Online-Only Supplemental Material

Replacement of red and processed meat with other food sources of protein and the risk of type 2 diabetes in European populations; the EPIC-InterAct study

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Supplemental Table S1–Dietary assessment methods used to estimate total protein and food sources of protein across countries/centres in the EPIC-InterAct case-cohort study and correlation coefficients reported for total protein and food sources of protein

Country	**Centres (where methods differed)***	**Dietary questionnaire***	**Administered***	**Correlation coefficient for questionnaire vs twelve 24-h recalls***						
				Protein†	Protein (biomarker)#	Meat	Fish	Dairy products	Eggs	Cereals
France		Quantitative	Self	0.59 (F)‡	0.37	0.43	0.39	0.67	0.40	0.56
Italy				0.48 (F) / 0.35 (M)	0.31 / 0.19	0.38 / 0.39	0.47 / 0.42	0.66 / 0.78	0.23 / 0.50	0.51 / 0.44
	Florence, Turin, Varese	Quantitative	Self							
	Ragusa	Quantitative	Face-to-face							
	Naples	Semi-quantitative	Face-to-face							
Spain		Quantitative	Face-to-face	0.51 (F) / 0.58 (M)	0.45 / 0.12	0.59 / 0.44	0.55 / 0.42	0.74 / 0.77	0.49 / 0.36	0.69 / 0.72
United Kingdom		Semi-quantitative	Self							
	Oxford			0.66 (F)						
	Cambridge			0.43 (F)§,‖	0.49§					
Netherlands		Quantitative	Self	0.67 (F) / 0.71 (M)	0.54 / 0.40	0.70 / 0.47	0.38 / 0.32	0.77 / 0.73	0.43 / 0.41	0.68 / 0.75
Germany		Quantitative	Self	0.54 (F) / 0.47 (M)	0.36 / 0.24	0.41 / 0.63	0.22 / 0.41	0.46 / 0.54	0.38 / 0.40	0.19 / 0.39
Sweden				0.43 (F) / 0.61 (M)	0.07 / 0.27	0.42 / 0.57	0.24 / 0.23	0.67 / 0.70	0.64 / 0.50	0.53 / 0.63
	Umeå	Semi-quantitative	Self							
	Malmö	Semi-quantitative and 14-day record of hot meals	Self							
Denmark		Semi-quantitative	Self	0.26 (F) / 0.52 (M)¶						

F, female; M, male.

*From: Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public health nutrition* 2002; **5**(6B): 1113-24.

†Validity coefficients in all centres except EPIC-Norfolk and Denmark represent Pearson correlation coefficients of total protein measured by dietary questionnaires versus twelve 24-h recalls (reference method), and were deattenuated and energy-adjusted. Values obtained from: Kaaks R, Slimani N, Riboli E. Pilot phase studies on the accuracy of dietary intake measurements in the EPIC project: overall evaluation of results. European Prospective Investigation into Cancer and Nutrition. *International journal of*

epidemiology 1997; **26 Suppl 1**: S26-36., unless indicated otherwise.
‡Same gender for entire row following the same sequence.
§Validity coefficients in the EPIC-Norfolk arm in the UK were estimated by Spearman correlation coefficients of total protein measured by dietary questionnaires versus 16-day weighted records.
||Values obtained from: Bingham SA, Gill C, Welch A, et al. *International journal of epidemiology* 1997; **26 Suppl 1**: S137-51.
¶Values obtained from Tjonneland A, Overvad K, Haraldsdottir J, Bang S, Ewertz M, Jensen OM. *International journal of epidemiology* 1991; **20(4)**: 906-12.
#Questionnaire vs. urinary nitrogen

