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Independent Risk Factors for Gallstone Formation in a Region with High Cholelithiasis Prevalence

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Key Words
Gallstones · Gallstone formation, risk factors · Cholelithiasis, general population · Study of Health in Pomerania (SHIP)

Abstract
Background/Aims: Cholelithiasis is a common disorder in north-eastern Germany. Analyses of risk factors for gallstone formation in this population may have high explanatory power. Gender-specific risk factors for gallstone formation and their interactions were investigated by using data of the population-based Study of Health in Pomerania (SHIP). ***Methods:*** Data of 4,202 persons aged 20–79 years were available. Cholelithiasis was defined by either a prior history of cholecystectomy or the presence of gallstones on abdominal ultrasound. Multivariable analyses were performed to identify independent risk factors for gallstone formation. ***Results:*** There were 468 persons (11.1%) with previous cholecystectomy and 423 persons (10.1%) with sonographic evidence of gallstones. Women had a twofold higher risk for cholelithiasis compared to men. Age, body mass index and low serum HDL cholesterol levels were independently associated with cholelithiasis in both men and women. In the male population, low alcohol and high coffee consumption and in the female population, low physical activity, were further independently related to gallstone formation. Additionally, sex-specific interactions between risk factors were found. ***Conclusions:*** Female sex, age and being overweight are major risk factors for gallstone formation in this region where cholelithiasis is a frequent disorder. Additional factors and interactions contribute to a gender-specific gallstone risk.

Introduction

Cholelithiasis represents one of the major sources of morbidity in industrialized countries. Advanced age and female gender are well-established risk factors for gallstone disease and among the avoidable risk factors, food pattern, a sedentary lifestyle, and being overweight have been found to be associated with the risk of gallstone formation [1]. However, several studies could not confirm those findings [2–6]. Inconsistent results may be explained by different study designs (clinically-based versus population-based selection of study participants), by varying definitions of endpoints (e.g. symptomatic gallstone disease versus sonographical diagnosis), by insufficient numbers of subjects, by disregarding gender-re-

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lated differences and by a limited spectrum of potential risk factors considered for multivariable statistical analyses. Methodological differences may further account for conflicting results with respect to specific factors such as alcohol and coffee. Some studies [4, 7–10] found a protective effect of alcohol consumption on the risk of gallstone, whereas other studies [2, 11] could not confirm this relation. One study [12] found an increased risk of cholelithiasis among coffee drinkers, but other studies [13, 14] observed an inverse relation between coffee consumption and gallstone formation.

Previous studies [15] that were conducted in the northeastern part of Germany identified a high cholelithiasis prevalence proportion of greater than 30 and 55% in men and women who were >65 years old, respectively. Analyses of risk factors for gallstone formation in this high-risk population may provide an insight into the pathobiology of this disease with high explanatory power. Additionally, this would allow for an investigation of interactions between risk factors and modifiers, whereby an interaction (or effect-measure modification) describes departure from additivity of effects on the chosen outcome scale. To the best of our knowledge, there are currently no studies available that systematically analyzed interactions in order to explore their impact on gallstone formation.

The aim of the present analysis was to investigate the gallstone risk in a high-risk population, to describe gender-specific risk factor profiles and to further explore possible interactions between risk factors and effect modifiers in this context.

Methods

Study Population

The Study of Health in Pomerania (SHIP) is a cross-sectional population-based survey in West Pomerania, a region in north-eastern Germany [16]. The total population comprised 212,157 inhabitants. A random sample from the population aged 20–79 years was drawn. The sample was selected using population registries and only individuals with German citizenship and principal residency in the study area were included. A total number of 7,008 subjects were sampled, with 292 men and 292 women in each of the twelve 5-year age strata. The net sample (after exclusion of migrated or deceased persons) comprised 6,267 eligible subjects. All subjects received a maximum of three written invitations. In case of nonresponse, letters were followed by several phone calls or by home visits if contact by phone was not possible. The SHIP population finally comprised 4,310 participants, corresponding to a final response rate of 68.8% [16]. The study was approved by the Ethics Committee of the University of Greifswald.

Among the 4,310 participants, 3 persons refused abdominal ultrasonography altogether. These individuals and a further 105 participants with uncertainty regarding the diagnosis of cholelithiasis were excluded from further analysis. This resulted in a total study population of 4,202 participants who were available for the present analysis.

