Nut consumption and type 2 diabetes risk: a systematic review and meta-analysis of observational studies

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ABSTRACT

Background: Previous meta-analyses, with some methodological controversies, have assessed the relation between nut consumption and type 2 diabetes (T2D) risk and pointed to contradictory results, making desirable the performance of an updated meta-analysis.

Objectives: We aimed to systematically review and meta-analyze all the published studies investigating the relations of total nuts and different types of nuts—i.e., walnuts, peanuts, peanut butter, and total tree nuts—with the prevalence and incidence of T2D.

Methods: A systematic search was conducted in the PubMed and Cochrane databases through 12 August, 2020. The inverse variance method with fixed-effect models was used to pool data across studies, expressed as risk ratios (RRs) or ORs and 95% CIs for prospective cohort and cross-sectional studies, respectively. The Cochran Q test and I^2 statistics were used to test and quantify heterogeneity, respectively. Dose-response meta-analysis was also conducted.

Results: Eight studies (5 prospective and 3 cross-sectional) were included in the quantitative synthesis. Meta-analyses of cross-sectional studies and prospective cohort studies, comparing the highest with the lowest categories, revealed a nonsignificant association between total nut consumption and T2D. Meta-analyses of prospective cohort studies showed an inverse association between peanut butter consumption and T2D incidence (RR: 0.87; 95% CI: 0.77, 0.98; $I^2 = 50.6\%$; $P_{\text{heterogeneity}} = 0.16$), whereas no association was observed between peanuts or tree nuts and T2D. There was no evidence of a linear dose-response or nonlinear dose-response gradient for total nut and peanut consumption in prospective cohort studies. The certainty of the evidence using NutriGrade was very low for all the exposures.

Conclusions: Current results do not demonstrate an association of total nut, peanut, or tree nut consumption with T2D. Peanut butter consumption may be inversely associated with this disease. This review protocol was registered at www.crd.york.ac.uk/prospero/ as CRD42020149756. *Am J Clin Nutr* 2021;113:960–971.

Keywords: nuts, peanuts, walnuts, tree nuts, peanut butter, type 2 diabetes, meta-analysis

Introduction

Nuts are nutrient-dense foods, with a complex matrix of different macro- and micronutrients. They are low in sodium and high in unsaturated fatty acids, dietary fiber, magnesium, plant protein, and phytochemicals, some of which may act synergistically to produce a wide range of health benefits (1–5). It has been consistently demonstrated that substituting

Supported in part by Institució Catalana de Recerca i Estudis Avançats (ICREA) under the ICREA Academia program (to JS-S); Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición (CIBEROBN), an initiative of Instituto de Salud Carlos III (ISCIII) of Spain, which is financed by European Regional Development Fund, "A way to make Europe"/"Investing in your future" grant CB06/03; ISCIII; Juan de la Cierva-Formación postdoctoral fellowships FJC2018-036016-I (to NB-T) and FJCI-2017-32205 (to PH-A); Spanish Ministry of Education, Culture, and Sports grant FPU 17/01925 (to IP-G); and a Diabetes Canada Clinician Scientist Award (to JLS).

Supplemental Tables 1 and 2 and Supplemental Figures 1–5 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: HbA1c, glycated hemoglobin; NHS, Nurses' Health Study; RR, risk ratio; T2D, type 2 diabetes.

Received June 15, 2020. Accepted for publication November 6, 2020.

First published online January 20, 2021; doi: https://doi.org/10.1093/ajcn/nqaa358.

TABLE 1 PICOS criteria for inclusion and exclusion of studies

Parameter	Inclusion criteria	Exclusion criteria
Population	General population of adults	Aged <18 y
Intervention/exposure	Nut consumption including total nuts or subtypes of nuts (walnuts, almonds, peanuts, peanut butter, hazelnuts, tree nuts, etc.)	Dietary exposure does not include nuts as exposure or includes nuts plus other foods (e.g., seeds, legumes)
Comparison	Extreme quantiles	Risk estimates reported on a continuous scale
Outcome	Prevalence or incidence of type 2 diabetes	Other chronic diseases as outcomes
Study design	Cross-sectional and prospective cohort studies	Case-control, ecological, retrospective observational studies, clinical trials, and nonhuman studies

carbohydrates for nuts reduces the glycemic response of the meal with potential metabolic benefits (6, 7). Nuts are a component of numerous dietary patterns, such as the Mediterranean, vegetarian, and Portfolio dietary patterns, that are associated with the prevention of noncommunicable diseases including benefits for type 2 diabetes (T2D) and glycemic control (8–10). Limited research has evaluated the long-term effect of nut consumption on glycemic markers. A recent pooled analysis from intervention trials conducted in individuals with or without diabetes demonstrated that nut consumption reduced fasting insulin and HOMA-IR, whereas no effects on glycated hemoglobin (HbA1c) and fasting glucose were observed (11). The results were slightly different in a meta-analysis including only individuals with T2D, where tree nut intake decreased fasting glucose and HbA1c, but not fasting insulin or HOMA-IR (12).

Regarding epidemiological studies, different meta-analyses have been conducted analyzing the associations between the frequency of nut consumption and diabetes risk, with controversial results. Most of them did not report any significant association when comparing the highest with the lowest categories nor in the dose-response analysis (13–17). Only the meta-analysis conducted by Afshin et al. (18) reported a significant inverse association. However, the validity of the aforementioned analysis has been questioned because of the inclusion of studies with nuts plus peas as exposure and the omission of 1 important prospective study (19). Similarly, other previous meta-analyses also included studies combining nuts plus other plant-foods as the exposure (14, 17), so their results could not be considered as describing a nuts-specific association with T2D.

Hence, to update the analysis and provide clarity on the findings we undertook a systematic review and meta-analysis of all published studies investigating the relations of total nuts and different types of nuts—i.e., walnuts, peanuts, peanut butter, and total tree nuts—with T2D incidence and prevalence. We hypothesized that highest total nut consumption compared with lowest consumption is inversely associated with T2D incidence and prevalence and that, given the differences in their nutritional profiles, different types of nuts are differently associated with this disease.

Methods

The protocol of the present systematic review and meta-analysis is available at https://www.crd.york.ac.uk/PROSPERO/ (CRD42020149756) and followed the methodology described in the Cochrane Handbook for Systematic Reviews of Interventions (20). The results are reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (21).

