

## An Assessment of Knowledge towards Acute Cholecystitis among General Population of Albaha City

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### ABSTRACT

**Background:** Acute cholecystitis is an acute inflammation of the gallbladder, and it is the most common cause of acute pain in the right upper quadrant. It is a critical clinical problem representing up to 5% of emergency room visits. **Objective:** The aim of the present study was to assess the knowledge of the general population of Albaha City, Saudi Arabia towards acute cholecystitis (AC). **Methods:** A representative sample of 634 subjects from both sexes, aged from 18-80 years who completed a standardized questionnaire was involved in the study. **Results:** Only 48 subjects had history of the disease with a prevalence rate of 7.57%. More than half of the participants (58.7%) recorded family history of AC in one of their direct relatives. Great percent of the study participants considered obesity, high cholesterol and high triglycerides responsible for increased incidence of AC (59.9%, 54.3% and 66.9%). A high percentage of the participants (55.2%, 48.3%, 38.2%, 62.8%, 36.9% and 54.3%) did not know whether their food or habits could predispose to AC. Higher percentages considered intolerance to fatty meals, nausea and vomiting as symptoms of AC (55.5%, 48.9% and 46.7% respectively). Most of the participants (75.7%) did not receive any information about AC prevention. Their established information was highly or to some extent effective in changing the participants' life style (39.0% and 42.9% respectively). **Conclusion:** This survey has been useful in determining the current regional knowledge towards AC among general population in Albaha city. Such study emphasizes the need for more efforts that focus on novel preventive strategies to overcome the onset of gallstones. Further much bigger collaborative national studies are recommended.

**Keywords:** acute cholecystitis; gall stone; risk factor; survey; Saudi Arabia.

### INTRODUCTION

Acute cholecystitis (AC) is an inflammatory disease of the gall bladder, and it is the most common cause of acute pain in the right upper quadrant (RUQ). It has been reported that cholecystitis represents one of the most common emergency admissions in surgical practice. More than 90% of AC cases are associated with gallstones. Gallstones are the primary triggering factors of cholecystitis, and they are present in more than 10% of the population and their presence increases with age. It is the most common indication for abdominal surgery in the elderly, with a prevalence of 21.4% in the age group of 60-69 years and 27.5% in individuals over 70 years<sup>(1-3)</sup>. Diabetes mellitus, pregnancy, cirrhosis, and hemolytic disease are considered key factors for the formation of gallstones. Risk factors for gallstones include family history and genetic predisposition. Obesity, rapid weight loss, and a high calorie diet are considered to be modifiable risk factors. In addition, certain drugs, such as estrogen replacement therapy and thiazide diuretics, can promote gallstone formation<sup>(3)</sup>. Children who are at a higher risk for developing cholecystitis include seriously ill children, those with sickle cell disease, those on prolonged total parenteral nutrition, those with hemolytic conditions, and those with congenital and biliary anomalies<sup>(4)</sup>. The most common presenting symptom of AC is upper

abdominal pain. However, pediatric population may present without many of the classic findings. Signs of peritoneal irritation may be present, and in some patients, the pain may radiate to the right shoulder or scapula. Frequently, the pain begins in the epigastric region and then localizes to the RUQ. Although the pain may initially be described as colicky, it becomes constant virtually. Nausea and vomiting are generally present, and patients may report fever<sup>(5)</sup>. High prevalence of AC has been reported in Saudi Arabia. **Reda et al.**<sup>(5)</sup> reported that summer season is a major aggravating factor for acute cholecystitis. The frequency and severity is significantly higher during summer as compared to other seasons of the year. People should be aware regarding practices used for prevention of gallbladder stones formation and inflammation. Diet plays a key role in gallstones formation. Sugar, high fat diet, and alcohol intake increase the incidence of gallstone formation. In contrast, monosaturated fat found in nuts and olive oil, fibre, and vegetables decrease the risk. Similarly, weight loss and exercise prevent the formation of gallstones and protect against inflammation<sup>(6)</sup>. Good understanding of the causes, symptoms, and risk factors associated with AC would play an important role in preventing or decreasing its complications. Hence, this study was done to assess the knowledge about AC, and to evaluate the awareness and attitudes towards the

causes and risk factors of AC among general population of Albaha city in Saudi Arabia.

