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# Vegetable Protein and Fiber from Cereal Are Inversely Associated with the Risk of Hypertension in a Spanish Cohort

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*Background.* Some cross-sectional studies suggest that fiber and protein intake can be associated with lower levels of blood pressure, but results from prospective cohorts are scarce and none have been conducted outside the U.S.

*Methods.* The SUN cohort followed-up prospectively 5880 men and women older than 20 years of age, all university graduates. Dietary information was gathered at baseline with a previously validated semiquantitative food frequency questionnaire. New cases of medically diagnosed hypertension (HT) were identified through responses to a mailed questionnaire after at least 2 years from recruitment.

*Results.* One hundred and eighty new cases of HT were ascertained after a median follow-up of 28 months. After adjustment for potential confounders and several dietary factors, participants in the highest quintile of vegetable protein intake had a lower risk of incident HT compared with those in the lowest quintile (hazard ratio (HR) = 0.5, 95% confidence interval (CI) 0.2−0.9, $p$ for trend = 0.06). Similarly, fiber from cereals was inversely associated with a lower risk of HT (HR comparing fifth vs. first quintile = 0.6, 95% CI 0.3–1.0, $p$ for trend = 0.05). Risk reduction was more important among men and obese and older individuals. Total or animal protein and total fiber as well as fiber from other sources different from cereal were not associated with the risk of HT.

*Conclusions.* In this Mediterranean cohort, dietary intake of vegetable protein and fiber from cereals were associated with a lower risk of HT when other nutrients were also taken into consideration. 

*Key Words:* Fiber, Protein, Hypertension, Prospective studies, Mediterranean diet, Spain.



## Introduction

The most recent statement on the primary prevention of hypertension (HT) published by the National High Blood Pressure Education Program Coordinating Committee accepted the role of some dietary factors in a multifactorial approach for the prevention of this disorder. Nonetheless, it also recognized that further research is still needed. Particularly, the statement that recommends investigating the role of dietary protein and fiber intake in the prevention of HT (1). So far, the effect of both nutrients in the pathogenesis and prevention of this condition remains elusive.

Recently, two meta-analyses of randomized trials have shown that fiber supplementation can exert a small beneficial effect on blood pressure (BP) levels, particularly among hypertensives (2–3). But the trials included in both studies assessed short-term interventions (<6 months). Results from well-conducted cohort studies consistently suggest that fiber, especially from cereals, can reduce the risk of coronary heart disease (4–7), stroke (8,9) and peripheral arterial disease (10,11). A possible mechanism to explain this effect could be a reduction in BP values. But

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prospective studies that have assessed the role of fiber in the incidence of HT are scarce (12–14), failing on occasion to separate the effect of different types of fiber (15), and they have been conducted exclusively in the U.S.

The study of the relationship between protein intake and BP presents similar problems. Most studies have been cross-sectional, did not discriminate between animal and vegetable protein, or did not adjust for potential dietary confounders (15–19).

There are no published results from large prospective studies in Mediterranean countries assessing the role of diet on the development of HT. The high consumption of fruit, vegetables, and cereal in these countries, which also implies a higher between-subject variability, makes them an excellent setting to address the role of dietary fiber and protein, particularly vegetable protein, in the prevention of HT.

The objective of our study was to assess the role of different nutritional factors, especially protein and fiber from different sources, on the risk of incident HT in a cohort of Spanish university graduates.

## Materials and Methods

### *Study Population*

The Seguimiento Universidad de Navarra (SUN, University of Navarra) Follow-up Study is a Mediterranean cohort of university graduates. A detailed description of its methods has been published elsewhere (20). Briefly, beginning in December 1999 an explanatory letter and a mailed questionnaire were sent to all former students of the University of Navarra (Spain), and to members of some Spanish professional associations. The follow-up of those who responded to the initial questionnaire is being carried out through biennial mailed questionnaires. From December 1999 to January 2002, we recruited 9,907 participants. From these, 8,646 (87%) answered the first follow-up questionnaire to July 2004.

For the present analysis we excluded those participants who reported a diagnosis of cancer, cardiovascular disease, or baseline diabetes or were prevalent cases of baseline HT. Those with missing values for any of the variables considered in the analysis or with implausible or extreme caloric intakes ($<$400 or $>$3500 kcal/day for women, and $<$600 or $>$4200 kcal/day for men) were also excluded, thus leaving 5,880 participants available for analysis.

### *Dietary Assessment*

The baseline questionnaire included a semiquantitative food frequency questionnaire, previously validated in a Spanish population (21). This type of dietary questionnaire is a good method for measuring the long-term normal diet (22). The questionnaire asked the frequency of consumption of 136 items in the previous year. There were nine possible answers (ranging from never/almost never to 6+ times per day). For each food, a standard portion size was specified. Nutrient intakes were calculated by multiplying the frequency of consumption by the nutrient content of the specified portion, using data from Spanish food composition tables (23,24).

