Increased Risk of Major Depressive Disorder After Cholecystectomy: A Nationwide Population-Based Cohort Study in Korea

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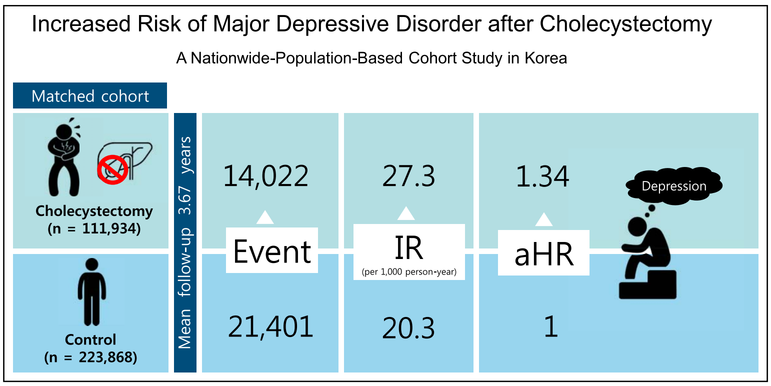
INTRODUCTION: **This study investigated the risk of depression in Korean adults who underwent cholecystectomy and appeared for subsequent long-term follow-ups. A national population-based data set was used for analysis.**

METHODS: **All patients (n = 111,934) aged 40 years and older who underwent cholecystectomy between 2010 and 2015 and a control population (n = 223,868), matched for age and sex, were identified from the database of the Korean National Health Insurance Corporation. The hazard ratio (HR) and 95% confidence interval (CI) of depression were estimated after cholecystectomy, and a Cox regression analysis was performed.**

RESULTS: **The incidence of depression in the cholecystectomy group was 27.3 per 1,000 person-years and that in the control group was 20.3 per 1,000 person-years. Patients who underwent cholecystectomy showed an increased risk of major depressive disorder (MDD) with an adjusted HR (aHR) of 1.34 (95% CI: 1.31–1.37, *P* < 0.001). The mean follow-up period after a 1-year lag was 3.67 ± 1.79 years. In the subgroup analysis, the risk of developing MDD after cholecystectomy was relatively high in patients aged 40–49 years (aHR 1.51, 95% CI: 1.44–1.58) and in participants without diabetes mellitus (aHR: 1.36, 95% CI: 1.33–1.39), hypertension (aHR: 1.38, 95% CI: 1.34–1.42), or dyslipidemia (aHR: 1.35, 95% CI: 1.32–1.38).**

DISCUSSION: **Compared with the control population, patients who underwent cholecystectomy exhibited an increased incidence of MDD. Thus, physicians should implement an enhanced program of MDD screening for at least several years after cholecystectomy.**



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INTRODUCTION

The adoption of a laparoscopic approach for cholecystectomy has made this procedure one of the most commonly performed operations worldwide; thus, gallbladder removal is generally considered a relatively safe procedure. However, emerging evidence has indicated that cholecystectomy itself may lead to an excessive risk of metabolic disorders and associated complications, including dyslipidemia, nonalcoholic fatty liver disease, and hyperglycemia (1–3). Furthermore, the long-term medical consequences of cholecystectomy have not yet been fully established.

Major depressive disorder (MDD) is characterized by depressed mood, diminished interest, and disturbed sleep or appetite (4). One in 5 adults is expected to have at least 1 episode of MDD during their lifetime (5). MDD is the second leading contributor to chronic disease burden. Furthermore, MDD places a considerable burden on both society and the individual, and it can even lead to death by suicide (6). Although the etiology of MDD is multifactorial, the risk of developing MDD is strongly associated with its heritability and environmental factors. No single mechanism established thus far can explain all aspects of the disease.

In the context of cholecystectomy and its relation to MDD, we note that depression is relatively prevalent in patients before and after various surgeries, and it can originate from suppressed immune function, postoperative pain, and decreased social activity (7). In this regard, a recent study has reported an increased risk of depressive disorder among women after cholecystectomy (8). Meanwhile, another cohort study has indicated that patients with symptomatic gallstones are at a higher risk of developing depression, whereas the risk of depression reduces after cholecystectomy (9). These conflicting findings can be attributed to these studies' relatively small population sizes and short follow-up periods. Consequently, in this study, we investigated the risk of depression in Korean adults who underwent cholecystectomy and appeared for subsequent long-term follow-ups. For our analysis, we used a national population-based data set obtained from the Korean National Health Insurance Service.

