NIH Public Access
Author Manuscript
Am J Clin Nutr. Author manuscript; available in PMC 2008 February 1.

Published in final edited form as:
Am J Clin Nutr. 2007 November ; 86(5): 1486–1494.

Prospective study of dietary pattern and risk of Parkinson disease[1,2,3]

Xiang Gao, **Honglei Chen**, **Teresa T Fung**, **Giancarlo Logroscino**, **Michael A Schwarzschild**, **Frank B Hu**, and **Alberto Ascherio**

1 *From the Departments of Nutrition (XG, TTF, FBH, and AA) and Epidemiology (GL, FBH, and AA), Harvard School of Public Health, Cambridge, MA; the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (FBH and AA), Boston, MA; the Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC (HC); the Department of Nutrition, Simmons College, Boston, MA (TTF); and the Department of Neurology, Massachusetts General Hospital, Boston, MA (MAS).*

Abstract

Background—Several studies have shown associations between Parkinson Disease (PD) risk and individual foods and nutrients with inconsistent results.

Objective—We examined associations between dietary patterns and risk of PD in the Health Professionals Follow-Up Study (1986–2002) and the Nurses' Health Study (1984–2000).

Design—We included 49 692 men and 81 676 women free of PD at baseline and used principal components analysis to identify major dietary patterns and the Alternate Healthy Eating Index (AHEI) and the alternate Mediterranean Diet Score (aMed) to assess diet quality. Relative risks (RRs) were computed by using Cox proportional hazards models within each cohort and were pooled by using a random-effects model.

Results—We documented 508 new PD cases after 16 y of follow-up. The principal components analysis identified 2 dietary patterns: prudent and Western. The prudent dietary pattern, characterized by high intakes of fruit, vegetables, and fish, was inversely associated with PD risk, but the Western pattern was not. The pooled multivariate-adjusted RR for the top compared with the bottom quintiles of the prudent score was 0.78 (95% CI: 0.56, 1.07; *P* for trend = 0.04). For the AHEI, the pooled multivariate-adjusted RR for the top compared with the bottom quintile was 0.70 (95% CI: 0.51, 0.94; *P* for trend = 0.01) and for aMED was 0.75 (95% CI: 0.57, 1.00; *P* for trend = 0.07).

Conclusions—Dietary patterns with a high intake of fruit, vegetables, legumes, whole grains, nuts, fish, and poultry and a low intake of saturated fat and a moderate intake of alcohol may protect against PD. Benefits of a plant-based dietary pattern including fish to PD merit further investigation.

Keywords

Parkinson disease; dietary pattern; prospective study; dietary index; principal components analysis

[2]Supported by NIH/NINDS grant R01 NS048517 and by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences.

[3] Address reprint requests to X Gao, Department of Nutrition, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115. E-mail: xgao@hsph.harvard.edu.

The authors' responsibilities were as follows—XG, HC, GL, MAS, FBH, and AA: study concept and design; XG, HC, MAS, FBH, and AA: acquisition of data; XG, HC, TTF, GL, MAS, FBH, and AA: analysis and interpretation of data and critical revision of the manuscript for important intellectual content; XG and AA: drafting of the manuscript; XG, HC, TTF, and AA: statistical analysis; HC and AA: funding; HC, TTF, and AA: administrative, technical, or material support; and AA: study supervision. None of the sponsors participated in the design of study or in the collection, analysis, or interpretation of the data. None of the authors reported a conflict of interest.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disease in the United States and affects more than one million Americans (1). Several studies have investigated associations between PD risk and intake of individual foods and nutrients with inconsistent results (2–8). Previous studies, however, have not examined the overall quality of the diet or dietary patterns in relation to the risk of PD. The analysis of dietary patterns for possible complex interactions between nutrients has emerged as a valuable approach to assess the association between diet and many diseases, including Alzheimer disease (9,10).

Principal components analysis and diet-quality scores are 2 commonly used dietary pattern approaches. Principal components analysis is a data-driven (a posteriori) method that describes existing eating patterns of a certain population. It is based on the assumption that between-person variations can in part be explained by underlying unmeasured variables (factors). Correlations between the consumption of different food items in the study population are used to identify these underlying factors or patterns, and individuals are then ranked in terms of how closely they conform to the total pattern (9,11). In contrast, diet-quality scores are hypothesis-driven (a priori) approaches that measure the degree of adherence of each individual diet to recommended guidelines (9,11,12).

In this study we prospectively examined whether major dietary patterns identified by principal components analysis, or diet-quality scores as assessed by the Alternate Healthy Eating Index (AHEI) and the alternate Mediterranean Diet Score (aMed), were associated with risk of PD in 2 large ongoing cohorts: participants in the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Study (NHS).

SUBJECTS AND METHODS

Study population

The HPFS was established in 1986, when 51 529 male US health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40–75 y completed a mailed questionnaire about their medical history and lifestyle. The NHS cohort was established in 1976, when 121 700 female registered nurses responded to a similar questionnaire. Dietary intake data were collected since 1986 in the HFPS and since 1980 in the NHS. Follow-up questionnaires are mailed to participants every 2 y to update information on potential risk factors and to ascertain newly diagnosed diseases. We used 1986 as baseline for the HFPS. For the NHS, we used 1984 as the baseline because the 1980 food-frequency questionnaire did not include several major food items. Participants who reported an implausible energy intake (<800 kcal/d or >4200 kcal/d for men and <500 kcal/d or >3500 kcal/d for women), those who had ≥70 items left blank on the baseline dietary questionnaire, and those who had a previous diagnosis of PD were excluded, which left 49 692 men and 81 676 women for further analyses. Both studies were approved by the Human Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

Assessment of dietary and nondietary exposures

Dietary intakes were assessed with semiquantitative food-frequency questionnaires (131 food items for men and 116 for women) validated for use with these populations (13,14). In brief, participants were asked how often on average over the previous year they had consumed a specific amount of each food item with 9 possible responses ranging from "never" to "6 or more times per day." Food-composition values for nutrients were obtained from the Harvard University Food Composition Database derived from the US Department of Agriculture sources (15) and were supplemented with manufacturer information.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Information on age, weight, height, smoking status, physical activity, use of nonaspirin nonsteroidal antiinflammatory drugs, and postmenopausal hormone therapy was collected via questionnaires. Body mass index (BMI) was calculated as weight (kg)/height squared (m) (2).

