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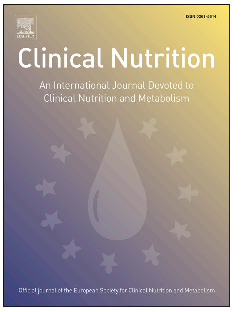

Legume consumption is inversely associated with type 2 diabetes incidence in adults: a prospective assessment from the PREDIMED study

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Legume consumption is inversely associated with type 2 diabetes incidence in adults: a prospective assessment from the PREDIMED study

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Running title: Legume consumption and type 2 diabetes incidence.

Foot note: Abbreviations used: International Diabetes Federation, IDF; cardiovascular disease, CVD; Mediterranean diet, MedDiet; PREvención con DIeta MEDiterránea, PREDIMED; Food Frequency Questionnaire, FFQ; intraclass correlation coefficient, ICC; hazard ratios, HRs; Confidence intervals, Cis; metabolic equivalent task, METs.

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

*__List of PREDIMED study investigators__ (Online Supplemental Material).

Abstract

Background & Aims: Legumes, a low-energy, nutrient-dense and low glycemic index food, have shown beneficial effects on glycemic control and adiposity. As such, legumes are widely recommended in diabetic diets, even though there is little evidence that their consumption protects against type 2 diabetes. Therefore the aim of the present study was to examine the associations between consumption of total legumes and specific subtypes, and type 2 diabetes risk. We also investigated the effect of theoretically substituting legumes for other protein- or carbohydrate-rich foods.

Methods: Prospective assessment of 3,349 participants in the PREvención con DIeta MEDiterránea (PREDIMED) study without type 2 diabetes at baseline. Dietary information was assessed at baseline and yearly during follow-up. We used Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (95%CIs) for type-2 diabetes incidence according to quartiles of cumulative average consumption of total legumes, lentils, chickpeas, dry beans and fresh peas.

Results: During a median follow-up of 4.3 years, 266 new cases of type 2 diabetes occurred. Individuals in the highest quartile of total legume and lentil consumption had a lower risk of diabetes than those in the lowest quartile (HR: 0.65; 95%CI: 0.43, 0.96; *P*-trend=0.04; and HR: 0.67; 95%CI: 0.46-0.98; *P*- trend=0.05, respectively). A borderline significant association was also observed for chickpeas consumption (HR 0.68; 95%CI: 0.46, 1.00; *P*-trend = 0.06). Substitutions of half a serving/day of legumes for similar servings of eggs, bread, rice or baked potato was associated with lower risk of diabetes incidence.

Conclusions: A frequent consumption of legumes, particularly lentils, in the context of a Mediterranean diet, may provide benefits on type 2 diabetes prevention in older adults at high cardiovascular risk.

Key words: Legumes; lentils; type 2 diabetes; PREDIMED-Study

BACKGROUND

Type 2 diabetes is recognised as a major public health issue worldwide. According to the International Diabetes Federation (IDF), type 2 diabetes affected 415 million adults in 2015 and it is estimated that this figure will increase to 642 million in 2040 [1]. Type 2 diabetes is associated with significant systemic consequences, including microvascular and macrovascular complications affecting the quality of life and decreasing the life expectancy [2]. Therefore, it is imperative to identify strategies to prevent and manage this condition.

In recent years, accumulating evidence from prospective studies and randomized controlled trials indicates that changes in diet and lifestyle are critical for the prevention of type 2 diabetes [3]. Legumes have been proposed as one of the dietary factors that may offer protection against type 2 diabetes. However, the independent association between non-soy legume intake and type 2 diabetes has scarcely been studied.

Legumes, including green beans and peas, peanuts, soybeans, lupine, alfalfa, clover, dry beans, broad beans, dry peas, chickpeas and lentils [4], are protein- and fiber-rich foods, and have a low glycemic index [5]. In addition, legumes contain sizeable amounts of B vitamins, particularly folate, as well as beneficial minerals such as, calcium, magnesium and potassium [6]. As a consequence of this unique nutritional value, several diabetes guidelines recommend them [7,8]. Furthermore, legumes are importantly present in healthy plant-based dietary patterns as the Mediterranean diet (MedDiet), vegetarian diets and prudent diets, which have consistently been associated with a lower risk of chronic diseases and type 2 diabetes [9,10]. Legumes consumption has also demonstrated beneficial effects on obesity, abdominal adiposity and metabolic syndrome [11–14] which are well recognized risk factors for type 2 diabetes. In addition, the replacement of red meat by legume consumption decreased peripheral inflammation, glycaemia and insulinemia in diabetic individuals [15,16].

To date, the few epidemiological studies evaluating these associations show inconsistent results. According to India's Third National Family Health Survey, compared to non-consumers, women who consumed legumes daily or weekly, but not men, showed a significant reduced prevalence of type 2 diabetes [17]. In contrast, this association was not observed in the Indian Migration Study [18]. Results from prospective studies are also controversial and highlight the paucity of studies on legumes and diabetes. Whereas several studies did not show any significant association between legume consumption and type 2 diabetes development [19–21], in the Shanghai Women's Health Study [22] consumption of total legumes (including soybeans) was associated with a reduced risk of type 2 diabetes incidence. Contrary, in the Nurse's health study a higher risk of type 2 diabetes was observed in the highest categories of total legume consumption [23].

