Risk factors for requiring cholecystectomy for gallstone disease in a prospective population-based cohort study

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Background: The relationship between different lifestyle factors and the risk of needing cholecystectomy for gallstone disease is not clear. This study aimed to assess the association between anthropometric, lifestyle and sociodemographic risk factors and the subsequent risk of requiring cholecystectomy for gallstone disease during long-term follow-up in a defined population cohort.

Methods: Data from a large population-based cohort study performed from 1995 to 1997 were used (the second Norwegian Nord-Trøndelag health study, HUNT2). Following HUNT2, from 1998 to 2011, all patients operated on for gallstone disease with cholecystectomy at the two hospitals in the county, Levanger Hospital and Namsos Hospital, were identified. A Cox proportional hazards model was used for multivariable risk analysis.

Results: The HUNT2 cohort included 65 237 individuals (69·5 per cent response rate), aged 20–99 years. During a median follow-up of 15·3 (range 0·6–16·4) years, 1162 cholecystectomies were performed. In multivariable analysis, overweight individuals (body mass index (BMI) 25·0–29·9 kg/m^2) had a 58 per cent increased risk of cholecystectomy compared with individuals with normal weight (BMI less than 25·0 kg/m^2). Obese individuals (BMI 30 kg/m^2 or above) had a twofold increased risk. Increasing waist circumference independently increased the risk of cholecystectomy. In women, current hormone replacement therapy (HRT) increased the risk, whereas hard physical activity and higher educational level were associated with reduced risk of cholecystectomy.

Conclusion: High BMI and waist circumference increased the risk of having cholecystectomy for both sexes. In women, the risk was increased by HRT, and decreased by hard physical activity and higher educational level.

Introduction

In Europe and North America, gallstones are the leading cause of inpatient admissions for gastrointestinal disease[1], and cholecystectomy for gallstone disease is one of the most common elective operations performed[2]. Cholecystectomy rates in North America increased during the 1990s, probably explained by increased incidence of cholelithiasis, an increased frequency of symptomatic gallstone disease, improved diagnostic expertise and a lowered threshold for surgery[1]. However, in the late 1990s the cholecystectomy rate stabilized following the introduction of the laparoscopic technique[3–5], as also demonstrated in Europe[6–8]. In Nord-Trøndelag County, Norway, the cholecystectomy rate increased during the years following introduction of laparoscopic surgery, from 6·2 per 100 000 person-years in 1990–1992 to 10·0 per 100 000 in 1998–2003, and has remained stable since[7].

The estimated prevalence of gallstones in Europe and North America is 5–25 per cent, and 50–80 per cent of patients are asymptomatic[1,8]. In addition, the prevalence of gallstone disease in a population appears to have little influence on the incidence of gallbladder surgery[9]. Several studies have assessed risk factors for gallstones[10–12]. However, they focused on the risk of gallstone formation and did not consider symptomatic disease or cholecystectomy as an endpoint. The subsequent risk factors for having a cholecystectomy performed have been less well investigated.

Seven of ten cholecystectomies are performed in women, both in the past and present era[13]. Overweight, parity, hormone replacement therapy (HRT) and use of contraceptive medications have been suggested as risk factors for cholecystectomy[12,14−16]. However, most previous studies have been performed in selected groups of patients, mainly postmenopausal women, and not in an unselected general population. The aim of this investigation was to examine lifestyle-related risk factors for cholecystectomy in a large and unselected prospective population-based cohort study.

Methods

The study base was the population of Nord-Trøndelag County, Norway (*Fig. 1*). The population structure of Nord-Trøndelag is stable and representative for Norway, except for slightly lower income and the absence of larger cities[17]. During 1995–1997, all residents in Nord-Trøndelag aged 20 years or more were invited to participate in the second wave of the Nord-Trøndelag health study (HUNT2), a survey consisting of written questionnaires on health-related topics, physical examinations and blood sampling[18,19].

