PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

ELSEVIER

World J Gastroenterol 2005;11(43):6800-6806
World Journal of Gastroenterology ISSN 1007-9327

• *CLINICAL RESEARCH* •

Pregnancy is not a risk factor for gallstone disease: Results of a randomly selected population sample

Thomas Walcher, Mark Martin Haenle, Martina Kron, Birgit Hay, Richard Andrew Mason, Alexa Friederike Alice von Schmiesing, Armin Imhof, Wolfgang Koenig, Peter Kern, Bernhard Otto Boehm, Wolfgang Kratzer

Thomas Walcher, Mark Martin Haenle, Richard Andrew Mason, Alexa Friederike Alice von Schmiesing, Bernhard Otto Boehm, Wolfgang Kratzer, Department of Internal Medicine I, University Hospital Ulm, Ulm, Germany
Martina Kron, Birgit Hay, Department of Biometry and Medical Documentation, University of Ulm, Ulm, Germany
Armin Imhof, Wolfgang Koenig, Department of Internal Medicine II, University Hospital Ulm, Ulm, Germany
Peter Kern, Department of Internal Medicine III, Section of Infectious Diseases and Clinical Immunology, University Hospital Ulm, Ulm, Germany
Co-first-authors: Thomas Walcher and Mark Martin Haenle
Correspondence to: W. Kratzer, PD Dr Med., University Hospital Ulm, Department of Internal Medicine I, Robert-Koch-Str. 8, D-89081 Ulm,
Germany. wolfgang.kratzer@medizin.uni-ulm.de.
Telephone: +49-731-50024536 Fax: +49-731-50024867
Received: 2005-04-11 Accepted: 2005-05-24

Abstract

AIM: To investigate the prevalence, risk factors, and selection of the study population for cholecystolithiasis in an urban population in Germany, in relation to our own findings and to the results in the international literature.

METHODS: A total of 2 147 persons (1 111 females, age 42.8 ± 12.7 years; 1 036 males, age 42.3 ± 13.1 years) participating in an investigation on the prevalence of *Echinococcus multilocularis* were studied for risk factors and prevalence of gallbladder stone disease. Risk factors were assessed by means of a standardized interview and calculation of body mass index (BMI). A diagnostic ultrasound examination of the gallbladder was performed. Data were analyzed by multiple logistic regression, using the SAS statistical software package.

RESULTS: Gallbladder stones were detected in 171 study participants (8.0%, *n* = 2 147). Risk factors for the development of gallbladder stone disease included age, sex, BMI, and positive family history. In a separate analysis of female study participants, pregnancy (yes/no) and number of pregnancies did not exert any influence.

CONCLUSION: Findings of the present study confirm that age, female sex, BMI, and positive family history are risk factors for the development of gallbladder stone disease. Pregnancy and the number of pregnancies, however, could not be shown to be risk factors. There seem to be no differences in the respective prevalence for gallbladder stone disease in urban and rural populations.

Key words: Cholecystolithiasis; Pregnancy; Risk factors; Selection bias; Ultrasonography

Walcher T, Haenle MM, Kron M, Hay B, Mason RA, von Schmiesing AFA, Imhof A, Koenig W, Kern P, Boehm BO, Kratzer W. Pregnancy is not a risk factor for gallstone disease: Results of a randomly selected population sample. *World J Gastroenterol* 2005; 11(43): 6800-6806
http://www.wjgnet.com/1007-9327/11/6800.asp

INTRODUCTION

Disorders of the gallbladder are a major cause of morbidity and a leading indication for hospital admissions in the United States[1-4] and in Europe[5,6]. In these developed nations, the economic impact of gallstone disease is high[1-5]. In the United States, more than 500 000 cholecystectomies are performed annually and direct costs for the diagnosis and treatment of gallbladder stones are estimated at 5 billion US Dollar per year[7,8]. For the treatment of gallstone disease in Germany, 200 inpatient hospital days per 10 000 health insured persons accumulate every year[9]. This creates costs of more than ½ billion[10]. Gallstone disease is not only an unsolved problem in Western industrialized nations but also in African nations[11,12] as well as in Asian countries like China, India, Bangladesh, and Japan[13-17]. Cholelithiasis is one of the commonest surgical diseases in China and accounted for 11.5% of overall hospitalized patients during the period from 1985 to 1995[18].

The most important risk factors for the development of gallstone disease currently being discussed in the literature include age[19-23], female gender[14,20-22,24], obesity[6,25-28] and heredity[19,20,29-31]. Other factors like pregnancy or number of pregnancies are still discussed are contradictory[12,21,32-34].

To our knowledge, there are no publications that assess the influence of the selection of study population on gallstone disease prevalence.

The present prospective ultrasound-based survey investigates the prevalence and risk factors for cholecystolithiasis in an urban population and also addresses the effect of selection of study population on the different risk factors.