Supplemental Table S2–Definition of individual food groups

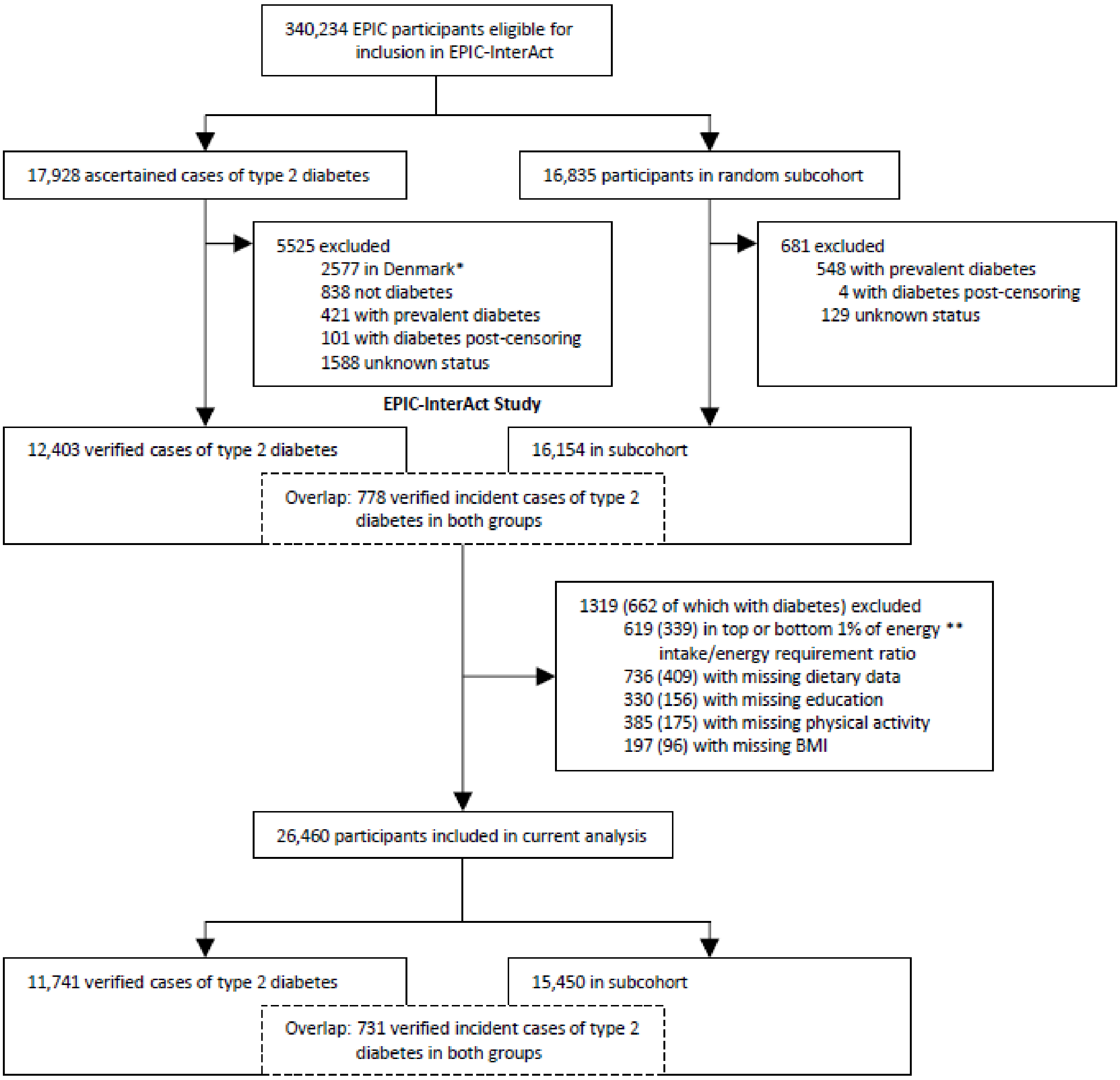
Food group	Included foods
Red meat	Unprocessed beef, pork, veal, mutton, lamb, goat and horse, hamburgers, meatballs and minced meat
Processed meat	Bacon-, ham- and liver-containing foods and foods such as black pudding, chorizo, sausage and corned beef
Poultry	Chicken, hen, turkey, duck, rabbit and goose
Fish	Lean and fatty fish, fish products, fish roe, fish liver and shellfish
Milk	Liquid dairy milks such skimmed, semi-skimmed, whole-fat types and buttermilk
Yogurt	Yogurt and thick fermented milks (e.g. sour milk)
Cheese	Hard and soft cheese
Eggs	Whole eggs and egg from egg products
Legumes	Red kidney beans, haricot beans, chickpeas, split peas and lentils
Nuts	Tree nuts, peanuts*, seeds, coconut and chestnut
Cereals	Bread, rice, pasta and other types of cereals†

*Peanuts were included as nuts, although they botanically belong to legumes, because they are usually consumed as nuts.
†We were not able to differentiate cereals into refined and whole grains in our data material.

