# Substitution of red meat with legumes and risk of primary liver cancer in 126,744 UK Biobank participants: a prospective cohort study

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## Abstract

Objective:

Research Design and Methods:

Results:

Conclusions:


## Introduction

## Research Design and Methods

#### Study population

The UK Biobank, a population-based prospective cohort, were initiated in 2006. [1] During 2006-2010, more than 500,000 participants, aged 40-69, were recruited and assessed at designated assessment centres across the UK. Data on sociodemographic factors (education, ethnicity, Townsend deprivation Index) and lifestyle factors (smoking, alcohol consumption, physical activity) were collected via touch screen questionnaires and computer-assisted interviews. Anthropometric data (BMI, waist circumference) were collected via physical measurements (reference to UKB document here).

#### Dietary assessment

A web-based diet questionnaire was administered at the end of the initial assessment visit for the last 70,000 recruited participants (reference from UKB document here). In the period February 2011 to April 2012, 320,000 participants who had provided an e-mail address were invited on four separate occasions to complete the diet questionnaire, of which 210,947 participants completed at least one. The questionnaire comprised the Oxford WebQ, an online 24-hour dietary recall assessment tool covering 206 foods and 32 beverages commonly consumed in the UK with intake categories ranging from 0 to +3 units of measurement (e.g. servings, cups, slices). [2] The Oxford WebQ has been validated with interviewer-based 24-hour recalls and biomarkers [3, 4].

Researchers classified 79 food groups and 14 beverage groups from the Oxford WebQ food groups using UK National Diet and Nutrition Survey (NDNS) categories [3, 4]. We used this classification to categorise intake of foods groups to match our substitution analysis. Legume intake was defined as intake of dietary pulses, baked beans, tofu-based products, peas, hummus, soy drinks, and soy-based desserts and yoghurt;

red meat intake was defined as intake of beef, pork, lamb, or other meat, including offal. Processed meat intake was defined as sausages, bacon (with and without fat), ham, or liver pate. Other food groups included were animal-based foods, unhealthy plant-based foods, healthy plant-based foods, and alcoholic beverages (supplemental table 1). animal-based and plant-based food groups were calculated in line with previous studies that used these food categories to construct a healthy plant-based diet index and an unhealthy plant-based diet index [5–8]. An overview of included foods in each food group is displayed in supplemental table 1.

Due to the incapability of a single 24-hour dietary recall evaluation to properly assess variation in diet over time (reference to nutritional epi methods here?), only participants who completed two or more questionnaires were eligible for inclusion in our study (reference to nutritional epi methods that two 24-hour recall is sufficient to capture variation in diet here?).

**Liver cancer assessment**

Liver cancer was defined according to ICD-10 diagnosis codes C22.0 Hepatocellular carcinoma (HCC) or C22.1 Intrahepatic cholangiocarcinoma (ICC). Incident and prevalent cases of liver cancer and corresponding diagnosis dates were obtained via linkage to central cancer registers or hospital inpatient episodes [1].

**Assessment of confounders**

Confounders were defined *a priori* from a literature review of diet components as exposure and liver cancer as the outcome and illustrated using directed acyclic graphs (supplemental fig. 1.). The following confounding variables were selected: age (years [continuous]), sex (male, female [categorical]), educational level (high: College or University degree, intermediate: A levels/AS levels, O levels/GCSEs, or equivalent, low: none of the previous mentioned [categorical]), Townsend Deprivation Index [continuous], Living alone (yes, no [categorical]), waist circumference (cm [continuous]), physical activity (above/below the 2017 UK Physical activity guidelines of 150 minutes of moderate activity per week or 75 minutes of vigorous activity, or missing data [categorical]), smoking (pack years as a proportion of lifespan exposed to smoking [continous]), and alcohol intake (grams/day continuous). All confounders except age were selected from the initial assessment visit before the start of follow-up.

