Dietary Protein Intake and Incidence of Type 2 Diabetes in Europe: The EPIC-InterAct Case-Cohort Study

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OBJECTIVE

The long-term association between dietary protein and type 2 diabetes incidence is uncertain. We aimed to investigate the association between total, animal, and plant protein intake and the incidence of type 2 diabetes.

RESEARCH DESIGN AND METHODS

The prospective European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct case-cohort study consists of 12,403 incident type 2 diabetes cases and a stratified subcohort of 16,154 individuals from eight European countries, with an average follow-up time of 12.0 years. Pooled country-specific hazard ratios (HRs) and 95% CI of prentice-weighted Cox regression analyses were used to estimate type 2 diabetes incidence according to protein intake.

RESULTS

After adjustment for important diabetes risk factors and dietary factors, the incidence of type 2 diabetes was higher in those with high intake of total protein (per 10 g: HR 1.06 [95% CI 1.02–1.09], $P_{trend} < 0.001$) and animal protein (per 10 g:

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1.05 [1.02–1.08], P_{trend} = 0.001). Effect modification by sex ($P < 0.001$) and BMI among women ($P < 0.001$) was observed. Compared with the overall analyses, associations were stronger in women, more specifically obese women with a BMI >30 kg/m^2 (per 10 g animal protein: 1.19 [1.09–1.32]), and nonsignificant in men. Plant protein intake was not associated with type 2 diabetes (per 10 g: 1.04 [0.93–1.16], P_{trend} = 0.098).

CONCLUSIONS

High total and animal protein intake was associated with a modest elevated risk of type 2 diabetes in a large cohort of European adults. In view of the rapidly increasing prevalence of type 2 diabetes, limiting iso-energetic diets high in dietary proteins, particularly from animal sources, should be considered.

Dietary proteins are advocated to have positive effects on weight loss and weight maintenance due to properties related to satiety and diet-induced thermogenesis (1). Doubling the relative protein content of the diet under ad libitum conditions for 12 weeks reduces food intake and can lower body weight by >6% (2). Therefore, increasing protein intake seems a promising approach to tackle the obesity epidemic and therewith to reduce the incidence of chronic diseases.

In contrast, long-term observational studies report an association of high protein intake with a higher risk of type 2 diabetes (3,4). Suggested beneficial acute effects of dietary protein on insulin secretion and glycemic control (5) do not seem to persist mid- and long-term (6,7). An iso-energetic high-protein diet compared with a low-protein high-fiber diet reduced insulin sensitivity after 6 weeks (6), and participants with a habitually high- compared with a normal-protein diet showed signs of reduced insulin sensitivity (7). The few epidemiological studies that addressed the association between protein intake and type 2 diabetes all found an increased type 2 diabetes risk with high protein and/or meat protein intake (3,4,8–10). However, most of these studies had small sample sizes, ranging from 140 (8,9) to 1,200 (10) participants. Of two large cohort studies with >35,000 participants (3,4), Sluijs et al. (3) did not observe a significant association for total protein after adjustment for BMI and waist circumference in the Dutch cohort of European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct. Based on subanalyses, the authors concluded that only for participants with a BMI <25 kg/m^2 does high protein intake increase type 2 diabetes risk (3).

Besides total and animal protein, prior research suggests that the protein source could be of relevance. Type 2 diabetes risk is associated with higher meat consumption, particularly red and processed meat (11–13). Type 2 diabetes risk is reported to be lower in subjects with high dairy use (14–17) and/or high plant product consumption, especially of legumes (18) and nuts (19). Data on the relation between fish consumption and type 2 diabetes reached mixed conclusions (20–22), and a recent study in the EPIC-InterAct case cohort reported no association (23). It is unclear whether it is the protein or other nutrients in such food groups that explain the association with type 2 diabetes.

Within the setting of EPIC-InterAct, we were able to study the association between protein intake and risk of type 2 diabetes in a large case cohort in eight countries in Europe: the largest cohort of type 2 diabetes so far (24). The characteristics of this study made it possible to explore the association between protein intake and type 2 diabetes according to plant or animal origin and by protein source.

RESEARCH DESIGN AND METHODS

Study Design

The participants, methods, study design, and measurements have previously been described (24). Briefly, the InterAct project was initiated to investigate how genetic and lifestyle behavioral factors, particularly diet and physical activity, interact to lead to type 2 diabetes. As part of the wider InterAct project, consortium partners have established a case-cohort study of incident type 2 diabetes (EPIC-InterAct case cohort) based on cases occurring in EPIC cohorts between 1991 and 2007 in 8 of 10 EPIC countries. A case-cohort study is comparable with a cohort study but it is more efficient, as it uses a random sample of the cohort to compare cases with. The case-cohort design combines the advantages of a prospective cohort with the efficiency and power of a large case-control study.

Type 2 Diabetes Case Ascertainment

We followed a pragmatic high-sensitivity approach for case ascertainment with the aim of *1*) identifying all potential incident type 2 diabetes cases and *2*) excluding all individuals with prevalent type 2 diabetes. Prevalent and incident type 2 diabetes was identified using multiple sources of evidence including self-report, linkage to primary care registers and secondary care registers, medication use (drug registers), hospital admissions, and mortality data. Further details have previously been published (24).

Subcohort

A subcohort of 16,835 individuals was randomly selected stratified by center. After exclusion of 548 individuals with prevalent type 2 diabetes, 129 individuals without information on reported diabetes status, and 4 individuals with postcensoring type 2 diabetes, 16,154 subcohort individuals remained.