Measurements

Sociodemographic and medical characteristics, and in women the histories of pregnancies and child births as well as current and/or previous use of oral contraceptives and hormone replacement therapy, were assessed by computer-assisted personal interviews. Education was categorized into three levels (low (<10 years), medium (10 years), high (>10 years), categories based on the Eastern German three-level school system). The current marital status comprised four categories (never married, married, divorced, widowed). To characterize social relations the social support survey score [17] and the Social Network Index [18] were calculated with higher levels indicating good social relations. Alcohol intake during the previous week was used as a proxy for general intake and the mean daily alcohol consumption was calculated using beverage-specific pure ethanol volume proportions [19]. Subjects were divided into four categories with respect to the mean daily alcohol consumption: 0, <20, 20–60 and >60 g. Binge drinking was assumed when an intake of >5 drinks on at least 1 day during the previous month was reported. According to smoking habits, participants were categorized into current, former and never-smokers. Diabetes was defined as self-reported physician diagnosis of diabetes, or serum hemoglobin A1c >7%. Individuals who participated in physical training during summer or winter for at least 1 h/week were classified as being physically active. Information on the use of coffee, decaffeinated coffee and tea was obtained. Food categories were selected from a food-frequency questionnaire and the classifications were summarized to a dietary pattern score for each subject [20]. Sex-specific tertiles of this score reflected the food quality: lower tertile = unfavorable dietary pattern (<12 for men, <14 for women), medium tertile = normal dietary pattern (12–14 for men, 14–16 for women), upper tertile = favorable dietary pattern (>14 for men, >16 for women). Information on the current use of drugs was classified according to the anatomic, therapeutic and chemical (ATC) code. The systemic use of glucocorticoids (ATC H02AB, H02B), HMG-CoA reductase inhibitors (ATC C10AA), and fibrates (ATC C10AB) were considered for the present analyses.

Height and weight as well as waist and hip circumferences were measured for the calculation of the body mass index (BMI = weight (kg)/height^2 (m^2)) and the waist-to-hip ratio (WHR), respectively. Overweight was defined as a BMI of ≥ 25 kg/m^2 and obesity as a BMI of ≥ 30 kg/m^2. Non-fasting blood samples were drawn from the cubital vein in the supine position. The two analytical laboratories involved in this study participated semi-annually in the official national German tests for quality assurance. In addition, duplicate blood samples were analyzed for internal quality assurance every week. Serum total, LDL and HDL cholesterol were measured photometrically (Hitachi 704, Roche, Mannheim, Germany). Lipoprotein (a) concentrations were determined with use of an immunoluminometric assay (Magic Lite Analyzer II, Ciba Corning, Mass., USA).

Trained physicians examined the liver using a 5-MHz transducer and a high-resolution instrument (Vingmed VST Gateway, Santa Clara, Calif., USA). The sonographers were unaware of the participant's clinical and laboratory characteristics. Hepatic steatosis was defined as the presence of an ultrasonographic pattern of a

