Total and subtypes of dietary fat intake and risk of type 2 diabetes mellitus in the Prevención con Dieta Mediterránea (PREDIMED) study[1–3]

Marta Guasch-Ferré,[4,6,7] Nerea Becerra-Tomás,[6,7] Miguel Ruiz-Canela,[7,9] Dolores Corella,[7,10] Helmut Schröder,[8,11] Ramon Estruch,[7,12] Emilio Ros,[7,13] Fernando Arós,[7,14] Enrique Gómez-Gracia,[15] Miquel Fiol,[7,16] Lluís Serra-Majem,[7,17] José Lapetra,[7,18] Josep Basora,[6,7] Nerea Martín-Calvo,[7,9] Olga Portoles,[7,10] Montserrat Fitó,[8,11] Frank B Hu,[4,5,19] Lluís Forga,[20] and Jordi Salas-Salvadó,[6,7]**

Departments of [4]Nutrition and [5]Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA; [6]Human Nutrition Unit, University Hospital of Sant Joan de Reus, Department of Biochemistry and Biotechnology, Faculty of Medicine and Health Sciences, Pere Virgili Health Research Institute, Rovira i Virgili University, Reus, Spain; Biomedical Research Networking Center for the [7]Pathophysiology of Obesity and Nutrition and [8]Epidemiology and Public Health, Carlos III Health Institute, Madrid, Spain; [9]Department of Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain; [10]Department of Preventive Medicine, University of Valencia, Valencia, Spain; [11]Cardiovascular Risk and Nutrition, Hospital del Mar Medical Research Institute, Barcelona, Spain; [12]Department of Internal Medicine and [13]Lipid Clinic, Endocrinology and Nutrition Service, August Pi i Sunyer Institute of Biomedical Research, Hospital Clinic, University of Barcelona, Barcelona, Spain; [14]Department of Cardiology, Organización Sanitaria Integrada Araba, University Hospital, University of the Basque Country, Universidad del País Vasco/Euskal Herriko Unibertsitatea, Vitoria-Gasteiz, Spain; [15]Department of Preventive Medicine, University of Malaga, Malaga, Spain; [16]Institute of Health Sciences, University of Balearic Islands and Son Espases Hospital, Palma de Mallorca, Spain; [17]Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Las Palmas, Spain; [18]Department of Family Medicine, Research Unit, Primary Care Division of Sevilla, Sevilla, Spain; [19]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and [20]Department of Endocrinology and Nutrition, Complejo Hospitalario de Navarra, Navarra Institute of Sanitary Research, Pamplona, Spain

ABSTRACT

Background: The associations between dietary fat and cardiovascular disease have been evaluated in several studies, but less is known about their influence on the risk of diabetes.

Objective: We examined the associations between total fat, subtypes of dietary fat, and food sources rich in saturated fatty acids and the incidence of type 2 diabetes (T2D).

Design: A prospective cohort analysis of 3349 individuals who were free of diabetes at baseline but were at high cardiovascular risk from the PREvención con DIeta MEDiterránea (PREDIMED) study was conducted. Detailed dietary information was assessed at baseline and yearly during the follow-up using a food frequency questionnaire. Multivariable Cox proportional hazards models were used to estimate T2D HRs and 95% CIs according to baseline and yearly updated fat intake.

Results: We documented 266 incident cases during 4.3 y of follow-up. Baseline saturated and animal fat intake was not associated with the risk of T2D. After multivariable adjustment, participants in the highest quartile of updated intake of saturated and animal fat had a higher risk of diabetes than the lowest quartile (HR: 2.19; 95% CI: 1.28, 3.73; and P-trend = 0.01 compared with HR: 2.00; 95% CI: 1.29, 3.09; and P-trend $<$ 0.01, respectively). In both the Mediterranean diet and control groups, participants in the highest quartile of updated animal fat intake had an ∼2-fold higher risk of T2D than their counterparts in the lowest quartile. The consumption of 1 serving of butter and cheese was associated with a higher risk of diabetes, whereas whole-fat yogurt intake was associated with a lower risk.

Conclusions: In a Mediterranean trial focused on dietary fat interventions, baseline intake of saturated and animal fat was not associated with T2D incidence, but the yearly updated intake of saturated and animal fat was associated with a higher risk of T2D. Cheese and butter intake was associated with a higher risk of T2D, whereas whole-fat yogurt intake was associated with a lower risk of T2D. This trial was registered at www.isrctn.com as ISRCTN35739639. *Am J Clin Nutr* 2017;105:723–35.

Keywords: dietary fat, fat subtypes, saturated fat, monounsaturated fat, ω-3 fatty acids, type 2 diabetes, PREDIMED study

[1] Supported by grants from the Carlos III Health Institute [grant RTIC G03/140 (to RE); grant RTIC RD 06/0045 (to MAM-G)], National Center of Cardiovascular Research (grant CNIC 06/2007), European Regional Development Fund (grants PI04–2239, PI 05/2584, CP06/00100, PI07/0240, PI07/1138, PI07/0954, PI 07/0473, PI10/01407, PI10/02658, PI11/01647, P11/02505, and PI13/00462), Ministry of Science and Innovation (grants AGL-2009–13906-C02 and AGL2010–22319-C03), Mapre Foundation, Regional Government of Andalusia Ministry of Health (grant PI0105/2007), Autonomous Government of Catalonia Department of Health (grants ACOMP06109, GVA-COMP2010–181, GVACOMP2011–151, CS2010-AP-111, and CS2011-AP-042), and Regional Government of Navarra (grant P27/2011). Patrimonio Comunal Olivarero, Hojiblanca SA, California Walnut Commission, Borges SA, and Morella Nuts SA donated the olive oil, walnuts, almonds, and hazelnuts, respectively, used in the study.

[2] None of the funding sources played a role in the design, collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

[3] Supplemental Tables 1–5 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

*To whom correspondence should be addressed. E-mail: marta.guasch@urv.cat (M Guasch-Ferré), jordi.salas@urv.cat (J Salas-Salvadó).

Received July 12, 2016. Accepted for publication January 10, 2017.

First published online February 15, 2017; doi: 10.3945/ajcn.116.142034.

INTRODUCTION

The global epidemic of type 2 diabetes (T2D)[21] has become a public health challenge in the past few decades. In 2015, 415 million adults (8.8%) worldwide suffered from T2D, and it is estimated that these rates will increase to 642 million (10.4%) in 2040 (1). T2D accounted for 14.5% of deaths in 2015 and is a serious burden for the health systems of many countries (1). Accruing evidence has demonstrated that the combination of several unhealthy lifestyle factors, including a Western-style diet, reduced physical activity, smoking, overweight, and obesity, explained ~90% of T2D cases (2). Dietary fats, especially the type of fat consumed, have been in the spotlight because of their effects on health. Although the 2015 dietary guidelines for Americans encouraged the consumption of vegetable fats and oils and discouraged the consumption of animal fats (3), past research has mainly focused on evaluating the associations between the quality of fats and the risk of cardiovascular disease (4), and less is known about its influence on the risk of T2D.

Previous observational studies have indicated that total fat intake is not associated with a higher incidence of T2D (5–8), but the evidence for specific types of fat remains inconsistent. For example, the consumption of PUFAs was associated with a lower risk of T2D in the Nurses' Health Study (NHS) (6), but no association was found in the Iowa Women's Health Study (7) despite the fact that both studies included middle-aged women and evaluated diets with the use of food-frequency questionnaires (FFQs). On the other hand, although SFAs have been related to insulin resistance (9), no significant associations were found between SFA intake and the incidence of T2D in several epidemiologic studies (10). Dietary SFAs represent a heterogeneous category of fatty acids that can be obtained from different food sources, including dairy products, meats, processed meats, and eggs. Because of the complexity of these fatty acids and the food matrix in which they are present, SFAs can have different biological effects on human health (11). A meta-analysis of randomized controlled trials (12) has shown that consuming more unsaturated fats (MUFAs and PUFAs) in place of either carbohydrates or SFAs may improve glycated hemoglobin A1C and HOMA-IR. PUFA consumption in particular showed additional benefits on insulin secretion capacity.

Previous data from the Prevención con Dieta Mediterránea (PREDIMED) study (ISRCTN35739639) demonstrated that a dietary pattern high in vegetable fat, primarily nuts and olive oil, decreased the risk of T2D and its complications (13, 14), but to our knowledge, the associations between total and subtypes of fat intake on the incidence of T2D have not been evaluated in Mediterranean individuals at a high risk for cardiovascular disease. Therefore, we prospectively investigated the associations between total and specific types of dietary fat in relation to the risk of T2D in participants free of diabetes at baseline from PREDIMED. We also examined the associations between animal food sources rich in SFAs and T2D risk.

[21] Abbreviations used: FFQ, food-frequency questionnaire; NHS, Nurses' Health Study; PREDIMED, Prevención con Dieta Mediterránea; T2D, type 2 diabetes.

METHODS

Study population

This study was a prospective cohort analysis of individuals free of T2D at baseline in the framework of PREDIMED, a multicenter, parallel-group, randomized clinical trial aimed at evaluating the effects of the Mediterranean diet on the primary prevention of cardiovascular disease in individuals at a high risk for cardiovascular disease (15, 16). From October 2003 to June 2009, 7447 participants were recruited. Participants in PREDIMED were men aged 55–80 y and women aged 60–80 y who were free of cardiovascular disease at baseline but were at a high risk because they had either T2D or ≥3 of the following cardiovascular disease risk factors: current smoking, hypertension, hypercholesterolemia, low HDL cholesterol, overweight or obesity, or family history of premature coronary artery disease. Exclusion criteria were the presence of any severe chronic illness, alcohol or drug abuse, BMI (in kg/m^2) ≥40, and allergy or intolerance to olive oil or nuts (16). For this analysis, we further excluded those participants who had T2D at baseline (n = 3614), lacked measures of blood glucose control (n = 292), were not followed up (n = 94), had implausible daily energy intake (<500 or >3500 kcal/d for women and <800 or >4000 kcal/d for men), or had not completed the baseline FFQ (n = 98). The final analyses included 3349 individuals free of T2D at baseline. The institutional review boards of all recruiting centers approved all procedures. Written informed consent was obtained from all study participants.

