European Journal of Clinical Nutrition (2017), 1–5

www.nature.com/ejcn

ORIGINAL ARTICLE

Vegetarian diet as a risk factor for symptomatic gallstone disease

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BACKGROUND/OBJECTIVES: Previous small studies have shown either no difference or a lower risk of symptomatic gallstone disease in vegetarians than in non-vegetarians. 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: The data were analysed from 49 652 adults enroled in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study, one-third of whom were vegetarian. The 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 1182 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.
CONCLUSIONS: 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.

European Journal of Clinical Nutrition advance online publication, 8 March 2017; doi:10.1038/ejcn.2016.252

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 BMI[1]—factors associated with lower rates of gallstone disease in previous large prospective cohort studies.[2–13] 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 design.[14–16] 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 women.[17]

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 AND METHODS

Study population

The Oxford component of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford) comprises 65 411 participants throughout the United Kingdom. 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 factors.[1] 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 questionnaire.[18] Participants were also asked whether they ate meat, fish, eggs or dairy products, and, where appropriate, the ages at which they stopped eating these foods, and were categorised 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 $\geqslant 15$ cigarettes per day) or heavy smoker (current smokers of $\geqslant 15$ cigarettes per day). Alcohol consumption was categorised in terms of grams of ethanol per day (< 1, 1–7, 8–15 or 16 g per day). Educational attainment was classified as some secondary school, higher secondary school, or university degree or equivalent, and an index of deprivation[19] 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

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Received 10 March 2016; revised 9 October 2016; accepted 6 November 2016

($n = 7629$) 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 the 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 ninetieth birthday were censored at age 90 and treated as non-cases. This resulted in the data from 49 652 participants being included in the analysis.

Table 1. Number of cases by diagnostic code

ICD code	*Description*	*Cases*
574.1	Calculus of gallbladder with other cholecystitis	1
574.2	Calculus of gallbladder without mention of cholecystitis	5
K80.0	Calculus of gallbladder with acute cholecystitis	72
K80.1	Calculus of gallbladder with other cholecystitis	226
K80.2	Calculus of gallbladder without cholecystitis	585
K80.3	Calculus of bile duct with cholangitis	10
K80.4	Calculus of bile duct with cholecystitis	4
K80.5	Calculus of bile duct without cholangitis or cholecystitis	110
K80.8	Other cholelithiasis	6
K81.0	Acute cholecystitis	48
K81.1	Chronic cholecystitis	63
K81.9	Cholecystitis, unspecified	52

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

Table 2. Lifestyle and dietary characteristics of participants by gender and vegetarian status

	Men (n = *11 592*)		*Women* (n = *38 060*)	
	Non-vegetarian (n = *7545*)	*Vegetarian* (n = *4047*)	*Non-vegetarian* (n = *25 931*)	*Vegetarian* (n = *12 129*)
Age (y)	50.5 (13.7)	42.3 (13.7)	46.9 (13.2)	38.6 (13.0)
BMI (kg/m^2)	24.6 (3.3)	23.3 (3.2)	23.9 (4.0)	22.6 (3.4)
Alcohol consumption (g per day)	16.4 (18.1)	13.9 (17.8)	8.1 (9.9)	7.7 (10.1)
Current smoker (%)	14.4	11.4	11.2	9.8
Physically active (%)[a]	74.6	80.6	74.9	79.2
University degree (%)[a]	44.5	49.9	32.3	41
Richest quartile (%)[a]	27.9	20.4	25.8	21.4
Self-reported prior diabetes (%)[a]	2.5	1.2	1.5	0.5
Self-reported prior hypertension (%)[a]	14.1	6.9	13.1	6.5
Self-reported prior hyperlipidaemia (%)[a]	10.8	3.2	6.5	2.3
Long-term use of medication (%)[a]	28.5	18.2	28.3	19.8
Use of oral contraceptives (%)[a]	—	—	73.5	78.8
Use of hormone replacement therapy (%)[a]	—	—	22.4	7.6
Regular use of dietary supplements (%)[a]	44.2	44.3	60.8	60
Dietary characteristics				
Vegetarian for more than 5 years at recruitment (%)	—	68.2	—	66.3
Non-vegetarian at follow-up (%)[a]	97.4	10.4	97.5	16.3
Vegetarian at follow-up (%)[a]	2.6	89.6	2.5	83.7
Meat intake (g per day)	70.9 (58.7)	—	58.0 (51.9)	—
Fish intake (g per day)	41.2 (30.9)	—	41.4 (30.1)	—
Dairy milk intake (g per day)[a]	343 (202)	234 (235)	306 (182)	233 (198)
Cheese (g per day)	19.9 (17.8)	24.3 (25.1)	22.8 (20.7)	27.7 (25.6)
Fresh fruit (g per day)	225 (190)	258 (227)	281 (214)	293 (244)
Fresh vegetables (g per day)	231 (124)	276 (147)	266 (139)	300 (169)
Energy (MJ/d)	9.13 (2.46)	8.67 (2.41)	7.95 (2.11)	7.54 (2.10)
Total fat (%E)	31.7 (5.8)	30.6 (6.4)	31.3 (6.0)	30.1 (6.7)
Saturated fat (%E)	11.6 (3.3)	10.0 (3.6)	11.2 (3.3)	10.2 (3.5)
Monounsaturated fat (%E)	10.8 (2.3)	9.9 (2.6)	10.4 (2.3)	9.6 (2.7)
Polyunsaturated fat (%E)	6.3 (2.0)	7.4 (2.6)	6.5 (2.0)	7.0 (2.5)
Protein (%E)	15.6 (2.8)	13.0 (2.0)	16.7 (3.0)	13.8 (2.1)
Carbohydrate (%E)	47.4 (6.6)	51.8 (7.0)	49.0 (6.3)	53.2 (6.7)
Total sugars (%E)	23.3 (5.5)	23.9 (6.4)	24.7 (5.9)	25.8 (6.6)
Added sugars (%E)	9.7 (4.7)	8.9 (4.7)	8.2 (4.5)	8.3 (4.6)
Intrinsic sugars (%E)	13.6 (5.3)	15.0 (6.5)	16.5 (6.0)	17.4 (6.8)
Starch (%E)	24.1 (5.1)	27.9 (5.8)	24.2 (4.9)	27.4 (5.5)