Residents were included if they had completed the questionnaires and anthropometric measurements. Surgery for gallstone disease was performed only at the two hospitals in the county, Levanger Hospital and Namsos Hospital. All patients operated on for gallstone disease were included, identified using surgical codes for cholecystectomy in the patient administrative system at the hospitals during 1998–2011. Participants who had undergone surgery for gallstone disease with cholecystectomy and had participated in HUNT2 were included as 'patients' and the remaining HUNT2 participants were included as 'controls'. Those who had a cholecystectomy during 1990–1997 (preceding HUNT2), who were operated on
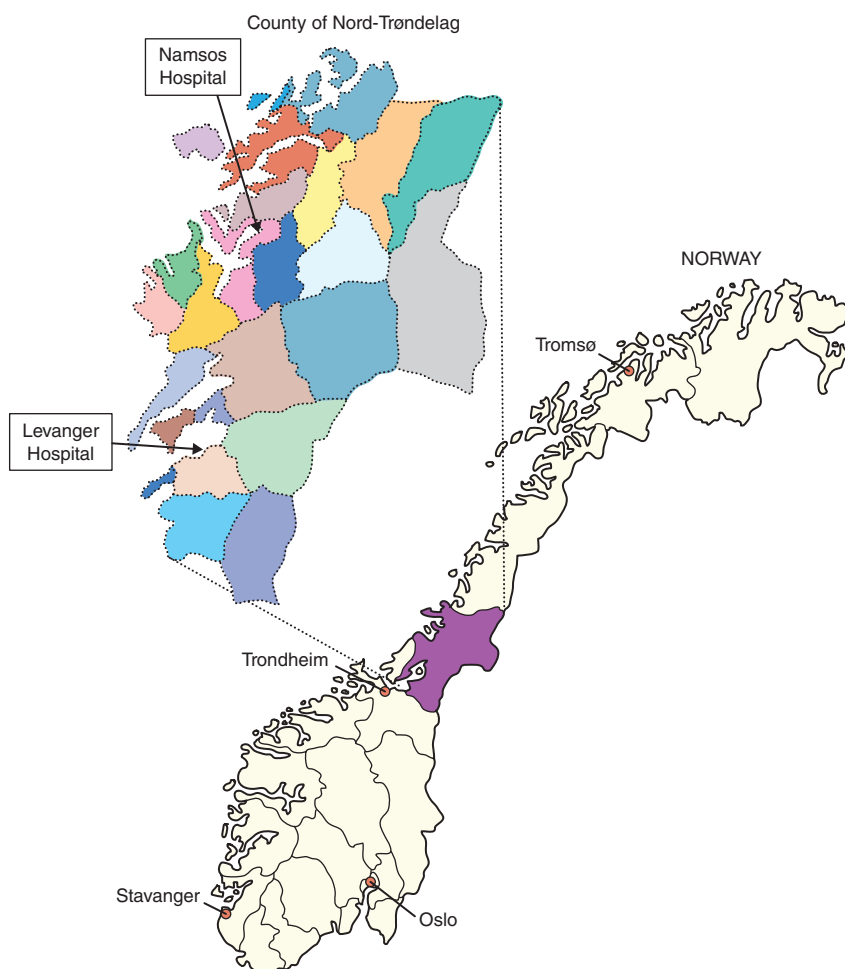

Fig. 1 The HUNT study area: the 25 (now 24) municipalities in Nord-Trøndelag County, Norway