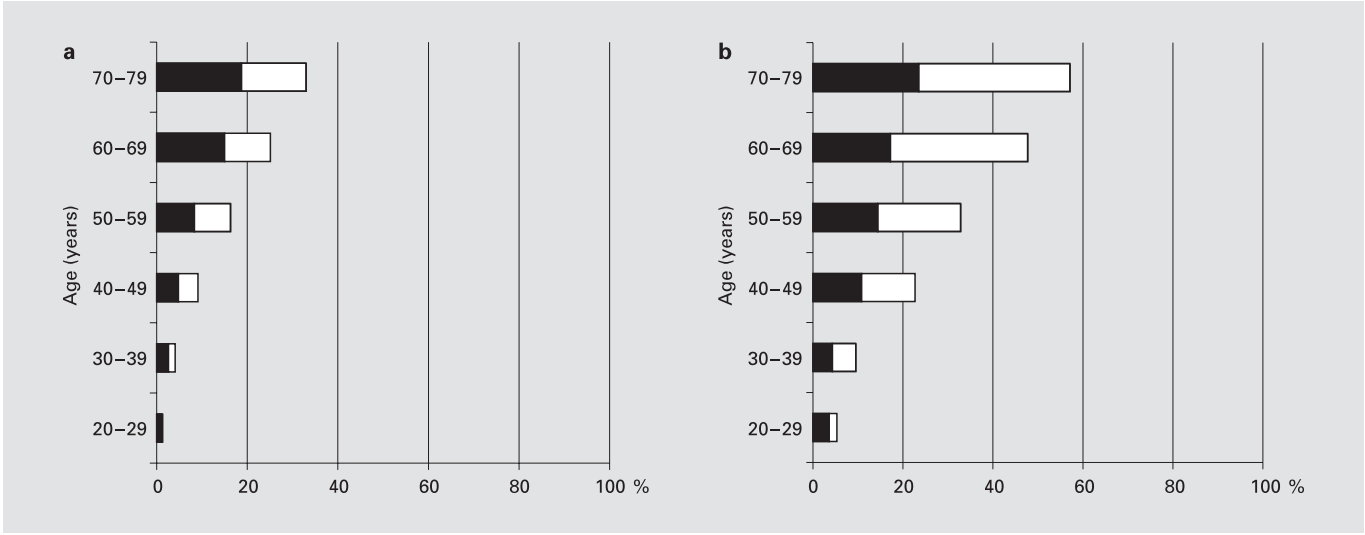

Fig. 1. Age-stratified prevalence of sonographically diagnosed gallstones (■) and positive history of cholecystectomy (□) in the male (**a**) and female (**b**) population.

bright liver, with evident contrast between hepatic and renal parenchyma. Cholelithiasis was present if the gallbladder contained echoes that moved with gravity. Stone movement was not a criterion for cholelithiasis if stones were large, septa existed in the gallbladder or if there was an enclosed infundibulum [6].

Statistical Analysis

Data on quantitative characteristics are expressed as median and range. Data on qualitative characteristics are expressed as percent values or absolute numbers as indicated. The adjusted gallstone prevalence was calculated by using sex- and age group-specific weighting factors reflecting the sex- and age distribution of the total population of Western Pomerania [21]. Subjects were divided into two groups with respect to the absence or presence of cholelithiasis (current gallstones and prior cholecystectomy). Comparisons between groups were made using χ^2 test (qualitative data) or ANOVA (quantitative data). Multivariable logistic regression analyses were carried out to identify independent risk factors for cholelithiasis. Ninety-eight men and 70 women had to be excluded from the models due to missing values in various variables. All multivariable analyses were fitted separately for each gender and performed in two steps. In a first step, regression models were run for the two study groups including all variables as main factors. A sequence of backward and forward stepwise regression analyses were performed in order to reduce the number of potential risk factors to a basic set. Only those variables remained in the model that achieved a consistent p value of <0.1. In a second step, a sequence of backward and forward stepwise regression analyses incorporated three-way and two-way interaction effects between the independent risk factors into the model [22]. The decision to maintain an interaction was made based on the likelihood ratio (consistent p value of <0.1). For interactions, the β and its standard error (SE) were calculated. All multivariable analyses were repeated after persons with prior history of cholecystectomy were excluded in order to evaluate the sensitivity of the results with respect to changes in lifestyle that might have occurred following the operation. Odds ratio (OR) and its 95% confidence interval (95% CI) are given. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software (SPSS GmbH Software, Munich, Germany).

Power analyses were performed using the Quanto software (http://hydra.usc.edu/gxe/). A gallstone prevalence rate of 20% and a frequency of risk factor A and B of 30% were assumed and the OR for A and B with respect to the risk of gallstone formation was estimated to be 1.5. Given a statistical power of 80% and using a two-sided test, the size of the present study population would have allowed to establish an OR of 1.6 for an interaction between the risk factors A and B with respect to the endpoint investigated.

Results

Description of the Study Population

Among the 4,202 SHIP participants there were 468 with previous cholecystectomy (11.1%). Gallstones were present in a further 423 participants (10.1%). Thus, the frequency of cholelithiasis was 21.2% in the SHIP population corresponding to a standardized prevalence proportion of 18.8% in the general population. Only 121 persons of those with sonographically detected cholelithiasis (28.7%) were aware of their gallstones. The prevalence of cholelithiasis was strongly age-dependent in men as well as in women (fig. 1a, b). Sonographic evidence for gallstones and previous history of cholecystectomy were

Table 1. Sociodemographic characteristics and data of risk behavior among subjects with and without cholelithiasis