Participants

We used a case-cohort design, including incident diabetes cases (n = 12,403) and a representative subcohort (n = 16,154, including 778 cases of incident type 2 diabetes) selected from the EPIC cohort (24). After exclusion of participants with missing information on dietary data (n = 117; 70 case subjects, 47 subcohort) or other missing covariates, i.e., physical activity, educational, and smoking status (n = 790; 357 case subjects, 433 subcohort), and participants who fell in the top or bottom 1% of the "energy intake/energy requirement ratio" (n = 619; 339 case subjects, 280 subcohort), our analysis included 26,253 participants (10,901 incident type 2 diabetes case subjects and a subcohort of 15,352 participants including 736 cases of incident type 2 diabetes).

All EPIC study participants gave written informed consent, and the study was approved by the national ethics committees and the International Agency for Research on Cancer.

Protein Intake and Other Variables

Dietary intake, over the 12 months before enrollment, was assessed by self- or interviewer-administered dietary questionnaires (mainly food frequency

questionnaires [FFQ]), developed and validated within each country, to estimate the usual individual food intakes of the study participants (for more detail, see Riboli et al. [25]). Protein intake (g/day) was adjusted for total energy intake by the residual method (26) and categorized in quintiles according to the data of the subcohort. As part of EPIC, standardized information on lifestyle exposures was collected by self-administered national questionnaires at baseline (25). Physical activity during work and leisure time was classified in four categories according to the Cambridge Physical Activity Index (27). Weight, height, and waist circumference were recorded using a standard protocol during a visit at the research center, except in Oxford (U.K.) and France, where only self-reported height and weight were available (25).

Statistical Analysis

The association between energy-adjusted protein intake and type 2 diabetes risk was examined in hazard ratios (HRs) and 95% CIs using Cox proportional hazards models adapted to case-cohort designs according to the Prentice-weighted method (28). We stratified all analyses by country, mainly because of the large dietary heterogeneity between countries, specifically between northern and southern Europe, e.g., relatively high protein intake in Spain and low protein intake in Germany and Sweden. We used random-effect meta-analyses to pool the country-specific HRs. Between-country heterogeneity was tested by I^2 statistic. Linear associations between protein intake and type 2 diabetes were estimated per 10-g increment of protein intake and by analyzing linear trends across protein intake categories using the median value of each quintile as a continuous variable. We adjusted for type 2 diabetes risk factors and nutritional factors using a stepwise approach, with age as the underlying time scale. Model 1 included protein intake, total energy (kilocalories per day), center, and sex. In model 2, we added type 2 diabetes risk factors, i.e., smoking status (never, former, or current), education (low, secondary, or high), physical activity (inactive, moderately inactive, moderately active, or active), and alcohol use (0, >0–6, >6–12, >12–24, or >24 g/day). Model 3 was additionally adjusted for soft drinks, tea, coffee, and the following residual adjusted nutrients: fiber, saturated fatty acids, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and cholesterol. It was not adjusted for carbohydrates to estimate the effect of increasing protein at the expense of carbohydrates. Model 4 was additionally adjusted for BMI (measured as weight in kilograms divided by the square of height in meters) and waist circumference (centimeters).

Effect modification was examined by various dietary and lifestyle factors, i.e., sex, BMI, waist circumference, physical activity, smoking, menopausal status, hyperlipidemia, and hypertension. A country-specific multivariate Wald test was used to evaluate interactions by continuous interaction terms. In case of significant interactions, HRs were stratified. The association between protein intake and type 2 diabetes risk was estimated within each country by sex (11,241 men; 15,012 women) and by BMI (normal: BMI <25 kg/m^2, n = 8,317; overweight: BMI 25–30 kg/m^2, n = 10,951; obese: BMI ≥30 kg/m^2, n = 6,985) and meta-analyzed. Models for sources of animal and plant protein and sequentially excluding main sources of protein, e.g., meat, were designed to explore the contribution of various protein sources to the associations of protein type with type 2 diabetes risk. Finally, sensitivity analyses were performed by excluding individuals who might have made dietary adjustments and/or lifestyle changes because of chronic disease at baseline (i.e., hypertension, hyperlipidemia, myocardial infarction, and/or stroke) and by excluding misreports of energy according to Goldberg criterion categories, defined as "under-reporters" with a ratio of energy intake to basal metabolic rate <1.14 and "over-reporters" with a ratio of >2.1 (29). Data analysis was performed using SAS 9.2, and the meta-analyses were conducted in STATA11.

RESULTS

Our analysis of this case-cohort study consisted of 10,901 incident type 2 diabetes cases and a subcohort of 15,352 participants (including 736 type 2 diabetes cases) with an mean ± SD follow-up time of 12.0 ± 2.3 years. FFQ-based median estimated energy-adjusted total protein intake was 90.4 g/day for men and 91.0 g/day for women, mainly consisting of animal protein. It was highest in Spain (102.5 g/day) and lowest in Germany and Sweden (respectively, 80.0 and 80.8 g/day) (Supplementary Fig. 1). Main animal protein sources in order of proportion were meat, dairy, and fish; main plant protein sources were bread, pasta and rice, potatoes, and vegetables (Table 1).

In the subcohort, participants with high intake of total protein (highest vs. lowest quintile) had higher mean BMI and waist circumference and higher intake of MUFAs, dietary fiber, dietary cholesterol, calcium, and β-carotene, whereas educational level and mean intake of carbohydrates, saturated fatty acids (SFAs), coffee, tea, and soft drinks were lower (Table 1). Additionally, with increasing protein intake women were less physically active, drank less alcohol, and were less often smokers, whereas men were more often smokers. With increasing quintiles of total protein intake, the number of type 2 diabetes cases in the subcohort increased (Table 1).