Abbreviation: BMI, body mas index. Values are mean (s.d.) except where indicated. %E denotes percentage of energy intake. [a]Unknown for some participants (percentages are calculated after excluding participants with unknown values.

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. X^2 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 $\geqslant 35$ kg/m^2. 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 1182 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 had. 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 5 years at recruitment, and around 85% were still vegetarian at follow-up ~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 in 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 nonsignificant 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; 95% CI: 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.

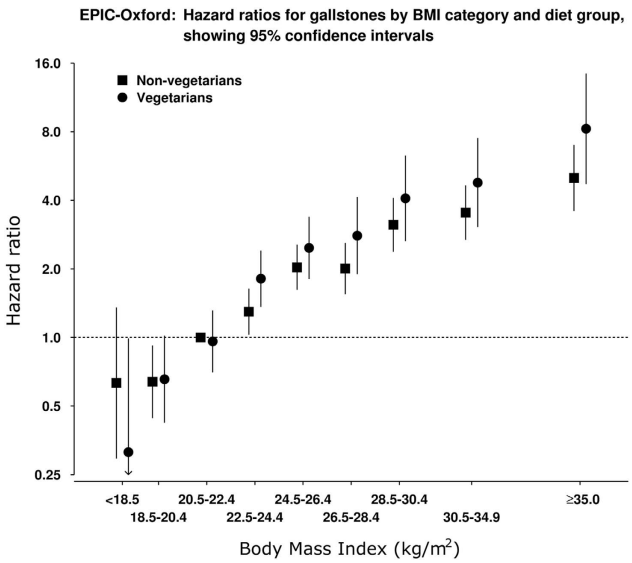

Figure 1. Hazard ratios for symptomatic gallstones by BMI for vegetarians and non-vegetarians in the EPIC-Oxford study.

Table 3. Risk of symptomatic gallstone disease in vegetarians compared with non-vegetarians in the EPIC-Oxford study[a]

	No. of cases	*HR (95% CI)*	
		Model 1[b]	*Model 2*[c]
Non-vegetarian	865	1	1
Vegetarian	317	1.08 (0.94–1.24)	1.22 (1.06–1.41)
P-*value*[d]		0.291	0.006

[a]EPIC, European Prospective Investigation into Cancer and Nutrition. [b]Analysis stratified by sex, method of recruitment and region of residence and adjusted for smoking, alcohol intake, education level, Townsend deprivation index, long-term medical treatment and HRT use in women [c]Analysis further adjusted for BMI. [d]*P* value for difference in risk calculated using a X^2 test.

DISCUSSION

In this study of nearly 50 000 individuals followed-up for a mean of just under 14 years, there were more than 1000 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 with that in 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.*[15] conducted a cross-sectional study of gallstone prevalence and self-reported vegetarian diet in 2417 individuals. 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

Table 4. Gallstone risk by sex-specific quintile of intake for selected macronutrients

