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ARTICLE

Association between dietary meat consumption and incident type 2 diabetes: the EPIC-InterAct study

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Abstract
Aims/hypothesis A diet rich in meat has been reported to contribute to the risk of type 2 diabetes. The present study aims to investigate the association between meat consumption and incident type 2 diabetes in the EPIC-InterAct study, a large prospective case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study.
Methods During 11.7 years of follow-up, 12,403 incident cases of type 2 diabetes were identified among 340,234 adults from eight European countries. A centre-stratified random subsample of 16,835 individuals was selected in order to perform a case-cohort design. Prentice-weighted Cox regression analyses were used to estimate HR and 95% CI for incident diabetes according to meat consumption.
Results Overall, multivariate analyses showed significant positive associations with incident type 2 diabetes for increasing consumption of total meat (50 g increments: HR 1.08; 95% CI 1.05, 1.12), red meat (HR 1.08; 95% CI 1.03, 1.13) and processed meat (HR 1.12; 95% CI 1.05, 1.19), and a borderline positive association with meat iron intake. Effect modifications by sex and class of BMI were observed. In men, the results of the overall analyses were confirmed. In women, the association with total and red meat persisted, although attenuated, while an association with poultry consumption also emerged (HR 1.20; 95% CI 1.07, 1.34). These associations were not evident among obese participants.
Conclusions/interpretation This prospective study confirms a positive association between high consumption of total and red meat and incident type 2 diabetes in a large cohort of European adults.

Keywords Case-cohort study · Diet · Meat · Type 2 diabetes

Abbreviations
EPIC European Prospective Investigation into Cancer and Nutrition
I^2 Index of between-study heterogeneity

Introduction

Recent estimates from the International Diabetes Federation indicate that, in the year 2011, 366 million people in the world had diabetes and this estimate is projected to increase to 552 million by 2030 [1]. In the European Union, type 2 diabetes and impaired glucose tolerance currently represent two of the major public health concerns [2]. Moreover, at present there is no real cure for type 2 diabetes but only long-term treatment with glucose-lowering drugs or insulin. In this scenario the identification of primary prevention strategies for type 2 diabetes represents an important issue.

While individual characteristics such as age, overweight or obesity, family history, sedentary lifestyle, ethnicity, hypertension and hyperlipidaemia are established risk factors for type 2 diabetes [3], less is known about the influence of dietary factors.

Three recent meta-analyses of prospective studies emphasised that a diet rich in red and processed meat consumption is an important and independent contributor to type 2 diabetes risk [4–6]. In these meta-analyses a large

The InterAct Consortium list of authors is shown in the Appendix.

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proportion of the available studies of the association between dietary habits and type 2 diabetes risk were conducted in the USA. More recently, several studies have been conducted in European countries confirming the association between meat consumption and risk of type 2 diabetes in European populations [7–11].

The present study aims to investigate the association between consumption of total meat and meat subtypes and incident type 2 diabetes in a large collaborative project including adults from 26 cohorts in eight European countries participating in the 'InterAct project, an examination of the interaction of genetic and lifestyle factors on the incidence of type 2 diabetes' [12], thus taking into account differences in meat consumption patterns across Europe [13, 14].

Methods

Study design The EPIC-InterAct study is a large prospective case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) [15]. Its aim is to investigate the influence of lifestyle and genetic factors (and their interaction) on the risk of developing type 2 diabetes in a large cohort of adults from eight European countries [12]. The EPIC study was initiated in the late 1980s as a collaboration between 23 research institutions in ten European countries (Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden, UK, Greece and Norway). Greece and Norway did not participate in the EPIC-InterAct study. The EPIC study has been previously described by Riboli et al [15].

During a mean follow-up of 11.7 years a total of 12,403 verified newly diagnosed cases of type 2 diabetes were identified among 340,234 EPIC participants (men and women aged 20-80 years at baseline with a stored blood sample and reported diabetes status). Using a case-cohort design, a centre-stratified random subcohort of 16,835 participants (5%) was selected from the 340,234 EPIC participants. After exclusions of participants with prevalent diabetes (n=548) or those with missing data on diet (n=117), smoking status (n=241), BMI (n=169), physical activity (n=289) or education (n=479), as well as those who fell in the top or bottom 1% of the 'energy intake/energy requirement ratio' (n=619), a total of 26,088 individuals remained for the analysis (14,529 subcohort non-cases, 729 subcohort type 2 diabetes cases and 10,830 non-subcohort type 2 diabetes cases).

All participants in the EPIC cohorts involved in the InterAct project gave their informed consent. The EPIC-InterAct study has been approved by the responsible ethics committees.

Dietary exposure assessment At baseline, in the EPIC study, total daily consumption of food items was assessed for each participant by country-specific validated dietary questionnaires [16]. The total daily intake of each nutrient and the total daily energy intake were calculated [17]. The mean daily intake of meat iron was calculated as the mean of the total daily intake of iron (both heme and non-heme iron) from all types of meat. Glycaemic index and glycaemic load values were calculated based on glucose as a reference [18].

In the present study, the food group 'red meat' included the daily consumption (g) of unprocessed beef, pork, veal, mutton, lamb, goat and horse, hamburgers, meatballs and minced meat. The food group 'poultry' included chicken, hen, turkey, duck and goose; also domestic rabbit was added to this group. The food group 'processed meat' included bacon-, ham- and liver-containing items and all other processed meats (black pudding, chorizo, sausages, corned beef). The category 'offals' included liver, kidney, tripe, tongue, heart and sweetbread. A 'red and processed meat' group was created by combining the 'red meat' and the 'processed meat' groups. A 'total meat' group was also created by combining all types of meat.

Non-dietary exposure assessment At baseline, in the EPIC study, information on lifestyle habits (including tobacco smoking, alcohol drinking and physical activity), education, occupation, previous diseases and reproductive history was collected by means of a specific lifestyle questionnaire. Height, weight, waist and hip circumference of participants were also collected.

