

Dietary intake and gallbladder disease: a review

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Abstract

Objective: Dietary intake has long been looked upon as a potentially modifiable risk factor for gallbladder disease (GBD), here defined as either having gallstones or having had surgery for gallstones. This paper reviews the epidemiological evidence for an association between dietary intake and GBD, focusing on six dietary factors that have received the most attention in studies in this area: energy intake, fatty acids, cholesterol, carbohydrates and fibre, calcium and alcohol. The objectives of this review are to evaluate the potential usefulness of altering the diet to prevent GBD and to consider future research in this area.

Design: We reviewed all English-language epidemiological studies on diet and cholelithiasis that were cross-sectional, cohort or case–control in design and that were indexed in the Medline database from 1966 to October 1997.

Results: A positive association was suggested with simple sugars and inverse associations with dietary fibre and alcohol. No convincing evidence was found for a role for energy intake or intake of fat or cholesterol. Variable means of ascertaining cases and inaccurate measurement of dietary intake may contribute to variation in results across studies.

Conclusions: Some specific components of the diet that may affect GBD include simple sugars, fibre and alcohol, but whether risk for GBD can be reduced by altering intake of a specific dietary factor has not been established. Although no specific dietary recommendations can be made to reduce risk of GBD *per se*, a ‘healthy’ diet aimed at reducing risk of other diseases might be expected to reduce risk for GBD as well.

Keywords
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Gallbladder disease is an exceptionally common source of morbidity in the United States, where an estimated 20 million people either have gallstones or have had surgery for gallstones¹. While most cases are asymptomatic, over 500 000 cholecystectomies are performed annually, and over 800 000 people are hospitalized because of gallstones, resulting in an annual cost of over US\$5 billion¹. The most common manifestation of gallstones is biliary pain, but serious complications including gallbladder inflammation, pancreatitis and bile duct obstruction may result. Gallstones may also contribute to the development of gallbladder cancer¹. Given the prevalence of the disease, measures towards preventing GBD could potentially lessen a large public health burden.

Diet has long been suspected as a modifiable risk factor for GBD, primarily because of indirect evidence from ecological studies and because of its link with obesity. Following a brief discussion of aetiology, this paper will discuss some methodological issues pertinent to studies on dietary intake and GBD and

review the epidemiological evidence for an association between the two. Here, GBD is defined as either having gallstones or having had surgery for gallstones. The objectives of this review are to identify possible dietary measures to prevent GBD, and to make recommendations for future research in this area.

The studies we reviewed were identified by searching the Medline database from 1966 to October 1997; the key search terms were ‘cholelithiasis’ and ‘diet’. Additional studies on diet and GBD were identified from the reference lists of articles identified from our Medline search or other review articles^{1–3}. Our criteria for including studies in this review were: (i) language of the article had to be English; (ii) studies had to be case–control, cohort, or cross-sectional in design; (iii) the study outcome had to be incident or prevalent cholelithiasis, including gallstones, cholecystectomy, or both; and (iv) the study ‘exposure’ had to be dietary intake. Other aspects related to diet and known to be related to GBD such as weight loss⁴ or total parenteral nutrition^{5–7} were not considered, and

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studies on gallstone recurrence were also not included. In addition, although most studies do not distinguish among the different types of gallstones, conclusions from this review are presumed to apply to cholesterol stones, the more common type found in western and developed countries². Finally, our review focuses on studies on humans or human populations. Although extensive research on gallstones has been conducted in animal models, no other animal besides the human is known to spontaneously develop cholesterol gallstones⁸; thus, while animal models may offer information on specific aspects of the lithogenic process, their findings are not considered here.

Pathogenesis

Gallstones are solid masses that form in the gallbladder from cholesterol, bilirubin and calcium salts precipitated from the bile. The large majority of gallstones in western countries have cholesterol as their primary constituent, whereas a much smaller number are composed primarily of calcium salts of bilirubin and phosphate⁹. Three essential pathogenetic conditions precede the occurrence of cholesterol gallstones: lithogenic bile, gallbladder stasis and short nucleation time¹.