Dietary pattern factors and diet-quality scores

We used baseline dietary intake data (1986 for the HPFS and 1984 for the NHS) to identify dietary pattern factors by using principal components analysis, as reported in earlier studies from our cohorts (16–19). This method was based primarily on the correlation between the food groups. In brief, we collapsed food items (131 for men and 116 for women) collected by FFQ to 40 (men) or 38 (women) foods or food groups on the basis of the similarity of nutrient composition and biological origin. Details of food groupings were described elsewhere (20). We then used SAS PROC FACTOR to conduct a principal components analysis. To achieve better interpretability, we used an orthogonal rotation procedure that results in factors (ie, dietary patterns) that are not correlated with each other. We determined the number of factors to retain by the amount of variation explained by each pattern and the natural interpretation of each pattern generated. We identified 2 major dietary pattern factors: the "prudent" pattern and the "Western" pattern, as described previously (16–19). The factor score for each pattern was constructed by summing observed intakes of the component food items weighted by factor loadings, and each individual received a factor score for each identified pattern. A higher score suggests better adherence to a certain dietary pattern. In a previous validation study, we found that the dietary pattern scores derived by using the FFQ were highly correlated with the scores derived by using diet records in a subgroup of the HPFS (n = 127) (20). The correlation coefficient was 0.52 for the prudent dietary pattern and 0.74 for the Western dietary pattern.

The AHEI was developed by McCullough et al (12) and modified from the US Department of Agriculture Healthy Eating Index. It includes 9 components (vegetables, fruit, nuts and soy, ratio of white to red meat, cereal fiber, *trans* fats, ratio of poly-unsaturated to saturated fat, long-term multivitamin use, and alcohol), each of which has a minimum score of 0 and a maximum score of 10 with an exception of multivitamin use. The possible score for the multivitamin component was either 2.5 or 7.5 to avoid overweighting. The total scores range from 2.5 (worst) to 87.5 (best) (Appendix A). A higher score suggests a higher dietary quality. The aMED was based on the Mediterranean diet scale by Trichopoulou et al (21,22). Fung et al (23,24) modified the scale and developed an aMED with use of an FFQ developed in the United States. The aMED is based on intake of 9 items: vegetables (without potato products), legumes, fruit, nuts, whole grains, fish, ratio of monounsaturated to saturated fat, alcohol, and, red and processed meat. Intake of first 7 items above the median of the study subjects received 1 point; all others received 0. For alcohol, 1 point was assigned for intakes between 5 and 15 g/d (Appendix B). For red and processed meat, an intake below the median received 1 point. The score ranges from 0 (worst) to 9 (best). In previous studies, the AHEI and aMED were shown to be inversely associated with the risk of coronary heart disease, stroke, and breast cancer (12,24–26).

Ascertainment of PD

As previously described (7,27), we identified new PD cases by biennial self-reported questionnaires. We then asked the treating neurologists to complete a questionnaire to confirm the diagnosis of PD or to send a copy of the medical records. A case was confirmed if a diagnosis of PD was considered definite or probable by the treating neurologist or internist or if the medical record included either a final diagnosis of PD made by a neurologist or evidence of ≥2 of the 3 cardinal signs (rest tremor, rigidity, and bradykinesia) in the absence of features suggesting other diagnoses. The review of medical records was conducted by the investigators, who were blind to the exposure status. Overall, >80% of the diagnoses were confirmed by the

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

treating neurologists. We also requested the death certificates of the deceased study participants and identified PD diagnoses that were not reported in the regular follow-up (<2%). In this analysis, we used only definite and probable cases of PD.

Statistical analysis

We computed person-time of follow-up for each participant from the return date of the baseline questionnaires to the date of the occurrence of the PD (PD first symptom), death from any cause, or end of follow-up (2002 for men and 2000 for women), whichever came first. We categorized baseline dietary pattern factors or diet-quality scores into quintiles, respectively. In primary analyses, we calculated relative risk (RR) by dividing the incidence rate in dietary pattern factors or score quintile by the corresponding rate in the reference quintile. Relative risks (RRs) were derived from Cox proportional hazard models in which for age (in mo), smoking status (never smoker, past smoker, current smoker of 1–14 cigarettes/d, or current smoker of ≥15 cigarettes/d), BMI (<23, 23–24.9, 25–26.9, 27–29.9, or ≥30), use of non-steroidal antiinflammatory drugs (yes or no), and intakes of total energy (kcal/d), caffeine (quintiles), and alcohol (0, 1–4.9, 5–9.9, 10–14.9, or ≥15 g/d for women; 0, 1–9.9, 10–19.9, 20–29.9, or ≥30 g/d for men) were controlled for. We adjusted for the use of nonsteroidal antiinflammatory drugs and caffeine intake because they have been shown to be inversely associated with PD risk (27,28). All covariates were derived from baseline data. Linear trends were tested for significance by using the median value for each quartile of intake and treating this value as a continuous variable. Log RR from the 2 cohorts were pooled by a random-effects model and weighted by the inverse of their variances (29). In our recent studies, we found that an empirical dietary urate index, comprising intakes of alcohol, dairy protein, fructose, and vitamin C, which reflects the overall effect of diet on plasma urate, was associated with PD risk in the HPFS (X Gao, H Chen, HK Choi, G Curhan, MA Schwarzschild, A Ascherio, unpublished observations, 2007). The urate index was calculated as follows: 0.013 × alcohol (g/d) + 0.008 × fructose (g/d) − 0.009 × dairy protein (g/d) − 0.0003 × vitamin C (mg/d). We therefore conducted secondary analyses further adjusted for urate index and dietary iron intake, which was suggested to be positively associated with PD risk in previous studies (4,8).