**The substitution model**

Substitutions were carried out in an equal-mass manner, i.e., substituting x grams of red meats with x grams of legumes. The size of the substitution was set to 15 grams of legumes for 15 grams of red meats to keep the substitution size below the mean intake any of the substituted food groups in the cohort. Substitutions were modelled using the leave-one-out-approach in which variables for every food group along with a variable for total food intake are included, except the food group that are to be substituted [9]. To estimate substitution of 15 grams of all red meats with 15 grams of legumes, the following model was defined:

$$log(h(t;x)) = log(h(0;t)) + \beta_1 Legumes(15g) + \beta_2 Total food intake(g) + \beta_3 Other food groups(g) + \beta_4 Covariates$$

When substituting red meat with legumes, processed meat was added to the model:

$$log(h(t;x)) = log(h(0;t)) + \beta_1 Legumes(15g) + \beta_2 Processed meat(15g) + \beta_3 Total food intake(g) + \beta_4 Other food groups(g) + \beta_5 Co$$

When substituting processed meat with legumes, red meat was added to the model:

$$log(h(t;x)) = log(h(0;t)) + \beta_1 Legumes(15g) + \beta_2 Red meat(15g) + \beta_3 Total food intake(g) + \beta_4 Other food groups(g) + \beta_5 Covariat$$

**Statistical analysis**

Multivariable-adjusted Cox proportional hazards regression models were used to estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI) with age as the underlying timescale. Participants were followed from the date of their last completed diet questionnaire until the event of interest occurred or due to right censoring, whichever came first. Participants were right censored due to one of the following events occurring: death, loss to follow-up, or administrative end of follow-up (set to Jan 31, 2022). Two levels of adjustments were added to the substitution model. A crude model was minimally adjusted for age, total weight of food intake, and all other foods groups to fit the substitution model. The adjusted model was further adjusted for sex, educational level, Townsend Deprivation Index, living alone, physical activity, smoking, alcohol intake, and waist circumference.

A stratified analysis on each cancer type was performed to test whether pooling of HCC and ICC as an outcome was justified. Further, the following sensitivity analyses were performed to test the robustness of the main analysis:

1. Exclusion of high alcohol consumers (more than 32 grams per day for men and 24 grams per day for women), exclusion of food intake misreporters ( 3200 or 16800 kJ/day for men and 2000 or 14000 kJ/day for women), exclusion of participants with any other liver disease before baseline, exclusion of participants with any type of cancer before baseline, and exclusion of the first two years of follow-up.

2. Inclusion criteria for number of completed diet questionnaires were set to 3 completed questionnaires.

3. (Mangler)

To estimate the effect of legume intake regardless of other dietary components, legume consumers (divided into quartiles) were compared to non-consumers.

All analyses were conducted in R with a significance level of 5 %.

# Results

After excluding participants with liver cancer and participants lost to follow-up before baseline, 126,744 participants remained who had completed two or more diet questionnaires. During a median follow-up time of 11.3 years, 173 participants developed liver cancer. Baseline characteristics are displayed in table 1. Participants who developed liver cancer were older at baseline, had a higher waist circumference, were less physically active, fewer had never smoked, and more were male, compared to all included participants.

Mean daily energy intake and food intake and median daily intake of all specified food groups are presented in table 2.

Main results are presented in table 3. In the crude model, no association was found for substituting 15 grams of legumes per day with 15 grams of total meat, red meat, or processed meat per day and risk of primary liver cancer (total meat: HR: 0.98 (95% CI: 0.93, 1.04), red meat: HR: 0.97 (95% CI: 0.91-1.03) and processed meat: HR 1.02 (95% CI:0.93, 1.13)). the results did not change when with further adjustments (total meat: HR: 1.02 (95% CI: 0.96, 1.08), red meat: HR: 1.00 (95% CI: 0.94-1.07) and processed meat: HR: 1.09 (95% CI: 0.98, 1.20).

