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Vegetarian diet as a risk factor for symptomatic gallstone disease

Running head

Vegetarian diet and risk of gallstone disease

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Support

Supported by the UK Medical Research Council MR/M012190/1 and Cancer Research UK 570/A16491.

Abbreviations

BMI, Body Mass Index; EPIC, European Prospective Investigation into Cancer and Nutrition; HES, Hospital Episode Statistics; HR, Hazard Ratio; HRT, Hormone Replacement Therapy; ICD, International Classification of Diseases; NHS, National Health Service; PEDW, Patient Episode Database for Wales; SMR, Scottish Morbidity Records.

Acknowledgements

We thank all the participants in the EPIC-Oxford cohort for their invaluable contribution to the study.

Conflicts of interest

Tim Key is a member of the Vegetarian Society

25 Thomas McConnell and Paul Appleby have no conflict of interests to declare

ABSTRACT

Background: Previous small studies have shown either no difference or a lower risk of symptomatic gallstone disease in vegetarians than in non-vegetarians.

Objectives: This study examined the incidence of symptomatic gallstone disease in a cohort of British vegetarians and non-vegetarians, and investigated the associations between nutrient intake and risk of symptomatic gallstone disease.

Subjects/Methods: Data were analysed from 49,652 adults enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study, one third of whom were vegetarian. Linked databases of hospital records were used to identify incident cases. Risk by diet group was estimated using Cox proportional hazards models. Further analysis quantified risk by intakes of selected macronutrients.

Results: There were 1,182 cases of symptomatic gallstone disease during 687,822 person years of follow-up (mean=13.85 years). There was a large significant association between increasing body mass index (BMI) and risk of developing symptomatic gallstone disease (overall trend $p<0.001$). After adjustment for BMI and other risk factors vegetarians had a moderately increased risk compared with non-vegetarians (HR 1.22; 95% CI 1.06-1.41; $p=0.006$). Although starch consumption was positively associated with gallstones risk ($p=0.002$ for trend) it did not explain the increased risk in vegetarians.

Conclusion: There is a highly significant association of increased BMI with risk of symptomatic gallstone disease. After adjusting for BMI there is a small but statistically significant positive association between vegetarian diet and symptomatic gallstone disease.

INTRODUCTION

Those consuming a vegetarian diet (containing no meat or fish) in the United Kingdom have been shown to consume more fibre, less fat and have a lower BMI¹; factors associated with lower rates of gallstone disease in previous large prospective cohort studies²⁻¹³. Therefore, it might be expected that vegetarian diets would have a protective effect for gallstone disease. Three previous studies have explored this topic and found either a protective association or no association but they have been limited by small sample size and a cross-sectional study design¹⁴⁻¹⁶. A recent cross-sectional study of Taiwanese vegetarians demonstrated a strong association between BMI and gallstone disease, with alcohol intake a significant risk factor in women¹⁷.

The objective of this study was to examine the incidence of developing symptomatic gallstone disease in a cohort of British vegetarians and non-vegetarians, and to investigate the associations between diet group, nutrient intake and gallstones risk.

MATERIALS & METHODS

Study population

The Oxford component of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford) comprises 65,411 participants throughout the UK. Recruitment was through general practices in Oxfordshire, Buckinghamshire and Greater Manchester, as well as postal recruitment of health conscious people through magazine advertisements, vegetarian and vegan societies, and snowballing techniques. Participants completed a baseline questionnaire detailing diet and past medical history amongst other factors¹. The protocol was approved by a Multicentre Research Ethics Committee, and all participants provided written informed consent.

Assessment of diet and lifestyle variables

Participants provided information about their dietary intake of 130 different food items over the previous 12 months using a validated semi-quantitative food frequency questionnaire¹⁸. Participants were also asked if they ate meat, fish, eggs or dairy products, and, where appropriate, the ages at which they stopped eating these foods, and were categorized as vegetarian if they did not eat meat or fish at the time of questionnaire response. Length of time as a vegetarian was estimated from the age at which the participant last reported eating meat or fish. Measured or self-reported height and weight were used to calculate BMI. Smoking was categorised as never smoker, former smoker, light smoker (all current smokers except those smoking ≥ 15 cigarettes/day) or heavy smoker (current smokers of ≥ 15 cigarettes/day). Alcohol consumption was categorized in terms of grams of ethanol per day (<1 , 1-7, 8-15 or 16g/day). Educational attainment was classified as some secondary school, higher secondary school, or university degree or equivalent, and an index of deprivation¹⁹ was calculated and grouped into quartiles. Participants were also asked to report if they were

receiving treatment for any long term medical condition at recruitment. An “unknown” category was added for variables with missing or incomplete information.