Ascertainment of T2D mellitus

The primary endpoint for this analysis was T2D incidence diagnosed according to American Diabetes Association criteria (17), namely fasting plasma glucose concentrations ≥7.0 mmol/L (≥126.1 mg/dL) or 2-h plasma glucose concentrations ≥11.1 mmol/L (≥200.0 mg/dL) after an oral dose of 75 g glucose or the recent use of an oral/insulin medication. A review of all medical records of participants was completed yearly in each center by physicians and investigators who were blinded to the intervention. When new-onset T2D cases were identified on the basis of a medical diagnosis reported in the medical charts or on a glucose test during routine biochemical analyses (done ≥1/y), these reports were sent to the PREDIMED Clinical Events Committee, whose members were also blinded to treatment allocation. Only when a second test with the use of the same criteria and repeated within the next 3 mo was available was the new T2D case definitively confirmed by the adjudication committee (13).

Dietary assessment

Dietary intake was measured with the use of a validated semiquantitative FFQ that trained dietitians completed in a face-to-face interview with the participant at baseline and yearly during the follow-up (18). This questionnaire, which has been validated in a populations at a high risk for cardiovascular disease risk from Spain (18), included 137 food items and 9-level scale-incremental frequencies of consumption for each food item (never or almost never; 1–3 times/mo; 1, 2–4, and 5–6 times/wk; and 1, 2–3, 4–6, and >6 times/d). We used Spanish food composition tables to estimate energy and nutrient intake (19).

Assessment of other covariates

At baseline and yearly during the follow-up, a questionnaire about lifestyle, educational achievement, medical history, and medication use was administered. Physical activity was assessed with the use of the validated Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire (20). Trained personnel took anthropometric and blood pressure measurements. We used calibrated scales and a wall-mounted stadiometer to measure weight and height, respectively, with participants in light clothing and no shoes; we used a validated oscillometer (HEM705CP; Omron) to measure blood pressure in triplicate with a 5-min interval between each measurement, and we recorded the mean of these 3 values. Participants were considered to be hypercholesterolemic or hypertensive if they had previously been diagnosed as such and/or were being treated with cholesterol-lowering or antihypertensive agents, respectively.

Statistical analysis

We calculated the follow-up time for each participant as the interval between the date of random assignment and T2D diagnosis, death from any cause, or the date of the last contact visit, whichever came first. The percentage of energy intake from total and specific dietary fats was calculated with the use of yearly updated measurements to better represent the long-term diet. We used data from baseline to the last FFQ before the onset of T2D to categorize participants into quartiles of dietary fat [MUFAs, PUFAs, SFAs, *trans* fat, animal fat, vegetable fat, marine ω-3 fatty acids, nonmarine ω-3 fatty acids, and ω-6 linoleic acid (18:2n–6)]. Baseline characteristics were presented for the total nondiabetic PREDIMED population and according to extreme quartiles of total and subtypes of fat intake, expressed as the mean ± SD for quantitative traits and *n* (%) for categorical variables. We calculated the correlations between MUFAs and SFAs with different food groups as well as fat type–adjusted residuals of SFAs and MUFAs.

We estimated HRs and 95% CIs of incident T2D according to quartiles of total and specific types of dietary fat. Time-dependent Cox regression analyses were conducted both for baseline and yearly updated measurements of dietary fat. Because the main intervention in PREDIMED was focused on recommendations about the intake of dietary fat and foods rich in dietary fats, which could produce bias from more compliant and health-conscious subjects achieving larger dietary changes, we conducted a stratified analysis for the intervention group (the 2 merged Mediterranean diet groups compared with the control group).

To assess a linear trend, we assigned the median intake within each quartile and modeled the variable as continuous. In addition, we estimated the risk of T2D modeling the updated total and specific fat intake (as percentage energy) with the use of continuous variables. Multivariable model 1 was adjusted for age, sex, BMI, smoking status, educational status, leisure-time physical activity, baseline hypertension or the use of antihypertensive medication, total energy intake, alcohol intake, quartiles of fiber, protein intake, and dietary cholesterol. Model 2 for specific types of fat also included as covariates quartiles of the other subtypes of fat. Model 3 was further adjusted for potential mediators of the associations, including hypercholesterolemia or the use of lipid-lowering drugs and fasting plasma glucose at baseline. All models were stratified by recruitment center, and the analyses for the total population were further adjusted for intervention group. To test the robustness of our findings, we conducted a sensitivity analysis that excluded those participants who developed T2D during the first year of follow-up ($n = 39$). When all types of fats (expressing them as percentages of total energy), protein, alcohol, total energy, and the other covariates are included simultaneously in the models, the coefficient from these models can be interpreted as the estimated differences in the risk of substituting a certain percentage of energy from total or specific types of fat for carbohydrates.

Finally, we also evaluated the association between the updated intake of 1 serving of animal food sources rich in SFAs (processed red meat, red meat, eggs, whole-fat milk, butter, whole-fat yogurt, and cheese) and the risk of T2D. The models were adjusted for the nondietary covariates listed previously and intakes of total energy, alcohol, vegetables, fruits, legumes, cereals, fish, meat, dairy, olive oil, nuts, and biscuits (except if the exposure was included in these food groups). Data were analyzed with the use of Stata version 12.1 (StataCorp LP), and statistical significance was set at $P < 0.05$.

RESULTS

During a median follow-up of 4.3 y, we documented 266 incident cases of T2D. At baseline, participants with a higher total fat intake had lower blood glucose concentrations, a lower intake of total energy, and a higher intake of all subtypes of fat. Participants with higher SFA and *trans* fat intake were more likely to smoke, were less physically active, and consumed less dietary fiber (**Table 1**). Baseline characteristics of the study population according to quartiles of animal and vegetable fat intake and subtypes of PUFA intake are described in **Supplemental Table 1**. At baseline, the mean intake of total fat in percentages of energy in the Mediterranean diet groups was 38.33% ± 6.30% and 37.95% ± 6.56% in the control group. At year 3, total fat intake in the Mediterranean diet group increased to 40.71% ± 5.49% and decreased to 37.40% ± 6.44% in the control group (**Supplemental Table 2**). The Spearman correlation coefficient between MUFAs and SFAs was 0.40. The respective coefficients for type-adjusted residuals of SFAs and cheese, red meat, and processed meat were 0.43, 0.36, 0.30, respectively (**Supplemental Table 3**).

The associations between baseline total and specific dietary fat intake and the risk of T2D are presented in **Table 2**. In the multivariable model, participants in the top quartile of baseline total fat intake had a higher risk of T2D than those in the reference quartile (HR: 1.69; 95% CI: 1.12, 2.54). For PUFAs, the corresponding HR was 1.56 (95% CI: 1.03, 2.35), and for vegetable fat it was 1.62 (95% CI: 1.07, 2.47). Baseline SFAs and animal fat were not significantly associated with T2D risk [multivariable model 3 for the fourth quartile compared with the first quartile: SFAs—HR: 1.16 (95% CI: 0.67, 1.99); animal fat—HR: 1.24 (95% CI: 0.78, 1.98)] (Table 2).

When analyzing yearly updated dietary fats in the total population in the multivariable model adjusted for cardiovascular disease risk factors, dietary factors, and baseline plasma glucose, a higher risk of T2D was observed for those participants in the highest quartile of updated SFA intake (fourth quartile compared with first quartile—HR: 2.19; 95% CI: 1.28, 3.73; P trend = 0.01) (**Table 3**). A 5% energy increment from SFA intake was consistently associated with a 2-fold higher risk of T2D (HR: 2.14; 95% CI: 1.30, 3.52; $P < 0.05$) (**Table 4**). Higher

TABLE 1
Baseline characteristics according to total dietary fat and specific types of fat[1]