Table 1 Baseline characteristics of the study population

	Women			Men		
	Controls (n = 32 454)	Patients (n = 813)	P*	Controls (n = 29 633)	Patients (n = 349)	P*
Age (years)			< 0·001			< 0·001
< 30	4408 (13·6)	120 (14·8)		3982 (13·4)	19 (5·4)	
30–39	5779 (17·8)	136 (16·7)		5349 (18·1)	45 (12·9)	
40–49	6799 (20·9)	185 (22·8)		6398 (21·6)	76 (21·8)	
50–59	5434 (16·7)	186 (22·9)		5197 (17·5)	80 (22·9)	
60–69	4446 (13·7)	128 (15·7)		4186 (14·1)	74 (21·2)	
70–79	4129 (12·7)	53 (6·5)		3489 (11·8)	53 (15·2)	
≥ 80	1459 (4·5)	5 (0·6)		1032 (3·5)	2 (0·6)	
Body mass index			< 0·001			< 0·001
Normal	14 595 (45·0)	223 (27·4)		10 449 (35·3)	61 (17·5)	
Overweight	11 977 (36·9)	341 (41·9)		14 963 (50·5)	194 (55·6)	
Obese	5882 (18·1)	249 (30·6)		4221 (14·2)	94 (26·9)	
Waist circumference			< 0·001			< 0·001
Normal	15 816 (48·7)	241 (29·6)		17 880 (60·3)	139 (39·8)	
Increased	7917 (24·4)	224 (27·6)		7645 (25·8)	125 (35·8)	
Substantially increased	8721 (26·9)	348 (42·8)		4108 (13·9)	85 (24·4)	
Highest educational level			0·015			0·240
Primary school	12 457 (38·4)	322 (39·6)		9111 (30·7)	118 (33·8)	
High school	8770 (27·0)	253 (31·1)		11 289 (38·1)	130 (37·2)	
Junior college	3202 (9·9)	74 (9·1)		2254 (7·6)	18 (5·2)	
University	6151 (19·0)	123 (15·1)		5631 (19·0)	64 (18·3)	
Missing	1874 (5·8)	41 (5·0)		1348 (4·5)	19 (5·4)	
Hard physical activity (h/week)			< 0·001			0·012
< 1	14 939 (46·0)	421 (51·8)		13 300 (44·9)	170 (48·7)	
≥ 1	6220 (19·2)	118 (14·5)		8883 (30·0)	81 (23·2)	
Missing	11 295 (34·8)	274 (33·7)		7450 (25·1)	98 (28·1)	
No. of children			0·014			
0	3872 (11·9)	68 (8·4)				
1–2	12 080 (37·2)	323 (39·7)				
≥ 3	12 062 (37·2)	323 (39·7)				
Missing	4440 (13·7)	99 (12·2)				
HRT use			< 0·001			
Never	20 412 (62·9)	470 (57·8)				
Former	1231 (3·8)	45 (5·5)				
Current	2558 (7·9)	117 (14·4)				
Missing	8253 (25·4)	181 (22·3)				
Ever used contraceptive medication			0·180			
No	9952 (30·7)	303 (37·3)				
Yes	12 585 (38·8)	344 (42·3)				
Missing	9917 (30·6)	166 (20·4)				

Values in parentheses are percentages. HRT, hormone replacement therapy. *Unconditional z-pooled test.

for malignant disease, or who lived outside the county were excluded.

The participants in HUNT gave written informed consent for medical research, including linkage to hospital patient records.

A full description of the questionnaires and measurements is given on the HUNT home page[18–20]. From HUNT2, information from questionnaires was used on physical activity, parity, contraceptive medication, HRT and data on anthropometric measurements. Height, weight and waist circumference were measured with standard methods by qualified personnel.

Based on the World Health Organization (WHO) classification, body mass index (BMI) was calculated and individuals were categorized as having normal weight (BMI less than 25·0 kg/m²), being overweight (25·0–29·9 kg/m²) or obese (30 kg/m² or more)[21]. Waist circumference was categorized according to WHO into three categories for each sex (men: normal (less than 94 cm), increased (94–101 cm) and substantially increased (102 cm or more); women: normal (less than 80 cm), increased (80–87 cm) and substantially increased (88 cm or more))[21].