Estimates seemed to go in opposite directions when substituting total meat or red meat with legumes for risk of HCC (total meat: HR: 1.08 (95% CI: 0.99, 1.19), red meat: HR: 1,07 (95% CI: 0.97, 1.18) and processed meat: HR: 1.12 (95% CI: 0.97, 1.30)) and ICC (total meat: HR: 0.97 (95% CI: 0.90, 1.05), red meat: HR: 0.95 (95% CI: 0.87, 1.03) and processed meat: HR: 1.06 (95% CI: 0.92, 1.22)) , but these trends were not statistically significant (supplementary table 2). Further, excluding high alcohol consumers or food intake misreporters or setting inclusion criteria to 3 completed diet questionnaires did not alter the estimates in any statistically significant way (supplementary tables 3 to 5). In the adjusted no substitution analysis, a mean intake of 6.3 grams of legumes per day was associated with a reduced risk of liver cancer, compared to no intake (HR: 0.59 (95% CI: 0.35, 0.98)); however, no associations were observed with further increase in legume intake (supplementary table 6).

## Conclusions

## Acknowledgements

## References


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## Tables

| | **All participants** | **Participants who developed liver cancer** |
|---|---|---|
| **Variable** | **N = 126,744**[1] | **N = 173**[1] |
| **Typical diet yesterday**[2] | 73,213 (58%) | 105 (61%) |
| **Age** | 60 (53, 65) | 64.0 (60.0, 68.0) |
| **Sex** | | |
| Female | 70,659 (56%) | 65 (38%) |

| | | |
|---|---|---|
| Male | 56,085 (44%) | 108 (62%) |
| **Educational level** | | |
| High | 59,416 (47%) | 76 (44%) |
| Intermediate | 41,817 (33%) | 52 (30%) |
| Low | 25,472 (20%) | 45 (26%) |
| Missing | 39 | |
| **Townsend Deprivation Index** | -2.4 (-3.8, 0.0) | -2.6 (-3.7, -0.7) |
| Missing | 149 | |
| **Living alone** | 22,658 (18%) | 34 (20%) |
| Missing | 171 | |
| **Physical activity**[3] | | |
| Above | 58,111 (46%) | 61 (35%) |
| Below | 50,712 (40%) | 79 (46%) |
| Missing | 17,921 (14%) | 33 (19%) |
| **Smoking** | | |
| Never | 72,583 (57%) | 75 (43%) |
| Ever | 54,122 (43%) | 98 (57%) |
| Missing | 39 | |
| **Alcohol intake [g/day]** | 11 (0, 26) | 11 (0, 29) |
| **Waist circumference [cm]** | 88 (79, 97) | 98 (89, 107) |
| Missing | 168 | |

[1]n (%); Median (IQR)
[2]Participants who reported eating a typical diet yesterday for all completed diet questionnaires.
[3]Above or below the 2017 UK Physical activity guidelines of 150 minutes of moderate activity per week or 75 minutes of vigorous activity.

| | **Cohort** | **Liver cancer** |
|---|---|---|
| **Daily food intake** | **N = 126,744**[1] | **N = 173**[1] |
| Total food intake [kJ/day] or [g/day] | | |
| **Energy [kJ]** | 8,643 (2,171) | 8,903 (2,281) |
| **Weight [g]** | 3,210 (715) | 3,221 (714) |
| Food groups [g/day] | | |
| **Legumes** | 11 (0, 34) | 8 (0, 35) |
| **Red and processed meat** | 53 (15, 86) | 60 (30, 95) |
| **Red meat** | 30 (0, 60) | 45 (0, 73) |
| **Processed meat** | 9 (0, 30) | 8 (0, 31) |
| **Other animal-based foods** | 475 (361, 603) | 448 (322, 604) |
| **Healthy plant-based foods** | 1,806 (1,454, 2,198) | 1,791 (1,365, 2,158) |
| **Unhealthy plant-based foods** | 472 (324, 662) | 491 (365, 698) |
| **Alcoholic beverages** | 132 (0, 342) | 144 (0, 375) |

[1]mean (±SD) for total energy and food intake; median (IQR) for food groups

| | Crude[1] | | Adjusted[2] | |
|---|---|---|---|---|
| **15 g/day substitution** | **HR** | **95% CI** | **HR** | **95% CI** |
| Legumes for total meat | 0.98 | 0.93, 1.04 | 1.02 | 0.96, 1.08 |
| Legumes for red meat | 0.97 | 0.91, 1.03 | 1.00 | 0.94, 1.07 |
| Legumes for processed meat | 1.02 | 0.93, 1.13 | 1.09 | 0.98, 1.20 |

[1]Adjusted for age (as underlying timescale), other food groups and total food intake to fit the substitution model.
[2]Further adjusted for sex, educational level, Townsend Deprivation Index, living alone, physical activity, smoking, alcohol intake and waist circumference.