Search strategy

We performed a systematic search without language restriction and limited to human studies in the Cochrane Library and MEDLINE (PubMed) databases through 30 September, 2019. Searches were updated on 12 August, 2020. **Table 1** depicts the Population, Intervention/exposure, Comparison, Outcome, and Study design criteria used for the present study. The search was complemented with a manual search of all the reference lists of the retrieved articles. **Supplemental Table 1** depicts the complete search strategy.

Study selection

Three independent reviewers (NB-T, IP-G, and PH-A) performed the initial screening of all titles and abstracts of the potentially eligible studies to select those that complied with the eligibility criteria. We only included cross-sectional and prospective studies (with ≥1 y of follow-up) evaluating the association between total nut or specific types of nut consumption and T2D, and reporting effect estimators as ORs, risk ratios (RRs), or HRs and the corresponding 95% CIs for the associations. When >1 report from the same study were identified (22, 23), we included both if different types of exposures were analyzed—i.e., peanut butter in Jiang et al. (22) and walnuts, total tree nuts, and peanuts in Pan et al. (23). If the same exposure was analyzed, the one with the longest follow-up was considered for inclusion (23). We did not include proceedings or published abstracts in the present systematic review and meta-analysis. Although peanuts are legumes from a botanical point of view, owing to their similarities with nuts in terms of nutritional composition, they have also been considered for inclusion in the present systematic review and meta-analysis (1, 24).

Data extraction

Two independent reviewers (NB-T and IP-G) went over the full texts of all the selected reports from the first phase of the screening process and extracted relevant data from the studies that met all the eligibility criteria, including author, year and journal of publication, study name, design and location, total sample size, subject characteristics, time of follow-up (only in prospective cohort studies), funding sources, statistical analyses performed, and effect estimators—OR, RR, HR, and 95% CI.

We extracted multivariable-adjusted estimates, which included BMI as a potential confounder. Moreover, if available, we also extracted multivariable-adjusted estimates without BMI. Three corresponding authors (25–27) were contacted by e-mail to ask for the effect estimates of only nuts as exposure because they reported in their original reports the association between nuts plus other foods, such as seeds or legumes, as exposure and T2D. Unfortunately, only 1 replied (25), stating that nut consumption was very infrequent during the period when the baseline of the Finnish Mobile Clinic was carried out. Therefore, these 3 studies were not included in the analyses.

Assessment of the quality of the included studies

Two different tools were used to evaluate the quality of the included studies according to the study design. For prospective cohort studies, the Newcastle-Ottawa scale was implemented (28). This ranking system consists in a 0- to 9-point scale, where points are given based on 3 different domains: *1*) population selection—maximum of 4 points; *2*) outcome assessment—maximum of 3 points; and *3*) comparability of the groups—maximum of 2 points. A total score of ≥6 points was needed to consider a study as high quality.

For cross-sectional studies, the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used. This tool consists of 14 different questions that guided the authors to arrive at a summary judgment of the overall quality of the study—good, fair, or poor—by taking into account the answers to each item. Any discrepancy was solved by reaching consensus between researchers.

Outcomes

The primary outcome of the present systematic review and meta-analysis was T2D incidence. The secondary outcome was the prevalence of T2D.

Statistical analyses

All data analysis was performed using Stata version 14 software (StataCorp LP). Because <5 study comparisons (29) were included for each analysis, the generic inverse variance method with the fixed-effects model was used to pool the ln-transformed ORs, RRs, and HRs comparing the highest with the lowest categories of nut consumption. For the primary meta-analyses, we used the reported RR from multivariable models with the most complete adjustment for potential confounders and including BMI as a covariate. Separate meta-analyses were conducted for cross-sectional and prospective cohort studies.

A fixed-effect linear dose-response gradient for total nut consumption, peanut consumption, and T2D incidence was estimated following the 2-stage generalized least-squares trend using the method developed by Greenland and Longnecker (30) as described by Orsini et al. (31). This consists of a 2-stage analysis where in the first stage the method fits the dose-response model within each study; then, in the second stage, the study-specific trends are combined. To carry out this method, data on effect estimates with their corresponding 95% CIs, doses, and the total numbers of participants and cases for ≥3 categories of exposure were needed. We assigned the mean or median of nut consumption in each category if it was directly reported. For studies that reported ranges, we converted it to specific doses. If open-ended extreme categories were reported, the median of the smallest group was estimated assuming that the beginning was 0, and for the largest dose group, the median minus the beginning value of the adjacent category was added to the beginning value of the last group. Some studies reported the information on nut consumption in servings and others in grams. Therefore, we standardized dose to the same unit, converting servings into grams per day, considering 28 g as 1 serving, unless otherwise indicated by the authors in the original report. When studies did not report sample size or person-years per category, we considered the categories of equal size. When cases per category were not available, we imputed them using the method described by Bekkering et al. (32).

To model the potential nonlinear associations between the aforementioned types of nuts and T2D incidence, we used restricted cubic splines (MKSPLINE procedure in Stata), which were combined using multivariate meta-analysis. To test for evidence of nonlinearity we used the Wald test, which constrains the regression coefficient for the second spline as equal to 0 (33). P values < 0.05 indicated nonlinearity.

For all meta-analyses, interstudy heterogeneity was estimated by the Cochran Q statistic and quantified by the I^2 statistic, where $I^2 \geq 50\%$ and $P_{\text{heterogeneity}} < 0.10$ were considered as substantial heterogeneity.

We conducted a sensitivity analysis by excluding 1 study at a time from the meta-analyses with >2 study comparisons and recalculating the summary risk estimates. When the removal of a study changed the magnitude (by >10%), the significance, and/or the direction of the association, or the evidence of heterogeneity, it was considered as influential. Because BMI could be not only a confounder, but also a mediator between nut consumption and T2D, whenever possible we repeated the meta-analyses on the multivariable-adjusted model without adjustment for BMI.

We could not explore sources of heterogeneity or publication bias because <10 study comparisons were included in each analysis (20).

Grading the evidence

Two independent researchers (NB-T and IP-G) rated the overall quality and the strength of the evidence of the meta-analysis using the NutriGrade system (34). A meta-analysis receives a maximum of 10 points according to the 8 different items that compose this tool: risk of bias/study quality/study limitations (0–2 points); precision (0–1 point); heterogeneity (0–1 point); directness (0–1 point); publication bias (0–1 point); funding bias (0–1 point); effect size (0–2 points); and dose-response (0–1 point). Based on the total NutriGrade score obtained, the overall quality of the meta-evidence was considered as very low (0–3.99 points), low (4–5.99 points), moderate (6–7.99 points), or high (8–10 points). Dissimilarities between researchers were resolved by consensus.