Lithogenicity of the bile is determined by the relative concentrations of the three main components of bile; these are bile acids, phospholipids and cholesterol. Generally, lithogenic bile occurs with disruption of cholesterol homeostasis, leading to increased cholesterol secretion and subsequent cholesterol supersaturation of the bile^{10,11}. Gallbladder stasis increases the opportunity for supersaturated bile concentrated in the gallbladder to form gallstones. Gallbladder stasis results when motility of the gallbladder is altered, leading to incomplete emptying of bile, increased fasting and residual volume of the gallbladder, and formation of biliary sludge, which enhances adherence of cholesterol crystals to form cholesterol gallstones^{11–14}. Both supersaturated bile and sludge occur normally but often disappear without subsequent problems. However, a critical determinant of the formation of gallstones appears to be the activity of pronucleating and antinucleating factors which promote or inhibit cholesterol precipitation in supersaturated bile and, hence, affect nucleation time¹; a difference in nucleation time appears to be a major discriminant between people with and without gallstones¹⁴. While lithogenic bile, gallbladder stasis and short nucleation time are often discussed separately, the three are not independent of each other¹².

Issues relevant to studies on diet and GBD

Numerous studies have been published on diet and GBD, but whether or not altering dietary intake can

alter disease risk has not been established. Two specific issues may contribute to the overall inconclusiveness of findings: problems in disease definition and ascertainment, and difficulties in measuring dietary intake. A discussion of these issues may provide background knowledge with which to evaluate studies on diet and GBD.

Disease definition and ascertainment

Disease definition and ascertainment in studies on GBD are particularly problematic because as many as two-thirds of cases with gallstones are asymptomatic or silent¹⁵. Generally, asymptomatic cases can be identified only in screening studies, which use one of two primary techniques to detect the presence of gallstones: oral cholecystography and ultrasonography. In oral cholecystography, a contrast agent is administered to ensure opacification and radiographic visualization of the gallbladder. In ultrasonography, gallstones are detected as opacities in the gallbladder that reflect the ultrasound beam, produce a distal shadow and move with change in the individual's position, demonstrating the higher specific gravity of stones relative to bile¹⁶. Because of its non-invasiveness as well as its relative convenience, ultrasonography has become the standard method used to detect gallstones.

Since cholecystectomy is the most common procedure for treating gallstones, individuals who have undergone cholecystectomy, or surgical removal of the gallbladder, are also commonly included as gallstone cases and presumably represent cases with symptomatic gallstones. Non-screening studies, which include most case–control and prospective cohort studies, primarily identify clinically diagnosed, symptomatic cases, usually through hospital records or self-report. Unless gallstones are confirmed by oral cholecystography or ultrasonography, however, clinically diagnosed cases may include individuals with conditions that mimic gallstone symptoms or who underwent surgery for other reasons, such as acalculous cholecystitis. Identification of cases through hospital records or self-report may also produce some detection bias if individuals with certain characteristics are more likely to be ascertained.

Depending on how disease was defined and cases were ascertained, findings from a given study may apply either to development of gallstones or more specifically to development of symptom-associated gallstones. If the former is of interest, complete screening is needed to identify all cases of gallstones, including those without symptoms. If the latter is of interest, then gallstones should be confirmed in the cases identified.

Distinguishing between factors contributing to gallstone formation and factors contributing to development

of symptoms requires making two comparisons: symptomatic gallstone cases with silent gallstone cases, and silent gallstone cases with non-cases. Comparing the findings of screening and non-screening studies may also help distinguish the two types of factors because screening studies are weighed more heavily towards silent gallstone cases, while non-screening studies would include primarily symptomatic cases. Inconsistent results and the potential for other types of biases, however, make such a comparison difficult. Hence, the relative contributions of risk factors in development and progression of the disease remain unclear.

The problem of disease ascertainment is exacerbated by disease heterogeneity. Studies are generally unable to distinguish between cholesterol and pigment stones although the two have distinctly different aetiologies and risk factors¹⁷. However, because cholesterol stones are the more common type of gallstones in western countries², most of our knowledge of the aetiology and epidemiology of gallstones applies specifically to cholesterol stones.

Measurement of dietary intake

A second limitation of studies on diet and GBD involves measurement of dietary intake. Measurement of intake is problematic in general given the difficulties involved in accurately recalling past diet. Categorizing individuals based on information from a 24-hour recall may also have led to substantial misclassification in some studies since the reported intake was unlikely to be representative of usual intake.

In addition, the relevant period of aetiological interest is unknown. In research using environmental carbon-14 to date gallstones, the average growth rate of gallstones was found to be 2.6 mm year⁻¹ for both asymptomatic and symptomatic cases, and the average latency period between gallstone formation and symptom development was almost 12 years; however, these analyses were based on only 15 cases¹⁸. In general, the appropriate risk period of interest is unknown, and dietary exposures in previous studies may not have been measured for the appropriate period.