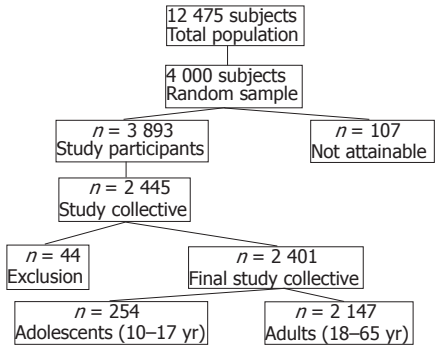

Figure 1 Study collective and participation.

MATERIALS AND METHODS

Study collective and participation

A random sample of 4 000 subjects was selected from the population of a city in southwestern Germany (total population: 12 475) for participation in a seroprevalence study for *Echinococcus multilocularis*. Of the 4 000 randomly selected and invited subjects, 107 could not be included in the final evaluation due to factors such as non-response to repeated invitations or incompetent legal status (n = 39), or moved away with no forwarding address (n = 68), resulting in a total random sample size of 3 893 subjects. Out of this pool, a total of 2 445 persons actually participated in the study (response rate: 62.8%). The following inclusion and exclusion criteria determined the composition of the collective studied for gallbladder stone disease (Figure 1):

Only persons in the age of 10-65 years were included into the study. Written consent for the examination and collection of personal health information was required.

Failure to visualize and assess the gallbladder or poor or restricted examination conditions lead to the exclusion from the study collective (n = 26 subjects). Significant contraction of the gallbladder following an inadequate fasting period (when no clinical signs of cholecystitis were identified) (n = 9 subjects), a history of cholecystectomy for gallbladder polyps or cholecystectomy of unknown reason (n = 4 subjects) or subject's refusal to undergo examination (n = 1 subject) also constituted exclusion criteria. Missing or invalid data acquisition (n = 4 subjects). Patients with prior cholecystectomy for gallbladder stones were added in the calculations of the gallbladder stone prevalence.

The total collective of subjects undergoing ultrasound examination of the gallbladder was 2 401 persons. In order to enhance comparability with published studies, we explicitly examined adult subjects aged 18-65 years. This non-selected adult collective consisted of 2 147 subjects (1 036 males, 48.3%; 1 111 females, 51.7%).

Subjects' informed written consent was obtained for examination and collection of personal health information. The study met the international agreements of the Helsinki Declaration from 1996 and was approved by the research Ethics Committee of the Baden-Württemberg General Medical Council (Landesärztekammer Baden-Württemberg).

Questionnaire and physical examination

Under the guidance of a trained interviewer, each subject completed a comprehensive questionnaire covering the following parameters: Demographic information (age, sex, nationality, marital status, education, occupation), recreational activities (sports, exercise), medical history (gallbladder stones, gastrointestinal, hepatic, cardiovascular, respiratory, endocrine, renal, rheumatic, or malignant diseases), dietary behavior (meal patterns including intake of certain foods; fluid intake including alcohol, use of tobacco products), family history (gall bladder stone disease, diabetes mellitus, overweight, history of cancer) and medication history.

Based on the recommendations of the WHO[35] for anthropometric measurements, patients then underwent determination of body height and weight and waist and hip circumference. BMI was calculated according to the common formula[35].

Ultrasound examination

Study participants were asked to present for the examination following a 4-h fasting period. All subjects underwent ultrasound examination of the upper abdomen under standard conditions to assure exact evaluation of the gallbladder. In order to enhance visualization of the gallbladder, subjects were asked to raise their right arm over their head, which increases both the intercostal spaces and the distance between the lower margin of the rib cage and the iliac crest. Examination was performed upon deep inspiration and with outward pressure on the abdominal wall.

The gallbladder was examined in three planes (longitudinal, cross-sectional and diagonal), providing the examiner with a three-dimensional impression of the organ. In cases in which cholecystolithiasis was present, the mobility of the stone(s) was assessed. Subjects, in whom differentiation between mobile stones and wall-adhering polyps was difficult, were examined again in standing position in order to reliably distinguish between stone and polyps on the basis of their mobility. The thickness of the gallbladder wall was measured and, in subjects with gallbladder stones, the number, size, and localization of stones before mobilization were determined. Ultrasound examinations were performed by a group of six examiners trained in gallbladder sonography. These examiners worked under supervision of an experienced specialist (>4 000 examinations per year), who also reviewed all questionable findings. Examinations were performed using four identical, state-of-the-art HDI-5000 ultrasound scanners (Advanced Technology Laboratories Ultrasound, Philips Medical Systems, Bothell, WA, USA).