Statistical analysis

Analyses were performed using SPSS® statistics version 22 (IBM, Armonk, New York, USA) and StatXact 9 (Cytel, Cambridge, Massachusetts, USA). The study endpoint

Table 2 Univariable Cox proportional hazards analysis of risk factors for cholecystectomy

	Women			Men		
	n	Hazard ratio	*P*	*n*	Hazard ratio	*P*
Age (years)						
< 30	4528	1·00 (reference)		4001	1·00 (reference)	
30–39	5915	0·87 (0·68, 1·11)	0·255	5394	1·76 (1·03, 3·01)	0·039
40–49	6984	1·00 (0·80, 1·26)	0·991	6474	2·49 (1·50, 4·11)	< 0·001
50–59	5620	1·26 (1·00, 1·59)	0·049	5277	3·24 (1·97, 5·34)	< 0·001
60–69	4574	1·08 (0·84, 1·38)	0·554	4260	3·79 (2·29, 6·27)	< 0·001
70–79	4182	0·50 (0·36, 0·69)	< 0·001	3542	3·34 (1·98, 5·65)	< 0·001
≥ 80	1464	0·13 (0·05, 0·33)	< 0·001	1034	0·42 (0·10, 1·80)	0·241
Body mass index						
Normal	14 818	1·00 (reference)		10 510	1·00 (reference)	
Overweight	12 318	1·86 (1·57, 2·21)	< 0·001	15 157	2·22 (1·67, 2·96)	< 0·001
Obese	6131	2·77 (2·31, 3·32)	< 0·001	4315	3·81 (2·76, 5·26)	< 0·001
Waist circumference						
Normal	16 057	1·00 (reference)		18 019	1·00 (reference)	
Increased	8141	1·86 (1·55, 2·23)	< 0·001	7770	2·12 (1·66, 2·70)	< 0·001
Substantially increased	9069	2·63 (2·23, 3·10)	< 0·001	4193	2·70 (2·06, 3·53)	< 0·001
Educational level						
Primary school	12 779	1·00 (reference)		9229	1·00 (reference)	
High school	9023	1·10 (0·93, 1·30)	0·262	11 419	0·88 (0·69, 1·13)	0·307
Junior college	3276	0·88 (0·68, 1·13)	0·322	2272	0·61 (0·37, 1·00)	0·050
University	6274	0·77 (0·62, 0·94)	0·011	5695	0·87 (0·64, 1·18)	0·362
Hard physical activity (h/week)						
< 1	15 360	1·00 (reference)		13 470	1·00 (reference)	
≥ 1	6338	0·67 (0·55, 0·82)	< 0·001	8964	0·71 (0·55, 0·93)	0·011
No. of children						
0	3940	1·00 (reference)				
1–2	12 403	1·52 (1·17, 1·97)	0·002			
≥ 3	12 385	1·53 (1·17, 1·98)	0·002			
HRT use						
Never	20 882	1·00 (reference)				
Former	1276	1·58 (1·17, 2·15)	0·003			
Current	2675	1·98 (1·62, 2·42)	< 0·001			

Values in parentheses are 95 per cent confidence intervals. HRT, hormone replacement therapy.

was cholecystectomy for gallstones. Observation time was measured from the date of participation in HUNT2 to the date of admission for cholecystectomy, death, moving out of Nord-Trøndelag County or end of the study (31 December 2011), whichever occurred first. Women and men were analysed separately. Proportions were compared using the unconditional z-pooled test, which is the unconditional version of Pearson's χ^2 test. The exact Cochran–Armitage test was used to test for trends in proportions. A Cox proportional hazards model was used for multivariable analysis of risk factors for cholecystectomy for gallstone disease. Estimates of hazard ratios (HRs) were accompanied by 95 per cent confidence intervals (c.i.). All tests were two-tailed, and statistical significance was set at $P < 0.050$.