However, to the best of our knowledge, no previous prospective studies have been conducted in Mediterranean populations who customarily consume sizeable amounts of non-soy legumes, or in individuals at high cardiovascular risk. Moreover, the effect of substituting legumes for other food sources rich in proteins or carbohydrates, has not been previously assessed. Therefore, the aim of the current study was to examine the association between the consumption of total non-soy legumes and its different subtypes (dry beans, chickpeas, lentils, and fresh peas), and the risk of type 2 diabetes development in a Mediterranean population at high cardiovascular risk. We also investigated the effect of substituting legumes for other protein- and carbohydrate-rich foods.

RESEARCH DESIGN AND METHODS

Study population

The present data was analyzed using an observational prospective design conducted within the frame of the PREDIMED (PREvención con DIeta MEDiterránea) trial (PREDIMED website: http://www.predimed.es) [24]. The PREDIMED study (registered at http://www.controlled-trials.com as ISRCTN35739639) was a randomized, multi center, parallel-group clinical trial conducted in Spain between October 2003 and December 2010. The main aim of the trial was to evaluate the effectiveness of the MedDiet on the primary prevention of CVD; the principal results have been published elsewhere [25]. Briefly, the study included 7,447 men (aged 55–80 years) and women (aged 60–80 years) without CVD at enrolment but who were at high cardiovascular risk. They were eligible if they had either type 2 diabetes or at least three of the following cardiovascular risk factors: hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or taking antihypertensive drugs), hypercholesterolemia (high LDL cholesterol ≥160mg/dL or taking hypolipidemic medication), low high-density lipoprotein (≤50 mg/dL in women or ≤40 mg/dL in men), overweight/obesity (BMI ≥ 25 kg/m^2), current smoking or family history of premature coronary heart disease. Exclusion criteria included alcohol or drug abuse, severe chronic illness, presence of BMI ≥ 40kg/m2 and allergy or intolerance to olive oil or nuts. For the current analysis, we excluded participants with type 2 diabetes at baseline (n=3,614), and those who lacked measures of blood glucose control (n=292), who had implausible daily energy intake (<500 or >3500kcal/d for women and <800 or > 4000kcal/d for men [26]) or who had not completed the baseline Food Frequency Questionnaire (FFQ) (n=98). We also excluded participants without follow-up (n=94). The final analysis included 3,349 non-diabetic individuals. The protocol was approved by the institutional review boards of the respective recruiting centers, and written informed consent was provided by all participants included in the study.

Dietary assessment

Trained dietitians quantified dietary intake using a validated semi-quantitative FFQ at baseline and yearly during the follow-up [27]. The Pearson correlation coefficient and the intraclass correlation coefficient (ICC) were used to explore the reproducibility of the FFQ for food groups and energy and nutrient intake. The reproducibility and validity of the FFQ for legumes were 0.47 (ICC 0.63), and 0.29 (ICC 0.40), respectively [27]. Legumes consumption was assessed using four items from the FFQ (lentils, chickpeas, dry beans and fresh peas). The consumption frequency was measured in nine categories (ranging from never or almost never to >6 servings/day) for each food item. The responses to each item were transformed to daily frequency and then multiplied by the portion size (in grams) in order to obtain grams per day consumed during the follow-up. The consumption of energy, nutrients and food groups was calculated using Spanish food composition tables [28,29].

Assessment of other covariates

At baseline and yearly during the follow-up, participants completed a 47-item questionnaire about lifestyle, medical history and medication use and a validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire [30]. To assess adherence to the MedDiet, a 14-item validated questionnaire was filled in for each participant [31]. One question was about legume consumption, two questions about meat and one about fish [31]. In order to control for the overall dietary pattern, we used this MedDiet questionnaire score but removed the variable related to legume consumption for the main analysis. Therefore, a 13-point score was used as a covariate in the models. For the substitution analysis of meat and fish, we used an 11-point score after additionally removing the variables related to meat intake and a 12-point score after removing the variable related to fish intake as covariates in the models.

Fasting blood samples, and anthropometric and blood pressure measurements were collected from all participants by trained personnel. Blood pressure was measured in triplicate (recording the mean of the three values), with an interval of 5 minutes between each measurement, using a validated oscillometer (Omron HEM705CP, Hoofddorp, The Netherlands), Weight and height were measured with participants in lightweight clothing and no shoes using calibrated scales and a wall-mounted stadiometer.