METHODS

Database

This retrospective cohort study relied on data from the Korean National Health Insurance Corporation (NHIC) database. Approximately 97% of the Korean population is registered with the Korean NHIC, a single public health insurance program managed by the Korean government. The NHIC database contains beneficial information for each patient, such as age, sex, place of residence, income, and medical claims information, including disease codes and procedure codes. In Korea, the monthly insurance premium is determined by income level rather than health risk; therefore, it can be used as a proxy for economic status. Individuals in the lowest income bracket are covered by the Medicaid program funded by general taxes. Korean researchers can use the NHIC database after approval by the official review

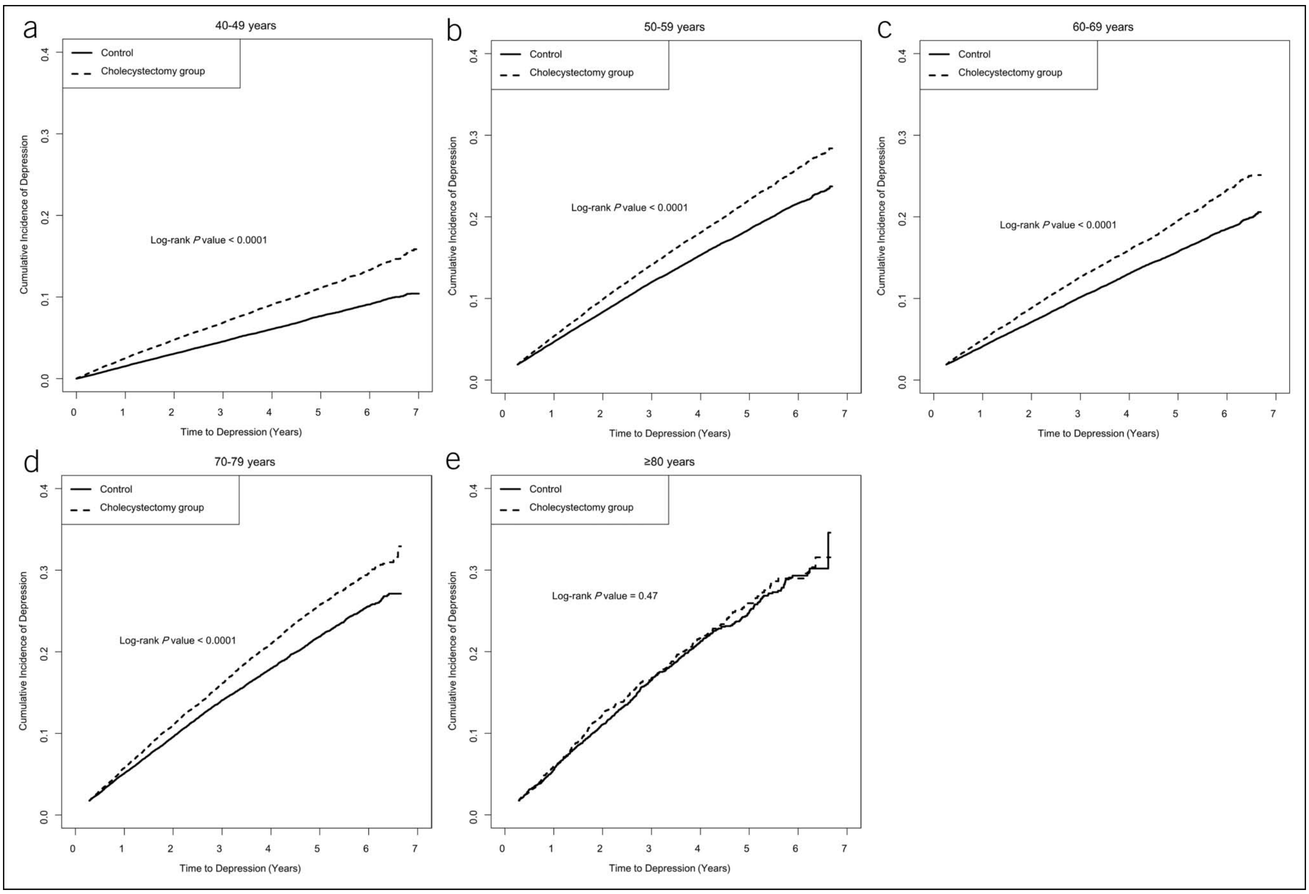

Figure 1. The Kaplan-Meier curves showing the cumulative incidence of depression in cholecystectomy and control groups according to age stratification; (**a**) 40–49, (**b**) 50–59, (**c**) 60–69, (**d**) 70–79, and (**e**) ≥80 years old. Statistical analysis was performed by the log-rank test.