Results

In HUNT2, 65 237 individuals attended (69·5 per cent response rate). Of these, 63 249 were included in the present study and 1988 were excluded after not answering the questionnaires (*Fig. 2*). In total, 1841 individuals were
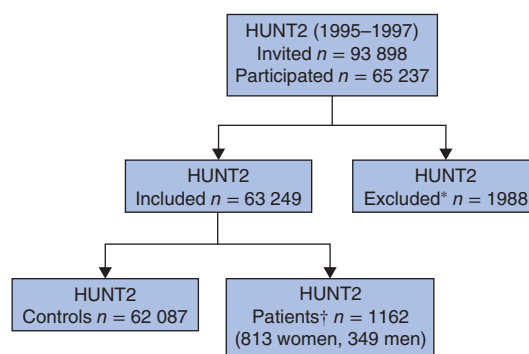

Fig. 2 Flow diagram showing inclusion of patients in the second Norwegian Nord-Trøndelag health study (HUNT2).
*Did not complete health questionnaire or height/weight were not recorded. †Some 1841 individuals were operated on in the time interval; 1162 (63·1 per cent) participated in HUNT2

operated on, of whom 1162 (63·1 per cent) participated in HUNT2. The included participants contributed 957 403 person-years of follow-up from 1996 to 2011, and were

followed for a median of 15·3 (range 0·6–16·4) years. Some 511 patients who had a cholecystectomy during the period from 1990 until their participation in HUNT2 were excluded from the study.

Baseline characteristics

The mean age of the cohort at the start of the study was 50 (range 20–99) years, and 33 267 (52·6 per cent) were women. Cholecystectomy was performed in 813 (2·4 per cent) of these women and in 349 (1·2 per cent) of 29 982 men during follow-up. The mean age at operation was 57 (range 26–90) years in women and 62 (28–90) years in men. The sex-specific distribution of baseline characteristics according to cholecystectomy is shown in *Table 1*.

Risk of having a cholecystectomy

The rate of cholecystectomy was highest among middle-aged individuals (40–60 years) in both sexes.

There was an increased rate of cholecystectomy with increasing BMI and increasing waist circumference in both women and men. In women, the rate of cholecystectomy was lower among those with a higher educational level, but no such relationship was found in men. In both sexes, the rate of cholecystectomy was lower among those who had reported hard physical activity of 1 h or more per week. The rate of cholecystectomy was higher with increasing parity and with use of HRT, whereas use of oral contraceptives showed no association with the rate of cholecystectomy.

Among 679 individuals who had undergone surgery but did not participate in HUNT2 (excluded from the present study), 501 (73·8 per cent) were women and the mean age at operation was 38 (range 20–99) years, compared with 52·6 per cent women and mean age at operation of 60 (26–90) years among those included in the present study. Median time to surgery was 7·9 (range 0·1–16·0) years for women and 8·2 (0·1–16·2) years for men.

Table 3 Multivariable Cox proportional hazards analysis of risk factors for cholecystectomy

