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

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Abstract: Purpose: Primary liver cancer is on the rise worldwide, partially due to poor diets and sedentary lifestyles. Shifting to more plant-based diets may lower the risk. We aimed to estimate the effect of replacing unprocessed red meat, processed red meat and total red meat with legumes on primary liver cancer in a free-living population. Methods: We analyzed data from 126,744 UK Biobank participants who completed $\geq$ 2 24-hour diet recalls. Baseline characteristics were collected from the initial assessment visit. Information on liver cancer diagnoses was collected via external linkage to inpatient hospital episodes or central cancer registries. Cox proportional hazards regression models were used to estimate substitution of 15 g/day of legumes with 15 g/day of total red meat, unprocessed red meat or processed red meat on liver cancer risk, using the leave-one-out food substitution model. Results: During a median follow-up time of 11.3 years, 173 participants developed liver cancer. In the fully adjusted models, no association was observed when substituting 15 g/day of legumes with total red meat (HR: 1.02 (95% CI 0.96-1.08)), unprocessed red meat (HR: 1.00 (95% CI 0.94-1.06)) or processed red meat (HR: 1.09 (95% CI 0.99-1.21)). Conclusion: Overall, little evidence of an association between replacing red meat with legumes and liver cancer was observed. Further research in larger study populations with longer follow-up time is warranted.

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

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1. Supplementary materials

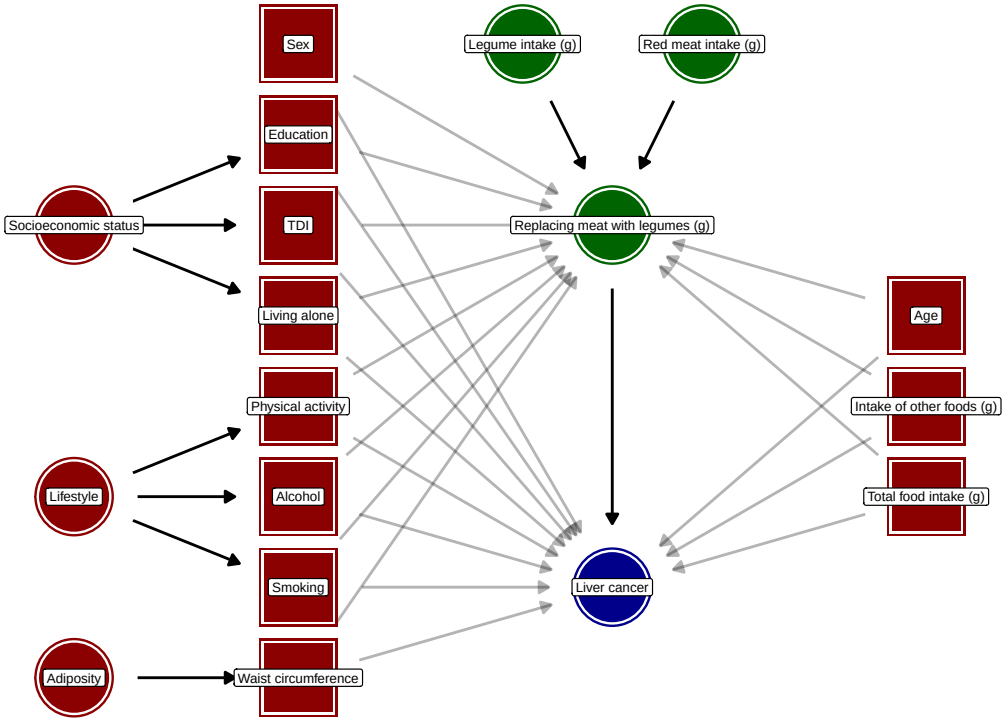

Figure S1. Simplified directed acyclic graph (DAG) visualizing the hypothesised causal relationship between replacing red meat with legumes and liver cancer based on assumptions of biasing paths. Red nodes represent confounders. Square nodes represent the minimal sufficient adjustment set for estimating 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	Poultry, fish, dairy, eggs, mixed dishes, and sauces and condiments
Healthy plant-based foods	Whole grains, fruits, nuts, plant oils, beverages (water, tea and coffee), vegetables
Unhealthy plant-based foods	Refined cereals, potatoes, fruit juice, mixed dishes (vegetarian), sweets & snacks, and sugar sweetened beverages
Alcoholic beverages	Beer and cider, spirits and other alcoholic drinks, fortified wine, red and rose wine, white wine

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

	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, and additionally stratified on sex, age, and attended assessment centre.
[2]Further adjusted for 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, and additionally stratified on sex, age, and attended assessment centre.
[2]Further adjusted for educational level, Townsend deprivation index, living alone, physical activity, smoking, alcohol intake, and waist circumference.

Table S4. Sensitivity analyses

	Exclusion of participants with:						
	High alcohol intake[1]	**Implausible food intake**[2]	**Liver disease before baseline**[3]	**Any cancer before baseline**[4]	**Fewer than 3 Oxford WebQs**	**Death register as source of liver cancer events**	**Exclusion of waist 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: 1400-2399.