committee; this study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (IRB number: X-2003/601–904). The requirement for informed consent was waived because this study was based on routinely collected medical claim data.

Study population

We designed a nested case-control study. Data of patients who underwent cholecystectomy at ages ≥40 years were selected from January 2010 through December 2015 from the NHIC data set (n = 52,034,424). Cholecystectomy was defined by the insurance claim code (Q7380). The primary endpoint of this study was newly diagnosed depression that was defined as a patient being diagnosed by a psychiatrist with a specific *International Classification of Disease* (*ICD*)*-10* code (F32 [MDD, single episode] or F33 [MDD, recurrent]). To avoid enrolling patients with pre-existing depression, individuals diagnosed with depression before the index date or within 1 year after the index date (1-year lag period) were excluded. In this period, we enrolled a total of 111,934 participants who underwent cholecystectomy at ages ≥40 years through this process.

The cholecystectomy patients were matched 1:2 with participants (control group) who did not undergo cholecystectomy between 2010 and 2015 from the NHIC data set. A total of 223,868 control participants were randomly selected from the population who were evaluated at the same time as each cholecystectomy group participant (index date) and were matched for age and sex after excluding pre-existing depression. To avoid selection bias, the control participants were sorted using random order and then selected from top to bottom.

Covariates

Age groups were classified by 10-year intervals. Five age groups were designated (40–49 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years). A patient's income status was categorized by the associated insurance premium; those with premiums of <20% and Medicaid eligibility were defined as belonging to the low-income group. Places of residence were categorized as either metropolitan, city, or rural areas. Hypertension (I10–I15 and antihypertensive medication), diabetes (E11–E14 and antidiabetes medication), and dyslipidemia (E78 and lipid-lowering medication) were defined by the occurrence of at least 1 claim per year for the relevant prescription. Subsequently, we analyzed the characteristics of participants undergoing cholecystectomy stratified according to age group, with or without comorbidity, and follow-up periods (1, 2, 3, 4, and 5+ years).

Statistical analyses

In this study, we present the basic characteristics of the study population using descriptive statistics. The χ^2 test or Fisher exact test was used to compare ages and comorbidities between the cholecystectomy and control groups as categorical variables. The incidence of depression in the 2 groups was calculated per 1,000 person-years. We next analyzed the hazard ratio (HR) and 95% confidence interval (CI) of depression after cholecystectomy, and a Cox regression analysis was subsequently performed. The HR was calculated as the ratio of depression in the cholecystectomy group relative to that in the control group, and it was adjusted for age, sex, income, place of residence, and the presence of hypertension, diabetes mellitus, or dyslipidemia. We also analyzed the characteristics of participants undergoing cholecystectomy stratified according to age group.

Table 1. Demographics of the study population

	Matched control subjects (n = 223,868)	Cholecystectomy cohort (n = 111,934)	*P* value
Age, yr			1.00
40–49	78,738 (35.17)	39,369 (35.17)	
50–59	73,008 (32.61)	36,504 (32.61)	
60–69	44,932 (20.07)	22,466 (20.07)	
70–79	22,922 (10.24)	11,461 (10.24)	
≥80	4,268 (1.91)	2,134 (1.91)	
Age (mean ± SD)	55.3 ± 10.68	55.3 ± 10.68	1
No. of men	136,878 (61.14)	68,439 (61.14)	1.00
Low-income individuals[a]	51,040 (22.8)	24,044 (21.48)	<0.0001
Place of residence			0.0278
Metropolitan	141,042 (63)	70,015 (62.55)	
City	60,535 (27.04)	30,726 (27.45)	
Rural	22,291 (9.96)	11,193 (10)	
Comorbidity			
Hypertension	21,733 (9.71)	17,490 (15.63)	<0.0001
Diabetes mellitus	56,392 (25.19)	37,469 (33.47)	<0.0001
Dyslipidemia	33,453 (14.94)	22,642 (20.23)	<0.0001

Data are presented as percentages or mean values ± SDs.
[a]Low-income is defined as a premium of <20% and Medicaid eligibility.