Data treatment

Incidence of symptomatic gallstones was determined through health record linkage. Hospital Episode Statistics for England (HES) and Wales (PEDW) and Scottish Morbidity Records (SMR) were sought for each participant. These databases recorded diagnosis and procedure codes for day case and inpatient treatment in hospital using International Classification of Diseases 9th edition (ICD-9) or ICD-10 codes.

The baseline data were combined with the HES/PEDW/SMR data and 934 participants who were not resident in England, Scotland or Wales or were untraceable were excluded.

Participants who only completed an initial assessment and not the detailed dietary and lifestyle questionnaire (n=7,629) were excluded. Fifty-nine participants who were below the age of 20 or over the age of 90 at recruitment were also excluded, as were participants with no follow up (n=380), prevalent malignant cancers except non-melanoma skin cancer (n=1382) or self-reported prior malignant cancer (n=585). Participants with unknown smoking status were also excluded (n=293) as were those with either unknown diet group or unreliable dietary data (n=1227), or self-reported prior gallstones (n=1542). Participants with unknown BMI were also excluded (n=1719) as well as those with an incident gallstones diagnosis preceding recruitment (n=9). Thirteen participants diagnosed after their 90th birthday were censored at age 90 and treated as non-cases. This resulted in data from 49,652 participants being included in the analysis.

Outcome

Cases were participants with an incident symptomatic gallstone disease diagnosis defined according to ICD-9 codes 574, 575.0 and 575.1 and the equivalent ICD-10 codes K80 and K81.

Statistical analysis

Person years were calculated from the latest of the date of recruitment or the beginning of hospital records data according to the participant's country of residence until the date of first hospital diagnosis of symptomatic gallstone disease, death, emigration or other loss to follow-up, or end of the follow-up period, whichever occurred first. Hazard ratios (HR) with 95% confidence intervals were calculated using Cox proportional hazards regression with an underlying time variable of age. All analyses were stratified by sex, method of recruitment, and region of residence, and adjustment was made for smoking, alcohol intake, education level, Townsend deprivation index, long-term medical treatment for any condition and HRT use in women. Chi-square likelihood test statistics were used to assess the differences in risk. Further analyses were additionally adjusted for BMI categorised as <18.5, 18.5-20.4, 20.5-22.4, 22.5-24.4, 24.5-26.4, 26.5-28.4, 28.5-30.4, 30.5-34.9 and ≥ 35 kg/m². Additional analysis was carried out for risk by sex specific fifths of intake of selected macronutrients, further adjusted for energy intake where appropriate. Subgroup analyses were conducted with the cases subdivided by gender and categories of BMI, age at recruitment, smoking status, education level and long term medical treatment for any condition. Statistical analysis was conducted using STATA statistical software release 13 (StataCorp, College Station, TX, USA). Two-sided p values <0.05 were considered statistically significant.

RESULTS

There were 1,182 cases of symptomatic gallstone disease during 687,822 person years of follow-up (mean=13.85 years). The distribution of diagnostic codes is shown in Table 1, with a mixture of diagnoses with and without cholecystitis.

Women made up 77% of participants, and 33% of participants were vegetarians (Table 2).

Non-vegetarians were older on average than vegetarians, and non-vegetarian men and women both had higher mean BMI and alcohol consumption than vegetarian men and women.

Physical activity was greater in vegetarian men and to a lesser extent in vegetarian women than in non-vegetarians. Around two thirds of vegetarians had followed a vegetarian diet for more than five years at recruitment, and around 85% were still vegetarian at follow up approximately 5 years later. Just over 2% of non-vegetarians had become vegetarians at follow up. Prevalence of self-reported hypertension, hyperlipidaemia, diabetes and use of long term medication was lower in vegetarians. Non-vegetarian women were more likely to have used HRT and less likely to have used oral contraceptives. Use of dietary supplements was more common in women than men but similar for vegetarians and non-vegetarians.

BMI had a large, highly significant association with gallstone risk (Figure 1). After adjusting for smoking, alcohol intake, education level, Townsend deprivation index, long-term medical treatment and HRT use in women and stratifying by sex, method of recruitment and region of residence, there was no significant difference in gallstones risk for vegetarians vs non-vegetarians. When further adjustment was made for BMI a significant difference emerged with a hazard ratio of 1.22 (95% CI 1.06-1.41, $p=0.006$) for vegetarians compared with non-vegetarians (Table 3).