Criteria for the diagnosis of gallstones were as follows: one or more hyperechoic structure(s) in the gallbladder with dorsal shadow; one or more hyperechoic structure(s) in the gallbladder without dorsal shadow but which by means of examination in multiple planes and/or attempt at mobilization can be certainly distinguished from a gallbladder septum, Heister's valve or a gallbladder polyp; a strongly hyperechoic structure with dorsal shadow in

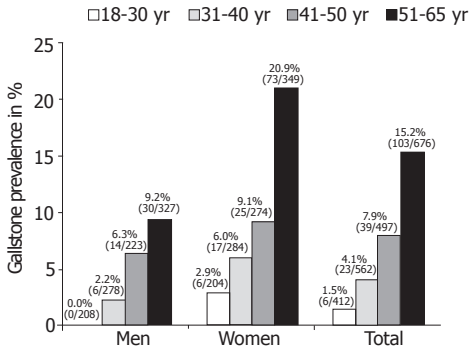

Figure 2 Distribution of gallbladder stone prevalence in relation to sex and age.

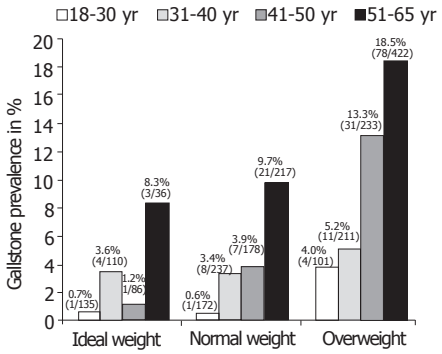

Figure 3 Prevalence of gallbladder stones in relation to BMI and age.

the anatomic location of gallbladder, with no or only slight visualization of residual gallbladder lumen; failure to delineate the gallbladder lumen in patients who have undergone prior cholecystectomy and who demonstrate corresponding surgical incisions in the right upper abdominal quadrant; presence of a significant amount of gallbladder sludge filling at least one-quarter of the gall bladder lumen with corresponding dorsal shadow.

Subjects, who because of recent food intake or other reasons, such as overlying intestinal gas, presented unfavorable examination conditions, were excluded from the study.

Statistical analysis

Multiple logistic regression[36] was performed to assess the impact of the known risk factors age, sex, BMI, and positive family history on the development of gallbladder stones. Two further multiple logistic regression models were fitted for female study participants in order to assess the impact of pregnancy and number of pregnancy, whereby in both models odds ratios were adjusted for the known risk factors like age, BMI, and positive family history for gallbladder stones. Odds ratios with 95% confidence interval and corresponding *P*-value are given. Statistical analyses were performed using the SAS statistical software package (version 8.02).

RESULTS

Prevalence in relation to age and sex

Gallbladder stones were detected at upper abdominal ultrasound examination in 87 of 2 147 subjects examined (4.1%), while gallbladder sludge was identified in two subjects (0.1%). A further 84 subjects (3.9%) had undergone prior cholecystectomy for the treatment of gallbladder stone disease. Thus, 171 subjects satisfied the inclusion criteria for cholecystolithiasis, representing an overall prevalence of cholecystolithiasis of 8.0% in the study population.

Among females, the proportion of subjects with current or prior gallbladder stone disease stood at 10.9% (121 of 1 111 subjects), while 4.8% of males (50 of 1 036 subjects) fulfilled the criteria for the diagnosis of cholecystolithiasis. The prevalence of gallbladder stone disease was higher for females than for males in all age classes. The highest prevalence was found in the group of females aged 51-65 years (20.9%; 73 of 349 subjects; Figure 2). Overall, the prevalence of gallbladder stones (defined as current and past cholecystolithiasis) increases with advancing age from 1.5% among subjects aged 18-30 years to 15.2% in the 51-65 years age group.

Prevalence in relation to BMI

BMI was calculated in 99.6% of study participants (n = 2 138). Mean BMI for the subcollective of subjects without gallbladder stone disease was 25.8±4.9 kg/m^2 (median 25.1 kg/m^2; range: 14.1-52.6 kg/m^2). Corresponding value for subjects with current or prior cholecystolithiasis was 29.2±5.9 kg/m^2 (median 28.7 kg/m^2; range: 17.6-51.5 kg/m^2). For description, BMI results were assigned to one of three classes defined according to the recommendations of the World Health Organization (WHO; Figure 3).

Class I, defined as at or below a subject's respective ideal weight (BMI <21 kg/m^2 in females and <22 kg/m^2 in males), included 367 subjects (17.2%). Class II (BMI 21-25 kg/m^2 in females and 22-26 kg/m^2 in males) included 804 subjects (37.6%), while 967 subjects (45.2%) met the criteria for Class III (BMI >25 kg/m^2 in females and BMI >26 kg/m^2 in males), and thus were considered as overweight. Only 9 subjects (2.5%) in BMI Class I exhibited evidence of gallbladder stone disease compared to 37 subjects (4.6%) in Class II and 124 subjects (12.8%) in Class III (Figure 3).

