

*Article*

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

**Niels Bock1[](https://orcid.org/0009-0005-7373-1589), Fie Langmann1[](https://orcid.org/0000-0003-3474-9346), Luke W. Johnston1,2[](https://orcid.org/0000-0003-4169-2616), Daniel B. Ibsen1,2,3,4[](https://orcid.org/0000-0002-7038-4770), Christina C. Dahm1,**∗[](https://orcid.org/0000-0003-0481-2893)

1 Department of Public Health, Aarhus University, Aarhus, Denmark;

2 Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus N, Denmark;

3 Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark;

4 MRC Epidemiology Unit, School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom;

**\*** Correspondence: [CCD@ph.au.dk](mailto:CCD@ph.au.dk).

**Abstract:** Purpose: Primary liver cancer is on the rise worldwide, partially due to poor diets and 1 sedentary lifestyles. Shifting to more plant-based diets may lower the risk. We aimed to estimate 2 the effect of replacing unprocessed red meat, processed red meat and total red meat with legumes 3 on primary liver cancer in a free-living population. Methods: We analyzed data from 126,744 4 UK Biobank participants who completed *≥* 2 24-hour diet recalls. Baseline characteristics were 5 collected from the initial assessment visit. Information on liver cancer diagnoses was collected via 6 external linkage to inpatient hospital episodes or central cancer registries. Cox proportional hazards 7 regression models were used to estimate substitution of 15 g/day of legumes with 15 g/day of total 8 red meat, unprocessed red meat and processed red meat on liver cancer risk, using the leave-one-out 9 food substitution model. Results: During a median follow-up time of 11.3 years, 173 participants 10 developed liver cancer. In the fully adjusted models, no association was observed when substituting 11 15 g/day of legumes with total red meat (HR: 0.98 (95% CI 0.93-1.04)), unprocessed red meat (HR: 12

0.97 (95% CI 0.91-1.03)) or processed red meat (HR: 1.02 (95% CI 0.93-1.13)). Conclusion: Overall, little 13 evidence of an association between replacing red meat with legumes and liver cancer was observed. 14 Further research in larger study populations with longer follow-up time is warranted. 15

**Keywords:** Food Substitutions; liver cancer; red meat; legumes. 16

**Citation:** Bock, N; Langmann, F; Johnston, LW; Ibsen, DB; Dahm, CC. Substitution of red meat with legumes and risk of primary liver cancer in 126,744 UK Biobank participants: a prospective cohort study. *Nutrients* **2024**, *1*, 0. [https://doi.org/](https://doi.org/10.3390/nu1010000)

Received:

Revised:

Accepted:

Published:

**Copyright:** © 2024 by the authors. Submitted to *Nutrients* for possible open access publication under the terms and conditions of the Creative Commons Attri- bution (CC BY) license ([https://](https://creativecommons.org/licenses/by/4.0/) [creativecommons.org/licenses/by/](https://creativecommons.org/licenses/by/4.0/) 4.0/).

1. **Introduction** 17

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and 18

the third leading cause of cancer-related death with viral hepatitis being the leading risk 19

factor [[1](#_bookmark9)]. In low-infection populations, modifiable risk factors, such as dietary habits, 20

may play an increasing role in HCC pathogenesis as non-alcoholic fatty liver disease 21

(NAFLD) has become the leading cause of liver cirrhosis [[2](#_bookmark10),[3](#_bookmark11)] that may in turn progress 22

to HCC. A western dietary pattern high in fats and red meats and concurrently low in 23

fruits, vegetables, and whole grains has been associated with NAFLD progression [[4](#_bookmark12)]. The 24

prevalence of NAFLD-related HCC cases is an increasing global problem [[2](#_bookmark10)]. It is estimated 25

that the prevalence of NAFLD-related HCC in the US will increase by 146%, while incident 26

NAFLD-related HCC cases will increase by 137% by 2030 [[5](#_bookmark13)]. 27

The second most common primary liver cancer is the intrahepatic cholangiocarcinoma 28

(ICC) [[6](#_bookmark14)]. While HCC emerges from the liver parenchyma, ICC emerges from the bile 29

duct. Despite being a relatively rare cancer, ICC is characterized by its aggressiveness, late 30

diagnosis and poor survival [[7](#_bookmark15)]. It is estimated that the incidence of ICC is increasing in 31

populations that are not burdened by known infectous and environmental risk factors [[8](#_bookmark16)]. 32

Recent meta-analyses of observational studies and clinical trials have shown a significant 33

adverse association between NAFLD and ICC [[9](#_bookmark17),[10](#_bookmark18)]. 34

Version June 7, 2024 submitted to *Nutrients* <https://www.mdpi.com/journal/nutrients>

The impact of specific food groups on liver cancer risk is not well known. Observa- 35 tional studies suggest that intake of coffee, vegetables and whole grains may lower HCC 36 risk [[11](#_bookmark19)–[14](#_bookmark21)]. The protective properties of these foods are proposedly due to their content 37 of dietary fibers and polyphenols, which are also defining components of legumes. The 38 health benefits of legumes extend to improved glycemic control and hypotensive and anti- 39 carcinogenic properties with observed inverse associations with cardiovascular disease and 40 colorectal cancer [[15](#_bookmark22),[16](#_bookmark23)]. Two large prospective cohort studies found evidence of inverse 41 associations between legume consumption and risk of HCC [[11](#_bookmark19),[13](#_bookmark20)]. However, replacement 42 foods were not specified in these studies, which fails to reflect that an increase in intake of 43 one food is at the expense of a concomitantly decreased intake of another food. Studies 44 on substituting plant-based proteins for animal-based proteins are important if we are to 45 lower the climate impacts of our diets [[17](#_bookmark24)]. Although previous research has investigated 46 substitution of animal-based proteins with plant-based proteins in relations to NAFLD [[18](#_bookmark25)], 47 research on substituting meats with legumes in relation to risk of HCC and ICC is sparse. 48 This leaves a substantial gap in the current knowledge on the beneficial effects on primary 49 liver cancer from substituting red meat with legumes. 50

The low incidence of liver cancer in populations not burdened by viral hepatitis 51

complicates observational prospective research designs; nonetheless, the prospects of the 52

burden of liver cancer on public health warrant investigation of preventative measures. 53 Thus, the main aim of this study was to estimate the association between replacing unpro- 54 cessed red meat, processed red meat and total red meat with legumes on primary liver 55

cancer in a free-living population. 56

1. **Materials and Methods** 57
   1. *Study population* 58

The UK Biobank is a population-based prospective cohort initiated in 2006. [[19](#_bookmark26)] 59