We also examined interactions of the dietary pattern factors or diet-quality scores with baseline age (<60 compared with ≥60 y), baseline smoking status (never compared with ever), estrogen use (never compared with ever, for women only), baseline caffeine intake (above or below the median), and baseline lactose intake (above or below the median). To test significance of interactions, we included multiplicative terms in the Cox models, with adjustment for other potential confounders. To address the possibility that dietary changes caused by early symptoms of PD might affect the results, we conducted lag analyses by excluding the first 4 y of follow-up. To evaluate the robustness of our results, we also conducted sensitivity analyses by excluding subjects with cancer or stroke at baseline. We used the SAS statistical package (version 9; SAS Institute, Cary, NC) for all analyses.

RESULTS

We documented 318 PD cases in men and 190 in women. Two major dietary pattern factors were identified (Table 1) in both men and women from principal components analysis: the prudent dietary pattern and the Western pattern. The prudent dietary pattern was characterized by high intakes of fruit, vegetables, legumes, whole grains, poultry, and fish; the Western dietary pattern was characterized by high intakes of red meats, processed meats, refined grains, French fries, desserts and sweets, and high-fat dairy products. The prudent dietary pattern is consistent with higher scores on the AHEI or aMED; in contrast, the Western patterns was correlated with a lower score (Appendix C). Furthermore, participants with a higher prudent pattern, AHEI, or aMED scores also had similar healthy population characteristics: they

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

exercised more, smoked less, had lower intakes of caffeine, and had higher intakes of energy, dietary α-tocopherol, and vitamin C (Table 2 and Table 3). In contrast, participants with a higher Western pattern score smoked more, exercised less, and reported higher intakes of caffeine and lower intakes of dietary α-tocopherol and vitamin C.

We observed an inverse association between the prudent dietary pattern factor and risk of PD in men and women combined (Table 4). After adjustment for age, smoking, caffeine, physical activity, and other potential confounders, the pooled RR comparing the top with the bottom quintile of the prudent pattern score was 0.78 (95% CI: 0.56, 1.07; *P* for trend = 0.04). The association between Western dietary scores and PD risk was not statistically significant. A higher score on the AHEI or aMED was also associated with a reduced risk of PD (Table 5). For the AHEI, the pooled multivariate-adjusted RR for the top compared with the bottom quintile was 0.70 (95% CI: 0.51, 0.94; *P* for trend = 0.01). Similarly, participants in the highest aMED quintile were less likely to develop PD than were those in the bottom aMED quintile (RR = 0.75; 95% CI: 0.57, 1.00; *P* for trend = 0.07). After further adjustment for physical activity, dietary urate index, and iron, the associations between dietary pattern factors or diet-quality scores and PD risk did not materially change (data not shown). We also examined the association between use of multivitamins and PD risk. The pooled multivariate-adjusted RR for users compared with nonusers was 0.98 (95% CI: 0.82, 1.18; *P* = 0.86). Further adjustment for multivitamin use did not materially change the statistical association between dietary pattern and indexes and PD risk. Because dairy intake was not included in the AHEI and aMED, we further adjusted for dairy intake, and the results did not change (data not shown).

We further explored possible interactions of the dietary patterns with age, BMI, cigarette smoking, caffeine intake, lactose intake, and, in women, use of postmenopausal estrogens. We found no significant interactions (*P* for interaction >0.05 for all), except for smoking and the Western dietary pattern (*P* for interaction = 0.009). The Western pattern tended to be positively associated with the risk of PD among never smokers, but not among ever smokers; however, neither association was statistically significant (*P* for trend >0.2 in both analyses). It remains unclear whether this significant association was driven by chance. Associations between the dietary factors or indexes and PD risk did not change materially when participants with PD during the first 4 y of follow-up or participants with cancer or stroke at baseline were excluded (data not shown).

DISCUSSION

In these 2 large prospective cohorts of men and women, we found that the prudent dietary pattern, characterized by high intakes of fruit, vegetables, whole grains, legumes, poultry, and fish was associated with a lower risk of PD. Similar results were obtained for higher AHEI or aMED scores, which suggests that a healthy dietary pattern with greater intakes of plant food and fish and moderate intakes of alcohol is inversely associated with PD risk. The associations were independent of smoking, caffeine intake, and other PD risk factors.

Compared with traditional single-food or nutrient methods, the dietary pattern approach is appealing for several reasons. In reality, people eat combinations of food and nutrients, which leads to a high collinearity among many of the nutrients and foods. It is often difficult to identify the effect of a single food or nutrient on health outcomes. Dietary patterns represent a combination of nutrients and foods; thus, they may be a more powerful predictor of health outcomes than any single nutrient alone (9). Furthermore, a dietary pattern analysis offers an approach for better understanding the complexities of eating behaviors of different population groups and subgroups and may be used to effectively develop dietary intervention strategies for target groups (30–33).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

The healthy diet, as identified in our analysis, was characterized by a high consumption of fruit, vegetables, legumes, and cereals and a low consumption of meats. This diet provides plenty of dietary antioxidants and folate and a limited amount of saturated fat, which may contribute to the lower PD risk of individuals with healthy diets. There is substantial evidence of a role of oxidative stress in PD (34–36), including increased oxidation in autopsy samples of substantia nigra from brains of persons with PD (34,35), and that oxidative stress promotes α-synuclein aggregation, which is most likely an important event in the pathogenesis of PD (36). We previously observed an inverse association between dietary intakes of vitamin E, but not of vitamin E from supplements, and PD risk in the NHS and HPFS population (7). A recent meta-analysis also suggested that greater dietary vitamin E intakes might protect against PD (2). The apparent discrepancy between vitamin E from foods and from supplements, however, remains unexplained.

