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Protocol: Substituting meat, poultry, and fish with legumes and risk of gallbladder diseases in a large prospective cohort

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Contents

Study information

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Description

Western diets high in animal foods and saturated fats has been shown to cause a multitude of non-communicable diseases while also having great and negative impacts on the environment. Based on a combined environmental and health related focus, legumes are increasingly being recommended as a meat substitute. Previous research has however indicated an increased risk of developing gallbladder related diseases when consuming large amounts of legumes and this study therefore investigates the association between substituting legumes for meats, poultry, and fish and the risk of developing gallbladder diseases.

This research will use the UK Biobank Resource under Application Number 81520.

Objectives and hypotheses

Background

The EAT-Lancet reference diet was introduced in 2019 as a globally sustainable and healthy diet emphasizing plant-based proteins instead of animal-based proteins, e.g., with a recommendation of 100 g legumes daily (Springmann et al., 2020; Willett et al., 2019).

Consumption of pulse-rich diets has been associated with overall better diet quality and greater health (Mitchell et al., 2009; Papanikolaou & Fulgoni, 2008). However, pulses contain a range of bioactive compounds, which may increase the biliary cholesterol secretion. This may consequently have implications for the risk of gallstone development and related comorbidities (Chavez-Santoscoy et al., 2014; Li et al., 2013; Li & Gao, 2019).

As legumes are a source of both carbohydrates and proteins, research frequently compares legumes with other carbohydrate sources (Belski et al., 2011; Jayalath et al., 2014; Lee et al., 2008; Linlawan et al., 2019; Sievenpiper et al., 2009). Observed associations for foods may be due to the specific foods themselves. However, the associations could also represent the effect of the dietary pattern in which the specific food is consumed. 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 (Ibsen et al., 2020; Ibsen & Dahm, 2022). The association of such food intake will not only be caused by the increased consumption of one food, but rather the substitution effect including various foods.

Consumption of legumes in Western countries has been negligible to date and the impact of markedly increasing intakes of legumes on gallbladder diseases is understudied. Therefore, this study aims to investigate the association between replacing red and processed meat, poultry, or fish with pulses and the risk of gallbladder diseases (gallstone, inflammation of the gallbladder, and removal of the gallbladder) contingent on potential confounders of the associations. As it might be more feasible for Western populations to include pulses and substituting dietary components that are not animal-based, this study also aimed to investigate the association between overall increased consumption of legumes and the risk of gallbladder diseases.

Hypothesis

- Replacing meat intakes with legumes is associated with an increased risk of gallbladder diseases.
- Replacing poultry or fish intakes with legumes is not associated with the risk of gallbladder diseases.
- Consuming more legumes without altering other dietary components is associated with increased risk of gallbladder disease.

Design plan

Study type

Observational Study. Data is collected from study subjects that are not randomly assigned to a treatment. This includes surveys, natural experiments, and regression discontinuity designs.

Blinding

No blinding is involved in this study.

Study design

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 (Biobank, 2007; Sudlow et al., 2015). All participants gave written, informed consent before 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).

Sampling plan

Existing data

Registration prior to analysis of the data. As of the date of submission, the data exist and you have accessed it, though no analysis has been conducted related to the research plan (including calculation of summary statistics). A common situation for this scenario when a large dataset exists that is used for many different studies over time, or when a data set is randomly split into a sample for exploratory analyses, and the other section of data is reserved for later confirmatory data analysis.

Explanation of existing data

The UK Biobank is a large national cohort of participants in the UK, with data collected in a standardized format the the sole purpose of providing a data resource for researchers to use for health research. All information about collection procedures, limitations, and sources of bias are well established and described by the UK Biobank resource.

Because of its size of data collected, it is near impossible to a priori see patterns in the data that might influence how the analysis will be conducted, unless specifically looked for or previously published on. In this way, we feel pre-analysis bias is minimal.

Data collection procedures

Study population and setting

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 (Fry et al., 2017). Professionally trained staff did physical, anthropometric, and biomedical measures following standardized procedures (Sudlow, Gallacher, Allen, Beral, Burton, Danesh, Downey, Elliott, Green, Landray, Liu, Matthews, Ong, Pell, Silman, Young, Sprosen, Peakman, & Collins, 2015). Diet was assessed through a touchscreen questionnaire at baseline and a 24-hour dietary assessment tool (Oxford WebQ) designed for the UK Biobank study. The 24-hour dietary assessment tool was completed by participants up to five times and 210,965 individuals completed one or more 24-hour dietary assessments (Biobank, 2021).

