JGH Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.15568

ORIGINAL ARTICLE - BILIARY AND PANCREATIC

Association between metabolic syndrome and incidence of cholelithiasis in the Korean population

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Key words
Blood pressure, Central obesity, Cholelithiasis, Fasting blood glucose, GB stone, HDL cholesterol, Low HDL cholesterol, Metabolic components, Metabolic syndrome, Triglycerides.

Accepted for publication 5 June 2021.

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Declaration of conflict of interest: All authors have nothing to disclose.
Author contribution: Jae-Hong Ryoo is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Yeji Kim contributed to the manuscript preparation and editing as the first author. Chang-Mo Oh, Sung Keun Park, and Ju Young Jung contributed to the study design and manuscript preparation. Eunhee Ha participated in data analysis, interpretation, and manuscript review. Jae-Hong Ryoo contributed to data acquisition, quality control of data and algorithms, data analysis and interpretation, and statistical analysis.
Financial support: This work was supported by the National Research Foundation of Korea in 2020 (grant number: 2020R1G1A1102257). The funding organization had no role in the design or conduct of this study.

Abstract

Background and Aim: Cholelithiasis is one of the most common gastrointestinal diseases worldwide. The metabolic syndrome (MetS), a combination of various metabolic abnormalities, is also common with a continually increasing prevalence. These diseases are associated with several risk factors. However, data on the association between MetS components and cholelithiasis are insufficient. This study aimed to analyze the association of MetS and its components with the incidence of cholelithiasis using national data from the Korean population.
Methods: Data were obtained from the National Health Insurance Corporation of Korea, and 207 850 individuals without cholelithiasis in 2009 were enrolled and followed up until 2013. A multivariate Cox proportional hazard model was used to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of cholelithiasis according to the presence of MetS and the number of MetS components. Furthermore, the risk of cholelithiasis was evaluated in individuals with a single metabolic component.
Results: The multivariate adjusted HRs and 95% CIs for incident cholelithiasis according to 1, 2, 3, and 4–5 MetS components were 1.08 (0.93–1.24), 1.22 (1.06–1.41), 1.35 (1.17–1.57), and 1.35 (1.15–1.57), respectively ($P < 0.001$). This increasing trend was observed in both sexes. Compared with participants with no metabolic components, those with low high-density lipoprotein (HDL) cholesterol had a significantly increased risk for cholelithiasis (adjusted HR, 1.39 [95% CI, 1.05–1.85]).
Conclusions: Metabolic syndrome is a potential risk factor for cholelithiasis. Low HDL cholesterol level is the most relevant factor among MetS components for incident cholelithiasis.

Introduction

Metabolic syndrome (MetS) is a combination of metabolic abnormalities, including high fasting blood glucose, high blood pressure (BP), high triglycerides, low high-density lipoprotein (HDL) cholesterol, and central obesity.[1] The clustering of these metabolic factors increases the risk of cardiovascular-disease and type 2 diabetes.[2] The prevalence of MetS is rapidly increasing worldwide. According to the data from the National Health and Nutrition Examination Survey from 2003 to 2012, the age adjusted prevalence of MetS increased from 32.9% to 34.7% over 10 years

in the US population.[3] In Asia, the trend rose more sharply, which was attributed to the westernization of lifestyle.[4] According to the data from the Korea National Health and Nutrition Examination Survey between 1998 and 2007, the overall prevalence of MetS increased from 24.9% to 31.3% over 10 years. In addition, among metabolic components, the level of low HDL cholesterol increased the most, by 13.8% over the 10 years.[5]

Cholelithiasis (gallstone disease) is one of the most common gastrointestinal diseases worldwide.[6] In the USA, the prevalence of cholelithiasis ranged from 7.9% in men to 16.6% in women from 1988 to 1994.[7] Cholelithiasis is a major health burden. The estimated direct and indirect cost of cholelithiasis was $6.2 billion annually in the USA in 2004.[8] Cholelithiasis is a potential risk factor for cholecystitis, cholangitis, pancreatitis, and gallbladder cancer.[9] In addition, because cholecystectomy is the first treatment choice for symptomatic cholelithiasis,[10] it represents one of the most common diseases requiring surgical intervention.[11]

Previous studies have shown a significant association between cholelithiasis and MetS.[12–17] These studies have suggested that the presence of MetS is potentially associated with an increased risk of cholelithiasis. However, few studies have longitudinally investigated the effect of MetS on the incidence of cholelithiasis in a large sample size. Moreover, limited published data are available to identify the risk of cholelithiasis based on the number of metabolic components.