Ascertainment and verification of type 2 diabetes incident cases In each InterAct centre a list of all ascertained type 2 diabetes incident cases was created including individuals with evidence of type 2 diabetes from self-reported history of diabetes during follow-up contacts, linkage to primary and secondary care registers, type 2 diabetes-specific medication use and type 2 diabetes diagnosis reported in hospital admissions records or in mortality data. A detailed description of the ascertainment and verification procedure in all InterAct centres is provided elsewhere [12]. Follow-up was censored at the date of diagnosis, 31 December 2007 or the date of death, whichever came first.

Statistical analysis Sex-specific quintiles of daily consumption of total meat, red meat, processed meat, red and processed meat, poultry and meat iron were obtained based on the subcohort sample. Sex-specific tertiles were obtained for offals due to their small daily consumption.

Within the subcohort sample the distribution of the main baseline non-dietary characteristics according to sex-specific quintiles of total meat consumption were explored. Generalised linear models, adjusted for age and daily energy intake at enrolment, were used to explore the baseline dietary variables.

Cox regression, with an estimation procedure for case-cohort designs according to the Prentice weighting method [19], was used to estimate HR and 95% CI of incident diabetes according to sex-specific quantiles of consumption of total meat, red meat, processed meat, red and processed meat, poultry, offals and meat iron. The time at entry was age at recruitment; exit time was the age at which participants were diagnosed with diabetes, died, were lost-to-follow-up or were censored at the end of the follow-up period, whichever came first. HR and 95% CI were computed with the lowest quantile of consumption as reference. Tests for linear trend in HR were based on medians across quantiles. In the basic model the baseline hazard function was stratified by centre and adjusted for sex and energy intake (natural log kJ). In multivariate model 1, analyses were performed stratified by centre and adjusted for sex, energy intake, smoking status (dummy variables for former and current smokers; never smokers as reference), alcohol (quintiles of daily intake), physical activity (four levels) and educational level (five levels) based on a priori knowledge of the main risk factors for type 2 diabetes [3, 20–22]. In multivariate model 2, a term for BMI (continuous) was added. The same models were performed with each type of meat and meat iron as continuous variables (50 g increments for total meat, red meat, processed meat, red and processed meat, and poultry; 10 g increments for offals; 1 mg increments for meat iron). Further analyses were performed with adjustment for intake of other foods and nutrients such as potatoes, total vegetables, bread and pasta, fish, cakes, soft drinks, coffee (50 g increments), total fats, magnesium, fibre and glycaemic load (continuous). Further analyses were also performed with meat consumption values scaled by additive calibration [23].

Possible effect modification by sex was tested by adding to multivariate model 2 the corresponding interaction terms obtained from quantiles of intake of the several meat items. The likelihood ratio test was used to assess the significance of the interaction terms. Multivariate model 2 was then performed separately by sex. Possible effect modification by BMI was also tested by adding to the model the corresponding interaction terms. Models were performed separately by BMI categories (<25, 25–30, ≥30 kg/m^2).

Sex-specific models, simultaneously adjusted for red meat, processed meat, poultry and offals (sex-specific quantiles of consumption) were also performed in order to explore the effect of the different meat groups adjusting for each other.

Random-effect meta-analysis was used to assess heterogeneity (I^2 statistic) among countries in the association between meat consumption (overall and by specific types) or meat iron intake and occurrence of type 2 diabetes.

Sensitivity analyses were performed by excluding participants with myocardial infarction, angina, stroke, hypertension or hyperlipidaemia at baseline and by excluding the first 2 years of follow-up.

Analyses were performed with Stata 9.2 (StataCorp, TX, USA).

Results

The baseline non-dietary characteristics of the subcohort sample according to quintiles of consumption of total meat are reported in Table 1. In comparison with individuals in the lowest quintile of total meat consumption, those in the highest quintile were less educated, had higher waist circumference and BMI and were more frequently current smokers. The baseline non-dietary characteristics of the subcohort sample according to country are reported in electronic supplementary material (ESM) Table 1. The mean estimates of daily consumption of the main foods and nutrients in subcohort participants according to quintiles of consumption of total meat are shown in Table 2.

The mean daily consumption of the several types of meat in the subcohort sample is reported in ESM Table 2. Mean daily consumption of total meat by country ranged from 85.2 g/day (SD 54.1) in the UK to 134.3 g/day (SD 60.2) in Denmark.

In Table 3, a positive association with type 2 diabetes was observed in the basic model, comparing highest vs lowest quantile of consumption of total meat, red meat, processed meat, offals, poultry and meat iron. In multivariate model 1, the association was significant for increments of total meat (50 g: HR 1.18; 95% CI 1.15, 1.22), red meat (HR 1.18; 95% CI 1.13, 1.23), processed meat (HR 1.24; 95% CI 1.18, 1.31), offals (10 g: HR 1.08; 95% CI 1.03, 1.14), poultry (HR 1.12; 95% CI 1.05, 1.20) and meat iron (1 mg: HR 1.05; 95% CI 1.03, 1.08). In multivariate model 2 (including adjustment for BMI), the association was still significant for total meat (HR 1.08; 95% CI 1.05, 1.12), red meat (HR 1.08; 95% CI 1.03, 1.13) and processed meat (HR 1.12; 95% CI 1.05, 1.19). A borderline suggestion remained for meat iron (HR 1.02; 95% CI 0.998, 1.04). No association persisted for poultry and offals. Results from crude and adjusted models according to quantiles of consumption are also shown. After performing multivariate model 2 with further adjustment for consumption of other foods (total vegetables, bread, pasta, fish and cakes) the results did not materially change: total meat HR 1.08 (95% CI 1.04, 1.11); red meat HR 1.07 (95% CI 1.02, 1.13); processed meat HR 1.12 (95% CI 1.05, 1.18); meat iron HR 1.02 (95% CI 0.996, 1.03). When meat consumption was scaled by additive calibration, significant associations with type 2 diabetes were lightly strengthened. Non-significant associations remained unchanged.

