Oxford University Press, 1998.
26. WHO. WHO Technical Report Series. Diet, nutrition, and the prevention of chronic diseases. Report of a Joint WHO/FAO Expert Consultation. Geneva, Switzerland: World Health Organization, 2003.
27. Huijbregts P, Feskens E, Rasanen L, et al. Dietary pattern and 20 year mortality in elderly men in Finland, Italy, and The Netherlands: longitudinal cohort study. BMJ 1997;315:13–7.
28. Enghardt Barbieri H, Lindvall C. Swedish Nutrition Recommendations Objectified (SNO): basis for general advice on food consumption for healthy adults. 2005. Available from: http://www.slv.se/upload/dokument/rapporter/mat_naring/Report_20_2005_SNO_eng.pdf (cited 4 February 2010).
29. Nordic Nutrition Recommendations NN. Integrating nutrition and physical activity. 4th ed. Copenhagen, Denmark: Nordic Council of Ministers, 2004.
30. Alhassan S, Kim S, Bersamin A, King AC, Gardner CD. Dietary adherence and weight loss success among overweight women: results from the A TO Z weight loss study. Int J Obes (Lond) 2008;32:985–91.
31. Buckland G, Bach A, Serra-Majem L. Obesity and the Mediterranean diet: a systematic review of observational and intervention studies. Obes Rev 2008;9:582–93.
32. Knoops KT, Groot de LC, Fidanza F, Alberti-Fidanza A, Kromhout D, van Staveren WA. Comparison of three different dietary scores in relation to 10-year mortality in elderly European subjects: the HALE project. Eur J Clin Nutr 2006;60:746–55.
33. Foo SY, Heller ER, Wykrzykowska J, et al. Vascular effects of a low-carbohydrate high-protein diet. Proc Natl Acad Sci USA 2009;106:15418–23.
34. Phillips SA, Jurva JW, Syed AQ, et al. Benefit of low-fat over low-carbohydrate diet on endothelial health in obesity. Hypertension 2008;51:376–82.