	No cholelithiasis n = 3,311	Cholelithiasis n = 891	p*
Age, years	47.1 ± 15.9	61.0 ± 13.1	<0.05
Gender (female)	1,564 (47.2%)	586 (65.8%)	<0.05
School education			
Low (<10 years)	1,134 (34.5%)	524 (59.3%)	<0.05
Medium (10 years)	1,600 (48.7%)	281 (31.8%)	
High (>10 years)	554 (16.8%)	79 (8.9%)	
Marital status			
Single	740 (22.4%)	61 (6.9%)	<0.05
Ever married	2,123 (64.3%)	605 (68.1%)	
Divorced	242 (7.3%)	68 (7.7%)	
Widowed	195 (5.9%)	154 (17.3%)	
Social support survey score	15.4 ± 5.4	15.0 ± 6.1	0.08
Social Network Index			
I (low)	1,071 (33.1%)	338 (39.1%)	<0.05
II	1,265 (39.1%)	331 (38.3%)	
III	718 (22.2%)	152 (17.6%)	
IV (high)	182 (5.6%)	44 (5.1%)	
Cigarette smoking habits			
Never-smoker	1,080 (32.7%)	419 (47.2%)	<0.05
Former smoker	1,095 (33.2%)	314 (35.4%)	
Current smoker	1,123 (34.1%)	154 (17.4%)	
Daily alcohol consumption			
0 g	1,035 (32.0%)	423 (47.7%)	<0.05
>0–20 g	1,124 (34.1%)	301 (34.0%)	
>20–60 g	844 (25.6%)	144 (16.3%)	
>60 g	272 (8.3%)	18 (2.0%)	
Binge drinking	1,074 (33.7%)	149 (17.8%)	<0.05
Physical activity	1,492 (45.2%)	276 (31.1%)	<0.05
Cups of coffee per day			
0	570 (17.3%)	139 (15.7%)	<0.05
1–2	1,124 (34.1%)	312 (35.2%)	
3–4	1,073 (32.6%)	363 (40.9%)	
≥ 5	529 (16.0%)	73 (8.2%)	
Use of decaffeinated coffee	301 (9.1%)	136 (15.3%)	<0.05
Use of tea	537 (16.3%)	130 (14.7%)	0.24
Dietary pattern, sum score			
Unfavorable	502 (32.3%)	137 (23.5%)	<0.05
Medium	506 (32.6%)	201 (34.5%)	
Optimal	544 (35.1%)	245 (42.0%)	

* χ^2 test (nominal data) or ANOVA (interval data).

Table 2. Clinical characteristics and laboratory data in subjects with and without cholelithiasis

	No cholelithiasis n = 3,311	Cholelithiasis n = 891	p*
Diabetes mellitus	211 (6.4%)	154 (17.4%)	<0.05
Known liver cirrhosis	5 (0.2%)	2 (0.2%)	0.81
Hepatic steatosis	874 (26.7%)	349 (39.9%)	<0.05
Glucocorticoids	33 (1.0%)	21 (2.4%)	<0.05
HMG-CoA reductase inhibitors	182 (5.5%)	93 (10.5%)	<0.05
Fibrates	37 (1.1%)	18 (2.0%)	<0.05
Body mass index, kg/m^2	26.7 ± 4.5	29.2 ± 5.0	<0.05
Waist-to-hip ratio	0.86 ± 0.09	0.87 ± 0.09	0.02
Cholesterol, mmol/l	5.74 ± 1.24	5.92 ± 1.25	<0.05
HDL cholesterol, mmol/l	1.46 ± 0.44	1.41 ± 0.45	<0.05
LDL cholesterol, mmol/l	3.55 ± 1.16	3.69 ± 1.16	<0.05
Lipoprotein (a), mg/l	211 ± 278	220 ± 296	0.41

HDL = High-density lipoprotein; LDL = low-density lipoprotein.

* χ^2 test (nominal data) or ANOVA (interval data).

found approximately twice as often in women compared to men for each age decade. The highest prevalence of gallstones was observed in women who were 70–79 years old. In this age group, 57.1% of women had either a previous history of cholecystectomy or current sonographic evidence for gallstones (fig. 1b).