The plasma homocysteine concentration has been shown to be inversely associated with the prudent dietary pattern factor in a subgroup of the HPFS (17). In an animal model, folate deficiency and elevated homocysteine significantly sensitized dopaminergic neurons to a subtoxic dose of 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (37). Homocysteine may have a neurotoxic effect by activating the *N*-methyl-D-aspartate receptor, which leads to cell death (38,39), or may be converted into homocysteic acid, which also has an excitotoxic effect on neurons (38,40). Polymorphism of methylenetetrahydrofolate reductase C677T, a major determinant of plasma homocysteine, has been shown to be associated with risk of PD in the Rotterdam Study (41), although no significant association was seen in a case-control study conducted in Germany (42).

Our previous analysis indicated that the prudent dietary pattern or higher AHEI and aMED scores were significantly associated with lower plasma inflammatory biomarker concentrations (18,23), which may further contribute to lower PD risk among individuals with such a diet. Chronic neuroinflammation may play a role in the pathogenesis of PD (43) and we previously reported that the use of a nonsteroidal antiinflammatory drug was associated with a lower risk of PD in this cohort and in another prospective cohort (28,44).

We did not observe a significant association between the Western dietary pattern and risk of PD. The Western dietary pattern has been shown to be significantly associated with high plasma homocysteine and inflammatory biomarkers in the HPFS and NHS (17,18). However, in some case-control studies individuals with PD had significantly lower intakes of meat and eggs than did controls (45,46). A greater intake of red meats or processed meats, which are major dietary sources of purine, has been reported to be associated with higher plasma uric acid concentrations (47). Two prospective studies showed that a higher plasma uric acid concentration was significantly associated with a lower risk of PD (48,49). After further adjustment for a dietary urate index, which reflects the effect of diet on plasma urate, the association between a Western dietary pattern and PD risk became slightly stronger (RR for quintile 5 versus quintile 1 increased from 1.29 to 1.35), although it remained nonsignificant (*P* for trend = 0.4). Furthermore, we cannot exclude the possibility that a lack of association between the Western dietary pattern and PD risk was due to chance. More studies are needed to clarify this.

Because of the prospective design of the study, our results are unlikely to be significantly affected by recall or selection bias. We also carried out several sensitivity analyses that produced similar significant results. Known PD risk factors were adjusted in our analysis; however, we cannot exclude the possibility of residual confounding by unknown risk factors. Moreover, the dietary patterns defined by principal components analysis were data-driven but not established a priori. The prudent pattern, therefore, does not necessarily define an optimal

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

diet. However, similar results were obtained using a priori defined dietary indexes that measured adherence to a healthy diet.

In conclusion, the results of this large prospective study suggest that dietary patterns with a high intake of fruit, vegetables, legumes, whole grains, nuts, fish, and poultry and a low intake of saturated fat and moderate intake of alcohol may protect against PD. The benefits of a plant-based dietary pattern including fish to PD merit further investigation.

References

1. Lang AE, Lozano AM. Parkinson's disease. First of two parts. N Engl J Med 1998;339:1044–53. [PubMed: 9761807]
2. Etminan M, Gill SS, Samii A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. Lancet Neurol 2005;4:362–5. [PubMed: 15907740]
3. Chen H, Zhang SM, Schwarzschild MA, et al. Folate intake and risk of Parkinson's disease. Am J Epidemiol 2004;160:368–75. [PubMed: 15286022]
4. Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD, Checkoway H. Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes. Neurology 2003;60:1761–6. [PubMed: 12796527]
5. Chen H, Zhang SM, Hernan MA, Willett WC, Ascherio A. Diet and Parkinson's disease: a potential role of dairy products in men. Ann Neurol 2002;52:793–801. [PubMed: 12447934]
6. Logroscino G, Marder K, Graziano J, et al. Dietary iron, animal fats, and risk of Parkinson's disease. Mov Disord 1998;13(suppl 1):13–6. [PubMed: 9613713]
7. Zhang SM, Hernan MA, Chen H, Spiegelman D, Willett WC, Ascherio A. Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk. Neurology 2002;59:1161–9. [PubMed: 12391343]
8. Johnson CC, Gorell JM, Rybicki BA, Sanders K, Peterson EL. Adult nutrient intake as a risk factor for Parkinson's disease. Int J Epidemiol 1999;28:1102–9. [PubMed: 10661654]
9. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol 2002;13:3–9. [PubMed: 11790957]
10. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006;59:912–21. [PubMed: 16622828]
11. Jacques PF, Tucker KL. Are dietary patterns useful for understanding the role of diet in chronic disease? Am J Clin Nutr 2001;73:1–2. [PubMed: 11124739]
12. McCullough ML, Feskanich D, Stampfer MJ, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. Am J Clin Nutr 2002;76:1261–71. [PubMed: 12450892]
13. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6. [PubMed: 8320406]
14. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67. [PubMed: 2621022]
15. USDA. UDSA nutrient database for standard reference, release 10: Nutritient Data Laboratory homepage. 1993 [(accessed 4 September 2007)]. Internet: http://www.nal.usda.gov/fnic/foodcomp
16. Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB. Dietary patterns and the risk of coronary heart disease in women. Arch Intern Med 2001;161:1857–62. [PubMed: 11493127]
17. Fung TT, Rimm EB, Spiegelman D, et al. Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. Am J Clin Nutr 2001;73:61–7. [PubMed: 11124751]
18. Lopez-Garcia E, Schulze MB, Fung TT, et al. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2004;80:1029–35. [PubMed: 15447916]
19. Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. Am J Clin Nutr 2000;72:912–21. [PubMed: 11010931]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