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 (Liu et al., 2011; Perez-Cornago et al., 2021). The Oxford WebQ was compared with interviewer-administered 24-hour dietary recalls and validated for macro nutrients and total energy intake using recovery biomarkers and compared with a single food frequency questionnaire (Carter et al., 2019; Greenwood et al., 2019; Liu, Young, Crowe, Benson, Spencer, Key, Appleby, & Beral, 2011). Recently, the Oxford WebQ nutrient calculation was updated to provide more detailed information on nutrient intakes and to incorporate new dietary variables (Perez-Cornago, Pollard, Young, Uden, Andrews, Piernas, Key, Mulligan, & Lentjes, 2021). 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 (Kelly et al., 2021).

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 (FAO, 2018). Therefore, this study will include varying numbers of 24-hour dietary assessments to ensure that we capture the usual intake of legumes. Usual intake will be estimated as a daily average across available 24-hour dietary assessments.

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 will be defined as oily fish, white fish and tinned tuna, fried fish with batter or breadcrumbs, and shellfish.

Gallbladder diseases Incident cases of gallbladder diseases includes incident cholelithiasis, cholecystitis, and cholecystectomy assessed through linkage to the National Health Service registers. Diagnosis after hospital admission or primary care visits were coded according to the International Classification of Diseases and Related Health Problems 10th edition disease codes (ICD-10) or operative procedure codes (OPCS) (Biobank, 2020; Digital, 2021a; 2021b). Cholecystitis and cholelithiasis can occur more than once, but only the first and incident diagnosis will be included as an outcome. Diagnosis can only provide information on presence of inflammation or gallstone but no information on whether the patient recovers completely. Further, individuals can have undiagnosed gallstones with no symptoms, while previous incidence of symptomatic cholelithiasis or cholecystitis is associated with a higher risk of developing symptoms in the future. Individuals do not necessarily develop new gallstones, but experience symptoms due to the gallstones already present in the gallbladder (NHS, 2021). Date of first diagnosis will be used as the precise measure of each outcome. Incident cases of cholelithiasis were diagnosed with ICD- 10-codes K80.0-K80.8 at first admission to the hospital or through OPCS-4 codes J21.1, J24.2-3, J26.1, J33.1-J33.2, J41.1, J41.3, J49.1, J49.2, and J52.1. Incident cases of cholecystitis were diagnosed with ICD-10-codes K81.0-K81.9. Incident cases of cholecystectomy were diagnosed with OPCS-4 codes J18.1-3 and J18.8-9 (Biobank, 2020; Digital, 2021a; 2021b).

Covariates Directed acyclic graphs will be used to illustrate the potential and known association between covariates of the association between substituting meat, poultry or fish for legumes and development of gallbladder disease. Information on covariates will include information on all other dietary components based on total weight by food group intakes as g/week 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), ethnic group (white or other), socioeconomic status (Townsend deprivation score, educational level, yearly income [< 18,000£; 18,000-30,999£; 31,000-51,999£; 52,000-100,000£; > 100,000£]), geographical region of recruitment (ten UK regions), cohabitation (alone, with spouse/partner, with other non-partner, no answer), anthropometry (BMI [kg/m2]), physical activity (low [≤918 MET-min/week], moderate [918-3706 MET-min/week], high [≥3706 MET-min/week], and unknown) (Cassidy et al., 2016), smoking status (never, former, current 1-15 cigarettes per day, current ≥15 cigarettes per day, unknown), rapid weight loss (yes, no), history of gallbladder related conditions (participants' diagnosis of diabetes, elevated cholesterol, use of hormone replacement therapy drugs for women [yes, no], used of oral contraceptives for women [yes, no]), and family history of diabetes (yes, no). Blood samples were drawn at baseline for all participants to measure total bilirubin levels as there has been found a causal association between elevated total bilirubin and risk of gallbladder diseases (Sun et al., 2023).

Sample size

For this cohort study, only participants with two or more 24 h dietary assessments and complete information on covariates will be included in the analyses.

Variables

Measures variables

Exposures: g/week consumption of legumes, meats, poultry, and fish

Outcomes: gallstone, gallbladder inflammation, gallbladder removal

Covariates: g/week consumption of fruits, vegetables, cereal products, dairy products, egg products, nuts, mixed dishes, condiments, added sugar and sweets, non-alcoholic beverages, and alcoholic beverages. Sex, age, ethnic group, Townsend deprivation score, educational level, yearly income, geographical region of recruitment (ten UK regions), cohabitation, obesity, physical activity, smoking status, rapid weight loss, own and family history of gallbladder related conditions.

