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Gallstone disease

Population based studies on risk factors, symptomatology and complications

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Veritatem dies aperit

To my family, Anna, Markus, Anders, Peter and Rebecka

Abbreviations

AC-Acute Cholecystitis
BMI-Body Mass Index
CBD-Common Bile Duct
ci-confidence interval
ERCP-Endoscopic retrograde cholangiopancreaticography
ESWL-Extracorporal Shockwave Lithotripsy
HDL-High Density Lipoprotein
LC-Laparoscopic cholecystectomy
LDL-Low Density Lipoprotein
MC-Minilaparotomy cholecystectomy
MRCP-Magnetic resonance cholangiopancreaticography
NHP-Nottingham Health Profile
ns-non-significant
OC-Open cholecystectomy
OR-Odds Ratio
USG-Ultrasonography
VAS-Visual Analogue Scale

CONTENTS

Abstract

Background & aims: Gallstone disease is common, costly and its complications are sometimes life threatening. The aim of this thesis is to determine the prevalence and incidence in relation to putative risk factors in the general population. Furthermore, to identify individuals with asymptomatic gallstones who are at risk of developing complications and, finally, to identify those who are at risk of an unsatisfactory outcome after cholecystectomy.

Material & methods: A sample of the adult (35-85 y.) general population was screened with ultrasound examination, blood tests and a questionnaire regarding digestive symptoms, life-style and quality of life. After excluding 115 subjects, who previously had a cholecystectomy, 739 participated. The examination was repeated after a minimum of five years. The individuals who were shown to have gallstones were followed in order to identify risk factors for developing complications. 200 consecutive symptomatic patients were operated with cholecystectomy on defined indications. They completed a questionnaire regarding digestive symptoms, life-style and quality of life before and three and twelve months after surgery.

Results: The crude prevalence of gallstone disease was 17.2 % for women and 12.4% for men. It increased with age and was higher among women. Symptoms did not differ between subjects with and without gallstones, but those previously operated with cholecystectomy did worse both regarding symptoms and quality of life. The estimated crude annual gallstone incidence was 1.5%. This increased with age, but did not differ between the sexes. Gallstone development was positively related to elevated blood lipids and negatively related to alcohol consumption. Fourteen of 120 subjects with gallstones at the primary screening developed a complication demanding treatment during a follow-up interval of 87 (3-146) months. In the patient series operated on strict indications, 91.3 % of those who had reported typical gallstone related pain preoperatively, experienced total or partial pain relief 3 months postoperatively. With atypical pain preoperatively, the corresponding figure was 77.1 %. The findings 12 months postoperatively were similar. In the logistic regression analysis, young age, frequency of pain episodes, atypical pain, specific food intolerance and disturbing abdominal gas were positively related to the frequency of abdominal pain 12 months after surgery.

Conclusion: The prevalence of gallstones was positively related to age and female gender. Previous cholecystectomy was associated with more symptoms and worse quality of life. The annual gallstone incidence of 1.5 % was high in comparison with other studies, but our population was older. In general, neither prevalent nor incident gallstones in the general population were associated with specific symptoms. The cumulative risk of developing a complication to gallstone disease during a 5-year follow-up interval was 7.6 % with no tendency to level off.

Patients with typical pain had a better outcome after cholecystectomy. Young age, atypical pain and frequent pain episodes before surgery were major risk factors for a worse outcome in terms of persistent pain.

Original papers

This thesis is based on the following papers, which are referred to in the text by their roman numerals:

I. K. Borch, K.-Å. Jönsson, J. Zdolzek, I. Halldestam, E. Kullman. Prevalence of gallstone disease in a Swedish population sample. Relations to occuption, childbirth, health status, life style, medications and blood lipids. Scand J Gastroenterol 1998; 33 (11): 1219-1225.

II. I. Halldestam, E.-L. Enell, E. Kullman, K. Borch. Development of symptoms and complications in individuals with asymptomatic gallstones. Br J Surg 2004; 91: 734-738.

III. I. Halldestam, E. Kullman, K. Borch. Incidence of gallstone disease in a general population sample - relations to symptomatology and potential risk factors. Submitted.

IV. I. Halldestam, E. Kullman, K. Borch. Defined indications for elective cholcystectomy for gallstone disease. Br J Surg 2008; 95: 620-626.

Introduction

Gallstones occur commonly in the western world[1-6]. Most are asymptomatic, but still, gallstone disease contributes substantially to health care costs, and its complications are sometimes life threatening. In the US, more than 700 000 cholecystectomies are performed each year[7]. Hospitalisation due to gallstone disease and its resulting complications costs more than five billion dollar, each year in the US only. The prevalence differs not only between countries but also between ethnic groups. Age and gender also influence the prevalence of gallstone disease.

It is well documented that other mechanisms also influence the cholecystectomy rates since there is a weak correlation to prevalence. Other possible explanations are differences in health care organisation, non-operative options and the surgeons´ attitude towards indications for surgery, especially regarding patients with mild or moderate pain[8]. Cholecystectomy rates in Scandinavia are in the range of 0.7-1.4/1000 inhabitants per year[9]. In Sweden, approximately 10 000 cholecystectomies are performed each year. This makes cholecystectomy one of the most common surgical procedures. In Sweden, the cholecystectomy rate was 4/1000 inhabitans / year in the 1940s and remained at that magnitude until the early 1970s. Thereafter it fell to approximately 1/1000 inhabitans / year[10]. After the introduction of laparoscopic cholecystectomy (LC) and day-care surgery in the late 1980s several studies revealed an increase in cholecystectomy rates of approximately 20%. As a consequence, even small changes in indications for cholecystectomy have a major impact on health care costs[11].

Since the introduction of LC, many studies have discussed and high-lighted the importance of adequate surgical technique in order to improve the outcome of the operation and timing of sugery. Comparisons to open cholecystectomy, with or without minimal incision, have also been high-lighted[12-14].

Most patients with symptomatic gallstone disease benefit from cholecystectomy[15, 16]. However, pain persists in a considerable number of cases and therefore, it is of great importance to identify these patients in order to avoid the so called post-cholecystectomy syndrome. Moreover, complications resulting from gallstone disease, such as gallstone related pancreatitis, cholecystitis, jaundice and/or cholangitis due to obstruction of the common bile duct (CBD) contribute substantially to morbidity and mortality, as well as health care costs. Identifying those at risk of developing such complications is therefore of critical importance.

History

Reports on gallstone disease are mentioned as early as 2000 BC, when the Babylonians first described the bile duct system. Gallstones were found in a Mummy from the 21st Dynasty, 1085-945 BC. The Italian physician Gentile de Foligna was the first to describe gallstones in man in the beginning of the 14th century, while biliary colic was first described in 1661 by Thomas Bartholinus, who ascribed the pain to stone passage

through the CBD. The first chemical analysis of the composition of gallstones was made in 1789 by Fourcroy. In those days, the treatment for gallstone disease consisted of enemas and mineral water. Health resorts like Marienbad and Karlsbad were famous for their treatment of gallstones. Surgical treatment was first introduced in1867 by John Bobbs in the US, who performed a cholecystotomy, i.e. the removal of the gallstones without removing the gallbladder[17]. Other surgeons adopted this operation. Carl Langenbuch in Berlin believed that this was not a curative operation since stones would recur. He introduced cholecystectomy, i.e. removal of the gallbladder with the stones in 1882[18, 19]. This operation soon became the common surgical procedure and only seven years later, it was introduced in Sweden. The first laparoscopic cholecystectomy was performed by Eric Mühe in 1986[20]. This was first not noticed and it was not until the French surgeon, Philippe Mouret performed a LC that it started to become widespread[21]. Three years later, it was introduced in Sweden and only a few years after that it became the "Gold standard" for elective treatment of symptomatic gallstone disease[22, 23]. As an alternative to LC, open cholecystectomy with minimal incision i.e. minilaparotomy cholecystectomy (MC), was introduced in the late 1980s. This method has not gained the same general acceptance as LC.

Today, the demonstration of gallstones is fundamental before an operation, but it was first in the late 1890s that gallstones could be detected on plain x-ray examination. However, this detection demands that the stones are calcified which only occurs in 10-15% of all cholesterol gallstones. Graham and Cole introduced oral cholecystography in 1924[24]. This form of detection of gallstones became the "Gold standard" until the beginning of the 1970s when ultrasonography (USG) replaced it. The main advantage of USG is that it is non-invasive, detects all kinds of stones and offers possibilities to examine other organs in the abdomen. No preparations except 6 hours of fasting are needed, making the method suitable for emergency examinations.

Gallstone development and pathophysiology

Depending on their composition, gallstones are often divided into three major types: cholesterol-, black pigment- and brown pigment stones. Black pigment stones are more common among patients with haemolytic diseases (hereditary spherocytosis, sickle cell anaemia, and Thalassaemia) and liver cirrhosis[25-29]. Brown stones are often caused by stasis and infection in the biliary system. In the Western world, the major constituent of gallstones is cholesterol, which comprises 50-98 % of the dried substance of the stone. Other constitues may include fatty acids, triglycerides, proteins, polysaccharides, as well as calcium bilirubinate, calcium carbonate and calcium bicarbonate. Gallbladder stones vary in size from less than a millimeter up to a few centimeters in diameter. Most patients only harbour stones in the gallbladder, but in 10-15 % the stones have migrated into the common bile duct[30].

Important factors in the development of cholesterol stones are supersaturation of cholesterol in bile, nucleation and growth of crystals in the gallbladder and gallbladder dysmotility resulting in impaired emptying.
The gallbladder stores and concentrates bile during fasting. After gastric emptying, especially after a fatty meal, and mediated by the hormone cholecystokinin, the gallbladder contracts simultaneously with relaxation of the sfincter Oddi, resulting in an extrusion of concentrated bile which mixes with food in the duodenum[31].
Biliary colic is considered to be caused by the impaction of one or more stones in the neck of the gallbladder. The raised intraluminal pressure, contraction and distension of the gallbladder give rise to biliary pain (colic).

Prevalence
As mentioned, gallstones are common in the Western world. The prevalence among adults is approximately 10-15% for men and 20% for women in Europe and North America (caucasians). Age, gender and ethnicity are the most important factors affecting prevalence[2]. The prevalence is high in Scandinavia[4, 32, 33] and other Northern European countries, but low in sub-Sahara Africa and Asia[34]. American Indians and Mexican Americans have higher prevalence in comparison to Afro-Americans. Pima Indians in southern Arizona account for the highest recorded prevalence of gallstone disease, with figures of above 70% in women aged 25 years or more[35]. Gallstones are rare before the age of 20 years, except in these high-risk groups.
Scandinavian studies on selected adult age groups show prevalence figures for gallstone disease of 13-18% in men and 15-25% in women. As for most other studies, these studies show that age increases prevalence and that there is a preponderance among women.
The prevalence of gallstone disease in Sweden has previously mainly been investigated in autopsy series[36] and in vivo in selected age groups[4, 33, 37].

