# **Legume consumption and risk of hepatic and biliary disease in the UK Biobank Study**

## Background

To reduce climate impacts of our diets the EAT-Lancet reference diet was introduced in 2019 as a globally sustainable and healthy diet with a large emphasis on plant-based proteins instead of animal-based proteins, e.g., with a recommendation of 100 g legumes daily (1-3). Legumes are the pods and fruits from the Leguminosae or Favaceae plant families (4). The climate impact of legumes is undoubtedly low (4-7), however the scientific evidence to support that 100 g of legumes/day improves health is sparse. Legumes are good sources of protein, low in saturated fat and energy density, and rich in dietary fibre; all components associated with a healthy diet (8, 9).

**Animal** studies imply that legume consumption **minimizes the risk of non-alcoholic fatty liver diseases (NAFLD) by reducing build-up of fats in the liver** (10-14)**.** NAFLD is the most prevalent chronic liver disease in the Western countries with a prevalence of 15-45 % (15, 16). NAFLD is caused by Western diet high in red meat, fats, and sugars, obesity, physical inactivity, and smoking (15-18), and even children can develop the disease (19). NAFLD is the liver manifestation of Metabolic Syndrome with shared causes and comorbidities such as abdominal adiposity, increased blood glucose levels, hypertension, and generally associated with increased risk of cardiovascular diseases (20, 21). Consumption of legume-rich compared to Western diets has been associated with overall better diet quality and greater health (22-32). Most evidence is derived from studies of dietary patterns including higher legume consumption, such as vegetarian diets. Thus, the evidence of an association is indirect and **limited (9).**

**As legumes are a source of both carbohydrates and proteins, research frequently compare legumes with other carbohydrate sources (9, 33-36).** When individuals limit intake of certain food groups, they will most often increase the intake of certain other food groups, in an otherwise stable diet (37, 38). **Replacing protein from animal sources with protein from plant sources has previously been associated with a substantially lower mortality rate (39).** An Asian study substituting a whole serving of animal-based foods with a whole serving of plant-based foods has shown to be beneficial against NAFLD (11). The key question remains, how the replacement of different amounts of meats, poultry, or fish with legumes impacts the risk of NAFLD. Consumption of legumes in the Western countries has been negligible to date and the impact of markedly increasing intakes of legumes on hepatobiliary and other diseases is understudied. Therefore, this study aims to investigate the association between replacing meats, poultry, or fish with legumes and the risk of non-alcoholic steatotic hepatitis (NASH) or NAFLD contingent on potential confounders of the associations. As it might be more feasible for Western populations to include legumes and substituting dietary components that are not meats, this study will also aim to investigate the association between total consumption of legumes and NAFLD and NASH.

**Hypotheses**

* Replacing meats and poultry intakes with legumes is associated with a lower risk of NAFLD and NASH.
* Replacing fish intake with legumes is not associated with a lower risk of NAFLD and NASH

## Methods

**Study population and setting**

The initial recruitment of participants for the UK Biobank started in 2006 and ran until June 2010. Of 9.2 million people identified from the National Health Service registers and invited to participate in the study, 5.5% participated, approximately 500,000 participants, aged 37-73 years at baseline. The study protocol and more information are available elsewhere (40, 41). At baseline, participants provided detailed information on several sociodemographic, physical, lifestyle, and health-related characteristics via self-completed touch-screen questionnaires and a computer assisted personal interview (42). Professionally trained staff did physical, anthropometric, and biomedical measures following standardized procedures (40). Diet was assessed through a touchscreen questionnaire at baseline and a 24-hour dietary assessment tool designed for the UK Biobank study. 210,965 individuals completed one or more 24-hour dietary assessments (43). All participants gave written, informed consent prior to baseline, and the study was approved by the National Information Governance Board for Health and Social Care and the National Health Service North West Multicentre Research Ethics Committee (reference number 06/MRE08/65).

For the current study, only participants with two or more 24 h dietary assessments will be included in the analyses, while missing information on covariates will be filled in by statistical imputations where applicable.

**Assessment of diet**

The Oxford WebQ was designed as an internet based 24-hour dietary assessment tool for measuring diet on repeated occasions. The questionnaire is a short set of food frequency questions on commonly eaten food groups in the British population on the day before. The questionnaire aims to measure the type and quantity of food and beverages consumed in the last 24 hours and estimate nutrients from the entered information through the UK Nutrient Databank Food Composition Tables (44, 45). The Oxford WebQ was compared with interviewer administered 24-hour dietary recalls and validated for macronutrients and total energy intake using recovery biomarkers and comparing with a single food frequency questionnaire (44, 46, 47). Recently, the Oxford WebQ nutrient calculation was updated to provide more detailed information on nutrient intakes and to incorporate new dietary variables (45).

Participants recruited between April 2009 and September 2010 completed the Oxford WebQ at baseline (n=70,747). The Oxford WebQ was not available until April 2009 and participants recruited before that date who provided a valid email address were invited to complete the four subsequent 24-hour dietary assessments online (48).

**Legumes**

Legume consumption will be estimated based on participants reported diets from the self-administered online 24-hour dietary assessments, the Oxford WebQ. Consumption of legumes and pulses will be based on total weight by food group intakes estimated from participants’ responses in the Oxford WebQ. Despite the high detail level of the Oxford WebQ, a single 24-hour dietary assessment cannot capture habitual intake of legumes in a UK-setting (49). Therefore, this study will include varying numbers of 24-hour dietary assessments to ensure that we capture usual intake of legumes.