20. Hu FB, Rimm E, Smith-Warner SA, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. Am J Clin Nutr 1999;69:243–9. [PubMed: 9989687]
21. 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. [PubMed: 12826634]
22. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. BMJ 1995;311:1457–60. [PubMed: 8520331]
23. Fung TT, McCullough ML, Newby PK, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2005;82:163–73. [PubMed: 16002815]
24. Fung TT, Hu FB, McCullough ML, Newby PK, Willett WC, Holmes MD. Diet quality is associated with the risk of estrogen receptor-negative breast cancer in postmenopausal women. J Nutr 2006;136:466–72. [PubMed: 16424129]
25. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive medications. Circulation 2006;114:160–7. [PubMed: 16818808]
26. Kurth T, Moore SC, Gaziano JM, et al. Healthy lifestyle and the risk of stroke in women. Arch Intern Med 2006;166:1403–9. [PubMed: 16832006]
27. Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA, Speizer FE. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology 2003;60:790–5. [PubMed: 12629235]
28. Chen H, Jacobs E, Schwarzschild MA, et al. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. Ann Neurol 2005;58:963–7. [PubMed: 16240369]
29. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology 1993;4:218–28. [PubMed: 8512986]
30. Millen BE, Quatromoni PA, Gagnon DR, Cupples LA, Franz MM, D'Agostino RB. Dietary patterns of men and women suggest targets for health promotion: the Framingham Nutrition Studies. Am J Health Promot 1996;11:42–52. 52–3. [PubMed: 10163450]
31. Gao X, Wilde PE, Lichtenstein AH, Bermudez OI, Tucker KL. The maximal amount of dietary alpha-tocopherol intake in U.S. adults (NHANES 2001–2002). J Nutr 2006;136:1021–6. [PubMed: 16549468]
32. Gao X, Wilde PE, Lichtenstein AH, Tucker KL. Meeting adequate intake for dietary calcium without dairy foods in adolescents aged 9 to 18 years (National Health and Nutrition Examination Survey 2001–2002). J Am Diet Assoc 2006;106:1759–65. [PubMed: 17081826]
33. Gao X, Wilde PE, Lichtenstein AH, Tucker KL. The 2005 USDA Food Guide Pyramid is associated with more adequate nutrient intakes within energy constraints than the 1992 Pyramid. J Nutr 2006;136:1341–6. [PubMed: 16614427]
34. Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. Nat Rev Drug Discov 2004;3:205–14. [PubMed: 15031734]
35. Rao AV, Balachandran B. Role of oxidative stress and antioxidants in neurodegenerative diseases. Nutr Neurosci 2002;5:291–309. [PubMed: 12385592]
36. Maguire-Zeiss KA, Short DW, Federoff HJ. Synuclein, dopamine and oxidative stress: co-conspirators in Parkinson's disease? Brain Res Mol Brain Res 2005;134:18–23. [PubMed: 15790526]
37. Duan W, Ladenheim B, Cutler RG, Kruman II, Cadet JL, Mattson MP. Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease. J Neurochem 2002;80:101–10. [PubMed: 11796748]
38. Parnetti L, Bottiglieri T, Lowenthal D. Role of homocysteine in age-related vascular and non-vascular diseases. Aging (Milano) 1997;9:241–57. [PubMed: 9359935]
39. Lipton SA, Kim WK, Choi YB, et al. Neurotoxicity associated with dual actions of homocysteine at the *N*-methyl-D-aspartate receptor. Proc Natl Acad Sci U S A 1997;94:5923–8. [PubMed: 9159176]
40. Beal MF, Kowall NW, Swartz KJ, Ferrante RJ. Homocysteic acid lesions in rat striatum spare somatostatin-neuropeptide Y (NADPH-diaphorase) neurons. Neurosci Lett 1990;108:36–42. [PubMed: 1689475]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

41. de Lau LM, Koudstaal PJ, van Meurs JB, Uitterlinden AG, Hofman A, Breteler MM. Methylenetetrahydrofolate reductase C677T genotype and PD. Ann Neurol 2005;57:927–30. [PubMed: 15929053]
42. Wullner U, Kolsch H, Linnebank M. Methylenetetrahydrofolate reductase in Parkinson's disease. Ann Neurol 2005;58:972–3. [PubMed: 16315277]
43. McGeer PL, McGeer EG. Inflammation and neurodegeneration in Parkinson's disease. Parkinsonism Relat Disord 2004;10(suppl 1):S3–7. [PubMed: 15109580]
44. Chen H, Zhang SM, Hernán MA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson's disease. Arch Neurol 2003;60:1059–64. [PubMed: 12925360]
45. Fall PA, Fredrikson M, Axelson O, Granerus AK. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Mov Disord 1999;14:28–37. [PubMed: 9918341]
46. Ma L, Zhang L, Gao XH, et al. Dietary factors and smoking as risk factors for PD in a rural population in China: a nested case-control study. Acta Neurol Scand 2006;113:278–81. [PubMed: 16542169]
47. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2005;52:283–9. [PubMed: 15641075]
48. Davis JW, Grandinetti A, Waslien CI, Ross GW, White LR, Morens DM. Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. Am J Epidemiol 1996;144:480–4. [PubMed: 8781463]
49. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum uric acid levels and the risk of Parkinson disease. Ann Neurol 2005;58:797–800. [PubMed: 16240356]

APPENDIX A Alternate Healthy Eating Index

Component	Criteria	Score
Vegetables	5 servings/d	10; 1 point less for each 10% less than intake required for full score
Fruit	4 servings/d	Same as above
Nuts and soy	1 serving/d	Same as above
Ratio of white to red meat	4	Same as above
Cereal fiber	15 g/d	Same as above
trans Fat	≤0.5% of energy >0.5 but <4% of energy	10 1 point less for each 10% increment in this range
	≥4%	0
Ratio of polyunsaturated to saturated fat	≥1	10; 1 point less for each 10% less than intake required for full score
Long-term multivitamin use	≥5 y	7.5 points for ≥5 y regular use; 2.5 for all others
Alcohol		
	Men: 1.5–2.5 servings/d; women: 0.5–1.5 servings/d	10
	Intake < ideal	1 point less for each 10% less than ideal intake
	Intake > ideal	1 point less for each 10% above ideal intake
	Men: 0 or >3.5 servings/d; women: 0 or >2.5 servings/d	0

APPENDIX B Alternate Mediterranean Diet Score

Component	Criteria for 1 point[1]
Vegetables	Greater than median intake (servings/d)
Legume	Same as above
Fruit	Same as above
Nuts	Same as above
Whole grains	Same as above
Cereal fiber	Same as above
Fish	Same as above
Red and processed meat	Less than median intake (servings/d)
Ratio of monounsaturated to saturated fat	Greater than median intake (servings/d)
Alcohol	5–25 g/d

Component	Criteria for 1 point[1]

[1] 0 points if these criteria are not met.