Incidence
Few studies have been published on the incidence of gallstone disease with the exception of one attempt to calculate the incidence from prevalence data[38] and a follow-up study from Sirmione[3] published as an abstract[39], the only studies are those given below.

A Swedish retrospective study from 1986 determined the incidence of symptomatic gallstone disease among patients with abdominal complaints[40]. During the study period, cholecystography was used as the routine examination for the detection of gallbladder stones. Since the proportion of cholecystographies showing gallstones decreased over time, it was concluded that the incidence of gallstone disease had de-

creased. There is no Swedish study on the incidence of gallstone disease in the general population.

In a large Danish study published in 1991, an age and sex stratified random population sample (ages 30, 40, 50 and 60 years) of Danish origin was followed up with ultrasonography after five years[41]. Re-screening was done on 82.8% (2987/3608). The five-year incidence of gallbladder stones in each age group was 0.3, 2.9, 2.5 and 3.3% among men and 1.4, 3.6, 3.1 and 3.7% among women. The overall annual incidence was 0.93 %. The study also showed that gallstones could have disappeared due to dissolution or spontaneous passage in 4.5 % of the patients over a 5-year period. The incidence was related to age and gender, although the difference between women and men decreased with increasing age.

The GREPCO group[42] studied the natural history of gallstones and the incidence of gallstones in a 10-year ultrasonographic follow-up study of 253 (59.4%) out of 426 initially examined women aged 20-69 years at baseline. The overall incidence of gallbladder stones was 6.3% (16 subjects), including 0.8% (2 subjects) without stones at baseline, but who were undergoing cholecystectomy during follow-up. The incidence was positively related to age. Moreover, BMI and parity were positively related to gallstone development.

In the Sirmione study it was shown that incidence rates are time-dependent[39]. There was a difference between1982-87 with a rate of 0.60 % per year in comparison to 1987-92 when the rate was 0.34 %. The incidence did not differ between women and men, but increased with age.

No study has attempted to establish the incidence of gallstone disease and to relate the findings to symptomatology and putative predisposing or protective factors.

Risk factors

As mentioned, the most common risk factors for developing gallstone disease are increasing age, female gender and ethnicity. There is a high prevalence in Europe and North America to extremely high prevalence among Pima Indians in Arizona[35], while prevalence in sub-Sahara Africa and Asia is low. Other putative predisposing and protective factors will be discussed in this chapter.

Estrogen therapy

In a large Danish study Jorgensen et al showed that differences in prevalence between men and women could be explained by estrogen therapy and childbirth[43]. Novacek in Austria reached the same conclusion[44]. Scragg et al found an age-dependent risk of developing gallstones related to the use of oral contraceptives[45], the risk being greatest among women younger than 29 years of age. In a large North American study which included more than 22 500 post-menopausal women, the promoting effect of estrogen

therapy on gallstone development was studied[46]. The probability of biliary tract surgery was almost twice as high in the group with estrogen therapy as compared to the group receiving placebo.

Parity

Most studies document an elevated risk associated with childbearing and parity[3, 42-44, 47, 48]. However, with regard to pregnancy two large studies, one in Germany and one in France could not verify these findings[49, 50].

Obesity

Several studies identify obesity as a major risk factor for developing gallstones[7, 42, 43, 51-54] gender disregarded, although the relationship is usually stronger in women than in men. Biliary hypersecretion of cholesterol, which is an important determinant in gallstone formation, is profoundly exacerbated by obesity. Rapid weight loss is also associated with an increased risk of developing gallstones[53]. After bariatric surgery such as Roux-en-Y gastric bypass (but not gastric banding) with rapid weight loss, approximately 40% of the patients form stones. This could justify prophylactic cholecystectomy in these patients.

Heredity

Most[5, 55, 56], but not all studies[57] show a relationship of gallstone occurrence with a family history of the disease. Unless such studies are based on screening for gallstones among relatives, the results are highly unreliable since most gallstones are asymptomatic and non-operated. The high prevalence among PIMA Indians is most probably due to heredity[35, 48]. However, when studying these populations, other predisposing factors are also overrepresented, for instance, the female/male ratio is higher as well as the frequency of obesity and parity. In some ethnical groups in South America the prevalence of gallstones is high. A study from Chile showed that cholesterol lithogenic genes are widely spread among Chilean Indians and Hispanics.

Occupation

Occupation/education is sometimes used as a measurement of socioeconomic status or life-style. In the Italian MICOL study, a higher risk of gallstone disease was found among housewives and in men with higher education[51]. The opposite was noticed in a British study which showed a relationship between gallstone disease and low social class[58]. An American study investigated differences between Mexican Americans and non-Hispanic whites and found that the prevalence of gallstone disease was twice as high among Mexican American women. These ethnic differences persisted after strati-

fication for age, parity and BMI. Interestingly, after controlling for age, parity, BMI and ethnicity, the prevalence among women was inversely related to level of education, income, occupation and habitat, all measurements of socioeconomic status[47].

Smoking

Data in the literature is conflicting as to wether smoking is predisposing or protective. It has been suggested that smokers are protected against the development of gallstones through a mechanism which leads to a decrease in prostaglandin synthesis and mucus production in the gallbladder epithelium[59]. Another study by Stampfer et al. came to the opposite conclusion when they found smoking to be an independent risk factor in women smoking heavily (>35 cigarettes/day)[60]. In a large British cohort study, smoking was identified as an important risk factor for developing symptomatic gallstone disease[58].

In a study from Australia, a risk of mis-estimating the risk in case-control studies was shown, since even first exposure to smoking among women was associated with an increased risk. Late occurring cases seem to have a different relation to the exposure factor than do the early[61].

Diabetes mellitus

It has been suggested that gallstone development is associated with common metabolic disorders such as, obesity, diabetes mellitus and dyslipidemia which supports the hypothesis that gallstone disease is part of the metabolic syndrome[62, 63].

Another pathophysiological link between insulin resistance and gallstone development is the increase of cholesterol saturation in gallbladder bile. This is related to an increase in body cholesterol synthesis and hypersecretion of biliary cholesterol as observed in obesity[7, 51]. This idea was supported by the findings in epidemiological studies[51, 64-67], but the matter is controversial since other studies found no such correlation[63, 68, 69].

NSAID

In a study carried out twenty years ago it was suggested that gallstone formation could be prevented by the intake of NSAID[70]. This could not be verified in a large randomised study on aspirin usage of more than 1g/daily[71] or in an experimental study on hamsters[72].

Chrons disease

The pathogenesis of the association between Chrons disease and gallstone disease is unclear. Previously it was believed to be attributable to bile acid malabsorption in the diseased or resected ileum segment, causing hepatic excretion of cholesterol supersatu-

rated bile. This explanation was not supported in a study showing that bile cholesterol saturation is significantly lower in patients with Chrons disease than in controls. A correlation between gallstone disease and Chrons disease was found in a large study which also showed an association of gallstone disease to the site of Chrons disease at diagnosis, as well as to the number and site of bowel resections[73].
It is surprising, however, that the incidence of cholecystectomies is not increased among patients with Chrons disease and that after ileal resection few patients require cholecystectomy[74]. Hence, simultaneous or prophylactic cholecystectomy is not justified.

Alcohol
Alcohol consumption has been shown to be associated with a lower prevalence of symptomatic[48, 75], as well as asymptomatic, gallstone disease[54, 60, 76, 77]. The intake of alcoholic beverages was also inversely related to the risk of cholecystectomy[78]. A large prospective study in men showed an inverse relation of alcohol beverage to symptomatic gallstone disease, but interestingly, the association was not present when consumption was less than 1-2 days a week[79]. In contrast, a large study from Germany found no relation to alcohol consumption[80].

Physical activity
The exact role that physical activity plays in preventing the formation of gallstones is unknown. One suggested mechanism behind the protective effect of physical activity is a reduced colonic transit time associated with a reduced intestinal bile salt dehydroxylation and an increased gallbladder motility[81]. Most of the epidemiological studies found no such correlation, gender disregarded[48, 82-84]. Leitzman et al, however, found a significant inverse relation between physical activity and gallstone disease among men[85]. These authors also performed a larger study on more than 60 000 women and showed recreational physical activity to be associated with a decreased risk of cholecystectomy[86]. This association was independent of other risk factors, such as obesity and recent weight loss.

Natural history of asymptomatic gallstones
Asymptomatic gallstone disease is being increasingly diagnosed today as a result of the widespread use of ultrasonography in the evaluation of patients with abdominal complaints[87].
Abdominal symptoms are common both in subjects with gallbladder stones and the population in general[87]. Muhrbeck et al. found no differences in the frequency of abdominal symptoms between persons with and without gallstones[88]. Similar results were found in a prospective radiological study in Italy[89].

Epidemiological studies have shown that 80% of subjects with stones are asymptomatic[1, 3, 90, 91]. No differences regarding minor dyspeptic symptoms were shown in a large study performed by the GREPCO-group in Italy[92]. Serious symptoms appear in one to two per cent annually among persons with asymptomatic gallbladder stones. In a study by Attili et al. [93], 118 persons with asymptomatic gallbladder stones were followed for ten years and the total risk of developing complications was less than 3%. Complications rarely develop without preceding episodes of biliary colic[94]. The most common complication is acute cholecystitis. Follow-up studies show that, other complications such as obstructive jaundice, cholangitis, pancreatitis and carcinoma of the gallbladder are infrequent[95]. Fewer complications develop later on than soon after the gallbladder stones have been diagnosed[95]. Ransohof et al. studied the difference in outcome between cholecystectomy and watchful waiting among patients with silent gallstones. They found no significant differences that could justify cholecystectomy[96].

A Swedish longitudinal follow-up study, published more than 20 years ago showed that over a 20-year period, only 18% developed biliary pain[97]. The annual probability of developing pain was 2% during the first 5 years and levelled off with time. There were no deaths related to gallstone disease.

Angelico et al followed a group of females with gallstones that had been detected in a screening study, for 10 years. At re-examination 61.5 % still were asymptomatic, 15.4 % had experienced at least one episode of biliary pain and 23.1% were submitted to elective cholecystectomy[42].

Since, in general, the course of the disease is benign and there are no specific risk factors indicating future complications among most people with asymptomatic gallstones, the descision to avoid cholecystectomy and instead apply watchful waiting is justified [98, 99].

Symptomatology

In symptom complexes associated with acute cholecystitis, acute pancreatitis or jaundice, the diagnosis is commonly easy to establish. Among those complaining of a single symptom, such as abdominal pain, the diagnosis is much more difficult to establish, since such symptoms often occur without gallstones[100]. Thus, it is difficult to define symptoms specific for gallstones and to distinguish between asymptomatic and symptomatic gallstones. Anamnestic data about abdominal symptoms in patients with suspected gallstone disease were compared with those in a matched control group. Only 23% of patients were shown to have gallstone disease. No symptom was commoner among the patients than among those with a normal cholecystography[101].