## METHODS

### Ethical considerations

This study design was approved by the institutional review board of the Faculty of Medicine, Albaha University. An informed consent was obtained from each participant.

### Study design

This study had a random cross-sectional design, and it was carried out from the beginning of May, 2017 to the end of July, 2017, among the general population of Albaha city, Saudi Arabia.

A sample size of 634 participants (both males and females), aged between 18 to 60 years were randomly recruited from the population in Albaha city (population size 100,000 person, confidence level of 95%, confidence interval of 4).

People who approved to participate in the study were included, but those not achieving inclusion criteria and those with incomplete data were excluded from the study. A self-administered questionnaire was used for data collection. The questionnaire had two parts. The first part was about demographic data of the participants. The second one consists of 17 questions assessing the knowledge regarding the causes, symptoms and risk factors of acute cholecystitis. The questionnaire was distributed to the participants by direct contact with them. Data were confirmed then coded and entered to a personal computer. Thanks and appreciations were used to inspire the participants to be involved in the study.

### Statistical design

All statistical analyses were done using SPSS v20. Qualitative data were represented as numbers and percentages in brackets. Quantitative data were tested for normality by Shapiro Wilk test and represented as mean  $\pm$  SD. Pearson's Chi-Square test was used to examine associations between two variables. Significance was adopted at  $p < 0.05$  for interpretation of results of tests.

## RESULTS

The present study was carried out on 634 participants who completed the questionnaire. The characteristics of the study participants are shown in **table 1**. Their age ranged from 18 to 80 years with greater percent (41.4%) belongs to the age group 18-28, and 79.2% of them were males. Most of the study participants were students and employers (25.2% and 20.3% respectively). Married participants constituted 65.1% while single ones were 33.7%. All the participants were educated with higher percentage (66.9%) of them in the level of higher education. Their weight ranged from 41.0 –

123.0 kg with a mean of  $75.24 \pm 15.94$  kg and the mean height was  $168.18 \pm 8.96$  (range, 130.0-190.0 cm). In this study, most of the participants (84.86%) did not develop acute cholecystitis (AC) while only 48 (7.57%) subjects gave past history of the disease. **Table 2** demonstrates the participant's information about dietary ingredients and habits that may predispose to acute cholecystitis. Among all the participants, considerable percentages considered smoking, coffee and beef as predisposing factors (52.4%, 46.7% and 33.8% respectively). Alternatively, fewer numbers of participants deliberated fish, nuts and chocolate (2.8%, 6.9% and 20.5%). Those who developed AC gave the same opinion and ranked smoking, coffee and beef greater than other ingredients (66.7%, 54.2%, 33.3% versus 0.0%, 12.5% and 33.3%). It was also observed that the higher percentages of the participants (55.2%, 48.3%, 38.2%, 62.8%, 36.9% and 54.3%) did not know whether their food or habits could predispose to AC. The awareness of the study participants about risk factors of acute cholecystitis was illustrated in **table 3**. More than half of the participants (58.7%) recorded family history of AC in one of their direct relatives. Moreover, higher percent (66.7%) was given by subjects with previous AC. Age as a risk factor was only reported by 36.9% and similar percent did not know its risk. Great percent of the study participants considered obesity, high cholesterol and high triglycerides responsible for increased incidence of AC (59.9%, 54.3% and 66.9%). Regarding diabetes mellitus, nearly half of the participants (48.6%) did not know the association between it and AC while, 30.0% categorized it as a risk factor. The useful HDL was not known by 50.8% of the participants and a lower percent (23.0%) considered it as a risk factor. This table shows also non-significant differences between individuals with or without history of AC regarding their knowledge about these risk factors ( $p > .05$ ). **Table 4** demonstrates the participant's information about symptoms of AC. Among all participants, higher percentages considered intolerance to fatty meals, nausea and vomiting as symptoms of AC (55.5%, 48.9% and 46.7% respectively). Whereas, symptoms like heart burn, epigastric pain, heaviness and bloating were considered by 39.7%, 36.3%, 32.2% and 30.0% respectively. In addition, nearly half of the participants (48.9%) didn't know whether localized pain in the right hypochondrium might be a symptom of AC and only low percent (20.5%) selected it. Concerning all these symptoms, higher frequencies were reported by those with previous attack of AC compared to healthy ones but with no significant differences ( $p > .05$ ) except for