# Figures

# Supplemental Material

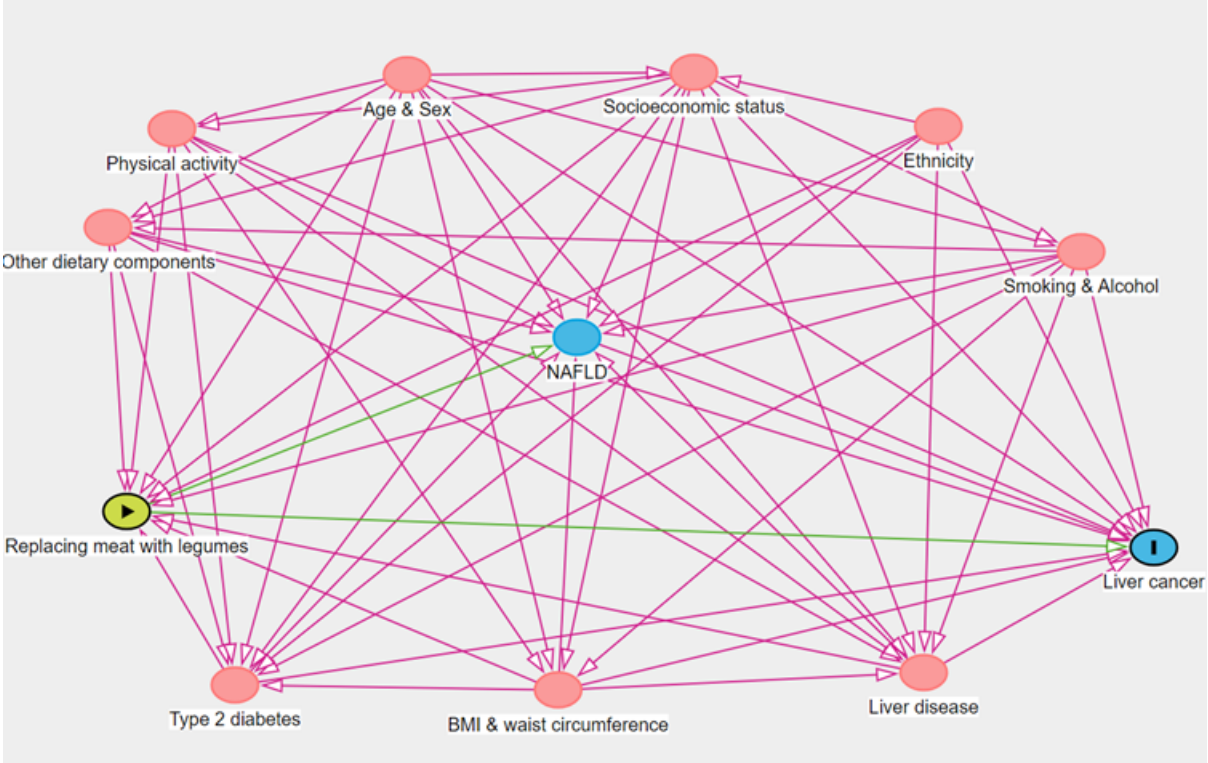


Figure 1: Figure 1. Directed acyclic graph visualizing the relationship between the exposure, replacing meat with legumes, and the outcome, liver cancer. Red circles indicate ancestors of exposure and outcome with red arrows being biasing paths. The NAFLD circle is blue to indicate that it is an ancestor of the outcome. The green arrows are causal paths.