High total protein intake was associated with a 13% higher incidence of type 2 diabetes (HR 1.13 [95% CI 1.08–1.19]) for every 10-g increment after adjustment for energy, center, sex, type 2 diabetes risk factors, and dietary factors (Table 2; Supplementary Fig. 2). Animal protein intake showed comparable results (1.12 [1.07–1.17]). Additional adjustment for waist circumference and BMI attenuated the associations to some extent for total protein to a 6% higher incidence of type 2 diabetes (1.06 [1.02–1.09]) and to 5% for animal protein (1.05 [1.02–1.08]). Analyzing total and animal protein intake by quintile (high vs. low) showed comparable results (1.17 [1.00–1.38], $P_{trend} < 0.001$ and 1.22 [1.06–1.40], $P_{trend} < 0.001$). Between-country heterogeneity was low (I^2 0.0–45.3%) (Supplementary Fig. 2).

For the association between total and animal protein intake and type 2 diabetes, effect modification by sex ($P < 0.001$) and by BMI among women ($P < 0.001$) was present. The association between 10-g increment of total and animal protein intake and type 2 diabetes was confirmed in women (HR 1.10 [95% CI 1.06–1.14] and 1.09 [1.05–1.14], respectively) in model 4 (Fig. 1;

Table 1—Sex-specific characteristics and dietary consumption of the EPIC-InterAct subcohort by categories of total protein intake* (*n* = 15,352)

	Men			Women		
	Q1: 68.9 g/day (63–73)	Q3: 89.0 g/day (87–91)	Q5: 113.5 g/day (109–121)	Q1: 73.5 g/day (69–77)	Q3: 90.6 g/day (89–92)	Q5: 109.5 g/day (105–116)
n cases/*N*	45/1,162	76/1,162	105/1,161	51/1,909	83/1,909	96/1,909
Characteristics						
Age (years)	53.0 ± 9.4	53.5 ± 9.0	51.4 ± 7.8	51.1 ± 9.9	53.0 ± 8.9	51.3 ± 8.6
Follow-up (years)	11.8 ± 2.6	11.8 ± 2.7	12.2 ± 2.6	11.8 ± 2.1	11.9 ± 2.2	12.3 ± 2.1
BMI (kg/m^2)	25.6 ± 3.5	26.5 ± 3.5	27.9 ± 3.6	24.2 ± 3.9	25.7 ± 4.4	27.1 ± 4.8
<25 (%)	44.6	32.9	20.2	66.4	50.3	36.8
25–30 (%)	44.8	52.9	54.0	25.1	33.7	40.4
>30 (%)	10.7	14.2	25.8	8.5	16.0	22.7
Waist (cm)	92.8 ± 10.1	94.7 ± 9.6	97.9 ± 9.6	77.6 ± 10.0	81.1 ± 10.7	84.5 ± 11.6
Family history of diabetes (%)						
Yes	15.8	17.1	11.7	20.4	22.1	21.4
Smoker (%)						
Never	34.5	30.7	30.2	52.9	57.1	59.8
Former	36.8	37.9	33.4	23.5	21.3	20.3
Smoker	28.7	31.4	36.4	23.7	21.7	20.0
Hypertension (%)						
Yes	18.1	18.9	18.1	16.9	18.8	18.5
Do not know	2.1	3.9	3.9	1.5	0.9	1.0
Hyperlipidemia (%)						
Yes	22.6	20.9	23.2	16.1	14.1	13.8
Do not know	9.3	12.9	7.3	6.4	7.1	4.8
Educational level (%)						
Long education (incl. university degree)	28.5	24.5	19.0	23.5	17.7	14.4
Physical activity (%)						
Active	24.2	22.8	27.2	20.0	17.4	13.6
Postmenopausal (%)	—	—	—	45.8	51.7	41.1
Country, *n*						
France, ♀ 526 (%)	—	—	—	3.4	5.9	6.8
Italy, ♂ 639, ♀1,300 (%)	7.5	13.6	6.7	10.7	16.1	11.4
Spain, ♂ 1,333, ♀ 2,154 (%)	2.5	15.5	58.7	3.1	19.1	49.9
U.K., ♂ 423, ♀ 661 (%)	7.8	7.6	4.2	6.9	6.0	8.6
The Netherlands, ♂ 226, ♀ 1,139 (%)	2.4	5.3	3.0	8.3	15.0	9.8
Germany, ♂ 845, ♀ 1,176 (%)	26.7	15.6	4.1	28.7	9.2	1.6
Sweden, ♂ 1,231, ♀ 1,625 (%)	40.5	20.2	4.6	31.8	16.1	2.4
Denmark, ♂ 1,110, ♀ 964 (%)	12.6	22.3	18.7	7.0	12.5	9.6
Dietary intake						
Total energy (kcal/day)	2,564.2 ± 673.6	2,361.0 ± 594.2	2,664.3 ± 674.5	2,061.2 ± 567.5	1,857.7 ± 485.3	2,005.1 ± 525.2
Total protein (energy %)	12.8 ± 1.2	16.5 ± 0.6	20.7 ± 1.9	13.2 ± 1.2	17.2 ± 0.8	21.6 ± 2.4
Animal protein (energy %)	6.8 ± 1.7	10.2 ± 1.4	14.4 ± 2.5	6.8 ± 1.8	10.6 ± 1.5	15.1 ± 2.8
From red meat (g/day)*	6.6 (3–12)	13.7 (8–21)	19.0 (11–28)	6.6 (4–10)	11.9 (8–17)	16.3 (10–23)
From processed meat (g/day)*	5.4 (3–8)	5.8 (3–9)	6.2 (3–12)	4.8 (3–7)	5.3 (3–8)	6.0 (4–10)
From poultry (g/day)*	2.6 (1–4)	4.8 (3–8)	9.8 (5–16)	2.7 (2–4)	5.1 (3–8)	10.3 (6–16)
From milk and dairy (g/day)*	5.3 (1–11)	7.0 (2–14)	7.5 (3–15)	5.4 (2–10)	8.5 (5–14)	10.9 (6–17)
From cheese (g/day)*	5.2 (2–9)	6.8 (3–12)	7.0 (3–15)	7.2 (4–10)	9.0 (6–13)	9.5 (5–16)
From fish (g/day)*	2.6 (1–5)	5.6 (3–9)	11.8 (6–19)	3.2 (2–5)	5.8 (3–9)	10.3 (6–16)
From eggs (g/day)*	1.2 (0–3)	2.0 (1–3)	3.0 (1–5)	1.5 (1–3)	2.2 (1–3)	2.9 (2–4)
Plant protein (energy %)	4.4 ± 1.3	5.0 ± 1.3	5.4 ± 1.4	4.7 ± 1.4	5.2 ± 1.3	5.3 ± 1.3
From bread (g/day)*	10.0 (7–14)	11.0 (8–15)	11.4 (8–17)	10.4 (8–13)	11.4 (9–15)	11.2 (8–14)
From potatoes (g/day)*	2.0 (1–3)	2.2 (1–3)	1.7 (1–3)	1.5 (1–2)	1.6 (1–2)	1.4 (1–2)
From pasta and rice (g/day)*	1.2 (0–2)	1.6 (1–3)	1.8 (1–3)	1.5 (1–3)	1.9 (1–3)	1.9 (1–3)
From legumes (g/day)*	0.2 (0–1)	0.5 (0–2)	3.1 (0–6)	0.6 (0–1)	1.1 (1–2)	2.1 (1–4)
Total carbohydrates (energy %)	46.0 ± 7.7	43.1 ± 6.8	38.7 ± 6.6	48.0 ± 7.2	45.1 ± 6.1	40.9 ± 6.2