Results

Study selection process

Figure 1 depicts the flow diagram of the selection process. We identified 1111 articles; after removing duplicates, 1004

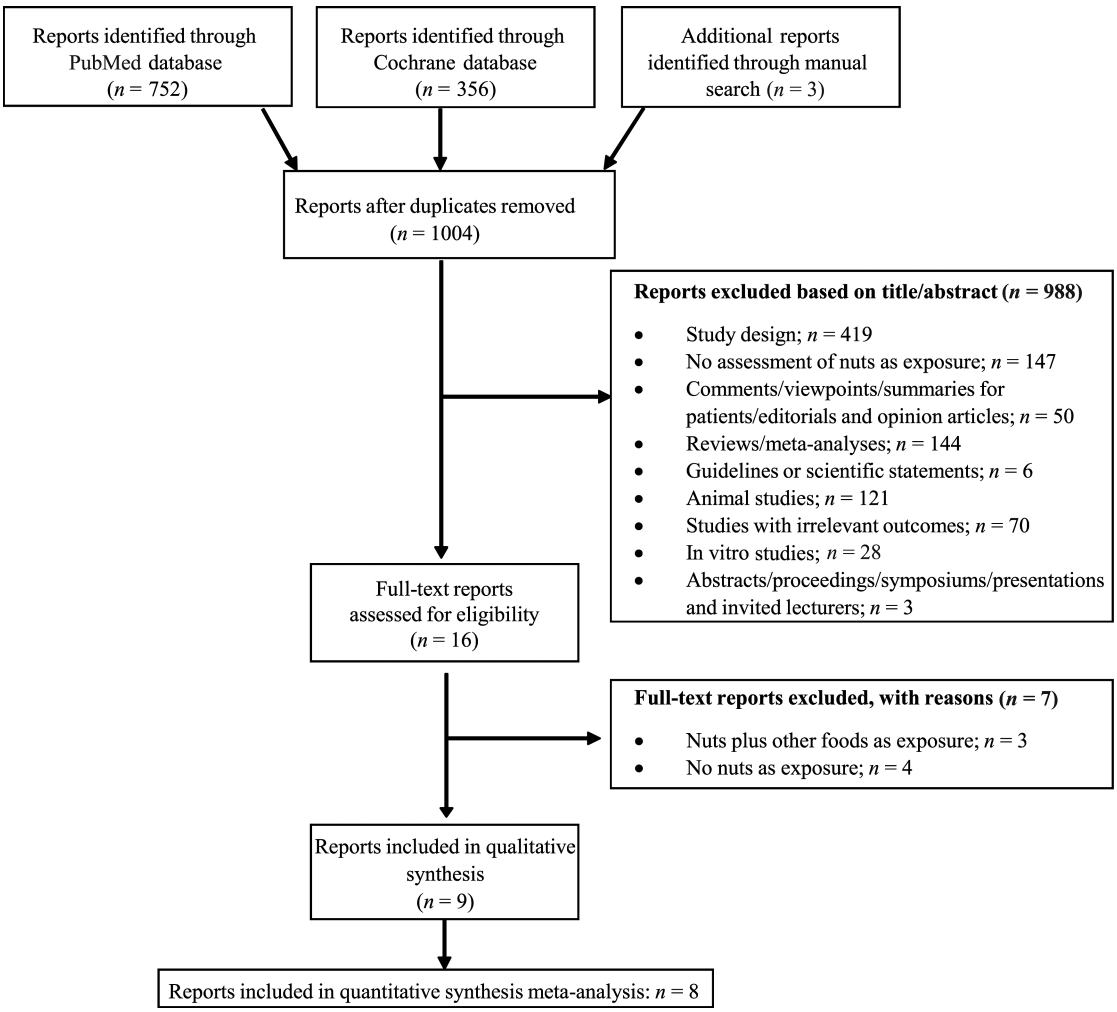

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

articles were checked for eligibility based on the title and abstract. Finally, 9 studies were selected for the present systematic review and meta-analysis: 3 cross-sectional study comparisons for total nuts (35–37); 1 cross-sectional study comparison for walnuts (36); 4 prospective cohort study comparisons (3 reports) for total nuts (23, 38, 39); 3 prospective cohort study comparisons (2 reports) for peanuts (23, 40); 2 prospective cohort study comparisons for peanut butter (22, 38); 2 prospective cohort study comparisons (1 report) for total tree nuts (23); and 1 prospective cohort study comparison for walnuts (23).

One of the selected prospective cohort studies (41) reported the risk estimate on the continuous scale instead of using quantiles of total nut consumption. As a consequence, we did not include this report when comparing the highest with the lowest category nor in the dose-response analysis.

Characteristics of the included studies

Table 2 shows the characteristics of the 9 included reports. The year of publication ranged from 2002 to 2018. Five studies were conducted in the United States, 3 in Europe, and 1 in Asia. For prospective cohort studies, the follow-up length ranged from 4.6 to 22 y. Five studies included only females, 1 only males, and 3 both. Nut consumption was assessed by an FFQ in all the studies except for 1 that used a 24-h dietary recall (36). Of the prospective cohort studies, only 2 were considered as low quality, whereas the quality of all the cross-sectional studies was judged as fair because of characteristics inherent to the study design. All selected studies included BMI as a covariate in their multivariable-adjusted model. Only 1 cross-sectional study (37) and 1 prospective cohort (23) reported multivariable-adjusted estimates with and without BMI.

Meta-analyses of cross-sectional studies

Figure 2 shows the superplot of the summary estimates for the fixed-effect meta-analyses of the associations of total nut and walnut consumption with T2D prevalence.

Three cross-sectional studies involving 72,559 participants and 7559 cases analyzed the association between total nut consumption and T2D prevalence (**Supplemental Figure 1**). No association was observed comparing the highest and lowest categories of consumption (OR: 0.91; 95% CI: 0.83, 1.01; $I^2 = 0\%$; $P_{\text{heterogeneity}} = 0.39$).