Biliary colic is usually defined as severe pain in the upper right quadrant or epigastrium[92], sometimes radiating to the back or the subscapular region and persisting for one to five hours[102]. Typically, the patient walks around. Sleep may be disrupted by the pain which is sometimes also exaggerated by meals. Nausea and vomiting may

occur. Classically, as opposed to cases of acute cholecystitis, there is no fever or local abdominal tenderness. Most commonly, the pain is constant without free intervals.
Biliary colic is the best predictor of gallstone related pain. It has a high negative predictive value for pain in the right upper abdominal quadrant[88, 100], or in other words, the absence of pain makes the presence of gallstones less probable. Women are predisposed to experience more pain since they form gallstones earlier in life[3, 37, 50, 103].

Jorgensen et al found ”right upper quadrant pain during the night” to be the most specific symptom in men and “strong and oppressive pain, provoked by fatty meals” to be the symptom best correlating with the presence of gallstones in women[100]. Other digestive symptoms, such as food intolerance, acid regurgitation, heartburn, bloating, constipation and diarrhoea, which are also common in the general population, often co-exist among persons with gallstone disease[3, 57, 104, 105]making it difficult to select the right patients for cholecystectomy. Sometimes these symptoms are relieved by a cholecystectomy, but there is a consensus that these symptoms not ought to be an indication for surgery. Symptoms may even be aggravated by cholecystectomy in these patients[106-108]. There is no evidence that supports the diagnosis “symptomatic gallstone disease” on any single symptom other than biliary colic[91].
Once the patients become symptomatic, the risk of developing biliary complications and the subsequent need for an operation is 6-8%[95].This figure decreases with increasing age.
In a study by Vertrhus et al.[109], patients with symptomatic gallstone disease were randomized to either cholecystectomy or watchful waiting. In the group randomized to watchful waiting, 35 out of 69 eventually underwent a cholecystectomy. This rate seemed to level off after four years. Despite the high rate of cholecystectomy (51%) in the group randomized to watchful waiting, they considered watchful waiting a safe alternative.
In a prospective 6-year follow-up study of 153 patients with gallstones, diagnosed by oral cholecystography, it was found that young age and several episodes of biliary colic could predict future complications that would demand cholecystectomy. They also found the annual incidence of an acute biliary complication to be 3.1%. It was concluded that patients with mild or with no symptoms, did best with watchful waiting[110].
Placing the patients on a waiting list with a mean time to surgery of 12 months causes morbidity to rise. As many as 23.7% developed complications needing an emergency operation[111]. In the case of otherwise healthy symptomatic patients aged 80 years and more, operative management seems to be the best option, since the mortality related to gallstone complications is higher than the mortality of surgery[112]. Another author considered all geratric patients with symptomatic gallstone disease to be candidates for

LC, due to the high risk of gallstone related complications and the low risk of surgical complications [113].

Although most symptomatic gallstones follow a benign course, some cause complications which are much more difficult to handle and which carry a high morbidity. This means that if the diagnosis is already established, there is no need to prolong time to surgery[114, 115]. Biliary pain is usually relieved by cholecystectomy[116], leading to a reduced utilisation of health care[117].

Indications for cholecystectomy

The evaluation of the indication for cholecystectomy must include the risk of developing complications to gallstone disease[55], the risk of complications to surgery[118-120] and, obviously, the expected effect on symptomatology[105, 121]. The cost for society must also be taken into consideration[122].

Cholecystectomy rates vary between and within countries, and there is no unambiguous relation to the prevalence of gallstone disease[9, 123]. Thus, there must be other explanations for the variations in cholecystectomy rates, such as organizational, economic and the physicans´ attitude regarding mild, moderate or atypical symptoms[123, 124]. Using strict indications or a standard preoperative assesement could be a way of improving the results of surgery[125, 126].

In screening studies there is an association between biliary colic (upper right abdominal quadrant pain) and occurrence of gallstones[87, 100, 127], making biliary colic the only predictor for gallstone disease[50, 127, 128]. However, several studies show that one pain episode will not necesserily be followed by more episodes within a reasonably long time-span. This seems to justify a policy of watchful waiting after the first pain episode, at least among adults[98, 110].

Therefore guidelines usually only recommend cholecystectomy to patients with repeat pain episodes or a complication resulting from gallstone disease[129]. When the stones are symptomatic, some even recommend operation without delay in order to minimize costs and complications[114, 130].

Complications

Most studies show that approximately 20% of gallbladder stones are- or become symptomatic. In the symptomatic gallstone population complications to the disease are more common[131]. In the Italian GREPCO study[57], such complications occured with an annual incidence of 0.7-2.0%.

In a large Swedish survey, Kullman et al concluded that when the rate of elective cholecystectomies decreased, the rate of cholecystectomies due to acute cholecystitis increased[132]. This finding was supported by a large American study from 2005 showing that the increase in cholecystectomies with the introduction of LC was associated

with a reduction in the incidence of acute cholecystitis[133]. In a study from a large hospital in New Zealand, where few patients undergo elective cholecystectomy, a large proportion of those treated conservatively returned with recurrent problems[134].

Acute cholecystitis

The cystic duct connects the gallbladder to the common bile duct. When it is obstructed for a longer time period by a gallstone, an acute inflammatory response occurs. The patient usually presents with fever, pain and a localized tenderness in the upper right quadrant or epigastrium. Blood analyses reveal an elevated CRP and white blood cell count. The diagnosis is clinical, but supported by ultrasonography which usually reveals gallbladder stones and signs of inflammation with edema and thickening of the gallbladder wall. Patients with severe acute cholecystitis may have a slight jaundice caused by compression of the CBD by the gallbladder or edema of the biliary tract. If the jaundice is more pronounced one may suspect Mirizzi´s syndrome[135, 136] or choledocholithiasis. Most authors recommend that an operation should not be delayed in this situation. It should preferably be performed within 3 days of the onset of symptoms[137, 138].

Jaundice

If gallstones migrate from the gallbladder to the common bile duct, they can cause an obstruction of the bile flow to the small intestine. Less commonly, an impacted stone in the Hartman´s pouch may compress the CBD. In both instances, the patient presents with jaundice with or without cholangitis. Acute suppurative cholangitis carries a high mortality unless the biliary tree is drained. Age, comorbid neurological disease and peripapillary diverticula are all identified as independent risk factors in this course of events[139].

Acute pancreatitis

Small gallstones[140], or so called microlithiasis[141], are generally the cause of acute gallstone pancreatitis. Most patients (80-90%) usually have a mild form that is conservatively treated with fast and intravenous fluids[142]. These patients recover within three to five days[143]. The remaining 15% develop the more aggressive necrotising pancreatitis, which is often complicated by bacterial translocation from the gut causing an infection of the initially sterile inflammation. These patients may develop multiple organ failure requiring intensive care treatment. Unfortunately, no causative treatment is available for the already developed pancreatitis [144]. However, in the case of stones retained in the CBD causing jaundice or cholangitis, an emergency ERCP with sphincterotomy and stoneextraction may be life saving[145-147]. If sphincerotomy is not performed, pro-

phylactic cholecystectomy should take place as soon as possible after the acute episode[148-150].

Gallstone ileus

In progressive acute cholecystitis, the inflammation, in combination with stones may lead to a fistula between the gallbladder and the small intestine or stomach. If they are large enough, the stones may become impacted in the small bowel causing obstruction. This condition accounts for 1-4% of all cases with small bowel obstruction[151, 152]. However, in persons over 65 years of age and particulary among females, this condition is much more common and accounts for over 25% of all cases of small bowel obstruction[153].The diagnosis is sometimes difficult to establish. Typically, the patient presents with symptoms of small bowel obstruction. Plain x-ray reveals signs of small bowel obstruction, sometimes with air in the biliary tract and more rarely, with a visible, calcified gallstone in the small bowel. Much more seldom, a stone penetrates into the stomach, where it is entrapped, causing the so called Bouveret´s syndrome[154, 155],with signs of intermittent gastric outlet obstruction.

Gallbladder carcinoma

Gallstone disease is considered to be the most important risk factor in the development of gallbladder carcinoma[156]. In its advanced stages it is associated with a high mortality[157]. Therefore, some physicians advocate prophylactic treatment of asymptomatic gallstones[158]. However, few subjects with gallstone disease (0.3 %) develop this malignancy. Accordingly, there is a general consensus not to treat asymptomatic gallstones, since the mortality associated with cholecystectomy is at least at the same level as that of gallbladder carcinoma[159].

Treatment

More than a century after the introduction of the open cholecystectomy by Karl Langenbuch, the removal of the gallbladder is the optimal treatment of gallstone disease. However, alternative therapies do exist. These include oral dilution therapy and ESWL (Extracorporal shock-wave lithotripsy) alone or in combination[160-162]. Complications and contraindications are few, but long-term success is limited due to gallstone recurrence. Langenbuch postulated that unless the gallbladder is removed, the gallbladder stones will recur. Today, the role of ESWL is mainly in combination with ERCP for selected patients with complex biliary tract stones[163-166]. In old patients with severe coexisting diseases and acute cholecystitis, ultrasound guided percutaneous drainage of the gallbladder can serve as a “bridge to surgery” or, in some cases, as the only treatment[167-169]. MRCP (Magnetic resonance cholangiopancreaticography) has partly replaced ERCP as a diagnostic tool for investigating diseases in the biliary tree[8].

Hence, ERCP has gradually become a therapeutic tool. It is used for sfincterotomy and stone removal from the bile duct whether the stone has caused jaundice, cholangitis or severe gallstone pancreatitis [170] [149, 171].
As mentioned, gallstone disease is still a surgical challenge and cholecystectomy is the treatment of choice for most patients[172]. Since the disease is very common and complications are costly, small changes in indications for cholecystectomy and the choice of surgical approach have a great impact on health care costs[173]. There are major differences in cholecystectomy rates between the Scandinavian countries. In Finland and Sweden, rates are twice as high as in Denmark and Norway. This difference has not been influenced by the introduction of LC[9]. It has been reported that there is an inverse relation between the rate of elective cholecystectomies and the rate of gallstone related complications, especially acute cholecystitis[132] and a study from Canada has shown that an increase in cholecystectomy rates is followed by a decline in the number of operations needed for acute cholecystitis[133].

Three major approaches for cholecystectomy exist and their advantages and disadvantages will be briefly discussed. Laparoscopic cholecystectomy (LC) was introduced in 1989, whereafter it spread rapidly in the Western world. There was a transient parallel increase in cholecystectomy rates after a decrease during previous decades[10, 11, 119, 120]. The gallstone prevalence seemed to be unchanged, so the only explanation for this transient increase was probably a change in indications for cholecystectomy[8, 11, 174, 175].