APPENDIX C Pearson's correlation coefficients for dietary pattern scores and diet quality indexes at baseline in the Health Professionals Follow-Up Study (1986) and the Nurses' Heath Study (1984)

	Western dietary pattern	Alternate Healthy Eating Index	Alternate Healthy Eating Index
Men			
Prudent dietary pattern	−0.08[1]	0.72[1]	0.68[1]
Western dietary pattern		−0.13[1]	−0.12[1]
Alternate Healthy Eating Index			0.81[1]
Women			
Prudent dietary pattern	−0.0001	0.69[1]	0.70[1]
Western dietary pattern		−0.11[1]	−0.04[1]
Alternate Healthy Eating Index			0.76[1]

[1] $P < 0.0001$.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

TABLE 1

Pearson's correlation coefficients for the relation between baseline food intakes and factors representing dietary patterns in the Health Professionals Follow-Up Study (1986) and the Nurses' Health Study (1984)[1]

	Men		Women	
Food	**Factor 1 (prudent)**	**Factor 2 (Western)**	**Factor 1 (prudent)**	**Factor 2 (Western)**
Other vegetables	0.75	—	0.67	—
Leafy vegetables	0.64	—	0.63	—
Yellow vegetables	0.63	—	0.60	—
Cruciferous vegetables	0.63	—	0.61	—
Legumes	0.61	—	0.55	—
Fruit	0.58	—	0.60	—
Tomatoes	0.56	—	0.45	—
Fish	0.51	—	0.50	—
Garlic	0.42	—	0.34	—
Poultry	0.36	—	0.43	—
Whole grains	0.35	—	0.41	—
Red meat	—	0.62	—	0.56
Processed meats	—	0.58	—	0.56
Refined grains	—	0.49	—	0.58
Desserts and sweets	—	0.47	—	0.44
French fries	—	0.46	—	0.47
High-fat dairy products	—	0.44	—	0.36
Eggs	—	0.38	—	—
High-sugar drinks	—	0.39	—	0.34
Snacks	—	0.37	—	—
Condiments	—	0.35	—	0.43
Margarine	—	0.35	—	0.33
Potatoes	—	0.34	—	0.42
Low-fat dairy	—	—	0.35	—
Olive oil	—	—	0.33	
Mayonnaise	—	—	—	0.31
Pizza	—	—	—	0.35

[1] Correlation coefficients <0.3 were omitted for simplicity.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

TABLE 2

Age-adjusted lifestyle characteristics by quintile (Q) of baseline dietary pattern in the Health Professionals Follow-Up Study (1986) and the Nurses' Health Study (1984)[1]

	Prudent dietary pattern				Western dietary pattern			
	Q1	Q3	Q5	*P* for trend	Q1	Q3	Q5	*P* for trend
Men								
Age (y)	52.9 ± 0.1[2]	55.0 ± 0.1	56.0 ± 0.1	<0.001	56.3 ± 0.1	54.7 ± 0.1	53.3 ± 0.1	<0.001
Current smokers (%)	15.0	8.6	5.7	<0.001	5.7	9.0	13.9	<0.001
Past smokers (%)	38.7	42.3	43.2	<0.001	43.9	41.3	40.6	<0.001
BMI (kg/m^2)	25.6 ± 0.03	25.5 ± 0.03	25.4 ± 0.03	<0.001	25.1 ± 0.03	25.5 ± 0.03	25.9 ± 0.03	<0.001
Physical activity (METs/wk)	15.3 ± 0.3	21.0 ± 0.3	28.4 ± 0.3	<0.001	24.9 ± 0.3	20.8 ± 0.3	18.3 ± 0.3	<0.001
Use of NSAIDs (%)	5.6	6.0	5.2	0.22	4.8	5.7	5.9	0.007
Total energy intake (kcal/d)	1691 ± 5.9	1950 ± 5.7	2365 ± 5.8	<0.001	1428 ± 4.4	1903 ± 4.2	2736 ± 4.3	<0.001
Alcohol intake (g/d)	10.8 ± 0.2	11.5 ± 0.2	11.6 ± 0.2	<0.001	10.5 ± 0.2	11.6 ± 0.2	12.1 ± 0.2	<0.001
Caffeine intake (mg/d)	313 ± 2.5	237 ± 2.4	181 ± 2.5	<0.001	216 ± 2.6	247 ± 2.5	243 ± 2.5	<0.001
Dietary α-tocopherol intake (mg/d)	8.6 ± 0.03	10.3 ± 0.03	12.1 ± 0.03	<0.001	11.3 ± 0.03	10.2 ± 0.03	9.8 ± 0.03	<0.001
Dietary vitamin C intake (mg/d)	116 ± 0.7	163 ± 0.7	224 ± 0.7	<0.001	200 ± 0.8	163 ± 0.8	141 ± 0.8	<0.001
Women								
Age (y)	48.8 ± 0.06	50.6 ± 0.06	52.1 ± 0.06	<0.001	52.5 ± 0.06	50.4 ± 0.06	48.8 ± 0.06	<0.001
Current smokers (%)	34.8	22.7	16.8	<0.001	20.1	23.8	27.9	<0.001
Past smokers (%)	25.6	32.6	37.6	<0.001	37.8	31.5	27.5	<0.001
BMI (kg/m^2)	24.9 ± 0.04	25.0 ± 0.04	25.3 ± 0.04	<0.001	24.5 ± 0.04	24.9 ± 0.04	25.7 ± 0.04	<0.001
Physical activity (METs/wk)	10.0 ± 0.2	13.8 ± 0.2	19.7 ± 0.2	<0.001	17.9 ± 0.2	13.5 ± 0.2	11.6 ± 0.2	<0.001
Use of NSAIDs (%)	5.1	5.0	5.6	0.02	5.1	5.0	5.5	0.01
Total energy intake (kcal/d)	1433 ± 3.8	1728 ± 3.8	2095 ± 3.8	<0.001	1233 ± 3.6	1689 ± 4.0	2372 ± 3.9	<0.001
Alcohol intake (g/d)	7.4 ± 0.09	6.8 ± 0.09	6.6 ± 0.09	<0.001	6.9 ± 0.08	7.1 ± 0.09	6.6 ± 0.09	0.03
Caffeine intake (mg/d)	362 ± 1.8	311 ± 1.8	280 ± 1.8	<0.001	299 ± 1.7	317 ± 1.8	328 ± 1.8	<0.001
Dietary α-tocopherol intake (mg/d)	6.6 ± 0.02	7.9 ± 0.02	9.5 ± 0.02	<0.001	8.6 ± 0.02	7.8 ± 0.02	7.5 ± 0.02	<0.001
Dietary vitamin C intake (mg/d)	100 ± 0.5	136 ± 0.4	176 ± 0.4	<0.001	157 ± 0.4	135 ± 0.5	121 ± 0.5	<0.001