While the issues discussed above may make it harder to detect associations, other biases may lead to observation of spurious associations. In studies in which diet was assessed after disease diagnosis, case responses may have been biased, leading to inflated measures of association for some dietary factors. Cases may also have altered their diets as a result of symptoms or disease diagnosis, leading to 'protopathic bias'¹⁹. Even in screening studies in which untreated cases of gallstones were identified, cases could not be assumed to be completely asymptomatic, or their responses free of either recall or protopathic bias; in one screening

study, as many as 40% of untreated gallstone cases were aware of their disease¹⁹.

Dietary risk factors

Diet has long been a suspected risk factor for gallstones. One source of evidence for this is the presumed link between cholesterol and gallstones. In fact, cholesterol overfeeding is the primary means of inducing supersaturated bile and cholesterol gallstones in animal models²⁰. The observed relationship between obesity and GBD further implicates diet as an important risk factor. A strong positive association has been found consistently between GBD and various measures of obesity²¹⁻⁴⁶, with some showing evidence of a dose-response relation^{28,36,39,40,42}.

Finally, ecological comparisons offer indirect evidence that diet may be an important factor in gallstone development. Early comparisons showed considerably higher prevalence of GBD in westernized than in non-westernized countries⁴⁷⁻⁴⁹, and other research has shown that GBD prevalence can differ substantially between communities that differ in culture and in diet⁵⁰. Observed trends in GBD over time also suggest a role for diet. Dietary changes, most notably a rise in caloric, lipid and animal protein intake⁵¹, may have contributed to the increase in GBD prevalence in European countries after World War II⁴⁷. Secular changes in diet since World War II may also have contributed to an increase in cholesterol gallstones in Japan, where pigment stones were more common previously⁵².

The main dietary hypotheses proposed have focused on six dietary factors: energy intake, fatty acids, cholesterol, highly refined carbohydrates and dietary fibre, calcium and alcohol. Evidence for each of these is discussed below, and findings from cross-sectional, case-control and prospective cohort studies are summarized in Tables 1, 2 and 3, respectively.

Energy intake

Excessive energy intake is thought to increase risk for gallstones primarily by contributing to obesity. Obesity increases risk for gallstones by contributing to an elevated flux of cholesterol from the liver. Obesity has been associated with increased cholesterol synthesis, possibly in part through its association with hyperinsulinaemia, as well as increased biliary cholesterol secretion and cholesterol supersaturation of the bile^{8,47}.

A positive association between energy intake and GBD has been observed in relatively few studies^{39,44,53-55} (Tables 1-3). Among the earliest reports of an association between energy intake and GBD is one by Sarles *et al.*⁵³, who found a 15% higher mean caloric intake in gallstone patients than in

Table 1 Cross-sectional studies on energy, macronutrients and GBD

Study population, year (reference)	No. of cases*	No. in study population	Method of dietary assessment	Energy	Total fat	Cholesterol	Carbohydrates	Simple sugars	Fibre	Protein
Gila River Indian Reservation, Pima/Papago Indians, [†] before 1971 (Reid <i>et al.</i> 1971) ⁶³	48	64	Diet history	N	N	N	N	N	N	N
France [†] before 1978 (Sarles <i>et al.</i> 1978) ⁵¹	11	214	Questions on usual diet	N	N	N	N			N
San Antonio, TX, US, 1979–82 (Diehl <i>et al.</i> 1989) ⁶⁶	35M 154F	2064	24-hour recall	N	- ^{††} + ^{‡§}	- [†]	N [‡]	+ [†]	+ [†]	N [‡]
Maryland, US, breast cancer study participants, [†] 1974–83 (Wysowski <i>et al.</i> 1986) ⁶⁴	43	265	Food frequency questionnaire		N					
Copenhagen, Denmark, 1982–84 (Jørgensen & Jørgensen 1989) ⁶⁵	47	3608	Diet history, intake during past month	N	+ [†]	N		+ [†]	-	N [†]
Sirmione, Italy, before 1985 (Sama <i>et al.</i> 1985) ⁹⁸	210	1930	24-hour recall (means compared in analysis)			N	-	N	-	
Kashmir, India, before 1989 (Khuroo <i>et al.</i> 1989) ³³	67	1104	Not specified	N	N					

N, no association; +, positive association; -, inverse association; blank indicates the factor was not examined.

