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Body mass index, alcohol, tobacco and symptomatic gallstone disease: a Swedish twin study

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Abstract. Katsika D, Tuvblad C, Einarsson C, Lichtenstein P, Marschall H-U (Karolinska Institutet, University Hospital Huddinge; and Karolinska Institutet, Stockholm; Sweden). Body mass index, alcohol, tobacco and symptomatic gallstone disease: a Swedish twin study. *J Intern Med* 2007; **262**: 581–587.

Background/Aims. Both genetic and environmental factors are involved in the pathogenesis of gallstone disease (GD). We aimed to examine the association between symptomatic GD and overweight (body mass index, BMI, 25–30 kg m^{-2}), obesity (BMI > 30 kg m^{-2}), alcohol, smoking and smoke-free tobacco by analysing a large twin population.

Methods. The Swedish Twin Registry (STR) was linked to the Swedish Hospital Discharge and Causes of Death Registries for GD and GD-surgery related diagnoses. Weight, height, use of alcohol, smoking and smoke-free tobacco were provided by STR and analysed for possible associations by conditional logistic regression.

Results. Overweight and obesity were associated with a significantly higher risk for symptomatic GD in the whole study population (OR 1.86 and OR 3.38; CI: 1.52–2.28 and 2.28–5.02 respectively). High alcohol consumption was associated with a lower risk for GD in the whole population (OR 0.62; CI: 0.51–0.74) with no difference between discordant monozygotic and dizygotic twins (OR 1.08 and OR 0.96; CI: 0.82–1.42 and 0.79–1.16). Smoking or smoke-free tobacco was not correlated with GD.

Conclusion. Consistent with epidemiological studies, we found positive associations between BMI and the development of symptomatic GD. High alcohol consumption was associated with a decreased risk against GD. Tobacco use has no impact on GD.

Keywords: alcohol, Body mass index, conditional logistic regression, gallstones, obesity, overweight, smoke-free tobacco, smoking, Swedish Twin Registry, tobacco.

Abbreviations: GD, gallstone disease; MZ, monozygotic; DZ, dizygotic; BMI, body mass index; OR, odds ratio; Ow/Ob, overweight/obesity; STR, Swedish Twin Registry.

Introduction

The pathogenesis of gallstones is complex [1, 2]. Gallstone formation appears to be a complex trait influenced by genes and environment, and their interaction [3]. Recently we estimated the contributions of genetic and environmental factors to symptomatic gallstone disease (GD) with data from the Swedish Twin Registry (STR) [4]. Genetic effects accounted for 25%, shared environmental effects for 13% and unique environmental effects for 62% [4] of the liability.

Overweight is the best-known, age-independent risk factor for GD [5, 6] that itself is genetically influenced [7–9]. Obese subjects are at even higher risk of GD during weight reduction [10]. Delayed gallbladder emptying, and decreased small bowel motility and sensitivity to cholecystokinin have been associated

with obesity and GD [11]. Increased risk of cholesterol gallstones formation was confirmed in obese diabetics with hypertriglyceridaemia [12]. Also, plasma cholesterol levels were found to correlate to GD [13]. Alcohol consumption was found to be inversely associated with the risk for GD [14–17]. Moderate alcohol intake may lower the risk for cholesterol GD by reducing bile cholesterol saturation and raising HDL-cholesterol levels [18]. However, the negative effect of alcohol on GD may be overestimated due to reduction of alcohol use because of symptoms related to clinical GD [19] or due to alcohol association with lower obesity [20].

Even more conflicting data are available for the association between GD and smoking. Two recent studies from Japan found either no association between cigarette smoking and GD [21] or an inverse correlation [22]; however, both studies confirmed the assumption that alcohol consumption protects against gallstone formation [21, 22]. Cross-sectional studies from Denmark [23] and Germany [24] either found a significant association between smoking and GD [23] or no relationship between alcohol consumption, tobacco use and GD at all [24]. Case–control studies from UK [25] and Australia [26] described symptomatic GD both as a disease of nonsmokers [25] and of cigarette smoking women [26], the latter surprisingly at maximal increased risk when young and currently smoking [26].

Investigations on GD risk factors should ideally adjust the results for potential effects by genetic predisposition and shared environmental factors. The co-twin control method, which compares twins who are discordant for a disease, provides a valid tool to achieve this aim. The STR, the largest population-based twin registry in the world, offers a particularly strong basis for exploring the importance of potential lifestyle risk factors with controlling for genetic background [27].

