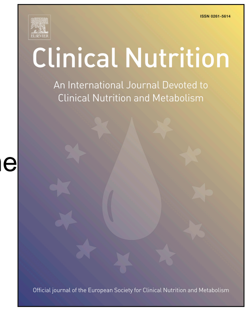

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Legume consumption and risk of all-cause, cardiovascular, and cancer mortality in the PREDIMED study

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Abbreviations: CVD (cardiovascular disease), MedDiet (Mediterranean diet), FFQ (food frequency questionnaire), PREDIMED (PREvención con DIetaMEDiterránea)

ABSTRACT

Background & aims: Limited prospective studies have examined the association between legumes consumption and mortality, whereas scarce, if at all, previous studies have evaluated such associations taking into consideration specific grain legumes. We aimed to investigate the association between total legumes consumption and grain legumes species (dry beans, chickpeas, lentils, and fresh peas) with all-cause, cardiovascular disease (CVD), cancer and other-cause mortality among elderly Mediterranean individuals at high CVD risk.

Methods: We prospectively assessed 7,216 participants from the PREvención con DIeta MEDiterránea study. Dietary intake was assessed at baseline and yearly during follow-up by using a validated food frequency questionnaire.

Results: During a median follow-up of 6.0 years, 425 total deaths, 103 CVD deaths, 169 cancer deaths and 153 due to other-causes deaths occurred. Hazard ratios (HRs) [95% confidence interval (CI)] of CVD mortality were 1.52 (1.02-2.89) (*P*-trend= 0.034) and 2.23 (1.32-3.78) (*P*-trend= 0.002) for the 3rd tertile of total legumes and dry beans consumption, respectively, compared with the 1st tertile. When comparing extreme tertiles, higher total legumes and lentils consumption was associated with 49% (HR: 0.51; 95% CI: 0.31-0.84; *P*-trend= 0.009) and 37% (HR: 0.63; 95% CI: 0.40-0.98; *P*-trend= 0.049) lower risk of cancer mortality. Similar associations were observed for CVD death in males and for cancer death in males, obese and diabetic participants.

Conclusions: These findings support the benefits of legumes consumption for cancer mortality prevention which may be counterbalanced by their higher risk for CVD mortality.

Keywords: Legumes; Cardiovascular; Cancer; Mortality; PREDIMED

Trial registration: The trial is registered at http://www.controlled-trials.com (ISRCTN35739639). Registration date: 5th October 2005.

INTRODUCTION

Cardiovascular diseases (CVDs) and cancer remain two of the most common causes of death and in 2012 accounted for 17.5 and 8.2 million deaths worldwide, respectively (1, 2). Lifestyle factors, mainly smoking, physical inactivity, unhealthy diet and excessive alcohol consumption, may adversely impact both conditions (3, 4). It has also been suggested that several deaths from CVDs (5) and one third of all cancer deaths (6) could be avoided through appropriate dietary modification. Recently, the PREDIMED trial highlighted the importance of the Mediterranean diet (MedDiet) in the primary prevention of major CVD events (7). In addition, findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) study showed that during a median follow-up of 8.7 years, a greater adherence to the MedDiet was associated with a lower overall cancer risk (8). Several reports have suggested that key MedDiet components are associated with reduced CVD (7) and cancer risk (9, 10). Legumes, a key food of the MedDiet, has been proposed as one of the dietary factors that may offer protection against CVD (11, 12) and cancer of the oral cavity and pharynx, esophagus, larynx, stomach, colorectum, kidney, upper aerodigestive tract (13), prostate (14) and breast (15). Legumes may protect against CVD and cancer through various mechanisms. Legumes are rich in dietary fiber and are good sources of polyunsaturated fatty acids, vitamin E, pyridoxine, folate, selenium, flavonoids and lignans with potential CVD and cancer preventive effects (16, 17). However studies evaluating the association of legumes consumption with CVD and cancer mortality are sparse. In this context, the EPIC study (18) evaluating the association between total legumes (including soybeans) and the risk of all-cause and cause-specific mortality among 10,449 participants with self-reported diabetes, found that increased consumption of legumes was not associated with the relative risk of death from CVD or cancer, but with reduced risk of all-cause mortality. Similarly, the Prospective Urban Rural Epidemiology [PURE] study observed that legume (non-soy) consumption was inversely associated with non-CVD and total mortality (19). On the other hand, in the Melbourne Collaborative Cohort Study, those participants consuming legumes two or more times per week had a significantly reduced risk of CVD mortality as compared to those who never ate legumes (20). However, in these studies, the assessment of legumes consumption was limited to a certain point of time (at baseline) which may have led to random measurement error caused by within-person variation and dietary changes during follow-up (21). Furthermore, in the above studies, the effect of different grain legumes was not analysed separately.

No prospective study has as yet assessed the association between consumption of different non-soy grain legumes species with mortality. Taking the above into account, the present study used yearly repeated measurements of dietary information to examine the possible associations of total legumes consumption and different grain legumes (dry beans, chickpeas, lentils, and fresh peas) with all-cause, CVD, cancer and other-cause mortality among elderly Mediterranean individuals at high CVD risk.