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Table 1—Continued

	Men			Women		
	Q1: 68.9 g/day (63–73)	Q3: 89.0 g/day (87–91)	Q5: 113.5 g/day (109–121)	Q1: 73.5 g/day (69–77)	Q3: 90.6 g/day (89–92)	Q5: 109.5 g/day (105–116)
Starch (energy %)	24.0 ± 6.6	24.6 ± 6.3	23.3 ± 6.1	24.0 ± 6.4	24.1 ± 6.0	22.0 ± 5.8
Sugar (energy %)	21.0 ± 7.2	17.8 ± 5.8	15.0 ± 5.3	23.4 ± 7.1	20.5 ± 5.8	18.5 ± 5.9
Total fat (energy %)	34.4 ± 7.0	34.1 ± 5.5	35.4 ± 5.6	35.1 ± 6.4	34.9 ± 5.6	35.5 ± 5.9
Saturated fat (energy %)	14.1 ± 4.0	13.0 ± 3.4	11.9 ± 3.3		13.3 ± 3.1	12.6 ± 3.3
Monounsaturated fat (energy %)	12.3 ± 2.8	12.9 ± 2.9	14.7 ± 3.8	12.5 ± 3.0	13.1 ± 3.6	14.2 ± 4.0
Polyunsaturated fat (energy %)	5.5 ± 2.0	5.4 ± 1.8	5.8 ± 2.2	5.7 ± 1.9	5.6 ± 1.7	5.7 ± 2.2
Fiber (g)*	20.1 ± 7.0	22.2 ± 6.1	23.9 ± 7.5	23.0 ± 6.6	23.5 ± 5.5	24.1 ± 5.9
Cholesterol (mg)*	274.4 ± 118.4	334.9 ± 108.3	422.6 ± 138.0	288.0 ± 93.2	342.2 ± 91.6	405.5 ± 105.9
Calcium (mg)*	792.7 ± 286.0	941.9 ± 335.4	1,026.5 ± 501.6	923.2 ± 247.5	1,054.3 ± 265.9	1,188.8 ± 453.7
Magnesium (mg)*	383.7 ± 107.8	379.5 ± 98.8	429.3 ± 110.3	330.1 ± 93.6	315.8 ± 86.7	353.8 ± 96.5
Vitamin B1 (mg)*	1.4 ± 0.5	1.4 ± 0.5	1.8 ± 0.6	1.2 ± 0.4	1.2 ± 0.4	1.4 ± 0.5
β-Carotene (μg)*	2,232.9 ± 2,048.6	2,596.7 ± 2,124.2	2,817.9 ± 2,483.3	3,119.4 ± 2,490.5	3,194.8 ± 2,403.8	3,493.4 ± 2,917.0
Vitamin C (mg)*	109.8 ± 64.8	110.7 ± 59.1	140.7 ± 79.8	129.9 ± 79.9	121.9 ± 60.3	141.0 ± 70.8
Vitamin D (mg)*	4.6 ± 3.0	4.6 ± 2.9	5.1 ± 3.8	4.1 ± 2.2	4.1 ± 2.1	4.4 ± 2.2
Vitamin E (mg)*	12.5 ± 6.0	11.7 ± 5.2	14.7 ± 6.8	11.7 ± 5.4	10.4 ± 4.2	11.9 ± 5.1
Soft drinks (g/day)*	37.9 (0–150)	15.9 (0–86)	0.0 (0–29)	13.3 (0–90)	2.4 (0–57)	0.0 (0–28)
Coffee (g/day)*	429.8 (190–621)	311.1 (100–611)	130.6 (43–450)	357.1 (120–580)	261.3 (89–500)	160.0 (52–450)
Tea (g/day)*	10.3 (0–150)	4.9 (0–146)	0.0 (0–12)	21.4 (0–250)	6.6 (0–238)	0.0 (0–119)
Alcohol (g)						
0 (%)	4.7	4.2	5.4	7.3	9.0	12.9
♂ 0–12, ♀ 0–6 (%)	42.0	39.1	39.6	46.6	53.6	55.4
♂ 12–24, ♀ 6–12 (%)	18.1	22.4	20.4	17.2	15.0	13.4
♂ >24, ♀ >12 (%)	35.3	34.3	34.5	28.9	22.4	18.4