Prevalence in relation to positive family history of gallbladder stones

Of 2 147 subjects, 105 (4.9%) were unable to provide information on their biological parents; thus, evaluation of the influence of hereditary predisposition was limited to a subcollective of 2 042 subjects. Gallbladder stones were diagnosed more frequently in subjects with a positive family history of cholecystolithiasis. In subjects with a positive family history involving one biological parent, the prevalence of gallbladder stones stood at 12.6% (51 of 405 subjects) and at 14.3% (3 of 21 subjects) in subjects, both of whose biological parents suffered from gallbladder stone disease. In the remaining 1 616 subjects with negative family history of gallbladder stone disease, prevalence of cholecystolithiasis stood at only 6.3% (n = 102).

Table 1 Classical risk factors of cholecystolithiasis in multiple logistic regression

Classical risk factors	Odds ratio (OR)	95%CI	*P*
Age (per yr)	1.06	1.05–1.08	<0.001
Female sex	2.78	1.91–4.07	<0.001
BMI (per kg/m^2)	1.12	1.08–1.15	<0.001
Positive family history	1.89	1.30–2.75	<0.001

Table 2 History of pregnancy and the number of prior pregnancies in the multiple logistic regression model (only females)

Factor tested	Odds ratio (OR)	95%CI	*P*
Age (per yr)	1.06	1.04–1.08	<0.001
BMI (per kg/m^2)	1.11	1.07–1.15	<0.001
Positive family history	1.99	1.28–3.07	0.002
Positive history of pregnancy	0.76	0.44–1.31	0.321

Prevalence in relation to pregnancy

All female study subjects were questioned about their pregnancy status. Fifteen women declined to provide information on prior pregnancy. Of the remaining 1 096 subjects included in this analysis, 26.3% (n = 288) reported never having been pregnant. The group of women with positive history of pregnancy (n = 808, 73.7%) was broken down into the group with one to two pregnancies (560 women, 51.1%) and those with three or more pregnancies (248 women, 22.6%). Gallbladder stones were detected in 22 of 288 nulliparae (7.6%). In the group of 560 women with one or two pregnancies, 55 subjects (9.8%) were positive for past or present cholecystolithiasis, compared to 43 subjects (17.3%) in the group of patients with three or more pregnancies.

Multiple logistic regression analysis

Multiple logistic regression showed a strong association of the factor "age" with the development of gallbladder stones (OR 1.11 per year of age; 95%CI: 1.05-1.08; P<0.001; Table 1). The comparison of females to males yielded an odds ratio of 2.78 (95%CI: 1.91-4.07; P<0.001; Table 1). Body mass index (BMI in kg/m^2) also was an important risk factor (OR 1.12 per-unit; 95%CI: 1.08-1.15; P<0.001; Table 1). Compared to study subjects without known gallbladder stone disease in the biological parents, persons with a positive parental history of cholecystolithiasis showed an odds ratio of 1.89 (95%CI: 1.30-2.75; P<0.001; Table 1).

In separate logistic regression models for females including the risk factors age, BMI, and family history, neither pregnancy nor number of pregnancies showed an association with the development of gallbladder stone disease. The first model revealed an OR of 0.76 for pregnancy yes *vs* no (95%CI: 0.44-1.31; P = 0.321; Table 2) and the second model an OR of 0.65 for one or two pregnancies *vs* no pregnancy and an OR of 1.04 for three or more pregnancies *vs* no pregnancy (95%CI: 0.37-1.15 and 0.56-1.94; P = 0.104; Table 3).

Table 3 Number of pregnancies in the multiple logistic regression model (only females)

Factor tested	Odds ratio (OR)	95%CI	*P*
Age (per yr)	1.06	1.04–1.08	<0.001
BMI (per kg/m^2)	1.11	1.07–1.15	<0.001
Positive family history	2.09	1.34–3.25	<0.001
Number of pregnancies			0.104
One or two *vs* none	0.65	0.37–1.15	
Three or more *vs* none	1.04	0.56–1.94	

DISCUSSION

The present ultrasound-based epidemiological survey is, to our knowledge, the first study conducted in a collective drawn from an urban population in Germany. The prevalence of gallbladder stone disease in our unselected collective stands at 8.0%. Our findings are comparable, on one hand, with those documented in a rural population and in a collective of blood donors in Germany[19,20], and, on the other, with the prevalence figures reported from Italian, British, and Danish studies[21,27,33,37], but our results are not comparable with the low prevalences from Eastern countries such as China, India, Japan, Taiwan, and Thailand[14,16,17,23,38] (Figure 4).

The prevalence of gallbladder stone disease (predominantly cholesterol gallstones) reported from a majority of European and American studies shows a clear female dominance. In Asian countries with a higher prevalence of pigment gallstones, the female dominance is less distinct[6,23,38]. In the present study, female sex was also found to be a clear risk factor (OR = 2.78; 95%CI: 1.91-4.07; P<0.001) and the ratio of males with gallbladder stone disease to females stood at 1 to 2.3. Due to the great importance of the risk factors, age and especially female sex, the selection modalities of study collectives gain paramount importance[6,37]. Comparing gallbladder stone prevalence in women in relation to the method of selecting the study population, the highest prevalence is observed in studies conducted as a cross sectional sample of the total population[20–22] or large random samples[14,24] (Table 4). Most large European studies were conducted either as random samples[24,39,40] or as surveys of entire factories or governmental departments[32,41] (Table 4).