During 2006-2010, more than 500,000 participants, aged 40-69, were recruited and visited 60

designated assessment centres across the UK. Participants provided information about age, 61

sex, sociodemographic factors (education, Townsend deprivation index, living alone) and 62

lifestyle factors (smoking, alcohol consumption, physical activity) via touch screen ques- 63

tionnaires, and computer-assisted interviews. Anthropometric data (waist circumference) 64

were collected via physical measurements [[20](#_bookmark27)]. 65

* 1. *Dietary assessment* 66

A web-based 24-hour dietary recall was administered at the end of the initial assess- 67

ment visit for the last 70,000 recruited participants [[21](#_bookmark28)]. From February 2011 to April 68

2012, 320,000 participants who had provided an e-mail address were invited on four sepa- 69

rate occasions to complete the 24-hour dietary recall, the Oxford WebQ, of which 210,947 70

participants completed at least one. The Oxford WebQ covered 206 food items and 32 71

beverage items commonly consumed in the UK. Intakes were reported in standard units of 72

measurements, e.g., servings, cups, slices, etc. with intake categories ranging from 0 to 3+ 73

units [[22](#_bookmark29)]. The Oxford WebQ has been validated against interviewer-based 24-hour dietary 74

recalls and biomarkers [[23](#_bookmark30),[24](#_bookmark31)]. 75

Researchers defined 79 food categories and 14 beverage categories from the Oxford 76

WebQ using the UK National Diet and Nutrition Survey categories [[22](#_bookmark29)]. These food and 77

beverage groups were used when defining the food groups used in the substitution analyses 78

(Table [S1](#_bookmark5)). Legumes were defined as legumes and dietary pulses, baked beans, tofu-based 79

products, peas, hummus, soy drinks, and soy-based desserts and yogurt. Red meat intake 80

was defined as intake of beef, pork, lamb, or other meat, including offal. Processed red meat 81

intake was defined as sausages, bacon (with and without fat), ham, or liver pate. Other 82

food groups included were animal-based foods, unhealthy plant-based foods, healthy 83

plant-based foods, and alcoholic beverages (Table [S1](#_bookmark5)). Animal-based and healthy and 84

unhealthy plant-based food foods were grouped based on plant-based diet indices from 85

previous studies [[25](#_bookmark32)–[28](#_bookmark33)]. 86

As a single 24-hour dietary recall does not assess habitual dietary intake and variation 87 in diet over time at an individual level [[29](#_bookmark34),[30](#_bookmark35)], only participants who completed two or 88 more Oxford WebQs were eligible for inclusion in this study. 89

* 1. *Liver cancer assessment* 90

Liver cancer was defined according to ICD-10 diagnosis codes C22.0 for Hepatocel- 91

lular carcinoma (HCC) or C22.1 for Intrahepatic cholangiocarcinoma (ICC) and ICD-9 92

diagnosis codes 1550 Malignant neoplasm of liver, primary or 1551 Malignant neoplasm 93

of intrahepatic bile ducts. Incident and prevalent cases of liver cancer and corresponding 94

diagnosis dates were obtained via external linkage to central cancer registries or hospital 95

inpatient episodes [[31](#_bookmark36),[32](#_bookmark37)]. 96

* 1. *Assessment of confounders* 97

Confounders were defined *a priori* from a review of the background literature and 98

illustrated using directed acyclic graphs (Figure [S1](#_bookmark4)). The following confounding variables 99

were selected: age at baseline (years, continuous), sex (male, female), educational level 100

(high: College or University degree, intermediate: A levels/AS levels, O levels/GCSEs, 101

or equivalent, low: none of the previous mentioned), Townsend Deprivation Index (con- 102

tinuous), living alone (yes, no), waist circumference (cm, continuous), physical activity 103

(above/below the 2017 UK Physical activity guidelines of 150 minutes of moderate activity 104

per week or 75 minutes of vigorous activity, or unknown), smoking (pack years as a propor- 105 tion of lifespan exposed to smoking, continuous), and alcohol intake (g/day, continuous). 106 Information on all confounders except age were collected at the initial assessment visit 107

before the start of follow-up. 108

* 1. *The substitution model* 109

The substitution analyses were conducted by modelling replacement of an equal mass 110

of meat with legumes. The portion size of the substitution was set to 15 g/day of legumes 111

for 15 g/day of red meat to ensure that substitutions were below the mean intake of any of 112

the substituted food groups in the cohort. The substitutions were modeled using the leave- 113

one-out-approach in which variables for every food group intake along with a variable for 114

total food intake were included, except the food group that were to be substituted [[33](#_bookmark38)]. To 115

estimate replacing of 15 g/day of all red meats (unprocessed and processed) with 15 g/day 116

of legumes, the following model was defined: 117

log(*h*(*t*; *x*)) = log(*h*0(*t*)) + *β*1Legumes (15g) +

*β*2Total food intake (g) + *β*3Other food groups (g) + *β*4Covariates (1)

When substituting only unprocessed red meat with legumes, processed red meat was 118

added to the model: 119

log(*h*(*t*; *x*)) = log(*h*0(*t*)) + *β*1Legumes (15g) + *β*2Processed red meat (15g) +

*β*3Total food intake (g) + *β*4Other food groups (g) + *β*5Covariates (2)

When substituting only processed red meat with legumes, red meat was added to the 120

model: 121

log(*h*(*t*; *x*)) = log(*h*0(*t*)) + *β*1Legumes (15g) + *β*2Unprocessed red meat (15g) +

*β*3Total food intake (g) + *β*4Other food groups (g) + *β*5Covariates (3)

The performance of the leave-one-out model when modeling equal mass substitutions has 122

been validated against simulated data [[34](#_bookmark39)]. 123

* 1. *Statistical analysis* 124

Multivariable-adjusted Cox proportional hazards regression models were used to esti- 125

mate hazard ratios (HR) with corresponding 95% confidence intervals (CI) with age as the 126

underlying timescale. Participants were followed from the date of their last completed Ox- 127

ford WebQ until the occurrence of the event of interest or due to right censoring, whichever 128

came first. Participants were right censored in the event of death, loss to follow-up, or 129

administrative end of follow-up (October 31, 2022). Two levels of adjustments were added 130

to the substitution model. Model 1 was minimally adjusted for age (as the underlying 131

timescale) total weight of food and beverage intake, and all other food groups to fit the 132

substitution model. Model 1 was additionally stratified on age at recruitment (<45, 45-49, 133