**Meat, poultry, and fish**

Consumption of red and processed meats, poultry, and fish will be based on total weight by food group intakes estimated from participants’ responses to the Oxford WebQs.

Red and processed meat will be defined as beef, pork, lamb, and other meats including offal, and processed meat including sausages, bacon, ham, and liver paté. Poultry will be defined as poultry with or without skin, and fried poultry with batter or breadcrumbs. Fish iwill be defined as oily fish, white fish and tinned tuna, fried fish with batter or breadcrumbs, and shellfish.

**Non-alcoholic fatty liver**

Incident cases of NASH and NAFLD will be assessed through linkage to the National Health Service registers where diagnosis after hospital admission or primary care visits are coded according to the International Classification of Diseases and Related Health Problems (ICD-10) (50). Incident cases of NAFLD are diagnosed with ICD-10-code K76.0 at first admission to hospital while incident cases of NASH are diagnosed with ICD-10-code K75.8 (51).

**Covariates**

The directed acyclic graph presented below (Figure 1) illustrates the potential and known association between covariates of the association between legume consumption and development of any of the outcomes.

Information on covariates will include information on all other dietary components based on total weight by food group intakes as g/day and kcal/day retrieved from the Oxford WebQ (fruits, vegetables, cereal products, dairy products, egg products, nuts, mixed dishes, condiments, added sugar and sweets, non-alcoholic beverages, and alcoholic beverages), sex (male, female), age (years), alcohol consumption (g ethanol/day as restricted cubic splines), ethnic group (white, mixed background, Asian, black, other, and unknown), socioeconomic status (Townsend deprivation score [quintiles], educational level), geographical region of recruitment (ten UK regions), lives with a wife or partner (yes, no), anthropometry (BMI [kg/m2]), physical activity (low [0-9.9 METs/week], moderate [10-49.9 METs/week], and high [≥50 METs/week], unknown), smoking status (never, former, current 1-15 cigarettes per day, current ≥15 cigarettes per day, current but number of cigarettes per day unknown, and smoking status unknown); history of metabolic diseases (ICD-codes [E10-E14, E78, I10-I15], and self-reported [yes, no, unknown] own or family members’ diagnoses of diabetes, hypertension, high cholesterol).

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Figure 1. Directed Acyclic Graph representing the association between replacement of animal foods with legumes and risk of non-alcoholic fatty liver and the assumed relationship with covariates. \*Own or family history with diabetes, hypertension, or high cholesterol.

**Statistical analyses**

Standard summary statistics will be performed to describe the distribution of total legume consumption as an average g/day based on participants’ 24-h WebQ responses and across baseline characteristics of participants in the study.

Multi-variable adjusted Cox Proportional Hazards regression models will be used to estimate the hazard ratios for each of the outcomes based on replacing meats and/or fish with legumes.

* Replacing red and processed meats, poultry, and fish with legumes (e.g., per 30 g/day)
* Replacing red and processed meats, poultry, and fish with legumes (e.g., per 40 kcal/day)

Age will be used as the underlying time scale in the analyses. Follow-up time will begin with participants’ last completed Oxford WebQ. As participants in UKB are still followed-up today, participants will be right censored at the date of the most recent registry update of full follow-up for the outcomes. Otherwise, censoring will occur at the event of death, loss to follow-up from the study, or date of diagnosis of NAFLD or NASH, whichever comes first.

The substitution analyses will be conducted with different adjustment levels. Model 1 will be minimally adjusted for strata of age at recruitment (<45, 45-49, 50-54, 55-59, 60-64, ≤65 years) and geographical region of recruitment (ten UK regions), sex, and intake of all other dietary components apart from the substitute components (red and processed meats; poultry; fish). When substituting g legumes/day, the unit for all dietary components will be g/day and the analyses will be adjusted for total amount of consumed foods in g/day. When substituting calories of legumes, the unit for all dietary components will be calories/day and the analyses will be adjusted for total amount of consumed calories/day. Model 2 will be further adjusted for alcohol consumption, ethnic group, socioeconomic status, lives with a wife or partner, physical activity, smoking status, and history of metabolic diseases. As obesity may either confound or mediate the association between replacing red and processed meats and/or poultry and/or fish with legumes and risk of NAFLD, model 3 will further adjust for anthropometry (BMI [kg/m2]).

**Secondary and sensitivity analyses**

To evaluate the association between overall legume intake and hepatobiliary disease risk, quintiles of legume intake (g/day) will be evaluated with adjustment levels similar to the substitution models.

Peas are increasingly used as a plant-based meat alternative in the food industry (52). Despite this, peas are also included in the NHS 5 A Day recommendations for fruits and vegetables (53). Therefore, in sensitivity analyses consumption of legumes will include participants self-reported intake of legumes and pulses together with consumed peas. The amount of peas consumed will be estimated based on participants’ reported portion sizes consumed with a portion size of peas weighing 80 g/day (54).

To evaluate the robustness of the main analyses, sensitivity analyses will include varying numbers of Oxford WebQ returns, imputations of missing information, and removal of participants with increased serum levels of alanine-aminotransferase (>45 U/L for women and >70 U/L for men) and aspartate-aminotransferase (>35 U/L for women and >45 U/L for men). Sensitivity analyses will further include removal of participants with alcoholic liver disease and removal of those with previous diseases of the liver, although not necessarily NAFLD, as they may be predisposed for developing further liver diseases. All analyses will be conducted in R with a significance level of 5%.

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