Ascertainment of type 2 diabetes mellitus

Type 2 diabetes was a prespecified secondary outcome in the PREDIMED trial. New-onset type 2 diabetes was identified following the American Diabetes Association criteria [32]; namely, fasting plasma glucose levels of $\geq$7.0 mmol/L ($\geq$126.1 mg/dL) or 2-h plasma glucose levels of $\geq$11.1 mmol/L ($\geq$200.0 mg/dL) after an oral dose of 75 g of glucose. Yearly, physicians-investigators of each center, who were blinded to the intervention, completed a review of all the participants' medical records. When new cases of type 2 diabetes were identified based on a diagnosis reported in the medical charts or on a fasting blood glucose values during routine biochemical analyses (done at least once per year), these reports were sent to the PREDIMED Clinical Events Committee, whose members were also blinded to treatment allocation. Only when the new onset type 2 diabetes case was verified within the next 3 months, using the same criteria, the adjudication committee definitively confirmed the end point [10]. Only confirmed diabetes events that occurred between 1 October 2003 and 1 December 2010 were included in the analyses.

Statistical analyses

To take advantage of the yearly dietary assessment and to better represent the long term diet [33], we used the cumulative average from baseline to the last FFQ before the new-onset of type 2 diabetes or to the last available FFQ (in those individuals without type 2 diabetes incidence). Participants were categorized into quartiles of consumption of total legumes, lentils, chickpeas, dry beans and fresh peas adjusted for energy intake using the residuals method [26].

The baseline characteristics of the study population were presented as means ± SD for quantitative variables, and percentages and numbers for categorical variables. One way ANOVA and Chi-square tests were used to assess differences in baseline characteristics according to quartiles of energy-adjusted cumulative average consumption of total legumes and the different subtypes. Cox regression models were fitted to assess the hazard ratios (HRs) and 95% confidence intervals (CIs) of type 2 diabetes according to quartiles of consumption of total legumes, lentils, chickpeas, dry beans and fresh peas. To appraise the linear trend, the median consumption within each quartile was included in the Cox regression models as a continuous variable. Model 1 was adjusted for sex, age (continuous), intervention group, baseline leisure time physical activity (METs-min/day), smoking status (never, current or former), educational level (primary education, secondary education or academic/graduate), fasting plasma glucose ($<$100mg/dL or $\geq$100mg/dL), prevalence of hypertension (yes/no), prevalence of hypercholesterolemia (yes/no), use of antihypertensive medication (yes/no), use of hypolipidaemic medication (yes/no) and cumulative average alcohol consumption in grams per day (continuous and adding a quadratic term). Model 2 was additionally adjusted for cumulative average of the 13-point screener (excluding legumes) of MedDiet adherence as a continuous variable. Model 3 was further adjusted for BMI (kg/m^2). All models were stratified by recruitment center. The first quartile was used as a reference category in all models. For each participant, we calculated the time variable as the interval between the randomization and the date of type 2 diabetes diagnosis, death from any cause or the last visit, whichever came first. To test the statistical interaction between quartiles of total legumes, lentils, chickpeas, dry beans, fresh peas and potential confounding variables such as sex, intervention group and BMI, the product terms were included in the multivariable model. Because no significant interactions were observed, the product terms were removed. We conducted subsequent multivariate analyses to examine the HRs of substituting half a serving/day of legumes (30g in raw) for half a serving/day of another protein-rich food, such as meat (75g), fish (75g) and eggs (30g), and another carbohydrate-rich food, such as bread (38g), rice (30g raw), baked potato (100g) and pasta (30g raw). These dietary variables were included as continuous variables in the same model, adjusted for the covariates listed above. The differences in their β-coefficients, 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 two sensitivity analyses: a) adjusting for updated BMI instead of baseline BMI to evaluate the impact of changes in body weight; and b) censoring participants at the time of diagnosis of cancer or CVD (myocardial infarction, stroke) because these diseases may lead to changes in diet [34]. Data were analyzed using a commercially available software program Stata 14 (StataCorp) and statistical significance was set at a 2-tailed P value <0.05.

RESULTS

During a median follow-up of 4.3 years, 266 incident cases of type 2 diabetes were documented. Baseline characteristics of the study population according to energy-adjusted quartiles of total legume intake are presented in **Table 1**. Participants in the highest quartile of total legume consumption were less likely to have higher education and had higher BMI and fasting plasma glucose levels than those in the bottom quartile. They also had a lower intake of total energy, dietary fat and alcohol but a higher intake of carbohydrates, protein and dietary fiber. Baseline characteristics according to quartiles of different type of legume consumption are described in **Supplemental table 1**.

During follow-up, the median cumulative average intake was 19.76 g/d for total legumes, 6.58g/d for lentils, 4.98g/d for chickpeas, 4.69 g/d for dry beans and 2.76 g/d for fresh peas (**Table 2**).

In multivariable analyses (**Table 3**), participants in the highest quartile of consumption of total legumes had a lower risk of developing type 2 diabetes even after adjusting for the overall dietary pattern score and BMI (HRs: 0.65; 95%CI: 0.43, 0.96; *P* trend = 0.04) than those in the lowest quartile. Likewise, those in the highest quartile of lentil intake had a 33% lower risk of type 2 diabetes incidence (HRs 0.67; 95%CI: 0.46-0.98; *P* trend = 0.05) than those in the bottom quartile. Comparing the 4^{th} *vs* the 1^{st} quartile of chickpeas consumption a borderline significant inverse association with type 2 diabetes development was observed (HRs 0.68; 95%CI: 0.46-1.00; *P* trend = 0.06). No significant associations were observed between fresh peas and dry beans, and the risk of type 2 diabetes. The results were similar when the consumption of total legumes, lentils, chickpeas, dry beans and fresh peas was modelled as a continuous variable per 30g/day increase (**Supplemental Table 2**). We observed an inverse association between total legumes (HR: 0.55; 95%CI: 0.32, 0.93; *P*-value = 0.03) and lentil consumption (HR: 0.18; 95%CI: 0.05, 0.65; *P*-value = 0.01) with incident type 2 diabetes, while consumption of chickpeas, dry beans and fresh peas was unrelated.