Furthermore, we analyzed the HR for depression as per the follow-up periods. All statistical analyses were performed using SAS version 9.4 software, and results with 2-sided P values of $<$0.05 were considered significant.

RESULTS

A total of 111,934 cholecystectomy patients and 223,868 age- and sex-matched comparison participants were included in the final analysis (Figure 1). The mean age of the participants was 55.3 ± 10.68 years, and 61.1% of the study population were men. Compared with the control group, a lower proportion of individuals in the cholecystectomy group reported the lowest income level and resided in rural areas. The cholecystectomy group included a higher proportion of individuals with hypertension, diabetes mellitus, or dyslipidemia than the control group. In the cholecystectomy group, 15.6% had hypertension, 33.5% had diabetes mellitus, and 20.2% had dyslipidemia (Table 1).

In the total study population, the mean follow-up period after a 1-year lag was 3.67 ± 1.79 years (3.59 ± 1.81 years for the cholecystectomy group and 3.71 ± 1.78 years for the control group). The maximum follow-up interval after cholecystectomy was 7 years. The incidence of MDD in the cholecystectomy group was 27.3 per 1,000 person-years and that in the control group was 20.3 per 1,000 person-years. After adjusting for age, sex, income, place of residence, diabetes mellitus, hypertension, and dyslipidemia, the participants who underwent cholecystectomy had a higher relative risk of MDD than those who did not undergo cholecystectomy (adjusted HR [aHR] 1.34, 95% CI: 1.31–1.37, $P < 0.001$) (Table 2).

In subgroup analyses according to age stratification, the incidence rates of MDD were 18.9, 40.6, 35.3, 47.8, and 48.4 per 1,000 person-years who underwent cholecystectomy in the 40–49, 50–59, 60–69, 70–79, and ≥80 years' age subgroups, respectively (Table 2). In the control group, the incidence rates of MDD were 12.5, 32.9, 27.1, 39.9, and 46.1 per 1,000 person-years, respectively, in the same age subgroups. The multivariable analysis-estimated aHRs for MDD in the cholecystectomy group were 1.51 (95% CI: 1.44–1.58) in 40–49 years, 1.22 (95% CI: 1.18–1.26) in 50–59 years, 1.30 (95% CI: 1.24–1.35) in 60–69 years, 1.17 (95% CI: 1.11–1.24) in 70–79 years, and 1.00 (95% CI: 0.87–1.14) in ≥80 years (Figure 1). The overall incidence rate of MDD increased with age, but the aHR for MDD after cholecystectomy was the highest in the younger group (40–49 years).

Subgroup analyses were performed according to comorbidities, the presence of diabetes mellitus, hypertension, or dyslipidemia (Table 3). Among participants who had diabetes mellitus, the cholecystectomy group showed a higher incidence rate of MDD (34.2 per 1,000 person-years) than the control group (30.0 per 1,000 person-years). Among participants without diabetes mellitus, the cholecystectomy group also showed a higher incidence rate

Table 2. Incidence of MDD in the cholecystectomy and control groups according to age-group classification

Group	n	Event	Person-years	Incidence rate[a]	HR (95% CI) Model 1	HR (95% CI) Model 2	HR (95% CI) Model 3
All							
Control	223,868	21,401	1,054,969.97	20.2859	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	111,934	14,022	513,836.6	27.2888	1.367 (1.337, 1.398)	1.367 (1.337, 1.398)	1.339 (1.309, 1.369)
Age, yr							
40–49							
Control	78,738	4,737	378,576.76	12.5127	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	39,369	3,500	185,418.03	18.8763	1.533 (1.466, 1.603)	1.533 (1.466, 1.603)	1.508 (1.441, 1.578)
50–59							
Control	66,722	9,983	303,187.99	32.9268	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	33,361	5,979	147,155.52	40.6305	1.251 (1.209, 1.293)	1.251 (1.209, 1.293)	1.217 (1.176, 1.259)
60–69							
Control	44,932	5,712	210,631.49	27.1185	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	22,466	3,587	101,697.13	35.2714	1.329 (1.272, 1.388)	1.329 (1.272, 1.388)	1.295 (1.239, 1.354)
70–79							
Control	22,922	4,042	101,318.55	39.894	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	11,461	2,356	49,247.01	47.8405	1.199 (1.136, 1.266)	1.199 (1.136, 1.266)	1.171 (1.109, 1.237)
≥80							
Control	4,268	773	16,764.57	46.1092	1(Ref.)	1(Ref.)	1 (Ref.)
Cholecystectomy	2,134	410	8,473.69	48.3851	1.041 (0.914, 1.186)	1.041 (0.914, 1.186)	0.999 (0.874, 1.141)