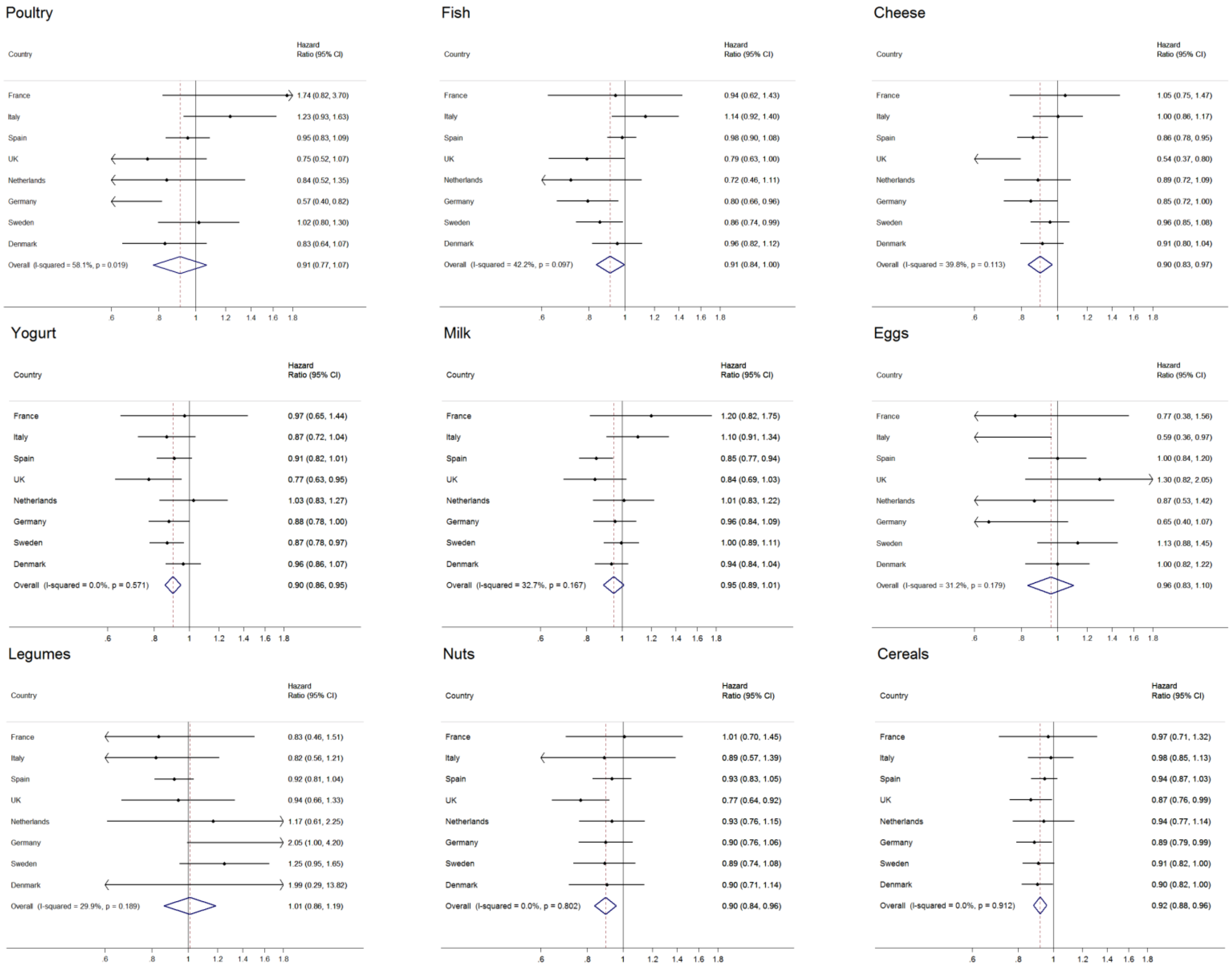
Supplemental Table S3–Analysis comparing replacement models with and without adjustment for serum ferritin

Replacement of red and processed meat with	β-coefficient	P value for attenuation of β	HR (95% CI)
Poultry			
Model 2 (ref)	-0.105		0.90 (0.83, 0.97)
Model 2 + ferritin	-0.059	<0.001	0.94 (0.87, 1.02)
Model 3 (ref)	-0.071		0.93 (0.85, 1.02)
Model 3 + ferritin	-0.043	0.002	0.96 (0.87, 1.05)
Fish			
Model 2 (ref)	-0.076		0.93 (0.87, 0.98)
Model 2 + ferritin	-0.030	<0.001	0.97 (0.91, 1.03)
Model 3 (ref)	-0.012		0.99 (0.92, 1.06)
Model 3 + ferritin	0.014	<0.001	1.01 (0.95, 1.09)
Cheese			
Model 2 (ref)	-0.173		0.84 (0.80, 0.88)
Model 2 + ferritin	-0.118	<0.001	0.89 (0.85, 0.94)
Model 3 (ref)	-0.114		0.89 (0.85, 0.94)
Model 3 + ferritin	-0.078	<0.001	0.93 (0.88, 0.97)
Yogurt			
Model 2 (ref)	-0.209	<0.001	0.81 (0.78, 0.85)
Model 2 + ferritin	-0.162		0.85 (0.81, 0.89)
Model 3 (ref)	-0.108	<0.001	0.90 (0.86, 0.94)
Model 3 + ferritin	-0.079		0.92 (0.88, 0.97)
Milk			
Model 2 (ref)	-0.139	<0.001	0.87 (0.83, 0.91)
Model 2 + ferritin	-0.084		0.92 (0.88, 0.96)
Model 3 (ref)	-0.062	<0.001	0.94 (0.89, 0.99)
Model 3 + ferritin	-0.032		0.97 (0.92, 1.02)
Eggs			
Model 2 (ref)	-0.002		1.00 (0.91, 1.09)
Model 2 + ferritin	0.038	0.02	1.04 (0.94, 1.14)
Model 3 (ref)	-0.047		0.95 (0.85, 1.07)
Model 3 + ferritin	-0.017	0.01	0.98 (0.88, 1.10)
Legumes			
Model 2 (ref)	-0.175		0.84 (0.78, 0.91)
Model 2 + ferritin	-0.125	0.006	0.88 (0.81, 0.96)
Model 3 (ref)	-0.051		0.95 (0.86, 1.04)
Model 3 + ferritin	-0.018	0.009	0.98 (0.90, 1.08)
Nuts			
Model 2 (ref)	-0.205		0.81 (0.77, 0.86)
Model 2 + ferritin	-0.141	<0.001	0.87 (0.82, 0.92)
Model 3 (ref)	-0.156		0.86 (0.78, 0.94)
Model 3 + ferritin	-0.114	<0.001	0.89 (0.82, 0.98)
Cereals			
Model 2 (ref)	-0.193		0.81 (0.77, 0.86)
Model 2 + ferritin	-0.143	<0.001	0.87 (0.82, 0.91)
Model 3 (ref)	-0.089		0.92 (0.88, 0.95)
Model 3 + ferritin	-0.060	<0.001	0.94 (0.90, 0.98)