	Total population	Total fat		MUFAs		PUFAs		SFAs		*trans* Fat	
		Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
Participants, *n*	3349	838	837	838	837	838	837	838	837	838	837
Age, y	67 ± 6	67 ± 6	66 ± 6	67 ± 6	67 ± 6	67 ± 6	67 ± 6	67 ± 6	66 ± 6	67 ± 6	66 ± 6*
Women, *n* (%)	2082 (62.2)	481 (57.4)	583 (69.7)*	508 (60.6)	571 (68.2)*	523 (62.4)	516 (61.7)	497 (59.3)	574 (68.6)*	543 (64.8)	542 (64.8)*
BMI, kg/m^2	30.0 ± 3.6	29.8 ± 3.3	30.3 ± 3.9*	29.8 ± 3.4	30.3 ± 3.8*	30.2 ± 3.5	29.8 ± 3.7	29.6 ± 3.4	30.5 ± 3.8*	29.6 ± 3.4	30.2 ± 3.7*
Smoking status, *n* (%)											
Never	2092 (62.5)	513 (61.2)	557 (66.6)	509 (60.7)	556 (66.4)	523 (62.4)	523 (62.5)	528 (63.0)	537 (64.2)*	557 (66.5)	525 (62.7)*
Former	732 (21.9)	183 (21.8)	159 (19.0)	193 (23.0)	159 (19.0)	177 (21.1)	193 (23.1)	180 (21.5)	159 (19.0)*	164 (19.6)	171 (21.9)*
Current	525 (15.7)	142 (17.0)	121 (14.5)	136 (16.2)	122 (14.6)	138 (16.5)	121 (14.5)	130 (15.5)	141 (16.9)*	117 (14.0)	141 (15.7)*
Intervention group, *n* (%)											
Mediterranean diet + EVOO	1114 (33.3)	283 (33.8)	278 (33.2)	268 (32.0)	269 (32.1)	294 (35.1)	255 (30.5)*	286 (34.1)	276 (33.0)	270 (32.2)	267 (31.9)
Mediterranean diet + nuts	1165 (34.8)	263 (34.4)	304 (36.3)	269 (32.1)	298 (35.6)	240 (28.6)	327 (39.1)*	281 (33.5)	280 (33.5)	279 (33.3)	297 (35.5)
Control group	1070 (32.0)	292 (34.8)	255 (30.5)	301 (35.9)	270 (32.3)	304 (36.3)	255 (30.5)*	271 (32.3)	281 (33.6)	289 (34.5)	273 (32.6)
Education, *n* (%)											
Primary	2540 (75.8)	656 (78.3)	624 (74.6)	650 (77.6)	609 (72.8)	643 (76.7)	636 (76.0)	649 (77.5)	617 (73.7)	667 (79.6)	616 (73.6)
Secondary	541 (16.2)	108 (12.9)	148 (17.7)	120 (14.3)	165 (19.7)	128 (15.3)	140 (16.7)	115 (13.7)	153 (18.3)	109 (13.0)	148 (17.7)
University or graduate	268 (8.0)	74 (8.8)	65 (7.8)	68 (8.1)	63 (7.5)	67 (8.0)	61 (7.3)	74 (8.8)	67 (8.0)	62 (7.4)	73 (8.7)
Fasting blood glucose, mg/dL	98.2 ± 14.9	99.0 ± 16.5	97.1 ± 13.7*	99.2 ± 16.8	97.6 ± 14.3	98.8 ± 14.3	98.9 ± 15.2	99.0 ± 16.3	98.5 ± 16.5	98.4 ± 15.0	98.9 ± 17.0
Physical activity, MET min/d	232 ± 222	246 ± 250	223 ± 201	242 ± 250	225 ± 200	222 ± 228	256 ± 240*	253 ± 239	207 ± 207*	254 ± 234	207 ± 205*
Hypertension, *n* (%)	3092 (92.3)	774 (92.4)	776 (92.7)	780 (93.1)	764 (91.3)	776 (92.6)	786 (93.9)	768 (91.7)	781 (93.3)	762 (90.9)	773 (92.4)
Hypercholesterolemia, *n* (%)	2857 (85.3)	732 (87.4)	705 (84.2)	727 (86.8)	709 (84.7)	693 (82.7)	718 (85.8)	750 (89.5)	680 (81.2)*	732 (87.4)	691 (82.6)*
Energy and nutrient intake											
Total energy intake, kcal/d	2261 ± 523	2292 ± 565	2175 ± 446*	2307 ± 548	2141 ± 421*	2219 ± 532	2331 ± 516*	2266 ± 548	2282 ± 504	2176 ± 519	2289 ± 532*
Carbohydrates, % energy	42.9 ± 6.9	50.2 ± 5.5	35.8 ± 4.4*	49.6 ± 5.8	36.6 ± 4.8*	47.4 ± 6.4	40.0 ± 6.5*	48.5 ± 6.3	38.2 ± 5.6*	45.3 ± 7.1	40.6 ± 6.4*
Protein, % energy	16.3 ± 2.7	16.6 ± 2.8	16.01 ± 2.4*	16.7 ± 2.7	15.8 ± 2.3*	16.7 ± 3.0	15.8 ± 2.4*	16.0 ± 2.7	16.7 ± 2.7*	16.2 ± 2.8	16.4 ± 2.6
Total fat, % energy	38.2 ± 6.4	30.0 ± 3.1	46.3 ± 3.0*	30.9 ± 4.2	45.5 ± 3.7*	33.0 ± 5.2	41.7 ± 5.7*	32.3 ± 5.2	43.2 ± 5.0*	35.9 ± 6.7	40.8 ± 5.8*
MUFAs, % energy	19.0 ± 4.2	14.3 ± 2.3	23.8 ± 2.8*	13.7 ± 1.8	24.5 ± 2.0*	16.6 ± 3.3	19.6 ± 4.4*	16.0 ± 3.6	21.3 ± 3.9*	18.4 ± 4.5	19.9 ± 4.1*
PUFAs, % energy	6.1 ± 2.0	4.8 ± 1.5	7.2 ± 2.0*	5.6 ± 2.2	6.6 ± 1.6*	4.1 ± 0.5	8.8 ± 1.6*	5.7 ± 2.0	6.3 ± 1.8*	5.9 ± 1.9	6.2 ± 2.0*
SFAs, % energy	9.7 ± 2.2	7.8 ± 1.6	11.5 ± 2.0*	8.3 ± 2.0	11.0 ± 2.0*	9.1 ± 2.3	9.8 ± 2.1*	7.1 ± 0.9	12.6 ± 1.4*	8.0 ± 1.7	11.6 ± 2.1*
trans Fat, % energy	0.22 ± 0.13	0.17 ± 0.11	0.27 ± 0.15*	0.19 ± 0.12	0.24 ± 0.15*	0.20 ± 0.13	0.23 ± 0.14*	0.13 ± 0.08	0.34 ± 0.15*	0.08 ± 0.02	0.41 ± 0.11*
Animal fat, % energy	13.9 ± 4.3	12.0 ± 3.5	15.7 ± 4.3*	13.0 ± 4.0	14.7 ± 4.1*	13.9 ± 4.3	13.3 ± 3.8*	10.2 ± 2.6	18.0 ± 3.8*	11.1 ± 3.3	16.6 ± 4.3*
Vegetable fat, % energy	24.2 ± 6.2	17.9 ± 3.9	30.5 ± 4.8*	17.9 ± 4.2	30.8 ± 4.3*	19.1 ± 4.8	28.4 ± 5.5*	22.1 ± 5.7	25.2 ± 6.3*	24.9 ± 6.6	24.1 ± 6.2
Marine ω-3 FAs, % energy	0.32 ± 0.19	0.30 ± 0.18	0.34 ± 0.19*	0.30 ± 0.19	0.33 ± 0.19*	0.27 ± 0.17	0.34 ± 0.20*	0.32 ± 0.18	0.31 ± 0.19	0.35 ± 0.21	0.29 ± 0.18*
Nonmarine ω-3 FAs, % energy	0.55 ± 0.23	0.44 ± 0.17	0.66 ± 0.25*	0.50 ± 0.23	0.60 ± 0.21*	0.40 ± 0.09	0.78 ± 0.29*	0.50 ± 0.24	0.60 ± 0.20*	0.53 ± 0.25	0.59 ± 0.22*
Linoleic acid, % energy	5.0 ± 1.8	3.9 ± 1.4	6.1 ± 1.9*	4.6 ± 2.1	5.5 ± 1.4*	3.2 ± 0.5	7.5 ± 1.6*	4.7 ± 1.8	5.2 ± 1.7*	4.8 ± 1.7	5.3 ± 1.9*
Dietary fiber, g/d	25.3 ± 8.6	28.85 ± 10.1	21.6 ± 6.2*	29.1 ± 10.1	21.7 ± 6.1*	25.6 ± 9.0	26.3 ± 9.5*	29.4 ± 10.3	21.9 ± 6.7*	27.2 ± 9.7*	23.4 ± 7.6*
Alcohol, g/d	9.11 ± 14.9	11.5 ± 18.7	6.2 ± 10.0*	10.2 ± 17.4	6.7 ± 10.5*	10.2 ± 17.7	8.8 ± 13.5	11.3 ± 18.8	6.4 ± 10.0*	8.8 ± 14.9	7.5 ± 11.4*

[1] All values are means ± SDs unless otherwise indicated. *$P < 0.05$. All quartiles were included in the analyses. Pearson's chi-square test was used for categorical variables, and 1-factor ANOVA was used for continuous variables. EVOO, extra-virgin olive oil; FA, fatty acid; MET, metabolic equivalent task; Q, quartile.

TABLE 2
Risk of type 2 diabetes according to baseline quartiles of total dietary fat and specific types of fat[1]

	Quartiles				
	1	2	3	4	*P*-trend
Total fat					
Cases/person-years	52/3279.04	65/3480.73	64/3521.3	85/3516.2	
Median, % energy	30.55	36.23	40.43	45.53	
Model 1	1 (ref)	1.13 (0.76, 1.67)	1.18 (0.79, 1.75)	1.54 (1.03, 2.31)	0.03
Model 2	1 (ref)	—	—	—	—
Model 3	1 (ref)	1.06 (0.69, 1.61)	1.03 (0.67, 1.57)	1.69 (1.12, 2.54)	0.01
MUFAs					
Cases/person-years	60/3286.3	63/3402.9	60/3563.7	83/3544.3	
Median, % energy	14.12	17.54	20.31	23.90	
Model 1	1 (ref)	0.96 (0.66, 1.39)	0.93 (0.63, 1.37)	1.23 (0.84, 1.79)	0.27
Model 2	1 (ref)	0.88 (0.60, 1.28)	0.82 (0.55, 1.24)	1.02 (0.66, 1.56)	0.89
Model 3	1 (ref)	0.83 (0.55, 1.28)	0.87 (0.57, 1.33)	1.10 (0.71, 1.71)	0.54
PUFAs					
Cases/person-years	55/3423.8	62/3433.04	67/3452.6	82/3487.8	
Median, % energy	4.14	5.20	6.23	8.28	
Model 1	1 (ref)	1.13 (0.77, 1.65)	1.22 (0.84, 1.78)	1.49 (1.05, 2.12)	0.02
Model 2	1 (ref)	1.10 (0.74, 1.63)	1.16 (0.78, 1.74)	1.44 (0.99, 2.08)	0.03
Model 3	1 (ref)	1.25 (0.81, 1.91)	1.32 (0.85, 2.05)	1.56 (1.03, 2.35)	0.03
SFAs					
Cases/person-years	48/3392.9	71/3416.9	68/3522.4	79/3464.9	
Median, % energy	7.29	8.92	10.31	12.21	
Model 1	1 (ref)	1.48 (1.00, 2.17)	1.34 (0.89, 2.02)	1.51 (0.99, 2.30)	0.12
Model 2	1 (ref)	1.46 (0.96, 2.23)	1.36 (0.84, 2.19)	1.53 (0.90, 2.63)	0.21
Model 3	1 (ref)	1.31 (0.84, 2.06)	1.21 (0.74, 1.98)	1.16 (0.67, 1.99)	0.83
trans Fat					
Cases/person-years	56/3554.3	74/3404.3	68/3414.2	68/3424.5	
Median, % energy	0.08	0.15	0.23	0.38	
Model 1	1 (ref)	1.30 (0.89, 1.90)	1.12 (0.77, 1.63)	1.16 (0.78, 1.72)	0.81
Model 2	1 (ref)	1.20 (0.81, 1.78)	0.97 (0.64, 1.49)	0.98 (0.61, 1.55)	0.62
Model 3	1 (ref)	1.59 (1.03, 2.45)	1.22 (0.77, 1.95)	1.26 (0.76, 2.11)	0.83
Animal fat					
Cases/person-years	55/3339.7	71/3476.6	67/3453.5	73/3467.5	
Median, % energy	9.37	12.48	15.01	18.57	
Model 1	1 (ref)	1.19 (0.81, 1.74)	1.11 (0.75, 1.65)	1.13 (0.73, 1.74)	0.70
Model 2	1 (ref)	1.23 (0.84, 1.82)	1.19 (0.79, 1.78)	1.29 (0.83, 2.02)	0.32
Model 3	1 (ref)	1.22 (0.79, 1.86)	1.22 (0.80, 1.87)	1.24 (0.78, 1.98)	0.41
Vegetable fat					
Cases/person-years	55/3333.5	66/3468.4	70/3519.7	75/3475.6	
Median, % energy	17.07	21.97	26.31	31.48	
Model 1	1 (ref)	1.24 (0.86, 1.79)	1.26 (0.87, 1.84)	1.57 (1.06, 2.34)	0.03
Model 2	1 (ref)	1.25 (0.87, 1.81)	1.30 (0.89, 1.89)	1.66 (1.10, 2.49)	0.02
Model 3	1 (ref)	0.97 (0.64, 1.45)	1.27 (0.86, 1.87)	1.62 (1.07, 2.47)	0.01
Marine ω-3 FAs					
Cases/person-years	64/3509.9	77/3436.4	64/3374.2	61/3476.7	
Median, % energy	0.14	0.23	0.32	0.57	
Model 1	1 (ref)	1.26 (0.89, 1.80)	1.06 (0.73, 1.55)	1.11 (0.75, 1.65)	0.91
Model 2	1 (ref)	1.25 (0.87, 1.80)	1.07 (0.73, 1.57)	1.10 (0.73, 1.65)	0.96
Model 3	1 (ref)	1.28 (0.87, 1.88)	1.06 (0.69, 1.61)	1.10 (0.71, 1.72)	0.95
Nonmarine ω-3 FAs					
Cases/person-years	56/3322.3	64/3438.6	74/3476.7	72/3559.7	
Median, % energy	0.35	0.44	0.55	0.80	
Model 1	1 (ref)	1.11 (0.76, 1.60)	1.16 (0.80, 1.70)	1.31 (0.91, 1.88)	0.14
Model 2	1 (ref)	1.02 (0.69, 1.52)	0.97 (0.63, 1.50)	0.97 (0.62, 1.53)	0.84
Model 3	1 (ref)	1.20 (0.78, 1.84)	1.20 (0.75, 1.93)	1.19 (0.72, 1.97)	0.68