MATERIALS AND METHODS

Study design and participants

For the present study, data from the PREDIMED trial (ISRCTN35739639) has been analyzed as an observational prospective cohort study. The design of this trial has been described in detail elsewhere (7, 22). In brief, from 2003 until 2009 the study recruited 7,447 men (aged 55-80 years) and women (aged 60-80 years) without CVD at enrolment but who were at high CVD risk. Participants were eligible if they had either type 2 diabetes or at least three of the following CVD risk factors: hypercholesterolemia, low high-density lipoprotein, overweight/obesity, hypertension, current smoking or family history of premature coronary heart disease. Exclusion criteria were: alcohol or drug addiction, severe chronic illness, body mass index (BMI) ≥ 40kg/m^2 and allergy or intolerance to olive oil or nuts. Participants were allocated to a MedDiet supplemented with extra-virgin olive oil; a MedDiet supplemented with mixed nuts, or a control diet consisting of advice to reduce the consumption of all sources of fat according to American Heart Association. The analyses for the current study were based on an extended observational follow-up until 30 June 2012 as described below. The Institutional Review Boards of the recruitment centers approved the study protocol, and participants provided written informed consent.

Dietary assessment

Dietary intake was assessed with the use of a validated 137-item semi-quantitative food frequency questionnaire (FFQ) at baseline and yearly during the follow-up (23). Reproducibility and validity of the FFQ for legumes, estimated by the Pearson correlation coefficient and the intraclass correlation coefficient (ICC) were 0.47 (ICC 0.63), and 0.29 (ICC 0.40), respectively (23). Information on consumption of legumes was derived from the FFQ using four items [lentils (lens culinaris), chickpeas (Cicer arietinum), dry beans (Phaseolus vulgaris) and fresh peas (Cajanus cajan)]. The consumption frequency was measured in nine categories (ranging from never or almost never to >6 servings/day) for each food item. The responses were transformed to grams per day during the follow-up by multiplying the portion sizes (grams) by the consumption frequency and making the corresponding division for the assessed period. Energy and nutrient intake were estimated using Spanish food composition tables (24).

Assessment of covariates

At baseline and yearly during the follow-up, participants completed a 47-item questionnaire related to lifestyle variables, educational level, smoking status, medical history and medication use. A validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire was administered to evaluate physical activity (25). To assess the degree of adherence to the MedDiet, a 14-item validated questionnaire was filled in for each participant (26). In order to control for the overall dietary pattern, we used this MedDiet questionnaire score but removing the variable related to legume consumption for the main analysis. Therefore, a 13-point score was used as a covariate in the models. Participants were considered to have type 2 diabetes, hypercholesterolemia or hypertension if they had previously been diagnosed as such conditions and/or if they were being treated with antihypertensive medication, antidiabetic agents or statins. Anthropometric and blood pressure measurements were undertaken by trained personnel. We used a validated oscillometer (Omron HEM-705CP, Hoofddorp, the Netherlands) to measure blood pressure, three times with a 5-minute interval between each reading, and the mean of the three values was recorded. Weight and height were measured with participants in light clothing and no shoes using calibrated scales and a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

Primary endpoints

For the present study, we used the following 4 different endpoints: 1) all-cause death 2) CVD death 3) cancer death, and 4) death from other causes. The following sources were used to ascertain death: 1) yearly repeated questionnaires and examinations to all participants, 2) contacts with general practitioners who were performing routine care of participants, 3) yearly consultation of the National Death Index, and 4) a comprehensive yearly review of medical records of all participants by physicians who were “blinded” with respect to the treatment allocation and dietary information. The Event Adjudication Committee, who was unaware of the information regarding diet, examined all medical records related to the aforementioned endpoints. Only those endpoints that were recorded between 1 October 2003 and 30 June 2012 were included in the present analysis.

Statistical analyses

Participants who had extremes daily energy intake (<500 or >3500kcal/d for women and <800 or > 4000kcal/d for men) or missing information on the FFQ at baseline or without follow-up information were excluded from the present analysis. To minimize the random measurement error caused by within-person variation and to better represent the long-term legumes consumption (21), we used the cumulative average from baseline to the last FFQ before death. Participants were categorized into tertiles of intake of total legumes, lentils, chickpeas, dry beans and fresh peas adjusted for energy intake using the residual method (27). Baseline characteristics according to tertiles of total legumes and its different subtypes are presented as means ± SD for quantitative variables, and percentages (%) and numbers (n) for categorical variables. One-way analysis of variance (ANOVA) and Chi-square tests were used to assess differences in baseline characteristics according to tertiles of energy-adjusted cumulative average consumption of total legumes and its different subtypes.

Person time of follow-up was calculated as the interval between the randomization date and death from any cause, or date of the last contact visit, whichever came first. Time-dependent Cox regression models were used to assess the associations between total legumes, lentils, chickpeas, dry beans and fresh peas intake and death from any cause during the follow-up. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated by using the lowest tertile as the reference category.

Multivariable model 1 for total legumes, lentils, chickpeas, dry beans and fresh peas was adjusted for sex, age (continuous) and intervention group. Model 2 was further adjusted for prevalence of diabetes, prevalence of hypertension, hypercholesterolemia, baseline BMI (kg/m^2), smoking status, educational level, physical activity, use of antihypertensive medication, use of antidiabetic agents, use of statins and cumulative average of alcohol intake in grams per day. Model 3 was additionally adjusted for cumulative average of the 13-point screener of MedDiet adherence. All models were stratified by the recruitment center. To appraise the linear trend, the median consumption within each tertile was included in the Cox regression models as a continuous variable.

Further, we conducted stratified analyses to investigate whether the observed association between total legumes and risk of CVD mortality and cancer mortality was modified by sex, age group (<67 yrs *vs.* ≥67 yrs), BMI (<30 or ≥30kg/m^2) and type 2 diabetes status. The tests for interaction were performed by means of likelihood ratio tests, which involved comparing models with and without cross product terms between the baseline stratifying variable and tertiles of total legume consumption as an ordinal variable.