TABLE 2 Characteristics of studies included in the systematic review and meta-analysis[1]

Study	Country	Study name	Design	Population	Nut consumption assessment method	Type of nuts	Nut intake	RR/HR/OR (95% CI)[2]	Age, y	Follow-up,[3] y	Incident cases	Funding source	Quality[4]
Jiang et al. (22)	USA	Nurses' Health Study	Prospective	83,818 F	FFQ (self-administered)	Total nuts and peanut butter	≥5 times/wk vs. never/almost never	0.71 (0.57, 0.87)	35–59	16	3206	Agency	5
Parker et al. (38)	USA	Iowa Women's Health Study	Prospective	35,988 F	FFQ (not specified)	Total nuts (not specified)	≥5 times/wk vs. <1/mo	1.51 (1.13, 2.04)	55–69	11	1831	Agency	6
						Peanut butter		0.97 (0.80, 1.18)					
Villegas et al. (40)	China	Shanghai Women's Health Study	Prospective	64,191 F	FFQ (face-to-face visit)	Peanuts	Quintile 5 vs. quintile 1	0.80 (0.68, 0.93)	40–70	4.6	1605	Agency	7
Kochar et al. (39)	USA	Physicians' Health Study I	Prospective	20,224 M	FFQ (self-administered)	Total nuts (peanuts and tree nuts)	≥7/wk vs. <1/wk	0.87 (0.61, 1.24)	40.7–87.1	19.2	1828	Agency–industry	4
von Ruesten et al. (41)	Germany	EPIC-Potsdam	Prospective	9098 M; 14,433 F	FFQ (self-administered)	Total nuts (peanuts, walnuts, Para nuts)	Continuous: 5-g/d increase	0.95 (0.90, 1.01)	35–65	8	837	Agency	8
Pan et al. (23)	USA	Nurses' Health Study I	Prospective	58,063 F	FFQ (self-administered)	Total nuts	≥5 servings/wk vs. never/rarely	1.00 (0.87, 1.14)	55–77	22	5121	Agency–industry	6
						Tree nuts		1.00 (0.86, 1.15)					
						Peanuts		1.05 (0.92, 1.19)					
		Nurses' Health Study II		79,893 F		Total nuts		1.02 (0.85, 1.23)	35–52	18	4098		
						Tree nuts		0.94 (0.75, 1.17)					
						Peanuts		1.01 (0.81, 1.25)					
		Nurses' Health Study I and II		137,956 F		Walnuts	≥2 servings/wk vs. never/rarely	0.76 (0.62, 0.94)	NHSI = 55–77 NHSII = 35–52	NHSI = 22 NHSII = 18	9219		
Ibarrola-Jurado et al. (35)	Spain	PREDIMED Study	Cross-sectional	3067 M; 4143 F	FFQ (face-to-face visit)	Total nuts (peanuts, almonds, hazelnuts, walnuts, pine nuts, pistachios, macadamia, and cashews)	<1 serving/wk vs. never/rarely	0.87 (0.78, 0.99)	55–80	—	3506	Agency	Fair
Brown et al. (37)	England, Wales, and Scotland	UK Women's Cohort Study	Cross-sectional	34,831 F	FFQ (self-administered)	Total nuts (almonds, cashews, peanuts, pecans, pistachios, and walnuts)	>Daily vs. no nuts	0.89 (0.32, 2.46)	35–69	—	630	Agency	Fair
Arab et al. (36)	USA	NHANES	Cross-sectional	34,121 M&F	24-h dietary recall	Total nuts (walnuts and other nuts)	Consumers vs. nonconsumers	1.01 (0.84, 1.20)	18–80	—	3423	Industry	Fair
						Walnuts		0.47 (0.31, 0.72)			3116		

[1]EPIC, European Prospective Investigation into Cancer and Nutrition; NHS, Nurses' Health Study; PREDIMED, Prevención con Dieta Mediterránea study; RR, risk ratio.
[2]For the highest compared with the lowest categories unless for continuous nuts exposure. ORs for cross-sectional studies and RRs or HRs for prospective studies.
[3]Mean or median.
[4]Assessed by the Newcastle-Ottawa Scale for prospective cohort studies and Study Quality Assessment Tools from the National Heart, Lung, and Blood Institute for cross-sectional studies.