Data are means ± SD or median (25th percentile–75th percentile) unless otherwise indicated. ♂ men, ♀ women; incl., including; Q, quintile. Family history of diabetes was not collected in Italy, Spain, Heidelberg, or Oxford (missing *n* = 7,723). *FFQ-estimated intake energy adjusted by the residual method.

Supplementary Table 1). In men, no association was present (both total and animal protein, 1.02 [0.98–1.06]). Compared with overweight women (1.07 [1.01–1.14]) and normal-weight women (1.11 [0.99–1.25]), obese women had a stronger association between animal protein intake and type 2 diabetes (1.19 [1.09–1.32]) (Table 3). In the sensitivity analyses, exclusion of "under-reporters" (*n* = 8,096) and "over-reporters" (*n* = 1,206) did not change the overall and sex-specific associations for both total and animal protein intake and type 2 diabetes (data not shown). Excluding the effect of possible lifestyle changes as a result of a medical condition (i.e., baseline self-reported hypertension, hyperlipidemia, myocardial infarction, and stroke, *n* = 11,043; 3,641 case subjects and 7,402 subcohort) strengthened the associations between both total and animal protein intake and type 2 diabetes in women (1.15 [1.04–1.27] and 1.12 [1.03–1.22], respectively) (Supplementary Table 2). No specific group of protein sources was accountable for the positive association between animal protein and type 2 diabetes; excluding protein from dairy, fish, or meat from total animal protein did not alter the association.

Plant protein intake per 10 g was not associated with type 2 diabetes, with an HR of 0.92 (95% CI 0.80–1.04), $P_{trend} = 0.507$, in model 1 and 1.04 (0.93–1.16), $P_{trend} = 0.098$, in model 4 (Table 2; Supplementary Fig. 2) and 1.12 (0.98–1.29) in the sensitivity analysis additionally adjusting for possible lifestyle changes as a result of a medical condition (Supplementary Table 2). No effect modification by sex or BMI was present. Excluding specific groups of plant protein sources did not alter the overall absent association between plant protein and type 2 diabetes.

CONCLUSIONS

Our study, the largest of its kind in terms of sample size, number of cases, and follow-up years, is the first to investigate the association between type 2 diabetes incidence and protein intake at a general European level. We found that high total protein at the exchange of carbohydrates is associated with a small elevated risk of type 2 diabetes. This association was largely explained by animal protein intake. BMI and waist circumference attenuated the associations. Plant protein intake was not associated with type 2 diabetes incidence in our cohort.

In this current study, with low heterogeneity between the eight countries, we observed a positive association for total and animal protein and type 2 diabetes risk, independent of known type 2 diabetes risk factors and dietary factors including fat, saturated fat, and fiber intake. We observed that type 2 diabetes incidence was 17% higher in individuals with the highest total protein intake compared with individuals with the lowest intake and that type 2 diabetes incidence increased 6% per 10-g increment of total protein intake at the expense of carbohydrates. A 10-g increment represents ~50 g meat or fish, a glass of milk, or 50 g nuts. We reviewed

Table 2—Meta-analyzed (pooled) HRs (95% CI) for the association between protein intake and type 2 diabetes in the EPIC-InterAct case-cohort study