Significant interactions with sex were observed for consumption of total meat, red meat, processed meat, poultry

Table 1 Distribution (%) of the EPIC-InterAct subcohort sample (15,258 participants, 62.2% women, mean age 52.4 years) according to the main individual characteristics and sex-specific quintiles of total meat consumption at baseline

Baseline non-dietary characteristic	Quintiles of total meat consumption				
	1	2	3	4	5
Median total meat intakes					
Men (g/day)	61.6	99.3	129.7	164.4	228.1
Women (g/day)	38.3	66.9	90.0	114.1	155.4
Smoking status					
Never	49.70	48.85	46.26	44.04	45.31
Former	29.02	27.03	28.10	26.97	24.77
Current	21.28	24.12	25.62	29.00	29.91
BMI class[a]					
Normal weight	54.57	46.26	43.00	43.45	35.22
Overweight	35.34	39.88	40.92	40.73	42.76
Obese	11.00	13.86	16.06	15.83	22.02
Waist circumference[b]					
Above WHO cut-off[c]	18.43	22.29	25.14	25.93	30.99
Hypertension[b,d]	19.63	20.03	18.13	18.51	18.30
Hyperlipidaemia[b,d]	18.96	20.25	19.10	17.84	17.52
Cambridge physical activity index[e]					
Inactive	24.03	24.38	24.41	22.08	23.20
Moderately inactive	32.49	33.19	34.27	33.45	34.86
Moderately active	23.80	22.15	22.48	23.07	21.92
Active	19.67	20.28	18.84	21.49	20.02
Educational level					
None	6.36	6.29	6.82	7.93	10.94
Primary school	28.00	31.65	34.76	33.94	37.88
Technical/professional school	23.48	25.16	22.97	23.26	21.26
Secondary school	16.75	14.94	15.53	14.45	14.02
Longer education	25.41	21.95	19.92	20.41	15.89

Median intakes for quintiles of total meat consumption are reported separately for men and women

[a]Normal weight: BMI<25 kg/m^2; overweight: BMI≥25 to <30 kg/m^2; obese: BMI≥30 kg/m^2

[b]Number of participants with missing information were as follows: 1,013 for waist circumference, 328 for hypertension, 3,869 for hyperlipidaemia

[c]WHO values: women cut-off, 88 cm; men cut-off, 102 cm

[d]Individuals with the disease are defined as either self-reported disease or treatment for disease or both

[e]Including physical activity at work and the sum of cycling and sport

and meat iron intake (all $p \leq 0.01$). In the overall models a 50% lower point estimate for HR in all quintiles was observed in women compared with men, while the linear relationship between total meat consumption and type 2 diabetes risk had a similar slope in both sexes (ESM Fig. 1). Results from sex-specific analyses (Table 4) showed a weakening of the association and a consequent lack of significance for processed meat and red and processed meat consumption in women but not in men. A significant positive association with type 2 diabetes risk was confirmed, however, in women, for total and red meat (p for trend 0.003 and 0.042, respectively) and for poultry consumption (p for trend 0.015). Similar results were obtained after further adjustment for menopausal status (data not shown). In men, the results obtained in the total sample were all confirmed. In sex-specific models simultaneously adjusted for consumption of red meat, processed meat, poultry and offals, the significant positive associations between red and processed meat and type 2 diabetes risk were confirmed among men, while no association emerged for offals and poultry. Among women only the significant positive association between poultry and incident type 2 diabetes persisted (data not shown).

A significant interaction with BMI was observed for the association with total meat, red meat, processed meat and poultry consumption (all $p<0.0001$). Results from the analyses performed separately for BMI classes showed a progressive attenuation of the positive associations between meat consumption and incident type 2 diabetes from normal-weight to obese individuals (ESM Table 3). The positive associations between quintiles of consumption of total meat, processed meat, and red and processed meat with type 2 diabetes risk were indeed statistically significant in normal-weight and overweight individuals, but were borderline or not significant among obese individuals.

Country-specific random-effect meta-analyses showed overall a significant between-country heterogeneity for poultry consumption (Fig. 1d; I^2=58.3%; p=0.019). Among women the meta-analyses showed, in all countries except the UK, a positive association between

Table 2 Mean daily consumption of the main foods, food groups and nutrients in the 15,258 EPIC-InterAct subcohort sample according to quintiles of total meat consumption at baseline