(Continued)

TABLE 2 (*Continued*)

	Quartiles				
	1	2	3	4	*P*-trend
Linoleic acid					
Cases/person-years	53/3438.6	61/3414.1	71/3476.9	81/3467.7	
Median, % energy	3.24	4.21	5.20	7.11	
Model 1	1 (ref)	1.15 (0.79, 1.68)	1.28 (0.89, 1.86)	1.52 (1.05, 2.18)	0.02
Model 2	1 (ref)	1.13 (0.76, 1.67)	1.23 (0.80, 1.89)	1.50 (0.97, 2.32)	0.05
Model 3	1 (ref)	1.46 (0.95, 2.25)	1.47 (0.91, 2.37)	1.59 (0.96, 2.63)	0.13

[1] All values are HRs (95% CIs) unless otherwise indicated. Time-dependent Cox regression models were used for all assessments. Multivariable model 1 was adjusted for age, sex, intervention group, BMI (in kg/m^2), smoking status, educational status, leisure-time physical activity, baseline hypertension or the use of antihypertensive medication, total energy intake, alcohol intake, quartiles of fiber, protein intake, and dietary cholesterol; model 2 was additionally adjusted for specific types of fat that were also included as covariates quartiles of the other subtypes of fat; and model 3 was further adjusted for potential mediators of the associations, including hypercholesterolemia or the use of lipid-lowering drugs and fasting plasma glucose at baseline. All models were 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. FA, fatty acid; ref, reference.

SFA intake was associated with T2D in the Mediterranean diet group but not in the control group; however, the interaction between SFAs and intervention group on T2D was not significant (*P*-interaction = 0.19). No significant associations were found for updated total fat intake and T2D incidence in multivariable models adjusted for cardiovascular disease risk factors and dietary factors (**Supplemental Table 4**), but when the model was further adjusted for baseline glucose, higher total fat intake was nonsignificantly associated with the risk of T2D (*P*-trend = 0.06) (Table 3). No significant associations were observed for the updated intake of MUFAs, PUFAs, or *trans* fat and the risk of T2D. In the stratified analysis, the *P*-trend for the updated intake of PUFA consumption in the Mediterranean group was 0.05 (HR: 1.35; 95% CI: 0.85, 2.14). When it was modeled as a continuous variable, the HR of T2D was 1.56 (95% CI: 1.04, 2.34; $P < 0.05$) per each 5% increase in energy from PUFA consumption (Table 4). Similarly, no significant associations were found between the updated intake of marine ω-3 fatty acids, nonmarine ω-3 fatty acids, linoleic acid intake, and T2D (Table 3). Consistent findings were observed when these dietary fats were analyzed as continuous variables per each 5% increase in energy intake (Table 4), but when the intake of marine ω-3 fatty acids was modeled as a continuous variable, we found an inverse association with T2D incidence for the total population analysis (Table 4). In the stratified analysis, each 5% increase in energy intake from linoleic acid was significantly associated with a higher risk of T2D in the Mediterranean diet group (Table 4).

Animal fat intake was strongly associated with a higher risk of T2D in the total population analyses (fourth quartile compared with first quartile—HR: 2.00; 95% CI: 1.29, 3.09; *P*-trend < 0.01) after adjusting for baseline fasting plasma glucose (Table 3). Participants in the higher quartile of updated animal fat intake had an ~2-fold higher risk of T2D than their counterparts in the lower quartile in both the Mediterranean diet and control groups (Table 3). Per each 5% increase in energy intake from animal fat, the risk of T2D increased by 26% (HR: 1.26; 95% CI: 1.04, 1.53; *P*-trend = 0.02) (Table 4). In the stratified analysis that used continuous variables, animal fat intake was associated with a higher risk of T2D only in the Mediterranean diet group. In the total population analyses, although vegetable fat showed a trend toward a higher risk of T2D in model 3 adjusted for baseline plasma glucose (HR: 1.50; 95% CI: 0.99, 2.25; *P*-trend = 0.09) (Table 3), no significant associations were found in the multivariable models not adjusted for plasma glucose (**Supplemental Table 5**) when analyzed as a continuous variable in the sensitivity analysis and when stratified by intervention group.

When we conducted sensitivity analysis by excluding those participants who developed T2D during the first year of follow-up ($n = 39$), the results were consistent with those of the primary analysis. The updated intake of SFAs and animal fat was consistently associated with a higher risk of T2D [multivariable model 3 for the fourth quartile compared with the first quartile: SFAs—HR: 2.46 (95% CI: 1.38, 4.38) and *P*-trend = 0.01; animal fat—HR: 1.87 (95% CI: 1.18, 2.97) and *P*-trend = 0.01], whereas a 5% increase in energy from marine ω-3 fatty acids was associated with a lower risk of TD (HR: 0.32; 95% CI: 0.13, 0.77; $P < 0.01$).

Figure 1 shows the risk of T2D by the updated intake of 1 serving of animal food sources rich in SFAs. Increasing the intake of 12 g butter and 30 g cheese was associated with a higher risk of T2D [HR: 2.42 (95% CI: 1.42, 4.13) and $P < 0.01$ compared with HR: 1.32 (95% CI: 1.15, 1.52) and $P < 0.01$, respectively], whereas the intake of whole-fat yogurt was associated with a lower risk of T2D (HR: 0.65; 95% CI: 0.45, 0.94; $P = 0.02$). No significant associations between red meat, processed meat, eggs, or whole-fat milk and diabetes were observed.

DISCUSSION

In this prospective study of participants at a high risk for cardiovascular disease, we found that the yearly updated intake of SFAs and animal fat, but not the baseline intake, were strongly associated with the risk of T2D after controlling for recognized classical potential confounders and plasma glucose concentrations at baseline. Butter and cheese intake, food sources rich in SFAs, were associated with a higher incidence of T2D, whereas whole-fat yogurt intake was associated with a lower incidence. These findings suggest a potential different role of SFAs on the risk of T2D depending on the food matrix in which they are consumed.

Given that our analyses were conducted in the context of PREDIMED, a nutritional trial that emphasized the intake of nuts

TABLE 3
Risk of type 2 diabetes according to updated quartiles of total and specific types of dietary fat stratified by intervention group[1]