With LC, day-care surgery was introduced for most patients requiring elective cholecystectomy, making it possible to decrease the numbers of hospital beds in surgical clinics[176-178].
Before the introduction of LC, several reports were published about operations through smaller inscions (MC). The spread of MC decelerated due to the rapid spread of LC. Majeed et al. [179] published a paper in the mid 1990s, showing that MC had the same advantages as LC regarding hospital stay and postoperative recovery, but MC was performed faster. A shorter operation time, but longer sick leave and time to recovery for MC as compared to LC was reported in a Swedish study[180]. A study of differences between LC and MC with special reference to obese persons, showed no differences in recovery time, but a significantly shorter operating time for MC, making it suitable even for obese persons[12]. Data in the literature regarding which type of operation is less expensive conflicts. One was in favour for LC[181], whereas another showed no difference in a high volume center using reusable instruments. Results were in favour of MC in hospitals performing few operations[122]. In spite of various advantages and disadvantages with these methods, LC is now the method of choice for elective cholecystectomy in most centers[182].

As minimally invasive techniques have gained dominance, training in open surgery has decreased. Jenkins et al. [183] studied the role of open cholecystectomy in the laparoscopic era. Primary open cholecystectomy is still an important alternative among those with a history of a previous abdominal operation and in patients with peritonitis. Furthermore, in laparoscopic surgery, conversion to open cholecystectomy must be considered as part of the method. Thus, familiarity with open surgery is crucial for all surgeons performing surgery on the gallbladder. Referring young surgeons to training programmes in LC cannot be justified without training in OC[184].

Post-cholecystectomy syndrome

The most commonly used indication for cholecystectomy is abdominal pain, but unfortunately some patients still experience pain after an operation. Unchanged, worsened or even new symptoms after cholecystectomy are major problems. Persistent pain or the so called "Post-cholecystectomy syndrome" varies in frequency between 6-47%[15, 106, 108, 185], even after excluding causal factors such as retained common bile duct or cystic duct stones, postoperative bile duct stenosis and sphincter Oddi dysfunction[186-190].

The technique of performing cholecystectomy seems to be of no significance for the occurrence of persistent pain[191]. However, with LC which favours a long cystic duct remnant, persistent postoperative pain could be due to a remnant stone in the duct[192]. Case reports concerning incomplete gallbladder resection as a cause of unchanged symptomatology after laparoscopic operations have also been published[193].

Digestive symptoms other than abdominal pain are common in the general population and may co-exist with pain in subjects with gallstone disease[125]. The occurrence of these symptoms raises the probability of a worse outcome after cholecystectomy[107, 108, 190]. There is also a relation between an unfavourable outcome and psychiatric disorders or vulnerability such as depression, neuropathy and anxiety[191, 194, 195]. Lack of social support and rumination were shown to occur among patients with persistent pain[195].

Low quality of life seems to be a predictor of a worse outcome[196]. A young age is related to an increased risk of persistent pain[121, 197]. Long lasting pain and pain intensity before surgery also seem to be related to an unfavourable outcome in terms of pain[121, 198, 199].

Aims of the study

- To establish the prevalence and the incidence of gallstone disease in a sample of the adult general population.

- To evaluate the role of putative predisposing and protective factors in gallstone development.

- To monitor symptomatology and the natural history, including complications and treatment, of gallstone disease detected in the general population.

- To study symptomatology and quality of life before and after cholecystectomy for symptomatic gallstone disease when strict indications for surgery are employed.

Materials and methods

Paper I

Study population

In order to come as close as possible to the true prevalence of gallstone disease it was important to minimize the time required to screen the study population. With the resources available it was considered realistic to examine a maximum of 1200 individuals within three years. According to the literature, 15% of individuals who are 40 years of age, and 25% of individuals 60 years of age, should be expected to have gallstones. The participation of an adequate number of younger persons was considered difficult to achieve and in these age groups, the gallstone prevalence is low. Therefore it was decided to invite subjects aged 35 years or more. The expected participation rate was set to at least 70% in each of five age groups (35-44, 45-54, 55-64, 65-74, 75-) with equal numbers of men and women. With an expected participation rate of 70%, 168 participants were needed in each age group. This rate would be sufficient, since with a power of 0.95 and alpha 0.05, the number of participants needed in each age group to show a difference of 10% in gallstone prevalence, was calculated to 140 (140/240=58%).

Approval by the local Ethical Committee for the study was obtained and since the approval was for baseline- and re-examinations in the study population, this approval was used in papers I-III.

From the files of the local population register, 1200 subjects aged 35-85 years (12 men and 12 women for each year of age) were selected at random. 854 subjects agreed to participate but, 115 who previously had undergone cholecystectomy for gallstone disease were not examined, unless they so desired after information about the main aim of the study. Thus, after informed written consent, a total of 739 subjects with the gallbladder in situ attended an examination with ultrasound and blood sampling.

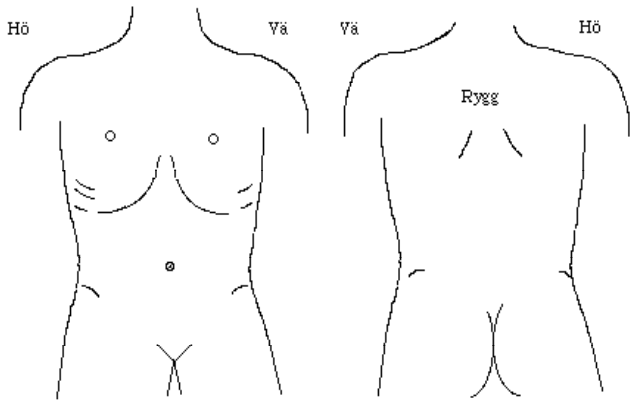
Methods

After fasting for a minimum of 6 hours, ultrasound examination of the gallbladder was performed with the subject in supine and left lateral position, using an Echo Camera SSD-630 (Aloka Co. Ltd., Tokyo, Japan) real-time scanner. Two experienced examiners performed all the examinations.

Immediately preceding the ultrasound examination, blood samples were drawn for analysis of plasma triglycerides, total cholesterol, LDL (low density lipoprotein) cholesterol, HDL (high density lipoprotein) cholesterol, and lipoprotein A. Height and weight were checked at the examination and body mass index (BMI) was calculated.

Within one month before the examination, all subjects received a questionnaire about their body weight and height; previous or present main occupation; smoking habits; use of alcohol; number of children; previous and present regular use of contraceptives

or postmenopausal estrogen substitution; present use of NSAIDs; and the frequency (or occurrence or not) of digestive symptoms during the last 3 months. The localisation of abdominal pain was marked on a schematic torso.



The Nottingham Health Profile (NHP), translated and weighted for Swedish conditions was used to assess quality of life[200-202].

NOTTINGHAM HEALTH PROFILE (NHP)

Energy	3q	100%
Pain	8q	100%
Emotional reaction	9q	100%
Sleep	5q	100%
Social isolation	5q	100%
Physical mobility	8q	100%
Maximum possible score	38q	600%

This consists of two parts. The first contains 38 statements which may be answered by "yes" or "no" and which fall into the six categories of energy (3 statements), emotional reactions (9 statements), social isolation (5 statements), sleep (5 statements), pain (8 statements), and physical mobility (8 statements). If all the statements within a category are answered by "yes", the score for that category is 100%. The higher the scores, the worse the quality of life. The second part of the NHP explores ("yes" or "no") whether the condition of the subject causes problems with social life such as employment, work around the house, family relations, sex life, hobbies, and holidays. Results are given as frequencies of ”yes” answers.
P-LDL cholesterol could not be analysed if triglyceride levels were above 3.9 mmol/l. Moreover in some cases it was impossible to perform a vein puncture or the blood drawn was insufficient.

Paper II

The study population consisted of the population described in paper I. Of the 739 individuals examined, 123 individuals with gallstones, cholesterolosis or sludge formed the basis of the study. For all the individuals screened, a patient record had been established at baseline. Records of the Statistics Sweden (SCB) were searched for causes and dates of death in the study population. Death certificates and post-mortem reports, when available, were collected and reviewed. During May 2003, the records of all 123 subjects were checked for hospital admissions or outpatient visits for complications or symptoms related to the gallstones.
Three subjects were lost for follow-up and 15 of the remaining 120 individuals had died during the follow-up interval. Except for one death of gallbladder carcinoma (7.5 years after baseline examination), the causes of death were unrelated to gallstone disease.

Paper III

The design is a random population sample, which is followed as a prospective cohort. Still living and available subjects in the study population described in paper I were offered a re-screening after a minimum interval of 5 years. A total of 14 subjects had been treated for gallstone disease and were therefore excluded. During follow-up, 69 persons had died. Apart from one death in gallbladder carcinoma, there were no deaths related to gallstone disease. Moreover, 73 persons were lost for follow up, unfit, or refused re-examination. Altogether, 583 subjects underwent re-examinations which were the same as those performed at baseline. For comparative reasons, we used the same symptom questionnaire that was used in our previous studies instead of a more recent one, such as the Rome III[203]. NHP was used for the same reason.

Paper IV

With a power of 0.95 and a significance level of 0.05, 177 patients were required to detect a difference in proportions of persistent pain of 15 % between the two groups.

The study population consisted of 200 (161 women) consecutive patients. The median age was 46.5 (range 24-79) years. Indications for elective cholecystectomy were occurrence of pain located in the upper right abdominal quadrant or the epigastrium (with or without radiation to the back and/or right subscapular region) and a history of at least two pain episodes during the last three months, or at least three pain episodes during the last year. Exclusion criteria were previous or current cholecystitis, pancreatitis, and/or previous endoscopic sphincterotomy. After inclusion, the patients were registered on a waiting list. One week before cholecystectomy, they received the same self-administered questionnaire that was used in previous studies. The location of abdominal pain was indicated on a drawing of a torso and pain intensity was indicated on a non-graded 100 mm visual analogue scale (VAS). The NHP was used to measure quality of life.

Cholecystectomy was performed by consultants and/or registrars at our surgical department. Each operation started laparoscopically. Conversion to open surgery was made on 17 patients, the most common reason being technical difficulties (13 patients). Other reasons for conversion were bleeding (3 patients) and, in one case, a cut in the common bile duct. Intraoperative cholangiography was successfully performed on 191 patients. Five patients were diagnosed with bile duct stones. Postoperative endoscopic sphincterotomy with stone extraction was successfully performed in all five cases.

Three and 12 months postoperatively, the patients completed the same questionnaires as they had done before the operation.

Statistical analysis

Continous numeric data are summarised as median with range (Paper II-IV) or when appropiate mean with SD (Paper I). A two-tailed P-value<0.05 was considered significant.

Paper I: In the evaluation of differences between groups, the Students t-test was used for continous data and the Mann-Whitney U-test for nominal data. Differences in proportions were evaluated by Fisher's exact test or chi-square test, when appropriate. The Mantel-Haenszel method was used to calculate odds ratio (OR) weighted for age and sex (10 strata). Weighted ORs are given with 95% confidence limits.

Paper II: The Mann–Whitney U test was used to evaluate differences between groups. Qualitative data were compared with Fisher's exact test or the $\chi 2$ test, as appropriate. Kaplan–Meier cumulative hazard analysis was used to estimate the risk of being hospitalized and treated for complications or symptoms related to gallstones during the follow-up interval.