Daily consumption	Quintiles of total meat consumption				
	1	2	3	4	5
Meats (g)					
Total meat	50.4 (0.5)	82.3 (0.5)	105.4 (0.5)	130.7 (0.5)	186.0 (0.6)
Red meat	18.6 (0.5)	32.8 (0.5)	45.6 (0.5)	58.7 (0.5)	81.5 (0.5)
Processed meat	19.4 (0.5)	28.4 (0.5)	32.7 (0.5)	39.0 (0.5)	56.2 (0.5)
Red and processed meat	38.0 (0.6)	61.3 (0.6)	78.3 (0.6)	97.7 (0.6)	137.7 (0.6)
Offals	1.1 (0.1)	1.6 (0.1)	2.2 (0.1)	2.8 (0.1)	4.3 (0.1)
Poultry	8.7 (0.4)	15.7 (0.4)	20.6 (0.4)	26.1 (0.4)	37.7 (0.4)
Other foods (g)					
Fruit	247.9 (3.5)	240.0 (3.4)	242.1 (3.4)	232.0 (3.4)	227.6 (3.5)
Vegetables	175.4 (2.2)	168.7 (2.1)	177.2 (2.1)	188.8 (2.1)	204.1 (2.2)
Potatoes	93.2 (1.4)	96.1 (1.3)	98.1 (1.3)	101.7 (1.3)	103.2 (1.4)
Fat-rich foods[a]	87.2 (0.8)	80.5 (0.8)	74.0 (0.8)	69.3 (0.8)	63.0 (0.8)
Fish	33.1 (0.6)	36.2 (0.6)	39.0 (0.6)	39.5 (0.6)	42.3 (0.6)
Dairy products	383.9 (4.4)	351.4 (4.2)	337.1 (4.2)	323.2 (4.2)	283.6 (4.4)
Coffee	344.6 (7.2)	369.0 (6.9)	396.3 (6.9)	413.7 (6.9)	396.7 (7.2)
Soft drinks	73.1 (2.8)	67.4 (2.8)	67.8 (2.7)	66.9 (2.8)	67.7 (2.9)
Nutrients					
Alcohol (g)	13.0 (0.3)	13.4 (0.3)	12.9 (0.3)	14.0 (0.3)	14.0 (0.3)
Total fibre (g)	24.2 (0.1)	22.8 (0.1)	22.5 (0.1)	22.3 (0.1)	22.1 (0.1)
Total iron (mg)	12.5 (0.05)	12.7 (0.05)	13.2 (0.05)	13.6 (0.05)	14.9 (0.05)
Meat iron (mg)	1.2 (0.02)	1.9 (0.02)	2.4 (0.02)	2.9 (0.02)	4.0 (0.02)
Magnesium (mg)	359.2 (1.3)	346.1 (1.3)	345.5 (1.3)	350.2 (1.3)	353.4 (1.3)
Total fats (g)	80.8 (0.3)	80.7 (0.3)	82.0 (0.3)	83.6 (0.3)	88.7 (0.3)
Total energy (kJ)	7,540.1 (44.1)	8,290.6 (44.1)	8,805.0 (44.1)	9,467.8 (44.1)	10,628.9 (44.1)
Glycaemic load	144.8 (0.5)	137.3 (0.5)	131.7 (0.4)	126.2 (0.5)	118.5 (0.5)
PUFA/SFA[b]	0.44 (0.004)	0.43 (0.004)	0.44 (0.004)	0.46 (0.004)	0.49 (0.004)

Means adjusted for age at recruitment and daily energy intake. Standard errors of the means (SEM) are reported

[a] Butter, margarine, vegetable oils, nuts and seeds, cakes and cookies

[b] Polyunsaturated/saturated fatty acid ratio

poultry consumption and type 2 diabetes risk that reached statistical significance in France, Italy and Sweden (ESM Fig. 2a; I^2=37.7%; p=0.129). Among men a significant between-country heterogeneity emerged for poultry consumption (ESM Fig. 2b; I^2=53.0%; p=0.047). Country-specific random-effect meta-analysis also showed a significant between-country heterogeneity for meat iron intake overall (Fig. 1f; I^2=61.0%; p=0.012). Among men a significant between-country heterogeneity emerged for meat iron intake (ESM Fig. 3b; I^2=59.0%; p=0.023). For all the other types of meat no significant heterogeneity emerged (Fig. 1).

The results did not materially change when sensitivity analyses were performed that excluded a total of 9,865 individuals reporting a history of myocardial infarction (n=547), angina (n=522), stroke (n=261), hypertension (n=6,863) or hyperlipidaemia (n=4,402) at baseline, or that excluded those with a diagnosis of type 2 diabetes in the first 2 years after recruitment (n=1,037).

Discussion

In this large European prospective study we found an overall positive association between consumption of meat and risk of type 2 diabetes. Individuals in the highest quintiles of consumption of total meat had a higher risk of developing type 2 diabetes compared with those in the lowest quintile of consumption. According to specific types of meat, we observed a higher risk of type 2 diabetes in high consumers of

Table 3 HR and 95% CI of type 2 diabetes by quintiles (Q) of consumption and by increments of several types of meat and meat iron in the 26,088 individuals of the EPIC-InterAct case-cohort study (14,529 subcohort non-cases, 729 subcohort type 2 diabetes cases and 10,830 non-subcohort type 2 diabetes cases)