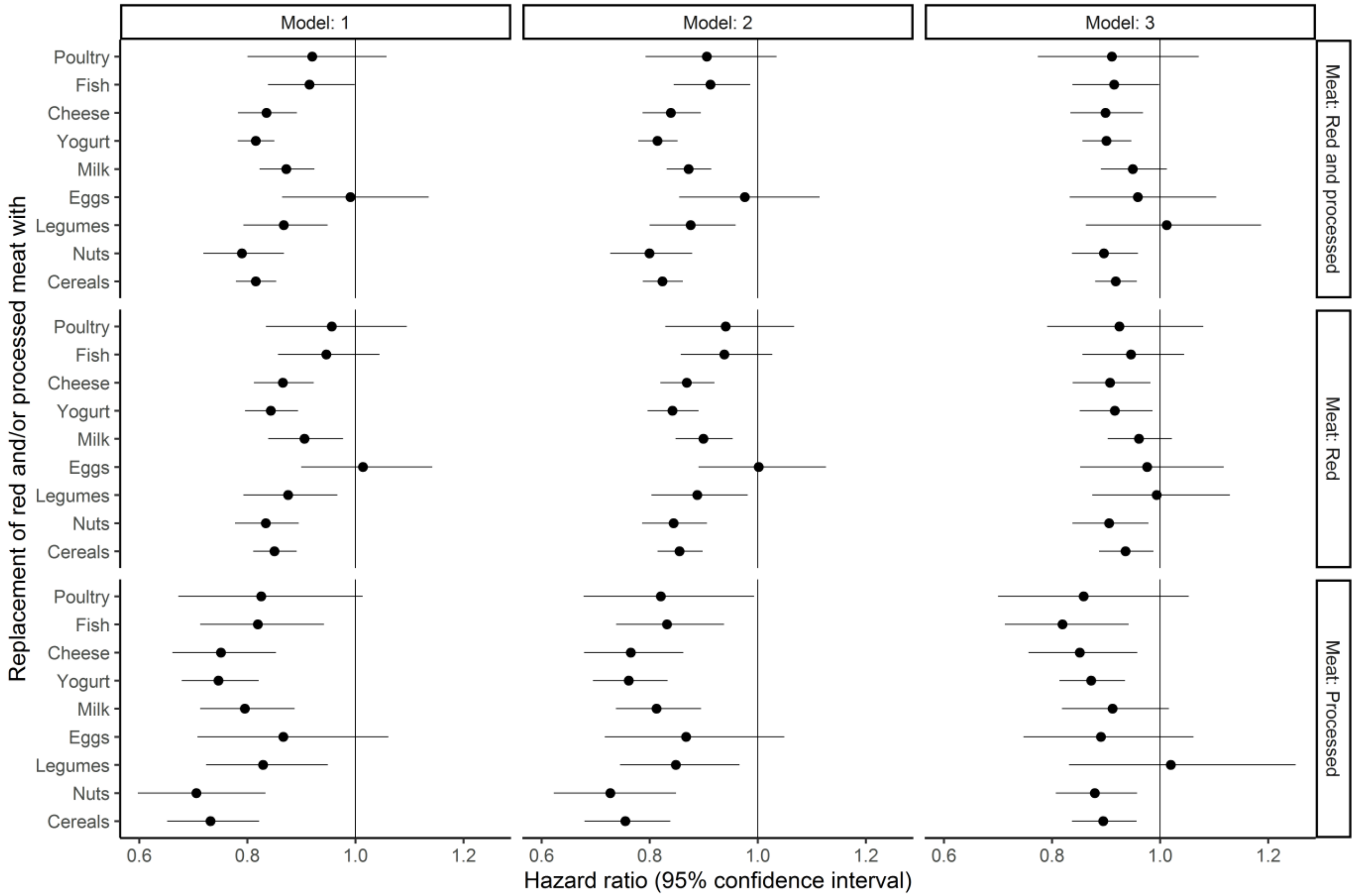
Model 2 adjusted for: age (underlying timescale), sex, country, education, physical activity, smoking status, total energy intake, alcohol consumption, fruit, vegetables, sweets, soft drinks, coffee, tea and other dairy products. Model 3 further adjusted for body mass index (n total = 24,611, n cases = 10,769). Serving sizes were 50 g/day for red and processed meat, poultry, fish, eggs and legumes, 30 g/day for cheese and cereals and 10 g/day for nuts. P value is from a one-sided Wald test.