	Q1 (low)	Q2	Q3	Q4	Q5 (high)	P_{trend}	Per 10 g
Total protein *N* (cases)	5,023 (2,048)	5,080 (2,144)	5,180 (2,265)	5,354 (2,425)	5,616 (2,755)		26,253 (11,637)
Median protein*	71.8	82.1	90.0	98.1	111.0		90.0
Model 1	1	1.08 (0.96–1.22)	1.20 (1.02–1.40)	1.40 (1.11–1.76)	1.63 (1.37–1.93)	<0.001	1.14 (1.09–1.19)
Model 2	1	1.10 (0.97–1.26)	1.19 (1.01–1.40)	1.38 (1.09–1.75)	1.57 (1.33–1.84)	<0.001	1.13 (1.09–1.18)
Model 3	1	1.12 (0.97–1.31)	1.19 (0.99–1.43)	1.39 (1.08–1.79)	1.55 (1.25–1.91)	<0.001	1.13 (1.08–1.19)
Model 4	1	1.00 (0.85–1.19)	1.02 (0.86–1.20)	1.13 (0.91–1.42)	1.17 (1.00–1.38)	<0.001	1.06 (1.02–1.09)
Animal protein *N* (cases)	4,950 (1,972)	5,034 (2,073)	5,207 (2,315)	5,351 (2,436)	5,711 (2,841)		26,253 (11,637)
Median protein*	36.0	47.4	55.6	64.3	78.1		55.6
Model 1	1	1.06 (0.95–1.19)	1.22 (1.08–1.37)	1.35 (1.18–1.54)	1.62 (1.35–1.94)	<0.0001	1.12 (1.08–1.17)
Model 2	1	1.07 (0.94–1.21)	1.24 (1.08–1.41)	1.35 (1.18–1.54)	1.61 (1.34–1.93)	<0.0001	1.12 (1.08–1.16)
Model 3	1	1.05 (0.90–1.22)	1.20 (1.01–1.42)	1.31 (1.11–1.56)	1.51 (1.20–1.91)	<0.001	1.12 (1.07–1.17)
Model 4	1	1.01 (0.85–1.20)	1.11 (0.96–1.29)	1.12 (0.99–1.27)	1.22 (1.06–1.40)	0.001	1.05 (1.02–1.08)
Plant protein *N* (cases)	5,536 (2,614)	5,243 (2,320)	5,144 (2,205)	5,128 (2,197)	5,202 (2,301)		26,253 (11,637)
Median protein*	18.6	23.1	26.2	29.6	35.9		26.2
Model 1	1	0.92 (0.82–1.04)	0.88 (0.78–0.99)	0.93 (0.73–1.19)	0.91 (0.72–1.15)	0.507	0.92 (0.80–1.04)
Model 2	1	0.94 (0.84–1.05)	0.89 (0.80–0.99)	0.94 (0.75–1.18)	0.92 (0.75–1.12)	0.416	0.91 (0.82–1.02)
Model 3	1	1.03 (0.94–1.13)	1.02 (0.92–1.13)	1.15 (0.99–1.34)	1.18 (1.02–1.36)	0.006	1.02 (0.95–1.10)
Model 4	1	1.05 (0.92–1.19)	0.97 (0.83–1.15)	1.09 (0.91–1.31)	1.22 (0.98–1.52)	0.098	1.04 (0.93–1.16)

Model 1 includes age (= time scale) and covariates energy, center, and sex. Model 2, see model 1 plus covariates smoking, education, physical activity, and alcohol. Model 3, see model 2 plus covariates fiber, SFA, MUFA, PUFA, cholesterol, soft drinks, tea, and coffee (not adjusted for carbohydrates; i.e., a substitution model). Model 4, see model 3 plus covariates BMI and waist. Q, quintile. *FFQ-estimated intake, adjusted for energy by the residual method.

the associations with increasing protein intake at the expense of carbohydrates because this is the most suitable source to replace protein, which is reflected by the lower carbohydrate intakes of participants with high-protein intakes. Furthermore, in clinical trials carbohydrates are also the source of choice to replace protein. Analyses of protein intake at the expense of fat intake were comparable with the substitution of carbohydrates. The HRs with increasing intake of protein over the quintiles show a linear dose-response relation. The association between total protein intake and type 2 diabetes appears to be largely explained by animal protein, with a 22% higher type 2 diabetes incidence when comparing highest versus lowest quintile and 5% higher incidence per 10-g increment of animal protein intake. The magnitude of the increased type 2 diabetes risk associated with high total protein intake is comparable with the results of the earlier Dutch cohort study (3), a biomarker-calibrated cohort in the U.S. (4), two small cross-sectional studies in Asian populations (n <150) (8,9), and one small (n = 1,190) Greek population (10).

We observed that type 2 diabetes incidence was 38% higher in women with the highest animal protein intake compared with women with the lowest intake and that type 2 diabetes incidence increased 9% per 10-g increment of animal protein intake. In obese women, the association was even stronger, with a risk increase of 19% per 10-g increment of animal protein intake. In men, only a weak nonsignificant association was present. A difference between men and women has been observed in a prior study, though it as most evident in men (30). In our study, it cannot be explained by differences in total protein intake and/or protein sources. On average, women did have a 20% lower absolute intake of total, animal, and plant protein, but the energy percentage of protein in the diet was equal for men and women. Also, the contribution of protein sources did not differ between sexes. Most dietary and lifestyle factors, associated with protein intake, did not differ substantially between men and women; only women with high protein intake were less likely to be physically active and were more restricted alcohol consumers. Further, the association remained similar after adjustment for BMI and waist in women but was attenuated in men. So, it seems that measures of abdominal obesity largely explain the association of protein intake and type 2 diabetes for men, which is not the case in women. Further research is required to explore why animal protein intake was found to be positively associated with type 2 diabetes risk in women only.

In our study, the association between protein intake and type 2 diabetes was attenuated by measures of body composition, most evident in men. This is in line with earlier research (3,4) and could be explained by the strong independent effect of abdominal obesity on type 2 diabetes risk and the positive correlation of protein intake with overweight and obesity (31). We found that the association between protein intake and type 2 diabetes was strongest in obese women in contrast to prior research declaring weaker associations with increasing BMI (3). Our findings may be explained by the fact that higher total protein intake, and/or higher protein intake from animal sources, is associated with weight and weight gain (31,32). In our data, this effect would be stronger in women than in men. More research is needed to explain these mixed results. Unfortunately, it was not possible to consider weight change as a mediating factor between protein intake and type 2 diabetes incidence because data on weight change in our cohort were ascertained at fixed time intervals after baseline recruitment, so there is the potential for information bias.