* Cases were gallstone and/or cholecystectomy cases identified as part of screening by ultrasound or oral cholecystography except studies in the Gila River Indian Reservation,⁶³ San Antonio, Texas⁶⁶ and Maryland, US⁶⁴ which identified only clinically diagnosed cases.

[†] Women only.

[‡] Adjusted for energy intake.

[§] Men only.

Table 2 Case-control studies on energy, macronutrients and GBD

Study location, year (reference)	No. of cases*	No. of controls	Method of dietary assessment	Energy	Total fat	Cholesterol	Carbohydrates	Simple sugars	Fibre	Protein
Melbourne, Australia, 1964-65 (Wheeler <i>et al.</i> 1970) ⁵⁶	396	397 (hospital)	Diet history	N	-	-	-	-	-	-
Marseilles, France, before 1969 (Sarles <i>et al.</i> 1969) ⁵³	101	101	Questions on diet 1 week before disease onset or diagnosis	+	N	N	N	-	-	N
France, † before 1978 (Sarles <i>et al.</i> 1978) ⁵¹	50	50	Questions on diet before first symptoms	N	N	N	N	-	-	N
Edmonton, Alberta, before 1979 (Smith <i>et al.</i> 1979) ⁵⁷	91	86	48-hour recall and crude fibre weekly intake questionnaire	-	N [‡]	N [‡]	N [‡]	-	N [‡]	N [‡]
Adelaide, Australia, 1978-80 (Scragg <i>et al.</i> 1984) ⁴⁴	241	359 (hospital), 241 (community)	105-item food frequency questionnaire on intake over several months before interview	+ [§]	+ [§]	- ^{†‡}	-	+	-	N
Italy, before 1982 (Alessandrini <i>et al.</i> 1982) ⁸⁶	160	160 (hospital)	Food frequency questionnaire on intake 5 years prior to diagnosis					+	-	
Oxford, UK, † before 1988 (Pixley & Mann 1988) ⁵⁸	109	109 (population)	4-day diary (means compared in analysis)	N	N	N	N	N	N	N
Manchester, UK, 1991 (Worthington <i>et al.</i> 1997) ⁵⁹	9	9	7-day weighted inventory	N	N	N	N	N	N	N
New Delhi, India, 1989-92 (Tandon <i>et al.</i> 1996) ⁵⁴	200	98 (hospital)	Diet history on intake during preceding month	+	+	+ [¶]	+	-	N	N
Madrid, Spain, 1992 (Ortega <i>et al.</i> 1997) ⁵⁵	54	46 (hospital)	Two 24-hour recalls (means compared in analysis)	+	+	+	+	-	-	N
Benha City, Egypt, before 1993 (Abdel-Rahman <i>et al.</i> 1993) ⁹⁴	100	100 (hospital)	Food frequency questionnaire on current intake				N			
India, before 1995 (Sarin <i>et al.</i> 1995) ⁶⁰	105	105	24-hour and 72-hour weekend recall (means compared in analysis)	N	N	N	N	-	N	N

N, no association; +, positive association; -, inverse association; blank indicates the factor was not examined.
 * Cases identified as patients diagnosed with gallstones in hospital or clinical setting except study by Pixley *et al.*,⁵⁸ identified in ultrasound screening.
 † Women only.
 ‡ Adjusted for energy intake.
 § Individuals under the age of 50 years.
 ¶ Men only.

Table 3 Prospective cohort studies on energy, macronutrients and GBD

Study population (reference)	No. of cases*	No. in study	Period of follow-up	Dietary assessment	Energy	Total fat	Cholesterol	Carbohydrates	Simple sugars	Fibre	Protein
Framingham, MA (Friedman <i>et al.</i> 1966) ³⁷	226	5209	1957–59	Questions on intake at fifth biennial exam, 8 years after initial exam		N	N				N
US [†] (Sichieri <i>et al.</i> 1991) ⁶¹	216	4730	1971–75 to 1982–84	24-hour recall	– [‡]	N [§]	N [§]	N [§]		–	
Nurses, US [†] (Maclure <i>et al.</i> 1989, 1990) ^{39,71}	612	88 837	1980–84	61-item food frequency questionnaire given in 1980	+	N [§]	N [§]	N [§]	N [§]	– [§]	N [§]
Zutphen, the Netherlands [¶] (Moerman <i>et al.</i> 1994) ⁶⁷	54	860	1960–85	Diet history taken in 1960	N	N	–	N	+ [§]	–	N
Japanese Americans, Oahu, HI [¶] (Kato <i>et al.</i> 1992) ⁴²	471	7831	1965–68 to 1990	24-hour recall and questions on usual monthly intake of alcohol	–	N		N			N

N, no association; +, positive association; –, inverse association; blank indicates the factor was not examined.