### *Other Covariate Assessments*

The baseline assessment also included questions to gather information about certain anthropometric measures (weight, height), lifestyle factors (smoking, physical activity), and clinical variables (family history of HT and cardiovascular disease, previous history of cancer, diabetes, hypercholesterolemia, use of medication). The validity of self-reported weight to compute body mass index (BMI) was assessed in a subsample of the cohort (25). The mean relative error in self-reported weight was 1.45% (95% CI: 0.86–2.03%). The correlation coefficient between measured and self-reported weight was 0.991 (95% CI: 0.986–0.994) and the weighted kappa statistic for BMI categories ($<$25, $\geq$25 and $<$30, and $\geq$30) was 0.98 (95% CI 0.84, 0.99).

The physical activity questionnaire inquired about the participation in 17 different activities. We assigned a multiple of resting metabolic rate [metabolic equivalent (MET) score] to each of these activities using previously published guidelines to quantify the average intensity of physical activity (26,27). The MET index of each activity was multiplied by the weekly time spent in each activity obtaining a value of overall weekly MET-hours for each participant. This variable represented the individual's volume and intensity of leisure-time physical activity. In a validation study there was a highly significant correlation between physical activity objectively measured through an accelerometer and the overall weekly MET-hours assessed using our questionnaire ($r = 0.51$, $p < 0.001$) (28).

### *Outcome Ascertainment*

Prevalent cases of HT at baseline were defined as those individuals reporting a medical diagnosis of HT in the initial questionnaire, taking anti-hypertensive medication (diuretics, beta-blockers, calcium antagonists, ACE inhibitors, other antihypertensive medication), or that reported a systolic BP $\geq$140 mmHg and/or diastolic BP $\geq$90 mmHg.

The follow-up questionnaire included the following question 'Since you completed the first questionnaire, have you received for the first time a medical diagnosis of hypertension?' and the approximate date (month and year) of the diagnosis. There was also a question asking whether the individual has her/his BP measured in the period between the completion of both questionnaires. We considered that a participant was an incident case of HT when she or he reported a diagnosis of HT in the follow-up questionnaire but was not hypertensive at baseline.

We carried out a validation study to determine the quality of the self-reported diagnosis of HT (29). Briefly, two study physicians (AA, JJB) performed two BP measures in a random sample of 127 participants in our cohort from the metropolitan area of Pamplona (Navarra, Spain). This study confirmed 82% (95% CI 73–93%) of the self-reported HT cases and 85% (95% CI 72–89%) of the self-reported normotensives. Other validation studies of self-reported HT have produced similar results (30,31). Self-reported information about a medical diagnosis of HT was used as a reliable outcome in previous epidemiologic studies that included highly educated participants (12,13,32).

### *Statistical Analysis*

Intake of each nutrient was adjusted for total energy intake using the residuals method. We applied separate models to adjust for energy among women and men (22). Energy-adjusted intake of a nutrient is computed using the residuals from a regression model in which the total energy intake is the independent variable and the intake of the particular nutrient is the dependent variable. The residuals represent the difference between the observed intake of the particular nutrient and the expected intake according to the individual energy intake of each participant. They are added to the expected intake of the nutrient if total energy intake is set at the mean of the sample.

We categorized each energy-adjusted nutrient using quintiles as cut-off points. In all statistical models, quintiles of nutrient intake were introduced as categorical variables, with the quintile corresponding to the lowest intake as the reference category. Linear trends were assessed assigning the median value to each quintile and modeling these values as a continuous variable.

Person-time of follow-up was computed for each participant in the cohort from the date of reception of the baseline questionnaire to the date of HT diagnosis or date of reception of the follow-up questionnaire, whichever occurred first. We used Cox proportional hazard models to assess the association between nutrient intake and the incidence of HT, adjusting for multiple known and potential risk factors of hypertension. For each nutrient, we ran an initial model including only age and sex as covariates. Next, we included in the model the following variables: BMI (with both a linear and a quadratic term), physical activity (4 categories), smoking (never/past/current smoker), alcohol consumption (5 categories), sodium intake (5 categories), total energy intake (continuous) and personal history of hypercholesterolemia (yes/no). Finally, to adjust for other dietary factors, we included in the model quintiles for the consumption of each of the following foods and nutrients: fruit, vegetables, low-fat dairy, potassium, magnesium, fiber, caffeine, saturated fatty acids, and monounsaturated fatty acids.

To assess the potential interaction (effect modification) between each nutrient and age, gender or BMI, we repeated the analysis after stratifying by gender, age ($<40$, $\geq 40$ years) and BMI ($<25$, $\geq 25$ kg/m$^2$). Statistical interactions between these variables and the nutrient of interest were evaluated through the likelihood ratio test comparing a model with a multiplicative term between both variables and a model without this term.

Finally, we ran a stepwise multiple linear regression model with cereal fiber intake as dependent variable and all food items that supplied cereal fiber as independent variables, to determine the main sources of this nutrient.

All $p$ values are two-tailed. Statements about statistical significance refer to the 0.05 cutoff.

