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ORIGINAL ARTICLE

Gallstone disease and mortality: a cohort study

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Abstract
Objectives The objective of this cohort study was to determine whether subjects with gallstone disease identified by screening of a general population had increased overall mortality when compared to gallstone-free participants and to explore causes of death.
Methods The study population ($N = 5928$) was examined 1982–1992 and included an abdominal ultrasound examination to assess gallstone status, a physical examination, blood samples, and a questionnaire about medical history. Participants were followed up through national registers until 2015. Multiple adjusted Cox regression models were built.
Results Gallstone disease was present in 10%. Mortality was 46% during median 24.7 years of follow-up with 1% lost. Overall mortality and death from cardiovascular diseases were significantly associated to gallstone disease. Death from unknown causes was significantly associated to gallstone disease and death from cancer and gastrointestinal disease was not associated. No differences in mortality for ultrasound-proven gallstones or cholecystectomy were identified.
Conclusions Gallstone disease is associated with increased overall mortality and to death from cardiovascular disease. Gallstones may be considered a possible cardiometabolic risk factor. Other unknown factors also seem to play a role.

Keywords Cholelithiasis · Epidemiologic studies · Gallbladder diseases · Gallstones · Ultrasonography · Epidemiology studies

Introduction

Gallstone disease has traditionally only been associated to colic, cholecystitis, jaundice, or pancreatitis and the mortality caused by these complications has been ever declining (Everhart and Ruhl 2009). Possible associations between gallstone disease and other morbidities have been discussed for decades (Friedman 1968; Kaye and Kern 1971; Patterson 1954; Paul et al. 1963), and a number of studies suggest associations to cardiometabolic risk factors and the metabolic syndrome (Diehl 2000). Limited knowledge about mortality in ultrasound-proven gallstone disease exists and only few cohort studies have identified associations to overall, cardiovascular, and cancer mortality (Ruhl and Everhart 2011; Schmidt et al. 2012).

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Gallstone disease is frequent in the general population with an overall prevalence of 10% (Jorgensen 2007), but only a small selected fraction is identified clinically (Shabanzadeh et al. 2016c). Since the majority of gallstone disease is 'silent', a population-based cohort study with ultrasound assessment of gallstones is necessary in order to explore associations between gallstone disease and mortality. Identifying morbidities causing death in subjects with gallstone disease might aim in understanding the risks of gallstone disease.

The objective of this cohort study was to determine whether participants with ultrasound-proven gallstones or cholecystectomy identified by screening of a general population had increased overall mortality when compared to gallstone-free participants and to explore the underlying causes of death.

Methods

The data of this study comprised three random samples of the general population, drawn by computer from the Civil Registration System, aged 30–70 years, and living in 11 municipalities in the western part of the urban area of Copenhagen. The cohorts were part of an international collaboration MONICA (Multinational mONItoring of trends and determinants in CArdiovascular disease). The aim of the MONICA studies was to examine cardiovascular risk factors in the general population. All were invited by letter and non-responders were re-invited and contacted by telephone. Free transportation and examinations that took place outside office working hours were offered if necessary. Subjects were invited for examinations which took place in the period 1982–1992. Participants appeared after 12 h of fasting and underwent a general health examination, including an abdominal ultrasound to assess gallstone status, a physical examination, blood samples, and a questionnaire about medical history. Studies on gallstone prevalence, incidence, and clinical follow-up have been published before (Jensen and Jorgensen 1991; Jorgensen 1987; Shabanzadeh et al. 2016a, b, c).

The explanatory variables were gallstones proven by ultrasound or history of cholecystectomy. At ultrasound gallstones were defined as acoustic shadows that moved with gravity in a gallbladder lumen. Exceptions from the mobility criteria included if a stone was wedged in the infundibulum of the gallbladder or otherwise impeded by size, septae, or folds. No intrahepatic or common bile duct gallstones were identified (Jorgensen 1987).