50-54, 55-59, 60-64 and *≥* 65), attented assessment centre, and sex. Model 2 was further 134

adjusted for educational level, Townsend Deprivation Index, living alone, physical activity, 135

smoking, alcohol intake, and waist circumference. Assumptions of proportional hazards 136

were checked using Shchoenfeld residuals. 137

In secondary analyses, each cancer type was analysed separately to evaluate if the 138

pooling of HCC and ICC as one outcome in the main analysis was justified. Furthermore, 139

to estimate the association of legume intake with liver cancer regardless of other dietary 140

components, legume consumers (divided into quartiles) were compared to non-consumers. 141

To evaluate the robustness of the main analyses, sensitivity analyses were performed 142

on subsamples of participants by excluding those with high alcohol intake (exclusion of 143

the upper decile of alcohol intake (g/day) by sex), implausible energy intake (exclusion 144

of participants below the 2.5th percentile and above the 97.5th percentile of energy intake 145

(kJ/day) by sex), any liver disease before baseline, any type of cancer before baseline, and 146

fewer than three completed Oxford WebQs. As neither the central cancer registries nor the 147

hospital inpatient registries were complete, liver cancer diagnoses retrieved from death 148

registries, which were updated more recently, were included in a sensitivity analysis to 149

test for outcome misclassification. Lastly, one of the causal assumptions was that anthro- 150

pometry confounded the causal relationship between replacing red meat with legumes and 151

liver cancer; however, strong arguments exist giving support to anthropometry being a 152

mediator between diet and health outcomes. Thus, to test for erroneously conditioning on 153

a potential mediator, as sensitivity analysis was adjusted following model 2 but without 154

waist circumference. All other sensitivity analyses were modeled as the fully adjusted 155

models in the main analyses. 156

All analyses were conducted in R (version 4.1.1) with a significance level of 5 %. 157

1. **Results** 158

After excluding participants with liver cancer before baseline, participants lost to 159

follow-up before baseline, and participants with errors in dietary data, 126,744 participants 160

who had completed two or more Oxford WebQs remained (Figure [1](#_bookmark0)). 161

During a median follow-up time of 11.3 years, 173 participants developed liver cancer. 162

Those who developed liver cancer were older at baseline, were more likely to be male, 163

have a higher waist circumference, be less physically active, and fewer had never smoked, 164

compared to all included participants (Table [1](#_bookmark1)). 165

Mean daily energy and total food intakes as well as daily intake of all specified food 166

groups in grams are presented in Table [2](#_bookmark2). 167

No evidence of associations was found for substituting 15 g/day of legumes with 15 168

g/day of total red meat, unprocessed red meat, or processed red meat and risk of primary 169

liver cancer in Model 1 (Table [3](#_bookmark3): total red meat: HR: 0.99, 95% CI: 0.93-1.05; unprocessed 170

red meat: HR: 0.97, 95% CI: 0.91-1.03; processed red meat: HR: 1.04, 95% CI: 0.94-1.15). 171

The estimated associations changed minimally with further adjustments. There was weak 172

evidence of an association between replacement of processed red meat with legumes ( HR: 173

1.09, 95% CI: 0.99-1.21; Table [3](#_bookmark3)). 174

In secondary analyses, when analyzing the associations between replacement of red 175

meat with legumes and HCC or ICC separately, weak evidence of a higher risk of HCC was 176

Two or more Oxford WebQs (n = 126,812)

1. Oxford WebQs (n = 48,108)
2. Oxford WebQs (n = 42,477)
3. Oxford WebQs (n = 30,463)
4. Oxford WebQs (n = 5,764)

UK Biobank (n = 502,369)

Exclusion of participants with:

No Oxford WebQ (n = 291,419) One Oxford WebQ (n = 84,138)

Included in study (n = 126,765)

Exclusions due to:

Liver cancer before baseline (n = 21)

Loss to follow−up before baseline or missing diet data (n = 47)

**Figure 1.** Flowchart of included participants. Missing diet data were merged with loss to follow-up before baseline due to n being less than 5. It should be noted that not all UK Biobank participants were invited to complete an Oxfords WebQ. Only the last 70,000 participants to visit an assessment center were asked to complete an Oxford WebQ at the end of their visit. Further Oxford WebQs were sent to 320,000 participants who provided an e-mail address.

observed (Table [S2](#_bookmark6), total red meat: HR: 1.06, 95% CI: 0.97-1.16; unprocessed red meat: HR: 177 1.04, 95% CI: 0.95-1.15; processed red meat: HR: 1.10, 95% CI: 0.96-1.27). This association 178 was opposite and inverse for replacement of total red meat and unprocessed red meat and 179 ICC (total red meat: HR: 0.97, 95% CI: 0.89-1.05; unprocessed red meat: HR: 0.94, 95% 180

CI: 0.87-1.02) but not for processed red meat ( HR: 1.07, 95% CI: 0.93- 1.23, Table [S2](#_bookmark6)). The 181 magnitude or direction of associations were not significantly different across strata of liver 182 cancer types. 183

In the adjusted non-substitution analysis, only the first quartile of legume intake (mean 184

intake 6.3 grams/day) was associated with a lower risk of liver cancer, compared to no 185

intake (HR: 0.60, 95% CI: 0.36-0.99); no associations were observed for quartiles 2, 3 or 4 186

compared to no intake (Table [S3](#_bookmark7)). 187

In sensitivity analyses, excluding participants based on high alcohol intake, implausi- 188

ble energy intake, any liver disease or cancer before baseline, or fewer than 3 completed 189

Oxford WebQs did not alter the estimates appreciably. Similar results were also found 190

when including death registries as a source of liver cancer cases and when excluding waist 191

circumference from the fully adjusted analysis (Table [S4](#_bookmark8)). 192

1. **Discussion** 193

Contrary to our hypothesis, this study showed little evidence of an association between 194

replacing 15 g/day of unprocessed or processed red meat with legumes on risk of primary 195

liver cancer. The estimates were robust to sensitivity analyses. When investigating liver 196

cancer types separately, replacing total red meat and unprocessed red meat with legumes 197

showed some weak evidence of an inverse association with ICC. The results for legume 198

intake without specified substitutions did not show a clear pattern of association. 199

The prospective longitudinal design of this study established temporality between 200

the diet exposure and liver cancer outcome, and the large sample size enabled analyses 201

# Table 1. Baseline characteristics of UK Biobank participants who completed *≥* 2 Oxford WebQ dietary recalls.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cohort** |  | **Liver cancer** |  |
| **Variable** | **N = 126,744***1* |  | **N = 173***1* |
| **Age, years Sex**  Female | 60 (53, 65)  70,659 (56%) |  | 64.0 (60.0, 68.0)  65 (38%) |  |
| Male | 56,085 (44%) |  | 108 (62%) |  |
| **Educational level***2*  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%) |
| Unknown | 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*Median (IQR) for continuous variables; n (%) for categorical variables

*2*High: College or University degree; Intermediate: A levels/AS levels, O levels/GCSEs, or equivalent; Low: none of the previous mentioned.