## Results

We included initially 9,907 participants in the baseline assessment of diet and other risk factors. From these, 1,045 were prevalent cases of HT, 813 reported a history of cardiovascular disease, cancer or diabetes, 1,018 were below or above the limits of caloric intake, and 784 had missing values for one or more potential confounding variable, with some participants included in more than one of these categories. Finally, 6,686 individuals were considered in the initial cohort; 5,880 (88%) answered the 2-year follow-up questionnaire. Table 1 shows the distribution of selected variables in the study population and among those ($n$ = 806) who were not prevalent cases of HT but did not respond to the follow-up questionnaire (lost to follow-up).

Total carbohydrates, glycemic load, protein and fat intake, and intake of different types of fat were not associated with the risk of HT when we took into consideration multiple potential confounding variables (Tables 2–5). Protein from vegetable sources but not total or animal protein was inversely associated with the risk of HT. The hazard ratio (HR) of HT among those with the highest intake of vegetable protein compared with those in the lowest intake category was 0.5 (95% confidence interval (CI): 0.2–0.9, $p$ for linear trend: 0.06) (Tables 2–5). When we additionally adjusted for folate intake, the estimates for vegetable protein did not substantially change (HR of HT in the fifth quintile compared with the first quintile 0.4, 95% CI 0.2–0.9, $p$ for trend 0.05).

Total fiber intake and fiber from fruits or vegetables were not associated with the risk of HT. However, fiber from cereals was associated with a statistically significant reduction in the risk of HT (HR highest vs. lowest quintile of cereal fiber intake 0.6, 95% CI 0.3–1.0), with a significant liner trend ($p$ = 0.05), suggesting a possible dose-response relationship (Tables 6 and 7). In this population, the main sources of fiber from cereals were whole grain bread (66% of total variability in cereal fiber intake), and white bread (27%).

In Table 8 we show the association between fiber from cereals or vegetable protein and HT stratified according

**Table 1.** Baseline characteristics of the SUN participants

| | Followed up | | Lost to follow-up | | *p* value* | |
|---|---|---|---|---|---|---|
| | Women (*n* = 3604) | Men (*n* = 2276) | Women (*n* = 510) | Men (*n* = 296) | Women | Men |
| Age (years) | 33.8 (9.8) | 38.9 (11.5) | 31.1 (9.7) | 36.0 (11.4) | <0.001 | <0.001 |
| BMI (kg/m$^2$) | 21.8 (2.8) | 25.1 (2.9) | 21.7 (3.1) | 25.4 (3.2) | 0.25 | 0.10 |
| Physical activity (MET-h/week) | 14.0 (17.0) | 21.2 (25.3) | 15.7 (21.1) | 21.8 (28.0) | 0.08 | 0.73 |
| Hypercholesterolemia (%) | 9.9 | 17.5 | 6.5 | 15.2 | 0.01 | 0.32 |
| Smoking status (%) | | | | | 0.03 | 0.03 |
| Never | 49.3 | 44.4 | 45.3 | 45.3 | | |
| Former | 27.8 | 27.1 | 33.5 | 32.8 | | |
| Current | 22.9 | 28.5 | 21.2 | 22.0 | | |
| Total energy intake (kcal/day) | 2,321 (573) | 2,527 (704) | 2,273 (632) | 2.529 (718) | 0.10 | 0.97 |
| Protein (% energy intake) | 18.2 (3.4) | 17.6 (3.3) | 18.4 (3.9) | 17.6 (3.2) | 0.14 | 0.79 |
| Carbohydrates (% energy intake) | 43.0 (7.3) | 42.9 (7.5) | 43.4 (7.4) | 41.7 (7.2) | 0.21 | 0.008 |
| Total fat (% energy intake) | 37.7 (6.6) | 36.7 (6.3) | 36.9 (6.8) | 37.7 (6.4) | 0.02 | 0.007 |
| Saturated fatty acids (% energy intake) | 12.8 (3.1) | 12.9 (3.3) | 12.6 (3.3) | 13.3 (3.2) | 0.22 | 0.05 |
| Monounsaturated fatty acids (% energy intake) | 16.3 (3.9) | 15.6 (3.4) | 15.6 (3.8) | 15.9 (3.5) | <0.001 | 0.08 |
| Intake of | | | | | | |
| Alcohol (g/day) | 3.8 (5.8) | 9.9 (12.4) | 3.8 (5.3) | 10.3 (13.3) | 0.84 | 0.57 |
| Sodium (g/day) | 3.2 (2.5) | 3.9 (2.6) | 3.1 (1.9) | 3.9 (2.2) | 0.51 | 0.93 |
| Potassium (g/day) | 4.7 (1.5) | 4.6 (1.6) | 4.8 (1.7) | 4.5 (1.5) | 0.41 | 0.40 |
| Magnesium (mg/day) | 408.2 (118.8) | 412.6 (128.6) | 409.6 (135.1) | 405.5 (129.2) | 0.82 | 0.37 |
| Fiber (g/day) | 27.3 (11.7) | 25.9 (12.1) | 27.4 (13.0) | 24.4 (11.2) | 0.92 | 0.06 |
| Caffeine (mg/day) | 44.8 (39.3) | 46.5 (43.2) | 47.1 (41.0) | 44.5 (38.3) | 0.21 | 0.41 |
| Fruit (g/day) | 343.1 (287.1) | 290.9 (277.3)) | 359.0 (306.6) | 258.2 (228.0) | 0.27 | 0.05 |
| Vegetable (g/day) | 543.1 (316.5) | 457.3 (306.5) | 551.4 (353.9) | 426.3 (279.3) | 0.61 | 0.10 |
| Low-fat dairy (g/day) | 238.3 (254.4) | 152.2 (222.3) | 263.0 (265.0) | 158.3 (238.8) | 0.04 | 0.66 |