Bivariate comparisons of baseline characteristics revealed persons with cholelithiasis to be older, more often of female gender, less well educated, less often unmarried and more frequently being a current smoker. Individuals with gallstones had lower levels for the Social Network Index and lower mean daily alcohol consumption. They were less physically active, had more often 3–4 but less often 5 or more cups of coffee per day, consumed more often decaffeinated coffee and had a higher food-frequency score (table 1). Persons with gallstones more often had diabetes, hepatic steatosis and used more often glucocorticoids, HMG-CoA reductase inhibitors and fibrates. They were further characterized by higher values for BMI and WHR, and they exhibited higher levels of total and LDL cholesterol and lower levels of HDL cholesterol (table 2). Women with cholelithiasis had used less often oral contraceptives, were more often pregnant and had given birth to more children than women without gallstones (table 3).

Independent Risk Factors for Cholelithiasis

In the male population, an advanced age, an increased BMI and low serum levels of HDL and LDL cholesterol were independently associated with the risk of cholelithiasis. The relation between alcohol drinking and the gallstone risk was inverse and dose-dependent with the lowest risk observed in men with a daily alcohol con-

Table 3. Comparison of females with and without cholelithiasis with respect to women-specific variables

	No cholelithiasis n = 1,564	Cholelithiasis n = 586	p*
Ever used oral contraceptives	1,177 (75.6%)	289 (49.5%)	<0.05
Duration of oral contraceptive use, years†	10.6 ± 9.9	10.2 ± 11.7	0.56
Ever used hormone replacement therapy (HRT)	283 (36.8%)	152 (31.7%)	0.07
Duration of HRT use, years‡	1.3 ± 0.6	1.3 ± 0.5	0.51
Never pregnant	267 (17.1%)	41 (7.0%)	<0.05
Pregnancies per woman	2.5 ± 1.4	2.7 ± 1.5	<0.05
Children per women	2.0 ± 1.1	2.4 ± 1.4	<0.05

* χ^2 test (nominal data) or ANOVA (interval data).
† Calculated only for women who ever took oral contraceptives.
‡ Calculated only for women who ever took HRT.

Table 4. Independent risk factors for cholelithiasis in men*

	OR	95%-CI	p*
Age, per 10-year increase	1.61	1.50–1.73	<0.05
Body mass index, per 5 kg/m^2	1.30	1.22–1.97	<0.05
HDL cholesterol, per 1 mmol/l	0.66	0.44–1.00	0.05
LDL cholesterol, per 1 mmol/l	0.88	0.77–0.99	<0.05
Daily alcohol consumption (ref. 0 g)			
>0–20 g	0.77	0.54–1.09	0.14
>20–60 g	0.72	0.51–1.03	0.07
>60 g	0.42	0.23–0.78	<0.05
Cups of coffee per day (ref. 0 cups)			
1–2	1.56	1.01–2.40	<0.05
3–4	2.42	1.57–3.72	<0.05
≥ 5	1.71	0.98–2.97	0.06
Use of tea	1.44	1.03–2.03	<0.05
Use of glucocorticoids	2.19	0.96–5.02	0.06

OR = Odds ratio; CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
* Logistic regression analysis, variables only included as main factors; all variables are listed which attained a statistical significance of $p < 0.1$.

Table 5. Independent risk factors for cholelithiasis in women*

	OR	95% CI	p*
Age, per 10-year increase	1.58	1.48–1.67	<0.05
Body mass index, per 5 kg/m^2	1.72	1.47–1.97	<0.05
HDL cholesterol, per 1 mmol/l	0.76	0.58–0.99	<0.05
LDL cholesterol, per 1 mmol/l	0.85	0.76–0.94	<0.05
Waist-to-hip ratio	7.39	1.02–53.51	<0.05
Parity	1.53	1.03–2.27	<0.05
Physical activity	0.76	0.60–0.96	<0.05
Cigarette smoking habits (ref. Never smoker)			
Former smoker	0.77	0.58–1.01	0.06
Current smoker	0.76	0.56–1.02	0.07

OR = Odds ratio; CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
* Logistic regression analysis, variables only included as main factors; all variables are listed which attained a statistical significance of $p < 0.1$.

sumption of >60 g. Coffee drinking was also independently related to cholelithiasis with the highest risk in persons who consumed 3–4 cups of coffee per day. Furthermore, the use of tea was independently related to the risk of cholelithiasis in men (table 4).