intolerance to fatty meals where significantly higher percentage was recorded by subjects with history of AC (70.8% versus 56.1%). As regards awareness about AC prevention, **table 5** shows that 42.6% of the study participants agreed that AC prevention is not expensive but, a greater percent (47.3%) did not know its costs. Higher percent (60.9%) did not know whether restricting calcium intake is good for AC prevention. In contrast, much higher percent (73.5%) agreed that dieting could prevent that disease and relative ratios (79.2% and 72.9%) were considered by those with or without history of AC. Most of the participants (75.7%) did not receive any information about AC prevention. Great percent of

individuals received awareness from physicians followed by the internet (46.1% and 35.5% respectively). The established information was highly or to some extent effective in changing the participants' life style (39.0% and 42.9% respectively). Considerations of the study participants about different lines of treatment of AC were illustrated in **table 6**. A significantly high percent (41.3%) reported endoscopic removal of gall bladder while, open surgery was only considered by 8.5%. The role of drugs in the treatment of AC was verified by 16.4%. Significantly high percent (51.7%) preferred to consult a cholecystitis physician if developed AC.

**Table 1: Socio-demographic characteristics of the study participants**

		N	%
Gender	Female	132	20.8
	Male	502	79.2
	Total	634	100.0
Age (years)	18-28	260	41.4
	29-39	184	29.3
	40-50	116	18.5
	51-61	56	8.9
	62-72	8	1.3
	>72	4	0.6
	Total	628	100.0
Marital status	Married	406	65.1
	Single	210	33.7
	Divorced	8	1.3
	Total	624	100.0
Educational level	Higher education	420	66.9
	Secondary education	154	24.5
	Post graduate	32	5.1
	Primary education	14	2.2
	Writing & reading	8	1.2
	Total	628	100.0
Occupation	Student	62	25.2
	Employer	50	20.3
	No	34	13.8
	Engineer	28	11.4
	Solider	22	8.9
	Teacher	16	6.5
	Retired	10	4.1
	House wife	10	4.1
	Shopkeeper	6	2.4
	accountant	2	0.8
	Doctor	2	0.8
	Police officer	2	0.8
	Professor	2	0.8
	Total	246	100.0
Wight (kg)	Range (mean ±SD)	41-123 (75.24±15.94)	
Height (cm)	Range (mean ±SD)	130-190(168.18±8.96)	

**Table 2: Information about dietary ingredients and drinks that may predispose to acute cholecystitis.**

		History of acute cholecystitis								Pearson Chi-Square	
		Yes N=48		No N=538		Don't know N=48		Total N=634		X <sup>2</sup>	P
		N	%	N	%	N	%	N	%		
Fish	Yes	0	0.0	16	3.0	2	4.2	18	2.8	8.85	.050
	No	12	25.0	232	43.1	22	45.8	266	42.0		
	Don't know	36	75.0	290	53.9	24	50.0	350	55.2		
Beef	Yes	16	33.3	186	34.6	12	25.0	214	33.8	3.051	.549
	No	6	12.5	98	18.2	10	20.8	114	18.0		
	Don't know	26	54.2	254	47.2	26	54.2	306	48.3		
Coffee	Yes	26	54.2	246	45.7	24	50.0	296	46.7	7.77	.100
	No	4	8.3	80	14.9	12	25.0	96	15.1		
	Don't know	18	37.5	212	39.4	12	25.0	242	38.2		
Nuts	Yes	6	12.5	32	5.9	6	12.5	44	6.9	6.099	.181
	No	12	25.0	168	31.2	12	25.0	192	30.3		
	Don't know	30	62.5	338	62.8	30	62.5	398	62.8		
Smoking	Yes	32	66.7	272	50.6	28	58.3	332	52.4	30.61	<.001*
	No	4	8.3	50	9.3	14	29.2	68	10.7		
	Don't know	12	25.0	216	40.1	6	12.5	234	36.9		
Chocolate	Yes	16	33.3	106	19.7	8	16.7	130	20.5	6.92	.140
	No	10	20.8	134	24.9	16	33.3	160	25.2		
	Don't know	22	45.8	298	55.4	24	50.0	344	54.3		