Values are expressed as mean (standard deviation) unless otherwise stated. BMI: body mass index.
*Comparison between followed-up and lost to follow up participants. $\chi^2$ test for categorical variables and Student's t-test for continuous variables.

to gender, age, and body mass index (BMI). For both vegetable protein and cereal fiber, the inverse association with HT was stronger among older than younger people, among men than women, and only for vegetable protein, among obese/overweight than among lean participants. But none of the interaction terms was statistically significant.

Finally, when we repeated the analysis including only those individuals who had their BP measured in the period between both questionnaires, the results were essentially the same (data not shown).

## Discussion

In this prospective Mediterranean cohort conducted in Spain, vegetable protein and fiber from cereal were inversely associated with the risk of HT, but only after taking into consideration multiple confounding factors. Fiber from other sources different from cereals and animal protein did not show any association with the incidence of HT. The inverse associations found for vegetable protein and cereal fiber were stronger among men, among older people, and among obese/overweight participants, i.e., those with a higher baseline risk. However, we were not able to show any statistically significant interaction (i.e., effect modification) for these differences.

Our study had potential limitations. First, the diet was evaluated using a food-frequency questionnaire. Although this questionnaire has been previously validated (21) and successfully used in other epidemiological studies (33), a certain degree of misclassification always occurs. However, usually this misclassification is non-differential resulting in risk estimates biased towards the null value. Then, the observed relationship between vegetable protein and fiber from cereals could not be explained through this source of error. But the lack of association between HT and other macronutrients or different sources of fiber can be a consequence of this nondifferential misclassification bias. Another limitation was the possible lack of statistical power. Again, this problem could not explain the observed associations but can account for the negative results for some of the other assessed nutrients.

Finally, our outcome was based in self-reported information. In the baseline questionnaire, we gathered information on usual BP values and a previous medical diagnosis of HT. Similarly, in the follow-up questionnaire we asked for a new medical diagnosis of HT. This ascertainment method could introduce misclassification error but, as we have explained in the Methods section and published elsewhere (29), both diagnosis of HT and values of BP based on the mailed questionnaires had adequate validity in this highly educated population (all participants were university

**Table 2.** Hazard ratios (95% confidence intervals) of hypertension according to quintiles of macronutrient (protein) intake in the SUN Cohort

| | Q1 | Q2 | Q3 | Q4 | Q5 | *p* for trend |
|---|---|---|---|---|---|---|
| Total protein intake | | | | | | |
| Cases of HT | 37 | 39 | 31 | 32 | 41 | |
| Person-years | 2,750.5 | 2,719.1 | 2,706.5 | 2,686.8 | 2,663.1 | |
| Age- and sex-adjusted HR | 1 (ref.) | 1.0 (0.6–1.6) | 0.8 (0.5–1.2) | 0.8 (0.5–1.2) | 0.9 (0.6–1.4) | 0.51 |
| Multivariate 1 HR | 1 (ref.) | 0.9 (0.6–1.5) | 0.7 (0.4–1.1) | 0.7 (0.4–1.1) | 0.8 (0.5–1.2) | 0.18 |
| Multivariate 2 HR | 1 (ref.) | 0.9 (0.6–1.5) | 0.7 (0.4–1.2) | 0.7 (0.4–1.1) | 0.8 (0.4–1.4) | 0.26 |
| Vegetable protein intake | | | | | | |
| Cases of HT | 34 | 25 | 40 | 35 | 46 | |
| Person-years | 2,722.3 | 2,727.1 | 2,721.6 | 2,709.2 | 2,645.7 | |
| Age- and sex-adjusted HR | 1 (ref.) | 0.6 (0.4–1.0) | 1.0 (0.6–1.5) | 0.7 (0.4–1.2) | 0.8 (0.5–1.2) | 0.46 |
| Multivariate 1 HR | 1 (ref.) | 0.6 (0.3–1.0) | 1.0 (0.6–1.5) | 0.7 (0.4–1.1) | 0.8 (0.5–1.2) | 0.57 |
| Multivariate 2 HR | 1 (ref.) | 0.5 (0.3–0.9) | 0.8 (0.5–1.4) | 0.5 (0.3–1.0) | 0.5 (0.2–0.9) | 0.06 |
| Animal protein intake | | | | | | |
| Cases of HT | 39 | 41 | 32 | 29 | 39 | |
| Person-years | 2,723.6 | 2,723.6 | 2,691.0 | 2,707.0 | 2,680.7 | |
| Age- and sex-adjusted HR | 1 (ref.) | 1.1 (0.7–1.7) | 0.9 (0.6–1.4) | 0.8 (0.5–1.3) | 1.1 (0.7–1.6) | 0.84 |
| Multivariate 1 HR | 1 (ref.) | 1.0 (0.7–1.6) | 0.8 (0.5–1.3) | 0.7 (0.4–1.1) | 0.9 (0.6–1.4) | 0.35 |
| Multivariate 2 HR | 1 (ref.) | 1.1 (0.7–1.8) | 0.9 (0.5–1.5) | 0.8 (0.4–1.3) | 1.0 (0.6–1.8) | 0.70 |