Our aim now was to: (i) examine associations between body mass index (BMI), alcohol and tobacco habits (smoking and use of smoke-free tobacco) and GD and (ii) to investigate whether potential associations between overweight or obesity, alcohol, tobacco and GD are confounded by shared environmental factors, by conducting a co-twin analysis.

Materials and methods

Study population

The STR was linked to the Swedish Hospital Discharge and Causes of Death Registries for twins born between 1886 and 1958 as recently described [4]. The study population comprised all 58 402 twins born 1886–1958 in the STR, consisting of 19 950 monozygotic (MZ) twins, 33 464 dizygotic (DZ) twins, 4988 twins of unknown zygosity; 27 692 were male and 30 710 female. In the separate analysis for each potential risk factor, we included those same-sexed twins in the STR who responded to a questionnaire in 1961 or 1973 regarding the risk factor studied [27].

Twins born between 1886 and 1925 (cohort C1) were evaluated in 1961 for smoking habits, in 1963 for smoking habits and BMI, and in 1967 and 1970 for smoking habits, alcohol and BMI [27]. If data on the same variable were available at different times, the most recent value was used. The 1973 questionnaire evaluated twins born between 1926 and 1958 (cohort C2) for alcohol, BMI, and smoking and smoke-free tobacco habits [27]. The follow-up times were 1 January, 1970 to 31 December, 2002 for C1; and 1 January, 1974 to 31 December, 2002 for C2. To avoid bias through later lifestyle changes, we excluded twins that had answered the questionnaires after the diagnosis of GD was made.

Covariates

Body mass index (kg m^{-2}) data were categorized according to the WHO [28] as normal (18.5–24.9), overweight (25.0–29.9) and obese (≥30.0). Alcohol was stratified according to the total amount consumed [29, 30] as nondrinkers (0 g $month^{-1}$ for both women and men), moderate consumers (>0–1800 g $month^{-1}$ for women, >0–2400 g $month^{-1}$ for men), and high consumers (>1800 g $month^{-1}$ for women, >2400 g $month^{-1}$ for men), i.e. statistically signifi-

cantly associated with increased risk for liver disease [29, 30]. Smoking was categorized as never, previous or current for all forms of smoking. The same principle was applied to smoke-free tobacco (snuff), an oral tobacco preparation popular in Sweden.

Cohort study comparing cases to unaffected unrelated twins

In the study population of 58 402 twins, we identified 1666 twins with GD. In this cohort, logistic regression analysis for gender, age, zygosity, BMI and alcohol and smoking habits was performed, including both concordant and discordant pairs, regardless of zygosity status. Dependence within twin pairs was accounted for by using Generalized Estimation Equation models (GEE) with SAS PROC GENMOD [31].

Co-twin study comparing cases to unaffected co-twins

Co-twin comparison of same-sexed twins was performed in 1527 cases with GD and where the co-twin was without a history of GD. The analysis was subdivided in MZ and DZ twin pairs to investigate genetic or shared environmental factors. The co-twin analyses were performed with conditional logistic regression by the maximum likelihood method using SAS PROC PHREG [32, 33]. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

By investigating the association within twin pairs discordant for GD, the influence of genetic and shared environmental factors is substantially reduced. Twins within the same pair share the same environment during infancy and childhood, so differences within MZ and DZ twin pairs should be independent of common environmental factors. In addition, within MZ twin pairs, differences are independent of genetic factors. If there were a causal effect of the risk factor on GD, we would expect the same association in GD discordant MZ and DZ twin pairs as in the whole study population that served as controls. On the other hand, if genetic effects were confounding the association we would expect the same association in discordant DZ twin pairs as well as in co-twins from the whole study population, but not in discordant MZ twin pairs. If shared environmental factors were confounding the association we would expect no difference between MZ and DZ twin pairs but a different association in co-twins from the whole study population. These conclusions are based on the assumption that any differences existing between MZ co-twins must necessarily originate from environmental influences including shared environmental factors. Differences between DZ co-twins could both be due to genetic and early environmental factors.

Results

The distributions of the covariates for twins with (cases) and without GD (controls) are presented in Table 1. There were more overweight twins with than without GD (32% vs. 23%). Moderate to high alcohol consumption was slightly more prevalent in twins without GD. The majority of the twins did not consume any tobacco products and the pattern of tobacco consumption was similar in the two groups.

In the cohort study, we included all twins and calculated the risk for GD and evaluated each parameter *per se* in comparison with unrelated twins. The crude risks for BMI, smoking, smoke-free tobacco and alcohol and GD are presented in Table 2. Women had a statistically significant, more than doubled, risk for GD. Overweight and obese twins had a higher risk for GD (OR1.86 and 3.38), which was statistically significant different from twins with normal BMI. Alcohol consumption at high levels had a statistically significant, negative effect against GD (OR 0.62). Previous or current smoking or use of smoke-free tobacco did not have a statistically significant impact on the development of GD (Table 2).