	Total population (n = 3349)		Mediterranean diet group (n = 2279)		Control group (n = 1070)	
	Cases/person-years	HR (95% CI)	Cases/person-years	HR (95% CI)	Cases/person-years	HR (95% CI)
Total fat						
Q1	55/3395.5	1 (ref)	40/2381.3	1 (ref)	21/1032.2	1 (ref)
Q2	71/3459.9	1.54 (1.03, 2.30)	41/2404.2	1.11 (0.69, 1.79)	26/1050.2	0.98 (0.52, 1.86)
Q3	66/3470.1	1.30 (0.87, 1.96)	43/2412.4	0.98 (0.60, 1.61)	19/1059.0	0.87 (0.44, 1.73)
Q4	74/3471.8	1.58 (1.03, 2.42)	44/2411.0	1.08 (0.65, 1.80)	32/1047.0	1.27 (0.70, 2.32)
P-trend		0.06		0.88		0.40
MUFAs						
Q1	65/3390.1	1 (ref)	41/2386.1	1 (ref)	20/1031	1 (ref)
Q2	74/3458.7	1.00 (0.69, 1.46)	45/2408.9	1.03 (0.65, 1.63)	23/1048	1.22 (0.60, 2.46)
Q3	59/3466.5	0.79 (0.51, 1.22)	39/2391.2	0.72 (0.41, 1.26)	30/1051	1.83 (0.86, 3.91)
Q4	68/3481.9	0.80 (0.50, 1.26)	43/2422.6	0.72 (0.41, 1.28)	25/1059	1.38 (0.60, 3.16)
P-trend		0.24		0.16		0.40
PUFAs						
Q1	68/3390.1	1 (ref)	44/2378.8	1 (ref)	21/1040	1 (ref)
Q2	59/3457.5	1.00 (0.67, 1.48)	28/2422.9	0.64 (0.38, 1.06)	20/1041	0.69 (0.35, 1.39)
Q3	66/3478.9	1.15 (0.78, 1.70)	47/2399.1	1.39 (0.89, 2.19)	28/1059	1.01 (0.51, 2.00)
Q4	73/3461.3	1.24 (0.82, 1.85)	49/2408.0	1.35 (0.85, 2.14)	29/1048	0.96 (0.50, 1.86)
P-trend		0.31		0.05		0.72
SFAs						
Q1	45/3421.1	1 (ref)	30/2378.2	1 (ref)	16/1041	1 (ref)
Q2	65/3474.4	1.63 (1.03, 2.58)	40/2430.1	1.50 (0.81, 2.78)	24/1047	1.32 (0.65, 2.69)
Q3	65/3438.7	1.61 (0.97, 2.66)	37/2397.0	1.32 (0.67, 2.59)	27/1045	1.30 (0.59, 2.89)
Q4	91/3463.0	2.19 (1.28, 3.73)	61/2403.6	2.07 (1.00, 4.29)	31/1056	1.43 (0.62, 3.31)
P-trend		0.01		0.09		0.47
trans Fat						
Q1	45/3486.1	1 (ref)	29/2420.9	1 (ref)	21/1066	1 (ref)
Q2	73/3434.8	1.49 (0.97, 2.28)	39/2394.9	1.51 (0.84, 2.71)	25/1039	1.06 (0.56, 2.00)
Q3	71/3440.7	1.22 (0.77, 1.93)	50/2398.4	1.65 (0.93, 2.94)	26/1040	0.93 (0.45, 1.91)
Q4	77/3435.7	1.21 (0.73, 2.01)	50/2394.7	1.51 (0.77, 2.93)	26/1044	0.96 (0.47, 1.97)
P-trend		0.94		0.46		0.85
Animal fat						
Q1	49/3450.0	1 (ref)	33/2397	1 (ref)	15/1042	1 (ref)
Q2	65/3453.5	1.45 (0.94, 2.23)	47/2410	1.63 (0.96, 2.78)	21/1048	1.27 (0.64, 2.51)
Q3	54/3449.8	1.27 (0.81, 2.00)	30/2403	1.08 (0.59, 1.98)	29/1044	1.70 (0.82, 3.50)
Q4	98/3445.0	2.00 (1.29, 3.09)	58/2399	1.92 (1.09, 3.41)	33/1054	1.99 (1.02, 3.88)
P-trend		<0.01		0.07		0.02
Vegetable fat						
Q1	68/3387.7	1 (ref)	42/2383	1 (ref)	24/1036	1 (ref)
Q2	67/3475.0	1.13 (0.78, 1.63)	42/2409	1.02 (0.64, 1.63)	19/1048	0.75 (0.40, 1.40)
Q3	60/3464.3	1.02 (0.68, 1.53)	37/2413	1.06 (0.65, 1.72)	27/1057	1.40 (0.77, 2.53)
Q4	71/3470.2	1.50 (0.99, 2.25)	47/2405	1.47 (0.89, 2.44)	28/1046	1.47 (0.79, 2.75)
P-trend		0.09		0.12		0.12
Marine ω-3 FAs						
Q1	81/3456.2	1 (ref)	54/2407	1 (ref)	27/1063	1 (ref)
Q2	73/3449.5	1.08 (0.75, 1.54)	46/2395	1.11 (0.69, 1.78)	30/1045	1.05 (0.59, 1.86)
Q3	53/3438.7	0.76 (0.51, 1.14)	30/2401	0.76 (0.45, 1.29)	19/1039	0.51 (0.26, 1.02)
Q4	59/3452.9	0.92 (0.61, 1.39)	38/2405	1.00 (0.59, 1.69)	22/1041	0.79 (0.43, 1.46)
P-trend		0.53		0.75		0.39
Nonmarine ω-3 FAs						
Q1	69/3388.9	1 (ref)	42/2374	1 (ref)	19/1031	1 (ref)
Q2	67/3455.2	1.01 (0.68, 1.51)	42/2417	1.38 (0.81, 2.36)	27/1049	1.16 (0.57, 2.36)
Q3	60/3487.0	0.99 (0.61, 1.61)	38/2406	1.09 (0.58, 2.06)	23/1057	0.95 (0.43, 2.10)
Q4	70/3466.1	1.18 (0.70, 2.00)	46/2412	1.14 (0.58, 2.25)	29/1052	0.98 (0.42, 2.29)
P-trend		0.70		0.77		0.75

(Continued)

TABLE 3 (*Continued*)

	Total population (n = 3349)		Mediterranean diet group (n = 2279)		Control group (n = 1070)	
	Cases/person-years	HR (95% CI)	Cases/person-years	HR (95% CI)	Cases/person-years	HR (95% CI)
Linoleic acid						
Q1	68/3396.1	1 (ref)	46/2373	1 (ref)	21/1041	1 (ref)
Q2	53/3464.1	0.89 (0.58, 1.38)	24/2428	0.53 (0.30, 0.94)	19/1043	0.62 (0.31, 1.25)
Q3	75/3474.8	1.25 (0.78, 1.98)	48/2401	1.22 (0.70, 2.13)	30/1058	1.16 (0.56, 2.43)
Q4	70/3462.3	1.01 (0.60, 1.69)	50/2407	1.23 (0.64, 2.38)	28/1046	1.05 (0.52, 2.15)
P-trend		0.97		0.30		0.54

[1] Time-dependent Cox regression models were used for all assessments. The multivariable model was adjusted for age, sex, BMI (in kg/m^2), smoking status, educational status, leisure-time physical activity, yearly updated total energy intake, alcohol intake, yearly updated quartiles of fiber, protein intake, dietary cholesterol, baseline hypertension or the use of antihypertensive medication, baseline hypercholesterolemia or the use of lipid-lowering drugs, and fasting plasma glucose at baseline. The multivariable model for specific subtypes of fat also included as covariates the other subtypes of fat. All models were stratified by recruitment center, and total population models were further adjusted by intervention group. Extremes of total energy intake (>4000 or <800 kcal/d in men and >3500 or <500 kcal/d in women) were excluded. The risk estimates for other models are shown in Supplemental Tables 4 and 5. FA, fatty acid; Q, quartile; ref, reference.

and olive oil (high in dietary fat), we evaluated both the associations between the intake of baseline total and specific fats as well as repeated measurements for the total population and stratified by intervention group in relation to T2D incidence to assess potential bias resulting from our intervention. We found a strong positive association between the yearly updated intake of SFAs and T2D but not for baseline SFA intake. Those participants who had a higher consumption of SFAs during 4.3 y of median follow-up had an ~2-fold higher risk of T2D than their counterparts with lower intakes of SFAs. Per each 5% increase in energy from SFA intake, the risk of T2D increased substantially. However, when we separated the analysis by intervention group, no significant associations between SFAs in relation to T2D were observed in the control group, probably because the Mediterranean diet intervention played an important role in reducing the risk of T2D in the PREDIMED population (13, 14). In addition, we observed a higher risk of T2D for higher intakes of PUFA and linoleic acid only in the Mediterranean diet groups, which could reflect a potential bias from compliance. Those participants who were most compliant (i.e., increasing MUFAs from nuts or olive oil and thereby decreasing other fats) probably had a lower risk of T2D.

Results from the baseline and updated analyses differed in this study. At baseline, the consumption of total fat, vegetable fat, and PUFAs but not SFAs or animal fat was significantly associated with a higher risk of T2D. However, the updated intake of SFAs and animal fat was associated with a higher risk of T2D in the overall population and in the Mediterranean diet group, whereas updated PUFA and linoleic acid intake was only associated with a higher risk of T2D in the Mediterranean diet group. Considering the trial design and differences between baseline and the yearly updated dietary fat intake on T2D, we cannot fully discard a potential bias of those participants who were more compliant and health-conscious and who achieved larger dietary changes as a result of participating in the trial.

Previous studies have been inconsistent in terms of the association between SFA intake and health outcomes. The FAO concluded that SFAs might be associated with insulin resistance and T2D (21), and findings from NHS also indicated that SFA intake was associated with a 34% a a higher risk of diabetes in multivariable models adjusted for diet, but the association was weakened after adjusting for BMI (22). In 2 other prospective studies, incident T2D and conversion to T2D were positively associated with SFA consumption (23, 24). On the other hand, null associations between SFA intake and type 2 diabetes have been shown in long-term cohorts and in a recent meta-analysis of observational studies (10). However, some of the studies included in the meta-analysis were small or did not include mutual adjustment for other types of fatty acids. In the Women's Health Initiative, reducing SFAs, when replaced with carbohydrates, did not reduce the risk of type 2 diabetes after 8.1 y of follow-up (25). Several reasons may account for this finding, including that participants were not at a higher risk of diabetes at baseline than those from other trials that may have included physical activity and weight loss as part of the intervention (25). More recently, a meta-analysis of randomized controlled trials demonstrated that replacing 5% of energy from carbohydrates with SFAs had no significant effect on fasting glucose but lowered fasting insulin. Replacing SFAs with PUFAs significantly lowered glucose, glycated hemoglobin A1C, and HOMA-IR (12). Together, it is important to consider the replacement nutrient when assessing the associations between dietary fat intake and chronic diseases.