Paper III: Wilcoxon's signed rank test or Mann-Whitney U-test was used for comparison of data within and between groups, respectively. Differences regarding categorical data were analysed with chi-square or Fischer`s exact test. Logistic regression analysis was used for multivariate analysis.

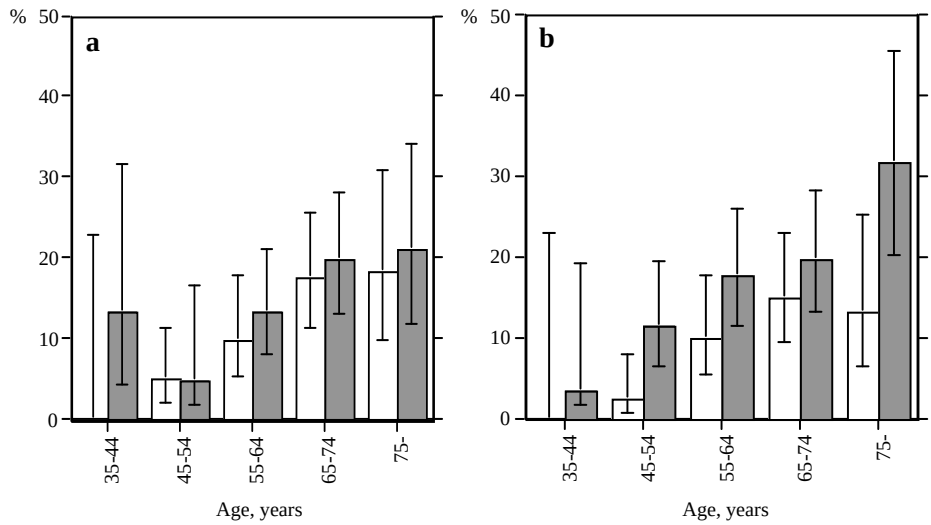
Paper IV: Differences between groups at the same time point were analyzed with Mann-Whitney U-test and differences between time points with Wilcoxon signed ranks test. Differences in proportions were evaluated with Fischer's exact test. Logistic regression analysis was used for multivariate analysis.

Results

Paper I

The median age was 61 (37-86) years in the 353 women and 62 (38-87) years in the 386 men who were successfully examined with ultrasound. Among subjects previously operated with cholecystectomy, the median age at cholecystectomy was 39 (17-75) years in women (n=75) and 51 (30-70) years in men (n=40) ($p<0.001$). Of the 739 subjects examined with ultrasound, 615 (83.2%) had no gallbladder pathology, 109 (14.7%) one or more gallstones, 9 (1.2%) gallbladder polyps (in most cases regarded as cholesterolosis), 5 (0.7%) sludge without stones, and 1 (0.1%) duplication of the gallbladder. Of the 109 subjects with gallstones, 61 were women and 48 men. Overall, 17.2% (61/353) of the women and 12.4% (48/386) of the men had gallstones. A solitary stone was found in 25 (41.0%) of the women and in 15 (31.2%) of the men (n.s.). The age and sex related prevalences of gallstones and previous cholecystectomy are shown in the figure.

Prevalence with 95% cis (bars) of current (a) and previously (b) operated gallstone disease in relation to age and sex in population sample of 854 subjects (white columns: men, shaded columns: women).



Both increased with age and in the oldest age group (=75 years-), 52.6% of the women and 31.7% of the men either had gallstones or were operated with cholecystectomy (women 31.6 %, men 13.3%). The fraction of subjects with gallstone disease who had

been operated with cholecystectomy was 55.1% (75/136) for women and 45.5% (40/88) for men (n.s.).

Considering age and sex matched groups, there were no differences regarding the prevalence of gallstones or previous cholecystectomy which were related to the category of present or previous (for those retired) main occupation to which the study subjects belonged. However, for subjects with an occupation requiring no specific education the OR was 1.0 (0.5-1.7) for current gallstones and 1.7 (1.0-2.9, $p<0.04$) for previous cholecystectomy.

Neither the number of siblings nor the number of children differed between age matched groups of women and men without gallstone disease, with gallstones, and previous cholecystectomy. For women with more than 3 children, the OR was 1.2 (0.3-3.7) for current gallstone disease and 1.9 (0.6-4.9) for previous cholecystectomy.

BMI in cholecystectomized women and men was significantly higher (26.0±4.5 and 26.2±3.3 kg/m2, respectively) than in matched subjects without gallstone disease (24.1±3.5 and 24.8±2.6 kg/m2, respectively) ($p<0.05$). Subjects with gallstones did not differ significantly from the other two groups with regard to BMI (women 25.0±3.8 and men 25.5±2.4 kg/ m2).

Blood lipid concentrations did not differ significantly between subjects with and without current gallstones. The OR of gallstones or previous cholecystectomy was not significantly changed in cigarette smokers or subjects using NSAIDs every week and there was no change in the OR of gallstones in subjects drinking wine or spirits every week (Table 1). However, the OR of previous cholecystectomy was reduced in subjects drinking wine or spirits every week. In women who had been taking drugs containing oestrogen for one year or more, the OR of gallstones was unchanged, whereas the OR of previous cholecystectomy was reduced.

Table 1. Weighted (for age and sex) odds ratios with 95% ci of current gallstones (GS+) or previous cholecystectomy (Op) in smokers, subjects drinking wine or spirits every week, subjects using NSAIDs every week, and women who had been taking drugs containing estrogen for more than one year.

Group	Smoking		Wine/spirits		NSAID		Estrogen	
GS+	1.0	(0.5-1.8)	0.8	(0.4-1.6)	1.2	(0.5-2.6)	0.8	(0.3-1.7)
Op	0.8	(0.4-1.5)	0.3	(0.1-0.4)[a]	1.3	(0.5-2.8)	0.3	(0.1-0.7)[a]

a: $p<0.01$ (Mantel-Haenszel).

When comparing matched groups, men without gallstones, with gallstones, and previously operated with cholecystectomy, did not differ significantly as regards to the frequency of digestive symptoms, except for acid regurgitation which was more frequent in cholecystectomized subjects. Women had digestive symptoms more frequently if they had previously been cholecystectomized. The frequency of intolerance to particular foods did not differ between any of the groups (Table 2).

Table 2. Mean values of frequencies (0: never, 1: occasionally, 2: once or a few times per month, 3: once or a few times per week, 4: daily) of digestive symptoms and fraction of subjects experiencing food intolerance, weight loss, and reduced appetite among subjects without gallstone disease (GS-), with gallstones (GS+), and previously operated with cholecystectomy (Op) during the last 3 months. The groups were matched for age. There were a total of 58, 57, and 67 women and 47, 46, and 35 men, respectively, in the 3 groups.

	Women			Men		
	GS-	GS+	Op	GS-	GS+	Op
Acid regurgitation	0.8	0.8	1.0	0.6	0.7	0.9[a]
Heartburn	0.6	0.8	0.9	0.8	0.6	0.6
Difficulties in swallowing	0.2	0.1	0.2	0.2	0.2	0.2
Pain during swallowing	0.1	0.1	0.1	0.1	0.1	0.1
Nausea	0.5	0.5	0.6	0.4	0.4	0.6
Vomiting	0.2	0.3	0.2	0.2	0.1	0.3
Bloating related to meals	0.9	0.7	1.2[a]	0.6	0.7	0.9
Bloating, not mealrelated	0.7	0.7	0.8	0.4	0.5	0.6
Disturbing abdominal gas	1.5	1.7	1.8	1.5	1.4	1.7
Constipation	1.1	1.2	1.4[a]	0.8	0.7	0.9
Diarrhéa	0.7	0.6	1.0	0.7	0.8	1.0
Abdominal pain, any type	0.6	0.5	1.0 [a]	0.4	0.4	0.8
Dull abdominal pain	0.5	0.4	0.9	0.3	0.3	0.6
Colic abdominal pain	0.3	0.3	0.6[b]	0.1	0.3	0.3
Dull abdominal pain, mealrelated	0.2	0.1	0.4	0.0	0.1	0.1
Colic abdominal pain, mealrelated	0.1	0.1	0.2	0.0	0.2	0.2
Dull abdominal pain, not mealrelated	0.3	0.3	0.5	0.3	0.2	0.5
Colic abdominal pain, not mealrelated	0.2	0.2	0.4	0.1	0.1	0.2
Upper rightsided abdominal pain, any type	0.2	0.1	0.5	0.1	0.1	0.3
Dull upper rightsided abdominal pain	0.2	0.1	0.4	0.0	0.1	0.2
Colic upper rightsided abdominal pain	0.1	0.1	0.2	0.1	0.1	0.1
Specific food intolerance	15/53	14/56	25/66	6/44	7/43	5/29
Reduced appetite	0/57	2/55	2/67	0/47	0/44	1/34
Weight loss	4/58	3/57	5/67	2/47	2/44	3/35

a: $p<0.05$, b: $p<0.02$, compared with GS- (Mann-Whitney u-test).

The ORs for experiencing different types of abdominal pain every week are given in table 3. It is evident that pain occurred more frequently and that it was frequently situated in the upper right part of the abdomen in subjects previously operated with cholecystectomy.

Table 3. Weighted (for age and sex) odds ratios with 95% ci of abdominal pain every week during the last 3 months in subjects with gallstones and subjects previously operated with cholecystectomy.

	Gallstones		Cholecystectomy	
Abdominal pain, any type	1.0	(0.2-3.2)	3.0	(1.3-7.0)[b]
Dull abdominal pain	1.2	(0.3-4.2)	2.9	(1.2-7.2)[b]
Colic abdominal pain	1.3	(0.1-7.8)	4.0	(1.0-13.4)[a]
Dull abdominal pain, mealrelated	2.2	(0.4-11.7)	2.2	(0.4-10.8)
Colic abdominal pain, mealrelated	5.6	(0.6-107.4)	2.6	(0.1-47.7)
Dull abdominal pain, not mealrelated	0.5	(0.0-4.1)	3.4	(1.0-9.6)[a]
Colic abdominal pain, not mealrelated	0.0	(0.0-4.9)	4.4	(0.9-16.3)
Upper rightsided abdominal pain, any type	1.0	(0.5-2.1)	2.3	(1.2-4.2)[b]
Dull upper rightsided abdominal pain	0.9	(0.3-2.1)	2.1	(1.0-4.0)[a]
Colic upper rightsided abdominal pain	1.5	(0.5-3.7)	2.2	(0.9-4.9)

a: $p<0.05$, b: $p<0.01$

For men, there was no significant difference between the three groups regarding their quality of life, estimated by part 1 of the NHP. Cholecystectomized women differed from women without gallstone disease in having both a higher score for pain and a higher mean total NHP part 1 score (Table 4).

Table 4.

A. Mean values of Nottingham Health Profile (NHP) part 1 scores (%) in subjects without gallstone disease (GS-), with gallstones (GS+), and previously operated with cholecystectomy (Op). The groups were matched for age. There were a total of 43, 47, and 57 women and 27, 29, and 26 men, respectively, in the 3 groups.