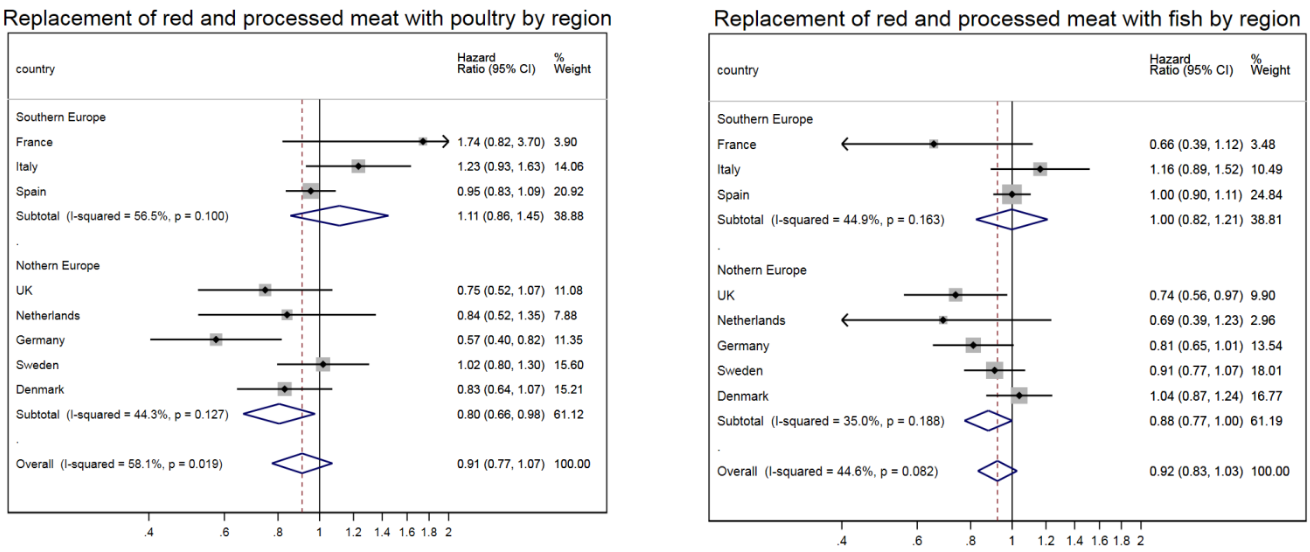
Supplemental Fig. S1–Flowchart of participants in the EPIC-InterAct case-cohort. *A random sample of 2055 type 2 diabetes cases from Denmark was included after the exclusion of 2577 cases. **n missing before exclusions.


Poultry
Country
Hazard Ratio (95% CI)
France 1.74 (0.82, 3.70)
Italy 1.23 (0.93, 1.63)
Spain 0.95 (0.83, 1.09)
UK 0.75 (0.52, 1.07)
Netherlands 0.84 (0.52, 1.35)
Germany 0.57 (0.40, 0.82)
Sweden 1.02 (0.80, 1.30)
Denmark 0.83 (0.64, 1.07)
Overall (I-squared = 58.1%, p = 0.019) 0.91 (0.77, 1.07)
.6 .8 1 1.2 1.4 1.6 1.8
Fish
Country
Hazard Ratio (95% CI)
France 0.94 (0.62, 1.43)
Italy 1.14 (0.92, 1.40)
Spain 0.98 (0.90, 1.08)
UK 0.79 (0.63, 1.00)
Netherlands 0.72 (0.46, 1.11)
Germany 0.80 (0.66, 0.96)
Sweden 0.86 (0.74, 0.99)
Denmark 0.96 (0.82, 1.12)
Overall (I-squared = 42.2%, p = 0.097) 0.91 (0.84, 1.00)
.6 .8 1 1.2 1.4 1.6 1.8
Cheese
Country
Hazard Ratio (95% CI)
France 1.05 (0.75, 1.47)
Italy 1.00 (0.86, 1.17)
Spain 0.86 (0.78, 0.95)
UK 0.54 (0.37, 0.80)
Netherlands 0.89 (0.72, 1.09)
Germany 0.85 (0.72, 1.00)
Sweden 0.96 (0.85, 1.08)
Denmark 0.91 (0.80, 1.04)
Overall (I-squared = 39.8%, p = 0.113) 0.90 (0.83, 0.97)
.6 .8 1 1.2 1.4 1.6 1.8
Yogurt
Country
Hazard Ratio (95% CI)
France 0.97 (0.65, 1.44)
Italy 0.87 (0.72, 1.04)
Spain 0.91 (0.82, 1.01)
UK 0.77 (0.63, 0.95)
Netherlands 1.03 (0.83, 1.27)
Germany 0.88 (0.78, 1.00)
Sweden 0.87 (0.78, 0.97)
Denmark 0.96 (0.86, 1.07)
Overall (I-squared = 0.0%, p = 0.571) 0.90 (0.86, 0.95)
.6 .8 1 1.2 1.4 1.6 1.8
Milk
Country
Hazard Ratio (95% CI)
France 1.20 (0.82, 1.75)
Italy 1.10 (0.91, 1.34)
Spain 0.85 (0.77, 0.94)
UK 0.84 (0.69, 1.03)
Netherlands 1.01 (0.83, 1.22)
Germany 0.96 (0.84, 1.09)
Sweden 1.00 (0.89, 1.11)
Denmark 0.94 (0.84, 1.04)
Overall (I-squared = 32.7%, p = 0.167) 0.95 (0.89, 1.01)
.6 .8 1 1.2 1.4 1.6 1.8
Eggs
Country
Hazard Ratio (95% CI)
France 0.77 (0.38, 1.56)
Italy 0.59 (0.36, 0.97)
Spain 1.00 (0.84, 1.20)
UK 1.30 (0.82, 2.05)
Netherlands 0.87 (0.53, 1.42)
Germany 0.65 (0.40, 1.07)
Sweden 1.13 (0.88, 1.45)
Denmark 1.00 (0.82, 1.22)
Overall (I-squared = 31.2%, p = 0.179) 0.96 (0.83, 1.10)
.6 .8 1 1.2 1.4 1.6 1.8
Legumes
Country
Hazard Ratio (95% CI)
France 0.83 (0.46, 1.51)
Italy 0.82 (0.56, 1.21)
Spain 0.92 (0.81, 1.04)
UK 0.94 (0.66, 1.33)
Netherlands 1.17 (0.61, 2.25)
Germany 2.05 (1.00, 4.20)
Sweden 1.25 (0.95, 1.65)
Denmark 1.99 (0.29, 13.82)
Overall (I-squared = 29.9%, p = 0.189) 1.01 (0.86, 1.19)
.6 .8 1 1.2 1.4 1.6 1.8
Nuts
Country
Hazard Ratio (95% CI)
France 1.01 (0.70, 1.45)
Italy 0.89 (0.57, 1.39)
Spain 0.93 (0.83, 1.05)
UK 0.77 (0.64, 0.92)
Netherlands 0.93 (0.76, 1.15)
Germany 0.90 (0.76, 1.06)
Sweden 0.89 (0.74, 1.08)
Denmark 0.90 (0.71, 1.14)
Overall (I-squared = 0.0%, p = 0.802) 0.90 (0.84, 0.96)
.6 .8 1 1.2 1.4 1.6 1.8
Cereals
Country
Hazard Ratio (95% CI)
France 0.97 (0.71, 1.32)
Italy 0.98 (0.85, 1.13)
Spain 0.94 (0.87, 1.03)
UK 0.87 (0.76, 0.99)
Netherlands 0.94 (0.77, 1.14)
Germany 0.89 (0.79, 0.99)
Sweden 0.91 (0.82, 1.00)
Denmark 0.90 (0.82, 1.00)
Overall (I-squared = 0.0%, p = 0.912) 0.92 (0.88, 0.96)
.6 .8 1 1.2 1.4 1.6 1.8