\*Significant

**Table 3: Awareness about risk factors of acute cholecystitis.**

		History of acute cholecystitis								Pearson Chi-Square	
		Yes N=48		No N=538		Don't know N=48		Total N=634		X <sup>2</sup>	P
		N	%	N	%	N	%	N	%		
History of AC in direct Relatives	Yes	32	66.7	314	58.4	26	54.2	372	58.7	4.91	.296
	No	8	16.7	152	28.3	12	25.0	172	27.1		
	Don't know	8	16.7	72	13.4	10	20.8	90	14.2		
Age	Yes	16	33.3	198	36.8	20	41.7	234	36.9	.84	.93
	No	14	29.2	140	26.0	12	25.0	166	26.2		
	Don't know	18	37.5	200	37.2	16	33.3	234	36.9		
Obesity	Yes	30	62.5	316	58.7	34	70.8	380	59.9	9.003	.054
	No	8	16.7	40	7.4	2	4.2	50	7.9		
	Don't know	10	20.8	182	33.8	12	25.0	204	32.2		
High cholesterol	Yes	26	54.2	294	54.6	24	50.0	344	54.3	2.33	.677
	No	4	8.3	54	10.0	8	16.7	66	10.4		
	Don't know	18	37.5	190	35.3	16	33.3	224	35.3		
High triglycerides	Yes	32	66.7	362	67.3	30	62.5	424	66.9	1.14	.901
	No	2	4.2	32	5.9	2	4.2	36	5.7		
	Don't know	14	29.2	144	26.8	16	33.3	174	27.4		
Diabetes mellitus	Yes	16	33.3	156	29.0	18	37.5	190	30.0	6.63	.157
	No	8	16.7	124	23.0	4	8.3	136	21.5		
	Don't know	24	50.0	258	48.0	26	54.2	308	48.6		
HDL	Yes	14	29.2	124	23.0	8	16.7	146	23.0	2.16	.705
	No	12	25.0	140	26.0	14	29.2	166	26.2		
	Don't know	22	45.8	274	50.9	26	54.2	322	50.8		

**Table 4: Knowledge about symptoms of acute cholecystitis**

		History of acute cholecystitis								Pearson Chi-Square	
		Yes N=48		No N=538		Don't know N=48		Total N=634		X <sup>2</sup>	P
		N	%	N	%	N	%	N	%		
Heart burn	Yes	26	54.2	210	39.0	16	33.3	252	39.7	5.39	.249
	No	8	16.7	140	26.0	14	29.2	162	25.6		
	Don't know	14	29.2	188	34.9	18	37.5	220	34.7		
Nausea	Yes	26	54.2	264	49.1	20	41.7	310	48.9	2.29	.683
	No	8	16.7	82	15.2	10	20.8	100	15.8		
	Don't know	14	29.2	192	35.7	18	37.5	224	35.3		
Vomiting	Yes	28	58.3	250	46.5	18	37.5	296	46.7	5.17	.270
	No	8	16.7	92	17.1	8	16.7	108	17.0		
	Don't know	12	25.0	196	36.4	22	45.8	230	36.3		
Bloating	Yes	16	33.3	164	30.5	10	20.8	190	30.0	5.41	.248
	No	10	20.8	146	27.1	10	20.8	166	26.2		
	Don't know	22	45.8	228	42.4	28	58.3	278	43.8		
Heaviness	Yes	20	41.7	168	31.2	16	33.3	204	32.2	4.46	.347
	No	8	16.7	80	14.9	4	8.3	92	14.5		
	Don't know	20	41.7	290	53.9	28	58.3	338	53.3		
Epigastric Pain	Yes	22	45.8	194	36.1	14	29.2	230	36.3	5.28	.260
	No	4	8.3	100	18.6	8	16.7	112	17.7		
	Don't know	22	45.8	244	45.4	26	54.2	292	46.1		
Right Hypochondrium pain	Yes	16	33.3	104	19.3	10	20.8	130	20.5	5.92	.205
	No	14	29.2	164	30.5	16	33.3	194	30.6		
	Don't know	18	37.5	270	50.2	22	45.8	310	48.9		
Intolerance to fatty meal	Yes	34	70.8	302	56.1	16	33.3	352	55.5	16.88	.002*
	No	6	12.5	56	10.4	10	20.8	72	11.4		
	Don't know	8	16.7	180	33.5	22	45.8	210	33.1		