Analysis plan

Statistical models

Main analyses

Standard summary statistics will be performed to describe the distribution of baseline characteristics and food consumption as an average g/week based on participants' 24-h WebQ responses. Multi-variable adjusted Cox Proportional Hazards regression models will be used to estimate the hazard ratios for gallbladder disease based on replacing meats, poultry, or fish with legumes.

- Replacing red and processed meats, poultry, or fish with legumes (e.g., per 80 g/week)

Age will be used as the underlying time scale in the analyses. Person-years at risk were calculated from the date of last completed Oxford WebQ to the date of death, loss to follow-up, diagnosis of any gallbladder disease, or right censoring, whichever occurred first. 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. The substitution analyses will be conducted with different adjustment levels.

Model 1 will be stratified for sex, age (<45, 45-49, 50-54, 55-59, 60-64, ≤65 years) at recruitment and geographical region of recruitment (ten UK regions), and adjusted for intake of all other dietary components apart from the two substitutes. When substituting g legumes/week, the unit for all dietary components will be g/week and the total weekly intake of all foods will be held stable in the analysis

Model 2 will be further adjusted for ethnic group (white or other), socioeconomic status (Townsend deprivation score, educational level, yearly income), cohabitation (alone, with spouse or partner, with non-partner, unknown), physical activity (low [≤ 918 METs/week], moderate [≥918 – 3706 METs/week], high [≤37069 METs/week], and unknown), smoking status (never, former, current 1-15 cigarettes per day, current ≥15 cigarettes per day, unknown), rapid weight loss (yes, no), female reproductive hormonal factors (use of hormonal replacement therapy drugs, use of oral contraceptives, and number of pregnancies), history of gallbladder related conditions (yes, no), and family history of gallbladder related conditions (yes, no).

Model 3 will be further adjusted for BMI (≥ 30 kg/m2 or < 30 kg/m2), as obesity may either confound or mediate the association between replacing red and processed meats, poultry, or fish with legumes and risk of gallbladder disease.

Secondary and sensitivity analyses

Cox proportional hazards regression substitution analyses will be conducted in a study sample restricted to consumers of legumes only (i.e. removing non legume consumers). To evaluate the association between overall legume intake and GBD risk, hazard ratios associated with a 80 g/week increase in legumes without substituting any other foods will be estimated following adjustment levels in model 2. This analysis was also conducted among consumers of legumes only. In these analyses, total weekly intake of all foods will not be held stable to ensure that no substitution is implied in the interpretation of results.

To evaluate the robustness of the main analyses, sensitivity analyses will include varying numbers of Oxford WebQ returns, removal of participants in the highest 90th percentile of total bilirubin levels, and exclusion of soy milk from the estimated legume consumption, as soy milk is unlikely to culinarily replace red and processed meat, poultry, or fish. Furthermore, consumption of legumes will include participants self-reported intake of legumes and pulses together with consumed peas. Peas are included in the NHS 5 A Day recommendations for fruit and vegetables consumption in the UK (Services, 2022). The amount of peas consumed will be estimated based on participants' reported daily portions consumed with a portion size of peas weighing 80 g (Services, 2021).

All secondary and sensitivity analyses will follow the adjustment level in model 2 from the main analysis (i.e. all covariates are included except BMI). All analyses will be conducted in R with a significance level of 5%.

Inference criteria

All analyses will be evaluated based on two-sided p-values. Values below 5% are classified as statistically significant. Inference on relevance and significance and the evaluation of, whether a result is meaningful will be based on the size of the estimate, and confidence intervals containing 1 or 0, for ratios or absolute measures respectively.

Data exclusion

Exclusion criteria Only participants with two or more completed Oxford WebQs are eligible for analyses. Participants who had their gallbladder removed or were diagnosed with cholelithiasis or cholecystitis before the last completed Oxford WebQ will be excluded from analyses.

Missing data

Missing data on covariates at baseline will also be a cause for exclusion of participants.