We conducted subsequent multivariable analyses to examine the HRs of substituting half a serving/day of total legumes (30g in raw) for half a serving/day of animal food sources, such as total meat (75g), fish (75g) and eggs (30g) for CVD and cancer mortality. These dietary variables were included as continuous variables in the same Cox regression model, adjusted for the covariates listed in model 3 and using a 13-item MedDiet score for the eggs replacement, 12-item MedDiet score for fish substitution and 11-item MedDiet score for meat, while additional adjustments were performed for cumulative average of energy intake. The differences in their βcoefficients, variance and covariance were used to calculate the β-coefficient ± SE for the substitution effect, and the HRs and 95% CI were calculated from these parameters.

To test the robustness of our results, we conducted sensitivity analysis adjusting for cumulative quintiles of consumption of individual food groups, including red meat, processed meat, fish, cereals, vegetables, fruits, nuts, olive oil and dairy products, instead of the modified MedDiet score.

Data were analyzed using the commercially available software program Stata 14 (StataCorp) and statistical significance was set at a 2-tailed *P*-value <0.05.

RESULTS

In the present study, analyses were carried out in 7,216 participants after excluding 153 participants who were outside the limits for total energy intake at baseline and 78 participants with missing baseline dietary information. Of the 7,216 participants who were followed for a median of 6 years, 425 died; 103 due to CVD, 169 due to cancer, and 153 due to other causes. Baseline characteristics of the participants according to cumulative energy-adjusted tertiles of total legumes consumption are presented in **Table 1**. As compared with participants in the lowest tertile of total legumes intake, those in the highest tertile were more likely to be older (*P*-value <0.001) and females (*P*-value = 0.003), to have secondary education (*P*-value <0.001), a higher BMI (*P*-value = 0.039) and a higher prevalence of hypercholesterolemia (*P*-value <0.001). They also had a higher fiber consumption (*P*-value <0.001) whereas a lower alcohol intake (*P*-value <0.001). Baseline characteristics according to tertiles of different types of legume intake are shown in **Supplemental Table 1**.

During follow-up, the median cumulative average consumption was 20.0 g/d for total legumes, 6.7 g/day for lentils, 5.2 g/day for chickpeas, 4.7 g/day for dry beans and 2.7 g/day for fresh peas (**Table 2**).

In the cumulative analysis, using yearly repeated measurements of diet, we did not find significant associations between total and specific subtypes of legumes consumption and all-cause mortality in the fully-adjusted models (*P*-trend >0.05) (**Table 3**).

In Table 4, the HRs for CVD, cancer and other-cause mortality according to tertiles of consumption of total legumes and its subtypes, are presented. For the fully adjusted model, HRs (95% CI) of CVD mortality and other-cause mortality was 1.72 (1.02-2.89) and 1.50 (0.99-2.27), respectively, for the 3rd tertile of total legumes consumption compared with the 1st tertile (*P*-trend= 0.034 and *P*-trend= 0.045, respectively). Compared with those in the 1st tertile, participants in the 3rd tertile of total legumes consumption had a HR of cancer mortality of 0.51 (95% CI: 0.31-0.84; *P*-trend= 0.009). Regarding grain legume species consumption, compared with those in the 1st tertile, participants in the highest tertile of lentils consumption had a HR of cancer mortality of 0.63 (95% CI: 0.40-0.98; *P*-trend= 0.049), whereas with respect to dry beans consumption, participants in the highest tertile had a HR of CVD mortality of 2.23 (95% CI: 1.32-3.78; *P*-trend= 0.002).

Stratified analysis

No statistically significant interactions were observed between legumes consumption and CVD or cancer mortality by sex, age (categorical variable), BMI (categorical variable) and type 2 diabetes status (*P*> 0.05). However, when results were stratified by sex, BMI and type 2 diabetes status the association between total legumes consumption and CVD mortality appeared stronger in males (HR: 2.33; 95% CI: 1.13-4.78; *P*-trend= 0.020) than in females (HR: 1.17; 95% CI: 0.51-2.70; *P*-trend= 0.794) (Figure 1). As concerns the association between total legumes consumption and cancer mortality stratified by the aforementioned variables, the results were only significant in males (HR: 0.52; 95% CI: 0.27-0.99; *P*-trend= 0.043), in diabetic subjects (HR: 0.51; 95% CI: 0.27-0.93; *P*-trend= 0.032) and in obese (HR: 0.38; 95% CI: 0.17-0.84; *P*-trend= 0.013 (Figure 2).

Substitution analysis

Replacing half a serving/day of animal food sources with half a serving/day of total legumes was not significantly associated with CVD and cancer mortality risk (P> 0.05).

Sensitivity Analysis

When we adjusted for individual food groups instead of the MedDiet score, the statistical significance persisted in the case of total legumes and CVD mortality (HR: 1.96; 95% CI: 1.15-3.36; *P*-trend= 0.011) as well as between total legumes and cancer mortality (HR: 0.50; 95% CI: 0.30-0.82; *P*-trend= 0.007). Regarding dry beans consumption, its association with CVD mortality was significant (HR: 2.47; 95% CI: 1.44-4.25; *P*-trend= 0.001), while lentils consumption had a HR of cancer mortality of 0.62 (95% CI: 0.39-0.97) but the *P*-trend did not reach the significant level (*P*-trend= 0.051).