Daily consumption	No. of cases	Basic model[a]		Multivariate model 1[b]		Multivariate model 2[c]	
		HR	CI	HR	CI	HR	CI
Total meat							
Q1 (m=61.6, w=38.3)	1,970	1.00		1.00		1.00	
Q2 (m=99.3, w=66.9)	2,070	1.16	1.06, 1.26	1.15	1.05, 1.25	1.01	0.91, 1.11
Q3 (m=129.7, w=90.0)	2,441	1.44	1.32, 1.57	1.39	1.27, 1.52	1.17	1.06, 1.30
Q4 (m=164.4, w=114.1)	2,347	1.50	1.37, 1.64	1.45	1.32, 1.59	1.19	1.07, 1.32
Q5 (m=228.1, w=155.4)	2,731	1.97	1.78, 2.16	1.82	1.65, 2.01	1.27	1.13, 1.42
p value for linear trend		<0.0001		<0.0001		<0.0001	
50 g increments		1.21	1.18, 1.24	1.18	1.15, 1.22	1.08	1.05, 1.12
Red meat							
Q1 (m=11.2, w=7.1)	2,061	1.00		1.00		1.00	
Q2 (m=30.8, w=20.4)	2,233	1.16	1.07, 1.27	1.16	1.06, 1.26	0.99	0.89, 1.11
Q3 (m=51.0, w=34.8)	2,285	1.26	1.16, 1.38	1.24	1.13, 1.36	1.10	1.00, 1.22
Q4 (m=76.3, w=52.1)	2,437	1.40	1.27, 1.53	1.33	1.21, 1.46	1.16	1.05, 1.29
Q5 (m=116.8, w=80.7)	2,543	1.57	1.42, 1.73	1.50	1.36, 1.56	1.20	1.07, 1.35
p value for linear trend		<0.0001		<0.0001		<0.0001	
50 g increments		1.20	1.15, 1.25	1.18	1.13, 1.23	1.08	1.03, 1.13
Processed meat							
Q1 (m=9.1, w=4.3)	2,015	1.00		1.00		1.00	
Q2 (m=23.2, w=13.2)	2,190	1.13	1.04, 1.22	1.13	1.04, 1.23	1.08	0.98, 1.19
Q3 (m=36.9, w=21.6)	2,275	1.20	1.10, 1.30	1.18	1.08, 1.28	1.03	0.94, 1.14
Q4 (m=55.7, w=34.4)	2,447	1.36	1.25, 1.48	1.31	1.20, 1.43	1.14	1.04, 1.26
Q5 (m=93.5, w=60.5)	2,632	1.61	1.47, 1.76	1.51	1.37, 1.65	1.16	1.04, 1.31
p value for linear trend		<0.0001		<0.0001		0.006	
50 g increments		1.30	1.23, 1.36	1.24	1.18, 1.31	1.12	1.05, 1.19
Red and processed meat							
Q1 (m=38.4, w=22.3)	1,991	1.00		1.00		1.00	
Q2 (m=71.0, w=45.4)	2,112	1.15	1.05, 1.25	1.11	1.01, 1.21	0.97	0.88, 1.08
Q3 (m=97.4, w=63.6)	2,328	1.34	1.23, 1.46	1.28	1.17, 1.40	1.08	0.97, 1.20
Q4 (m=129.0, w=85.3)	2,410	1.47	1.34, 1.61	1.39	1.26, 1.52	1.18	1.06, 1.31
Q5 (m=182.3, w=120.4)	2,718	1.84	1.67, 2.02	1.70	1.54, 1.88	1.18	1.04, 1.33
p value for linear trend		<0.0001		<0.0001		<0.0001	
50 g increments		1.23	1.1, 1.27	1.20	1.16, 1.24	1.09	1.05, 1.13
Offals							
Q1 (m=0.0, w=0.0)	5,862	1.00		1.00		1.00	
Q2 (m=0.9, w=0.6)	1,597	0.97	0.89, 1.06	0.99	0.90, 1.08	0.97	0.85, 1.07
Q3 (m=5.3, w=3.9)	4,100	1.11	1.04, 1.19	1.12	1.04, 1.19	1.04	0.96, 1.13
p value for linear trend		0.001		0.001		0.308	
10 g increments		1.09	1.0, 1.14	1.08	1.03, 1.14	1.00	0.94, 1.07
Poultry							
Q1 (m=0.6, w=0.3)	2,399	1.00		1.00		1.00	
Q2 (m=9.9, w=7.4)	2,208	0.95	0.87, 1.03	0.97	0.89, 1.06	0.98	0.89, 1.09
Q3 (m=16.9, w=15.2)	2,206	0.97	0.89, 1.06	1.00	0.91, 1.09	0.93	0.83, 1.03
Q4 (m=29.7, w=24.6)	2,356	1.05	0.97, 1.15	1.07	0.97, 1.16	0.99	0.89, 1.09
Q5 (m=53.8, w=49.3)	2,390	1.13	1.03, 1.24	1.12	1.02, 1.24	1.02	0.91, 1.13

Table 3 (continued)

Daily consumption	No. of cases	Basic model[a]		Multivariate model 1[b]		Multivariate model 2[c]	
		HR	CI	HR	CI	HR	CI
p value for linear trend		0.001		0.003		0.786	
50 g increments		1.15	1.08, 1.23	1.12	1.05, 1.20	1.03	0.95, 1.11
Meat iron							
Q1 (m=1.2, w=0.7)	1,979	1.00		1.00		1.00	
Q2 (m=2.1, w=1.3)	2,197	1.21	1.11, 1.32	1.18	1.08, 1.29	1.10	1.00, 1.22
Q3 (m=2.8, w=1.9)	2,232	1.26	1.16, 1.38	1.21	1.11, 1.33	1.08	0.98, 1.20
Q4 (m=3.8, w=2.5)	2,446	1.44	1.32, 1.58	1.37	1.25, 1.50	1.16	1.05, 1.29
Q5 (m=5.4, w=3.7)	2,705	1.67	1.52, 1.83	1.58	1.44, 1.74	1.16	1.04, 1.30
p value for linear trend		<0.0001		<0.0001		0.009	
1 mg increments		1.06	1.03, 1.08	1.05	1.03, 1.08	1.02	0.998, 1.04

Sex-specific median of daily consumption across quintiles and increments is shown in grams (mg for meat iron)

[a] Model stratified by centre (the hazard function was stratified by centre) and adjusted for energy intake (log kJ) and sex; total, n=26,088; cases, n=11,559

[b] Multivariate model 1: stratified by centre and adjusted for sex, energy intake (log kJ), smoking status (dummy variables for former and current smokers), alcohol consumption (quintiles of daily intake), physical activity (four levels) and educational level (five levels); total, n=26,088; cases, n=11,559

[c] Multivariate model 2: multivariate model 1 with addition of a term for BMI (continuous); total, n=26,088; cases, n=11,559

m, men; w, women

red and processed meat overall, in male high consumers of red meat, processed meat and meat iron and in female high consumers of poultry.

The large amount of information on health and lifestyle items collected at baseline allowed control for several possible confounders of the meat–diabetes association. After controlling for these well-known risk factors for type 2 diabetes (including sex, BMI, cigarette smoking, alcohol consumption, physical inactivity and educational level), the positive associations between total meat, red meat and processed meat and type 2 diabetes risk in the basic model were indeed largely attenuated, although the associations remained statistically significant. Nevertheless further residual confounding effects cannot be excluded.