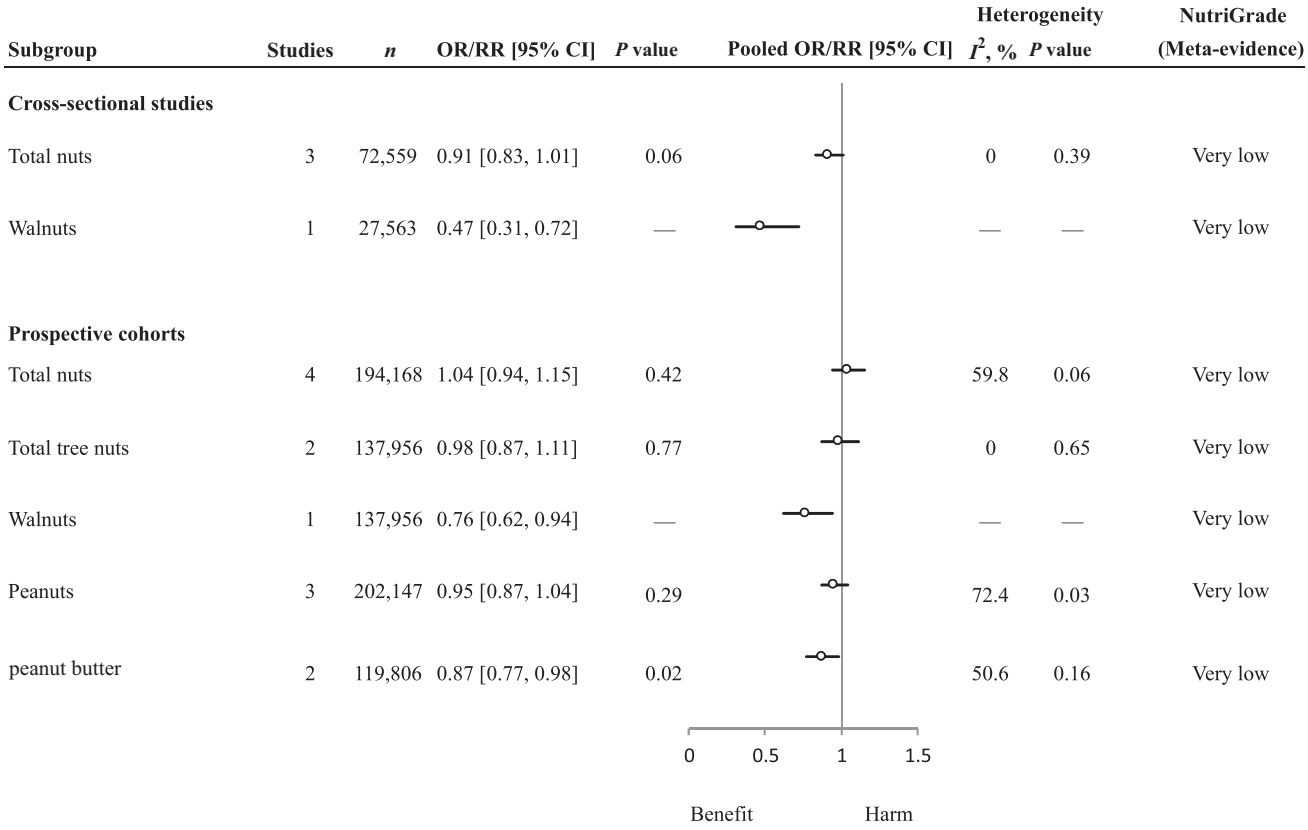

FIGURE 2 Summary of the pooled risk estimates of cross-sectional studies and prospective cohort studies assessing the associations of total nuts and different types of nuts with type 2 diabetes. Analyses were conducted using generic inverse variance fixed-effects models. The circles present the pooled risk estimates. $I^2 \geq 50\%$ indicates substantial heterogeneity. RR, risk ratio.

Only 1 cross-sectional study, including 27,563 participants and 3116 cases, analyzed the association between walnut consumption and T2D prevalence. The results showed that those individuals consuming walnuts with high certainty were at lower risk of having T2D than nonconsumers (OR: 0.47; 95% CI: 0.31, 0.72; $P < 0.01$). We could not undertake a meta-analysis for this exposure because only 1 study comparison was available for the analysis.

Meta-analysis of prospective cohort studies

Figure 2 depicts the superplot of the summary estimates for the fixed-effect meta-analyses of the associations of total nut, peanut, peanut butter, total tree nut, and walnut consumption with T2D incidence. **Supplemental Figures 2–5** show individual forest plots for each meta-analysis comparing the highest and lowest categories of consumption. There was no association between total nuts (RR: 1.04; 95% CI: 0.94, 1.15; $I^2 = 59.8\%$; $P_{\text{heterogeneity}} = 0.06$) or total tree nuts (RR: 0.98; 95% CI: 0.87, 1.11; $I^2 = 0\%$; $P_{\text{heterogeneity}} = 0.65$) and T2D incidence. Only 1 prospective cohort study (23) including 137,956 participants from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) has analyzed the association between walnut intake and the risk of T2D incidence. The results showed that those consuming ≥2 servings/wk had a 24% lower risk of developing T2D than those that never or almost never consumed walnuts. We were not able to perform a meta-analysis with this type of nut because of the inclusion of only 1 study comparison for this analysis. Regarding peanut consumption, no association was observed with T2D incidence (RR: 0.95; 95% CI: 0.87, 1.04; $I^2 = 72.4\%$; $P_{\text{heterogeneity}} = 0.03$). Peanut butter consumption was the only type inversely associated with T2D incidence (RR: 0.87; 95% CI: 0.77, 0.98; $I^2 = 50.6\%$; $P_{\text{heterogeneity}} = 0.16$).

There were no significant linear or nonlinear dose–response relations between total nuts or peanuts and T2D incidence (**Figures 3**, **4**).

Sensitivity analyses

Leave-one-out analysis.

Supplemental Table 2 displays the sensitivity analyses of the systematic removal of 1 study at a time and the recalculation of the association estimates in those meta-analyses with ≥3 study comparisons. The systematic exclusion of each of the cross-sectional studies from the meta-analysis of total nut consumption and T2D prevalence showed that the removal of Arab et al. (36) modified the significance of the association from nonsignificant (OR: 0.91; 95% CI: 0.83, 1.01; $I^2 = 0\%$; $P_{\text{heterogeneity}} = 0.39$) to significant (OR: 0.87; 95% CI: 0.77, 0.98; $I^2 = 0\%$; $P_{\text{heterogeneity}} = 0.97$). Regarding the association between total nuts and T2D incidence in prospective cohort studies, the removal

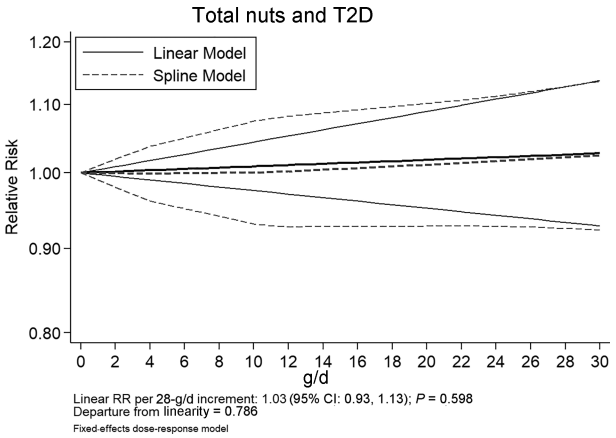

FIGURE 3 Linear and nonlinear dose–response relation between a 28-g increase in total nut intake and the risk of T2D ($n = 4$ study comparisons) in prospective cohort studies. The 2-stage generalized least-squares trend method was used for the linear dose-response and restricted cubic splines combined using multivariate meta-analysis for the nonlinear association. Each study was centered to the baseline reference dose for the estimation of the risk of increasing the dose. The risk ratios are plotted on the log scale. A dosage of 0 g/d served as the reference. RR, risk ratio; T2D, type 2 diabetes.

of Parker et al. (38) explained all the heterogeneity ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.73$). Finally, in the meta-analysis of prospective cohort studies of peanut consumption and T2D incidence, the removal of Pan et al. (23) NHSI changed the significance of the association from nonsignificant to significant (RR: 0.87; 95% CI: 0.76, 0.98; $I^2 = 65.7\%$; $P_{\text{heterogeneity}} = 0.09$), without changing the evidence for heterogeneity, or the direction or magnitude of the association. Furthermore, the exclusion of Villegas et al. (40) explained all the heterogeneity ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.76$).