Long-term follow-up was performed through linkage of the participants' personal registration number to The Central Person Registry and The Danish Register of Causes of Death. The Danish Central Person Registry contains daily updated information on migration and vital status of the entire nation (Schmidt et al. 2014). Causes of death have been registered by the Danish National Board of Health. Initially, the cause of death was interpreted through the information from the death certificates; however, since 2007 the medical doctor who verified the death registered the cause of death on the death certificate. Causes were coded in accordance to International Classification of Disease (ICD) 8 until 1994 and since then according to the ICD 10; the ICD 9 was never used in Denmark. The Danish Register of Causes of Death contains one underlying cause of death with a number of contributory causes (Helweg-Larsen 2011). The causes of death in this present study were defined as the underlying cause of death. Entrance into the study population was the day of examination and participants were followed until death, emigration, lost to follow-up, or censoring on December 13th 2015. Causes of death were registered until December 31st 2013.

Overall mortality and subgroups of causes of death were the main outcomes of this study. Overall mortality was explored for the entire cohort, but due to differences in dates of database updates, causes of death analyses were restricted to the population with registered causes of death. Causes of death subgroups included cardiovascular disease also including diabetes, hypertension, and the complications thereof, cancer, gastrointestinal diseases, and all other causes of death divided into probably lifestyle related and probably not lifestyle related diseases. The latter division of other causes of death has been performed in mortality analyses before (Bender et al. 2015). Diabetes and hypertension were included as cardiovascular disease due to the increased focus on disposing morbidities to cardiovascular disease in the period (Janssen and Kunst 2004) and due to the variations in interpretation of the causes leading to death in participants with cardiovascular diseases. For a detailed description of diagnosis codes included in the causes of death categories, see the supplemental Table.

Analyses were all adjusted for the covariates age and sex. Other factors included body mass index (kg/m^2), smoking status (never, past, or current), alcohol consumption (units per week), high density lipoprotein cholesterol (mmol/L), non-high density lipoprotein cholesterol (total cholesterol minus high density lipoprotein cholesterol, mmol/L), and a diagnosis of diabetes made by a medical doctor. Blood pressures were reported as means of two measurements on the right arm while seated. For the purpose of this study, systolic blood pressure was dichotomized at 140 mmHg and diastolic blood pressure at 90 mmHg in order to adjust for hypertension. The participants' social group was according to the five'-level definition from The Danish National Centre for Social Research which was based on education and occupation with level I indicating the highest social group (Jorgensen 1988). A first multiple adjusted models was built

by including covariates and variables with possible confounding associations for gallstone disease and causes of death based on directed acyclic graphs. A second multiple adjusted model was built excluding participants with known morbidities identified through the baseline examination medical history questionnaire. Thereby, cardiovascular disease was explored by excluding participants with coronary and cerebrovascular disease and other probably lifestyle-related diseases were explored by excluding participants with chronic bronchitis since death from chronic obstructive pulmonary disease was included in this group.

Sensitivity analyses of causes of death were performed for significant associations or non-significant associations with P value <0.20 in the first multiple adjusted model in order to explore the impact of the subgroup heterogeneity. The sensitivity analyses included the same covariates and variables as included in the first multiple adjusted model. Reporting was performed according to the STROBE Statement (von Elm et al. 2007) with the exception of reporting unadjusted estimates.

Statistical analyses

Medians with interquartile ranges (iqr) were reported for continuous variables and numbers with percentages were reported for categorical variables. Cumulative mortality proportions at 30-year follow-up were reported for both overall mortality and causes of death. In causes of death analyses, all alternative causes were included as competing risks. In all analyses, participants alive or lost to follow-up were censored on last date available in The Central Person Registry. Cox regression was used for statistical analyses. Hazard ratios (HR) with 95% confidence intervals (CI) were reported and significant associations were defined by a confidence interval not including 1. Each analysis of overall mortality or causes of death was performed in two sets, one with gallstone disease included as a three-level categorical variable (ultrasound-proven stones, cholecystectomy, no gallstones) and one with gallstone disease included as a dichotomous variable. A minimum of 10 outcome events per parameter was required in the multiple adjusted models. Plots of Martingale residuals were inspected for goodness of fit in the final multiple models and the assumption of proportional hazards was not violated in any of the analyses. All statistical analyses were performed with the "R Studio" software (RStudio Inc, Boston, MA) with the "survival" and "cmprsk" packages.