Results from the additional within-pair analyses, aimed to control for potential unmeasured confounding, are presented in Table 3. When we compared the cases with their healthy co-twins, we found a statistically significant decreased risk for GD when the healthy DZ co-twin was obese. No statistically significant difference was found in the association within discordant MZ and DZ twins regarding overweight or alcohol and GD. These results indicate that the posi-

Table 1 Sample information

Variable	Type	Prevalence: Twins with Gallstone disease *n* (%)	Prevalence: Twins without Gallstone disease *n* (%)
Gender	Female	1076 (65)	29 634 (52)
	Male	590 (35)	27 102 (48)
	Data missing	0	0
Zygosity	MZ	586 (35)	19 364 (34)
	DZ	941 (56)	32 523 (57)
	Unknown	139 (9)	4849 (9)
BMI	Normal	878 (63)	32 547 (74)
	Overweight	450 (32)	10 150 (23)
	Obese	70 (5)	1553 (4)
	Data missing	268	12 486
Alcohol	Never	1153 (81)	33 579 (73)
	Moderate Consumption	132 (9)	5383 (12)
	High consumption	139 (10)	7020 (15)
	Data missing	242	10 754
Smoking	Never	832 (55)	25 236 (51)
	Previous	498 (33)	16 853 (34)
	Current	169 (12)	7108 (14)
	Data missing	167	7539
Use of smoke-free tobacco	Never	691 (96)	26 024 (91)
	Previous	20 (3)	1981 (7)
	Current	7 (1)	524 (2)
	Data missing	948	28 207

Distribution of BMI, alcohol, smoking and use of smoke-free tobacco for twins with and without GD. GD, gallstone disease; MZ, monozygotic; DZ, dizygotic.

Table 2 Cohort study

	Variable	OR	CI
Gender	Female	1.00[a]	
	Male	0.47*	(0.39–0.56)
BMI	Normal	1.00[a]	
	Overweight	1.86*	(1.52–2.28)
	Obese	3.38*	(2.28–5.02)
Alcohol	Never	1.08	(0.96–1.20)
	Moderate consumption	1.00[a]	
	High consumption	0.62*	(0.51–0.74)
Smoking	Never	1.00[a]	
	Previous	1.15	(0.95–1.39)
	Current	0.99	(0.78–1.27)
Smoke-free tobacco	Never	1.00[a]	
	Previous	0.62	(0.37–1.04)
	Current	1.05	(0.49–2.23)

Crude odds ratios (OR) and 95% confidence intervals (CI) for gender, BMI, alcohol, smoking and smoke-free tobacco. Reference category marked by [a]. Significant differences marked by *.

Table 3 Co-twin analysis

Variable	Zygosity	OR	CI
Overweight	MZ	1.16	(0.86–1.56)
	DZ	1.17	(0.97–1.42)
Obesity	MZ	0.79	(0.59–1.05)
	DZ	0.83*	(0.69–0.99)
No alcohol consumption	MZ	0.84	(0.64–1.11)
	DZ	0.99	(0.82–1.20)
High alcohol consumption	MZ	1.08	(0.82–1.42)
	DZ	0.96	(0.79–1.16)
Previous smoker	MZ	1.17	(0.93–1.47)
	DZ	1.08	(0.91–1.28)
Current smoker	MZ	0.85	(0.68–1.07)
	DZ	0.90	(0.76–1.06)
Previous use of smoke-free tobacco	MZ	0.74	(0.32–1.75)
	DZ	0.78	(0.42–1.45)
Current use of smoke-free tobacco	MZ	1.20	(0.52–2.80)
	DZ	1.26	(0.68–2.36)

Odds ratios (OR) and 95% confidence intervals (CI) for symptomatic GD in same gender MZ and DZ twin pairs discordant for symptomatic GD. Significant differences marked by *. GD, gallstone disease; MZ, monozygotic; DZ, dizygotic.

tive association between overweight and GD, as well as the negative association of high alcohol consumption on GD observed in the cohort analyses probably have been confounded by shared environmental factors.

Discussion

The present study aimed to estimate the impact of BMI, alcohol, smoking and smoke-free tobacco for the development of symptomatic GD. Data from the cohort study confirmed our previous finding that women are at higher risk for GD [4]. Here we also could show that the risk increases with increasing BMI. Overweight and especially obese twins have a

substantially higher risk for GD (OR 1.86 and 3.38 respectively).