[1] METs, metabolic equivalents; NSAIDs, nonsteroidal antiinflammatory drugs. A generalized linear model was used to examine significance for trend for continuous variables; logistic regression was used for categorical variables.

[2] $\bar{x}$ ± SEM (all such values).

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

TABLE 3

Age-adjusted lifestyle characteristics by quintile (Q) of baseline diet quality index in the Health Professionals Follow-Up Study (1986) and the Nurses' Health Study (1984)[1]

	Alternate Healthy Eating Index				Alternate Mediterranean Diet Score			
	Q1	Q3	Q5	*P* for trend	Q1	Q3	Q5	*P* for trend
Men								
Age (y)	53.3 ± 0.1[2]	54.7 ± 0.1	55.8 ± 0.1	<0.001	52.8 ± 0.09	55.0 ± 0.1	56.0 ± 0.1	<0.001
Current smokers (%)	14.9	8.9	4.6	<0.001	15.0	9.4	5.1	<0.001
Past smokers (%)	37.4	42.3	44.8	<0.001	40.0	41.9	43.1	<0.001
BMI (kg/m^2)	26.0 ± 0.03	25.6 ± 0.03	24.9 ± 0.03	<0.001	25.9 ± 0.03	25.6 ± 0.03	25.1 ± 0.03	<0.001
Physical activity (METs/wk)	14.8 ± 0.3	20.0 ± 0.3	30.1 ± 0.3	<0.001	15.3 ± 0.3	19.8 ± 0.3	27.4 ± 0.3	<0.001
Use of NSAIDs (%)	5.6	5.7	5.4	0.22	5.8	5.4	5.2	0.08
Total energy intake (kcal/d)	1692 ± 5.9	1998 ± 5.9	2257 ± 5.9	<0.001	1774 ± 5.9	1954 ± 5.9	2216 ± 5.9	<0.001
Alcohol intake (g/d)	9.7 ± 0.2	11.4 ± 0.2	12.7 ± 0.2	<0.001	12.0 ± 0.2	11.2 ± 0.2	11.4 ± 0.2	<0.001
Caffeine intake (mg/d)	310 ± 2.5	236 ± 2.5	179 ± 2.5	<0.001	305 ± 2.5	243 ± 2.4	183 ± 2.5	<0.001
Dietary α-tocopherol intake (mg/d)	8.5 ± 0.03	10.3 ± 0.03	12.3 ± 0.03	<0.001	8.5 ± 0.03	10.3 ± 0.03	12.0 ± 0.03	<0.001
Dietary vitamin C intake (mg/d)	122 ± 0.8	166 ± 0.8	212 ± 0.8	<0.001	126 ± 0.8	164 ± 0.8	203 ± 0.8	<0.001
Women								
Age (y)	49.3 ± 0.06	50.4 ± 0.06	51.9 ± 0.06	<0.001	49.3 ± 0.05	50.6 ± 0.06	52.0 ± 0.05	<0.001
Current smokers (%)	31.6	23.6	16.4	<0.001	31.0	23.2	16.3	<0.001
Past smokers (%)	23.6	31.8	41.2	<0.001	27.1	32.4	38.1	<0.001
BMI (kg/m^2)	25.7 ± 0.04	25.1 ± 0.04	24.2 ± 0.04	<0.001	25.2 ± 0.04	25.1 ± 0.04	24.7 ± 0.04	<0.001
Physical activity (METs/wk)	9.5 ± 0.2	13.4 ± 0.2	20.1 ± 0.2	<0.001	10.6 ± 0.2	13.7 ± 0.2	18.9 ± 0.2	<0.001
Use of NSAIDs (%)	5.2	4.9	4.9	0.23	5.4	5.1	5.1	0.32
Total energy intake (kcal/d)	1509 ± 4	1741 ± 4	1973 ± 4	<0.001	1537 ± 4	1735 ± 4	1997 ± 4	<0.001
Alcohol intake (g/d)	5.8 ± 0.09	6.9 ± 0.09	7.9 ± 0.09	<0.001	6.7 ± 0.08	7.0 ± 0.09	7.0 ± 0.09	<0.001
Caffeine intake (mg/d)	350 ± 1.8	316 ± 1.8	281 ± 1.8	<0.001	348 ± 1.7	315 ± 1.8	278 ± 1.8	<0.001
Dietary α-tocopherol intake (mg/d)	6.6 ± 0.02	7.8 ± 0.02	9.5 ± 0.02	<0.001	6.7 ± 0.02	8.0 ± 0.02	9.2 ± 0.02	<0.001
Dietary vitamin C intake (mg/d)	100 ± 0.5	137 ± 0.5	171 ± 0.5	<0.001	108 ± 0.4	137 ± 0.5	168 ± 0.5	<0.001

[1] METs, metabolic equivalents; NSAIDs, nonsteroidal antiinflammatory drugs. A generalized linear model was used to examine significance for trend for continuous variables; logistic regression was used for categorical variables.

[2] $\bar{x}$ ± SEM (all such values).