Our findings from Leutkirch (total prevalence 8.0%) are comparable to those reported for populations in Römerstein (7.8%) and blood donors in Ulm (6.0%) as well as to Italian studies conducted in Sirmione (6.9%) and Chianciano (5.9%), all of which were conducted as cross-sectional sample of the total population[19–22] (Figure 4).

The prevalence of gallbladder stones in our study collective is lower in younger persons than in those belonging to older age groups. Similar trends toward higher gallbladder stone prevalence in older persons have been described in nearly all sonographic studies[6,19,20,23,25], as well as in autopsy studies[37] and in studies based on clinical symptoms[42] (Figure 4).

Using multiple regression analysis under consideration

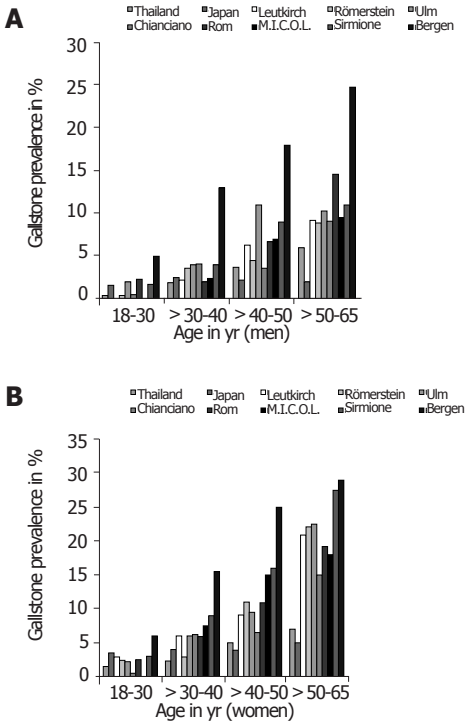

Figure 4 Age adjusted gallbladder stone prevalence in males and females in comparable large studies. **A:** in men; **B:** in women.

of the known risk factors age, sex, and family history, we found an association with study participants' current BMI (OR 1.12/unit; 95%CI: 1.08-1.15; $P<0.0001$). As in most other European studies, our findings showed an increased prevalence of gallbladder stone disease in overweight subjects[6,25–28]. The prevalence of gallbladder stones in subjects with a positive family history in the biological parents (12.7%) is more than twice as high as that in subjects with negative family history (6.3%). Our findings point to a strong effect for genetic factors in the pathogenesis of cholecystolithiasis (OR = 1.89; 95%CI: 1.30-2.75; $P<0.001$), although the mechanism of inheritance is not known. A familial accumulation of cholecystolithiasis cases has been observed in other sonographic screening studies in first-degree relatives of persons suffering from gallbladder stones[6,29-31,39].

The multiple logistic regression model failed to show an increased prevalence of gallbladder stones for female subjects with prior pregnancy (prevalence 12.1% *vs* 7.6%). One reason might be the much lower average age of the nulliparae (33.6±13.7 years) compared to women who had borne children (46.0±10.7 years), suggesting that the higher prevalence may actually be an age-related phenomenon. This effect is also apparent in the increased prevalence of gallbladder stones in women with three or more pregnancies (average age 48.9±9.7 years) compared with women who had been pregnant only one or two times (average age 44.7±10.9 years). The analysis of pregnancy as a risk factor for cholecystolithiasis has lead to different results in the literature[12,21,32–34] which range from no effect to a prevalence that is reduced by a factor of 40 in comparison of nulliparae to women who have been pregnant[15,43] (Table 5). The old clinical experience of an increased prevalence of gallbladder stones in women who have borne children could not be substantiated by the findings of the present study.

Table 4 Relative risk for gall bladder stones in relation to selection of study population

Place/region	Population selection	*n*	Sex distribution male:female
Chiayi[23]	Random sample	923	1:1.0
Rome[32]	Factory	2 325	1:1.1
Bergen[40]	Random sample	1 371	1:1.1
Ulm[19]	Blood donors	1 116	1:1.1
Copenhagen[44]	Random sample	4 807	1:1.4
Chiang Mai[38]	Random sample	6 146	1:1.5
Schwedt[41]	Factory	1 616	1:1.6
Okinawa[17]	Inhabitants of an island	2 584	1:1.7
Jiaotong[14]	Random sample	15 856	1:2.0
M.I.C.O.L[24]	Random sample	29 739	1:2.0
Römerstein[20]	Total survey	2 498	1:2.1
Sirmione[21]	Total survey	1 911	1:2.2
Cianciano[22]	Total survey	1 804	1:2.3
Leutkirch	Random sample	2 401	1:2.3

In conclusion, the classical risk factors age, female sex, body mass index (BMI), and positive family history have been confirmed by the findings of the present study. The female-specific factors of prior pregnancy and number of prior pregnancies, however, could not be shown to exert measurable influence on the prevalence of gallbladder stones. The selection of study populations affects study results i.e. the strength of the effect of female sex on the development of gallbladder stones. There does not appear to be a difference between the prevalence of gallbladder stones in urban and rural populations.