Similar to the male population, an advanced age, high BMI, and low serum HDL and LDL cholesterol levels were also associated with cholelithiasis in the female population. Further independent risk factors for gallstone formation in females were an increased WHR, parity and low physical activity. Additionally, cigarette smokers showed a lower risk of gallstones than non-smokers (table 5).

The food-frequency score was not identified as an independent risk factor for cholelithiasis in either males or females. Therefore, further analyses were repeated including each of the 15 specific items as a single variable into the model. Of note, none of these dietary factors met the criteria to be maintained in the final regression models. Additional analyses were also performed with different variations of the variable age (categorized to 6 and 12 strata, age^2). These analyses yielded similar results with respect to the independent risk factors identified with analyses that included age as a continuous variable.

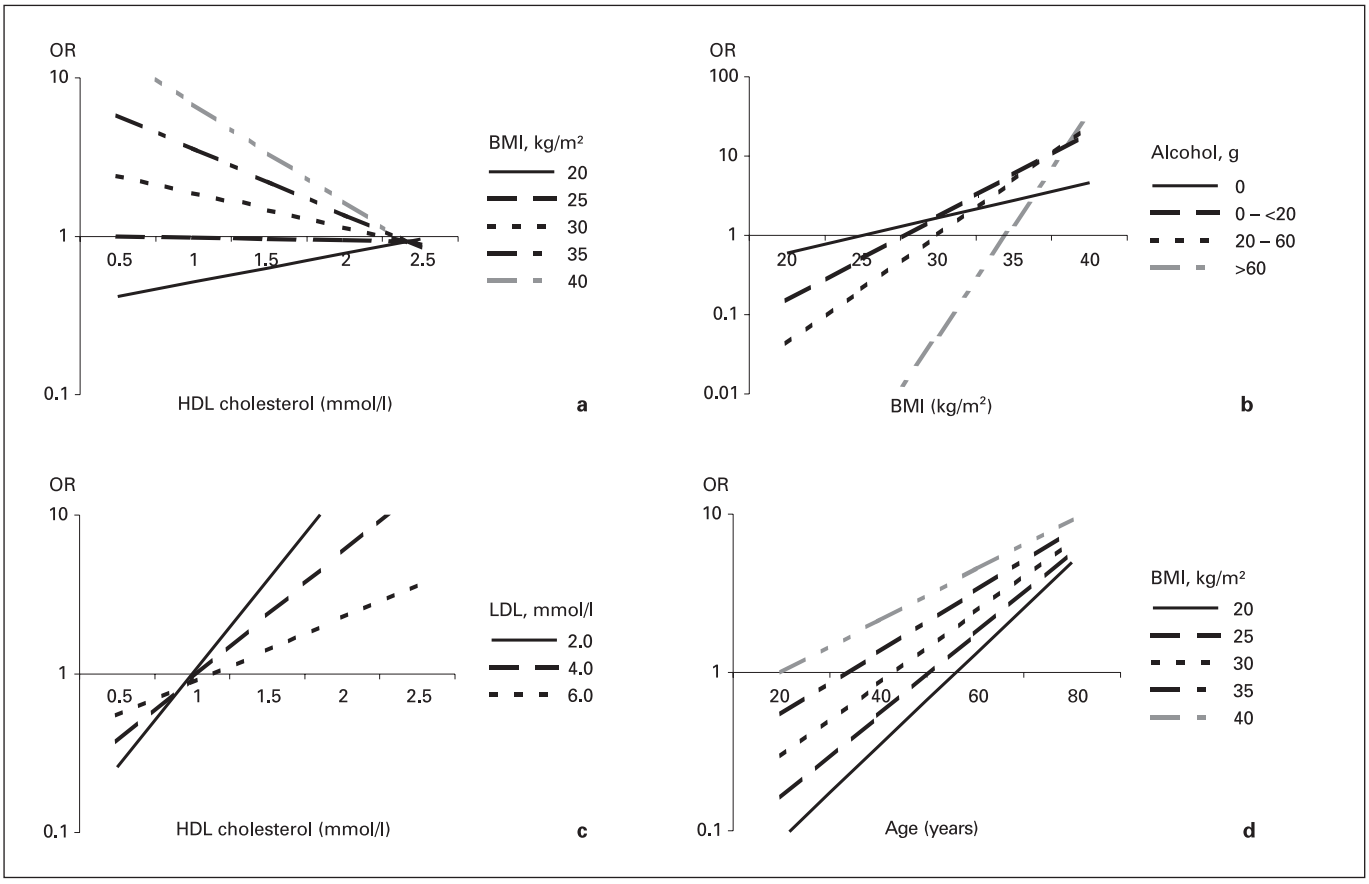

Fig. 2. Risk of cholelithiasis in the male population. **a** Interaction between HDL cholesterol and body mass index (BMI). **b** Interaction between mean daily alcohol intake and BMI. **c** Interaction between HDL and LDL cholesterol. **d** Risk of cholelithiasis in the female population. Interaction between age and BMI. OR = Odds ratio.