| Food group | Includes |
|---|---|
| **Legumes** | |
| Soya-based desserts & yogurt | Soya-based desserts |
| Legumes/pulses | Baked beans, pulses |
| Soy drink | Soya drinks (including calcium fortified) |
| Soy-based meals | Tofu-based products |
| Vegetable dips | Hummus, guacamole (assuming 50% hummus) |
| Peas/sweetcorn | Peas, sweetcorn (assuming 50% peas) |
| **Red meat** | |
| Beef | Beef |
| Lamb | Lamb |

| | |
|---|---|
| Other meat, offal | Other meat including offal |
| Pork | Pork |
| **Processed meat** | |
| Processed meat | Sausages, bacon (with and without fat), ham, liver pate |
| **Animal-based foods** | |
| Poultry | |
| Breaded/battered Chicken | Fried poultry with batter/breadcrumbs |
| Poultry | Poultry (with/without skin) |
| Fish | |
| Bre aded/battered Fish | Fried fish with batter/breadcrumbs |
| Oily fish | Oily fish, including salmon |
| Shellfish | Prawns, lobster, crab, shellfish |
| White fish & tinned tuna | Tinned tuna, white fish, other fish |
| Dairy | |
| Dairy fat spread lower fat | Spreadable/lower fat butter, dairy-based very low fat spread |
| Dairy fat spread | Spreadable normal fat butter, dairy-based normal fat spread (includi |
| Milk-dairy desserts | Ice cream, milk puddings, milk-based desserts, cheesecake |
| Milk-based & powdered drinks | Dairy-based smoothies, milk-based drinks, hot chocolate |
| Full fat yogurt | Whole milk yogurt (plain) |
| High fat cheese | Cheese >17.5 g fat per 100 g, including hard cheese, soft cheese, sprea |
| Low fat yogurt | Fat free and lower fat yogurt, plain or flavoured |
| Medium & low fat cheese | Cheese <=17.5g fat per 100 g, including hard and spreadable lower fa |
| Semi-skimmed milk | Semi-skimmed milk >1 g fat per 100 g (cow, other) |
| Skimmed milk | Skimmed milk <1 g fat per 100 g (cow, cholesterol lowering, powdere |
| Whole milk | Whole milk >3.6 g fat per 100 g (cow, goat, sheep) |
| Cream | Cream (cow's milk) |
| Eggs | |
| Egg and egg dishes | Whole eggs and processed (omelette, scotch eggs, other) |
| Sauces | |
| Sauces (higher fat) | Mayonnaise, salad dressing, pesto, cheese sauce, white sauce, gravy |
| Sauces (lower fat) | Yeast, chutney, olives, ketchup, brown sauce, tomato sauce |
| Mixed dishes | |
| Pizza | Pizza (including gluten free crust) |
| Savoury snacks | Crisps, savoury biscuits, cheese snacks, other savoury biscuits |
| Soups | Soups, homemade, powdered and canned |
| Sushi | Sushi |
| **Healthy plant-based foods** | |
| Whole grains | |
| Mixed bread, brown & seeded | Mixed, brown or seeded bread, sliced, baguette, bap, roll |
| Wholemeal bread | Wholemeal bread, sliced, baguette, bap, roll |
| Biscuit cereal | Wholewheat biscuit cereal |
| Bran cereal | Bran cereal |
| Oat cereal (non-sugar) | Porridge oats (including milk/dried fruit added) |
| Oat cereal (sugar) | Oatcrunch breakfast cereal |
| Muesli | Muesli (with or without dried fruit) |
| Wholemeal pasta, brown rice & other wholegrains | Brown and wholemeal pasta and rice |
| Fruits | |
| Apples & pears | Apples and pears |
| Berries | Blackberries, strawberries, blueberries, raspberries, cherries |
| Citrus | Grapefruit, orange, satsuma |
| Dried fruit | Dried fruit, prunes |
| Bananas & other fruit | Bananas, mixed fruit, grapes, mango, melon, peach, pineapple, kiwi, c |
| Stewed fruit | Stewed fruit, plums |
| Nuts | |