CI, confidence interval; HR, hazard ratio; MDD, major depressive disorder.
Model 1: nonadjusted.
Model 2: adjusted for age.
Model 3: adjusted for age, sex, income, place of residence, diabetes mellitus, hypertension, and dyslipidemia.
[a]Incidence rate: per 1,000 person-years.

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Table 3. Comorbidity and aHR of depression

Comorbidity	n	Event	Person-years	Incidence rate[a]	HR (95% CI) Model 1	Model 2	Model 3
Diabetes mellitus							
No							
Control	2 02,135	18,470	956,972.07	19.3005	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	94,444	11,369	436,207.81	26.0633	1.36 (1.328, 1.392)	1.376 (1.344, 1.408)	1.359 (1.327, 1.391)
Yes							
Control	21,733	2,931	97,997.9	29.9088	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	17,490	2,653	77,628.79	34.1755	1.148 (1.089, 1.21)	1.165 (1.105, 1.228)	1.166 (1.106, 1.229)
Hypertension							
No							
Control	1 67,476	14,125	794,826.97	17.7712	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	74,465	8,323	345,264.02	24.1062	1.365 (1.329, 1.403)	1.394 (1.357, 1.433)	1.378 (1.341, 1.416)
Yes							
Control	56,392	7,276	26 0,143	27.9692	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	37,469	5,699	168,572.59	33.8074	1.217 (1.176, 1.26)	1.253 (1.21, 1.297)	1.244 (1.201, 1.288)
Dyslipidemia							
No							
Control	1 90,415	17,046	905,510.6	18.8247	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	89,292	10,570	414,729.08	25.4865	1.363 (1.33, 1.396)	1.369 (1.336, 1.403)	1.349 (1.316, 1.382)
Yes							
Control	33,453	4,355	149,459.37	29.1384	1 (Ref.)	1 (Ref.)	1 (Ref.)
Cholecystectomy	22,642	3,452	99,107.52	34.8309	1.202 (1.15, 1.257)	1.24 (1.186, 1.297)	1.239 (1.185, 1.296)

aHR, adjusted HR; CI, confidence interval; HR, hazard ratio.
Model 1: nonadjusted.
Model 2: adjusted for age.
Model 3: adjusted for age, sex, income, place of residence, diabetes mellitus, hypertension, and dyslipidemia.
[a]Incidence rate: per 1,000 person-years

of MDD (26.1 per 1,000 person-years) than the control group (19.3 per 1,000 person-years). The overall incidence of MDD increased with accompanying diabetes mellitus, but the aHR of MDD after cholecystectomy was higher in participants without diabetes mellitus (aHR 1.36, 95% CI: 1.33–1.39) than in participants with diabetes mellitus (aHR 1.17, 95% CI: 1.11–1.23). Similarly, participants without hypertension and dyslipidemia (aHR: 1.38, 1.35) had a higher relative risk of MDD after cholecystectomy than participants who had these diseases (aHR: 1.24, 1.24).

Next, according to the follow-up period, we estimated the aHR for depression after cholecystectomy to be 1.39 (95% CI: 1.34–1.45) for the 2 years (13–24 months) relative to the control group. The aHR decreased slightly during the follow-up periods; values were 1.34, 1.27, and 1.30 for 3, 4, and 5 + years, respectively (Table 4).

DISCUSSION

Our study results indicated an increased relative risk of MDD after cholecystectomy compared with age- and sex-matched control participants (aHR: 1.34, 95% CI: 1.31–1.67). The incidence rate of MDD was 27.3 cases per 1,000 person-years in participants after cholecystectomy and 20.3 cases per 1,000 person-years in control participants during the mean follow-up period of 3.67 ± 1.79 years. In particular, the younger population (40–49 years, aHR 1.51) had the largest relative risk compared with the older population and a null effect in the oldest group (≥80 years, aHR 1.00). Participants without comorbidities observed a higher relative risk of MDD after cholecystectomy than participants with diabetes mellitus, hypertension, or dyslipidemia.