DISCUSSION

Higher consumption of non-soy legumes and grain legume species were hypothesized to decrease mortality, especially from cancer and CVD. In the present prospective study including a large sample of older adults at high risk of CVD, higher consumption of total legumes and lentils was associated with 49% and 37% respective lower risk of cancer mortality. To the best of our knowledge, no previous prospective study has revealed a protective role of legumes consumption against cancer mortality (18) or any specific type of cancer mortality (28). In the aforementioned studies, measurement error in the dietary assessment methods due to changes in dietary habits during follow-up may have resulted in the misclassification of individual intake and could have led to underestimation of the association between legumes intake and protection from cancer mortality. To overcome this limitation, we treated legumes as cumulative average intake (21).

Previous studies have observed inverse associations between legumes consumption and the risk of different cancers (13-15). The protective effect of total legumes and lentils consumption on cancer mortality risk can be explained by various potential mechanisms among which the most important seems to be their high polyphenol content (29), predominantly phenolic acids and flavonoids; the latter being at higher concentrations in cooked lentils compared to other cooked legumes (30). Potential anticancer mechanisms for phenolic acids and flavonoids are inhibition of cell proliferation, inflammation, oxidative stress, invasion, metastasis, and activation of apoptosis (31). Furthermore, legumes are good sources of dietary fiber, vitamin E and B, selenium, and lignans, all dietary components with recognized anti-cancer actions (17). However, in the current study the inverse association between legumes and cancer mortality that we found, reached the significant level only in males, diabetics and obese, suggesting that consumption of legumes is more beneficial for these groups of participants, compared to females, non-diabetics and non-obese. We considered the possibility that these groups may differ in terms of legumes consumption. However, the consumption of legumes did not differ greatly between them. Obesity and type 2 diabetes are associated with increased risk of many forms of cancer (32, 33) and inversely related to legumes consumption (34). Therefore, we can assume that these participants may have shown notable decreases in the risk of cancer mortality with higher intake of legumes because the higher cacostatic load of these conditions at baseline, and, therefore a potential increased sensitivity to detect any favorable effect of legumes intake. With regard to sex, since the cancer cases were substantially lower among females compared to males, one possible explanation for this finding may be the lack of statistical power to detect any significant associations in females.

On the other hand, the intake of total legumes and grain legume species was not associated with all-cause mortality. To date, three previous prospective studies (18-19, 35) have shown a significant inverse association between consumption of legumes and all-cause mortality. In the EPIC study (18), an increment in legumes consumption by 20 g/day was associated with a 7% significant risk reduction of all-cause mortality. A 8% significant risk reduction for every 20g increase in daily legume consumption has also been reported in the 'Food Habits in Later Life' study (35). Recently, an inverse association between at least 1 serving per month of legumes consumption and total mortality was observed in the PURE study (19). Differences in the study design and populations studied could partly explain the discrepancies observed between our results and those of the aforementioned studies.

Contrary to our hypothesis, higher intakes of total legumes and dry beans were associated to a higher risk of CVD mortality. Interestingly, the magnitude of the effect of dry beans compared to total legumes on CVD mortality was higher. It is unclear why legumes and particularly dry beans are responsible for the increased CVD mortality; with a number of different pathological processes are likely to be involved.

Spontaneous cases of cardiac arrest are reported, caused by gastric dilatation and elevated abdominal pressure, which can be possibly brought either by binge eating (36), or by the dyspepsia and discomfort associated with cowpeas (37) and dry beans in general (38). The vagus nerve, also called pneumogastric nerve, is involved in varied tasks as lowering the heart rate and controlling gastrointestinal peristalsis; whether dry beans consumption predisposes to cardiac arrest acting through this nerve (stomach-heart axis) in CVD patients is a hypothesis to be further tested. To strengthen the aforementioned possible explanation for the unexpected finding, we analyzed dry beans consumption in relation to sudden cardiac death and found strong significant associations after adjustment for modified MedDiet score (HR: 3.99; 95% CI: 1.35-11.82) and for individual food groups (HR: 4.93; 95% CI: 1.67-14.55), respectively. Residual confounding can drive another possible explanation. Usually, dry beans but not other legumes in Spain, are consumed as a dish made with processed red meat and lard (fabada), or as a side dish of sausages or other processed meat. After adjusting the analyses for red and processed meat, our results changed slightly (data not shown) suggesting that the association between this type of legume and CVD mortality may not be mediated by these types of meat. In the sex-stratified analysis, the association between legumes and increased risk of CVD mortality remained significant only in men. The lower CVD cases among women compared to men could significantly decrease the statistical power to detect any notable associations.

The present study has some limitations. First, although the FFQ used to assess dietary intake was validated and the cumulative average from baseline to the last FFQ before death was used, misclassification bias cannot be completely excluded. Second, given its observational nature, this study cannot support causal relationships between legumes consumption and mortality. Third, even though we adjusted for several potential confounders, residual confounding cannot be ruled out. Finally, participants were elderly Mediterranean individuals at high CVD risk and this may limit the generalizability of the findings to other age-groups or populations.

Conclusions

Our findings demonstrated for the first time that higher consumption of total legumes and lentils were associated with a decreased risk of cancer mortality whereas total legumes and especially dry beans were associated with an increased risk of CVD mortality, independent of traditional risk factors, in an elderly Mediterranean population at high CVD risk. From a public health perspective, these contradictory results may be proved important, and healthcare professionals should be aware of the possible benefits and dangers of legumes and dry beans consumption, respectively. An intriguing question, then, is whether some individuals are more prone to the effects of consuming legumes (i.e. dry beans), suggesting the need for future research.