References

References

Belski, R., Mori, T. A., Puddey, I. B., Sipsas, S., Woodman, R. J., Ackland, T. R., Beilin, L. J., Dove, E. R., Carlyon, N. B., Jayaseena, V., & Hodgson, J. M. (2011). Effects of lupin-enriched foods on body composition and cardiovascular disease risk factors: a 12-month randomized controlled weight loss trial. *Int J Obes (Lond)*, *35*(6), 810–819. https://doi.org/10.1038/ijo.2010.213

Biobank, U. (2007). *UK Biobank: Protocol for a large-scale prospective epidemiological resource*. UK Biobank Coordinating Centre. https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf

Biobank, U. (2020). *Hospital inpatient data*. https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=2000

Biobank, U. (2021). *Data-Field 105010*. https://biobank.ndph.ox.ac.uk/crystal/field.cgi?id=105010

Carter, J. L., Lewington, S., Piernas, C., Bradbury, K., Key, T. J., Jebb, S. A., Arnold, M., Bennett, D., & Clarke, R. (2019). Reproducibility of dietary intakes of macronutrients, specific food groups, and dietary patterns in 211 050 adults in the UK Biobank study. *J Nutr Sci*, *8*, e34. https://doi.org/10.1017/jns.2019.31

Cassidy, S., Chau, J. Y., Catt, M., Bauman, A., & Trenell, M. I. (2016). Cross-sectional study of diet, physical activity, television viewing and sleep duration in 233 110 adults from the UK Biobank; the behavioural phenotype of cardiovascular disease and type 2 diabetes. *BMJ Open*, *6*(3). https://doi.org/10.1136/bmjopen-2015-010038

Chavez-Santoscoy, R. A., Gutierrez-Uribe, J. A., Granados, O., Torre-Villalvazo, I., Serna-Saldivar, S. O., Torres, N., Palacios-Gonzalez, B., & Tovar, A. R. (2014). Flavonoids and saponins extracted from black bean (Phaseolus vulgaris L.) seed coats modulate lipid metabolism and biliary cholesterol secretion in C57BL/6 mice. *BRITISH JOURNAL OF NUTRITION*, *112*(6), 886–899. https://doi.org/10.1017/S0007114514001536

Digital, N. (2021a). *National Clinical Coding Standards OPCS-4 (2021) Accurate data for quality information*. https://classbrowser.nhs.uk/ref_books/OPCS-4.9_NCCS-2021.pdf

Digital, N. (2021b). *NHS Data Model and Dictionary International Classification of Diseases (ICD)*. The National Health Service,. https://datadictionary.nhs.uk/supporting_information/international_classification_of_diseases__icd_.html

FAO. (2018). *Dietary Assessment: A resource guide to method selection and application in low ressource settings*. https://www.fao.org/3/i9940en/I9940EN.pdf

Fry, A., Littlejohns, T. J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., & Allen, N. E. (2017). Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am J Epidemiol*, *186*(9), 1026–1034. https://doi.org/10.1093/aje/kwx246

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, N., Key, T. J., Liu, B., Morris, M. A., Mulla, U. Z., Petropoulou, K., Potter, G. D. M., Riboli, E., Young, H., Wark, P. A., & Cade, J. E. (2019). Validation of the Oxford WebQ Online 24-Hour Dietary Questionnaire Using Biomarkers. *Am J Epidemiol*, *188*(10), 1858–1867. https://doi.org/10.1093/aje/kwz165

Ibsen, D. B., & Dahm, C. C. (2022). Food substitutions revisited. *Am J Clin Nutr*, *116*(5), 1195–1198. https://doi.org/10.1093/ajcn/nqac222

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. (2020). Food substitution models for nutritional epidemiology. *Am J Clin Nutr*, *113*(2), 294–303. https://doi.org/10.1093/ajcn/nqaa315

Jayalath, V. H., Souza, R. J. de, Sievenpiper, J. L., Ha, V., Chiavaroli, L., Mirrahimi, A., Di Buono, M., Bernstein, A. M., Leiter, L. A., Kris-Etherton, P. M., Vuksan, V., Beyene, J., Kendall, C. W., & Jenkins, D. J. (2014). Effect of dietary pulses on blood pressure: a systematic review and meta-analysis of controlled feeding trials. *Am J Hypertens*, *27*(1), 56–64. https://doi.org/10.1093/ajh/hpt155

Kelly, R. K., Watling, C. Z., Tong, T. Y. N., Piernas, C., Carter, J. L., Papier, K., Key, T. J., & Perez-Cornago, A. (2021). Associations Between Macronutrients From Different Dietary Sources and Serum Lipids in 24 639 UK Biobank Study Participants. *Arterioscler Thromb Vasc Biol*, *41*(7), 2190–2200. https://doi.org/10.1161/atvbaha.120.315628

Lee, Y. P., Puddey, I. B., & Hodgson, J. M. (2008). Protein, fibre and blood pressure: potential benefit of legumes. *Clin Exp Pharmacol*