HT: hypertension; HR: hazard ratio.
Multivariate 1: Adjusted for age (continuous variable), sex, BMI (linear and quadratic term), physical activity (4 categories), alcohol consumption (5 categories), sodium intake (5 categories), total energy intake (continuous variable), smoking (never smokers, former smokers, current smokers), hypercholesterolemia (yes/no).
Multivariate 2: Additionally adjusted for fruit, vegetable, fiber, caffeine, magnesium, potassium, low-fat dairy, MUFA, and SFA intake (quintiles).

graduates and 48% were health professionals). Similarly, other studies conducted in populations with a high educational level have relied on the self-reported diagnosis of HT (12,13,32).

On the other hand, this study had several strengths. Its prospective design precluded changes in diet as a consequence of high BP values, a potential problem in cross-sectional studies. Assessment of diet and other potential confounding factors was carried out using validated and extensive questionnaires. The high level of education in our cohort (all participants were university graduates) increased the internal validity of the study and probably improved the quality of self-reported data.

Dietary protein has been associated with lower BP values in several cross-sectional studies (19,34,35). However, evidence from prospective studies is scarce. In the prospective Chicago Western Electric Study, a higher consumption of vegetable protein was inversely associated with changes in BP during follow-up. But their results were not adjusted for potassium or magnesium, which are nutrients correlated with vegetable protein that can also induce a reduction in BP and in the risk of HT (17). The CARDIA

**Table 3.** Hazard ratios (95% confidence intervals) of hypertension according to quintiles of macronutrient (carbohydrate) intake in the SUN Cohort

| | Q1 | Q2 | Q3 | Q4 | Q5 | *p* for trend |
|---|---|---|---|---|---|---|
| Total carbohydrate intake | | | | | | |
| Cases of HT | 28 | 29 | 44 | 38 | 41 | |
| Person-years | 2,717.2 | 2,713.3 | 2,696.0 | 2,703.3 | 2,696.3 | |
| Age- and sex-adjusted HR | 1 (ref.) | 0.9 (0.5–1.5) | 1.2 (0.8–2.0) | 0.9 (0.5–1.4) | 0.8 (0.5–1.3) | 0.30 |
| Multivariate 1 HR | 1 (ref.) | 0.9 (0.5–1.5) | 1.2 (0.7–2.0) | 0.9 (0.5–1.5) | 0.9 (0.5–1.5) | 0.57 |
| Multivariate 2 HR | 1 (ref.) | 0.9 (0.5–1.6) | 1.2 (0.7–2.2) | 1.0 (0.5–1.8) | 0.8 (0.4–1.7) | 0.60 |
| Glycemic load | | | | | | |
| Cases of HT | 26 | 40 | 35 | 38 | 41 | |
| Person-years | 2,719.7 | 2,653.7 | 2,726.0 | 2,729.5 | 2,697.0 | |
| Age- and sex-adjusted HR | 1 (ref.) | 1.4 (0.9–2.3) | 1.1 (0.7–1.8) | 1.0 (0.6–1.7) | 0.9 (0.6–1.5) | 0.30 |
| Multivariate 1 HR | 1 (ref.) | 1.4 (0.9–2.3) | 1.1 (0.6–1.8) | 1.0 (0.6–1.7) | 1.0 (0.6–1.7) | 0.55 |
| Multivariate 2 HR | 1 (ref.) | 1.4 (0.9–2.5) | 1.1 (0.6–1.9) | 1.0 (0.5–1.9) | 0.9 (0.4–1.8) | 0.38 |

HT: hypertension; HR: hazard ratio
Multivariate 1: Adjusted for age (continuous variable), sex, BMI (linear and quadratic term), physical activity (4 categories), alcohol consumption (5 categories), sodium intake (5 categories), total energy intake (continuous variable), smoking (never smokers, former smokers, current smokers), hypercholesterolemia (yes/no).
Multivariate 2: Additionally adjusted for fruit, vegetable, fiber, caffeine, magnesium, potassium, low-fat dairy, MUFA, and SFA intake (quintiles).