*3*Above or below the 2017 UK Physical activity guidelines of 150 minutes of moderate activity per

week or 75 minutes of vigorous activity.

of a rare cancer. Further, our specified substitution analyses have some strengths in 202 contrast to traditional methods in nutritional epidemiology through examining the effect 203 of consuming a food or nutrient while holding all other foods constant. The substitution 204 is easily interpretable and reflects the implications that an increased intake of a food is at 205 the expense a decreased intake of other foods. In that sense, the food substitution model 206 mimics some aspects of a randomized controlled design. A limitation of this research 207 design was that the low intake of the substituted foods in this population restricted the size 208 of the substitution, which may in turn have restricted findings of clinical relevance. 209

Information on dietary intake was collected using self-reported 24-hour diet recalls, 210

which may have introduced measurement error partly due to 24-hour recalls’ limited 211

ability to estimate habitual dietary intake. However, estimates were robust to exclusion 212

of participants with fewer than three completed Oxford WebQs, indicating that at least 213

two 24-hour diet recall measurements were sufficient to account for some of the natural 214

fluctuations in dietary intake over time. A validation study of the Oxford WebQ found some 215

person-specific biases within participants with a higher BMI having greater disparities 216

for correlation with true intakes for some nutrients [[24](#_bookmark31)]. Adjustment for BMI was not 217

included in this current study. However, adjusting for waist circumference did not change 218

the estimates significantly, lending some support to sufficient adjustment of person specific 219

bias. Finally, by specifying that the dietary exposure was collected on at least two occasions, 220

the study population suffered considerable attrition. This is unlikely to be completely at 221

random, and most likely resulted in a study population with greater focus on their dietary 222

habits compared to the general population. For example, the mean intake of processed 223

# Table 2. Daily dietary intake of food groups, total food, and total energy intake in UK Biobank participants who completed *≥* 2 Oxford WebQ dietary recalls.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cohort** |  | **Liver cancer** |  |
| **Daily food intake** | **N = 126,744***1* |  | **N = 173***1* |
| **Total food intake** |  |  |  |  |
| Energy, kJ | 8,430 (7,179, 9,856) |  | 8,579 (7,413, 10,048) |  |
| Weight, g | 3,144 (2,720, 3,621) |  | 3,162 (2,737, 3,659) |  |

**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*2* | 475 (361, 603) | 448 (322, 604) |
| Healthy plant-based foods*3* | 1,806 (1,454, 2,198) | 1,791 (1,365, 2,158) |
| Unhealthy plant-based foods*4* | 472 (324, 662) | 491 (365, 698) |
| Alcoholic beverages | 132 (0, 342) | 144 (0, 375) |

*1*Median (IQR)

*2*Other animal-based foods include poultry, fish, dairy, eggs, and mixed dishes with animal products. *3*Healthy plant-based foods include whole grains, vegetables, fruits, nuts, plant oils, and beverages (coffee, tea, water).

*4*Unhealthy plant-based foods include refined grains, potatoes, mixed vegetarian dishes, sweets and

snacks, fruit juice, and sugar sweetened beverages.

meat was low in our study population. If a diet consisting of higher intakes of healthier 224 plant-based foods is associated with lower liver cancer incidence, our study population 225 may be at lower risk overall, thus reducing the power of our study to detect an association. 226 Registries used to determine a diagnosis of liver cancer were incomplete or not up-to- 227

date at the time of analysis [[31](#_bookmark36)]. Data from external providers, such as the NHS England, 228 NHS Central Register or National Records of Scotland, were estimated to be mostly com- 229 plete by the UK Biobank at various dates, ranging from 31 December 2016 for cancer data 230 from Wales to 31 October 2022 for hospital inpatient data from England [[32](#_bookmark37)]. This could 231 introduce misclassification of the outcome, as individuals with liver cancer may not be iden- 232 tified as cases. However, the estimates were robust in a sensitivity analysis that included 233 death registries as an additional source of liver cancer diagnoses to accommodate missing 234 outcome events. Incorrectly classifying non-cases as cases would lead to attenuation of our 235 results, but this is unlikely due to register linkage. Though health registries may have been 236 only partially up to date, using registries almost eliminates selection bias due to loss to 237 follow-up. 238

# Table 3. Replacing 15/day of total red meat, unprocessed red meat, and processed meat with legumes and hazard ratios and 95% confidence intervals for primary liver cancer.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Model 1***1* |  | **Model 2***2* |  |
| **15 g/day of legumes replacing:** | **HR (95% CI)** |  | **HR (95% CI)** |
| Total red meat | 0.99 (0.93-1.05) |  | 1.02 (0.96-1.08) |  |
| Unprocessed red meat | 0.97 (0.91-1.03) |  | 1.00 (0.94-1.06) |  |
| Processed red meat | 1.04 (0.94-1.15) |  | 1.09 (0.99-1.21) |  |

*1*Multivariate Cox proportional hazards regression model adjusted for age (as underlying timescale), other food groups, and total food intake.

*2*Further adjusted for sex, educational level, Townsend deprivation index, living alone, physical

activity, smoking, alcohol intake, and waist circumference.