Further analysis of gallstone risk by sex-specific fifths of nutrient intake stratified and adjusted for the same variables reported above including BMI and sex-specific fifths of

energy intake showed a significant increased risk with consumption of starch (HR 1.37; 95% CI 1.13-1.66 in the highest compared with the lowest fifth of intake, $p=0.002$ for trend; Table 4). A similar but non-significant trend was found for added sugars (highest vs. lowest fifth HR 1.18; 95% CI 0.98-1.43, $p=0.059$) and total carbohydrate (highest vs. lowest fifth HR 1.19; 95% CI 0.98-1.45, $p=0.098$). A small but significant trend was found in the reverse direction for intrinsic sugars (highest vs. lowest fifth HR 0.86; 0.71-1.04, $p=0.041$). Further analysis did not reveal any of these variables to be intermediates for the effect of vegetarian diet (data not presented). No significant associations were found between intakes of energy, fat, cholesterol, protein or fibre and gallstones risk.

Subgroups analyses (Table 5) did not reveal any significant heterogeneity in risks for vegetarians compared with non-vegetarians in different subsets of participants defined by gender, BMI, age at entry, smoking status, education level and long-term medical treatment.

DISCUSSION

In this study of nearly 50,000 individuals followed up for a mean of just under 14 years there were more than 1,000 new cases of symptomatic gallstones. Adjusting for known risk factors including BMI a significantly higher risk for symptomatic gallstone disease was found in vegetarians compared to non-vegetarians. Examination of macronutrient intakes and gallstone risk revealed a link with carbohydrates and, in particular, starch; however, this did not account for the difference in risk between vegetarians and non-vegetarians.

Previous studies in Western populations exploring the effect of vegetarian diet have been limited by small sample sizes and cross-sectional study design. Pixley et al.¹⁶ found a significantly lower prevalence of gallstones on ultrasound scan amongst vegetarian women but the study was limited by a small sample size (15 cases in vegetarians). Walcher et al. conducted a cross-sectional study of gallstone prevalence and self-reported vegetarian diet in 2,417 individuals¹⁵. No association was found and the study was limited by the small number of cases in vegetarians (n=4). Studies in non-European or North American populations have not as yet shown any conclusive relationship between vegetarian diet and gallstone risk²⁰⁻²². Our results suggest that a vegetarian diet has no protective association with risk for symptomatic gallstones and, indeed, may confer a modest increase in risk once the relatively low BMI of vegetarians is taken into account.

Previous studies by Tsai et al.⁵ have provided strong evidence of a link between carbohydrate consumption and gallstone disease. Our findings suggest that starch may be a key macronutrient in determining gallstone risk, although this finding did not explain the increased risk for vegetarians. CCK is the dominant gastrointestinal polypeptide involved in gallbladder contraction²³ and is poorly stimulated by carbohydrates but better stimulated by fats²⁴. Higher levels of stimulation related to higher carbohydrate consumption resulting in less gallbladder stasis may explain this finding. Another large prospective cohort study found

a significant protective association with higher vegetable protein and a small and non-significant trend towards increased risk with higher meat consumption². Other studies have shown significantly higher risk of gallstones in those consuming low amounts of both poly- and mono-unsaturated fat and higher risk amongst those consuming higher amounts of saturated and trans-fats^{3, 6, 25}. No corresponding associations were found in this study.

BMI in our study was also found to be strongly associated with an increased risk of symptomatic gallstone disease. BMI has previously been reported to be a significant risk factor for gallstone development^{26, 27} with a recent large combined cohort and meta-analysis also demonstrating a significant association²⁸. A limitation of BMI is that it is only a proxy of body composition and relative obesity. Future work could explore the association of symptomatic gallstones with body composition rather than just BMI.

There does not appear to be a protective association with vegetarian diet and risk of symptomatic gallstone disease and instead the risk among vegetarians appears to be slightly increased. The modest positive association after adjustment for BMI found in this study is not explained by differences in consumption of a selection of macronutrients. Future work could explore whether a similar association is found in other large prospective cohort studies. The key public health message is the importance of maintaining a healthy weight in reducing the risk of symptomatic gallstone disease.

208 **Support**

209 Supported by the UK Medical Research Council MR/M012190/1 and Cancer Research UK
210 570/A16491.

211 **Acknowledgements**

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Figure Legends

Figure 1. Hazard ratios for symptomatic gallstones by BMI for vegetarians and non-vegetarians in the EPIC-Oxford study