Results were similar when model 3 was adjusted by quintiles of cumulative consumption of nuts, olive oil, fish and fruits and vegetables instead of using the MedDiet score (data not shown).

Figure 1 shows the potential impact on type 2 diabetes development of theoretically substituting half a serving/day of total legumes for half a serving/day of food rich in protein or carbohydrates. For foods rich in protein, the risk of type 2 diabetes was 50% lower when half a serving/day of legumes was substituted for half a serving/day of eggs. However, although there was a trend toward lower risk of type 2 diabetes, the association was non-significant when fish or meat were replaced with legumes [(HR: 0.58; 95%CI: 0.32, 1.05; *P*-value = 0.07) and (HR: 0.59; 95%CI 0.34, 1.03) *P*-value = 0.07), respectively]. For carbohydrate-rich food, a 44%, 47%, 52% and 51% lower risk of type 2 diabetes development was observed when wholemeal bread, white bread, rice and baked potato, respectively, were replaced with legumes.

Our results were significant in two different sensitivity analyses. When we examined the impact of changes in BMI on the association of legume consumption and type 2 diabetes risk adjusting for updated BMI instead of baseline BMI, total legumes lentils and chickpeas consumption was associated with a lower risk of type 2 diabetes [HR: 0.65; 95%CI: 0.43, 0.96; *P*-trend = 0.03 (fourth quartile *vs* first quartile of legumes consumption), HR: 0.68; 95%CI: 0.47, 0.98; *P*-trend = 0.05 (fourth quartile *vs* first quartile of lentils consumption)] and HR: 0.67; 95%CI: 0.46, 0.99; *P*-value = 0.05 (fourth quartile *vs* first quartile of chickpeas consumption). The associations were non-significant for the intake of dry beans and fresh peas. When study participants with cancer or CVD incidence during follow-up were censored after they were diagnosed – on the assumption that their diet could have changed after the diagnosis – the results were similar. Individuals in the highest quartile of total legumes and lentils consumption had a lower risk of type 2 diabetes development than those in the lowest quartile [(HR: 61; 95%CI: 0.40, 0.93; *P*-trend = 0.03) and (HR: 60; 95%CI: 0.41, 0.90; *P*-trend = 0.04), respectively]. Otherwise, chickpeas, dry-beans and fresh-peas consumption was not associated with type 2 diabetes incidence.

DISCUSSION

To the best of our knowledge, this is the first prospective study conducted in senior Mediterranean individuals at high cardiovascular risk evaluating the association between consumption of total legumes and its different varieties, and type 2 diabetes. The present study revealed that a higher consumption of total legumes, especially lentils, was associated with a lower risk of type 2 diabetes development. The consumption of chickpeas was borderline significantly associated with a lower risk of type 2 diabetes incidence. Nonetheless, the intake of dry beans and fresh peas was not associated with type 2 diabetes risk. It should be underlined that the theoretical effect of substituting half a serving/day of legumes for half a serving/day of other foods rich in protein or carbohydrates, including eggs, wholemeal and white bread, rice or baked potato, was associated with a significant lower risk of type 2 diabetes incidence. These findings provide new insights into the role of legume consumption in preventing type 2 diabetes.

To date there has been little evidence of the effect of legume consumption on the risk of type 2 diabetes. In agreement with our results, in the India's Third National Family Health Survey, total legume consumption was associated with a reduced prevalence of type 2 diabetes in adult women, but not in men [17]. In a similar manner, in the prospective Shanghai Women's Health Study, total legume consumption and the intake of three mutually exclusive legume groups (soybeans, peanuts and other legumes) were associated with a protection against type 2 diabetes development [22].

Other epidemiological studies, however, have not supported this protective role of total legume consumption on type 2 diabetes risk [18–21,23]. For example, in the Indian Migration Study, no cross-sectional association was observed between legume consumption and type 2 diabetes prevalence [18]. Likewise, Meyer and co-workers [19] found no association between legume consumption and type 2 diabetes incidence in older women during six year of follow-up. Similarly, no significant association was observed in the Malmö Diet and Cancer study [21] and in the Women's Health Study [20] after evaluating a large sample consisting of 27,140 men and women, and 38,018 female health professionals, respectively. Contrary to our results, in the Nurse's health Study [23], a higher risk of type 2 diabetes was observed in those individuals in the 5th quintile *vs* those in the 1st quintile of total legume consumption. However, when they analysed the consumption as an increase of one serving/day, non-significant association was observed.