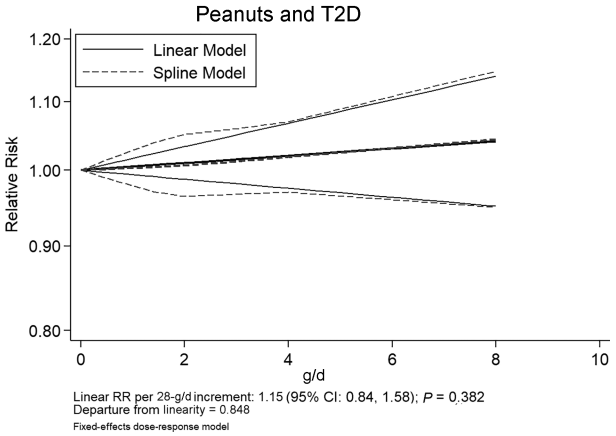

FIGURE 4 Linear and nonlinear dose–response relation between a 28-g increase in peanut intake and the risk of T2D ($n = 3$ study comparisons) in prospective cohort studies. The 2-stage generalized least-squares trend method was used for the linear dose-response and restricted cubic splines combined using multivariate meta-analysis for the nonlinear association. Each study was centered to the baseline reference dose for the estimation of the risk of increasing the dose. The risk ratios are plotted on the log scale. A dosage of 0 g/d served as the reference. RR, risk ratio; T2D, type 2 diabetes.

Including multivariable-adjusted estimates without BMI in the meta-analyses.

In cross-sectional studies, only Brown et al. (37) reported multivariable-adjusted estimates with and without BMI for the association between total nuts and T2D prevalence. Therefore, we were not able to repeat this meta-analysis because the other 2 included studies adjusted for BMI in their multivariable model. In the original article of Brown et al. (37), adjusting for BMI changed the OR (95% CI) from 0.54 (0.20, 1.50) to 0.89 (0.32, 2.46), without changing the significance of the results.

Regarding prospective cohort studies, only 2 reports (1 article including the NHSI and NHSII cohorts) reported both multivariable-adjusted estimates with and without BMI for the associations of total nuts, total tree nuts, and peanuts with T2D incidence (23). Therefore, we could only just repeat the meta-analysis for total tree nuts and T2D incidence, because other studies (38–40) that did not report the aforementioned information were included in the other analyses. The risk estimates for the meta-analysis of total tree nuts substantially changed from nonsignificant to significant when we did not consider BMI as a covariate in the adjustment model (RR: 0.85; 95% CI: 0.75, 0.95; $I^2 = 70.0\%$; $P_{\text{heterogeneity}} = 0.07$). In the original report of Pan et al. (23), when BMI was not included in the models as a covariate, individuals consuming ≥5 servings/wk had 13% and 23% lower risk of T2D incidence in the NHSI and NHSII cohorts, respectively, than those who almost never consumed total nuts. However, this association became no longer significant after adjusting for BMI. The nonsignificant association between peanuts and T2D incidence was not modified by the exclusion of BMI in the adjustment models, neither for NHSI nor for NHSII (23). Similarly, the significant protective association between walnut consumption, which was only studied in NHSI and NHSII combined, and T2D incidence was also not changed (RR: 0.67; 95% CI: 0.54, 0.82 for ≥2 servings/wk compared with never) when the authors did not include BMI as a potential confounder (23).

NutriGrade assessment.

Table 3 shows the NutriGrade evaluation for the overall certainty of the evidence for all the meta-analyses. The evidence was rated as very low for all the exposures. This was due to the presence of heterogeneity, indirectness (with the exception of total nuts in cross-sectional studies), and funding bias; the impossibility of estimating publication bias; and the absence of a dose–response relation.

Discussion

We conducted a systematic review and meta-analysis of 3 cross-sectional and 6 prospective cohort studies to evaluate the association between nut consumption and T2D prevalence or incidence. Pooled analyses of cross-sectional studies showed no significant association between total nut consumption and T2D prevalence. The results of the meta-analyses of prospective cohort studies suggest that peanut butter consumption is inversely associated with T2D incidence. No association was observed between total nut consumption and T2D incidence, nor between the type of nuts (peanuts, total tree nuts) and T2D incidence. A meta-analysis for walnut consumption could not be undertaken

TABLE 3 NutriGrade assessment of the systematic review and meta-analyses assessing the association between nut consumption and type 2 diabetes risk[1]

Study type	Studies, *n*	Effect Estimate (95% CI)	Risk of bias	Precision	Heterogeneity	Directness	Publication bias	Funding bias	Dose-response	Final score	Meta-evidence
Total nuts—cross-sectional studies	3 (observational studies)	OR: 0.91 (0.83, 1.01)	1	1	0	0	0	0	0	2	Very low
Total nuts—prospective studies	4 (observational studies)	RR: 1.04 (0.94, 1.15)	1	1	0	0	0	0	0	2	Very low
Total tree nuts—prospective studies	2 (observational studies)	RR: 0.98 (0.87, 1.11)	1	1	0	0	0	0	0	2	Very low
Peanuts—prospective studies	3 (observational studies)	RR: 0.95 (0.87, 1.04)	1	1	0	0	0	0	0	2	Very low
Peanut butter—prospective studies	2 (observational studies)	RR: 0.87 (0.77, 0.98)	1	1	0	0	0	0	0	2	Very low
Walnuts—cross-sectional studies	1 (observational study)	OR: 0.47 (0.31, 0.72)	0.5	1	0	0	0	0	0	1.5	Very low
Walnuts—prospective studies	1 (observational study)	RR: 0.76 (0.62, 0.94)	1	1	0	0	0	0	0	2	Very low

[1] RR, risk ratio.

because only 1 study comparison was detected in both cross-sectional and prospective cohort studies. However, both studies showed a significant inverse association between this type of nut and T2D.

Previous meta-analyses have also focused on summarizing data regarding nut consumption and T2D (13–17, 18). However, some of them included studies analyzing nuts plus seeds as the exposure (14, 17, 18), which may be considered as a limitation (i.e., lack of specificity) owing to the merged exposures. Moreover, in 1 of the previous meta-analyses, the authors also pooled studies assessing nuts as categories and as a continuous exposure in the same analysis (17) when conducting an analysis comparing extreme categories. With the present meta-analysis, we aimed to update findings and deal with these limitations by solely including those studies that specifically reported nut consumption as the exposure and T2D as the outcome.

To the best of our knowledge, this is the first systematic review and meta-analysis of cross-sectional studies evaluating the association between nut consumption and T2D prevalence. Our results found no association between consumption of total nuts and T2D, included data from 3 different populations, and are in line with the results observed in the meta-analysis of prospective cohort studies. Regarding walnut consumption, it is important to highlight that only 1 cross-sectional study was found (36), and even though the consumption was significantly and inversely associated with T2D, these findings need to be further studied.