To the best of our knowledge, this study is the first to investigate the incidence of MDD in South Korea, specifically in participants who underwent cholecystectomy. In this context, we note that the global prevalence of MDD is 4.7% (4.4%–5.0%) and the annual incidence is 3.0% (2.4%–3.8%) (10). In Asian countries, the prevalence of depression is relatively lower than in western countries; however, an increasing tendency has been observed (11,12). In this study, the annual incidence of MDD was estimated to be 2.73% in the cholecystectomy group and 2.03% in the control group. In a population-based study conducted in Taiwan, the incidence of depression was 3.51% and 2.36% in patients with and without cholecystectomy among 7,213 patients with an underlying gallbladder stone (8). This result may overestimate the incidence of depression because a patient with gallbladder stone has a higher risk of developing depression than the general population (9). They also showed increasing risk of MDD after cholecystectomy only in women (aHR: 1.61, 95% CI: 1.08–2.41). Since depression is

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Table 4. Adjusted HR for depression after cholecystectomy as related to follow-up periods

Follow-up period	n	Event	aHR (95% CI)	*P* value
2 yr (13–24 mo)				
Control	223,868	5,581	1 (Ref.)	<0.0001
Cholecystectomy	111,934	3,940	1.392 (1.336, 1.45)	<0.0001
3 yr (25–36 mo)				
Control	216,646	5,020	1 (Ref.)	<0.0001
Cholecystectomy	106,491	3,332	1.335 (1.277, 1.395)	<0.0001
4 yr (37–48 mo)				
Control	175,385	4,073	1 (Ref.)	<0.0001
Cholecystectomy	84,942	2,555	1.272 (1.21, 1.337)	<0.0001
≥ 5 yr (≥49 mo)				
Control	136,079	6,727	1 (Ref.)	<0.0001
Cholecystectomy	65,148	4,195	1.303 (1.253, 1.354)	<0.0001

Multivariate model adjusted for age, sex, income, place of residence, diabetes mellitus, hypertension, and dyslipidemia.
aHR, adjusted hazard ratio; CI, confidence interval.

generally common in women, the study would affect the results by enrolling more women (n = 742) than men (n = 455) in the cholecystectomy group. By contrast, we enrolled 68,439 (61.1%) men and 43,495 (38.9%) women in the cholecystectomy group. There was no sex difference in the total number of cholecystectomies in Korea (13), but our study included a larger male population because we excluded individuals with pre-existing depression among those who underwent cholecystectomy. In the general population, a point prevalence of MDD was 3.2% in men and 4.0% in women (14). In addition, by comparing them with age- and sex-matched controls, we could minimize the effect of sex differences on the incidence of depression.

We found a trend for increased risk of MDD with age. However, results of previous studies are inconsistent about whether depression increases or decreases with age (15). Because most studies use cross-sectional data to compare the relationship between age groups and depression, the limitation that age effects are inferred from interperson comparisons is present (16). Regarding age-related effects, the burden of medical comorbidities increases, and psychosocial stress may influence the development of depression in the elderly population (17). Similar to our findings, a previous Korean study found that the prevalence of depression increased with age in both men and women and gradually increased to 2.9%, 3.6%, 5.5%, and 9.4% in individuals aged 40s, 50s, 60s, and >70s, respectively (18). We found the incidence of MDD was the lowest in the 40–49 years' group with or without cholecystectomy, while the relative risk of MDD after cholecystectomy was the highest in this group. The incidence of MDD increased with age, but the relative risk of MDD after cholecystectomy decreased with age. There was no difference in the relative risk of MDD after cholecystectomy in the elderly people older than 80 years compared with the control participants. The dissociation mechanism between the incidence and relative risk of MDD is difficult to explain based on our research results. We speculated that cholecystectomy might contribute to a greater risk of developing depression in the younger population who generally have few risk factors for depression.