No screening for undiagnosed type 2 diabetes was done, while detailed information on clinical diabetes diagnosed before recruitment was collected at baseline. During the ascertainment and verification procedure for incident cases of type 2 diabetes, additional cases of prevalent diabetes not reported in the baseline questionnaire were also identified and excluded from these analyses.

In a series of sensitivity analyses we excluded participants with a diagnosis of myocardial infarction, angina, stroke, hypertension or hyperlipidaemia at baseline and participants with a diagnosis of type 2 diabetes in the first 2 years of follow-up. In these subgroups dietary changes towards a 'healthier' pattern might have occurred as a consequence of the clinical diagnosis of a chronic disease or prediabetic condition, possibly leading to a distortion of the real associations between meat and diabetes risk. After exclusions of these subgroups no relevant changes were observed in the association between meat consumption and type 2 diabetes.

Imprecise dietary assessment or inaccuracies in self-reporting of adjusting variables, as sources of potential residual confounding, may represent a limitation of all epidemiological studies, including the current one. Possible errors in the collection of individual dietary habits at baseline by country-specific food frequency questionnaires were partially overcome by the exclusion of individuals who fell in the top or bottom 1% of the 'energy intake/energy requirement ratio'.

Our conclusions are partially consistent with the results of three recent systematic reviews and meta-analyses. In the review by Aune et al (12 cohort studies from the USA, Europe, Asia and Australia) [4], a statistically significant positive association between total red meat and processed meat and type 2 diabetes risk emerged (21% and 41% increased risk for highest vs lowest intake, respectively), while total meat consumption was not significantly associated. In the review by Micha et al (seven cohort studies from the USA, Germany and China) [5], a statistically significant positive association emerged between processed meat and the combination of processed and unprocessed red meat and risk of type 2 diabetes (19% and 12% increased risk for 50 and 100 g/day, respectively), which is well in agreement with our estimates. Also, in the more recent review by Pan et al (nine cohort studies from the USA, Finland, Germany and

Table 4 Sex-specific HR and 95% CI of type 2 diabetes by quintiles (Q) of consumption and by increments of several types of meat in the 11,174 men and 14,914 women participating in the EPIC-InterAct study (results from the adjusted model)

Daily consumption	Men			Women		
	No. of cases	HR	CI	No. of cases	HR	CI
Total meat						
Q1 (m=61.6, w=38.3)	1,022	1.00		948	1.00	
Q2 (m=99.3, w=66.9)	977	0.92	0.78, 1.08	1,093	1.08	0.95, 1.23
Q3 (m=129.7, w=90.0)	1,283	1.24	1.06, 1.45	1,158	1.11	0.97, 1.27
Q4 (m=164.4, w=114.1)	1,177	1.27	1.08, 1.50	1,170	1.16	1.01, 1.33
Q5 (m=228.1, w=155.4)	1,302	1.38	1.15, 1.65	1,429	1.25	1.08, 1.45
p value for linear trend		<0.0001			0.003	
50 g increments		1.08	1.04, 1.13		1.09	1.04, 1.15
Red meat						
Q1 (m=11.2, w=7.1)	1,040	1.00		1,021	1.00	
Q2 (m=30.8, w=20.4)	1,151	1.07	0.92, 1.24	1,082	0.93	0.81, 1.08
Q3 (m=51.0, w=34.8)	1,145	1.14	0.98, 1.34	1,140	1.06	0.93, 1.22
Q4 (m=76.3, w=52.1)	1,203	1.27	1.08, 1.49	1,234	1.07	0.93, 1.23
Q5 (m=116.8, w=80.7)	1,222	1.30	1.09, 1.56	1,321	1.12	0.96, 1.30
p value for linear trend		0.001			0.042	
50 g increments		1.09	1.03, 1.17		1.06	0.98, 1.15
Processed meat						
Q1 (m=9.1, w=4.3)	993	1.00		1,022	1.00	
Q2 (m=23.2, w=13.2)	1,110	1.08	0.94, 1.24	1,080	1.07	0.94, 1.21
Q3 (m=36.9, w=21.6)	1,100	1.03	0.88, 1.20	1,175	1.03	0.91, 1.17
Q4 (m=55.7, w=34.4)	1,231	1.21	1.04, 1.40	1,216	1.10	0.97, 1.26
Q5 (m=93.5, w=60.5)	1,327	1.34	1.14, 1.57	1,305	1.07	0.92, 1.25
p value for linear trend		<0.0001			0.338	
50 g increments		1.15	1.07, 1.23		1.08	0.97, 1.20
Red and processed meat						
Q1 (m=38.4, w=22.3)	975	1.00		1,016	1.00	
Q2 (m=71.0, w=45.4)	1,067	1.01	0.87, 1.18	1,045	0.94	0.82, 1.07
Q3 (m=97.4, w=63.6)	1,173	1.16	0.99, 1.36	1,155	1.00	0.87, 1.15
Q4 (m=129.0, w=85.3)	1,227	1.31	1.12, 1.54	1,183	1.10	0.95, 1.26
Q5 (m=182.3, w=120.4)	1,319	1.42	1.19, 1.69	1,399	1.05	0.90, 1.23
p value for linear trend		<0.0001			0.122	
50 g increments		1.12	1.07, 1.17		1.07	1.00, 1.14
Poultry						
Q1 (m=0.6, w=0.3)	1,273	1.00		1,126	1.00	
Q2 (m=9.9, w=7.4)	1,148	0.95	0.81, 1.11	1,060	1.01	0.88, 1.15
Q3 (m=16.9, w=15.2)	1,081	0.87	0.74, 1.01	1,125	1.00	0.87, 1.16
Q4 (m=29.7, w=24.6)	1,139	0.90	0.78, 1.04	1,217	1.10	0.95, 1.27
Q5 (m=53.8, w=49.3)	1,120	0.89	0.76, 1.04	1,270	1.19	1.02, 1.38
p value for linear trend		0.115			0.015	
50 g increments		0.94	0.85, 1.03		1.20	1.07, 1.34
Meat iron						
Q1 (m=1.2, w=0.7)	997	1.00		982	1.00	
Q2 (m=2.1, w=1.3)	1,112	1.14	0.98, 1.33	1,085	1.08	0.95, 1.22
Q3 (m=2.8, w=1.9)	1,156	1.18	1.01, 1.38	1,076	1.00	0.87, 1.14
Q4 (m=3.8, w=2.5)	1,247	1.29	1.11, 1.51	1,199	1.09	0.95, 1.26
Q5 (m=5.4, w=3.7)	1,249	1.25	1.06, 1.49	1,456	1.14	0.98, 1.32