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Conflict of interest statement: The authors declare that they not have conflict of interest related to this article.

Authors Contribution:

ER, DC, RE, MF, LS-M, FA, MFiol, MA-MG, JL and JS-S *designed the research*. NB-T, CP, MB, DC, RE, ER, FA, MF, LS-M, JL, MFiol, MR-C and JS-S *conducted the research*. CP, NB-T and JS-S *analyzed the data*. CP, NB-T and JS-S *wrote the paper*. CP, NB-T and JS-S *had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis*. All authors revised the manuscript for important intellectual content, and read and approved the final manuscript.

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Table 1. Baseline characteristics of the study population according to cumulative average tertiles of energy-adjusted total legumes consumption*

	Tertiles of total legumes consumption			
	T1(lowest) n=2404	T2 n=2404	T3 (highest) n=2404	*P*-value†
Total legume, (g/day)	11.75	18.42	28.10	
Lentils, g/day	3.88	6.13	8.62	
Chickpeas, g/day	3.55	4.33	8.39	
Fresh peas, g/day	3.05	3.63	4.01	
Dry beans, g/day	3.24	4.21	8.95	
Age, years	67 ± 6	67 ± 6	67 ± 6	<0.001
Women, % (n)	55.32 (1,330)	60.11 (1,445)	56.95 (1,369)	0.003
Smoking habit, % (n)				0.040
Never	59.15 (1,422)	63.35 (1,523)	62.02 (1,491)	
Former	26.08 (627)	23.04 (327)	24.58 (591)	
Current	14.77 (355)	13.60 (327)	13.39 (322)	
Education, % (n)				<0.001
Primary	74.38 (1,788)	79.28 (1,906)	79.41 (1,909)	
Secondary	17.05 (410)	14.56 (350)	13.94 (335)	
University/graduate	8.57 (206)	6.16 (148)	6.66 (160)	
Intervention group, n (%)				0.730
MedDiet + EVOO	34.15 (821)	34.40 (827)	34.36 (826)	
MedDiet + Nuts	32.24 (775)	33.61 (808)	32.28 (776)	
Control group	33.61 (808)	31.99 (769)	33.36 (802)	
BMI, kg/m^2	30.00 ± 3.86	29.82 ± 3.77	30.10 ± 3.94	0.039

Leisure time physical activity, METs, min/day	234.42 ± 239.70	224.33 ± 227.04	234.53 ± 249.39	0.236
Hypertension, % (n)	82.20 (1,976)	82.53 (1,984)	83.49 (2,007)	0.470
Hypercholesterolemia, % (n)	71.21 (1,712)	70.55 (1,696)	74.92 (1,801)	0.001
Current medication use, % (n)				
Use of antihypertensive agents	72.09 (1,733)	72.13 (1,734)	73.96 (1,778)	0.250
Statin use	40.06 (963)	39.35 (946)	41.31 (993)	0.375
Oral antidiabetic agents	30.70 (738)	32.53 (782)	33.36 (802)	0.130
MedDiet score	8.33 ± 1.85	8.41 ± 1.75	8.44 ± 1.86	0.111
Red Meat, g/day	54.15 ± 37.80	52.31 ± 33.00	44.54 ± 34.03	<0.001
Processed red meat, g/day	27.58 ± 20.15	26.32 ± 16.77	24.25 ± 17.87	<0.001
Vegetables, g/day	309.22 ± 137.86	329.53 ± 132.20	363.39 ± 157.10	<0.001
Fruit, g/day	358.01 ± 199.42	362.23 ± 187.43	384.79 ± 199.00	<0.001
Cereals, g/day	228.08 ± 86.28	232.22 ± 78.12	215.27 ± 82.24	<0.001
Olive oil, g/day	40.41 ± 16.10	39.52 ± 16.32	37.22 ± 17.55	<0.001
Nuts, g/day	9.53 ± 13.52	10.20 ± 12.34	10.62 ± 13.51	0.016
Dairy products, g/day	373.00 ± 217.18	373.81 ± 204.18	393.97 ± 225.20	<0.001
Fish, g/day	95.13 ± 47.33	100.45 ± 47.44	102.14 ± 51.52	<0.001
Energy, kcal/day	2320.08 ± 577.75	2156.75 ± 511.32	2231.14 ± 528.54	<0.001
Carbohydrate, % of energy	41.00 ± 7.21	41.50 ± 6.93	42.82 ± 7.08	<0.001
Protein, % of energy	16.12 ± 2.77	16.80 ± 2.76	16.90 ± 2.84	<0.001
Fat, % of energy	40.02 ± 6.72	39.38 ± 6.64	38.23 ± 6.89	<0.001
Alcohol, g/day	9.51 ± 15.16	8.40 ± 12.32	7.07 ± 11.94	<0.001
Dietary fiber, g/day	22.78 ± 6.94	24.73 ± 6.41	28.20 ± 8.10	<0.001

Data are expressed as means ± SD or median for continuous variables and percentage and number (n) for categorical variables.
[†]*P*-value for differences between tertiles was calculated by chi-square or one-way analysis of variance test for categorical and

continuous variables, respectively.

All dietary variables were adjusted for total energy intake using the residual method.