The main contributors of the animal sources of SFA intake in our population were cheese (22.9%), red meat (17.6%), and processed meat (8.0%), followed by eggs and other dairy products (ranging from 1% to 5% of the animal SFA intake). Moderate correlations were observed for type-adjusted residuals of SFAs and red meat, processed meat, and total cheese but not for adjusted residuals of MUFAs and these food groups. Results from this study and previous findings from PREDIMED (26) suggest that dairy products, food sources of SFAs, are inversely associated with T2D. Nevertheless, the effect differs depending on the dairy product consumed, and one of the reasons may be the different type of SFAs that these products contain. Individual studies and meta-analyses have shown that higher dairy-fat biomarkers were inversely associated with the risk of T2D (27) but that red meats and processed meats were associated with an increased risk of T2D (28). We found that butter and cheese consumption was associated with a higher risk of T2D, whereas whole-fat yogurt intake was associated with a lower risk of T2D. Although cheese consumption was inversely associated with the risk of diabetes in some studies,

TABLE 4
Risk of type 2 diabetes associated with increases in the percentage of energy from updated total and specific types of dietary fat[1]

	Total population (n = 3349)	Mediterranean diet group (n = 2279)	Control group (n = 1070)
Total fat			
Model 1	1.08 (0.97, 1.21)	1.09 (0.93, 1.27)	1.11 (0.94, 1.31)
Model 2	—	—	—
Model 3	1.08 (0.96, 1.21)	1.09 (0.92, 1.28)	1.09 (0.91, 1.30)
MUFAs			
Model 1	1.02 (0.86, 1.22)	0.96 (0.75, 1.23)	1.13 (0.88, 1.44)
Model 2	0.85 (0.69, 1.04)	0.78 (0.59, 1.02)	0.99 (0.74, 1.34)
Model 3	0.88 (0.71, 1.08)	0.78 (0.59, 1.03)	1.08 (0.79, 1.49)
PUFAs			
Model 1	1.29 (0.92, 1.81)	1.37 (0.90, 2.09)	1.36 (0.83, 2.25)
Model 2	1.28 (0.93, 1.78)	1.43 (0.96, 2.15)	1.31 (0.77, 2.22)
Model 3	1.28 (0.91, 1.81)	1.56 (1.04, 2.34)*	1.17 (0.62, 2.20)
SFAs			
Model 1	1.75 (1.24, 2.46)*	2.18 (1.37, 3.45)*	1.29 (0.79, 2.10)
Model 2	2.34 (1.43, 3.84)*	2.56 (1.28, 5.15)*	1.80 (0.89, 3.66)
Model 3	2.14 (1.30, 3.52)*	2.29 (1.17, 4.50)*	1.54 (0.73, 3.24)
trans Fat			
Model 1	1.57 (0.56, 4.44)	4.57 (1.27, 16.48)*	0.36 (0.07, 1.78)
Model 2	0.39 (0.10, 1.57)	1.00 (0.15, 6.62)	0.12 (0.02, 0.85)*
Model 3	0.49 (0.12, 1.94)	1.42 (0.25, 8.13)	0.16 (0.02, 1.14)
Model 4[2]	1.59 (0.54, 4.72)	5.17 (1.45, 18.38)*	0.30 (0.05, 1.63)
Animal fat			
Model 1	1.26 (1.05, 1.51)*	1.41 (1.10, 1.81)*	1.07 (0.81, 1.41)
Model 2	1.32 (1.09, 1.59)*	1.48 (1.15, 1.92)*	1.13 (0.86, 1.50)
Model 3	1.26 (1.04, 1.53)*	1.36 (1.05, 1.77)*	1.09 (0.80, 1.47)
Vegetable fat			
Model 1	1.04 (0.92, 1.17)	1.01 (0.85, 1.19)	1.61 (0.94, 2.75)
Model 2	1.09 (0.97, 1.23)	1.09 (0.92, 1.28)	1.57 (0.92, 2.69)
Model 3	1.09 (0.97, 1.24)	1.10 (0.93, 1.30)	1.58 (0.91, 2.73)
Marine ω-3 fatty acids			
Model 1	0.45 (0.21, 1.00)	0.49 (0.18, 1.38)	0.47 (0.14, 1.56)
Model 2	0.47 (0.21, 1.04)	0.59 (0.22, 1.62)	0.37 (0.11, 1.28)
Model 3	0.45 (0.20, 0.99)	0.61 (0.22, 1.64)	0.26 (0.07, 0.92)*
Nonmarine ω-3 fatty acids			
Model 1	1.09 (0.62, 1.93)	1.16 (0.60, 2.23)	1.36 (0.53, 3.46)
Model 2	0.52 (0.24, 1.09)	0.34 (0.13, 0.91)*	0.76 (0.24, 2.45)
Model 3	0.74 (0.34, 1.59)	0.54 (0.19, 1.59)	0.74 (0.22, 2.56)
ω-6 Linoleic acid			
Model 1	1.06 (0.98, 1.14)	1.07 (0.98, 1.18)	1.06 (0.95, 1.18)
Model 2	1.12 (1.03, 1.22)	1.21 (1.07, 1.38)*	1.08 (0.96, 1.22)
Model 3	1.09 (0.98, 1.20)	1.18 (1.02, 1.37)*	1.06 (0.92, 1.22)

[1] All values are HRs (95% CIs). *$P < 0.05$. The percentage increases in energy for the types of fats assessed were 5% for total fat, MUFAs, PUFAs, SFAs, animal fat, and vegetable fat and 1% for *trans* fat, marine ω-3 fatty acids, nonmarine ω-3 fatty acids, and ω-3 linoleic acid, respectively. Multivariable model 1 was adjusted for age, sex, BMI (in kg/m^2), smoking status, educational status, leisure-time physical activity, baseline hypertension or the use of antihypertensive medication, updated total energy intake, alcohol intake, fiber, protein intake, and dietary cholesterol; model 2 was additionally adjusted for specific subtypes of fat that also included as covariates the other subtypes of fat; and model 3 was further adjusted for hypercholesterolemia or the use of lipid-lowering drugs and fasting plasma glucose at baseline. All models were stratified by recruitment center, and the total population analyses of models were further adjusted for intervention group. Extremes of total energy intake (>4000 or <800 kcal/d in men and >3500 or <500 kcal/d in women) were excluded.

[2] Removed saturated fat from the model.

(29, 30) not all studies agreed (31). Indeed, there is evidence suggesting that cheese intake in men was associated with a 5% higher T2D risk in a meta-analysis of 2 prospective studies (31). Because we did not differentiate between the type of cheese consumed and the intake of cheese is often combined with refined carbohydrates, this may explain the increased risk of T2D observed in our study; however, clinical trials are needed to confirm these associations. An inverse association between butter and T2D (RR: 0.96; 95% CI: 0.93, 0.99; P = 0.021) has been recently reported (32). Butter is a source of animal fat and *trans* fatty acids, and it has been previously observed that substituting butter for olive oil is beneficial for T2D prevention (33). Although a

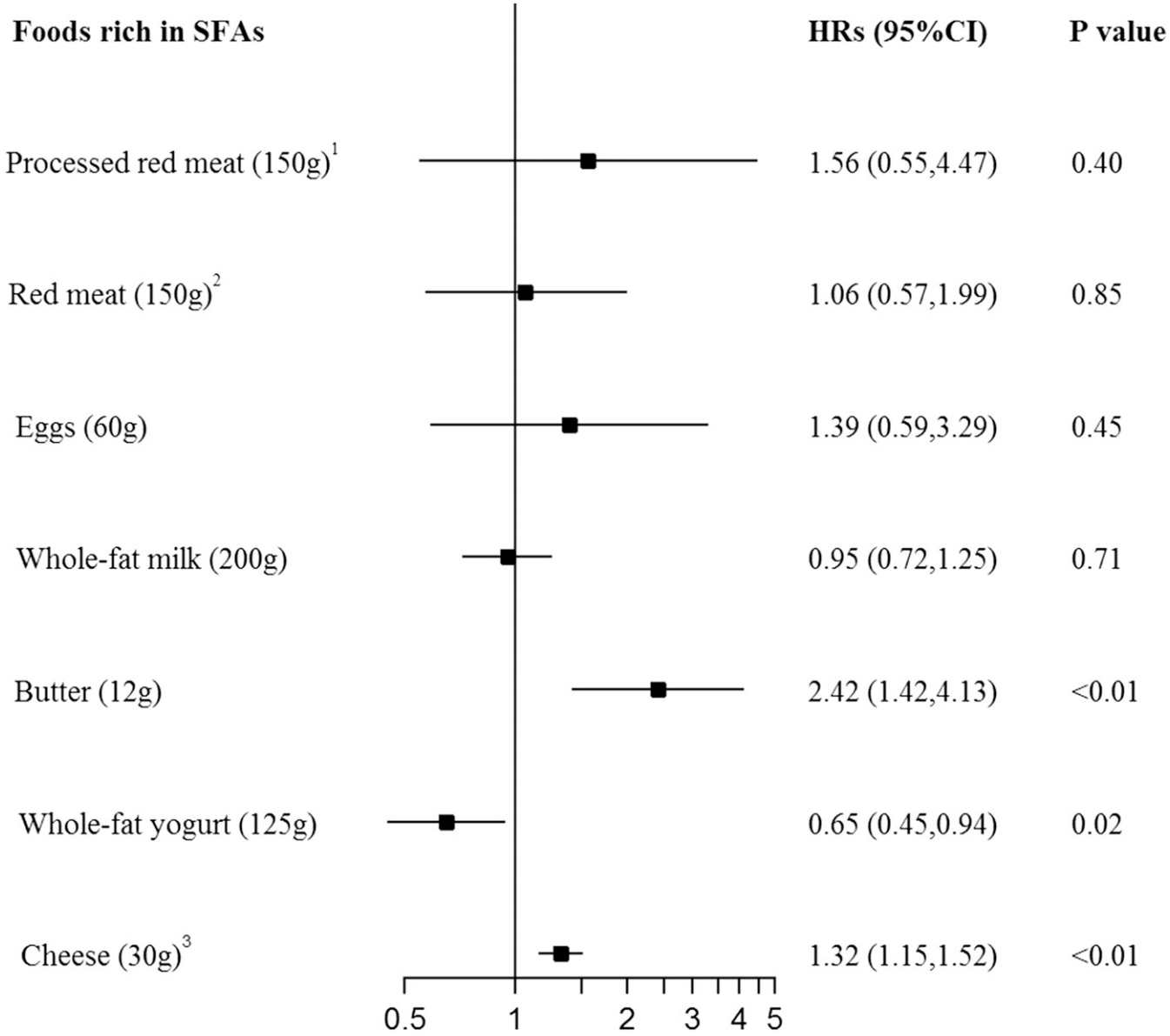

FIGURE 1 Adjusted HRs (95% CIs) of incident type 2 diabetes by increasing the consumption of 1 serving of the following food sources rich in saturated fat: processed red meat, red meat, eggs, whole-fat milk, butter, whole-fat yogurt, and cheese. The multivariable model was adjusted for age, sex, intervention group, BMI (in kg/m^2), smoking status, educational status, leisure-time physical activity, baseline hypertension or the use of antihypertensive medication, hypercholesterolemia or the use of lipid-lowering drugs, fasting plasma glucose, yearly updated total energy intake, alcohol intake, and the intake of vegetables, fruits, legumes, cereals, fish, meat, dairy, olive oil, nuts, and biscuits (except if the exposure was included in these food groups). The analyses were stratified by recruitment center. [1]Includes offal, ham, sausages, pâté, hamburgers, and bacon. [2]Includes pork, veal, beef, and lamb. [3]Includes petit Suisse, ricotta, cottage, spreadable, and semicured and cured cheeses.

higher risk of T2D has been demonstrated with the consumption of red meat and processed meat in previous studies (28, 34), we did not find significant associations between processed meat, red meat, and T2D in this study, possibly because residual confounding may have blunted the potential associations. However, total meat intake and processed meat intake were associated with a higher risk of metabolic syndrome and its components (including high fasting glucose) in a previous report of the PREDIMED Study (35).