The discrepancies between our results and those of the aforementioned studies, could be explained by differences in the study design. For instance, in the present analysis we used cumulative average consumption as exposure, while all the other prospective studies, except the Nurse's Health study and the Shanghai Women's Health Study [22,23], used a single measurement at baseline. Discrepancies could also be due to the different characteristics of the study population studied. Participants from the present study were European Mediterranean individuals at high risk of CVD. However, the other studies have been conducted in Asian [17,18,22], American [19,20,23] and

Northern European populations [21]. Another possible explanation is the way as the outcome was defined. In the present study, diabetes was defined following the definition of the American Diabetes Association, but in most of the studies [17,19,20,22,23] diabetes was self-reported. Finally, subtypes of legumes included in the analysis as well as the amount consumed also could explain the heterogeneity in the results. In the present study, we considered legumes as the sum of lentils, chickpeas, dry beans and fresh peas, and the main contributors to total legumes consumption were lentils and chickpeas (both subtypes inversely associated with type 2 diabetes risk in the current analysis). Nonetheless, of the 5 previous prospective published studies, only two of them distinguished between the different subtypes of legumes included [19,23], and contrary to us, they did not include lentils and chickpeas in the analysis.

Various mechanisms could explain the protective role of legume consumption against type 2 diabetes. Legumes are a low-energy but nutrient-dense food group [6] and their consumption, like that of other seeds, could improve cardiometabolic health due to their unique composition in bioactive nutrients and phytochemicals and the complex interplay among them [35]. Recently, the intake of vegetable protein, of which legumes are a good source, has been recently associated with a lower risk of type 2 diabetes in two large US prospective cohorts [36]. Legumes also contain significant amounts of calcium, potassium and magnesium, minerals which intake has been inversely related to type 2 diabetes risk [37–39]. Furthermore, legumes also contain high amounts of polyphenols [40], predominantly phenolic acids and flavonoids with antioxidant and anti-inflammatory properties[6], which may also protect against type 2 diabetes [41]. In addition, legumes are rich in fiber [6], which is associated with higher satiety [42] and improvements in the control of body weight [43], glucose metabolism [44] as well as lower risk of type 2 diabetes incidence [45]. Another explanation for the beneficial effect on type 2 diabetes risk may be the low glycemic index of legumes, which might blunt glycemic excursions and, therefore, pancreatic insulin secretion, both of which are mechanisms involved in the development of type 2 diabetes. In this context, a pooled analysis of randomized clinical trials demonstrated that the consumption of pulses alone or combined with a low glycemic index diet rich in fiber improves markers of long term glycemic control in individuals with or without type 2 diabetes [46]. In addition, a higher risk of type 2 diabetes has been associated with high glycemic index diets, which highlights the biological plausibility of these associations [47,48].

To date, no studies have evaluated the associations between the consumption of lentils, dry beans, chickpeas, or fresh peas and type 2 diabetes incidence. In our study, lentil consumption was significantly associated with a lower risk of type 2 diabetes. The higher flavonoid content in cooked lentils compared to other cooked pulses may explain this finding [49]. However, further studies are needed to better understand the effect of lentil consumption on the incidence of type 2 diabetes and elucidate the underlying biological mechanisms.

We also examined the effect of substituting legumes for other carbohydrate-or protein-rich foods on the risk of type 2 diabetes. Our novel results suggest that replacing eggs, bread, rice or baked potato with legumes has a beneficial effect on type 2 diabetes. These findings support our previous suggestions of legumes as a good substitute for energy dense animal protein sources [6] and other more rapidly digestible carbohydrates [50].

Our study has limitations. First, because type 2 diabetes was a secondary outcome of the PREDIMED study, these analyses conducted in a subgroup of participants without type 2 diabetes should be considered exploratory in nature. Second, our sample population was comprised of older elderly Caucasian individuals at high cardiovascular risk, which limits the extrapolation of our results to other populations. Third, although we used a validated FFQ to assess diet, measurement errors are inevitable.

Our study also has strengths, such as the use of repeated dietary measurements, which allows as to reduce the random measurement error produced by within-person variation and dietary changes during follow-up; the control for many potential confounding variables; the inclusion of sensitivity analyses; and the accurate and blind assessment of incident cases of type 2 diabetes.

CONCLUSIONS

In summary, the current data suggests that a frequent consumption of legumes and particularly lentils could provide benefits on type 2 diabetes development in senior adults at high cardiovascular risk. The substitution of legumes for other protein- or carbohydrate-rich foods is also associated with a lower risk of type 2 diabetes. The present study supports an increased consumption of legumes for type 2 diabetes prevention. However, given the mixed results from previous researches, further studies are needed to confirm our findings and elucidate which mechanisms are involved.

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Authors' responsibilities:

ER, DC, RE, MF, LS-M, FA, RML-R, M Fiol, JL and JS-S *designed the research*. NB-T, AD-L, NR-E, ER, PB-C, DC, RE, MF, LS-M, FA, RML-R, M Fiol, JMS-L, JD-E, OP and JS-S *conducted the research*. NB-T and JS-S *analyzed the data*. NB-T, AD-Land JS-S *wrote the paper*. NB-T and JS-S *had primary responsibility for final content*. All authors read and approved the final manuscript.