Results

The study population included 5928 participants with complete ultrasound examinations for assessment of gallstones. The participation proportion was 75.5% out of 7847 invited subjects. Ten percent had gallstone disease, of whom 6.8% had ultrasound-proven gallstones and 3.2% had cholecystectomies performed before baseline (Fig. 1). Participants with gallstone disease had higher age, higher BMI, were most often female, and differed on a number of other factors at baseline (Table 1).

The overall mortality proportion was 46% during median follow-up 24.7 years, iqr [18.9; 32.4] (21.8 years, iqr [12.2; 26.6] and 24.7 years, iqr [20.0; 32.5] in participants with and without gallstone disease, respectively). Lost to follow-up (1%) included 58 emigrations and four who had disappeared or changed their personal registration number (Fig. 1). The unadjusted cumulative overall mortality proportion was significantly increased in participants with gallstone disease and no differences in curves for ultrasound-proven gallstones and for cholecystectomy were seen (Fig. 2). Causes of death were available for 91% of deaths (2465/2710) and analyses were performed on a follow-up period of median 24.7 years, iqr [18.4; 32.5]. The most frequent causes of death were cancer (33.4%) and cardiovascular disease (30.4%) (supplemental Table).

Overall mortality was significantly associated to gallstone disease with a 25% relative increase in multiple adjusted analyses (Table 2).

Death from cardiovascular diseases was significantly associated to gallstone disease in all multiple adjusted models (Table 2). The significant association of cardiovascular disease and gallstone disease withheld when deaths from diabetes and hypertension were re-categorized as non-cardiovascular disease in sensitivity analyses (Table 3).

Deaths from cancer were non-significantly associated to gallstone disease with P value <0.20 in the multiple adjusted model (Table 2). Deaths from non-gastrointestinal cancers, colorectal cancer, and upper gastrointestinal cancers (gallbladder, other biliary, esophagus, gastric, duodenal, small bowel, pancreatic, hepatic) had no significant associations to gallstone disease in sensitivity analyses.

Deaths from other probably not lifestyle related diseases were significantly associated to gallstone disease (Table 2). When all subgroups of deaths from other probably not lifestyle related diseases (see supplemental Table) were explored only, the subgroup symptoms, signs, and abnormal clinical findings were significantly associated to gallstone disease (data not shown). When this subgroup was further divided, only the unknown causes of death or sudden death were significantly associated to gallstone disease (Table 3).

No difference in mortality was seen for the ultrasound-proven gallstones, cholecystectomy, or pooled gallstone disease except for the analyses of other probably not lifestyle related diseases (Table 2). No significant associations