B: NHP part 2 scores (fraction [%] of subjects reporting influence of present state of health on common activities). The groups were matched for age. Since some of the study subjects were retired, there were less answers to the questions about employment and holidays than for other questions in this part of the NHP (women: 18 [GS-], 19 [GS+], and 24 [Op]; men: 16 [GS-], 11 [GS+, and 12 [Op]).

A.

Women	Energy	Pain	Emotional reactions	Sleep	Social isolation	Physical mobility	Total score
GS-	7.6	9.4	3.4	14.5	3.7	6.4	44.9
GS+	10.5	11.5	6.4	13.3	2.5	7.7	51.9
Op	20.4	16.6[a]	13.6	18.8	11.8	12.3	93.5[a]

Men	Energy	Pain	Emotional reactions	Sleep	Social isolation	Physical mobility	Total score
GS-	15.3	7.3	11.9	13.3	2.9	5.3	56.0
GS+	6.4	9.0	5.7	15.8	4.6	5.3	46.9
Op	9.9	6.3	2.3	11.8	0.8	7.5	38.5

B.

Women	Employment	Work around the house	Social life	Family relations	Sex life	Hobbies	Holidays
GS-	6.7	12.8	2.6	0.0	2.9	11.1	5.6
GS+	12.5	17.4	8.7	6.5	7.3	10.5	5.3
Op	8.7	28.1	7.1	3.6	6.1	4.0	4.2

Men	Employment	Work around the house	Social life	Family relations	Sex life	Hobbies	Holidays
GS-	0.0	11.5	7.4	0.0	4.0	6.7	12.5
GS+	9.1	3.6	0.0	0.0	19.2	27.3	0.0
Op	0.0	8.0	0.0	0.0	25.0[b]	8.3	16.7

a: $p < 0.01$ when compared with GS- (Mann-Whitney u-test).

b: $p < 0.05$ when compared with GS- (Fisher's exact test).

Paper II

The subjects were followed until treatment or during a median interval of 87 (range 3–146) months. Out of 120 individuals, 14 were admitted to hospital and treated for symptoms or complications related to gallstones: recurrent biliary pain (7), acute biliary colic (1), acute cholecystitis (3), bile duct stones with jaundice (1), gallstone pancreatitis (1) and adenocarcinoma of the gallbladder (1). The patient with acute biliary colic was considered unfit for cholecystectomy and received conservative treatment, one patient had extracorporeal shockwave lithotripsy and the other 12 had surgery. Of those who underwent surgery, nine had cholecystectomy, one had a cholecystectomy followed by an endoscopic removal of bile duct stones, one underwent endoscopic removal of bile duct stones as the only procedure and the patient with gallbladder carcinoma had a palliative procedure. The cumulative risk of being admitted to hospital and treated for complications or symptoms was 7.6 (95% ci 2.8-12.4) % during the first five years of follow-up;

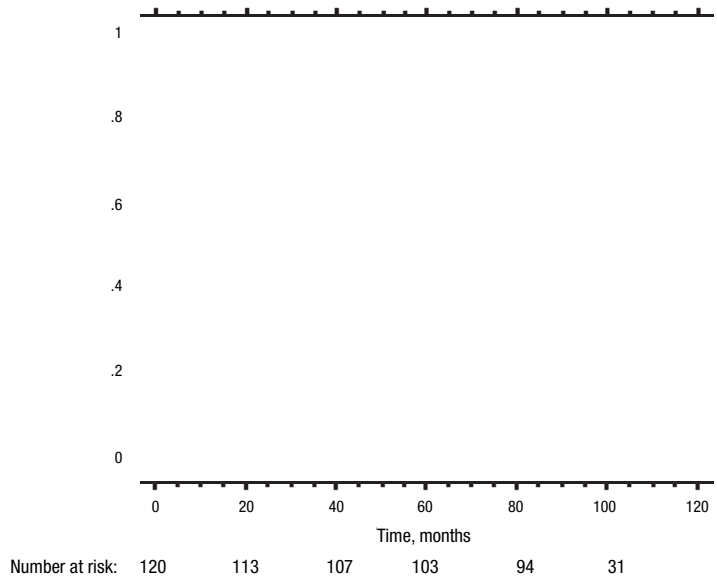


Figure. Cumulative risk of experiencing complications or symptoms leading to hospitalisation and treatment among 120 individuals with gallbladder stones detected at screening in the general population and followed for a median of 87 (range 3-146) months.

Although all the individuals who were treated reported the occurrence of one or more digestive symptoms at the initial screening, there was no difference between this group and those who were not treated. This was also the case regarding specific food intolerance (4 of 13 treated versus 19 of 98 untreated subjects). The occurrence of upper abdominal pain (central or right-sided, frequency disregarded) did not differ significantly between the treated and untreated subjects (dull pain: 2 of 14 versus 6 of 103; colicky pain: 2 of 14 versus 3 of 101).

The number of gallbladder stones detected at the initial screening did not differ between treated and untreated subjects (solitary stone: 5 of 12 versus 35 of 94 respectively). The median age at the initial screening was 58 (38–82) years for the treated and 67 (41–84) years for the untreated subjects (P=0.021).

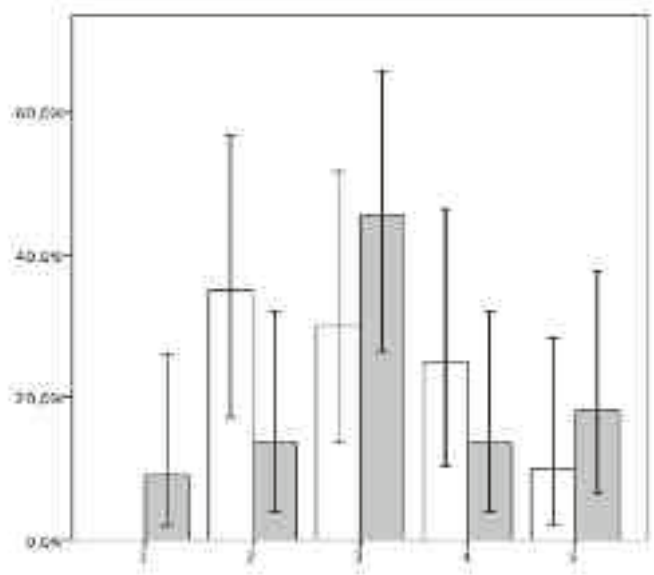
Paper III

Repeat ultrasound examination was performed in 583 of 739 subjects, resulting in a follow-up rate of 79%. Of the 503 subjects without gallbladder stones at baseline, 42 developed stones. None of the 503 subjects had undergone cholecystectomy for gallstone disease during follow-up. Thus, the overall incidence of gallstone disease was 8.3 (95% ci 6.0-10.7) %. With a median follow-up time of 67 (60-117) months, the estimated crude annual incidence was 1.5%.

The study population was divided into three groups; Group 0: subjects without stones at baseline and at follow-up (n=461); Group 1: subjects without stones at baseline but with stones at follow-up (n=42); and Group 2: subjects with stones at baseline and at follow-up (n=80).

There were no significant differences regarding gender or age at baseline between Group 0 and 1. In Group 2, the sex distribution did not differ from that in Group 0 and Group 1, whereas age was significantly higher both compared to Group 0 (P<0.001) and Group 1 (P=0.029). The median follow-up time did not differ significantly between the groups.

The age and sex distribution at baseline among subjects with newly developed stones is shown in the figure.



Age and sex distribution (%) at baseline among 42 subjects with newly developed stones at follow-up.
Error bars depict 95% ci. White bars=men, shaded bars=women.
Age (years): 1 = 35-44, 2 = 45-54, 3 = 55-64, 4 = 65-74, 5 =75-.

Table 1 shows the frequency of stones among women and men in each age group. There was no significant difference related to gender in any age group or overall (22/242 for women and 20/261 for men, P=0.630). The gallstone incidence was positively related to age among women (P=0.029), but not among men (P=0.834).

Table 1. Age and sex distribution at baseline among subjects with and without newly detected gallstones at follow-up.

Results of ultrasound examination at follow-up.	Age, years										Totals	
	35-44		45-54		55-64		65-74		75-			
	men	women	men	women	men	women	men	women	men	women	men	women
No stones	11	18	87	73	71	64	58	54	14	11	241	220
Stones	0	2	7	3	6	10	5	3	2	4	20	22
Totals	11	20	94	76	77	74	63	57	16	15	261	242
% with stones in each goup	0.0	10.0	7.4	3.9	7.8	13.5	7.9	5.7	12.5	26.7	7.7	9.1

The frequency scores of digestive symptoms at baseline and follow-up for subjects with newly developed stones (Group 1) were analysed. Except for a significant decrease in frequency scores for nausea and diarrhea, there were no significant changes. At the follow-up examination, the frequency scores for constipation and disturbing abdominal gas were higher in Group 1 than in Group 2 (P=0.022 and P=0.004). There were no significant differences between Group 0 and Group 1 or between Group 0 and Group 2.

In Group 1, the first part of the NHP score was 26.5 (0.0-211.8) % at baseline and 46.3 (0.0-296.6) % at follow-up (P=0.475). Except for a significant difference at follow-up between group 0 and group 1 (P=0.044), NHP scores did not differ significantly between groups at baseline or at follow-up.

BMI had increased over time in all three groups, but neither at baseline nor at follow-up were there any differences between the groups.

P-total cholesterol and P-LDL cholesterol concentrations at baseline were higher in Group 1 than in Group 0. At follow-up, the P-total cholesterol, P-LDL cholesterol and P-triglyceride concentrations were higher in Group 1 than in Group 0. There were no significant differences between Group 0 and Group 2. Only P-total cholesterol differed between Group 1 and Group 2. As compared to baseline, P-total cholesterol, P-HDL cholesterol and P-lipoprotein A concentrations at follow-up were lower in all three groups. The opposite trend was found regarding P-triglycerides.

The relations of gallstone development to other possible predisposing or protective factors are presented in table 2. Except for an inverse relation between a weekly use of wine or spirits and gallstone occurrence, there were no significant associations. Weekly use of alcohol was reported by 34.3% in Group 0 and 16.7% in Group 1.

Exchanging estrogen use during more than five years with use during more than one year, or more than ten years, did not change the results appreciably.

Table 2. Putative predisposing or protective factors present at baseline or at follow-up in relation to development of gallbladder stones.

G - = no stones. G + = newly developed stones

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		G -	G +	P-value
Smoking at baseline and/or follow-up	yes	108	13	0.351
	no	338	29	
Alcohol consumption at least every week at baseline and/or follow-up	yes	158	7	0.024
	no	303	35	
NSAID intake at least every week at baseline and/or follow-up	yes	110	9	0.709
	no	311	32	
Estrogen intake of total duration more than 5 years	yes	112	8	0.252
	no	98	13	
More than 3 pregnancies	yes	12	0	0.609
	no	205	22	
Qualified occupation, current or previous	yes	346	27	0.093
	no	107	15	
Diabetes mellitus at baseline or follow-up	yes	28	2	>0.999
	no	431	40	
Heredity (two or more first degree relatives operated for gallstones)	yes	21	2	>0.999
	no	431	40	

P-values are from Fischer exact test.