Interactions

Three two-way interactions among males were detected. Firstly, the effects of BMI were modulated by serum HDL cholesterol levels (β = –0.092; SE 0.048; p = 0.055). In slim persons and in individuals with normal BMI values, the risk of gallstones rose only slightly with increasing serum HDL levels. In overweight and obese individuals, however, the risk was especially high when low serum HDL cholesterol concentrations were also present (fig. 2a). Secondly, an interaction between the daily alcohol use and BMI was detected (β and SE for >0–20, >20–60 and >60 g alcohol/day, 0.144 ± 0.047, 0.104 ± 0.044 and 0.157 ± 0.064, respectively; p = 0.007). While alcohol consumption was inversely associated with the risk of cholelithiasis in subjects with lower BMI, such protective effects were not detectable in persons who were overweight or obese (fig. 2b). Thirdly, serum LDL cholesterol levels interacted with serum HDL cholesterol levels (β = –0.442; SE 0.161; p = 0.006). The beneficial effects of serum HDL cholesterol with respect to the cholelithiasis risk were especially relevant in persons with high serum LDL cholesterol concentrations (fig. 2c).

In women, two two-way interactions were found. Firstly, physical activity decreased the risk of gallstones in women who had never been pregnant by the factor 3.12, whereas in parous women the risk declined only by the factor 1.25 (β = 0.914; SE 0.484; p = 0.059). Secondly, the BMI modulated the effects of age on the risk of gallstones (β = –0.001; SE 0.001; p = 0.054). Increased BMI values were related to an increased risk of cholelithiasis at younger ages, whereas at older ages the BMI was less strongly associated with the gallstone risk (fig. 2d).

Risk Factors for Sonographically Detected Gallstones

All regression models were re-run after persons with a previous history of cholecystectomy had been excluded.

Among men, an advanced age (OR per 10-year increase 1.57, 95% CI 1.43–1.71) and an increased coffee consumption (OR for 3–4 cups of coffee vs. no coffee 2.22, 95% CI 1.28–3.85) were related to the risk of sonographically detected cholelithiasis. Alcohol consumption (OR for >60 g/day 0.33, 95% CI 0.13–0.80) and serum HDL cholesterol (OR per 1 mmol/l increase 0.53, 95% CI 0.31–0.89) showed an inverse relation to the gallstone risk. Furthermore, the interactions between alcohol and BMI (β and SE for >0–20, >20–60 and >60 g alcohol/day, 0.150 ± 0.058, 0.137 ± 0.057 and 0.113 ± 0.101, respectively; p = 0.045) and between serum HDL and LDL cholesterol levels (β = 0.407; SE 0.196; p = 0.038) attained again statistical significance.

In the female study population, an advanced age (OR per 10-year increase 1.50, 95% CI 1.38–1.62) and an increased BMI (OR per 5 kg/m^2 increase 1.27, 95% CI 1.10–1.44) could again be identified as independent risk factors for sonographically detected gallstones and physical activity showed protective effects against this risk (OR 0.61, 95% CI 0.45–0.84). The interaction between age and BMI also retained statistical significance (β = –0.003; SE 0.001; p = 0.007).

Discussion

In the present study the prevalence of cholelithiasis and its risk factors were analyzed using data from a population-based study that was conducted in a region where gallstone disease is a common disorder. The adjusted prevalence proportion of 18.8% observed in the adult population of this region is one of the highest ever reported [1]. Only native Americans exhibited a higher gallstone prevalence [23] and two European studies [15, 24], one from Norway [24] and the other from a neighboring region [15], revealed a similarly high prevalence.