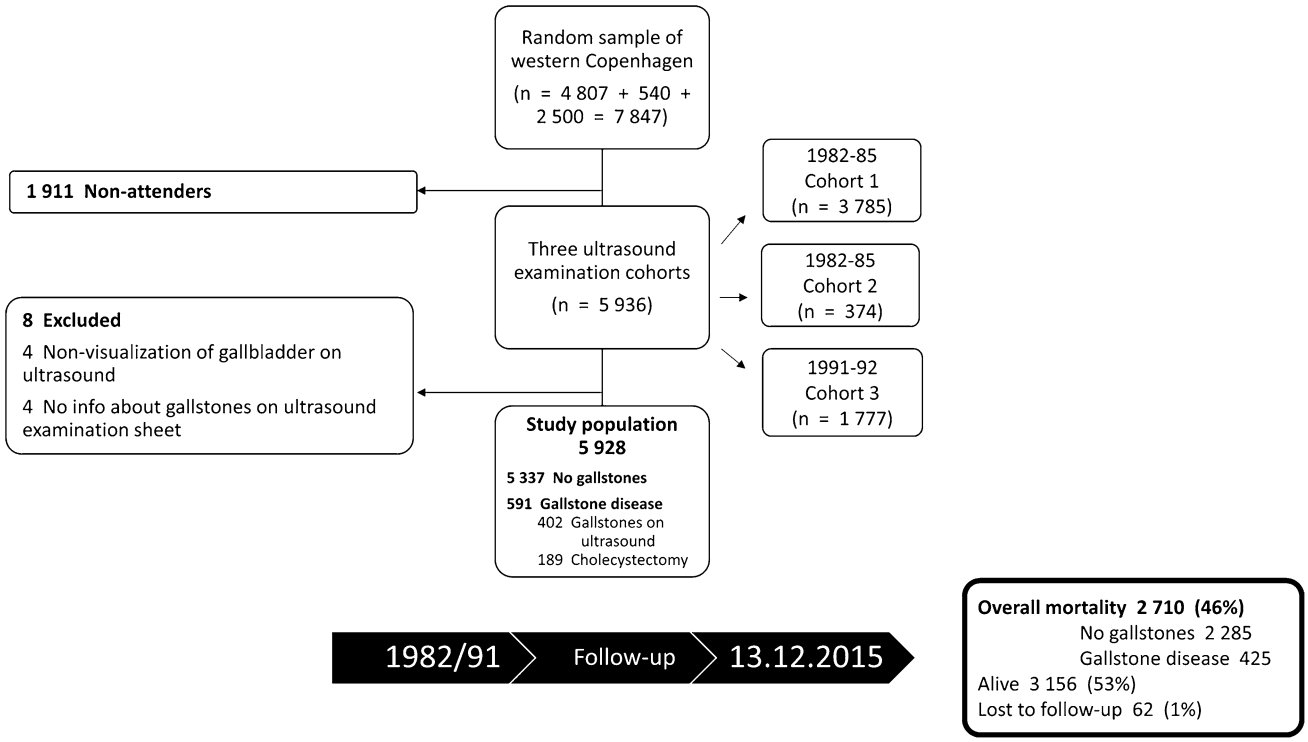

Fig. 1 Study design and participant flow (Denmark, 1982–2015)

Table 1 Baseline characteristics of the random population sample from Western Copenhagen (Denmark, 1982–1992)

Variable	Unit	No gallstones ($N = 5337$)	Gallstones ($N = 591$)	P value[a]	Missing
Age	Median [iqr]	50.0 [40.0; 60.0]	60.0 [50.0; 70.0]	<0.0001	
Sex	Female	2524 (47.3)	382 (64.6)	<0.0001	
	Male	2813 (52.7)	209 (35.4)		
Body mass index	Median [iqr]	24.2 [22.0; 27.0]	25.8 [23.2; 29.3]	<0.0001	2
High density lipoprotein cholesterol	mmol/L	1.4 [1.2; 1.7]	1.4 [1.2; 1.7]	0.25	16
Non-high density lipoprotein cholesterol	mmol/L	4.4 [3.6; 5.3]	4.7 [4.0; 5.6]	<0.0001	21
Systolic blood pressure	>140 mmHg	948 (17.8)	192 (32.5)	<0.0001	3
Diastolic blood pressure	>90 mmHg	690 (12.9)	122 (20.7)	<0.0001	3
Diabetes		125 (2.3)	30 (5.1)	0.0001	5
Coronary disease		95 (1.8)	25 (4.2)	0.0001	5
Cerebrovascular disease		53 (1.0)	22 (3.7)	0.0001	5
Chronic bronchitis		586 (11.0)	88 (14.9)	0.006	10
Smoking	Never (ref.)	1420 (26.6)	141 (23.9)		1
	Past	1079 (20.2)	142 (24.1)		
	Current	2838 (53.2)	307 (52.0)	0.07	
Alcohol consumption (units/week)	Median [iqr]	5.0 [2.0; 12.0]	3.0 [0.0; 9.0]	<0.0001	15
Social group	I (ref.)	255 (4.9)	15 (2.6)		118
	II	745 (14.2)	62 (10.9)		
	III	1258 (24.0)	137 (24.1)		
	IV	1713 (32.7)	187 (32.9)		
	V	1271 (24.2)	167 (29.4)	0.005	

[a] Chi-squared or Wilcoxon rank sum test

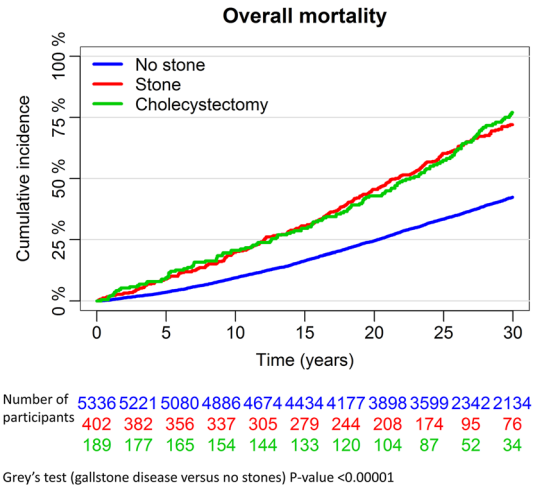

Fig. 2 Cumulative overall mortality proportions in participants with ultrasound-proven gallstones, cholecystectomy, or no gallstones at baseline during study period (Denmark, 1982–2015)

were identified for deaths from gastrointestinal disease or other probably lifestyle-related diseases and gallstone disease (Table 2).