	Women			Men		
	n	Hazard ratio	*P*	*n*	Hazard ratio	*P*
Age (years)						
< 30	3296	1·00 (reference)		3578	1·00 (reference)	
30–39	4059	0·77 (0·55, 1·07)	0·128	4657	1·36 (0·77, 2·39)	0·289
40–49	4154	0·69 (0·48, 0·98)	0·036	5250	1·85 (1·08, 3·16)	0·025
50–59	2686	0·56 (0·37, 0·86)	0·007	3858	2·30 (1·33, 3·98)	0·003
60–69	1355	0·52 (0·32, 0·84)	0·008	2497	2·69 (1·51, 4·79)	< 0·001
70–79	993	0·18 (0·09, 0·37)	< 0·001	1686	2·92 (1·58, 5·41)	< 0·001
≥ 80	343	0·11 (0·03, 0·46)	0·002	449	0·72 (0·16, 3·18)	0·667
Body mass index						
Normal	8346	1·00 (reference)		7910	1·00 (reference)	
Overweight	5946	1·58 (1·19, 2·10)	0·002	11 047	1·58 (1·10, 2·30)	0·014
Obese	2594	1·96 (1·33, 2·87)	< 0·001	3018	2·02 (1·22, 3·37)	0·007
Waist circumference						
Normal	9261	1·00 (reference)		13 840	1·00 (reference)	
Increased	3937	1·38 (1·03, 1·85)	0·029	5395	1·55 (1·12, 2·15)	0·009
Substantially increased	3688	1·72 (1·22, 2·43)	0·002	2740	1·51 (0·96, 2·39)	0·076
Educational level						
Primary school	4841	1·00 (reference)		5973	1·00 (reference)	
High school	5288	0·93 (0·73, 1·20)	0·584	8977	1·15 (0·84, 1·58)	0·373
Junior college	2293	0·72 (0·50, 1·04)	0·083	1966	1·07 (0·60, 1·91)	0·826
University	4464	0·64 (0·48, 0·87)	0·004	5059	1·21 (0·84, 1·75)	0·293
Hard physical activity (h/week)						
< 1	11 665	1·00 (reference)		13 147	1·00 (reference)	
≥ 1	5221	0·74 (0·59, 0·94)	0·012	8828	0·81 (0·62, 1·06)	0·124
No. of children						
0	2749	1·00 (reference)				
1–2	7762	1·47 (1·04, 2·07)	0·028			
≥ 3	6375	1·21 (0·83, 1·75)	0·329			
HRT use						
Never	14 443	1·00 (reference)				
Former	814	1·97 (1·37, 2·85)	< 0·001			
Current	1629	2·30 (1·73, 3·07)	< 0·001			

Values in parentheses are 95 per cent confidence intervals. HRT, hormone replacement therapy.

Associations between risk factors and cholecystectomy

The results for each sex are shown in *Table 2* (univariable analysis) and *Table 3* (multivariable analysis). In women, the risk of cholecystectomy decreased with higher age. In men, however, the risk increased with increasing age up to 70–79 years. In both sexes, the risk of cholecystectomy was higher with both increasing BMI and increasing waist circumference in a dose–response relationship. Among women, university-level education reduced the risk of cholecystectomy. This association was not present in men. In the univariable analysis, hard physical activity of 1 h or more per week was associated with a reduced risk of cholecystectomy in both sexes. This association was retained in women in the multivariable analysis, but not in men. In the univariable analysis, parity was associated with increased risk of cholecystectomy in a dose–response relationship, and the association was attenuated in the multivariable analysis. In women who had ever used HRT, the risk of cholecystectomy increased compared with that in never users. The use of contraceptive medication was not associated with the risk of cholecystectomy (results not shown).

Sensitivity analysis

Some variables had a substantial number of participants with missing values (*Table 1*), so the regressions were run using a missing value category for all variables with missing data. As the estimates did not change substantially and conclusions remained the same, the authors chose not to include the missing value category in the final analyses (results not shown).

Discussion

In this population-based cohort study with a median observation time of 15 years, overweight and obese individuals had a 1·5–2-fold increased risk of requiring cholecystectomy for gallstone disease compared with the risk in persons of normal weight. Increased waist circumference was independently associated with risk of cholecystectomy. In women, HRT increased the risk, whereas hard physical activity of 1 h per week or more and higher educational level were associated with a reduced risk of cholecystectomy. With increasing parity, there was a trend towards an increased risk. Contraceptive medication showed no association with the risk of cholecystectomy. Increasing age decreased the risk of cholecystectomy for gallstones in women, but increased the risk in men.