Table 4 (continued)

Daily consumption	Men			Women		
	No. of cases	HR	CI	No. of cases	HR	CI
p value for linear trend		0.005			0.095	
1 mg increments		1.02	1.00, 1.05		1.01	0.98, 1.05

Sex-specific cut-offs of quintiles and increments are shown in grams (mg for meat iron)

HR and 95% CI from multivariate model 2: stratified by centre and adjusted for energy intake (log kJ), BMI (continuous), smoking status (dummy variables for former and current smokers), alcohol consumption (quintiles of daily intake), physical activity (four levels) and educational level (five levels)

m, men; w, women

China) [6], both unprocessed and processed red meat were significantly associated with an increased risk of type 2 diabetes (19% and 51% increased risk for 100 and 50 g/day, respectively).

In a study aimed to examine the association between meat consumption and risk of type 2 diabetes in a large cohort of Finnish middle-aged male smokers [9], over 1,000 incident cases of diabetes were identified in 12 years of follow-up. High total and processed meat consumption emerged as risk factors for type 2 diabetes with 50% and 37% increased adjusted risks, respectively, in the highest vs the lowest quintiles.

In 2012, two prospective studies that aimed to investigate the association between meat consumption and type 2 diabetes were performed in two European countries. In the frame of a prospective study among 66,118 disease-free French women (1,369 cases of incident diabetes identified between 1993 and 2007), one serving increment of processed meat was associated with a 29% increased risk [10]. In a prospective cohort of 4,366 Dutch participants, 456 diabetes cases were confirmed during a median follow-up period of 12.4 years. In the highest category of red and processed meat consumption, compared with the lowest category, a 42% and 87% increased risk was shown, respectively [11]. These results from specific countries were confirmed in our study, which included, for the first time, a large series of adults from the general population of several European countries in the same analysis, thus allowing an evaluation of the association between meat consumption and diabetes independently of country-specific dietary patterns.

The results of the sex-specific analysis showed a significant positive association between total meat consumption and type 2 diabetes risk both for women and men, with women showing a 50% lower risk in comparison with men at all levels of consumption. This positive association seems, however, to be driven by different types of meat consumed among women and men (red and processed meat for men, red meat and poultry for women). The finding of a positive association between type 2 diabetes and poultry consumption in women is not consistent with findings in several previous studies [24–26]. In their meta-analysis, Pan et al [6] modelled the substitution of total red meat consumption with poultry consumption and showed a lower risk of type 2 diabetes. On the other hand, in a case–control study (192 cases of incident type 2 diabetes and 382 control subjects) nested in the population-based EPIC-Potsdam cohort a dietary pattern score inversely associated with diabetes-related biomarkers was derived by reduced rank regression. Low consumption of poultry, high-calorie soft drinks, beer, red meat, processed meat, legumes and white bread was associated with a substantially reduced incidence of type 2 diabetes [27].

The borderline or non-significant associations between consumption of total meat, red meat, processed meat, and red and processed meat and type 2 diabetes among obese participants and the effect modification by BMI categories could be explained by the strong independent effect of obesity on type 2 diabetes risk. The important role of overweight and obesity in the onset of new cases of type 2 diabetes was discussed in a recent meta-analysis [28], while obesity has been cited as an important factor accounting for more than half of new diabetes cases [20]. This is also evident from our analyses, as BMI was the covariate that induced the largest attenuation of risk estimates for type 2 diabetes. On the other hand, obese participants might have a greater tendency to under-report meat consumption, thus contributing to attenuation of the association between meat intake and type 2 diabetes.

The positive association with meat was also independent of the consumption of the other main food items that were added to the model. A number of possible hypotheses have been considered in order to clarify the mechanisms responsible for the positive association of meat consumption with incidence of type 2 diabetes. It has been observed that nitrites, frequently used for preservation of meat and meat products, may have a toxic effect on pancreatic beta cells, mediated by the formation of nitrosamines in the stomach or