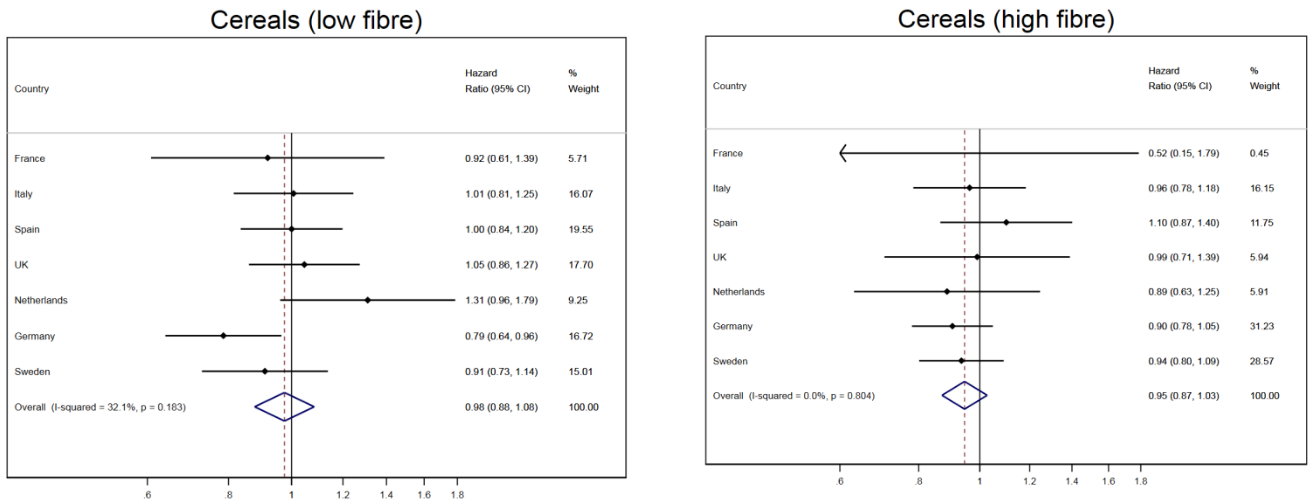
Supplemental Fig. S2–The estimated effect of replacing red and processed meat with poultry, fish, cheese, yogurt, milk, eggs, legumes, nuts or cereals on the incidence of type 2 diabetes across eight European countries from the EPIC-InterAct study (n total = 26,460, n cases = 11,741). Hazard ratios and 95% confidence intervals (CIs) were adjusted for: age (underlying timescale), sex, centre, education, physical activity, smoking status, total energy intake, alcohol consumption, fruit, vegetables, sweets, soft drinks, coffee, tea, other dairy products and body mass index. Serving sizes were 200 g/day for milk, 70 g/day for yogurt, 50 g/day for red and processed meat, poultry, fish, eggs and legumes, 30 g/day for cheese and cereals and 10 g/day for nuts.