Physiol, *35*(4), 473–476. https://doi.org/10.1111/j.1440-1681.2008.04899.x

Li, T., Francl, J. M., Boehme, S., & Chiang, J. Y. L. (2013). Regulation of cholesterol and bile acid homeostasis by the cholesterol 7α-hydroxylase/steroid response element-binding protein 2/microRNA-33a axis in mice. *Hepatology*, *58*(3), 1111–1121. https://doi.org/10.1002/hep.26427

Li, X., & Gao, P. (2019). Fatty liver increases gallstone disease risk in younger Chinese patients. *Medicine (Baltimore)*, *98*(22), e15940. https://doi.org/10.1097/md.0000000000015940

Linlawan, S., Patcharatrakul, T., Somlaw, N., & Gonlachanvit, S. (2019). Effect of Rice, Wheat, and Mung Bean Ingestion on Intestinal Gas Production and Postprandial Gastrointestinal Symptoms in Non-Constipation Irritable Bowel Syndrome Patients. *Nutrients*, *11*(9). https://doi.org/10.3390/nu11092061

Liu, B., Young, H., Crowe, F. L., Benson, V. S., Spencer, E. A., Key, T. J., Appleby, P. N., & Beral, V. (2011). Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. *Public Health Nutr*, *14*(11), 1998–2005. https://doi.org/10.1017/s1368980011000942

Mitchell, D. C., Lawrence, F. R., Hartman, T. J., & Curran, J. M. (2009). Consumption of dry beans, peas, and lentils could improve diet quality in the US population. *J Am Diet Assoc*, *109*(5), 909–913. https://doi.org/10.1016/j.jada.2009.02.029

NHS. (2021). *Gallstones Symptoms*. The National Health Service,. https://www.nhs.uk/conditions/gallstones/symptoms/

Papanikolaou, Y., & Fulgoni, 3., V. L. (2008). Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight, and a smaller waist circumference in adults: results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*, *27*(5), 569–576. https://doi.org/10.1080/07315724.2008.10719740

Perez-Cornago, A., Pollard, Z., Young, H., Uden, M. van, Andrews, C., Piernas, C., Key, T. J., Mulligan, A., & Lentjes, M. (2021). Description of the updated nutrition calculation of the Oxford WebQ questionnaire and comparison with the previous version among 207,144 participants in UK Biobank. *Eur J Nutr*, *60*(7), 4019–4030. https://doi.org/10.1007/s00394-021-02558-4

Services, U. N. H. (2021). *5 A Day: what counts?*. UK NHS. https://www.nhs.uk/live-well/eat-well/5-a-day/5-a-day-what-counts/

Services, U. N. H. (2022). *5 A Day portion sizes*. UK NHS. https://www.nhs.uk/live-well/eat-well/5-a-day/portion-sizes/

Sievenpiper, J. L., Kendall, C. W., Esfahani, A., Wong, J. M., Carleton, A. J., Jiang, H. Y., Bazinet, R. P., Vidgen, E., & Jenkins, D. J. (2009). Effect of non-oil-seed pulses on glycaemic control: a systematic review and meta-analysis of randomised controlled experimental trials in people with and without diabetes. *Diabetologia*, *52*(8), 1479–1495. https://doi.org/10.1007/s00125-009-1395-7

Springmann, M., Spajic, L., Clark, M. A., Poore, J., Herforth, A., Webb, P., Rayner, M., & Scarborough, P. (2020). The healthiness and sustainability of national and global food based dietary guidelines: modelling study. *BMJ*, *370*, m2322. https://doi.org/https://doi.org/10.1136/bmj.m2322

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., Liu, B., Matthews, P., Ong, G., Pell, J., Silman, A., Young, A., Sprosen, T., Peakman, T., & Collins, R. (2015). UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *Plos Med*, *12*(3), e1001779. https://doi.org/10.1371/journal.pmed.1001779

Sun, Y., Yang, S., Dai, W., Zheng, Z., Zhang, X., Zheng, Y., Wang, J., Bi, S., Duan, Y., Wu, S., & Kong, J. (2023). Causal association between serum total bilirubin and cholelithiasis: a bidirectional two-sample Mendelian randomization study. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1178486

Willett, W., Rockström, J., Loken, B., Springmann, M., Lang, T., Vermeulen, S., Garnett, T., Tilman, D., DeClerck, F., Wood, A., Jonell, M., Clark, M., Gordon, L. J., Fanzo, J., Hawkes, C., Zurayk, R., Rivera, J. A., De Vries, W., Majele Sibanda, L., … Murray, C. J. L. (2019). Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet*, *393*(10170), 447–492. https://doi.org/10.1016/s0140-6736(18)31788-4