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FIGURE LEGEND

Figure 1. The impact of substituting half a serving/day of legumes for half a serving/day of foods rich in proteins or carbohydrates on risk of type 2 diabetes. All HRs were adjusted for age (y), sex, intervention group, cumulative average of alcohol intake (continuous, adding a quadratic term), total energy intake (kcal/d), smoking status (never, former or current smoker), educational level (primary education, secondary education or academic/graduate), leisure-time physical activity (metabolic equivalent task minutes/d), baseline hypertension (yes/no), hypercholesterolemia (yes/no), use of lipid-lowering drugs (yes/no), use of antihypertensive drugs (yes/no), fasting plasma glucose at baseline (<100mg/dL or ≥ 100mg/dL), MedDiet adherence (13-point score) except for meat (11-point score) and fish (12-point score) and BMI (kg/m^2). 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.

Half a serving/day corresponds to 30g of raw legumes, eggs, pasta and rice; 38g of bread; 75g of fish and meat; 100g of baked potato.

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

	Quartile of total legume consumption				
	Q1 (lowest) n=838	Q2 n=837	Q3 n=837	Q4 (highest) n=837	*P*-value†
Total legume consumption, (g/day)	9.64 ± 3.55	16.09 ± 1.41	21.57 ± 1.89	34.60 ± 17.24	
Lentils, g/day	3.58 ± 2.31	5.26 ± 2.13	7.28 ± 2.34	9.97 ± 6.06	
Chickpeas, g/day	2.71 ± 2.02	4.31 ± 1.70	6.06 ± 2.051	9.17 ± 5.53	
Fresh peas, g/day	1.14 ± 1.92	2.57 ± 2.15	2.90 ± 2.84	6.24 ± 14.70	
Dry beans, g/day	2.20 ± 1.97	3.95 ± 1.85	5.32 ± 2.67	9.22 ± 6.22	
Age, years	66 ± 6	67 ± 6	67 ± 6	67 ± 6	0.31
Women, % (n)	59.90 (502)	62.37 (522)	63.80 (534)	62.60 (524)	0.42
Smoking habit, % (n)					0.31
Never	60.74 (509)	60.81 (509)	64.40 (539)	63.92 (535)	
Former	21.72 (182)	22.82 (191)	22.10 (185)	20.79 (174)	
Current	17.54 (147)	16.37 (137)	13.50 (113)	15.29 (128)	
Education, % (n)					0.01
Primary	72.43 (607)	75.87 (635)	76.58 (641)	78.49 (657)	
Secondary	16.59 (139)	16.97 (142)	16.01 (134)	15.05 (126)	
University/graduate	10.98 (92)	7.17 (60)	7.41 (62)	6.45 (54)	
Intervention group, n (%)					0.13
MedDiet + EVOO	32.22 (270)	33.09 (277)	34.65 (290)	33.09 (277)	
MedDiet + Nuts	35.20 (295)	35.72 (299)	36.56 (306)	31.66 (265)	
Control group	32.58 (273)	31.18 (261)	28.79 (241)	35.24 (295)	
BMI, kg/m^2	29.95 ± 3.65	29.68 ± 3.48	30.16 ± 3.54	30.17 ± 3.65	0.02

Leisure time physical activity, METs.min/day	234.21 ± 236.78	228.65 ± 214.85	226.27 ± 215.75	237.12 ± 220.54	0.74
Hypertension, % (n)	90.57 (759)	92.11 (771)	91.52 (766)	92.95 (778)	0.34
Hypercholesterolemia, % (n)	84.25 (706)	83.27 (697)	85.19 (713)	85.90 (719)	0.47
Current medication use, % (n)					
Use of antihypertensive agents	75.78 (635)	76.46 (640)	77.18 (646)	78.61 (658)	0.55
Use hypolipidemic agents	47.37 (397)	49.58 (415)	50.78 (425)	51.25 (429)	0.39
Fasting plasma glucose, mg/dayl	97.57 ± 15.22	97.26 ± 12.93	98.81 ± 16.51	99.32 ± 14.79	0.01
Nutrient intake‡					
Total energy, kcal/day	2381 ± 564	2196 ± 469	2239 ± 533	2230 ± 504	<0.01
Total fat, % of total energy	38.68 ± 6.53	39.13 ± 6.11	38.02 ± 6.15	37.00 ± 6.56	<0.01
Carbohydrate, % of total energy	42.37 ± 7.23	42.09 ± 6.57	42.89 ± 6.43	44.11 ± 7.19	<0.01
Protein, % of total energy	15.75 ± 2.70	16.19 ± 2.64	16.59 ± 2.641	16.69 ± 2.81	<0.01
Alcohol, g/day	10.52 ± 16.71	9.10 ± 12.11	9.09 ± 14.10	7.74 ± 12.33	<0.01
Dietary fiber , g/day	22.43 ± 7.02	24.02 ± 6.27	25.76 ± 6.93	28.98 ± 8.59	<0.01

*Data are expressed as means ± SD for continuous variables and percentage and number (n) for categorical variables.