Discussion

Gallstone disease in the general population had a relative increased overall mortality of 25% during long-term follow-up. No differences in mortality were identified for cholecystectomy or ultrasound-proven gallstones. Death from cardiovascular diseases and unknown causes of death were significantly associated to gallstone disease. No significant associations were found for death from cancer or gastrointestinal diseases. No significant confounding was identified through multiple adjusted analyses.

Other population-based cohort studies have found associations for ultrasound-proven gallstones or cholecystectomy and overall mortality, pooled cancer mortality (Ruhl and Everhart 2011; Schmidt et al. 2012), and cardiovascular mortality (Ruhl and Everhart 2011). To our knowledge, these two cohort studies of general populations from the US (Ruhl and Everhart 2011) and Norway (Schmidt et al. 2012) are the only studies similar to this study including ultrasound assessment of gallstones. In conflict with these previous studies, this present study found only a non-significant association for death from cancer and colorectal cancers ($P = 0.21$) in sensitivity analyses. Although cancer was the most frequent cause of death, the findings still can be due to type II error. Cancers have heterogeneous etiologies and hypotheses about occurrence of specific cancers in gallstone disease can therefore not be rejected with this study.

A number of cohort studies have explored the importance of clinically diagnosed gallstone disease to mortality and morbidity. The first cohort study of that kind, identified no association to overall mortality (Friedman et al. 1966); however, clinically diagnosed gallstones have since been associated to increased overall mortality and pooled cancer mortality in Pima Indians (Grimaldi et al. 1993). When focusing on incident morbidity, clinical gallstones have been associated to coronary heart disease (Bortnichak et al. 1985; Lv et al. 2015), stroke (Wei et al. 2014), cardiovascular disease (Olaiya et al. 2013; Wirth et al. 2015), as well as gastrointestinal cancers (Goldacre et al. 2012) and other site-specific cancers (Johansen et al. 1996; Li et al. 2011). However, less than one-fifth of gallstone carriers from a general population are detected clinically and specific determinants of clinically diagnosed gallstone disease have been identified (Shabanzadeh et al. 2016a, b). Studies including only clinically diagnosed gallstones, therefore, contain a selected group of gallstone carriers and control groups with unknown gallstone status, consequently, causing a differential misclassification bias.

The link between gallstone formation and cardiovascular disease might be through genetic variations of cholesterol transport proteins. The Apolipoprotein E protein functions as a blood cholesterol transporter and as ligands to hepatic lipoprotein receptors (Mahley 1988) and its *ε4* allele has been associated to both clinically diagnosed gallstones (Xue et al. 2012) and coronary artery disease (Bennet et al. 2007) in meta-analyses of observational studies. The underlying mechanisms are not completely understood (Bennet et al. 2007); however, altered affinity to the low density lipoprotein receptor has been suggested (Hatters et al. 2006). Second, the expression of the hepatic cholesterol transporter ABCG5/8 is promoted by hyperinsulinemia as seen in obesity and the metabolic syndrome (Biddinger et al. 2008). The D19H polymorphism of this transporter has been associated to gallstone disease (Jiang et al. 2014) and suggested as "gain of function" mutation enhancing cholesterol clearance from the hepatocyte into bile promoting gallstone formation (Hirschfield et al. 2013). The findings of no differences in mortality for cholecystectomy or ultrasound-proven gallstones support the hypothesis of common underlying mechanisms between gallstones and cardiovascular disease which, therefore, are not reversed by cholecystectomy.