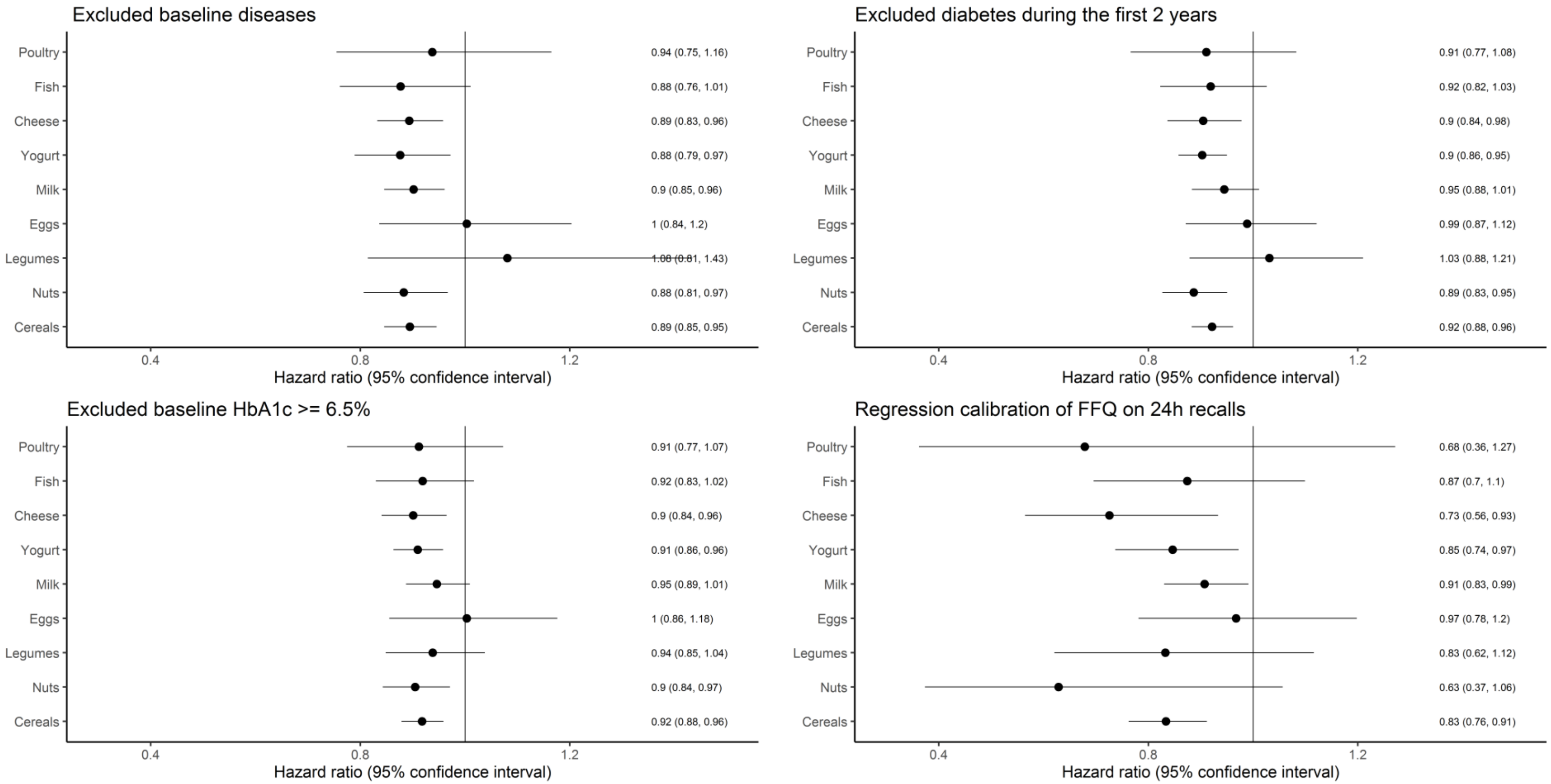
Supplemental Fig. S3–Replacement of red and/or processed red meat and hazard of type 2 diabetes. Country-specific estimates were combined using random effects meta-analysis. Model 1 adjusted for: age (underlying timescale), sex, centre, total energy intake, education, physical activity, smoking status and alcohol consumption. Model 2 further adjusted for fruit, vegetables, sweets, soft drinks, coffee, tea and other dairy products. Model 3 further adjusted for body mass index (n total = 26,460, n cases = 11,741). Serving sizes were 200 g/day for milk, 70 g/day for yogurt, 50 g/day for red and processed meat, poultry, fish, eggs and legumes, 30 g/day for cheese and cereals and 10 g/day for nuts.