| | |
|---|---|
| Nut-based spreads | Peanut-butter and chocolate-based spread |
| Unsalted nuts & seeds | Unsalted peanuts and nuts |
| Salted nuts & seeds | Salted peanuts and nuts |
| Plant oils | |
| Olive oil ( drizz ling/dunking) | Olive oil |
| Vegetable spread lower fat | Olive oil based lower fat spread, plant-based lower fat margarine and |
| Vegetable spread | Olive oil based spread, plant-based soft or hard margarine and soya-b |
| Beverages | |
| Coffee, caffeinated | Normal instant, filter, cappuccino, espresso coffee |
| Coffee, decaffeinated | Decaffeinated instant, filter, cappuccino, espresso coffee |
| Tea | Black, green and other tea |
| Tea, decaffeinated | Decaffeinated black, herbal tea, rooibos |
| Water/sparkling water | Plain water, sparkling water |
| Vegetables | |
| Allium vegetables | Garlic, leek, onion |
| Green l eafy/cabbages | Broccoli, cabbage, kale, cauliflower, spinach, sprouts |
| Raw salad | Mixed side salad, lettuce, watercress |
| Root vegetables | Beetroot, carrots, celery, parsnip, turnip |
| Tomatoes | Fresh and tinned tomatoes |
| Other vegetables (mushrooms, fruiting, mixed) | Mushrooms, mixed vegetables, avocado, broad beans, green beans, bu |
| Vegetable side dishes | Coleslaw, salad with added fat/mayonnaise |
| Vegetable dips | Hummus, guacamole (assuming 50% guacamole) |
| Peas/sweetcorn | Peas, sweetcorn (assuming 50% sweetcorn) |
| **Unhealthy plant-based foods** | |
| Refined cereals | |
| Biscuits | Chocolate biscuits, plain biscuits, sweet biscuits and cookies |
| Other bread | Naan, garlic bread, other bread (including gluten free) |
| White bread | White bread, sliced, baguette, bap, roll |
| Oat cereal (sugar) | Oatcrunch breakfast cereal |
| Savoury snacks | Crisps, savoury biscuits, cheese snacks, other savoury biscuits |
| White pasta & rice | White pasta, rice, couscous, gluten free pasta |
| Potatoes | |
| Potatoes/sweet potatoes ( baked/boiled) | Potatoes, sweet potatoes, boiled or baked |
| Fried/roast potatoes | Potatoes and chips, fried or roasted with fat |
| Mashed potatoes | Potatoes, mashed |
| Fruit juice | |
| Fruit juice | Orange, grapefruit drink and 100% fruit juice |
| Mixed dishes, vegetarian | |
| Grain dishes - added fat | Double and single crust pies, crumble pies, Yorkshire pudding, snackp |
| Samosa, pakora | Indian samosa, pakora snacks |
| Vegetarian meals | Quorn-based and vegetarian burgers and products |
| Sweets & snacks | |
| Added sugars & preserves | Table sugar, honey, jam and preserves |
| Chocolate confectionery | Chocolate bar (including white, milk and dark chocolate), chocolate-c |
| Desserts & cakes & pastries | Pancakes, croissant, Danish pastries, scones, fruitcakes, cakes, doughn |
| Other sweets | Hard and soft sweets (including sugar free) |
| Sugar sweetened beverages | |
| Rice/oat drink | Rice and oat vegetable drinks |
| Low/non sugar SSBs | Low calorie fizzy drinks and squash |
| SSBs & other sugary drinks | Fizzy sugary drinks, squash, fruit smoothies |
| Alcoholic beverages | |
| Beer & Cider | Beer and cider |
| Spirits | Spirits and other alcoholic drinks |
| Fortified wine | Fortified wine |

| | Crude[1] | | Adjusted[2] | |
|---|---|---|---|---|
| **15 g/day substitution** | **HR** | **95% CI** | **HR** | **95% CI** |
| Hepatocellular carcinoma | | | | |
| Legumes for total meat | 1.03 | 0.94, 1.12 | 1.08 | 0.99, 1.19 |
| Legumes for red meat | 1.03 | 0.93, 1.13 | 1.07 | 0.97, 1.18 |
| Legumes for processed meat | 1.03 | 0.89, 1.19 | 1.12 | 0.97, 1.30 |
| Intrahepatic cholangiocarcinoma | | | | |
| Legumes for total meat | 0.95 | 0.87, 1.02 | 0.97 | 0.90, 1.05 |
| Legumes for red meat | 0.93 | 0.85, 1.01 | 0.95 | 0.87, 1.03 |
| Legumes for processed meat | 1.02 | 0.89, 1.17 | 1.06 | 0.92, 1.22 |