In keeping with other studies [1, 4–8, 11, 15, 25–28] an advanced age and female gender were also major risk factors for cholelithiasis in the present study. Also in concordance with previous studies [7, 11, 25, 28–32], an increased BMI was independently associated with a higher risk of gallstones. In the total SHIP population, the adjusted prevalence proportion of being overweight and obesity were 63.4 and 24.0%, respectively. An increased BMI seems to be the most important avoidable risk factor in this population and therefore appears to largely account for the high gallstone prevalence in this region. The finding of an independent association between WHR and cholelithiasis that was present in the female subpopulation also reflects metabolic changes that play a pivotal role in gallstone development, especially in women.

In the present analyses, physical activity had an effect on the gallstone risk that was even independent from BMI and WHR in females. This finding is in line with previous studies [33] which could demonstrate beneficial effects of sports on gallstone formation in obese persons. High serum HDL cholesterol levels attenuated the gallstone risk related to high BMI in the male subpopulation also indicating the protective effects of physical activity in this context.

In good agreement with other studies [34], low serum HDL cholesterol concentrations were independently associated with the risk of gallstones in both subpopulations. Also in both sexes, low serum LDL cholesterol levels were associated with this risk. This finding was not expected, because in general increased rather than decreased serum LDL cholesterol levels predict the risk of gallstone disease [35, 36]. In the present study, effect modification and selection bias may explain this apparent discrepancy. Firstly, there was one two-way interaction between serum HDL and LDL cholesterol. In men, high serum HDL lowered the risk of cholelithiasis related to high serum LDL cholesterol. Secondly, further analyses that were performed after persons with previous cholecystectomy had been excluded, revealed no independent association between serum LDL cholesterol and the risk of sonographically detected gallstones. Although a decreased statistical power by a reduced size of the study population may also have led to the latter, the findings altogether indicate lifestyle changes after gallbladder surgery that had modified the effects of serum LDL cholesterol on the risk of cholelithiasis.

In line with other studies [4, 7–10, 27], alcohol drinking had protective effects on the gallstone risk in men. Also in agreement with other studies [12], coffee drinking increased this risk in men. Other studies [13, 14] yielded a low gallstone risk among coffee drinkers. The discrepancies may reflect gender- and ethnic-related differences and cultural aspects of nutrition that also play a role in the development of gallstones [32].

The present analyses demonstrated male tea drinkers to exhibit an elevated gallstone risk. This is in contrast to two prior studies [12, 37] that did not reveal tea drinking as a relevant risk factor for cholelithiasis. After persons with previous cholecystectomy were excluded from the analyses, the association between tea drinking and the gallstone risk was no longer present. This could argue for a change in habits after gallbladder surgery with respect to coffee consumption and thus for a spurious association

between tea drinking and cholelithiasis. An alternative explanation would be that gallstones become symptomatic earlier in tea drinkers or the disease is diagnosed earlier for other reasons in these persons. Similar confounding may also explain the association between smoking and cholelithiasis in women that likewise no longer attained statistical significance after persons with previous cholecystectomy were excluded from the analyses.

In contrast to previous studies [2, 14], none of the other nutritional factors that were considered as potential risk factors showed an independent association with gallstone risk. This may reflect the difficulties involved in accurately assessing nutrition in epidemiological studies. Moreover, variables such as BMI, WHR and serum lipid levels may be regarded as the net sum of single measurements of nutritional variables. Similar reasons may have caused the absence of an association between social factors and the risk of cholelithiasis.

This study has some limitations. Firstly, the present study is cross-sectional. Re-assessments of cohort studies may be useful to further explore the role of interactions with respect to gallstone formation and well-designed intervention studies are needed to investigate the protective effects of physical activity versus diet on the gallstone risk, especially in individuals who are overweight. Secondly, we did not adjust for multiple testing because of the exploratory nature of our analyses for interactions. This may have given rise to spurious associations. Thirdly, in order to reduce the number of analyses, interactions were only tested between those risk factors that attained a statistical significance of $p < 0.1$ in the regression models. Therefore, it cannot fully be excluded that some relevant effect modifiers may have been overseen.

In conclusion, female sex, an advanced age and an increased BMI are major risk factors for cholelithiasis in this region where cholelithiasis is a common disorder. Programs that are designed to prevent gallstone formation should not only be focused on BMI reduction by optimizing dietary factors but should also be aimed at increasing physical activity, especially among women.

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