**Table 4.** Hazard ratios (95% confidence intervals) of hypertension according to quintiles of macronutrient (fat) intake in the SUN Cohort

| | Q1 | Q2 | Q3 | Q4 | Q5 | *p* for trend |
|---|---|---|---|---|---|---|
| Total fat intake | | | | | | |
| Cases of HT | 41 | 26 | 38 | 38 | 37 | |
| Person-years | 2,692.0 | 2,692.4 | 2,690.3 | 2,728.2 | 2,723.1 | |
| Age- and sex-adjusted HR | 1 (ref.) | 0.7 (0.4–1.1) | 1.0 (0.6–1.5) | 1.0 (0.6–1.5) | 1.0 (0.6–1.6) | 0.68 |
| Multivariate 1 HR | 1 (ref.) | 0.7 (0.4–1.2) | 0.9 (0.6–1.5) | 0.9 (0.6–1.5) | 1.0 (0.6–1.6) | 0.73 |
| Multivariate 2 HR | 1 (ref.) | 0.7 (0.4–1.1) | 0.9 (0.5–1.4) | 0.8 (0.5–1.3) | 0.9 (0.5–1.4) | 0.75 |
| Saturated fat intake | | | | | | |
| Cases of HT | 39 | 33 | 30 | 40 | 38 | |
| Person-years | 2,675.7 | 2,690.8 | 2,724.3 | 2,717.2 | 2,717.9 | |
| Age- and sex-adjusted HR | 1 (ref.) | 0.9 (0.6–1.5) | 0.8 (0.5–1.4) | 1.1 (0.7–1.7) | 1.1 (0.7–1.8) | 0.48 |
| Multivariate 1 HR | 1 (ref.) | 0.9 (0.5–1.4) | 0.8 (0.5–1.3) | 1.1 (0.7–1.8) | 1.2 (0.7–1.8) | 0.36 |
| Multivariate 2 HR | 1 (ref.) | 0.8 (0.5–1.3) | 0.8 (0.5–1.3) | 1.0 (0.6–1.7) | 1.0 (0.6–1.7) | 0.68 |
| Monounsaturated fat intake | | | | | | |
| Cases of HT | 37 | 31 | 37 | 38 | 37 | |
| Person-years | 2,703.9 | 2,705.9 | 2,676.6 | 2,730.1 | 2,709.4 | |
| Age- and sex-adjusted HR | 1 (ref.) | 0.8 (0.5–1.4) | 1.0 (0.6–1.6) | 1.0 (0.7–1.6) | 1.0 (0.6–1.6) | 0.79 |
| Multivariate 1 HR | 1 (ref.) | 0.8 (0.5–1.4) | 1.0 (0.6–1.5) | 1.0 (0.6–1.6) | 1.0 (0.6–1.6) | 0.92 |
| Multivariate 2 HR | 1 (ref.) | 0.8 (0.5–1.4) | 0.9 (0.5–1.4) | 0.9 (0.6–1.5) | 0.8 (0.5–1.4) | 0.64 |

HT: hypertension; HR: hazard ratio

Multivariate 1: Adjusted for age (continuous variable), sex, BMI (linear and quadratic term), physical activity (4 categories), alcohol consumption (5 categories), sodium intake (5 categories), total energy intake (continuous variable), smoking (never smokers, former smokers, current smokers), hypercholesterolemia (yes/no).

Multivariate 2: Additionally adjusted for fruit, vegetable, fiber, caffeine, magnesium, potassium, and low-fat dairy intake (quintiles).

cohort of relatively young Americans did not find any association between dietary protein and HT. However, the possible different roles of animal and vegetable protein were not assessed (15). Finally, the Dietary Intervention Study in Children that followed-up 662 children aged 8–11 years with elevated low-density lipoprotein cholesterol for 3 years found an inverse association between protein intake and increase in BP, but the relationship disappeared after adjusting for other dietary factors (36). The role of dietary protein has also been studied in some clinical trials, but most of them had small sample size with a limited duration or were conducted exclusively among hypertensive patients (37). All these factors could restrict the applicability of their results to the general population.

Two recent meta-analyses have suggested a beneficial effect of fiber supplementation on BP, particularly among hypertensive individuals (2,3). However, the length of the intervention in the analyzed trials was $<24$ weeks in all cases. Hence, it is not possible to derive from these studies the longer-term effect of fiber intake. Nonetheless, there are several observational studies that have linked a high consumption of fiber, especially from cereals, with a lower risk of cardiovascular disease (4–11). Moreover, fiber has been associated with a lower risk of HT or lower levels of BP in some prospective studies (12,13,15). So far, there has been no available prospective information about the role of fiber on the risk of HT obtained in populations outside the U.S.

Little is known about the mechanisms through which fiber could reduce the risk of HT.

Dietary fiber has been shown to reduce insulin resistance (38) and this, in turn, could curtail increases in BP. In fact, cereal fiber was associated with a lower prevalence of the

**Table 5.** Hazard ratios (95% confidence intervals) of hypertension according to quintiles of macronutrient (polyunsaturated fat) intake in the SUN Cohort

| Polyunsaturated fat intake | Q1 | Q2 | Q3 | Q4 | Q5 | P for trend |
|---|---|---|---|---|---|---|
| Cases of HT | 30 | 32 | 38 | 49 | 31 | |
| Person-years | 2,698.5 | 2,701.3 | 2,692.2 | 2,729.1 | 2,704.8 | |
| Age and sex adjusted HR | 1 (ref.) | 1.1 (0.7–1.8) | 1.1 (0.7–1.8) | 1.3 (0.8–2.0) | 0.9 (0.5–1.5) | 0.85 |
| Multivariate 1 HR | 1 (ref.) | 1.0 (0.6–1.7) | 1.0 (0.6–1.7) | 1.3 (0.8–2.0) | 0.9 (0.6–1.5) | 0.93 |
| Multivariate 2 HR | 1 (ref.) | 1.0 (0.6–1.7) | 1.0 (0.6–1.7) | 1.2 (0.7–2.0) | 0.9 (0.5–1.5) | 0.69 |

HT: hypertension; HR: hazard ratio

Multivariate 1: Adjusted for age (continuous variable), sex, BMI (linear and quadratic term), physical activity (4 categories), alcohol consumption (5 categories), sodium intake (5 categories), total energy intake (continuous variable), smoking (never smokers, former smokers, current smokers), hypercholesterolemia (yes/no).