[1]Adjusted for age (as underlying timescale), other food groups and total food intake to fit the substitution model.
[2]Further adjusted for sex, educational level, Townsend Deprivation Index, living alone, physical activity, smoking, alcohol intake and waist circumference.

| | Crude[1] | | Adjusted[2] | |
|---|---|---|---|---|
| **15 g/day substitution** | **HR** | **95% CI** | **HR** | **95% CI** |
| Legumes for total meat | 0.97 | 0.91, 1.04 | 1.00 | 0.94, 1.07 |
| Legumes for red meat | 0.97 | 0.90, 1.04 | 0.99 | 0.92, 1.06 |
| Legumes for processed meat | 0.99 | 0.89, 1.11 | 1.04 | 0.93, 1.17 |

[1]Adjusted for age (as underlying timescale), other food groups and total food intake to fit the substitution model.
[2]Further adjusted for sex, educational level, Townsend Deprivation Index, living alone, physical activity, smoking, alcohol intake and waist circumference.

| | Crude[1] | | Adjusted[2] | |
|---|---|---|---|---|
| **15 g/day substitution** | **HR** | **95% CI** | **HR** | **95% CI** |
| Legumes for total meat | 0.98 | 0.92, 1.04 | 1.02 | 0.96, 1.08 |
| Legumes for red meat | 0.97 | 0.91, 1.03 | 1.00 | 0.94, 1.06 |
| Legumes for processed meat | 1.02 | 0.93, 1.13 | 1.09 | 0.98, 1.20 |

[1]Adjusted for age (as underlying timescale), other food groups and total food intake to fit the substitution model.
[2]Further adjusted for sex, educational level, Townsend Deprivation Index, living alone, physical activity, smoking, alcohol intake and waist circumference.

| | Crude[1] | | Adjusted[2] | |
|---|---|---|---|---|
| **15 g/day substitution** | **HR** | **95% CI** | **HR** | **95% CI** |
| Legumes for total meat | 1.00 | 0.93, 1.07 | 1.04 | 0.97, 1.12 |
| Legumes for red meat | 0.98 | 0.91, 1.07 | 1.02 | 0.94, 1.11 |
| Legumes for processed meat | 1.04 | 0.91, 1.19 | 1.11 | 0.97, 1.27 |

[1]Adjusted for age (as underlying timescale), other food groups and total food intake to fit the substitution model.
[2]Further adjusted for sex, educational level, Townsend Deprivation Index, living alone, physical activity, smoking, alcohol intake and waist circumference.

| | Crude[1] | | Adjusted[2] | |
|---|---|---|---|---|
| **Characteristic** | **HR** | **95% CI** | **HR** | **95% CI** |
| Legume category[3] | | | | |
| No intake | — | — | — | — |
| Q1 | 0.58 | 0.35, 0.96 | 0.59 | 0.35, 0.98 |
| Q2 | 0.84 | 0.54, 1.29 | 0.85 | 0.55, 1.32 |
| Q3 | 0.75 | 0.47, 1.19 | 0.75 | 0.47, 1.20 |
| Q4 | 1.02 | 0.66, 1.56 | 1.10 | 0.71, 1.69 |

[1]Adjusted for age (as underlying timescale), other food groups and total food intake to fit the substitution model.
[2]Further adjusted for sex, educational level, Townsend Deprivation Index, living alone, physical activity, smoking, alcohol intake and waist circumference.
[3]mean daily intake of legumes in grams for each quartile: Q1: 6.3, Q2: 15.7, Q3: 34.3, Q4 109.