The limitations of this study were the use of data from a database for causes of death which might have included varying interpretations of the underlying cause of death, either by the physician declaring death or by changes in the knowledge about causes of disease throughout the follow-up period. Underlying causes of death cannot be classified more precisely since autopsies no longer are performed by routine in Denmark. Another limitation includes the long

Table 2 Analyses of overall mortality ($N = 5928$ with median follow-up 24.7 years, iqr [18.9; 32.4]) and causes of death ($N = 5683$ with median follow-up 24.7 years, iqr [18.4; 32.5]) and gallstone disease (Denmark, 1982–2015)

Causes of death and gallstone status	Number of deaths/total	Unadjusted cumulative mortality proportion at 30 years (%)	Sex- and age-adjusted HR [95% CI]	Multiple adjusted model 1 HR [95% CI]	Multiple adjusted model 2 HR [95% CI][a]
Overall mortality					
No stones	2285/5337	42.4	Ref.	Ref.	
Stones at ultrasound	282/402	72.0	**1.28 [1.13; 1.46]**	**1.27 [1.12; 1.45]**[c]	
Cholecystectomy	143/189	77.1	**1.20 [1.01; 1.42]**	**1.22 [1.02; 1.46]**[c]	
Gallstone disease[b]	387/591	73.8	**1.25 [1.13; 1.40]**	**1.25 [1.12; 1.40]**[c]	
Cardiovascular disease					
No stones	603/5121	12.4	Ref.	Ref.	Ref.
Stones at ultrasound	97/384	26.5	**1.58 [1.27; 1.96]**	**1.36 [1.08; 1.70]**[d]	**1.39 [1.09; 1.78]**[d]
Cholecystectomy	49/178	28.8	**1.45 [1.12; 2.02]**	**1.43 [1.05; 1.95]**[d]	**1.47 [1.06; 2.04]**[d]
Gallstone disease[b]	146/562	27.3	**1.55 [1.29; 1.87]**	**1.38 [1.13; 1.67]**[d]	**1.42 [1.15; 1.75]**[d]
Cancer					
No stones	708/5121	14.6	Ref.	Ref.	
Stones at ultrasound	73/384	20.4	1.12 [0.88; 1.43]	1.11 [0.87; 1.43][c]	
Cholecystectomy	42/178	25.3	1.23 [0.90; 1.69]	1.23 [0.89; 1.70][c]	
Gallstone disease[b]	115/562	22.1	*1.16 [0.95; 1.42]*	*1.15 [0.94; 1.42]*[c]	
Gastrointestinal disease					
No stones	66/5121	1.3	Ref.	Ref.	
Stones at ultrasound	10/384	2.7	1.47 [0.75; 2.88]	1.38 [0.68; 2.81][e]	
Cholecystectomy	4/178	2.4	1.09 [0.39; 3.02]	1.16 [0.41; 3.24][e]	
Gallstone disease[b]	14/562	2.6	1.34 [0.74; 2.41]	1.30 [0.70; 2.42][e]	
Other probably lifestyle-related diseases					
No stones	217/5121	4.5	Ref.	Ref.	
Stones at ultrasound	18/384	5.0	0.87 [0.54; 1.42]	0.93 [0.57; 1.51][f]	1.07 [0.59; 1.95][f]
Cholecystectomy	10/178	4.9	0.88 [0.47; 1.68]	0.99 [0.52; 1.89][f]	0.76 [0.31; 1.87][f]
Gallstone disease[b]	28/562	5.0	0.88 [0.59; 1.31]	0.95 [0.63; 1.42][f]	0.96 [0.57; 1.60][f]
Other probably not lifestyle related diseases					
No stones	475/5121	10.0	Ref.		
Stones at ultrasound	66/384	18.7	**1.43 [1.10; 1.85]**		
Cholecystectomy	27/178	16.7	1.01 [0.68; 1.50]		
Gallstone disease[b]	93/562	18.1	**1.28 [1.02; 1.60]**		

Bold letters indicate significant associations and italic letters indicate a P value <0.20

[a] Presence of cardiovascular disease (coronary disease and cerebrovascular disease) was excluded in analyses of cardiovascular disease and chronic bronchitis was excluded in analyses of other probably lifestyle related diseases

[b] Gallstone disease included both ultrasound-proven gallstones and cholecystectomy at baseline examination

[c] Model includes age, sex, body mass index, social group I–V, smoking (never, past, current), alcohol consumption (units/week)