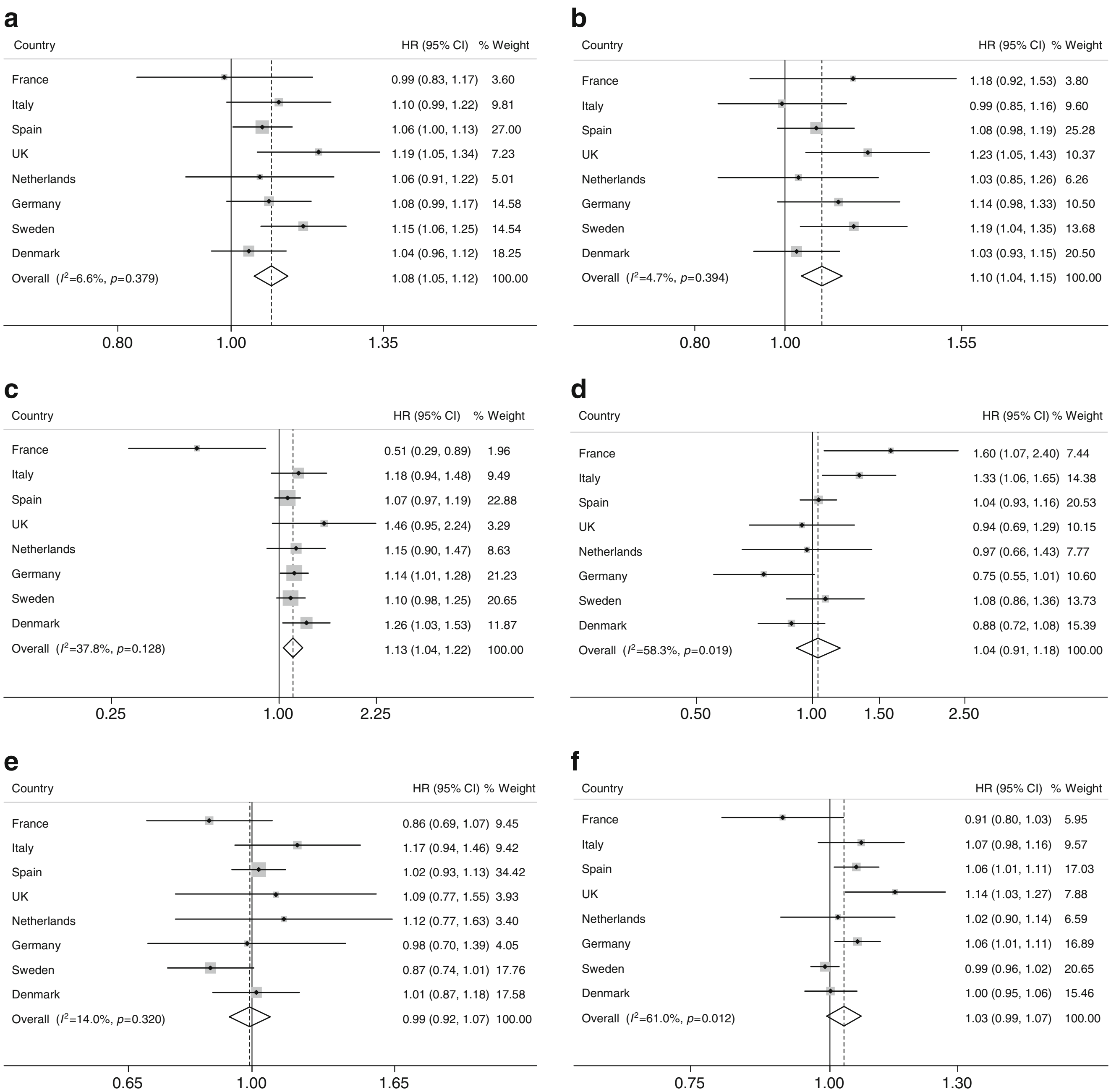

Fig. 1 Country-specific and overall HR for type 2 diabetes associated with 50 g increments of consumption of total meat (**a**), red meat (**b**), processed meat (**c**), poultry (**d**), offals (**e**) and meat iron intake (1 mg increments) (**f**) overall. HR and 95% CI derived by modified Cox proportional models stratified by centre and adjusted for sex, energy intake (log kJ), BMI (continuous), smoking status (dummy variable for former and current smokers), alcohol (quintiles of daily intake), physical activity (four levels) and education (five levels). Weights are from random effects analysis

in the meat product itself. Nitrosamines could also be produced in well cooked meat from heterocyclic amines or polycyclic aromatic hydrocarbons [29]. Some nitrosamines were found to be associated with type 1 diabetes in humans [30], while streptozotocin, a nitrosamine-related compound, was found to be associated with type 2 diabetes in animal models [31, 32]. Advanced glycation end-products, present in meat and meat products as a result of cooking or processing, have been associated with insulin resistance or type 2 diabetes both in animal models [33] and in humans [34]. A role in the onset of type 2 diabetes might be played by saturated and *trans*-fatty acids present in meat. Several studies suggested a detrimental effect of saturated fat (animal origin foods as main source) [35–38], or *trans*-fatty acids (main sources including also beef, lamb, mutton and derived products) [39] in the development of type 2 diabetes due to adverse metabolic effects on insulin sensitivity.

A diet rich in meat and meat products could lead to an increase in the body's iron stores, which is suspected to impair insulin sensitivity and increase blood glucose concentration thus leading to higher type 2 diabetes risk [40–42]. Heme iron is in fact more bioavailable than non-heme iron, since its absorption is partially independent of body iron status and is less influenced by consumption of various foods and nutrients [43, 44]. Heme iron could, moreover, promote the endogenous formation of nitrosamines [45]. In agreement with these hypotheses, in our study we found that intake of iron from meat (consisting of heme iron in large proportion [46]) was associated with a higher risk of type 2 diabetes. A further consideration should be kept in mind in relation to the different heme iron status in men and women. In premenopausal women a significant amount of iron is lost during menstrual cycles, leading to lower body iron stores than in men and postmenopausal women [43]. This could partially explain the weaker association observed in our study between red and processed meat consumption and type 2 diabetes in women compared with men.

A clear excess of diabetes has been reported among workers in the meat industry [47, 48], and it has been proposed that this might be related to exposures to zoonotic infective agents present in fresh cuts of meat, including poultry [49], although overweight might play a relevant role in this category of workers.

In conclusion this study involving a large cohort of European adults showed a positive association between high consumption of total and red meat and incident type 2 diabetes overall. Among men, a positive association between high consumption of total, red and processed meat and incident type 2 diabetes emerged. Among women, a positive association between high consumption of total meat, red meat and poultry and incident type 2 diabetes emerged. This study provides further evidence of the role of meat and meat products as risk factors to be considered in the identification of primary prevention strategies for type 2 diabetes.

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Appendix

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