†P value for differences between quartiles were calculated by chi-square or ANOVA tests for categorical and continuous variables, respectively.

‡All dietary variables were adjusted for total energy intake.

Abbreviations: Q, quartile; MedDiet, Mediterranean diet; EVOO, extra virgin olive oil; METs, metabolic equivalent

Table 2. Energy-adjusted cumulative average legume consumption during follow-up in the study population*

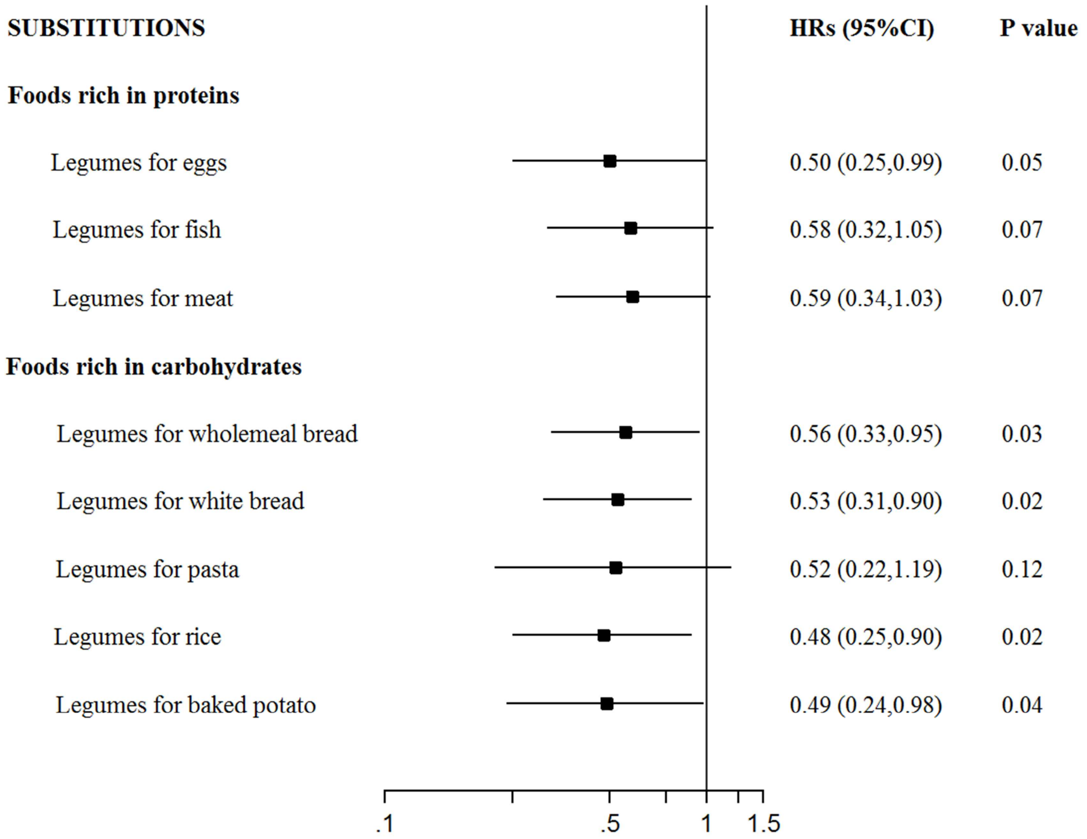
	Means ± SD	Median	Interquartile range
Legumes	20.84 ± 9.60	19.76	15.42 – 24.75
Lentils	6.73 ± 3.51	6.58	4.37 – 8.46
Chickpeas	5.67 ± 3.25	4.98	3.90 – 7.37
Dry beans	5.33 ± 3.59	4.69	3.48 – 8.70
Fresh peas	3.12 ± 5.15	2.76	0.92 – 4.18

*Data are expressed in raw grams per day

Table 3. HRs (95% CIs) of type 2 diabetes incidence according to energy-adjusted quartiles of cumulative average consumption of legumes and its specific subtypes