We observed a lack of an association between updated total fat intake and the risk of T2D after adjusting for cardiovascular disease risk factors and dietary factors, but a trend to an increased risk was observed when plasma glucose was included in the model, which may be a potential mediator of the associations. However, when separating the analysis by intervention group, nonsignificant associations were found. Although conflicting results have been found for total fat intake and T2D (36), in 3 previous prospective studies with a follow-up ranging from 6 to 14 y, including NHS (6), the Iowa Women's Health Study (7), and the Australian Longitudinal Study on Women's Health (8), total dietary fat intake was not significantly associated with the risk of diabetes. In line with our results, in 2 of these previous studies, MUFA intake was not significantly associated with the risk of T2D incidence (6, 7).

It is also worth noting that we found that total animal fat intake was associated with a higher risk of T2D in the total population but also when stratified by intervention group. In this sense, our results support the current dietary recommendations that favor plant-based fat diets over animal fats (37), encouraging the intake of healthy vegetable fat, such as olive oil or nuts. We found a nonsignificant suggestive trend of an increased risk of T2D by a higher intake of vegetable fat when evaluated in quartiles; however, the associations were no longer significant when evaluated as a continuous variable or when stratified by intervention group. The potential higher risk of T2D by a higher intake of vegetable fat may be explained because in addition to fruits, vegetables, and nuts, this food group also included other vegetable oils (such as palm oil), margarine, and processed pastries that may have driven the positive trend on an increased T2D risk in our population (38).

Our data suggests that a 1% increase in energy intake from marine ω-3 fatty acids was associated with an ∼50% lower risk of T2D, but no significant associations were found when analyzed as quartiles of intake or for other subtypes of PUFAs. Previous data regarding the associations with marine ω-3 fatty acids are inconsistent, and a meta-analysis that included 16 prospective cohort studies and >25,670 cases of diabetes concluded that the consumption of 250 mg/d ω-3 fatty acids from seafood was not significantly associated with T2D risk (RR: 1.04; 95% CI: 0.97, 1.10) (39). In addition, the results for linoleic acid in this study are consistent with a meta-analysis of 5 prospective cohort studies that showed no significant associations between the intake of ω-6 fatty acids and diabetes (40).

Finally, no association between *trans* fat and T2D was observed in our population, perhaps because the intake of this type of fat is very low in Spain (especially in the elderly Mediterranean population, who consume low amounts of processed food) and the lack of statistical power when separating the analysis by intervention. In agreement with these results, a meta-analysis that included 6 prospective cohort studies found no association between *trans* fat intake and T2D (HR: 1.10; 95% CI: 0.95, 1.27), although the authors reported that the interpretation of these findings is complicated because of the heterogeneity between the included studies (10).

Dietary fats could affect insulin resistance and consequently the risk of diabetes through several mechanisms that are yet not well understood. Dietary fatty acids may play a differential role on diabetes onset through the mediation of cell-membrane fatty-acid composition and functions, including membrane fluidity, ion permeability, and insulin-receptor binding and affinity (41). For instance, a greater SFA content of membrane phospholipids increases insulin resistance (41). Moreover, increased serum SFAs have been shown to be associated with insulin resistance, elevated serum glucose concentration, and tissue inflammation (42). Palmitic acid (16:0) might activate inflammatory cytokines and pose specific lipotoxicity to pancreatic β cells (43). On the other hand, MUFAs and PUFAs have been shown to have beneficial effects on serum lipids, inflammation, blood pressure, insulin resistance, endothelial function, and glycemic control (44–47).

Findings from this study cannot prove causality, and it is difficult to rule out residual confounding. We adjusted for several known risk factors for T2D, including several dietary factors, but measurement errors are inevitable in estimates of food and nutrient consumption. Finally, results from a Mediterranean population at a high risk for cardiovascular disease may not be generalizable to more diverse populations. Given that these analyses were conducted in the context of a clinical trial and because most developed countries have had dietary guidelines recommending the reduction of SFA intake for several decades, we acknowledge that it is difficult to disentangle the health consciousness of the population for reducing SFA intake from a true effect of SFAs on T2D. The strengths of our study include the prospective design, the use of the repeated measures of diet and lifestyle, and the accurate and blind assessment of incident case of T2D.

In summary, these data suggest that the intake of SFAs and animal fat was associated with a higher risk of T2D incidence in a Mediterranean population at a high risk for cardiovascular disease. Some animal food sources rich in SFAs such as cheese and butter were associated with a higher risk of T2D, whereas others such as whole-fat yogurt were associated with a lower risk of T2D. These findings may provide a deeper insight into the recommendations for dietary guidelines regarding the type of dietary fat to be consumed at a population level.

The authors' responsibilities were as follows—MG-F, NB-T, DC, RE, ER, FA, EG-G, M Fiol, LS-M, JL, M Fitó, and JS-S: designed the research; MG-F, NB-T, and JS-S: analyzed the data, wrote the manuscript, and took responsibility for the integrity of the data and accuracy of the data analysis; DC, RE, ER, FA, EG-G, M Fiol, LS-M, JL, M Fitó, and JS-S: coordinated subject recruitment at the outpatient clinics; and all authors: conducted the research and read and approved the final manuscript. RE has served on the board of and received lecture fees from the Research Foundation on Wine and Nutrition, has served on the boards of the Beer and Health Foundation and European Foundation for Alcohol Research, and has received lecture fees from Cerveceros de España and Sanofi-Aventis and grant support from Novartis. ER has served on the board of and received travel support as well as grant support from the California Walnut Commission; has served on the board of the Flora Foundation (Unilever); has served on the board of and received lecture fees from Roche; has served on the board of and received grant support from Amgen; has received consulting fees from Damm and Abbott Laboratories; has received consulting fees and lecture fees as well as grant support from Merck; has received lecture fees from Danone, Pace, AstraZeneca, and Rottapharm and lecture fees and payment for developing educational presentations as well as grant support from Ferrer; has received payment for developing educational presentations from Recordati; and has received grant support from Sanofi-Aventis, Takeda, Daiichi Sankyo, Nutrexpa, Feiraco, Unilever, and Karo Bio. FA has received funding for developing educational presentations from Menarini and AstraZeneca. LS-M has served on the boards of the Mediterranean Diet Foundation and Beer and Health Foundation. JS-S has served on the board of and received grant support from the International Nut and Dried Fruit Council and has received consulting fees from Danone and grant support from Eroski and Nestlé. None of the other authors reported a conflict of interest related to the study.

REFERENCES

1. International Diabetes Federation. IDF diabetes atlas. 7th ed. Brussels (Belgium): International Diabetes Federation; 2015.
2. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 2011;8:228–36.
3. US Department of Agriculture, US Department of Health and Human Services. Scientific report of the 2015 Dietary Guidelines Advisory Committee: advisory report to the Secretary of Health and Human Services and the Secretary of Agriculture. Washington (DC): US Department of Health and Human Services; 2015. [cited 2017 Jan 9]. Available from: https://health.gov/dietaryguidelines/2015-scientific-report.
4. Michas G, Micha R, Zampelas A. Dietary fats and cardiovascular disease: putting together the pieces of a complicated puzzle. Atherosclerosis 2014;234:320–8.
5. Hu FB, van Dam RM, Liu S. Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. Diabetologia 2001;44:805–17.