Logistic regression analysis was done with newly developed gallstones as a dependent variable. Table 3 shows a relation between gallstone development and follow-up interval, P-LDL cholesterol at baseline and weekly alcohol consumption. No other associations were found.

Exchanging plasma lipids at baseline with the difference in lipid concentrations between follow-up and baseline in the same analysis, yielded significance for P-triglycerides (OR 2.103 [1.030-4.296], P=0.041).

Performing the same analysis as in table 3 including women only and adding estrogen intake of a total duration of more than five years as well as parity (more than three pregnancies) showed similar results with the exception that there was no significant correlation to alcohol consumption. No association was found between development of gallstones and estrogen intake or parity.

Table 3.
Results of logistic regression analysis with newly developed gallstones at follow-up examination as the dependent variable. Values in parenthesis are 95 per cent cis.

Independent variable	Odds ratio	P
Follow-up interval	1.092 (1.013-1.177)	0.022
Age at baseline	1.016 (0.973-1.061)	0.473
Male gender	0.941 (0.340-2.606)	0.906
BMI at baseline	0.849 (0.703-1.024)	0.088
Heredity (more than 2 first degree relatives operated for gallstones)	1.538 (0.292-8.109)	0.612
Qualified current or previous occupation	0.447 (0.169-1.187)	0.106
Smoking at baseline and/or follow-up	1.182 (0.430-3.249)	0.746
Alcohol consumption at least every week at baseline and/or follow-up	0.291 (0.087-0.975)	0.045
NSAID intake at least every week at baseline and/or follow-up	0.877 (0.293-2.624)	0.814
Diabetes mellitus at baseline or follow-up	0.414 (0.047-3.613)	0.425
P-HDL cholesterol at baseline	1.291 (0.487-3.423)	0.607
P-LDL cholesterol at baseline	1.906 (1.255-2.897)	0.025
P-triglycerides at baseline	0.898 (0.423-1.904)	0.778
P-lipoprotein A at baseline	0.999 (0.997-1.001)	0.206

BMI: Body Mass Index. HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein.

PaperIV

It was shown that all digestive symptoms occurred rather commonly before cholecystectomy. For the majority of patients, these symptoms occurred at a frequency of less than once a week and, with the exception of bloating and disturbing abdominal gas, daily symptoms were infrequent. Compared to baseline there was a significant reduction in the frequency of all symptoms, except abdominal pain with atypical or multiple location and diarrhoea at 3 months after surgery. No more changes occurred thereafter. With regard to abdominal pain, 14 patients did not report any during the last 3 months prior the cholecystectomy. Although these patients had experienced pain previously and did fulfill the criteria for inclusion in the study when they were registered on the waiting list for cholecystectomy, they were excluded from further study. The remaining 186 patients also fulfilled the inclusion criteria at the time of registration on the waiting list. However, in 35 of these cases, atypical or multiple abdominal pain location was indicated in the symptom questionnaire at baseline. In the following, two groups are considered, patients with typical pain location (n=151) and patients with atypical or multiple pain location (n=35), as reported in the questionnaire at baseline. The frequencies of digestive symptoms other than pain in the two groups were compared at baseline and at 3 and 12 months after surgery. There were no significant differences.

Table 1. Changes in the frequency of abdominal pain episodes in patients with typical pain location and patients with atypical or multiple pain location at baseline.

Location of abdominal pain at baseline	No of patients		Change in frequency of abdominal pain episodes from baseline to 12 months postoperatively			
			No of patients (% of total)			
	Baseline	12 months	Disappeared	Improved	Unchanged	Worse
Typical	151	149	105 (70.5)	31 (20.8)	12 (8.0)	1 (0.7)
Atypical or multiple	35	35	25 (71.4)	2 (5.7)	5 (14.3)	3 (8.6)

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Table 1 shows changes in the frequency of pain episodes between baseline and 12 months. The disappearance, or reduced frequency of pain, was reported by 91.3% of patients with typical pain location at baseline. In the case of patients with atypical or multiple pain location at baseline, the corresponding figure was 77.1%. The difference between the two groups was significant (P= 0.034). Of the 149 patients with typical pain location at baseline, 31 (20.8%) reported pain with atypical or multifocal location at 12 months. In 17 of these 31 cases the frequency of pain episodes was less than once a month. With regard to the 35 patients with atypical or multiple pain location at baseline, 9 (25.7%) reported pain with typical location at 12 months, in 4 cases with a frequency of pain episodes of less than once a month. The frequency of a changed pain location at 12 months compared to baseline did not differ between the two groups (P=0.119).

There were no significant differences at any time point between patients with typical pain location and patients with atypical or multiple pain location with regard to frequency of pain episodes, pain intensity (VAS) and quality of life (NHP). However, there was a tendency (P=0.058) towards a lower frequency of pain episodes at baseline in the group with atypical or multiple pain location. There were significant improvements in both groups for all three variables when the baseline was compared with 3 months postoperatively. Differences between 3 and 12 months were not significant.

Logistic regression analysis was performed using the frequency of abdominal pain episodes (pain location disregarded) at 12 months as the dependent variable. The following baseline variables were independent: age, frequency of abdominal pain episodes, pain location, disturbing abdominal gas (at least every month at baseline) and specific food intolerance (yes/no). The overall NHP-score and the VAS-score for abdominal pain at baseline were also included as independent variables. The variables that emerged as being significantly correlated with the frequency of pain episodes at 12 months, are given in Table 3A.

Table 3B shows that exchanging specific food intolerance and disturbing abdominal gas at baseline with the same two variables at 12 months yielded, similar results. Fur-

thermore, the total NHP score at 12 months was related to the frequency of pain episodes at 12 months.

Table 3. Results of stepwise logistic regression analysis with frequency of abdominal pain episodes (episodes at least every month, yes/no; location disregarded) at 12 months as dependent variable.
A: Symptoms at baseline independent.
B: Disturbing abdominal gas, specific food intolerance and NHP at 12 months and age, frequency of pain episodes and location of pain at baseline independent.

A

Variable	**Odds ratio**	**95% ci**	**P-value**
Age at baseline, years	0.968	0.936-1.001	0.057
Pain episodes at least every month at baseline	4.553	1.173-17.673	0.028
Pain location atypical or multiple at baseline	3.061	1.131-8.284	0.028
Disturbing abdominal gas at least every month at baseline	5.329	1.950-14.564	0.001
Specific food intolerance at baseline	5.226	1.097-24.896	0.038

B

Variable	**Odds ratio**	**95% ci**	**P-value**
Age at baseline, years	0.955	0.922-0.989	0.011
Pain episodes at least every month at baseline	5.567	1.367-22.674	0.017
Pain location atypical or multiple at baseline	2.904	1.077-7.830	0.035
Disturbing abdominal gas at least every month at 12 at 12 months postoperatively	2.466	1.000-6.080	0.050
Specific food intolerance at 12 months postoperatively	2.229	0.962-5.445	0.061
Total NHP score at 12 months postoperatively	1.007	1.002-1.012	0.005

Discussion

The prevalence of gallstone disease at baseline was 17.2 % for women and 12.4 % for men (Paper I). These figures correspond well with other Scandinavian studies[4, 33, 37]. The prevalence is highest in North America and northern Europe and lowest in sub-Sahara Africa and Asia[34, 50, 55, 57, 67, 69, 127, 128]. The rates rise with increasing age and there is a female preponderance[76, 204-206]. In our study at an age of 75 years or more, 53 % of the women and 32 % of the men either had gallstones or had undergone a cholecystectomy (32 % and 13 % respectively).

We found that most subjects with gallstones are asymptomatic and no differences could be found in comparison with those without stones (Paper I). This is in agreement with several other studies[1, 3, 4, 57, 88, 89]. As in another study, the size and number of gallstones, did not influence symptomatology[32, 89]. On the other hand, size or volume is of importance regarding complications. Small or multiple stones are reportedly associated with increased risk of pancreatitis[140, 207, 208] and large volumes (multiple stones) with gallbladder carcinoma[156]. Since pancreatitis is a common and sometimes life threatening complication, some even recomend prophylactic cholecystectomy for cases with small or multiple stones, symptomatology disregarded[140].

Pain in the right upper quadrant is the only specific, although weak, predictor of symptomatic gallstone disease[50, 127]. In our study, as well as in a study by Jørgensen et al., it was shown that persons who previously had undergone a cholecystectomy experienced more pain[32, 100]. These persons also reported lower quality of life (Paper I). The question whether these symptoms and reduced quality of life are caused by, worsened or reduced by the cholecystectomy could not be answered in that study, but inspired to a study on postcholecystectomy syndrome (Paper IV).

The results from the incidence study led to the conclusion that gallstone development was not related to any significant change in digestive symptoms. Subjects who developed gallstones, reported a significant reduction in quality of life compared to persons without gallstone disease. One explanation could be that they were older than subjects who did not have newly developed gallstones.

Several putative predisposing and protective factors were analysed. Age and gender were mentioned above. High BMI is known to be associated with gallstone disease [2, 7, 53, 69, 75, 82, 209], but we found no such association, either in the prevalence study or in the incidence study. However, in the prevalence study, we found that subjects previously operated with cholecystectomy had a significantly higher BMI.

In our studies heredity was measured by the participant´s knowledge about gallstone operations among first-degree relatives. It is therefore, as in other studies, of question-

able value. Still, several studies claim heredity is an important risk factor for gallstone disease[5, 55, 56, 67]. As others, we found no such association[32, 57].

In some studies diabetes mellitus is described as a risk factor for gallstone disease [7, 64, 66, 67, 138, 210], but this association could not be verified in our study nor in that of Persson et al. [32, 68].

Data in the literature is conflicting as regards associations between occupation and life style and gallstone disease[47, 51, 58]. Although we could not find any associations to prevalent or incident gallstones, the OR of cholecystectomy was increased in the group of subjects with unqualified occupations (Paper I). In an American study Diehl et al. after controlling for age, obesity, parity and ethnicity showed, that socioeconomic factors such as low education and income, as well as an unqualified occupation were related to a higher prevalence of gallstone disease among women[47].

Several studies show a strong relation between estrogen intake or parity and gallstone disease[3, 44-48]. It has even been suggested that childbirth and estrogen intake together can explain the difference in prevalence between women and men[43]. However, like two large studies from Germany and France[49, 50] we found no relation between pregnancy or estrogen intake and the prevalence gallstone disease. Neither was there any such relation to gallstone development.

The prevention of gallstone reccurence with aspirin or NSAIDs has been described[70], but as in our studies, no such association was found in a large randomised trial[71] or in animal studies[72].