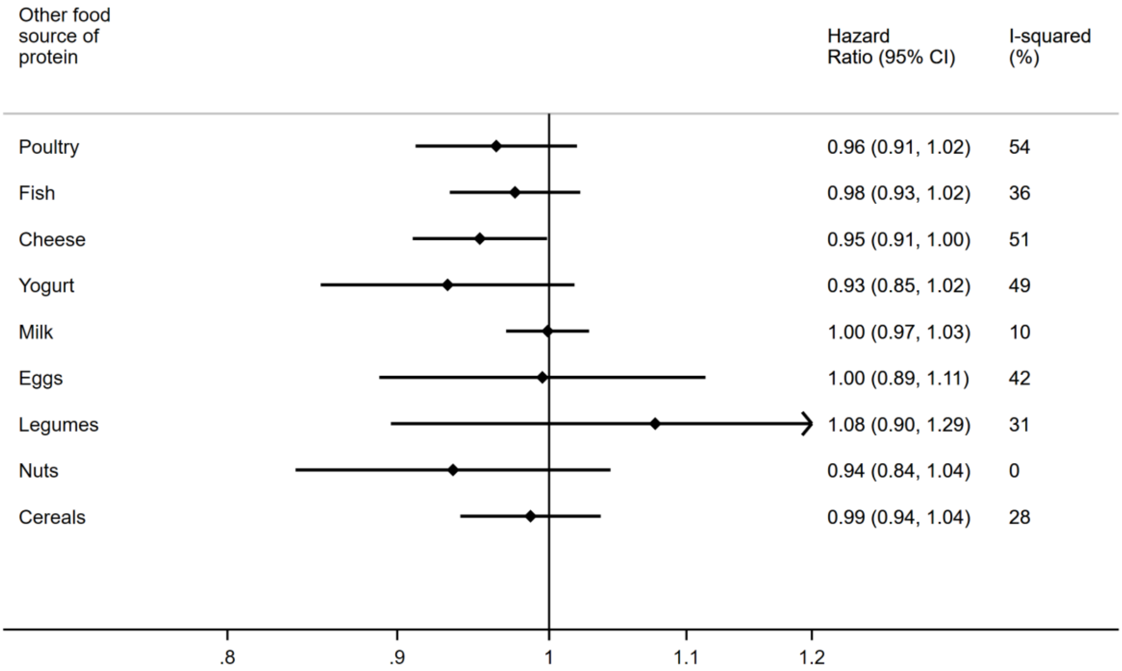
Supplemental Fig. S4–Stratified meta-analyses of replacements of red and processed meat with other food sources of protein and hazard of type 2 diabetes across eight European countries from the EPIC-InterAct Study. Stratified by European region based on a cut-point, including the Netherlands, above which was defined as the northern European region. Countries below the cut-point were defined as southern. All country-specific estimates were adjusted for: age (underlying timescale), sex, education, physical activity, smoking status, total energy intake, alcohol consumption, fruit, vegetables, sweets, soft drinks, coffee, tea, other dairy products and body mass index (n total = 26,460, n cases = 11,741). Serving sizes were 50 g/day for red and processed meat, poultry and fish.



Supplemental Fig. S5–Meta-analyses of replacements of red and processed meat with cereals stratified on high or low dietary fibre from cereals (low <8 g/day, n total = 9246, n cases = 3817; high ≥8 g/day, n total = 7785, n cases = 3289) and hazard of type 2 diabetes across seven European countries from the EPIC-InterAct Study. All country-specific estimates were adjusted for: age (underlying timescale), sex, education, physical activity, smoking status, total energy intake, alcohol consumption fruit, vegetables, sweets, soft drinks, coffee, tea, other dairy products and body mass index. Serving sizes were 50 g/day for red and processed meat and 30 g/day for cereals. Denmark was not included because the models would not converge as the Danes in general had a higher intake of cereal fibre compared with the other countries.



Supplemental Fig. S6–Sensitivity analyses excluding participants with baseline prevalent diseases (n cancer = 887, myocardial infarction = 529, stroke = 227, angina = 370, hypertension = 6141, hyperlipidaemia = 2385; n total = 15,921, n cases = 5699); developed diabetes during the first 2 years of follow-up (n diabetes during first 2 years of follow-up = 997; n total = 25,463, n cases = 10,744); baseline HbA1c levels ≥ 6.5% (n HbA1c levels ≥ 6.5% = 2241; n total = 24,219, n cases = 9584); and regression calibration of FFQ intakes using 24h recall data from 2271 participants. Serving sizes were 50 g/day for red and processed meat, poultry, fish, eggs and legumes, 30 g/day for cheese and cereals and 10 g/day for nuts. Denmark not included for replacement of red and processed meat with legumes in the regression calibration analysis due to too low intakes.



Supplemental Fig. S7–Sensitivity analysis of the estimated association of replacing red and processed meat (per 5 g protein/day) with other food sources of protein and the incidence of type 2 diabetes in the EPIC-InterAct case-cohort study (n total = 26,460, n cases = 11,741). Country-specific estimates were obtained and combined using random effects meta-analysis. Adjusted for: age (underlying timescale), sex, centre, education, physical activity, smoking status, total energy intake, total protein, alcohol consumption, fruit, vegetables, sweets, soft drinks, coffee, tea, other dairy products and body mass index.