ACKNOWLEDGMENTS

The study was initiated by the Government of the state of Baden-Württemberg, Germany. Financial support was granted via the work of the Baden-Württemberg state health office, District Government Stuttgart, Germany as well as the regional health office from Ravensburg, Germany. Further support was granted by the administration of the city of Leutkirch, Germany. Vials for blood samples and part of the laboratory testing were supplied by Sarstedt AG & Co., Nürnbrecht, Germany. BOB is supported by the German Research Council (GRK 1041). The authors wish to express their gratitude to Mr. Walter Feucht of the ULDO Backwaren Company, Neu-Ulm, Germany for his generous support of this study. Without his participation, the rapid evaluation and prompt analysis of the data would not have been possible. The following members of the EMIL-Study-Group contributed to the accomplishment of this study: Adler G, Armsen A, Banzhaf H-M, Bauerdick M, Bertling U, Boehm BO, Brandner BO, Brockmann SO, Deckert M, Dingler C, Eggink S, Fuchs M, Gaus W, Goussis H, Gruenert A, Haenle MM, Hampl W, Haug C, Hay B, Huetter M-L, Imhof A, Kern P, Kimmig P, Kirch A, Klass D, Koenig

Table 5 Review of published studies addressing the effect of the factor "pregnancy" on the prevalence of gallbladder stones

Factor by which the prevalence of gallstone disease in women with prior pregnancy is increased	1.0–1.5 times	1.6–2.5 times	2.6–10 times	11 – 50 times
Studies showing a quantitative relation between cholecystolithiasis and pregnancy	1966 Framingham[42] 1988 Sirmione[21] 1985 San Antonio[45] 1985 Maastricht[46]	1982 Oxford[47] 1982 Kopenhagen[44]	1979 Stockholm[48] 1982 Rom[32] 1986 Schwedt[41] 1986 Chianciano[22] 1991 Santiago[49]	1988 Srinagar[15]
Studies not showing a quantitative relation between cholecystolithiasis and pregnancy		1956 Birmingham[50] 1970 Pima reservation[51] 1980 Boston[52] 1982 Oberpfuss[53] 1983 Oxford[54] 1984 Adelaide[55] 1989 Soweto[12] 1990 Dublin[43] 1995 Ulm[19] 1996 Römerstein[20] 2002 Leutkirch		

W, Kratzer W, Kron M, Manfras B, Meitinger K, Mertens T, Oehme R, Pfaff G, Piechotowski I, Reuter S, Romig T, von Schmiesing AFA, Steinbach G, Tourbier M, Voegtle A, Walcher T, Wolff S.