Some suggest that smoking prevents gallstone development[36], but the matter is controversial since others found smoking to be a independent risk factor[58, 60]. We found no association in our prevalence and incidence studies.

Alcohol consumption was shown to be associated with a decreased risk of developing symptomatic gallstone disease[60, 78, 79, 211, 212]. Although these findings are not undisputed[80], theye are in accordance with our studies.

Increased triglyceride levels associated with gallstone disease have been demonstrated in several prevalence studies[3, 51, 84, 213]. In this study and other prevalence studies[32, 90, 214] this was not the case. However, in our incidence study P-triglyceride levels at follow-up were related to gallstone development.

P-total cholesterol at baseline was associated with the development of gallstones. This was explained by a positive relation to P-LDL cholesterol, since there was no significant relation to P-HDL cholesterol. No other incidence studies have included repeat analysis of blood lipids. However, one study showed that small gallstones, which could represent newly developed gallstones, were associated with increased levels of both P-total cholesterol and P-LDL cholesterol[214].

Of 583 subjects without gallbladder stones at baseline, 42 (8.3 %) had developed stones after a minimum follow-up interval of 5 years (Paper III), yielding an estimated crude annual incidence of 1.5 %. There are only two published reports on the inci-

dence of gallstone disease. Neither of these has related the incidence to symptomatology and risk factors. In 1991, Jensen et al. published a large ultrasound based study from Denmark, which included women and men aged 30, 40, 50 and 60 years. They were followed for a minimum of five years[41]. Re-screening was done in 82.8% (2987/3608). The five-year incidence of gallbladder stones in each age group was 1.4, 3.6, 3.1, and 3.7% among women and 0.3, 2.9, 2.5 and 3.3% among men.
An Italian group performed a 10-year ultrasonographic follow-up study of 253 (59.4 %) out of 426 initially examined women aged 20-69 years at baseline[42]. The overall incidence of gallbladder stones was 6.3% (16 subjects), including 0.8% (2 subjects) without stones at baseline, but who had a cholecystectomy during follow-up.
In our study, the overall five-year incidence was much higher (8.3%). On the other hand, the present study population was older compared with both the Italian and the Danish studies. Furthermore, the prevalence of gallstone disease is higher in Scandinavia than in southern Europe[215] which probably could explain some of the difference. Our study found a positive association to age among women, but not among men. With regard to women, our results agree with those of others[41]. We found no difference in incidence related to gender. This may also be due to a higher age in the present study population, since the difference in incidence between women and men seems to level off with increasing age[41].

Predicting a beneficial outcome of elective cholecystectomy is critical. Firstly, it is important, but difficult to identify those asymptomatic individuals who are at increased risk of developing complications to gallstone disease (Paper II). Secondly, it is important to identify those symptomatic patients who are at increased risk of an unsatisfactory outcome of surgery, i.e. persistent pain or the so-called “post-cholecystectomy syndrome” (Paper IV). Complications to gallstone disease are costly and sometimes life-threathening. The major mortality is among the elderly. Some complications (e.g. acute pancreatitis) even lack causative treatment. One could argue that part of this mortality could be avoided by operating all persons with known gallstones. This however is unrealistic since the prevalence is high, most stones are asymptomatic[216], and health care costs would increase enormously.The treatment related mortality should also be taken into consideration[159].Therefore, it is desirable to be able to predict which individuals with asymptomatic stones will develop a complication. At the moment watchful waiting is the best option[98].
We evaluated putative risk factors and estimated the risk of being treated for complications among 120 subjects with asymptomatic gallstones found at screening in 739 subjects (Paper II). They were followed for a median of 87 (range 3-146) months or until treatment was required. Fourteen subjects were admitted to hospital and treated for gallstone-related complications (six) or symptoms (seven). The cumulative risk of being treated during the first five years after detection of asymptomatic gallstones was

7.6 (95% ci 2.8 to 12.4) per cent. In a 10 year follow-up study of 118 asymptomatic persons with gallbladder stones 3 % developed complications[93].

There were no significant differences between treated and untreated subjects with regard to digestive symptoms or any of the risk factors monitored at baseline, although treated subjects were significantly younger.

In the case of patients with gallstones and abdominal pain, it is important to refer the right candidates for cholecystectomy in order to avoid "post-cholecystectomy syndrome". In our prevalence study, we found that subjects previously operated with a cholecystectomy did worse regarding abdominal pain and quality of life. Whether this pattern was already present before the operation or is a result of the operation is unknown. In order to elucidate these aspects, we performed a prospective study on 200 consecutive patients undergoing cholecystectomy on strict indications (Paper IV). In the group with typical pain location, only 8.7 % experienced unchanged or worsened pain, whereas the corresponding frequency among patients with atypical pain location was 22.9 %. The latter figure agrees with that in a recent study from Norway, which showed that 22 % of patients undergoing cholecystectomy had persistent pain five years postoperatively[197]. These studies emphasize the importance of proper patient selection.

Unique to our studies was the use of a drawing of a torso in which the patient could indicate pain location at home without the influences associated with a health care visit. This was very useful in the categorisation of the pain, i.e. typical and atypical pain location. We also used measurements of quality of life. Similar assements, including psychological factors, have been used in other studies[125, 126, 217-219].

In our study (Paper IV), the outcome of cholecystectomy in terms of changes in the frequency of abdominal pain episodes, pain intensity and quality of life were interrelated and stable after three months. An important observation was that patients with a high frequency of pain episodes at baseline had a lower chance of becoming pain free after cholecystectomy. These results are in accordance with two other recently published studies[121, 198].

One should expect that patients with atypical pain at baseline and related worse outcome after surgery should experience a worse quality of life postoperatively as compared to patients with typical pain. This was not the case. However, several other studies have shown such an association [32, 191, 196].

Patients with psychiatric diseases and vulnerability usually experience lower quality of life and a worse outcome after surgery[106, 194].

Finally, in accordance with other studies[121, 197], we found that young age is a major risk factor for an unsatisfactory outcome after cholecystectomy.

Conclusions

In our adult study population, the prevalence of gallstone disease was 17.2 % among women and 12.4 % among men. The prevalence rose with increasing age and was higher among women. The crude annual incidence was 1.5% and increased with age among women. The incidence did not differ between women and men.

There was a relation of elevated blood lipid levels to gallstone development. Furthermore, there was an inverse relation between alcohol consumption to gallstone prevalence and incidence.

There were no significant changes in symptomatology or quality of life related to gallstone development. Nearly one out of ten developed symptoms or complications demanding treatment during a follow-up interval of 87 months. This did not seem to level off with time.

After cholecystectomy, patients with typical abdominal pain experienced better symptom relief than did patients with atypical pain preoperatively. All patients did better after cholecystectomy as regards the frequency and intensity of pain as well as quality of life. The changes were stable after three months. High intensity of pain, atypical pain and young age preoperatively were related to an unsatisfactory outcome after cholecystectomy.

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Summary in Swedish/Populärvetenskaplig sammanfattning på svenska

Gallsten är i Sverige liksom i övriga västvärlden vanligt förekommande. De studier som finns är gamla och en del är baserade på obduktionsstudier. Förekomsten (prevalensen) av gallsten i relation till symptom och riskfaktorer är inte undersökt i Sverige. Internationella prevalensstudier med ultraljud visar att de flesta med sten i gallblåsan är besvärsfria. Endast ungefär 20 % har besvär som kan relateras till gallstenarna. Smärta är den vanligaste anledningen till galloperation. Gallstenssjukdomen och dess komplikationer orsakar stora kostnader för samhället och små ändringar i indikationerna för operation orsakar avsevärda skillnader i kostnader. Dess komplikationer såsom akut cholecystit, pankreatit och sten i djupa gallgången kan bli livshotande. När dessa inträffar blir kostnaden avsevärt större jämfört med en planerad operation. Det är därför viktigt att analysera vilka individer med gallstenssjukdom som löper störst risk att utveckla komplikationer. Vidare är det väl känt att en del av dem som genomgår en planerad operation har oförändrade, förvärrade eller till och med nytillkomna besvär efteråt. Vid en analys av bördan av gallstenssjukdomen på individ- och samhällsnivå är det av yttersta vikt att fastställa frekvensen av nyinsjuknande (incidensen) och att relatera den till symptom och riskfaktorer. Endast två internationella studier avseende incidensen är publicerade och ingen har satt den i relation till symptomatologi eller riskfaktorer.

Målen med studierna var att fastställa ålders- och könsrelaterad prevalens och incidens. Vidare att ställa gallstensförekomst i relation till livsstil såsom rökning, alkohol konsumtion, medicinförbrukning e.t.c. Ur befolkningsregistret i Linköping slumpades 1200 (lika många män och kvinnor) personer i åldrarna 35-85 år ut. De kallades till en ultraljudsundersökning av gallblåsan efter att ha fyllt i ett frågeformulär om symptom, livsvanor och livskvalitet. Blodfetter analyserades. Prevalensen av gallsten var 17,2 % för kvinnor och 12,4 % för män. Man såg som i andra studier en högre prevalens hos kvinnor än män och en ökning med stigande ålder. Ingen skillnad fanns mellan de med gallsten och de utan gallsten avseende symptom, blodfetter och livskvalitet. Anmärkningsvärt var att personer som tidigare blivit gallopererade hade såväl mera symptom som sämre livskvalitet.

De personer som befanns ha gallsten utan besvär (n=120) vid den första undersökningen informerades om att de hade gallsten men att behandling endast är aktuell vid besvär. Dessa personer följdes upp efter minst fem år för att se hur många som utvecklat en behandlingskrävande symptom eller komplikation. Under denna period blev ungefär var tionde person behandlad. Den vanligaste orsaken var återkommande smärtor. Inga av ett antal potentiella riskfaktorer registrerade vid den primära undersökningen skiljde sig mellan de som blev behandlade och de som inte blev det. Dock noterades att de som utvecklade en komplikation var avsevärt yngre.

Efter ett minimum intervall på fem år gjorde vi om samma undersökningar som i prevalens studien för att fastställa incidensen samt studera symptomutveckling och riskfaktorer. Den årliga incidensen av gallsten fastställdes till 1,5 %. Ingen nämnvärd förändring av symptombilden noterades bland dem som utvecklade gallsten. Utveckling av gallsten var positivt relaterad till uppföljningstiden och nivåerna av blodfetter. Vidare fanns en omvänd relation mellan alkoholkonsumtion och gallstensutveckling.
I en enkätstudie av 200 konsekutiva patienter opererade för gallstenssjukdom med strikt definierade kriterier för operation analyserades symptom och livskvalitet innan och 3 respektive 12 månader efter operationen. Vi fann att bland dem som enligt definition hade typisk gallstenssmärta var frekvensen av besvär efter operationen avsevärt lägre (8,7 %) än bland de med atypiska besvär före operationen (23.1 %). När symptom eller livskvalitet förbättrades hade detta redan skett efter tre månader. Atypisk buksmärta, ung ålder och frekventa smärtepisoder före operationen minskade sannolikheten att bli besvärsfri efter operationen.

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