Our results regarding prospective cohort studies are in line with previous meta-analyses (13, 14, 17), despite some of them (14, 17) not considering nut consumption alone. In fact, discrepancies with the results reported by Afshin et al. (18) might be due to the aforementioned methodological issues. Even though previous studies have assessed the possible association between total nut consumption and T2D risk, most did not specify the type of nut consumed, therefore we were only able to conduct analyses for total tree nuts, peanuts, and peanut butter, but not for other types of nuts. In our study, peanut butter consumption showed a significant inverse association with T2D risk. Results should be taken with caution because data for the analysis of peanut butter consumption and T2D were drawn from 2 cohorts of women: the NHSI and Iowa Women's Health Study (22, 38). Peanut butter intake is likely the greatest source of nuts in the US diet (42). Therefore, because the results come only from 2 American cohorts, this is likely why peanut butter consumption showed a significant association in this meta-analysis. However, other types of nut sources are under-consumed in the United States, which could make it more difficult to see an association. It is important to highlight that we detected 1 prospective cohort (23) study analyzing the association between walnut consumption and T2D risk. Although we could not perform a meta-analysis for this type of nut, the study reported an inverse significant association when comparing extreme categories of consumption. Importantly, this prospective study included data from 2 well-conducted American cohorts with repeated measures of nut consumption over time and after 10 y of follow-up. Differences in the nutritional characteristics of nuts and peanuts in terms of concentration and combinations of fatty acids, micronutrients, and bioactive compounds, as well as the choice of different portion sizes, suggest that certain types of nuts may be differently associated with risk of T2D (43). However, owing to the limited

number of studies included in previous meta-analyses and the present analyses, this association remains unclear.

It is important to highlight that even though the present results are in line with previous meta-analyses, they differ from those of short-term clinical trials where nut consumption has been shown to have a beneficial effect on glycemic control in individuals either with or without diabetes (11, 12) when compared with other foods. However, clinical trials vary in terms of the background diets and intervention comparators, which could clearly influence the outcome. Moreover, these clinical trials are testing a different hypothesis because they compare the effect of nuts with those of other foods, but not the association between the frequency or amount of nuts per se and T2D as in the present meta-analysis. This could be the reason for the divergent results along with the limitation of confounding in observational studies. Finally, these trials focused on intermediate outcomes, which call into question their relevance for T2D prevention because there are several pathways to clinical events (44). Nuts are rich in different nutrients that may interact synergistically to beneficially modify T2D risk factors. In particular, unsaturated fatty acids, fiber, polyphenols, arginine, and magnesium may play a role in glucose and/or insulin homeostasis and thus be protective against T2D incidence and/or progression (45). Moreover, despite being a high-energy food, nut intake seems not to induce weight gain and appears to reduce hunger (46). In addition, they have a decreased bioavailability of metabolizable energy, because the energy provided by nuts has been seen to be much less than that estimated by the Atwater factors (47, 48). Therefore, body weight may mediate the association between nuts and the risk of T2D. It may be also worth mentioning that nut intake is prospectively associated with decreased risk of overweight/obesity and weight gain (49). A reduction in weight gain (owing to greater satiety signaling and reduced bioavailability of energy) may be on the causal pathway between the exposure (nuts) and the outcome (T2D). The loss of significance with attenuation of the risk estimates in the primary analyses for tree nuts, compared with sensitivity analyses in which analyses were restricted to risk estimates without adjustment for BMI, support body weight changes as a mediator of the reduction in the risk of T2D. Considering our results, nuts' protective effect on T2D might be strengthened when they are included as part of a healthy dietary pattern. In fact, the most recent meta-analysis of 9 prospective studies (50) found that the negative association between plant-based dietary patterns and risk of T2D was increased when healthy plant-based foods (i.e., fruits, nuts, vegetables, whole grains, and legumes) were included in the definition of plant-based patterns (RR: 0.70; 95% CI: 0.62, 0.79). However, although a subanalysis of the PREDIMED (Prevención con Dieta Mediterránea) study conducted in only participants from the Reus center reported a beneficial effect of the Mediterranean diet enriched with tree nuts (walnuts, almonds, and hazelnuts) on T2D prevention (51), the results from the entire study showed a nonsignificant decrease in the incidence of T2D when compared with those participants in the low-fat dietary advice intervention (52).

The present systematic review and meta-analysis has some strengths that should be elucidated. First, a comprehensive systematic search strategy was used to identify all available prospective cohort and cross-sectional studies. Second, studies specifically reporting nut consumption as the exposure were included. Third, the certainty of the evidence was assessed using the NutriGrade approach. However, it also has some limitations that need to be further discussed. The present study focused on the T2D risk attributable to a sole food group (nuts). It has been argued that the overall dietary pattern appears to have a greater effect than individual food groups or nutrients on health, which may explain the difficulty in coming to a conclusion when analyzing an isolated food. However, although evidence from dietary patterns provides the foundation for the development of policy and dietary guidelines, this type of research does not allow us to identify which foods or nutrients are involved in the etiology of disease. Therefore, food-based research is crucial to enhance the mechanistic understanding of diet effects and to isolate the true causative agents (53). Subgroup analyses could not be performed because <10 study comparisons were available. Measurement error in the evaluation of nut consumption could not be ruled out because, except for 1 study, all included studies in the present analyses used self-report FFQs for this purpose. Although the FFQs were previously validated, only in the studies of Jiang et al. (22) and Pan et al. (23) the cumulative average method of nut consumption from FFQ, which reduces measurement error due to intraindividual variation (54), was used as the exposure. Moreover, FFQs follow a food-based design, which may underestimate nut intake more than dish-based FFQs because other ways of eating nuts, in muesli, cakes, nut bars, etc., are not considered. This makes it difficult to fully capture the true exposure. The combination of FFQs with other dietary assessment methods such as 24-h dietary recall or with biomarker concentrations could be a good option to improve the accuracy of the dietary intake assessment in future (55). It is important to highlight that in the case of cross-sectional studies reverse causation cannot be discarded. In addition, owing to the observational nature of the included studies, the possibility of residual confounding could not be ruled out. Another important limitation is that we were not able to repeat all primary meta-analyses including multivariable-adjusted estimates without BMI to explore the potential mediating effect of BMI in the association between nut consumption and T2D. However, our sensitivity analysis revealed that the association between total tree nuts and T2D incidence was largely mediated through BMI because the effect estimates changed from nonsignificant to significant when we repeated the analysis including multivariable-adjusted estimates without BMI. However, without appropriate statistical mediation analyses of repeated assessments, individual studies adjusting with or without BMI cannot claim if BMI is more a confounder or a mediator. Further studies using statistical methods to assess the mediation effect of BMI are needed to clarify if it is a potential confounder or a mediator of the associations of total nut and different types of nut consumption with T2D. Moreover, there was evidence of serious indirectness in all the exposures with the exception of total nuts (meta-analysis of cross-sectional studies) because studies included in the analyses were performed only in women or the results were based on only 1 study report, which limited the generalizability of our findings to men and other populations. Finally, the results are also limited by serious inconsistency because we were unable to explain the observed heterogeneity owing to the limited number of included studies. It is noteworthy that, although for total nuts (meta-analysis of prospective cohort studies) and peanuts there was evidence of substantial heterogeneity, the

removal of 2 studies [(23) and (39), respectively] explained it.