\*Significant

**Table 5: Information about prevention of acute cholecystitis**

		History of acute cholecystitis								Pearson Chi-Square	
		Yes N=48		No N=538		Don't know N=48		Total N=634		X <sup>2</sup>	P
		N	%	N	%	N	%	N	%		
Is AC prevention expensive?	Yes	4	8.3	56	10.4	4	8.3	64	10.1	8.51	.071
	No	26	54.2	216	40.1	28	58.3	270	42.6		
	Don't know	18	37.5	266	49.4	16	33.3	300	47.3		
Restricting calcium intake good for AC prevention?	Yes	2	4.2	94	17.5	10	20.8	106	16.7	10.35	.035*
	No	16	33.3	112	20.8	14	29.2	142	22.4		
	Don't know	30	62.5	332	61.7	24	50.0	386	60.9		
Could dieting prevent AC?	Yes	38	79.2	392	72.9	36	75.0	466	73.5	4.22	.370
	No	2	4.2	34	6.3	0	0.0	36	5.7		
	Don't know	8	16.7	112	20.8	12	25.0	132	20.8		
Did you receive any information about AC prevention?	Yes	16	33.3	128	23.8	10	20.8	154	24.3	2.52	.284
	No	32	66.7	410	76.2	38	79.2	480	75.7		
Source of information	Physicians	8	50.0	60	47.6	2	20.0	70	46.1	9.84	.083
	Internet	4	25.0	46	36.5	4	40.0	54	35.5		
	Brochures	2	12.5	10	7.9	4	40.0	16	10.5		
	TV	2	12.5	10	7.9	0	0.0	12	7.9		
Did this information help you?	Yes	6	37.5	52	40.6	2	20.0	60	39.0	2.35	.697
	No	2	12.5	24	18.8	2	20.0	28	18.2		
	To some extent	8	50.0	52	40.6	6	60.0	66	42.9		

\*Significant

**Table 6: Opinions about different lines of treatment for acute cholecystitis**

		History of acute cholecystitis				Pearson Chi-Square		
		Yes N=48	No N=538	Don't know N=48	Total N=634	X <sup>2</sup>	P	
Treatment	Drugs	N	4	92	8	104	42.87	<.001*
		%	8.3	17.1	16.7	16.4		
	Herbs	N	0	22	6	28		
		%	0.0	4.1	12.5	4.4		
	Frequent check-up	N	6	30	2	38		
		%	12.5	5.6	4.2	6.0		
	Extracorporeal Shock Wave Lithotripsy	N	0	4	2	6		
		%	0.0	0.7	4.2	0.9		
	Open surgery	N	10	44	0	54		
		%	20.8	8.2	0.0	8.5		
Operation with endoscopes	N	18	232	12	262			
	%	37.5	43.1	25.0	41.3			
Don't know	N	10	114	18	142			
	%	20.8	21.2	37.5	22.4			
Which doctor did you consult?	General surgeon	N	8	76	6	90	12.59	.043*
		%	16.7	14.1	12.5	14.2		
	Cholecystitis physician	N	22	288	18	328		
		%	45.8	53.5	37.5	51.7		
	General practitioner	N	16	128	22	166		
		%	33.3	23.8	45.8	26.2		
	Don't know	N	2	46	2	50		
		%	4.2	8.6	4.2	7.9		

\*Significant

## DISCUSSION

The present study assessed the knowledge of the general population of Albaha City, KSA towards acute cholecystitis. A representative sample of 634 subjects from both sexes, aged from 18-80 years completed a standardized questionnaire, and they were involved in the study.

To the best of our recent knowledge, this is the first study to through light on extent of information about AC disease and its risk factors in Albaha City. Our main goal was to find out preventive strategies in order to minimize incidence of AC.

The prevalence of AC among the studied population sample was 7.57% where only 48 subjects gave history of the disease. Worldwide, significant variations in prevalence of gall stone disease were observed based on both genetic and environmental factors. In Western countries, it is very common and ranged between 9 and 30%. In contrast, it is low in rural Africa, India, China and Japan<sup>(7,8)</sup>. In Saudi Arabia, gallstones prevalence at country level is not well defined. Only scattered reports on gallstone disease from different parts of Saudi Arabia were retrieved. **Abu-Eshy et al.**<sup>(9)</sup> reported overall prevalence of 11.7% in Abha region. The change in lifestyle among Saudis in recent years may suggest that the condition is of increasing health importance.