Abbreviations: T, tertile; MedDiet, Mediterranean diet; EVOO, extra virgin olive oil; MET, metabolic equivalent

Table 2. Energy-adjusted cumulative average of total and grain legume species consumption during follow-up in the study population*

	Means ± SD	Median	Interquartile range
Total legumes	21.18 ± 9.89	20.05	15.72 – 25.01
Lentils	6.89 ± 3.65	6.74	4.43 – 8.50
Chickpeas	5.75 ± 3.23	5.24	3.96 – 7.37
Dry beans	5.34 ± 3.70	4.67	3.49 – 6.91
Fresh peas	3.20 ± 5.48	2.70	1.02 – 4.22

*Data are expressed in raw grams per day

Table 3. HRs (95% CIs) of all-cause mortality according to energy-adjusted tertiles of cumulative average of total and grain legume species consumption

	Tertiles of legumes consumption			
	1 (lowest)	2	3 (highest)	*P*-trend
Legumes				
Cases/person-years	146/14294	146/14209	133/13961	
Median, g/day	13.95	20.05	27.34	
Multivariable model 1	1 (ref.)	0.99 (0.78, 1.25)	0.93 (0.72, 1.20)	0.656
Multivariable model 2	1 (ref.)	1.01 (0.80, 1.28)	0.99 (0.76, 1.28)	0.987
Multivariable model 3	1 (ref.)	1.08 (0.85, 1.37)	1.09 (0.84, 1.41)	0.503
Lentils				
Cases/person-years	163/14233	134/14262	128/13969	
Median, g/day	4.06	6.74	8.73	
Multivariable model 1	1 (ref.)	0.86 (0.68, 1.09)	0.87 (0.68, 1.11)	0.273
Multivariable model 2	1 (ref.)	0.88 (0.69, 1.11)	0.91 (0.71, 1.17)	0.461
Multivariable model 3	1 (ref.)	0.95 (0.75, 1.20)	0.99 (0.77, 1.27)	0.965
Chickpeas				
Cases/person-years	159/14219	133/14240	133/14005	
Median, g/day	3.48	5.24	8.23	
Multivariable model 1	1 (ref.)	0.83 (0.66, 1.04)	0.85 (0.67, 1.08)	0.334
Multivariable model 2	1 (ref.)	0.85 (0.67, 1.08)	0.88 (0.69, 1.11)	0.456
Multivariable model 3	1 (ref.)	0.90 (0.71, 1.14)	0.96 (0.75, 1.22)	0.933
Dry beans				
Cases/person-years	139/14224	138/14214	148/14026	
Median, g/day	2.67	4.67	7.95	
Multivariable model 1	1 (ref.)	1.00 (0.79, 1.28)	1.08 (0.84, 1.39)	0.606
Multivariable model 2	1 (ref.)	1.02 (0.80, 1.30)	1.12 (0.87, 1.46)	0.420
Multivariable model 3	1 (ref.)	1.04 (0.82, 1.34)	1.19 (0.92, 1.54)	0.225
Fresh peas				
Cases/person-years	149/14174	126/14236	150/14054	
Median, g/day	0.55	2.70	4.82	
Multivariable model 1	1 (ref.)	0.83 (0.65, 1.06)	1.03 (0.81, 1.31)	0.763
Multivariable model 2	1 (ref.)	0.84 (0.66, 1.07)	1.06 (0.84, 1.35)	0.604
Multivariable model 3	1 (ref.)	0.86 (0.68, 1.10)	1.07 (0.84, 1.36)	0.582

Cox regression models were used to assess the risk of all-cause mortality by tertiles of cumulative average of total and grain legume species consumption. Multivariable model 1 was adjusted for age (y), sex and intervention group. Model 2 was further adjusted for prevalence of diabetes (yes/no), prevalence of hypertension (yes/no), hypercholesterolemia (yes/no), baseline BMI (kg/m^2), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), physical activity (metabolic equivalent task units in min/day),use of antihypertensive medication (yes/no), use of antidiabetic agents (yes/no), statin use (yes/no) and cumulative average of alcohol intake (continuous and adding the quadratic term). Model 3 was further adjusted for cumulative average of the 13-point screener (excluding legumes) of Mediterranean diet adherence (continuous). All models were stratified by recruitment center. Extremes of total energy intake (>4000 or < 800 kcal/day in men and >3500 or <500 kcal/day in women) were excluded.