The relatively low number of events limited the possibility to adjust for confounding 239 factors. Excessive adjustment parameters per event can compromise the validity of the 240 multivariable Cox regression model, potentially causing biased estimates. To ensure statis- 241 tical validity, at least 10 events per variable were aimed for in the main analysis by limiting 242 the number of adjustment levels, using fewer and broader food groups, and fewer levels 243 for categorical covariates. This approach was guided by our *a priori* causal assumptions. 244 Although this method helped maintain statistical validity, it may have increased residual 245 confounding by diluting the importance of specific food groups. Additionally, risk factors 246 that could not be adjust for, such as aflatoxin B1, a known liver carcinogen, may have 247 contributed to additional residual confounding. 248

Contrary to our hypothesis, replacing processed red meat with legumes was associated 249

with a non-significant increase in risk of primary liver cancer, with a greater effect size 250

compared to unprocessed red meat. This pattern persisted across all sensitivity analyses. 251

However, the estimates for processed red meat were labeled with less confidence, partly 252

due to the low median intake. The findings of this current study align with other research in 253

the UK Biobank, where unprocessed red meat intake was associated with a non-significant 254

increase in liver cancer risk, with a greater effect size than processed meat (both white and 255

red meat) [[35](#_bookmark40)]. This supports the notion that processed meat may not be associated with 256

liver cancer risk in this population. 257

The literature on food substitutions, particularly in relation to liver cancer, is sparse. 258

Accordingly, an analysis of legume intake without specifying food substitutions was also 259

conducted. A recent meta-analysis of observational studies found a non-linear dose- 260

response relationship between legume intake and liver cancer risk, with a protective effect 261

observed between intakes of 8 g/day to 40 g/day [[36](#_bookmark41)]. This somewhat contrasts with 262

our findings where any increase above 6.3 g/day of legumes was not associated with a 263

decreased risk of liver cancer, compared to no legume intake. One recent meta-analysis of 264

observational studies showed no association between red or processed meat intake and 265

HCC [[37](#_bookmark42)] while another found a positive association between processed meat and HCC [[38](#_bookmark43)]. 266

Another study examined replacement of animal-based protein sources with plant-based 267

protein sources and NAFLD risk in two cohorts and found a near significant decrease in 268

NAFLD when replacing processed meat, but not unprocessed red meat, with legumes in 269

one cohort and a near significant increase in NAFLD risk when replacing total red and 270

processed meat with legumes in another cohort [[18](#_bookmark25)]. 271

1. **Conclusion** 272

Overall, little evidence of an association between replacing red meat with legumes 273

and liver cancer was observed. These results should be interpreted with caution due to the 274

low intake of the substituted foods and few liver cancer cases. Further research in larger 275

study populations with longer follow-up time is warranted. 276

**Funding:** This research received no external funding. 277

**Data Availability Statement:** This research has been conducted using the UK Biobank Resource 278

under Application Number 81520. Data can be accessed via application to the Access Management 279

System (AMS) at <https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>. Showcase 280

of the data are available at <https://biobank.ndph.ox.ac.uk/showcase/>. 281

**Conflicts of Interest:** The authors declare no conflict of interest. 282

**Abbreviations** 283

The following abbreviations are used in this manuscript: 284

285

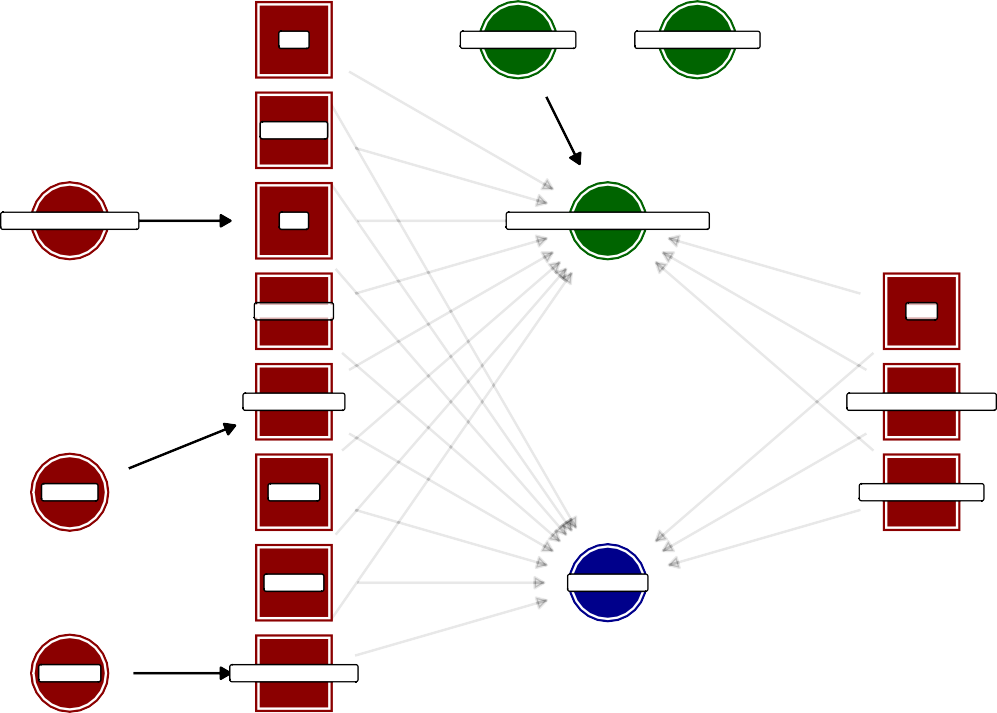
NAFLD Non-alcoholic fatty liver disease HCC Hepatocellular carcinoma

ICC Intrahepatic cholangiocarcinoma TDI Townsend deprivation index DAG Directed acyclic graphs

IQR Interquartile range

286

**Appendix A** 287



Sex

Legume intake (g)

Red meat intake (g)

Education

Socioeconomic status

TDI

Replacing meat with legumes (g)

Living alone

Age

Physical activity

Intake of other foods (g)

Lifestyle

Alcohol

Total food intake (g)

Smoking

Liver cancer

Adiposity

Waist circumference

**Figure S1.** Simplified directed acyclic graph (DAG) visualizing the hypothesised causal relationship between replacing red meat with legumes and liver cancer based on assumptions of biasing paths. Red nodes represent confounders. Square nodes represent the minimal sufficient adjustment set for estimating the effect of replacing red meat with legumes on liver cancer. Shadowed arrows represent biasing paths. DAG terminology demands visualisation of all hypothesized correlating relationships between variables, typically resulting in complex and hard-to-follow illustrations. To improve readability, inter-covariate arrows are hidden in the above DAG.