REFERENCES

1 National Institutes of Health Consensus Development Conference Statement on Gallstones and Laparoscopic Cholecystectomy. *Am J Surg* 1993; 165: 390-398
2 **Russo MW,** Wei JT, Thiny MT, Gangarosa LM, Brown A, Ringel Y, Shaheen NJ, Sandler RS. Digestive and liver diseases statistics, 2004. *Gastroenterology* 2004; **126**: 1448-1453
3 **Diehl AK.** Epidemiology and natural history of gallstone disease. *Gastroenterol Clin North Am* 1991; **20**: 1-19
4 **Sandler RS,** Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R. The burden of selected digestive diseases in the United States. *Gastroenterology* 2002; **122**: 1500-1511
5 **Kang JY,** Ellis C, Majeed A, Hoare J, Tinto A, Williamson RC, Tibbs CJ, Maxwell JD. Gallstones--an increasing problem: a study of hospital admissions in England between 1989/1990 and 1999/2000. *Aliment Pharmacol Ther* 2003; **17:** 561-569
6 **Kratzer W,** Mason RA, Kächele V. Prevalence of gallstones in sonographic surveys worldwide. *J Clin Ultrasound* 1999; **27**: 1-7
7 **Everhart JE**. US government printing office. *US government printing* 1994; 647-649
8 Hall MJ, Owings MF. 2000 National Hospital Discharge Survey. Adv Data 2002;:1-18
9 Bundesministerium für Gesundheit. Morbidität - Krankenhausfälle und Arbeitsunfähigkeit. In: Der Bundesminister für Gesundheit, editor. Daten des Gesundheitswesens. Baden-Baden: Nomos, 1993: 34-43
10 Bundesministerium für Gesundheit. Gallensteine (ICD 574). In: Der Bundesminister für Gesundheit, editor. Ernährungsabhängige Krankheiten und ihre Kosten. Baden-Baden: Nomos, 1993: 187-193
11 **Safer L,** Bdioui F, Braham A, Ben Salem K, Soltani MS, Bchir A, Saffar H. [Epidemiology of cholelithiasis in central Tunisia. Prevalence and associated factors in a nonselected population] *Gastroenterol Clin Biol* 2000; **24:** 883-887
12 **Walker AR,** Segal I, Posner R, Shein H, Tsotetsi NG, Walker AJ. Prevalence of gallstones in elderly black women in Soweto, Johannesburg, as assessed by ultrasound. *Am J Gastroenterol* 1989; **84**: 1383-1385
13 **Shi JS,** Ma JY, Zhu LH, Pan BR, Wang ZR, Ma LS. Studies on gallstone in China. *World J Gastroenterol* 2001; **7**: 593-596
14 **Zhao Y,** Zhang R, Hu Y, Li R, Liang L, Gang Y. An epidemiological survey of gallstones with gray-scale ultrasound *Huaxi Yike Daxue Xuebao* 1990; **21:** 217-220
15 **Khuroo MS,** Mahajan R, Zargar SA, Javid G, Sapru S. Prevalence of biliary tract disease in India: a sonographic study in adult population in Kashmir. *Gut* 1989; **30:** 201-205
16 **Dhar SC,** Ansari S, Saha M, Ahmad MM, Rahman MT, Hasan M, Khan AK. Gallstone disease in a rural Bangladeshi community. *Indian J Gastroenterol* 2001; **20:** 223-6
17 **Nomura H,** Kashiwagi S, Hayashi J, Kajiyama W, Ikematsu H, Noguchi A, Tani S, Goto M. Prevalence of gallstone disease in a general population of Okinawa, *Japan. Am J Epidemiol* 1988; **128:** 598-605
18 **Zhu X,** Zhang S, Huang Z. [The trend of the gallstone disease in China over the past decade] *Zhonghua Waike Zazhi* 1995; **33:** 652-658
19 **Kratzer W,** Kächele V, Mason RA, Hill V, Hay B, Haug C, Adler G, Beckh K, Muche R. Gallstone prevalence in Germany: the Ulm Gallbladder Stone Study. *Dig Dis Sci* 1998; **43**: 1285-1291
20 **Kratzer W,** Kron M, Hay B, Pfeiffer MM, Kächele V. Prevalence of cholecystolithiasis in South Germany--an ultrasound study of 2,498 persons of a rural population. *Z Gastroenterol* 1999; **37**: 1157-1162
21 **Barbara L,** Sama C, Morselli Labate AM, Taroni F, Rusticali AG, Festi D, Sapio C, Roda E, Banterle C, Puci A. A population study on the prevalence of gallstone disease: the Sirmione Study. *Hepatology* 1987; **7:** 913-917
22 **Loria P,** Dilengite MA, Bozzoli M, Carubbi F, Messora R, Sassatelli R, Bertolotti M, Tampieri A, Tartoni PL, Cassinadri M. Prevalence rates of gallstone disease in Italy. The Chianciano population study. *Eur J Epidemiol* 1994; **10**: 143-150
23 **Lu SN,** Chang WY, Wang LY, Hsieh MY, Chuang WL, Chen SC, Su WP, Tai TY, Wu MM, Chen CJ. Risk factors for gallstones among Chinese in Taiwan. A community sonographic survey. *J Clin Gastroenterol* 1990; **12:** 542-526
24 **Attili AF,** Carulli N, Roda E, Barbara B, Capocaccia L, Menotti A, Okoliksanyi L, Ricci G, Capocaccia R, Festi D. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholelithiasis (M.I.COL.) *Am J Epidemiol* 1995; **141:** 158-165
25 **Méndez-Sánchez N,** Chavez-Tapia NC, Motola-Kuba D, Sanchez-Lara K, Ponciano-Rodríguez G, Baptista H, Ramos MH, Uribe M. Metabolic syndrome as a risk factor for gallstone disease. *World J Gastroenterol* 2005; **11:** 1653-7
26 **Kono S,** Shinchi K, Todoroki I, Honjo S, Sakurai Y, Wakabayashi K, Imanishi K, Nishikawa H, Ogawa S, Katsurada M.

Gallstone disease among Japanese men in relation to obesity, glucose intolerance, exercise, alcohol use, and smoking. *Scand J Gastroenterol* 1995; **30**: 372-376

27 **Heaton KW,** Braddon FE, Mountford RA, Hughes AO, Emmett PM. Symptomatic and silent gall stones in the community. *Gut* 1991; **32**: 316-320

28 **Kodama H,** Kono S, Todoroki I, Honjo S, Sakurai Y, Wakabayashi K, Nishiwaki M, Hamada H, Nishikawa H, Koga H, Ogawa S, Nakagawa K. Gallstone disease risk in relation to body mass index and waist-to-hip ratio in Japanese men. *Int J Obes Relat Metab Disord* 1999; **23**: 211-216

29 **Barbara L,** Festi D, Morselli AM, Labate, Roda E, Rusticali AG et al. The sirmione study: familial frequency of gallstone disease. *Hepatology* 1984; **4**:1086