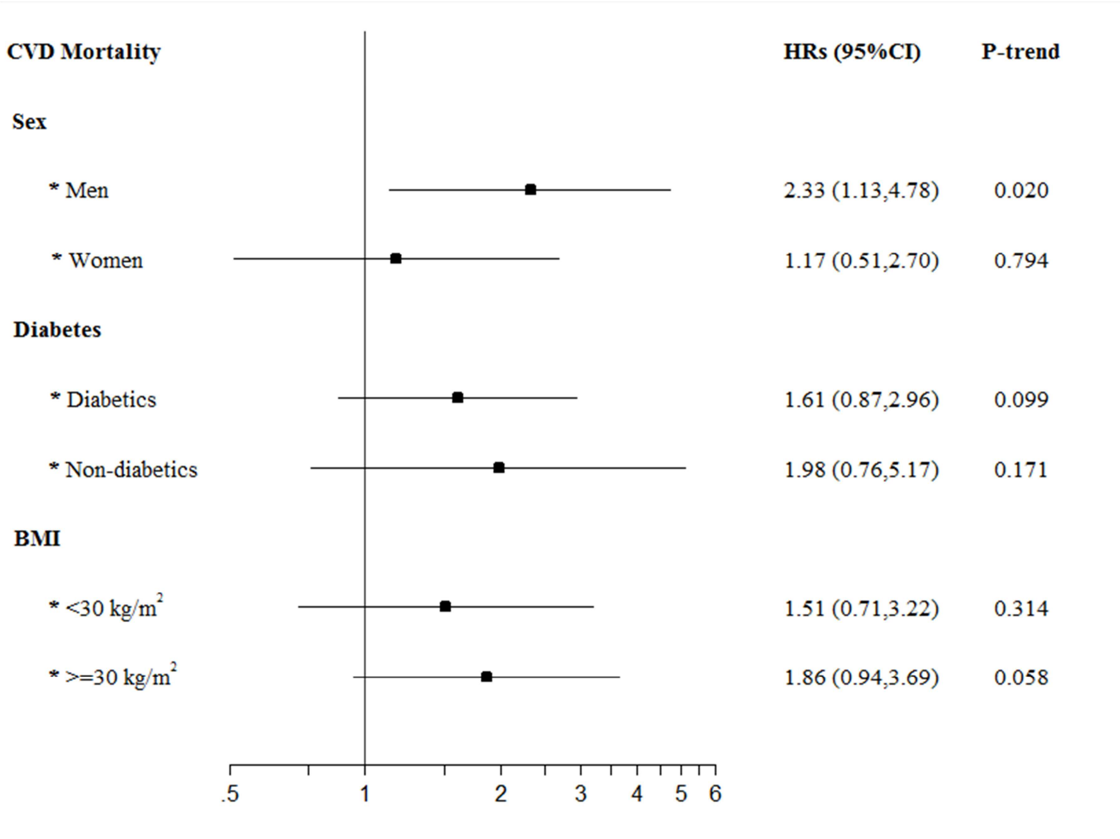
Table 4. HRs (95% CIs) for specific causes of death according to cumulative tertiles of total and grain legume species consumption

	CVD deaths (n=103)	Cancer deaths (n=169)	Other-cause deaths (n=153)
Total legumes			
Tertile 1 (13.95 g/day)*	1 (ref.)	1 (ref.)	1 (ref.)
Tertile 2 (20.05 g/day)	1.12 (0.68, 1.87)	1.19 (0.84, 1.68)	0.91 (0.59, 1.39)
Tertile 3 (27.34 g/day)	1.72 (1.02, 2.89)	0.51 (0.31, 0.84)	1.50 (0.99, 2.27)
P-trend	0.034	0.009	0.045
Lentils			
Tertile 1 (4.06 g/day)	1 (ref.)	1 (ref.)	1 (ref.)
Tertile 2 (6.74 g/day)	1.10 (0.68, 1.78)	0.81 (0.57, 1.16)	1.03 (0.68, 1.57)
Tertile 3 (8.73 g/day)	1.14 (0.69, 1.88)	0.63 (0.40, 0.98)	1.40 (0.93, 2.10)
P-trend	0.524	0.049	0.132
Chickpeas			
Tertile 1 (3.48 g/day)	1 (ref.)	1 (ref.)	1 (ref.)
Tertile 2 (5.24 g/day)	0.86 (0.51, 1.40)	0.83 (0.58, 1.18)	1.06 (0.71, 1.59)
Tertile 3 (8.23 g/day)	1.11 (0.69, 1.81)	0.67 (0.45, 1.00)	1.29 (0.85, 1.94)
P-trend	0.480	0.078	0.193
Drybeans			
Tertile 1 (2.67 g/day)	1 (ref.)	1 (ref.)	1 (ref.)
Tertile 2 (4.67 g/day)	1.17 (0.67, 2.06)	0.89 (0.61, 1.29)	1.17 (0.78, 1.78)
Tertile 3 (7.95 g/day)	2.23 (1.32, 3.78)	0.88 (0.58, 1.35)	1.09 (0.71, 1.67)
P-trend	0.002	0.507	0.831
Peas			
Tertile 1 (0.55 g/day)	1 (ref.)	1 (ref.)	1 (ref.)
Tertile 2 (2.70 g/day)	0.87 (0.55, 1.38)	0.69 (0.47, 1.01)	1.14 (0.75, 1.74)
Tertile 3 (4.82 g/day)	0.84 (0.53, 1.35)	0.95 (0.65, 1.38)	1.43 (0.94, 2.18)
P-trend	0.559	0.683	0.082

Cox regression models were used to assess the risk of specific causes of death according to tertiles of cumulative average of total and grain legume species consumption. Multivariable model was adjusted for age (y), sex and intervention group, prevalence of diabetes (yes/no), prevalence of hypertension (yes/no), hypercholesterolemia (yes/no), baseline BMI (kg/m^2), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), physical activity (metabolic equivalent task units in min/day),use of antihypertensive medication (yes/no), use of antidiabetic agents (yes/no), statin use (yes/no), cumulative average of alcohol intake (continuous and adding the quadratic term) and cumulative average of the 13-point screener (excluding legumes) of Mediterranean diet adherence (continuous).All models were stratified by recruitment center. Extremes of total energy intake (>4000 or < 800 kcal/day in men and >3500 or <500 kcal/day in women) were excluded.

*Median (all such values).