6. Salmerón J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019–26.
7. Meyer KA, Kushi LH, Jacobs DR, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. Diabetes Care 2001;24:1528–35.
8. Alhazmi A, Stojanovski E, McEvoy M, Garg ML. Macronutrient intake and type 2 diabetes risk in middle-aged Australian women. Results from the Australian Longitudinal Study on Women's Health. Public Health Nutr 2014;17:1587–94.
9. Morio B, Fardet A, Legrand P, Lecerf J-M. Involvement of dietary saturated fats, from all sources or of dairy origin only, in insulin resistance and type 2 diabetes. Nutr Rev 2016;74:33–47.
10. de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, Uleryk E, Budylowski P, Schünemann H, Beyene J, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ 2015;351:h3978.
11. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. Circulation 2016;133:187–225.
12. Imamura F, Micha R, Wu JHY, de Oliveira Otto MC, Otite FO, Abioye AI, Mozaffarian D. Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and meta-analysis of randomised controlled feeding trials. PLoS Med 2016;13:e1002087.
13. Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas M-I, Ibarrola-Jurado N, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med 2014;160:1–10.
14. Díaz-López A, Babio N, Martínez-González MA, Corella D, Amor AJ, Fitó M, Estruch R, Arós F, Gómez-Gracia E, Fiol M, et al. Mediterranean diet, retinopathy, nephropathy, and microvascular diabetes complications: a post hoc analysis of a randomized trial. Diabetes Care 2015;38:2134–41.
15. Martínez-González MÁ, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fiol M, Warnberg J, Arós F, Ruiz-Gutierrez V, Lamuela-Raventós RM, et al. Cohort profile: design and methods of the PREDIMED study. Int J Epidemiol 2012;41:377–85.
16. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–90.
17. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2008;31(Suppl 1):S55–60.
18. Fernández-Ballart JD, Piñol JL, Zazpe I, Corella D, Carrasco P, Toledo E, Perez-Bauer M, Martínez-González MA, Salas-Salvadó J, Martín-Moreno JM. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr 2010;103:1808–16.
19. Mataix J. Tablas de composición de alimentos. [Food composition tables.] 4th ed. Granada (Spain): University of Granada; 2003 (in Spanish).
20. Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota leisure time physical activity questionnaire in Spanish men. The MARATHOM investigators. Am J Epidemiol 1994;139:1197–209.
21. FAO. Fats and fatty acids in human nutrition—report of an expert consultation. Washington (DC): FAO; 2010.
22. van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. Diabetes Care 2002;25:417–24.
23. Marshall JA, Hoag S, Shetterly S, Hamman RF. Dietary fat predicts conversion from impaired glucose tolerance to NIDDM. The San Luis Valley Diabetes Study. Diabetes Care 1994;17:50–6.
24. Feskens EJ, Virtanen SM, Räsänen L, Tuomilehto J, Stengård J, Pekkanen J, Nissinen A, Kromhout D. Dietary factors determining diabetes and impaired glucose tolerance. A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetes Care 1995;18:1104–12.
25. Tinker LF, Bonds DE, Margolis KL, Manson JE, Howard BV, Larson J, Perri MG, Beresford SAA, Robinson JG, Rodríguez B, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. Arch Intern Med 2008;168:1500–11.
26. Díaz-López A, Bulló M, Martínez-González MA, Corella D, Estruch R, Fitó M, Gómez-Gracia E, Fiol M, García de la Corte FJ, Ros E, et al. Dairy product consumption and risk of type 2 diabetes in an elderly Spanish Mediterranean population at high cardiovascular risk. Eur J Nutr 2016;55:349–60.
27. Yakoob MY, Shi P, Willett WC, Rexrode KM, Campos H, Orav EJ, Hu FB, Mozaffarian D. Circulating biomarkers of dairy fat and risk of incident diabetes mellitus among US men and women in two large prospective cohorts. Circulation 2016;133:1645–54.
28. Pan A, Sun Q, Bernstein AM, Manson JE, Willet WC, Hu FB. Changes in red meat consumption and subsequent risk of type 2 diabetes mellitus: three cohorts of US men and women. JAMA Intern Med 2013;173:1328–35.
29. Gao D, Ning N, Wang C, Wang Y, Li Q, Meng Z, Liu Y, Li Q. Dairy products consumption and risk of type 2 diabetes: systematic review and dose-response meta-analysis. PLoS One 2013;8:e73965.
30. Aune D, Norat T, Romundstad P, Vatten LJ. Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. Am J Clin Nutr 2013;98:1066–83.
31. Gijsbers L, Ding EL, Malik VS, de Goede J, Geleijnse JM, Soedamah-Muthu SS. Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. Am J Clin Nutr 2016;103:1111–24.
32. Pimpin L, Wu JHY, Haskelberg H, Del Gobbo L, Mozaffarian D. Is butter back? A systematic review and meta-analysis of butter consumption and risk of cardiovascular disease, diabetes, and total mortality. PLoS One 2016;11:e0158118.
33. Guasch-Ferré M, Hruby A, Salas-Salvadó J, Martínez-González MA, Sun Q, Willett WC, Hu FB. Olive oil consumption and risk of type 2 diabetes in US women. Am J Clin Nutr 2015;102:479–86.
34. Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Willett WC, Hu FB. Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. Am J Clin Nutr 2011;94:1088–96.
35. Becerra-Tomás N, Babio N, Martínez-González MÁ, Corella D, Estruch R, Ros E, Fitó M, Serra-Majem L, Salaverria I, Lamuela-Raventós RM, et al. Replacing red meat and processed red meat for white meat, fish, legumes or eggs is associated with lower risk of incidence of metabolic syndrome. Clin Nutr 2016;35:1442–9.
36. Alhazmi A, Stojanovski E, McEvoy M, Garg ML. Macronutrient intakes and development of type 2 diabetes: a systematic review and meta-analysis of cohort studies. J Am Coll Nutr 2012;31:243–58.
37. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet 2014;383:1999–2007.
38. Mancini A, Imperlini E, Nigro E, Montagnese C, Daniele A, Orrù S, Buono P. Biological and nutritional properties of palm oil and palmitic acid: effects on health. Molecules 2015;20:17339–61.
39. Wu JHY, Micha R, Imamura F, Pan A, Biggs ML, Ajaz O, Djousse L, Hu FB, Mozaffarian D. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. Br J Nutr 2012;107(Suppl 2):S214–27.
40. Alhazmi A, Stojanovski E, McEvoy M, Garg ML. The association between dietary patterns and type 2 diabetes: a systematic review and meta-analysis of cohort studies. J Hum Nutr Diet 2014;27:251–60.
41. Storlien LH, Pan DA, Kriketos AD, O'Connor J, Caterson ID, Cooney GJ, Jenkins AB, Baur LA. Skeletal muscle membrane lipids and insulin resistance. Lipids 1996;31(Suppl):S261–5.
42. Odegaard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science 2013;339:172–7.
43. Sharma RB, Alonso LC. Lipotoxicity in the pancreatic beta cell: not just survival and function, but proliferation as well? Curr Diab Rep 2014;14:492.
44. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004;292:1440–6.
45. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. Am J Clin Nutr 1998;67:577S–82S.
46. Mensink RP, Zock PL, Kester ADM, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003;77:1146–55.
47. Hall WL. Dietary saturated and unsaturated fats as determinants of blood pressure and vascular function. Nutr Res Rev 2009;22:18–38.

APPENDIX A

List of other PREDIMED Study Investigators

Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer, Barcelona, Spain: M Serra-Mir, A Pérez-Heras, C Viñas, R Casas, A Medina-Renom, JM Baena, M García, M Oller, J Amat, I Duaso, Y García, C Iglesias, C Simón, L Quinzavos, L Parra, M Liroz, J Benavent, J Clos, I Pla, M Amorós, MT Bonet, MT Martín, MS Sánchez, J Altirriba, E Manzano, A Altés, M Cofán, C Valls-Pedret, A Sala-Vila, and M Doménech.

Rovira i Virgili University, Reus, Spain: M Bulló, N Babio, R González, C Molina, A Díaz-López, F Márquez, P Martínez, N Ibarrola, M Sorlí, J García Roselló, A Castro, F Martin, N Tort, A Isach, JJ Cabré, G Mestres, F Paris, M Llauradó, N Rosique-Esteban, R Pedret, J Basells, J Vizcaino, R Segarra, J Frigola, J Costa-Vizcaino, A Salas-Huetos, J Boj, D Montañes, and J Fernández-Ballart.

University of Valencia, Valencia, Spain: P Carrasco, C Ortega-Azorín, EM Asensio, R Osma, R Barragán, F Francés, M Guillén, JI González, C Sáiz, FJ Giménez, O Coltell, R Fernández-Carrión, P Guillem-Sáiz, I González-Monje, L Quiles, V Pascual, C Riera, MA Pages, D Godoy, A Carratalá-Calvo, S Sánchez-Navarro, and C Valero-Barceló.

Hospital del Mar Research Institute, Barcelona, Spain: S Tello, J Vila, R de la Torre, D Muñoz-Aguayo, R Elosua, J Marrugat, N Molina, E Maestre, A Rovira, O Castañer, and M Farré.

University of Navarra and Osasunbidea (Servicio Navarro de Salud), Primary Care Centres, Pamplona, Spain: E Toledo, B Sanjulián, A Sánchez-Tainta, S Eguaras, A Martí, P Buil-Cosiales, M Serrano-Martínez, J Diez-Espino, A García-Arellano, EH Martínez-Lapiscina, E Goñi, Z Vázquez, N Berrade, V Extremera-Urabayen, C Arroyo-Azpa, L García-Pérez, J Villanueva-Telleria, F Cortés-Ugalde, T Sagredo-Arce, MD Vigata-López, MT Arceiz Campo, A Urtasun-Samper, MV Gueto Rubio, and B Churio-Beraza.

University Hospital of Álava, Vitoria, Spain: I Salaverria, T del Hierro, J Algorta, S Francisco, A Alonso-Gómez, E Sanz, J Rekondo, MC Belló, and A Loma-Osorio.

University of Málaga, Málaga, Spain: J Wärnberg, R Benítez Pont, M Bianchi Alba, R Gómez-Huelgas, J Martínez-González, V Velasco García, J de Diego Salas, A Baca Osorio, J Gil Zarzosa, JJ Sánchez Luque, and E Vargas López.

Instituto de la Grasa, Consejo Superior de Investigaciones Científicas, Sevilla, Spain: V Ruiz-Gutiérrez, J Sánchez Perona, E Montero Romero, M García-García, and E Jurado-Ruiz.

Instituto de Investigación Sanitaria de Palma (IdISPa), Palma de Mallorca, Spain: D Romaguera, M García-Valdueza, M Moñino, S Munuera, M Vivó, F Bestard, JA Munar, L Coll, A Proenza, R Prieto, G Frontera, F Fiol, M Ginard, A Jover, and J García.

Department of Family Medicine, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain: JM Santos-Lozano, M Ortega-Calvo, L Mellado, FJ García-Corte, P Román, P Iglesias, Y Corchado, L Miró-Moriano, C Domínguez-Espinaco, JM Lozano-Rodriguez, and S Vaquero-Diaz.

School of Pharmacy, University of Barcelona, Barcelona, Spain: MC López- Sabater, AI Castellote-Bargalló, P Quifer-Rada, and A Tresserra-Rimbau.

Instituto Universitario de Investigaciones Biomédicas y Sanitarias (IUIBS) de la Universidad de Las Palmas de Gran Canaria, Las Palmas, Spain: J Álvarez-Pérez, EM Díaz-Benítez, A Sánchez-Villegas, LT Casañas-Quintana, J Pérez-Cabrera, C Ruano-Rodríguez, I Bautista-Castaño, F Sarmiento de la Fe, JA García Pastor, BV Díaz-González, JM Castillo Anzalas, RE Sosa-Also, and J Medina-Ponce.

Hospital Universitari de Bellvitge-IDIBELL, Hospitalet de Llobregat, Barcelona, Spain: E de la Cruz, M Fanlo-Maresma, A Galera, F Trias, I Sarasa, E Corbella, and X Corbella.

Primary Care Division, Catalan Institute of Health, Barcelona, Spain: C Cabezas, E Vinyoles, MA Rovira, L García, G Flores, JM Verdú, P Baby, A Ramos, L Mengual, P Roura, MC Yuste, A Guarner, A Rovira, MI Santamaría, M Mata, C de Juan, and A Brau.

Other investigators of the PREDIMED network: JA Tur (University of Balearic Islands), MP Portillo (University of Basque Country), and G Sáez (University of Valencia).

Clinical End Point Committee: F Arós (chair), M Aldamiz-Echevarría, AM Alonso-Gómez, J Berjón, J Gállego, A García-Layana, A Larrauri, J Portu-Zapirain, and J Timiraus-Fernández.