	Quartiles of legumes consumption				
	1 (lowest)	2	3	4 (highest)	P-trend
Legumes					
Cases/person-years	85/3479	72/3465	62/3456	47/3397	
Median (P25, P75), g/day	12.73 (10.38, 14.29)	17.63 (16.59, 18.70)	21.97 (20.85, 23.23)	28.75 (26.45, 32.66)	
Crude model	1 (ref.)	0.84 (0.61-1.15)	0.74 (0.54-1.03)	0.55 (0.37-0.81)	<0.01
Multivariable model 1	1 (ref.)	0.84 (0.61-1.15)	0.81 (0.58-1.12)	0.59 (0.40-0.87)	0.01
Multivariable model 2	1 (ref.)	0.85 (0.62-1.17)	0.84 (0.60-1.17)	0.62 (0.42-0.93)	0.03
Multivariable model 3	1 (ref.)	0.87 (0.63-1.19)	0.86 (0.61-1.20)	0.65 (0.43-0.96)	0.04
Lentils					
Cases/person-years	99/3465	60/3492	55/3465	52/3376	
Median (P25, P75), g/day	3.77 (2.89, 4.17)	5.62 (4.71, 6.15)	7.66 (7.12, 8.23)	8.88 (8.66, 9.49)	
Crude model	1 (ref.)	0.62 (0.45-0.86)	0.60 (0.43-0.85)	0.60 (0.42-0.87)	0.01
Multivariable model 1	1 (ref.)	0.67 (0.48-0.92)	0.61 (0.43-0.88)	0.63 (0.44-0.91)	0.02
Multivariable model 2	1 (ref.)	0.69 (0.50-0.96)	0.64 (0.45-0.92)	0.66 (0.45-0.96)	0.04
Multivariable model 3	1 (ref.)	0.69 (0.50-0.96)	0.66 (0.46-0.94)	0.67 (0.46-0.98)	0.05
Chickpeas					
Cases/person-years	79/3470	80/3477	60/3461	47/3390	
Median (P25, P75), g/day	3.05 (1.77, 3.57)	4.35 (4.14, 4.73)	6.15 (5.58, 6.71)	8.59 (7.99, 9.13)	
Crude model	1 (ref.)	1.08 (0.79-1.47)	0.80 (0.57-1.13)	0.60 (0.42-0.88)	0.01
Multivariable model 1	1 (ref.)	1.10 (0.80-1.50)	0.89 (0.62-1.27)	0.65 (0.45-0.96)	0.03
Multivariable model 2	1 (ref.)	1.10 (0.80-1.51)	0.92 (0.64-1.31)	0.67 (0.46-0.99)	0.05
Multivariable model 3	1 (ref.)	1.08 (0.79-1.49)	0.91 (0.64-1.30)	0.68 (0.46- 1.00)	0.06
Dry beans					
Cases/person-years	77/3453	75/3480	56/3455	58/3410	
Median (P25, P75), g/day	2.16 (0.68, 2.99)	4.16 (3.84, 4.46)	5.67 (5.08, 6.30)	8.45 (7.66, 9.22)	
Crude model	1 (ref.)	1.02 (0.74-1.40)	0.77 (0.55-1.08)	0.83 (0.57-1.19)	0.31
Multivariable model 1	1 (ref.)	1.03 (0.75-1.41)	0.80 (0.56-1.12)	0.87 (0.61-1.26)	0.50
Multivariable model 2	1 (ref.)	1.05 (0.76-1.44)	0.83 (0.59-1.17)	0.91 (0.62-1.31)	0.65
Multivariable model 3	1 (ref.)	1.05 (0.77, 1.45)	0.84 (0.59, 1.18)	0.93 (0.65, 1.35)	0.75
Fresh peas					
Cases/person-years	61/3418	76/3441	65/3487	64/3458	
Median (P25, P75), g/day	0.22 (0, 0.61)	1.85 (1.33, 2.32)	3.53 (3.15, 3.87)	5.06 (4.52, 7.06)	
Crude model	1 (ref.)	1.18 (0.84-1.66)	0.89 (0.62-1.28)	0.89 (0.61-1.29)	0.22
Multivariable model 1	1 (ref.)	1.26 (0.89-1.79)	1.03 (0.71-1.49)	0.97 (0.66-1.42)	0.51
Multivariable model 2	1 (ref.)	1.26 (0.89-1.79)	1.04 (0.72-1.50)	0.97 (0.66-1.41)	0.50
Multivariable model 3	1 (ref.)	1.27 (0.89-1.81)	1.04 (0.72-1.51)	0.97 (0.66-1.42)	0.49

Cox regression models were used to assess the risk of diabetes incidence by quartiles of cumulative average of intake of legumes and legume subtypes. Multivariable model 1 was adjusted for age (y), sex, intervention group, cumulative average consumption of alcohol (continuous and adding a quadratic term), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure-time physical activity (metabolic equivalent task minutes/day), baseline hypertension (yes/no), hypercholesterolemia (yes/no), use of antihypertensive medication (yes/no), use of lipid-lowering drugs (yes/no) and fasting plasma glucose at baseline (<100mgL or ≥100mg/dL). Model 2 was further adjusted for cumulative average of the 13-point screener (excluding legumes) of MedDiet adherence (continuous). Model 3 was additionally adjusted for BMI (kg/m^2). Extremes of total energy intake (>4000 or < 800 kcal/day in men and >3500 or <500 kcal/day in women) were excluded.


SUBSTITUTIONS
HRs (95%CI)
P value
Foods rich in proteins
Legumes for eggs
0.50 (0.25,0.99)
0.05
Legumes for fish
0.58 (0.32,1.05)
0.07
Legumes for meat
0.59 (0.34,1.03)
0.07
Foods rich in carbohydrates
Legumes for wholemeal bread
0.56 (0.33,0.95)
0.03
Legumes for white bread
0.53 (0.31,0.90)
0.02
Legumes for pasta
0.52 (0.22,1.19)
0.12
Legumes for rice
0.48 (0.25,0.90)
0.02
Legumes for baked potato
0.49 (0.24,0.98)
0.04
.1
.5
1
1.5