In contrast to suggested beneficial short-term effects of dietary protein on glycemic control (5,33), our study found that habitually high intake of

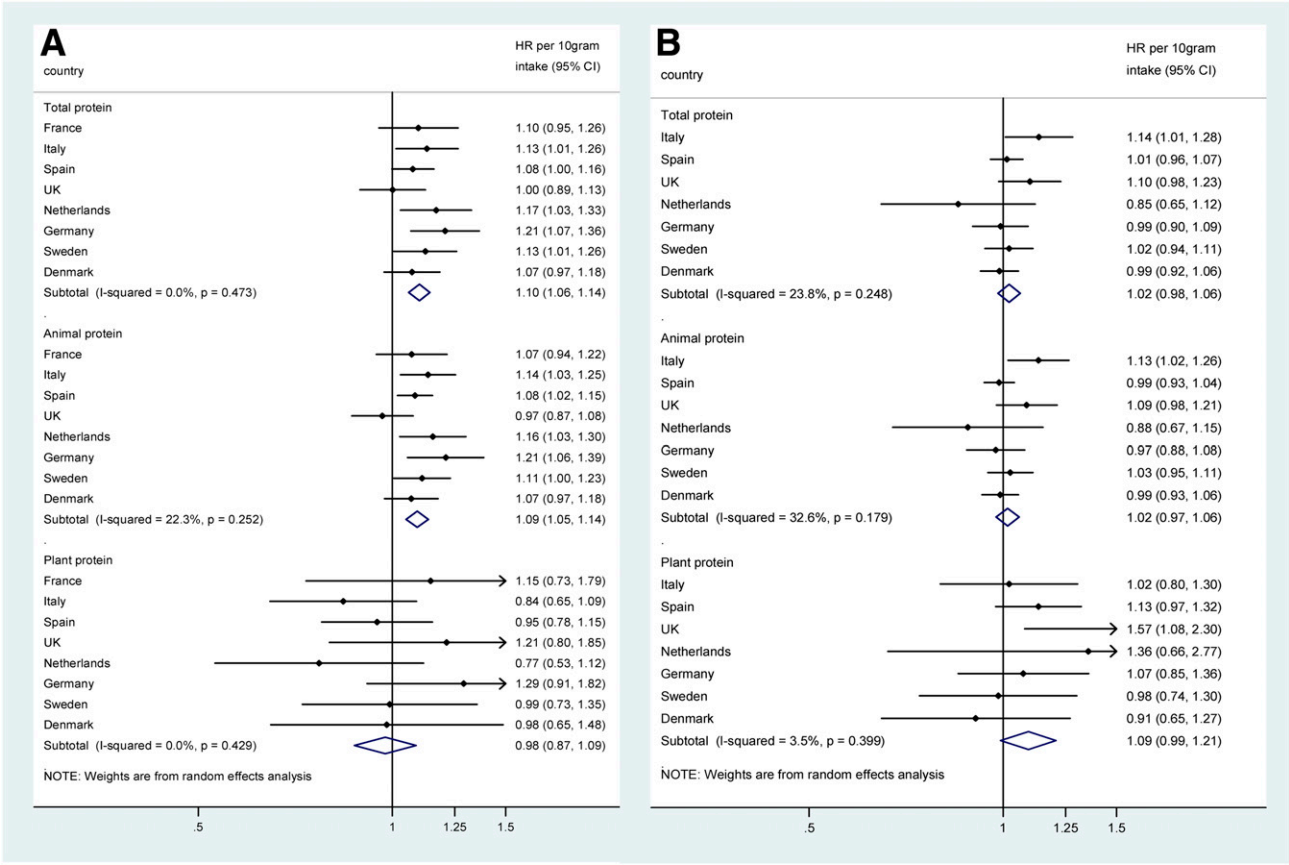

Figure 1—Meta-analyzed HRs of type 2 diabetes associated with 10-g increments of total, animal, and plant protein. Meta-analyzed (pooled country specific) HRs and 95% CI. Protein intake is FFQ-estimated intake, adjusted for energy using the residual method. *A*: Women. *B*: Men. The HRs are adjusted for energy, smoking, education, physical activity, alcohol, fiber, SFA, MUFA, PUFA, cholesterol, soft drinks, tea, coffee, BMI, and waist (not adjusted for carbohydrates; i.e., a substitution model).

protein increases type 2 diabetes risk. This discrepancy between short- and long-term effects of protein intake can be explained by differences in energy content and/or in long-term and acute effects of dietary protein. In energy-restricted diets, high-protein content as a percentage of total energy is found to be beneficial, while absolute protein intake is similar or only modestly increased compared with protein intake in energy balance. We observed that in the general population, in energy balance or positive energy balance, a high absolute protein intake is associated with increased type 2 diabetes risk. The mechanism of the potential harmful effect of high dietary protein intake on type 2 diabetes is largely unknown. It could be driven by high protein sources, such as red or

Table 3—BMI-specific meta-analyzed (pooled) HRs (95% CI) (per 10 g protein intake) for the association between protein intake and type 2 diabetes: results of the adjusted model (model 4)