[d] Model includes age, sex, body mass index, social group I–V, smoking (never, past, current), alcohol consumption (units/week), diabetes, systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, non-high density lipoprotein cholesterol, high density lipoprotein cholesterol

[e] Model includes age, sex, body mass index, social group (I II III vs. IV V)

[f] Model includes age, sex, body mass index, social group I–V, smoking (never, past, current), alcohol consumption (units/week)

follow-up which might have caused an underestimation of gallstone exposure in the presumed gallstone-free comparator group. These limitations might have caused a non-differential misclassification bias with hazard ratio estimates towards one and non-significant associations as a consequence. A larger sample size might, thereby, have strengthened the identified associations. These limitations must be outweighed against the unique possibilities of a comprehensive and long follow-up of a general population sample with ultrasound assessment of gallstones at

Table 3 Sensitivity analyses of causes of death ($N = 5628$ with median follow-up 24.7 years, iqr [18.9; 32.4]) and gallstone disease (Denmark, 1982–2013)

	Number of deaths/total	Adjusted analyses HR [95% CI]
Cardiovascular disease		
Coronary, cerebral, and peripheral ischemic disease		
No stones	536/5121	Ref.
Gallstone disease[a]	130/562	**1.39 [1.13; 1.71][b]**
Cancer		
Upper gastrointestinal cancers[c]		
No stones	101/5121	Ref.
Gallstone disease[a]	14/562	1.21 [0.67; 2.16][d]
Colorectal cancer		
No Gallstones	65/5121	Ref.
Gallstone disease[a]	14/562	1.44 [0.82; 2.53][d]
Non-gastrointestinal cancers		
No stones	524/5121	Ref.
Gallstone disease[a]	82/562	1.09 [0.86; 1.39][d]
Other probably not lifestyle related diseases: the subgroup Symptoms, signs, and abnormal clinical findings (data from the other subgroups not shown)		
All symptoms, signs, and abnormal clinical findings		
No stones	98/5121	Ref.
Gallstone disease[a]	27/562	**1.91 [1.23; 2.96][e]**
Unknown causes of death/sudden death		
No stones	55/5121	Ref.
Gallstone disease[a]	14/562	**1.91 [1.04; 3.50][e]**
Other symptoms, signs, or clinical findings		
No stones	420/5121	Ref.
Gallstone disease[a]	79/562	1.20 [0.94; 1.54][e]

Bold letters indicate significant associations

[a] Gallstone disease included both ultrasound-proven gallstones and cholecystectomy at baseline examination

[b] Model includes age, sex, body mass index, social group I–V, smoking (never, past, current), alcohol consumption (units/week), diabetes, systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, non-high density lipoprotein cholesterol, high density lipoprotein cholesterol

[c] Esophagus, gastric, duodenal, small bowel, pancreas, hepatic, gallbladder, and other biliary cancers (cholecystectomy at baseline excluded)

[d] Model includes age, sex, body mass index, social group (I II III vs. IV V), smoking (never, past, current), alcohol consumption (units/week)

[e] Model includes age and sex

baseline. Other strengths included the minimizing of confounding through adjustment for covariates associated to gallstone disease and to mortality.

The association of unknown causes of death or sudden death suggests that other factors might contribute to the increased overall mortality in gallstone disease. This study's design was not able to identify such alternative causes of death which was a limitation; however, since sudden death most often is caused by cardiac diseases, this finding might support the association between death from cardiovascular disease and gallstone disease even further. Future studies should explore these possible alternative causes further. This study supports the increasing body of evidence on the relationship between gallstone disease and cardiometabolic risk factors or the metabolic syndrome (Diehl 2000; Grundy 2004; Shabanzadeh et al. 2016c). Future population-based studies should explore the association between ultrasound-proven gallstones and the development of morbidity further. Clinical trials of cardiovascular interventions or prevention might also benefit from including ultrasound assessment of gallstones as a cardiometabolic risk factor.

To conclude, gallstone disease was associated to a relative increase of 25% in overall mortality and to death from cardiovascular disease. This evidence further supports the link between the metabolic syndrome and gallstone

disease. Gallstone disease may be considered a possible cardiometabolic risk factor in future trials. More research on long-term gallstone disease morbidity is needed.

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