This questionnaire-based survey revealed that high percentages of the participants did not know whether their dietary elements or habits could predispose to AC. Considerable number of the study participants deliberated smoking, coffee and beef as predisposing factors. Studies on the relationship between coffee intake and gall stone disease revealed conflicting information; some have observed a statistically significant positive association between coffee and gallstone risk<sup>(10,11)</sup>. In contrast, other studies have found a protective effect of coffee consumption against gallstones formation<sup>(12,13)</sup>. However, **Walcher et al.**<sup>(14)</sup> could not confirm this association. **Mendez-Sanchez et al.**<sup>(15)</sup> reported a strong positive relationship between hypercaloric diets including meat intake and cholesterol gall stones. Studies on nutritional approaches for prevention of gall stone disease revealed that Poly- and mono-unsaturated fats, specifically nut consumption, might be useful<sup>(6,16)</sup>.

In this study, the awareness of the study participants about risk factors of AC was variable. High percent of them considered obesity, high cholesterol and high triglycerides responsible for increased incidence of AC. In contrast, age, diabetes mellitus were not well known by the participants as risk factors. The useful HDL cholesterol was not known by half of the participants and a low percent considered it as a risk factor. Acute cholecystitis is

an inflammatory disease of the gall bladder. In more than ninety percent of cases is due to gall stones, which is known as acute calculous cholecystitis<sup>(17)</sup>. Many epidemiological studies have indicated that obesity, due to over nutrition and/or physical inactivity and diabetes mellitus are profoundly associated with cholesterol stones formation in the gall bladder<sup>(18-20)</sup>. Moreover, For every 5-unit increment in body mass index or the presence of diabetes, the risk of gall bladder disease was estimated to be 1.63 and 1.56<sup>(21,22)</sup>.

Sometimes acute cholecystitis occurs without cystic duct obstruction due to gallstones. This type is known as acute acalculous cholecystitis, and it accounts for 2–15 % of AC cases<sup>(23)</sup>. Traditionally, it is known to occur in critically ill patients and to have a poor prognosis<sup>(24)</sup>. The risk of AAC increases in patients with advanced age and cerebrovascular accidents<sup>(23)</sup>.

In this study, nearly two thirds of the participants who developed AC gave family history of its occurrence in one or more of their direct relatives. This finding is in accordance with that of **Hirschfield et al.**<sup>(25)</sup> who stated that gall stone disease has a familial nature, and they attributed this to the interaction between genetic and environmental factors. Genetic predisposition to gallstone formation is clearly evident and associations between multiple lithogenic gene variants and gallstone formation have been observed<sup>(7)</sup>.

In the study herein, the participants were concerned with different lines of treatment of AC. A significantly high percent favoured endoscopic removal of gall bladder while open surgery was the last choice. In addition, nearly half of them were oriented with the specialty of the treating physician and preferred to consult a cholecystitis physician if developed AC. Current treatment algorithms of AC are predominantly invasive and are based on surgery<sup>(17)</sup>. Laparoscopic cholecystectomy is the standard treatment for acute cholecystitis. It has been linked to a lower complication rate and shorter postoperative hospital stay compared with open cholecystectomy<sup>(26)</sup>.

In the current study, most of the participants did not get effective public health education about protective methods, healthy foods and life styles that help in AC prevention. Though high percent of them realized the role of dieting in disease prevention, and a number of them agreed that prevention is not expensive. The knowledge of gall stone disease is crucial to organize preventive strategies. These may decrease its incidence, complications and save its economic costs. In

normal risk individuals, lifestyle modifications with weight reduction, increased physical activity and dietary alterations are appropriate, whereas high-risk individuals might benefit from early prevention and diagnosis as well as targeted therapy with ursodeoxycholic acid, statins, ezetimibe and/or modulators of bile salt signaling pathways<sup>(27)</sup>. Rapid weight loss (>1.5 kg per week by a very-low-calorie diet or after bariatric surgery) are also associated with cholesterol-rich gallstones<sup>(28)</sup>.

## CONCLUSION

This survey has been useful in determining the current regional knowledge towards AC among general population in Albaha city. Such study emphasizes the need of more efforts that focus on novel preventive strategies to overcome the onset of gallstones not only in at-risk patients but also in the population in general. Further much intensive collaborative national studies are recommended.

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