* Cases were identified as patients diagnosed with gallstones in hospital or clinical setting.

[†] Women only.

[‡] Individuals under the age of 50 years.

[§] Adjusted for energy intake.

[¶] Men only.

controls (Table 2). However, a considerably larger hospital-based case–control study published soon afterward found no difference in caloric intake between cases and controls⁵⁶. Subsequent case–control studies also show inconsistent results, with some showing a positive association^{44,54,55} but others not^{51,57–60}. One relatively large case–control study conducted in Adelaide, Australia found a positive association but only among individuals under the age of 50, suggesting that some individuals may be more susceptible to the disease than others⁴⁴.

A positive association was also found in one prospective cohort study. In their study of a cohort of nurses, Maclure *et al.*³⁹ found a significantly higher risk of gallstones in women in the highest quintile of energy intake relative to those in the lowest (Table 3). Risk was especially increased in non-overweight women, for whom risk in the highest quintile was over twice that of women in the lowest. Although two cohort studies found inverse associations between energy intake and GBD^{42,61}, both categorized individuals based on a single 24-hour recall which may not have been representative of usual intake. Overall, results of diet–GBD studies provide little evidence of an association between energy intake and GBD. The null findings in the majority of studies reviewed may arise because energy intake is one of the most poorly measured aspects of the diet. The possibilities of underreporting, adoption of calorie-restricted diets⁴², or lower energy expenditure⁵⁷ in obese individuals at higher risk for the disease may also contribute to null findings.

Fatty acids

Dietary fatty acids have also been suggested as a risk factor for gallstones, although the mechanism by which they may affect gallstone development is unclear⁸. Several mechanisms specific to different types of fat have been proposed, but changing either the type or the amount of fat in the diet in human feeding studies has not produced any consistent effects on bile cholesterol content or on gallstone occurrence^{8,62}. High fat intake overall may also increase risk of gallstones by contributing to obesity.

Most cross-sectional studies^{33,51,63,64} show no association between fat intake and GBD (Table 1). However, in a large cross-sectional survey in Copenhagen, Denmark, Jørgensen *et al.*⁶⁵ found a non-significant increase in GBD prevalence with higher percentage of energy from fat. In a study in San Antonio, Diehl *et al.*⁶⁶ found a positive association for fat in men and an inverse association in women, but subjects were categorized based on a single 24-hour recall that may not have represented usual intake.

The majority of case–control studies are also null,

but several tend to be fairly small^{51,53,57–60} (Table 2). Of the two largest case–control studies on diet and GBD, one hospital-based study found an inverse association⁵⁶, while the other, using both hospital and population controls, found a positive association among younger subjects⁴⁴. None of the prospective cohort studies found an association between fat intake and GBD (Table 3).

In general, findings on dietary fat parallel results for total caloric intake and provide little evidence of an association with GBD. The studies, however, are similarly subject to biases discussed above for caloric intake, such as underreporting. Analyses on specific types of fat have not provided convincing evidence of a role for saturated, polyunsaturated or monounsaturated fatty acids^{55,59–61, 63,65–69}. In food-level analyses, some studies have found no association for fats or oils in diet^{45,70}, including butter or margarine^{71,72}, although others have^{55,73}. Positive associations have also been found for fried food consumption⁷² and preference for oily foods⁷⁰.

Recent experimental studies have brought attention to fish oils as a protective factor^{74,75}. No observational epidemiological studies have specifically investigated the association between fish oils and GBD. Among studies that identified types of foods associated with the disease, four^{55,72,73,76} found inverse associations with fish consumption, but three others did not^{67,70,71}.