These results are in agreement with a limited number of other population-based cohort studies of lifestyle factors related to risk of symptomatic gallstone disease or cholecystectomy[16,22−24]. Among these studies, only Tsai and colleagues[16] used cholecystectomy as endpoint, but their study was limited to women. They found that abdominal circumference and waist to hip ratio were associated with an increased risk of cholecystectomy, independent of BMI. Symptomatic gallstone disease was used as an endpoint by Hou and co-workers[22], but their study was also limited to women. These authors found that, regardless of adiposity level, being physically active reduced the risk of gallstone disease. Stender *et al.*[23] observed an association between raised BMI and increased risk of symptomatic gallstone disease, which was most pronounced in women. Banim and colleagues[24] concluded that an association between physical activity and risk of gallstone disease may be causal, as there are consistent experimental and epidemiological data regarding a protective effect of physical activity in both sexes. In the present study, an association was found between both raised BMI and waist circumference and increased risk of cholecystectomy for gallstone disease, and a negative (protective) association with physical activity, at least for women who performed hard physical activity for at least 1 h per week. However, the conclusions are based on self-assessment of physical activity and must therefore be interpreted with this in mind. Previous studies[10,12,25] have reported that HRT is a risk factor for gallstones and cholecystectomy, as in the present study. A possible increased risk of cholecystectomy in women with many children and in those taking oral contraceptives has been discussed in previous reports[11,15,26,27], but this was not confirmed in the present study.

Laparoscopic cholecystectomy was introduced in Nord-Trøndelag in 1992 and since 1998 (the baseline of the study) laparoscopic cholecystectomy has been the standard procedure. Open cholecystectomies were performed only in patients with advanced disease, and represented only around 10 per cent of procedures. The incidence of cholecystectomy in Nord-Trøndelag increased from 6·2 per 100 000 person-years in 1990–1992 to 10·0 per 100 000 in 1998–2003, and has been stable since[2]. This increase coincided with an increase in obesity documented during this time in the same county by the three HUNT studies[28]. Similarly, cholecystectomy rates increased during the 1990s in North America, parallel with the increase in obesity, and the rate stabilized in the late 1990s following introduction of the laparoscopic technique[3−5].

The population-based design with a large sample size, long observation time and completeness of cholecystectomy detection are strengths of the present study. That the HUNT2 study used objective standardized measurements of height, weight and waist circumference, performed

by qualified personnel, is also a clear advantage. The population structure of Nord-Trøndelag County is relatively stable, which makes accurate long-term follow-up possible.

A weakness of the study is the lack of records for patients operated on for gallstone disease before 1990. These patients, who could potentially have had a cholecystectomy, were treated as controls in the present study, together with all patients who truly had no operation before 1990. However, owing to the large number of controls, the effect of including individuals who underwent cholecystectomy before 1990 would be small, and would attenuate the risk estimates. Those who had undergone surgery but did not participate in HUNT2 had a mean age 22 years younger than those included in HUNT2. This difference in age may add to the uncertainty of the results of the present study, but age was adjusted for in the multivariable analysis. Whether the controls underwent surgery elsewhere is uncertain. However, in Nord-Trøndelag almost all healthcare is provided by universal health coverage in the county of residence, and surgery in private hospitals or outside the public hospital system is not common. The authors do not know whether the participants used as controls in this study had gallstones. However, gallstones *per se* are not an indication for cholecystectomy, which was the outcome of this study. Only about 10 per cent of individuals with gallstones develop symptoms that require surgery[14]. Before the era of laparoscopic surgery, the indication for cholecystectomy was one or more episodes of cholecystitis and gallstone-related pain. However, following the introduction of laparoscopic surgery in later years, many have been offered surgery only after episodes of gallstone colic[7]. In HUNT2, 32 per cent of the population did not participate[19]. A non-participant study performed after HUNT3 showed that the population not captured were the youngest (aged 20–39 years) and the oldest (aged 80 years or more) residents. More men than women did not participate, and non-participants had lower socioeconomic status and higher mortality and prevalence of several chronic diseases[19]. This must be kept in mind when generalizing the results.

Acknowledgements

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Snapshot quiz

Snapshot quiz 16/11

Answer: A 55-year-old woman presented with a 1-day history of generalized abdominal pain, distension and vomiting. The X-ray showed a classical coffee bean sign, representative of acute large bowel obstruction secondary to sigmoid volvulus (**a**). Flexible sigmoidoscopy revealed a large area of necrotic mucosa and a patch of viable mucosa (**b**). Following decompression and derotation, the patient was managed conservatively and recovered fully.