# Table S1. Supplementary table 1. Summary of included foods for each food group. Food group Includes

**Legumes** Soya-based desserts, Baked beans, pulses, Soya drinks (including calcium fortified), Tofu-based products, Hummus, Peas

**Red meat** Beef, Lamb, Other meat including offal, Pork

**Processed meat** Sausages, bacon (with and without fat), ham, liver pate

# Animal-based foods Healthy

**plant-based foods Unhealthy plant-based foods Alcoholic beverages**

Poultry, fish, dairy, eggs, mixed dishes, and sauces and condiments

Whole grains, fruits, nuts, plant oils, beverages (water, tea and coffee), vegetables

Refined cereals, potatoes, fruit juice, mixed dishes (vegetarian), sweets & snacks, and sugar sweetened beverages

Beer and cider, spirits and other alcoholic drinks, fortified wine, red and rose wine, white wine

# Table S2. Replacing 15/day of total meat, red meat and processed meat with legumes and hazard ratios and 95% confidence intervals for hepatocellular carcinoma and intrahepatic cholangiocarci- noma.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Model 1***1* |  | **Model 2***2* |  |
| **15 g/day of legumes replacing:** | **HR (95% CI)** |  | **HR (95% CI)** |
| **Hepatocellular carcinoma** |  |  |  |  |
| Total red meat | 1.02 (0.94-1.11) |  | 1.06 (0.97-1.16) |  |
| Unprocessed red meat | 1.02 (0.93-1.11) |  | 1.04 (0.95-1.15) |  |
| Processed red meat | 1.04 (0.90-1.19) |  | 1.10 (0.96-1.27) |  |

**Intrahepatic cholangiocarcinoma**

|  |  |  |
| --- | --- | --- |
| Total red meat | 0.94 (0.87-1.02) | 0.97 (0.89-1.05) |
| Unprocessed red meat | 0.92 (0.85-1.00) | 0.94 (0.87-1.02) |
| Processed red meat | 1.03 (0.90-1.18) | 1.07 (0.93-1.23) |

*1*Multivariate Cox proportional hazards regression model adjusted for age (as underlying timescale), other food groups, and total food intake.

*2*Further adjusted for sex, educational level, Townsend deprivation index, living alone, physical

activity, smoking, alcohol intake, and waist circumference.

# Table S3. No intake of legumes vs. quartiles of daily legume intake and hazard ratios and 95% confidence intervals for primary liver cancer.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | **Model 1***1* |  | **Model 2***2* |  |
| **Characteristic** | **Mean daily legume intake** | **HR (95% CI)** |  | **HR (95% CI)** |
| Categories: |  |  |  |  |  |
| No intake | 0.00 | — |  | — |  |
| Q1 | 6.3 | 0.59 (0.35-0.98) |  | 0.60 (0.36-0.99) |  |
| Q2 | 16 | 0.88 (0.57-1.35) |  | 0.90 (0.58-1.38) |  |
| Q3 | 34 | 0.73 (0.46-1.17) |  | 0.74 (0.47-1.19) |  |
| Q4 | 109 | 0.98 (0.64-1.52) |  | 1.07 (0.69-1.66) |  |

*1*Multivariate Cox proportional hazards regression model adjusted for age (as underlying timescale), other food groups, and total food intake.

*2*Further adjusted for sex, educational level, Townsend deprivation index, living alone, physical

activity, smoking, alcohol intake, and waist circumference.

Version June 7, 2024 submitted to *Nutrients* 11 of 13

# Table S4. Sensitivity analyses

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | **Exclusion of participants with:** |  | | | | | | | |
|  | **High alcohol intake***1* |  | **Implausible food** | **Liver disease before** | **Any cancer before** |  | **Fewer than 3 Oxford** |  | **Death register as source** |  | **Exclusion of waist** |  |
|  |  |  | **intake***2* | **baseline***3* | **baseline***4* |  | **WebQs** |  | **of liver cancer events** |  | **circumference from analysis** |  |
| **15 g/day of legumes replacing:** | **HR (95% CI)** |  | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |  | **HR (95% CI)** |  | **HR (95% CI)** |  | **HR (95% CI)** |  |
| Total red meat | 1.00 (0.94-1.06) |  | 1.01 (0.95-1.07) | 0.99 (0.93-1.06) | 1.03 (0.96-1.11) |  | 1.04 (0.96-1.12) |  | 1.02 (0.96-1.08) |  | 1.00 (0.94-1.06) |  |
| Unprocessed red meat | 0.98 (0.92-1.05) |  | 0.99 (0.93-1.05) | 0.97 (0.90-1.04) | 1.00 (0.93-1.08) |  | 1.02 (0.94-1.11) |  | 1.00 (0.94-1.07) |  | 0.98 (0.92-1.05) |  |
| Processed red meat | 1.06 (0.95-1.18) |  | 1.08 (0.98-1.20) | 1.08 (0.96-1.20) | 1.15 (1.01-1.30) |  | 1.11 (0.97-1.27) |  | 1.07 (0.98-1.18) |  | 1.06 (0.96-1.17) |  |

*1* Exclusion of the upper decile of alcohol intake (g/day) by sex.

*2* Exclusion of participants below the 2.5th percentile and above the 97.5th percentile of energy intake (kJ/day) by sex.

*3* ICD10 codes: K70-79, B16-19, Z94.4, I85, I86.4, and E83.0-1. ICD9 codes: 5710-5745, 0700-0709, V427 and 2750-2751.

*4* ICD10 codes: C00-C97 and D00-D48. ICD9 codes: 140-239.

**References** 288

1. Massarweh, N.N.; El-Serag, H.B. Epidemiology of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. *Cancer* 289

*Control* **2017**, *24*, 107327481772924. <https://doi.org/10.1177/1073274817729245>. 290

1. Younossi, Z.M.; Koenig, A.B.; Abdelatif, D.; Fazel, Y.; Henry, L.; Wymer, M. Global epidemiology of nonalcoholic fatty liver 291

disease—Meta-analytic [assessment](https://doi.org/10.1002/hep.28431) of prevalence, incidence, and outcomes. *Hepatology* **2016**, *64*, 73–84. [https://doi.org/10.1002/](https://doi.org/10.1002/hep.28431) 292

[hep.28431](https://doi.org/10.1002/hep.28431). 293

1. Younossi, Z.M.; Stepanova, M.; Younossi, Y.; Golabi, P.; Mishra, A.; Rafiq, N.; Henry, L. Epidemiology of chronic liver diseases in 294

the USA in the past three decades. *Gut* **2019**, *69*, 564–568. <https://doi.org/10.1136/gutjnl-2019-318813>. 295

1. Guo, W.; Ge, X.; Lu, J.; Xu, X.; Gao, J.; Wang, Q.; Song, C.; Zhang, Q.; Yu, C. Diet and Risk of Non-Alcoholic Fatty Liver 296