30 **Nürnberg D,** Berndt H, Pannwitz H. [Familial incidence of gallstones]. *Dtsch Med Wochenschr* 1989; **114**: 1059-1063

31 **Sarin SK,** Negi VS, Dewan R, Sasan S, Saraya A. High familial prevalence of gallstones in the first-degree relatives of gallstone patients. *Hepatology* 1995; **22**: 138-141

32 **Prevalence of gallstone disease in an Italian adult female population.** Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO). *Am J Epidemiol* 1984; **119**: 796-805

33 **Jørgensen T.** Gall stones in a Danish population: fertility period, pregnancies, and exogenous female sex hormones. *Gut* 1988; **29**: 433-439

34 **Hossain GA,** Islam SM, Mahmood S, Chakrabarty RK, Akhter N. Gall stone in pregnancy. *Mymensingh Med J* 2003; **12**: 112-116

35 **WHO Expert Committee** on Physical Status: the Use and Interpretation of Anthropometry: report of a WHO expert committee (WHO technical report series). *Genf: World Health Organization* 1995; 427-437

36 **Hosmer DWJr**, Lemeshow S. Applied logistic regression. *New York: Wiley*; 1989

37 **Brett M,** Barker DJ. The world distribution of gallstones. *Int J Epidemiol* 1976; **5**: 335-341

38 **Prathnadi P,** Miki M, Suprasert S. Incidence of cholelithiasis in the northern part of Thailand. J Med Assoc Thai 1992; 75: 462-470

39 **Jørgensen T.** Gallstones in a Danish population: familial occurrence and social factors. *J Biosoc Sci* 1988; **20**: 111-120

40 **Glambek I,** Kvaale G, Arnesjö B, Søreide O. Prevalence of gallstones in a Norwegian population. *Scand J Gastroenterol* 1987; **22**: 1089-1094

41 **Berndt H,** Nürnberg D, Pannwitz H. [Prevalence of cholelithiasis. Results of an epidemiologic study using sonography in East Germany] *Z Gastroenterol* 1989; **27**: 662-666

42 **Friedman GD,** Kannel WB, Dawber TR. The epidemiology of gallbladder disease: observations in the Framingham Study. *J Chronic Dis* 1966; **19**: 273-292

43 **Basso L,** McCollum PT, Darling MR, Tocchi A, Tanner WA. A study of cholelithiasis during pregnancy and its relationship with age, parity, menarche, breast-feeding, dysmenorrhea, oral contraception and a maternal history of cholelithiasis. *Surg Gynecol Obstet* 1992; **175**: 41-46

44 **Jørgensen T.** Prevalence of gallstones in a Danish population. *Am J Epidemiol* 1987; **126**: 912-921

45 **Diehl AK,** Rosenthal M, Hazuda HP, Comeaux PJ, Stern MP. Socioeconomic status and the prevalence of clinical gallbladder disease. *J Chronic Dis* 1985; **38**:1019-1026

46 **Thijs C,** Knipschild P, Leffers P. Pregnancy and gallstone disease: an empiric demonstration of the importance of specification of risk periods. *Am J Epidemiol* 1991; **134**: 186-195

47 **Layde PM,** Vessey MP, Yeates D. Risk factors for gall-bladder disease: a cohort study of young women attending family planning clinics. *J Epidemiol Community Health* 1982; **36**: 274-278

48 **Ahlberg J,** Angelin B, Einarsson K, Hellström K, Leijd B. Prevalence of gallbladder disease in hyperlipoproteinemia. *Dig Dis Sci* 1979; **24**: 459-464

49 **Valdivieso V,** Covarrubias C, Siegel F, Cruz F. Pregnancy and cholelithiasis: pathogenesis and natural course of gallstones diagnosed in early puerperium. *Hepatology* 1993; **17**: 1-4

50 **Horn G.** Observations on the aetiology of cholelithiasis. *Br Med J* 1956; **2**: 732-737

51 **Sampliner RE,** Bennett PH, Comess LJ, Rose FA, Burch TA. Gallbladder disease in pima indians. Demonstration of high prevalence and early onset by cholecystography. *N Engl J Med* 1970; **283**: 1358-1364

52 **Maclure KM,** Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. *N Engl J Med* 1989; **321**: 563-569

53 **Rhomberg HP,** Judmair G, Lochs A. How common are gallstones? *Br Med J (Clin Res Ed)* 1984; **289**: 1002

54 **Pixley F,** Wilson D, McPherson K, Mann J. Effect of vegetarianism on development of gall stones in women. *Br Med J (Clin Res Ed)* 1985; **291**: 11-12

55 **Scragg RK,** McMichael AJ, Seamark RF. Oral contraceptives, pregnancy, and endogenous oestrogen in gall stone disease--a case-control study. *Br Med J (Clin Res Ed)* 1984; **288**: 1795-1799

Science Editor Guo SY **Language Editor** Elsevier HK