Cholesterol

Increased cholesterol intake has been hypothesized to contribute to bile cholesterol saturation. However, results of human feeding studies have been inconsistent^{77–82}. The possibility that dietary cholesterol may be a risk factor for gallstones has received even less support from observational epidemiological studies. No cross-sectional or cohort studies have found a positive association between cholesterol and GBD (Tables 1 and 3). Findings from case–control studies vary considerably, with one of the largest showing an inverse association⁴⁴, two smaller, more recent studies showing a positive association^{54,55}, and two others showing no association^{58,59} (Table 2). As far as examining specific high cholesterol foods, no observational studies have found a positive association between egg consumption and GBD^{55,67,70–72,76,83}.

Highly refined carbohydrates and fibre

Consumption of highly refined carbohydrates coupled with low fibre intakes may increase risk of gallstone development. Insoluble fibre may protect against gallstone occurrence by speeding intestinal transit and reducing the generation of secondary bile acids such as deoxycholate^{84,85}, which has been associated with increased cholesterol saturation of the bile^{8,62}.

While studies on carbohydrate intake have been

generally null, several studies have found GBD to be inversely associated with fibre intake and positively associated with simple sugar intake (Tables 1–3). In the cross-sectional study in Copenhagen, Jørgensen *et al.*⁶⁵ found a non-significant trend of increased GBD prevalence with higher intake of refined sugar and a non-significant inverse trend for intake of dietary fibre (Table 1). A similar pattern of increased risk for sugar intake and decreased risk for fibre intake was also seen in two of the larger case–control studies, one in Adelaide, Australia⁴⁴ and the other in Italy⁸⁶ (Table 2), as well as in a prospective cohort study conducted in Zutphen, the Netherlands⁶⁷ (Table 3).

In contrast to the Zutphen study, which found a twofold greater risk of clinically diagnosed gallstones for the highest tertile of sugar intake relative to the lowest, there was no association between gallstones and sucrose intake in the nurses' cohort⁷¹ (Table 3). Whereas the nurses' study examined intake of sucrose specifically, other studies included mono- and disaccharides in their analyses of sugar intake^{44,67}. Furthermore, analyses in the nurses' cohort were performed on energy-adjusted sucrose intake while sugar intake was unadjusted for energy in most other studies. A non-significant decrease in risk was observed for dietary fibre in the nurses' cohort even when adjusted for energy intake, with women in the highest quintile 80% as likely to develop symptomatic gallstones relative to those in the lowest⁷¹.

Overall, results across studies and study designs suggest that some aspect of a diet that is high in fibre or low in simple sugars may protect against GBD. It is notable that only one of 15 studies with information on fibre intake noted a positive association, and none of 10 studies with information on simple sugar intake noted an inverse association. Interestingly, however, one intervention study found that a diet high in fibre and low in refined carbohydrates did not reduce the risk of recurrence of gallstones after dissolution⁸⁷.

At the food level, positive associations have been found for sugar or sugar products^{44,55,67,76}, dates⁸³, and pastries and cakes⁸⁸, although other researchers have not found positive associations for sugar-rich products^{45,71–73,76}.

Calcium and other vitamins and minerals

Calcium has been hypothesized to protect against gallstones by binding secondary bile acids including deoxycholate in the small intestinal lumen, thus reducing the deoxycholate and cholesterol content of the bile. Few studies have examined the association between calcium intake and GBD and, thus, evidence for such an association is extremely limited. While three found an inverse association between dietary calcium and GBD^{24,55,67}, others found no association^{53,59,61,63}. An inverse association has also

been observed with dairy or cheese products in some^{67,73,76} but not all^{55,70–72,83,88} studies.

There are few studies on other vitamins and minerals. Reid *et al.*⁶³ found no association for iron, magnesium, potassium or phosphorous. Ortega *et al.*⁵⁵ looked at a large number of vitamins and minerals and found that cases had a lower intake of folate and magnesium and, among women, of vitamin C. Worthington *et al.*⁵⁹ found that gallstone cases had a lower intake of 10 of 16 antioxidants examined in their study.