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

TABLE 4

Relative risks (and 95% CIs) of Parkinson disease according to quintile (Q) of dietary pattern score in the Health Professionals Follow-Up Study (1986) and the Nurses' Health Study (1984)[1]

	Dietary pattern factor scores					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***P* for trend**
Prudent pattern						
Men						
n	53	61	73	65	66	0.30
Age- and smoking-adjusted	1	0.92 (0.63, 1.33)	1.00 (0.70, 1.43)	0.87 (0.60, 1.26)	0.84 (0.58, 1.21)	0.08
Multivariate-adjusted[2]	1	0.89 (0.61, 1.30)	0.95 (0.66, 1.37)	0.80 (0.54, 1.17)	0.72 (0.48, 1.07)	
Women						
n	28	40	45	30	47	0.60
Age- and smoking-adjusted	1	1.20 (0.74, 1.94)	1.24 (0.77, 1.99)	0.75 (0.45, 1.26)	1.06 (0.66, 1.70)	0.24
Multivariate-adjusted[2]	1	1.13 (0.69, 1.84)	1.14 (0.70, 1.85)	0.67 (0.39, 1.14)	0.90 (0.53, 1.50)	0.04
Pooled[3]	1	0.97 (0.72, 1.31)	1.01 (0.76, 1.36)	0.75 (0.55, 1.02)	0.78 (0.56, 1.07)	
Western pattern						
Men						
n	57	86	59	62	54	0.73
Age- and smoking-adjusted	1	1.56 (1.12, 2.19)	1.12 (0.78, 1.62)	1.24 (0.86, 1.78)	1.24 (0.85, 1.81)	0.15
Multivariate-adjusted[2]	1	1.70 (1.20, 2.40)	1.29 (0.87, 1.92)	1.50 (0.98, 2.29)	1.68 (1.0, 2.84)	
Women						
n	40	47	39	36	28	0.86
Age- and smoking-adjusted	1	1.32 (0.86, 2.02)	1.24 (0.79, 1.93)	1.23 (0.78, 1.93)	1.08 (0.67, 1.77)	0.67
Multivariate-adjusted[2]	1	1.29 (0.83, 2.00)	1.15 (0.71, 1.87)	1.10 (0.64, 1.90)	0.91 (0.46, 1.81)	0.55
Pooled[3]	1	1.53 (1.16, 2.01)	1.23 (0.91, 1.68)	1.33 (0.96, 1.86)	1.29 (0.71, 2.34)	

[1] Cox proportional hazard models were used to calculate relative risks.

[2] Adjustment for age (in mo), smoking status (never smoker, past smoker, current smoker of 1–14 cigarettes/d, or current smoker of ≥ 15 cigarettes/d), BMI (<23, 23–24.9, 25–26.9, 27–29.9, or ≥30 kg/m^2), use of nonsteroidal antiinflammatory drugs (yes or no), and intakes of total energy (kcal/d), caffeine (quintiles), and alcohol (0, 1–4.9, 5–9.9, 10–14.9, or ≥15 g/d for women; 0, 1–9.9, 10–19.9, 20–29.9, or ≥30 g/d for men).

[3] Based on multivariate models. Random-effects models were used.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

TABLE 5

Relative risks (and 95% CIs) of Parkinson disease according to quintile (Q) of diet-quality score in the Health Professionals Follow-Up Study (1986) and the Nurses' Health Study (1984)[1]

	Diet-quality scores					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***P* for trend**
Alternate Health Eating Index						
Men						
n	60	62	73	60	63	
Age- and smoking-adjusted	1	1.00 (0.69, 1.45)	1.01 (0.70, 1.45)	0.82 (0.57, 1.19)	0.76 (0.52, 1.10)	0.07
Multivariate-adjusted[2]	1	0.98 (0.68, 1.42)	0.98 (0.68, 1.41)	0.77 (0.53, 1.14)	0.68 (0.46, 1.02)	0.02
Women						
n	39	24	47	35	45	
Age- and smoking-adjusted	1	0.58 (0.35, 0.97)	1.05 (0.68, 1.61)	0.71 (0.45, 1.13)	0.82 (0.53, 1.28)	0.62
Multivariate-adjusted[2]	1	0.56 (0.34, 0.94)	0.98 (0.63, 1.51)	0.64 (0.40, 1.03)	0.71 (0.45, 1.13)	0.27
Pooled[3]	1	0.77 (0.45, 1.31)	0.98 (0.74, 1.30)	0.72 (0.53, 0.97)	0.70 (0.51, 0.94)	0.01
Alternate Mediterranean Diet Score						
Men						
n	54	51	65	62	86	
Age- and smoking-adjusted	1	1.03 (0.69, 1.54)	1.16 (0.80, 1.69)	1.09 (0.75, 1.60)	0.90 (0.63, 1.29)	0.55
Multivariate-adjusted[2]	1	1.02 (0.68, 1.52)	1.13 (0.78, 1.65)	1.04 (0.71, 1.54)	0.84 (0.58, 1.22)	0.33
Women						
n	50	31	28	33	48	
Age- and smoking-adjusted	1	0.68 (0.43, 1.06)	0.57 (0.36, 0.91)	0.73 (0.47, 1.13)	0.75 (0.50, 1.12)	0.27
Multivariate-adjusted[2]	1	0.66 (0.42, 1.04)	0.54 (0.33, 0.86)	0.67 (0.42, 1.05)	0.66 (0.43, 1.00)	0.09
Pooled[3]	1	0.83 (0.54, 1.27)	0.79 (0.38, 1.65)	0.85 (0.55, 1.31)	0.75 (0.57, 1.00)	0.07

[1] Cox proportional hazard models were used to calculate relative risks.

[2] Adjustment for age (in mo), smoking status (never smoker, past smoker, current smoker of 1–14 cigarettes/d, or current smoker of ≥ 15 cigarettes/d), BMI (<23, 23–24.9, 25–26.9, 27–29.9, or ≥30 kg/m^2), use of nonsteroidal antiinflammatory drugs (yes/no), and intake of total energy (kcal/d), and caffeine (quintiles).

[3] Based on multivariate models. Random-effects models were used.