The biological mechanisms that may account for the observed association between a higher risk of MDD after cholecystectomy remain unclear. Persistent gastrointestinal symptoms, such as diarrhea or abdominal pain, could occur in a substantial subset of patients owing to bile acid–induced diarrhea and/or changes in the gut microbiome induced by cholecystectomy (19–22). These changes could have direct (through the microbiome) or indirect (through impaired health-related quality of life associated with diarrhea or pain) effects that modify the risk of developing MDD (23–25). Previous studies in patients undergoing cholecystectomy could provide important information about mediating factors that are associated with the risk of developing MDD (26,27).

Another mechanism for developing MDD may be the increased risk of abnormal metabolic consequences after cholecystectomy (2,28). Our results showed that the cholecystectomy group had a higher proportion of individuals with hypertension, diabetes mellitus, or dyslipidemia than the control group according to baseline demographics. For cholesterol gallstone disease, a strong association exists between this disease and highly prevalent metabolic disorders such as obesity, dyslipidemia, and diabetes mellitus (29). By contrast, cholecystectomy could influence the enterohepatic circulation and lipid/glucose metabolism and likely contribute to the development of metabolic diseases (30,31). In addition, a recent study indicated that patients who had cholecystectomy had a stronger relationship with metabolic syndrome than participants with gallstone or normal (28). Furthermore, abnormal metabolic consequences could be related to depressive mood through the dysregulation of the hypothalamic-pituitary-adrenal axis and insulin resistance (6,32). A recent meta-analysis suggested that metabolic syndrome and depression were significantly related after adjusting potential confounders (adjusted odds ratio: 1.34, 95% CI: 1.18–1.51). We observed the higher incidence of MDD in participants who had underlying hypertension, diabetes mellitus, or dyslipidemia regardless of cholecystectomy. Interestingly, participants without those diseases had a higher relative risk of MDD after cholecystectomy than participants who had those diseases. The reasons for this dissociation between incidence and relative risk of MDD are uncertain.

This study includes certain limitations. First, we used health insurance claim data for this study and considered the number of medical visits for depression based on *ICD* codes. The use of *ICD* codes reported on insurance claims allows for the possibility of misdiagnosis. However, the diagnosis of MDD has a very high validity relative to depressive symptoms reported by surveys. Second, although this study used age- and sex-matched control group, confounding factors such as postoperative pain, infection, marital status, education, occupational status, body mass index, smoking habits, and alcohol intake were not included in this study; all these factors can also influence the development of MDD. Third, we could not exclude participants who already had symptoms of depression but were not diagnosed with MDD before the index date. To minimize the inclusion of these participants, we excluded individuals who were diagnosed with depression within 1 year after the index date (1-year lag period). Finally, our capacity to explore any potential physiological mechanism was limited as we did not have any information on the diagnostic indications for cholecystectomy because a different indication for cholecystectomy (such as symptomatic gallbladder stone, gallbladder polyp, or acute cholecystitis) might play a different role in depressive symptoms. We excluded patients who underwent cholecystectomy for gallbladder cancer because it was defined as a different claim code (Q7410).

Our study suggested that participants who underwent cholecystectomy had a higher relative risk of new incidence of MDD than control participants based on the analysis of a national population-based data set over a 7-year follow-up period. The risk of developing MDD is relatively high in the younger middle-aged (40–49 years) population and participants without underlying metabolic disease and is highest within the 2 years after cholecystectomy. Thus, physicians should implement an enhanced program of MDD screening for at least several years after cholecystectomy.

CONFLICTS OF INTEREST

Guarantor of the article: Dong Ho Lee, MD, PhD.
Specific author contributions: Eun Hyo Jin, MD, PhD, and Kyungdo Han, PhD, are joint first authors. Conceptualization and supervision: D.H.L.; formal analysis and drafting the original article: E.H.J.; statistical analysis and investigation: K.H.; review and editing: C.M.S. and J.H.L.; methodology: H.Y. and N.K.; All authors have read and approved the final manuscript.
Financial support: None to report.
Potential competing interest: None to report.

Study Highlights

WHAT IS KNOWN

✓ The long-term medical consequences of cholecystectomy are not completely known.

WHAT IS NEW HERE

✓ Patients who underwent cholecystectomy had an increased incidence of major depressive disorder (MDD).
✓ The risk of MDD was the highest in cholecystectomy patients aged 40–49 years.

TRANSLATIONAL IMPACT

✓ Physicians should implement an enhanced program of MDD screening for at least several years after cholecystectomy.

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