Alcohol

Moderate alcohol intake may protect against gallstone development, possibly through its association with reduced biliary cholesterol saturation and higher serum high density lipoprotein (HDL)^{89,90}. A substantial proportion of studies with information on alcohol intake have found evidence of an inverse association between alcohol drinking and GBD, including all of the 10 studies with the largest number of cases (Table 4). The alcohol–GBD association has been presented as an example of protopathic bias, with the disease leading to a reduction in the putative risk factor. Thijs *et al.*¹⁹ showed a decreased risk of clinically diagnosed gallstones in drinkers relative to non-drinkers in one case–control study but no association between alcohol and gallstones in three other studies designed specifically to minimize protopathic bias. While such bias is possible, however, it is less likely to have occurred in prospective cohort studies, all of which appear to show evidence of an inverse association (Table 4). Two separate follow-ups from the nurses' cohort found significant trends of decreased risk with increased alcohol consumption, with those consuming ≥ 15 g of alcohol a day only 70% as likely to develop symptomatic gallstones as non-drinkers^{39,41}. In another large cohort study of Japanese American men, subjects in the highest category of alcohol consumption (≥ 24.7 oz alcohol month⁻¹ – 27 g alcohol per day) were 80% as likely to develop GBD as non-drinkers⁴². In summary, findings from studies regardless of study design overwhelmingly support an inverse association between alcohol intake and GBD.

A few studies have found an apparent dose–response relationship of decreased risk with increased alcohol intake^{29,39,43,90}, although the association between gallstones and alcoholic liver cirrhosis^{91,92} suggests that excessive alcohol intake may increase risk of gallstones. Cirrhosis appears to be specifically associated with pigment stones rather than cholesterol stones¹⁷.

Other foods or food patterns

Two studies suggest that vegetarians may be at

decreased risk for GBD^{27,93}. Other studies also show evidence of a protective effect for vegetables^{53,73}, vegetable fat^{71,83}, vegetable protein^{58,63,65,67,71}, or crude fibre from vegetables⁵⁷, although others have not^{51,55,59,71,72,76,88,94}. Inverse associations have also been observed for olive oil⁸⁸ and for the ratio of polyunsaturated fats to saturated fats⁶⁵. A majority of studies fail to implicate meat as a risk factor. Although some have found positive associations for meat^{55,73}, animal fat^{88,94} and animal protein⁵⁹, most have not^{51,53,58,63,65,67,70–72,76,83,88}.

Other specific foods of interest have included fruits^{53,55,57,70–73,76,88}, beans and pulses^{71,73,76,88} and caffeine^{31,43,45,70,72,73,93}, but the few studies with information on these have had inconsistent findings and have not provided convincing evidence of their association with GBD.

Conclusions and directions for future research

Overall, the studies reviewed here do not provide strong evidence of a role for energy intake or intake of fat or cholesterol, but they suggest an association with simple sugars and inverse associations with dietary fibre and alcohol. Factors that are understudied are fish oils, calcium and antioxidants.

The failure to find consistent associations of diet to GBD is rather remarkable. Gallstones can be induced in animal models with only dietary manipulation. Also, bile plays a major role in the digestive process and its major constituents, including cholesterol, are derived from dietary fats. Much of the difficulty in studying associations between dietary factors and GBD arises from our limited ability to measure dietary intake accurately and for the relevant time period. An additional issue of concern is the appropriateness of a single-nutrient approach. Whereas laboratory research provides valuable information on the biological effects of specific dietary factors, and statistical tools can be used to disentangle their effects in observational studies, such findings are of limited relevance to actual dietary practice, especially since dietary factors can be highly intercorrelated. In this context, more useful information might be gained from investigating the combined effects of dietary factors or from quantifying the aggregate risk associated with dietary patterns.

In drawing conclusions on the association between dietary intake and GBD, the role of obesity should also be emphasized. If diet affects GBD occurrence by contributing to energy imbalance leading to excessive weight gain and obesity, then other factors related to energy balance should also be examined thoroughly. Physical activity, for example, has been found to be inversely associated with GBD in some studies^{31,42,95}.

Other research could add to our understanding of the quality of case ascertainment in studies on GBD by addressing such issues as the proportions of clinically