Multivariate 2: Adjusted additionally for fruit, vegetable, fiber, caffeine, magnesium, potassium, and low-fat dairy intake (quintiles).

**Table 6.** Hazard ratios (95% confidence intervals) of hypertension according to quintiles of total fiber and fiber from different sources in the SUN cohort

| | Q1 | Q2 | Q3 | Q4 | Q5 | *p* for trend |
|---|---|---|---|---|---|---|
| Total fiber intake | | | | | | |
| Cases of HT | 30 | 33 | 32 | 42 | 43 | |
| Person-years | 2,764.3 | 2,737.1 | 2,704.3 | 2,684.3 | 2,636.0 | |
| Age- and sex-adjusted HR | 1 (ref.) | 1.0 (0.6–1.7) | 0.9 (0.5–1.4) | 1.1 (0.7–1.8) | 1.0 (0.6–1.6) | 0.88 |
| Multivariate 1 HR | 1 (ref.) | 1.0 (0.6–1.6) | 0.8 (0.5–1.4) | 1.1 (0.7–1.8) | 1.0 (0.6–1.7) | 0.73 |
| Multivariate 2 HR | 1 (ref.) | 1.2 (0.7–2.2) | 1.0 (0.5–2.0) | 1.2 (0.6–2.5) | 1.2 (0.5–3.0) | 0.88 |
| Fiber from fruit sources | | | | | | |
| Cases of HT | 26 | 45 | 32 | 41 | 36 | |
| Person-years | 2,717.2 | 2,761.2 | 2,706.3 | 2,667.5 | 2,673.8 | |
| Age- and sex-adjusted HR | 1 (ref.) | 1.5 (0.9–2.4) | 1.0 (0.6–1.7) | 1.2 (0.7–2.0) | 1.0 (0.6–1.7) | 0.44 |
| Multivariate 1 HR | 1 (ref.) | 1.4 (0.9–2.4) | 1.0 (0.6–1.7) | 1.2 (0.7–2.0) | 1.0 (0.6–1.7) | 0.48 |
| Multivariate 2 HR | 1 (ref.) | 1.2 (0.5–2.9) | 0.8 (0.3–2.5) | 1.5 (0.4–5.3) | 1.8 (0.4–7.7) | 0.36 |
| Fiber from cereal sources | | | | | | |
| Cases of HT | 36 | 32 | 38 | 42 | 32 | |
| Person-years | 2,689.2 | 2,725.0 | 2,697.8 | 2,699.2 | 2,714.8 | |
| Age- and sex-adjusted HR | 1 (ref.) | 0.9 (0.5–1.4) | 0.9 (0.6–1.4) | 0.9 (0.6–1.4) | 0.7 (0.4–1.1) | 0.19 |
| Multivariate 1 HR | 1 (ref.) | 0.9 (0.5–1.4) | 0.9 (0.5–1.4) | 0.9 (0.6–1.4) | 0.7 (0.4–1.1) | 0.18 |
| Multivariate 2 HR | 1 (ref.) | 0.9 (0.5–1.4) | 0.8 (0.5–1.3) | 0.8 (0.5–1.4) | 0.6 (0.3–1.0) | 0.05 |

HT: hypertension; HR: hazard ratio

Multivariate 1: Adjusted for age (continuous variable), sex, BMI (linear and quadratic term), physical activity (4 categories), alcohol consumption (5 categories), sodium intake (5 categories), total energy intake (continuous variable), smoking (never smokers, former smokers, current smokers), hypercholesterolemia (yes/no).

Multivariate 2: Additionally adjusted for fruit, vegetable, caffeine, magnesium, potassium, low-fat dairy, MUFA, and SFA intake (quintiles).

metabolic syndrome in the Framingham Offspring Cohort Study (39). Similarly, how dietary protein affect BP values is largely unknown. It has been hypothesized that protein intake could result in higher concentrations of some amino acids that could have a favorable effect on BP (40). Folate and vegetable protein intake are highly correlated, and folate intake has been recently associated with a lower risk of HT in the Nurses' Health Study I and II (32). However, when we additionally adjusted for folate intake, risk estimates did not change, suggesting that this micronutrient was not the element mainly responsible for the observed association. Nonetheless, it is not possible to rule out completely the possibility of residual confounding by other nutrients associated with both vegetable protein intake and the risk of HT.