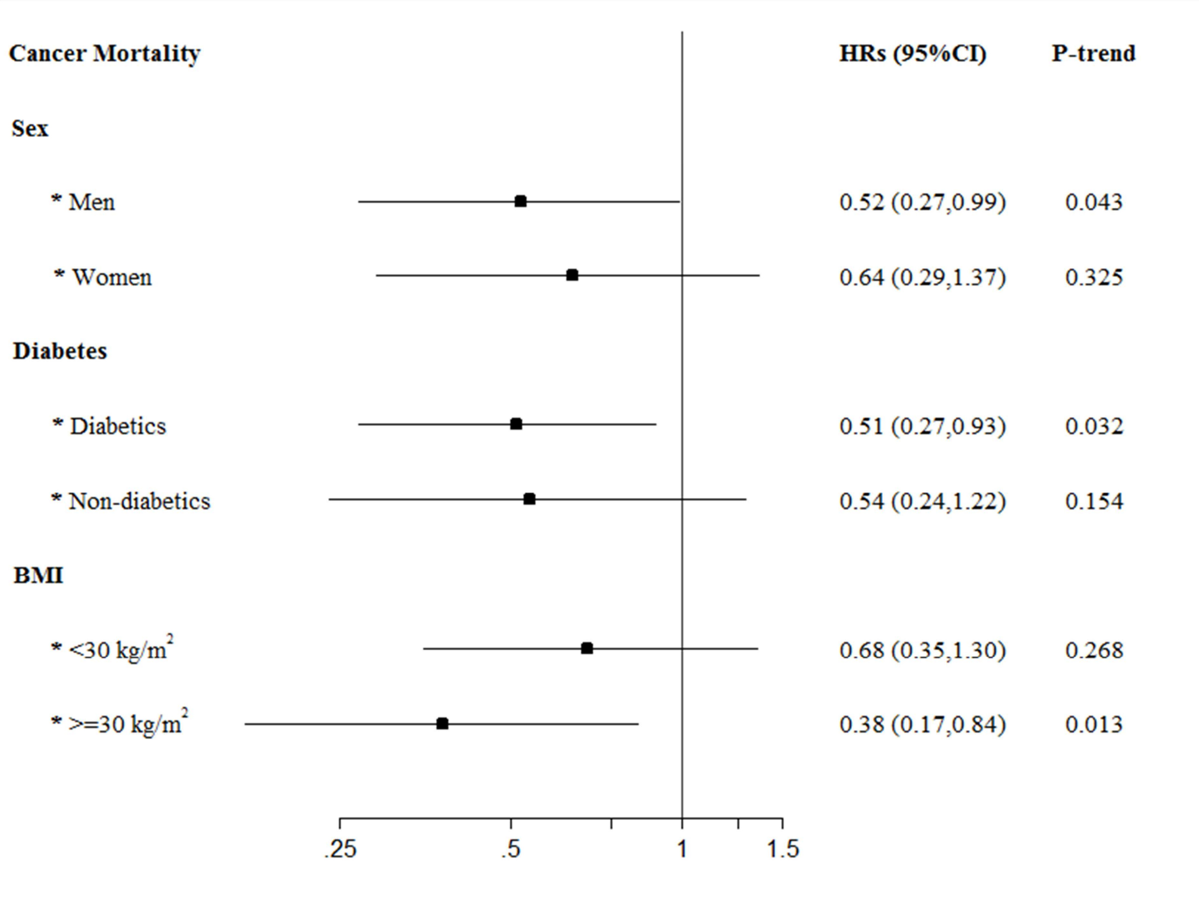
Figure 1



HRs (95% CIs) for CVD mortality according to legumes consumption stratified by sex, BMI and type 2 diabetes status. All HRs were adjusted for age (y), sex [number of CVD deaths (62 in men and 41 in women); in the case of sex stratification, adjustment for sex was excluded] and intervention group, prevalence of diabetes (yes/no) (in the case of diabetes stratification, adjustment for diabetes prevalence was excluded), prevalence of hypertension (yes/no), hypercholesterolemia (yes/no), baseline BMI (kg/m^2) (in the case of BMI stratification, adjustment for BMI was excluded), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), physical activity (metabolic equivalent task units in min/day), use of antihypertensive medication (yes/no), use of antidiabetic agents (yes/no), statin use (yes/no), cumulative average of alcohol intake (continuous and adding the quadratic term) and cumulative average of the 13-point screener (excluding legumes) of Mediterranean diet adherence (continuous). Stratified by recruitment center. Extremes of total energy intake (>4000 or <800 kcal/d in men and >3500 or <500 kcal/d in women) were excluded. *P*-interaction > 0.05.

Abbreviations: CVD, cardiovascular disease; BMI, body mass index.

Figure 2



HRs (95% CIs) for cancer mortality according to legumes consumption stratified by sex, BMI and type 2 diabetes status. All HRs were adjusted for age (y), sex [number of cancer deaths (108 in men and 61 in women); in the case of sex stratification, adjustment for sex was excluded] and intervention group, prevalence of diabetes (yes/no) (in the case of diabetes stratification, adjustment for diabetes prevalence was excluded), prevalence of hypertension (yes/no), hypercholesterolemia (yes/no), baseline BMI (kg/m2) (in the case of BMI stratification, adjustment for BMI was excluded), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), physical activity (metabolic equivalent task units in min/day),use of antihypertensive medication (yes/no), use of antidiabetic agents (yes/no), statin use (yes/no), cumulative average of alcohol intake (continuous and adding the quadratic term) and cumulative average of the 13-point screener (excluding legumes) of Mediterranean diet adherence (continuous). Stratified by recruitment center. Extremes of total energy intake (>4000 or <800 kcal/d in men and >3500 or <500 kcal/d in women) were excluded. P-interaction > 0.05.

Abbreviations: BMI, body mass index.