Table 4 Summary of findings on the association between alcohol and GBD

Cross-sectional		Cohort		Case-control	
Study population, year (reference)	No. of cases/ No. in study population	Study population, year (reference)	No. of cases/ No. in study population	Study population, year (reference)	No. of cases/ No. of controls
Inverse association					
San Antonio, TX, US, 1979–82 (Diehl <i>et al.</i> 1987) ⁹⁹	NS/2990*	Framingham, MA, US, follow-up 1957–59 (Friedman <i>et al.</i> 1966) ³⁷	216/5209	Meibourne, Australia, 1964–65 (Wheeler <i>et al.</i> 1970) ⁵⁶	396/397
Italy, 1983 (LaVecchia <i>et al.</i> 1994) ⁹⁰	2126/58462	San Francisco, CA, US, follow-up 1964–68 to 1971–76 (Klatsky <i>et al.</i> 1981) ¹⁰⁰	NS/80514	Adelaide, Australia, 1978–80 (Scragg <i>et al.</i> 1984) ⁴⁴	241/ 359 (hospital), 241 (community) 84/171
Copenhagen, Denmark, 1982–84 (Jørgensen & Jørgensen 1989) ⁶⁵	47/3608	Nurses, US, follow-up 1980–84 (Maclure <i>et al.</i> 1989) ³⁹	612/88837†	Athens, Greece, 1983 (Pastides <i>et al.</i> 1990) ⁷³	207/451
Hispanic Americans, US, 1982–84 (Maurer <i>et al.</i> 1990) ²¹	253/1325†	Zutphen, the Netherlands, follow-up 1960–85 (Moerman <i>et al.</i> 1994) ⁶⁷	54/860*	Maastricht, the Netherlands, before 1983–85 (Thijs <i>et al.</i> 1991) ¹⁹	195/1122
Sirmione, Italy, before 1985 (Sama <i>et al.</i> 1985) ⁹⁸	210/1930	Japanese American, Hawaii, US, follow-up 1965–68 to 1990 (Kato <i>et al.</i> 1992) ⁴²	471/7831*	Milan, Italy, 1987–89 (LaVecchia <i>et al.</i> 1991) ⁴³	
Fukuoka, Japan, 1986–90 (Kono <i>et al.</i> 1992) ²⁹	99/2739*	Nurses, US, follow-up 1989–91 (Grodstein <i>et al.</i> 1994) ⁴¹	425/96211†		
Fukuoka, Japan, 1991–92 (Kono <i>et al.</i> 1995) ³⁰	72/2215*				
No association					
San Antonio, TX, US, 1979–82 (Diehl <i>et al.</i> 1987) ⁹⁹	NS/2990†			Marseilles, France, before 1969 (Sartles <i>et al.</i> 1969) ⁵³	101/101
Rome, Italy, 1981–84 (GREPCO 1988) ³²	204/2320			Maastricht, the Netherlands, before 1983–85 (Thijs <i>et al.</i> 1991) ¹⁹	151/451
Hispanic Americans, US, 1982–84 (Maurer <i>et al.</i> 1990) ²¹	53/968*			Maastricht, the Netherlands, before 1983–85 (Thijs <i>et al.</i> 1991) ¹⁹	77/352
Maastricht, the Netherlands, before 1983–85 (Thijs <i>et al.</i> 1991) ¹⁹	63/852			Oxford, UK, before 1988 (Pixley & Mann 1988) ⁵⁸	109/109†
Aged 70, Copenhagen, Denmark, 1984–85 (Jørgensen <i>et al.</i> 1990) ²⁵	90/374			Athens, Greece, before 1989 (Linos <i>et al.</i> 1989) ⁸⁸	96/118
Pregnant women in Dublin, Ireland, 1990 (Basso <i>et al.</i> 1992) ⁴⁵	23/521			Madrid, Spain 1992 (Ortega <i>et al.</i> 1997) ⁵⁵	54/46
Ulm, Germany, 1994–95 (Kratzer <i>et al.</i> 1997) ⁹³	67/1116				
Positive association					
				Niigata, Japan, 1982–84 and 1986 (Kato <i>et al.</i> 1990) ⁷⁰	86/116

NS, not specified.

*Men only.

†Women only.

diagnosed cases or cholecystectomy cases who actually have or had gallstones. Future research should also distinguish asymptomatic from symptomatic gallstones in order to distinguish factors leading to development of gallstones from factors leading to progression to symptoms.

In sum, studies on diet and GBD overall suggest that dietary intake is associated with GBD, although the specific components of importance remain unclear. Dietary factors of particular interest are simple sugars, fibre, and alcohol. However, results of these studies cannot completely eliminate the possibility of confounding by other dietary or lifestyle factors, nor do they provide strong evidence that risk for GBD can be reduced by altering intake of a specific dietary factor. Although no specific dietary recommendations can presently be made to reduce the risk of GBD *per se*, implications of studies on GBD are at least consistent with recommendations to prevent other diseases. These include increasing the consumption of fibre-rich vegetables, fruits and grains, minimizing the consumption of fats and sweets, and drinking alcohol in moderation^{96,97}. Thus, a more generally 'healthy' diet that is promoted to reduce risk of other diseases might be expected to reduce risk for GBD as well.

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