Disease, Cirrhosis, and [Liver](https://doi.org/10.3390/nu14245335) Cancer: A Large Prospective Cohort Study in UK Biobank. *Nutrients* **2022**, *14*, 5335. [https:](https://doi.org/10.3390/nu14245335) 297

[//doi.org/10.3390/nu14245335](https://doi.org/10.3390/nu14245335). 298

1. Estes, C.; Razavi, H.; Loomba, R.; Younossi, Z.; Sanyal, A.J. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates 299

an exponential increase in burden of disease. *Hepatology* **2017**, *67*, 123–133. <https://doi.org/10.1002/hep.29466>. 300

1. Khan, S.A.; Tavolari, S.; Brandi, G. Cholangiocarcinoma: Epidemiology and risk factors. *Liver International* **2019**, *39*, 19–31. 301

<https://doi.org/10.1111/liv.14095>. 302

1. Kirstein, M.M.; Vogel, A. [Epidemiology](https://doi.org/10.1159/000453013) and Risk Factors of Cholangiocarcinoma. *Visceral Medicine* **2016**, *32*, 395–400. [https:](https://doi.org/10.1159/000453013) 303

[//doi.org/10.1159/000453013](https://doi.org/10.1159/000453013). 304

1. Bergquist, A.; von Seth, E. Epidemiology of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol* **2015**, *29*, 221–232. [https:](https://doi.org/10.1016/j.bpg.2015.02.003) 305

[//doi.org/10.1016/j.bpg.2015.02.003](https://doi.org/10.1016/j.bpg.2015.02.003). 306

1. Wongjarupong, N.; Assavapongpaiboon, B.; Susantitaphong, P.; Cheungpasitporn, W.; Treeprasertsuk, S.; Rerknimitr, R.; 307

Chaiteerakij, R. Non-alcoholic fatty liver disease as a risk factor for cholangiocarcinoma: a systematic review and meta-analysis. 308

*BMC Gastroenterology* **2017**, *17*. <https://doi.org/10.1186/s12876-017-0696-4>. 309

1. Corrao, S.; Natoli, G.; Argano, C. Nonalcoholic fatty liver disease is associated with intrahepatic cholangiocarcinoma and not 310

with extrahepatic form: definitive evidence from meta-analysis and trial sequential analysis. *Eur J Gastroenterol Hepatol* **2020**, 311

*33*, 62–68. <https://doi.org/10.1097/meg.0000000000001684>. 312

1. Zhang, W.; Xiang, Y.; Li, H.; Yang, G.; Cai, H.; Ji, B.; Gao, Y.; Zheng, W.; Shu, X. Vegetable-based dietary pattern and liver 313

cancer risk: Results from [the](https://doi.org/10.1111/cas.12231) Shanghai Women’s and Men’s Health Studies. *Cancer Science* **2013**, *104*, 1353–1361. [https:](https://doi.org/10.1111/cas.12231) 314

[//doi.org/10.1111/cas.12231](https://doi.org/10.1111/cas.12231). 315

1. Yang, Y.; Zhang, D.; Feng, N.; Chen, G.; Liu, J.; Chen, G.; Zhu, Y. Increased Intake of Vegetables, But Not Fruit, Reduces Risk for 316

Hepatocellular Carcinoma: A Meta-analysis. *Gastroenterology* **2014**, *147*, 1031–1042. <https://doi.org/10.1053/j.gastro.2014.08.005>. 317

1. Liu, X.; Yang, W.; Petrick, J.L.; Liao, L.M.; Wang, W.; He, N.; Campbell, P.T.; Zhang, Z.F.; Giovannucci, E.; McGlynn, K.A.; et al. 318 Higher intake of whole grains and dietary fiber are associated with lower risk of liver cancer and chronic liver disease mortality. 319 *Nature Communications* **2021**, *12*. <https://doi.org/10.1038/s41467-021-26448-9>. 320
2. Bhurwal, A.; Ratta, P.; Yoshitake, S.; Pioppo, L.; Reja, D.; Dellatore, P.; Rustgi, V. Inverse Association of Coffee with Liver 321

Cancer Development: An Updated Systematic Review and Meta-analysis. *Journal of Gastrointestinal and Liver Diseases* **2020**. 322

<https://doi.org/10.15403/jgld-805>. 323

1. Viguiliouk, E.; Glenn, A.J.; Nishi, S.K.; Chiavaroli, L.; Seider, M.; Khan, T.; Bonaccio, M.; Iacoviello, L.; Mejia, S.B.; Jenkins, 324

D.J.A.; et al. Associations between Dietary Pulses Alone or with Other Legumes and Cardiometabolic Disease Outcomes: An 325

Umbrella Review and Updated Systematic Review and Meta-analysis of Prospective Cohort Studies. *Advances in Nutrition* **2019**, 326

*10*, S308–S319. <https://doi.org/10.1093/advances/nmz113>. 327

1. Jin, S.; Je, Y. Nuts and legumes consumption and risk of colorectal cancer: a systematic review and meta-analysis. *European* 328

*Journal of Epidemiology* **2022**, *37*, 569–585. <https://doi.org/10.1007/s10654-022-00881-6>. 329

1. UN. Food and Climate Change: Healthy diets for a healthier planet. 330
2. Zhang, S.; Yan, Y.; Meng, G.; Zhang, Q.; Liu, L.; Wu, H.; Gu, Y.; Wang, X.; Zhang, J.; Sun, S.; et al. Protein foods from animal 331

sources and risk of nonalcoholic fatty liver disease in representative cohorts from North and South China. *Journal of Internal* 332

*Medicine* **2022**, *293*, 340–353. <https://doi.org/10.1111/joim.13586>. 333

1. Sudlow, C.; Gallacher, J.; Allen, N.; Beral, V.; Burton, P.; Danesh, J.; Downey, P.; Elliott, P.; Green, J.; Landray, M.; et al. UK Biobank: 334

An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS* 335

*Medicine* **2015**, *12*, e1001779. <https://doi.org/10.1371/journal.pmed.1001779>. 336

1. UK Biobank. Order of Data Collection, 2011. Accessed 21 May 2024. 337
2. UK Biobank. 24-hour dietary recall questionnaire (Oxford WebQ), 2024. Accessed 21 May 2024. 338
3. Piernas, C.; Perez-Cornago, A.; Gao, M.; Young, H.; Pollard, Z.; Mulligan, A.; Lentjes, M.; Carter, J.; Bradbury, K.; Key, T.J.; 339

et al. Describing a new food group classification system for UK biobank: analysis of food groups and sources of macro- and 340

micronutrients in 208,200 [participants.](https://doi.org/10.1007/s00394-021-02535-x) *European Journal of Nutrition* **2021**, *60*, 2879–2890. [https://doi.org/10.1007/s00394-021-025](https://doi.org/10.1007/s00394-021-02535-x) 341