Because we had data on twins, we could go one step further and investigate the aetiology of the association between BMI and GD. There were only minor non-significant increases in risks for GD in discordant DZ and MZ overweight twins (OR 1.17 and OR 1.16) with no difference between the zygosity groups. In contrast to the analysis with unrelated control twins, the co-twin analysis suggested significantly lower (OR 0.83) risk for GD for DZ obese twins. Obese MZs also had a lower (OR 0.79) yet not significant lower risk for GD. This surprising finding seems to contradict the association between GD and BMI. One might speculate that the obese twin of a DZ twin brother or sister did not present with typical gallstone symptoms or that he/she restrained from further evaluation and surgery for gallstones as he/she (or the physician involved) became afraid of possible discomfort and/or surgical complication.

In both overweight and obese twins there were no differences between the zygosity groups, but there was a difference compared to the whole population, suggesting that shared environmental factors confound the association between BMI and GD. Possible mechanisms for the shared environmental effect could be diet during childhood or maternal dietary or alcohol habits during pregnancy that influence both BMI and GD later in life, and could be an explanation to our previous findings of shared environmental factors for GD [4].

We were not able to unequivocally define the impact of alcohol consumption on GD. The OR was significantly decreased in twins with higher alcohol consumption (OR 0.62; CI: 0.51–0.74) when compared to twins with moderate alcohol consumption. However, there were no differences between twins with moderate alcohol consumption and the totally alcohol abstaining twins. Previous studies suggest that frequent, moderate intake of alcohol is associated with a lower risk for GD both in men and women [14–17]. In the high alcohol consumption groups, there was no difference within discordant DZ and MZ twins (OR 0.96 and OR 1.08; CI: 0.79–1.16 and 0.82–1.42) suggesting that this negative association of alcohol and GD effect is confounded by shared environment.

As to tobacco use, we did not find any significant association between the risk of GD and current or previous smoking or use of smoke-free tobacco, which is consistent with some [21, 24] but not all epidemiologic studies [21–26]. However, our data on tobacco habits, especially on smoke-free tobacco, were scarce, limiting the power of this evaluation.

Our study of lifestyle-related environmental factors, which includes overweight and obesity, has limitations. In particular, our study does not answer the question what fractions of GD specifically are due to obesity or heredity. This question could be addressed in a bivariate quantitative analysis that includes twins without GD. However, this was not possible in our study as the data set concerning BMI (and alcohol and smoking habits) of the large majority of twins without GD is incomplete. In addition, information about BMI, alcohol, smoking and smoke-free tobacco was self-reported, and it is possible that data on weight and drug habits were underestimated, in particular in the higher ranges. A large proportion of self-reports actually was incomplete and not suitable for evaluation which diminished the already relatively modest number (1666) of cases with symptomatic GD. Furthermore, the question on smoke-free tobacco habits was only addressed to cohort C1 and thus leading to a large number of missing values. Thus, despite the large number of twins screened, the study size might not have had sufficient power to reveal possibly significant differences. Twins that actually did answer the questionnaire have been assumed to be representative of the whole population, which would be a potential bias factor if this were not the case. Another factor not studied was the impact of co-morbidity, i.e. high BMI or cardiopulmonary disease, on the hospitalization decision. As the laparoscopic era progressed during the 90s, some patients might have been operated on an ambulatory basis and thus were not accounted for in the Hospital Discharge Registry whereas patients with risk factors, e.g. high BMI, certainly were hospitalized. On the other hand, patients with severe confounding illness, e.g. advanced lung

disease, and thus high operative risk were more likely to be treated conservatively on an outpatient basis. Finally, the Hospital Discharge Registry is complete only from 1987 on. Although including inpatients retroactively, some data were unavailable for many of the operated patients in the older cohort. Despite all these limitations, the present study is strengthened by its long follow-up time of upto 40 years and by the absence of recall bias as potential risk or protective factors were registered prior to the diagnosis of GD.

In conclusion, we confirm the association between increasing BMI and GD as well as a negative effect of increased alcohol consumption on GD when alcohol consumption reached levels associated with increased risk for liver disease. The co-twin analysis indicates in both cases that shared environmental factors rather than genetic mechanisms probably confound these associations. Diet during childhood, maternal alcohol habits or dietary factors during pregnancy could be of significance, though no data are available on the potential impact of these factors. Smoking or use of smoke-free tobacco did not have a significant impact on symptomatic GD and larger studies are required to identify a possible association.

Conflict of interest statement

No conflict of interest was declared.

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