	Overall	Men	Women
Animal protein *N* (cases)	26,253 (11,637)	11,241 (5,798)	15,012 (5,839)
BMI (kg/m^2)			
<25	1.08 (1.00–1.17); 52.4	1.02 (0.88–1.17); 50.2	1.11 (0.99–1.25); 53.1
25–30	1.04 (1.00–1.07); 57.4	1.07 (0.99–1.15); 56.7	1.07 (1.01–1.14); 58.2
>30	1.06 (1.00–1.11); 60.7	0.96 (0.91–1.02); 62.1	1.19 (1.09–1.32); 60.0
Plant protein *N* (cases)	26,253 (11,637)	11,241 (5,798)	15,012 (5,839)
BMI (kg/m^2)			
<25	1.04 (0.89–1.23); 25.9	0.97 (0.76–1.24); 26.1	1.15 (0.90–1.46); 25.8
25–30	1.06 (0.96–1.17); 26.5	1.13 (0.99–1.29); 26.3	1.01 (0.84–1.21); 26.6
>30	1.08 (0.87–1.33); 26.8	1.17 (0.93–1.47); 26.2	1.12 (0.78–1.61); 27.2

Data are HR (95% CI); median protein intake unless otherwise indicated. Median protein intake: FFQ-estimated intake, adjusted for energy using the residual method. Model 4 includes age (= time scale) and covariates energy, center, sex, smoking, education, physical activity, alcohol, fiber, SFA, MUFA, PUFA, cholesterol, soft drinks, tea, coffee, BMI, and waist (not adjusted for carbohydrates; i.e., a substitution model). The pooled HRs per 10 g protein intake did not include risk scores for Dutch men and French women because of the low number of obese subjects in these groups.

processed meat, and factors associated with protein intake or protein per se, e.g., based on amino acid profiles. Dietary proteins are known to increase glucagon, which could partially explain high blood glucose levels. Dietary proteins also increase insulin secretion, possibly leading to hyperinsulinemia, a risk factor for insulin resistance. A recent study suggested there could be a key role for the plasma amino acid levels of isoleucine, leucine, valine, tyrosine, and phenylalanine in the pathogenesis of type 2 diabetes (34), which have also been found to be associated with type 2 diabetes incidence in EPIC-Potsdam (35). High levels of these plasma amino acids predicted future diabetes, e.g., as found for single plasma amino acids, such as leucine, with an HR of 3.66 (95% 1.61–8.29), and for combinations of the amino acids isoleucine, tyrosine, and phenylalanine, with an HR of 5.99 (2.34–15.34) comparing the highest versus lowest quartile (34). This is in line with earlier experimental elevations of plasma amino acids by infusion, which resulted in impaired insulin-stimulated glucose disposal and insulin-mediated suppression of (hepatic) glucose production (36,37). The above-mentioned branched-chain amino acids and tyrosine and phenylalanine are mainly present in meat and dairy, though they are available in all protein-rich foods.

No specific group of protein sources accounted for the positive association of animal protein and type 2 diabetes incidence. Protein from meat did not explain the association in our cohort, and neither did protein from dairy or fish. So, although the well-established association between meat consumption and type 2 diabetes is suggested to be mainly due to other nutrients, such as iron, nitrites, sodium, or advanced glycation end products (12,38), a direct effect of protein from meat cannot be excluded. In our analyses, protein from dairy and protein from cheese were not accountable for the reported reduced type 2 diabetes risk associated with dairy (14–16) and cheese consumption. Fish consumption is not associated with type 2 diabetes (20–23,39), so possibly our observed association between animal protein and increased type 2 diabetes risk is counterbalanced by potential risk-reducing nutritional components of fish. The findings of this study did not confirm the suggested reduced type 2 diabetes risk associated with protein intake from plant products (especially legumes [18] and nuts [19]). This could be related to the large proportion of bread, pasta and rice, and potatoes among the plant protein sources and relatively low intake of vegetables, legumes, and nuts, although no indication for a risk-reducing effect of protein from vegetables, legumes, and nuts was present in our analyses. To estimate protein intake, we used uncalibrated results of FFQs, so the intake is not equal to the 24-h protein intake in EPIC reported by Halkjaer et al. (40).

Our study with a large sample size from eight European countries and long follow-up had several strengths. The prospective design, with data collection before the occurrence of type 2 diabetes, and the use of validated FFQs at baseline reduce possible biased recall of diet, although it is possible that diets have changed during follow-up, which could influence the results. The strict validation of diabetes cases reduced the probability of misclassifying non-cases as cases. In contrast, it cannot be ruled out that incident and prevalent type 2 diabetes cases have remained undiagnosed, which may lead to an underestimation of main effects and reduced power. Further, we were able to adjust our associations for a wide range of potential risk factors for type 2 diabetes and dietary factors, so the observed positive association between protein intake and type 2 diabetes is likely to be explained by proteins per se. The possibility of unmeasured or residual confounding cannot be ruled out, though. Information on *trans*-fatty acids was, for example, not available, but in Europe intake in non–margarine using, low–dairy using countries intake was probably low, and in margarine-using diary countries such as the Netherlands, *trans*-fatty acids correlate with PUFA intake. Because of the observational design, conclusions regarding causality cannot be drawn. The associations could for example relate to a less healthy diet and/or lifestyle, even though total and animal protein intake was not associated with known risk factors such as higher SFAs or lower fiber intake.

Overall, we conclude that a greater intake of total protein intake is associated with a higher type 2 diabetes incidence in European populations, but the effect of protein intake is small and known type 2 diabetes risk factors are also important. Our results show that protein of animal origin is largely responsible for the association—not plant protein. The association is confirmed in women, not in men, and is strongest in obese women. The association cannot be explained by a single food source. In view of the rapidly increasing prevalence of type 2 diabetes, limiting isoenergetic diets high in dietary proteins, particularly from animal sources, should be considered.

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