[35-x](https://doi.org/10.1007/s00394-021-02535-x). 342

1. Liu, B.; Young, H.; Crowe, F.L.; Benson, V.S.; Spencer, E.A.; Key, T.J.; Appleby, P.N.; Beral, V. Development and evaluation of the 343

Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. 344

*Public Health Nutrition* **2011**, *14*, 1998–2005. <https://doi.org/10.1017/s1368980011000942>. 345

1. Greenwood, D.C.; Hardie, L.J.; Frost, G.S.; Alwan, N.A.; Bradbury, K.E.; Carter, M.; Elliott, P.; Evans, C.E.L.; Ford, H.E.; Hancock, 346 N.; et al. Validation of the Oxford WebQ Online 24-Hour Dietary Questionnaire Using Biomarkers. *American Journal of* 347 *Epidemiology* **2019**, *188*, 1858–1867. <https://doi.org/10.1093/aje/kwz165>. 348
2. Thompson, A.S.; Tresserra-Rimbau, A.; Karavasiloglou, N.; Jennings, A.; Cantwell, M.; Hill, C.; Perez-Cornago, A.; Bondonno, N.P.; 349

Murphy, N.; Rohrmann, S.; et al. Association of Healthful Plant-based Diet Adherence With Risk of Mortality and Major Chronic 350

Diseases Among Adults in the UK. *JAMA Network Open* **2023**, *6*, e234714. <https://doi.org/10.1001/jamanetworkopen.2023.4714>. 351

1. Heianza, Y.; Zhou, T.; Sun, D.; Hu, F.B.; Qi, L. Healthful plant-based dietary patterns, genetic risk of obesity, and cardiovascular 352

risk in the UK biobank study. *Clinical Nutrition* **2021**, *40*, 4694–4701. <https://doi.org/10.1016/j.clnu.2021.06.018>. 353

1. Satija, A.; Bhupathiraju, S.N.; Spiegelman, D.; Chiuve, S.E.; Manson, J.E.; Willett, W.; Rexrode, K.M.; Rimm, E.B.; Hu, F.B. 354

Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults. *Journal of the American* 355

*College of Cardiology* **2017**, *70*, 411–422. <https://doi.org/10.1016/j.jacc.2017.05.047>. 356

1. Satija, A.; Bhupathiraju, S.N.; Rimm, E.B.; Spiegelman, D.; Chiuve, S.E.; Borgi, L.; Willett, W.C.; Manson, J.E.; Sun, Q.; Hu, F.B. 357

Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort 358

Studies. *PLOS Medicine* **2016**, *13*, e1002039. <https://doi.org/10.1371/journal.pmed.1002039>. 359

1. Thompson, F.E.; Subar, A.F., Dietary Assessment Methodology; Elsevier, 2013; pp. 5–46. [https://doi.org/10.1016/b978-0-12-3918](https://doi.org/10.1016/b978-0-12-391884-0.00001-9) 360

[84-0.00001-9](https://doi.org/10.1016/b978-0-12-391884-0.00001-9). 361

1. Gurinovic´, M.; Zekovic´, M.; Mileševic´, J.; Nikolic´, M.; Glibetic´, M., Nutritional Assessment; Elsevier, 2017. [https://doi.org/10.101](https://doi.org/10.1016/b978-0-08-100596-5.21180-3) 362

[6/b978-0-08-100596-5.21180-3](https://doi.org/10.1016/b978-0-08-100596-5.21180-3). 363

1. UK Biobank. Health Outcomes Overview, 2024. Accessed 21 May 2024. 364
2. UK Biobank. Data providers and dates of data availability, 2023. Accessed 21 May 2024. 365
3. Ibsen, D.B.; Laursen, A.S.D.; Würtz, A.M.L.; Dahm, C.C.; Rimm, E.B.; Parner, E.T.; Overvad, K.; Jakobsen, M.U. Food substitution 366

models for nutritional [epidemiolog](https://doi.org/10.1093/ajcn/nqaa315)y. *The American Journal of Clinical Nutrition* **2021**, *113*, 294–303. [https://doi.org/10.1093/ajcn/](https://doi.org/10.1093/ajcn/nqaa315) 367

[nqaa315](https://doi.org/10.1093/ajcn/nqaa315). 368

1. Tomova, G.; Gilthorpe, M.; Tennant, P. Theory and performance of substitution models for estimating relative causal effects in 369

nutritional epidemiology. *The American Journal of Clinical Nutrition* **2022**, *116*, 1379–1388. <https://doi.org/10.1093/ajcn/nqac188>. 370

1. Knuppel, A.; Papier, K.; Fensom, G.K.; Appleby, P.N.; Schmidt, J.A.; Tong, T.Y.N.; Travis, R.C.; Key, T.J.; Perez-Cornago, A. 371 Meat intake and cancer risk: prospective analyses in UK Biobank. *International Journal of Epidemiology* **2020**, *49*, 1540–1552. 372 <https://doi.org/10.1093/ije/dyaa142>. 373
2. Liu, K.; Chen, W.; Zhou, Y.; Xu, L.; Sun, X.; Mao, Y.; Ye, D. Associations between food groups and liver cancer: a systematic 374

review and meta-analysis of observational studies. *Nutrition Journal* **2023**, *22*. <https://doi.org/10.1186/s12937-023-00858-5>. 375

1. Di, Y.; Ding, L.; Gao, L.; Huang, H. Association of meat consumption with the risk of gastrointestinal cancers: a systematic review 376

and meta-analysis. *BMC Cancer* **2023**, *23*. <https://doi.org/10.1186/s12885-023-11218-1>. 377

1. Yu, J.; Liu, Z.; Liang, D.; Li, J.; Ma, S.; Wang, G.; Chen, W. Meat Intake and the Risk of Hepatocellular Carcinoma: A Meta-Analysis 378

of Observational Studies. *Nutrition and Cancer* **2022**, *74*, 3340–3350. <https://doi.org/10.1080/01635581.2022.2077386>. 379

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual 380

author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to 381

people or property resulting from any ideas, methods, instructions or products referred to in the content. 382