Taken together, the certainty of the evidence in the risk estimates was considered as very low. Future research is likely to alter substantially the risk estimates.

In conclusion, the present systematic review and meta-analysis provides the most updated and comprehensive summary estimates for the associations of total nut consumption and different subtypes of nut consumption with T2D prevalence or incidence. Current results do not demonstrate an association between total nut, peanut, or tree nut consumption and risk of T2D. Peanut butter consumption may be inversely associated with this disease. Based on the low certainty of the evidence, it is premature to conclude that increased nut consumption does not reduce the risk of T2D. The reduction in the risk of T2D seen in sensitivity analyses suggested that weight loss or decreased weight might mediate the reduction in risk, although appropriate statistical mediation analyses using repeated assessments are needed to confirm this assumption.

The authors' responsibilities were as follows—NB-T and JS-S: designed the research; NB-T and IP-G: conducted the research; NB-T: performed the statistical analysis; NB-T, PH-A, and JS-S: had primary responsibility for the final content; and all authors: wrote the paper and read and approved the final manuscript. JS-S reports serving on the boards of the International Nut and Dried Fruit Council (INC) and the Eroski Foundation and receiving grant support from these entities through his institution. He has received research funding from the Instituto de Salud Carlos III, Spain; Ministerio de Educación y Ciencia, Spain; Departament de Salut Pública de la Generalitat de Catalunya, Catalonia, Spain; and the European Commission. He has also received research funding from the California Walnut Commission, Sacramento, CA, USA; La Morella Nuts, Spain; and Borges SA, Spain. He reports receiving consulting fees or travel expenses from the California Walnut Commission, the Eroski Foundation, Nuts for Life, the Australian Nut Industry Council, Nestlé and Abbot Laboratories. He is on the Clinical Practice Guidelines Expert Committee of the European Association for the Study of Diabetes (EASD), and has served on the Scientific Committee of the Spanish Food and Safety Agency, and the Spanish Federation of the Scientific Societies of Food, Nutrition, and Dietetics. He is a member of the International Carbohydrate Quality Consortium (ICQC), and an Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD. DJAJ has received research grants from the Saskatchewan & Alberta Pulse Growers Associations; the Agricultural Bioproducts Innovation Program through the Pulse Research Network; the Advanced Foods and Material Network; Loblaw Companies Ltd.; Unilever Canada and Netherlands, Barilla; the Almond Board of California; Agriculture and Agri-food Canada; Pulse Canada; Kellogg's Company, Canada; Quaker Oats, Canada; Procter & Gamble Technical Centre Ltd.; Bayer Consumer Care, Springfield, NJ; Pepsi/Quaker; INC; Soy Foods Association of North America; Solae; Haine Celestial; the Sanitarium Company; Orafti; the International Tree Nut Council Nutrition Research and Education Foundation; the Peanut Institute; Soy Nutrition Institute (SNI); the Canola and Flax Councils of Canada; the Calorie Control Council; the Canadian Institutes of Health Research (CIHR); the Canada Foundation for Innovation; and the Ontario Research Fund. He has received in-kind supplies for trials as a research support from the Almond Board of California, Walnut Council of California, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, and WhiteWave Foods. He has been on the speaker's panel of, served on the scientific advisory board of, and/or received travel support and/or honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd., the Griffin Hospital (for the development of the NuVal scoring system), EPICURE, Diet Quality Photo Navigation, Better Therapeutics (FareWell), Verywell, True Health Initiative, Heali AI Corp, Institute of Food Technologists, SNI, Herbalife Nutrition Institute, the Saskatchewan & Alberta Pulse Growers Associations, Sanitarium Company, Orafti, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamentals for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, Abbott Laboratories, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Soy Foods Association of North America, the Nutrition Foundation of Italy, Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society, the ASN, Arizona State University, Paolo Sorbini Foundation, and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the USDA to present the 2013 WO Atwater Memorial Lecture. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association. He is a member of the ICQC. His wife, Alexandra L Jenkins, is a director and partner of Glycemic Index Laboratories, Inc., and his sister, Caroline Brydson, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for 1 of his studies. CWCK has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada, Almond Board of California, American Peanut Council, Barilla, CIHR, Canola Council of Canada, INC, International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd., Pulse Canada, and Unilever. He has received in-kind research support from the Almond Board of California, American Peanut Council, Barilla, California Walnut Commission, Kellogg Canada, Loblaw Companies, Quaker (PepsiCo), Primo, Unico, Unilever, and WhiteWave Foods/Danone. He has received travel support and/or honoraria from the American Peanut Council, Barilla, California Walnut Commission, Canola Council of Canada, General Mills, INC, International Pasta Organization, Loblaw Brands Ltd., Nutrition Foundation of Italy, Oldways Preservation Trust, Paramount Farms, Peanut Institute, Pulse Canada, Sun-Maid, Tate & Lyle, Unilever, and White Wave Foods/Danone. He has served on the scientific advisory board for the International Tree Nut Council, International Pasta Organization, McCormick Science Institute, and Oldways Preservation Trust. 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He has received in-kind food donations to support a randomized controlled trial from the Almond Board of California, California Walnut Commission, American Peanut Council, Barilla, Unilever, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, and WhiteWave Foods. He has received travel support, speaker fees and/or honoraria from Diabetes Canada, Dairy Farmers of Canada, FoodMinds LLC, International Sweeteners Association, Nestlé, Pulse Canada, Canadian Society for Endocrinology and Metabolism, GI Foundation, Abbott, Biofortis, ASN, Northern Ontario School of Medicine, INC Nutrition Research & Education Foundation, European Food Safety Authority, Comité Européen des Fabricants de Sucre, and the Physicians Committee for Responsible Medicine. He has or has had ad hoc consulting arrangements with Perkins Coie LLP, Tate & Lyle, and Wirtschaftliche

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Data Availability

Data described in the article, codebook, and analytic code will be made available upon request.

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