	Hazard ratio[a] *by quintile of intake (95% CI)*					P *for trend*[b]
	Lowest	*2*	*3*	*4*	*Highest*	
Energy (kJ)	1.00	0.99 (0.83–1.19)	0.94 (0.78–1.13)	1.01 (0.84–1.21)	0.97 (0.81–1.16)	0.888
Fat (%E)	1.00	0.92 (0.77–1.11)	1.03 (0.86–1.23)	0.98 (0.81–1.18)	0.85 (0.70–1.03)	0.22
SFA (%E)	1.00	0.87 (0.72–1.05)	1.05 (0.88–1.26)	0.95 (0.79–1.15)	0.90 (0.75–1.09)	0.511
MUFA (%E)	1.00	0.94 (0.78–1.13)	0.95 (0.79–1.14)	0.99 (0.83–1.20)	0.85 (0.70–1.03)	0.194
PUFA (%E)	1.00	1.07 (0.90–1.28)	0.89 (0.74–1.07)	0.98 (0.81–1.17)	1.02 (0.85–1.22)	0.873
Cholesterol (mg)	1.00	0.89 (0.73–1.09)	0.88 (0.72–1.07)	0.83 (0.67–1.02)	0.87 (0.70–1.09)	0.341
Protein (%E)	1.00	0.98 (0.80–1.21)	1.04 (0.85–1.27)	0.98 (0.80–1.20)	1.01 (0.83–1.23)	0.919
Carbohydrates (%E)	1.00	1.13 (0.94–1.35)	1.06 (0.87–1.28)	1.15 (0.95–1.39)	1.19 (0.98–1.45)	0.098
Total sugars (%E)	1.00	1.07 (0.89–1.29)	1.28 (1.07–1.54)	1.11 (0.92–1.34)	0.96 (0.79–1.17)	0.639
Added sugars (%E)	1.00	1.08 (0.89–1.30)	1.01 (0.83–1.22)	1.14 (0.94–1.37)	1.18 (0.98–1.43)	0.059
Intrinsic sugars (%E)	1.00	1.01 (0.84–1.20)	0.90 (0.75–1.09)	0.84 (0.70–1.02)	0.86 (0.71–1.04)	0.041
Starch (%E)	1.00	1.13 (0.95–1.35)	1.13 (0.94–1.36)	1.15 (0.95–1.38)	1.37 (1.13–1.66)	0.002
Fibre (g)	1.00	0.97 (0.81–1.17)	1.06 (0.88–1.28)	0.99 (0.81–1.21)	1.00 (0.80–1.24)	0.983

Abbreviations: CI, confidence interval; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid. [a]Stratified by sex, method of recruitment and region of residence, and adjusted for smoking, BMI, alcohol intake, education level, Townsend deprivation index, long-term medical treatment, HRT use in women and, where appropriate, sex-specific quintile of energy intake. [b]Trend tests were performed by replacing the categorical intake variable with a continuous variable equal to the median intake within each sex-specific quintile.

Table 5. Risk of gallstones for vegetarians compared with non-vegetarians in selected subgroups

Subgroup	*Number of cases*	*HR*[a] *(95% CI)*	*Test for heterogeneity*
Overall	*1182*	*1.22 (1.06, 1.41)*	
Sex			
Men	176	0.96 (0.66, 1.41)	
Women	1006	1.27 (1.09, 1.48)	$\chi^2_1 = 0.54$; $P = 0.463$
Body mass index			
< 25 kg/m^2	562	1.23 (1.02, 1.50)	
25–29 kg/m^2	412	1.24 (0.96, 1.60)	
$\geqslant 30$ kg/m^2	208	1.21 (0.84, 1.75)	$\chi^2_2 = 1.90$; $P = 0.387$
Age at recruitment			
< 50 years	583	1.30 (1.09, 1.55)	
$\geqslant 50$ years	599	1.07 (0.84, 1.36)	$\chi^2_1 = 1.00$; $P = 0.317$
Smoking status			
Never	641	1.24 (1.03, 1.50)	
Former	382	1.34 (1.04, 1.72)	
Current	159	1.02 (0.65, 1.59)	$\chi^2_2 = 0.87$; $P = 0.648$
Education level			
CSE/O-level or lower	518	1.22 (0.97, 1.54)	
HNC/A-level	274	1.39 (1.05, 1.83)	
Degree	268	1.23 (0.94, 1.61)	$\chi^2_2 = 0.59$; $P = 0.745$
Receiving long-term medical treatment			
No	696	1.25 (1.05, 1.48)	
Yes	376	1.18 (0.91, 1.53)	$\chi^2_1 = 0.08$; $P = 0.776$

[a]Hazard ratios are stratified by sex, method of recruitment and region of residence and adjusted for smoking, BMI, alcohol intake, education level, Townsend deprivation index, long-term medical treatment and HRT use in women.

any conclusive relationship between vegetarian diet and gallstone risk.[20–22] 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 contraction[23] and is poorly stimulated by carbohydrates but better stimulated by fats.[24] Lower levels of stimulation related to lower fat consumption resulting in increased gallbladder stasis may explain this finding. Another large prospective cohort study found a significant protective association with higher vegetable protein and a small and nonsignificant trend towards increased risk with higher meat consumption.[2] Other studies have shown significantly higher risk of gallstones in those consuming low amounts of both poly- and monounsaturated 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 association.[28] 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.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank all the participants in the EPIC-Oxford cohort for their invaluable contribution to the study. This work is supported by the UK Medical Research Council MR/M012190/1 and Cancer Research UK 570/A16491.

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