In conclusion, we have observed in a prospectively followed-up Mediterranean population that vegetable protein and fiber from cereals are inversely associated with the risk of developing HT. Interestingly, the risk reduction was only apparent when we took into consideration other dietary factors.

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**Table 7.** Hazard ratios (95% confidence intervals) of hypertension according to quintiles of total fiber and fiber from vegetable sources intake in the SUN Cohort

| Fiber from vegetable sources | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend |
|---|---|---|---|---|---|---|
| Cases of HT | 42 | 29 | 31 | 36 | 42 | |
| Person-years | 2,726.7 | 2,733.2 | 2,731.9 | 2,669.4 | 2,664.8 | |
| Age and sex adjusted HR | 1 (ref.) | 0.7 (0.4–1.1) | 0.7 (0.4–1.1) | 0.8 (0.5–1.3) | 0.9 (0.6–1.5) | 0.68 |
| Multivariate 1 HR | 1 (ref.) | 0.7 (0.4–1.1) | 0.7 (0.4–1.1) | 0.9 (0.5–1.3) | 0.9 (0.6–1.4) | 0.78 |
| Multivariate 2 HR | 1 (ref.) | 0.8 (0.4–1.5) | 0.7 (0.3–1.6) | 0.7 (0.2–1.8) | 0.7 (0.2–2.1) | 0.70 |

HT: hypertension; HR: hazard ratio

Multivariate 1: Adjusted for age (continuous variable), sex, BMI (linear and quadratic term), physical activity (4 categories), alcohol consumption (5 categories), sodium intake (5 categories), total energy intake (continuous variable), smoking (never smokers, former smokers, current smokers), hypercholesterolemia (yes/no).

Multivariate 2: Additionally adjusted for fruit, vegetable, caffeine, magnesium, potassium, low-fat dairy, MUFA, and SFA intake (quintiles).

**Table 8.** Hazard ratios (95% confidence intervals) of hypertension according to categories of vegetable protein and fiber from cereals in the SUN cohort, stratified by age, sex, and body mass index

| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend | *P* for interaction |
|---|---|---|---|---|---|---|---|
| Vegetable protein | | | | | | | |
| Gender | | | | | | | |
| Women | 1 (ref.) | 1.0 (0.4–2.4) | 1.2 (0.4–3.1) | 0.6 (0.2–1.9) | 0.9 (0.3–3.0) | 0.71 | 0.07 |
| Men | 1 (ref.) | 0.3 (0.1–0.7) | 0.5 (0.3–1.1) | 0.4 (0.2–0.9) | 0.3 (0.1–0.8) | 0.04 | |
| Age | | | | | | | |
| <40 years old | 1 (ref.) | 0.9 (0.4–2.0) | 1.2 (0.5–2.8) | 0.6 (0.2–1.7) | 0.9 (0.3–2.9) | 0.77 | 0.18 |
| ≥40 years old | 1 (ref.) | 0.3 (0.1–0.7) | 0.6 (0.3–1.2) | 0.4 (0.2–0.9) | 0.3 (0.1–0.7) | 0.02 | |
| BMI | | | | | | | |
| <25 kg/m$^2$ | 1 (ref.) | 0.7 (0.3–1.6) | 0.8 (0.3–1.8) | 0.4 (0.1–1.0) | 0.8 (0.3–2.1) | 0.54 | 0.24 |
| ≥25 kg/m$^2$ | 1 (ref.) | 0.4 (0.2–0.9) | 0.7 (0.3–1.6) | 0.6 (0.2–1.3) | 0.3 (0.1–0.8) | 0.03 | |
| Cereal fiber | | | | | | | |
| Gender | | | | | | | |
| Women | 1 (ref.) | 0.9 (0.4–2.1) | 0.9 (0.4–2.2) | 1.0 (0.4–2.3) | 0.6 (0.3–1.5) | 0.32 | 0.61 |
| Men | 1 (ref.) | 0.9 (0.5–1.6) | 0.7 (0.4–1.4) | 0.7 (0.4–1.4) | 0.5 (0.2–1.0) | 0.04 | |
| Age | | | | | | | |
| <40 years old | 1 (ref.) | 0.7 (0.3–1.6) | 1.1 (0.5–2.3) | 1.6 (0.7–3.4) | 0.7 (0.3–1.8) | 0.88 | 0.29 |
| ≥40 years old | 1 (ref.) | 1.1 (0.6–2.1) | 0.6 (0.3–1.1) | 0.5 (0.3–1.0) | 0.5 (0.2–1.0) | 0.03 | |
| BMI | | | | | | | |
| <25 kg/m$^2$ | 1 (ref.) | 0.6 (0.3–1.4) | 1.0 (0.5–2.2) | 0.9 (0.4–2.0) | 0.5 (0.2–1.3) | 0.24 | 0.77 |
| ≥25 kg/m$^2$ | 1 (ref.) | 1.1 (0.6–2.2) | 0.7 (0.3–1.4) | 0.7 (0.4–1.5) | 0.7 (0.3–1.5) | 0.30 | |

The hazard ratios are adjusted for variables in multivariable model 2 in Tables 2–5, 6–7.

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