We longitudinally evaluated the risk of cholelithiasis according to the number of metabolic components using medical data of 207 850 Koreans, derived from the National Health Insurance Service-National Sample Cohort database. Through this analysis, we could observe the effect of MetS and the number of MetS components on the incidence of cholelithiasis. Additionally, to identify any sex differences and the relative contribution of each metabolic component to incident cholelithiasis, we stratified the data according to sex and evaluated individuals with only one metabolic component to exclude the effects of others.

Methods

Data sources. The national health insurance system covers over 97% of the population living in South Korea. Therefore, the database of the national health insurance system represents the medical service usage of nearly the entire Korean population.[18] In addition, Koreans aged more than 40 years are required to undergo a medical health checkup at least once every 2 years. Information from which is collected and stored by the National Health Insurance Corporation (NHIC). In recent years, the national health insurance system in South Korea has provided a sample database for research purposes to establish the NHIS-NSC.

The NHIS-NSC database includes information from health checkups and the incidence of cholelithiasis from Statistics Korea. Ethical approval for the study protocol was obtained from the institutional review board of Kyung Hee University Hospital. The requirement for informed consent was waived because researchers retrospectively accessed a de-identified database for analysis purposes.

Study participants. The NHIS-NSC database included a total of 223 551 participants who underwent medical health checkups in 2009. Of these, we initially excluded 4039 individuals who had previously had cholelithiasis (International Classification of Disease [ICD] K80) between 2002 and the date of the medical health examination in 2009. Among the remaining 219 512 participants, 11 662 were excluded based on the following exclusion criteria that might influence cholelithiasis or MetS: 217 people with no information about MetS components, and 11 450 who were previously diagnosed with cancer (ICD C00-C97) between 2002 and the date of the medical health examination in 2009. Some participants had more than one exclusion criteria applied. A total of 207 850 participants were included in the final analysis and were observed for the incidence of cholelithiasis. The total follow-up period was 906 402.6 person-years, and the average follow-up period was 4.36 (standard deviation [SD], 0.51) person-years.

Health survey examinations and laboratory measurements. The general health checkup was conducted in two stages. The first stage of the examination was a massive screening test to determine the presence or absence of disease in the asymptomatic general population. The second stage of the examination included consultations for screening tests and a more detailed examination to confirm the presence of disease. These health examinations also included a questionnaire regarding lifestyle and medical history. Study data included level of physical activity, the information provided by the questionnaire, anthropometric measurements, and laboratory measurements. Smoking pattern was categorized into three status: never, former, and current smoker. Never smoker was defined as those who have smoked < 100 cigarettes or have never smoked in their lifetime. Participants who smoked ≥ 100 cigarettes in their lifetime were categorized into smoker. Out of smokers, participants who were currently smoking were defined as current smoker, and participants who were currently quitting smoking were defined as former smoker. The amount of smoking was determined by the number of packs per year, calculated from a smoking-related questionnaire. Alcohol intake was defined by alcohol consumption for more than three times per week. Physical activity was defined as moderate-intensity physical activity for at least 30 min per day for more than 4 days per week or vigorous-intensity physical activity for at least 20 min per day for more than 4 days per week.[19] BMI was calculated as weight (kg) divided by the square of height (m). Waist circumference (WC) was measured in a standing position at the level of the umbilicus.

Systolic and diastolic BP were measured by trained examiners, and the following laboratory data were measured at the same time that participants underwent health examinations: fasting blood glucose, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, serum creatinine (SCr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT). Kidney function was assessed through estimated glomerular filtration rate (eGFR), which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: $eGFR = 141 \times \min(SCr/K, 1)^{a} \times \max(SCr/K, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female], where SCr = serum creatinine, $K = 0.7$, for women and 0.9 for men, $a = -0.329$ for women and -0.411 for men, min indicates the

minimum of SCr/*K* (or 1), and max indicates the maximum SCr/*K* (or 1).[20]

The presence of MetS was determined based on the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention.[1] MetS was defined as the presence of three or more of the five metabolic components described as follows: BP was elevated when systolic and diastolic BP was ≥ 130/85 mmHg; fasting blood glucose was defined as elevated when ≥ 5.55 mmol/L; serum triglyceride levels were defined as high when ≥ 1.695 mmol/L; HDL cholesterol levels were defined as low when < 1.036 mmol/L in men and < 1.295 mmol/Lin women, and WC was elevated when ≥ 90 cm in men and ≥ 85 cm in women. Participants with baseline hypertension, diabetes, and dyslipidemia were regarded as having baseline metabolic components of elevated BP, elevated fasting glucose, and high triglycerides, respectively. The identification of baseline hypertension, diabetes, and dyslipidemia was based on the revision of the data for the ICD codes of hypertension (I10-I15), diabetes (E10-E14), and dyslipidemia (E78.0-E78.5) from 2002 to the date of reception of the medical health checkup data in 2009.

Outcome definitions. Incident cholelithiasis was identified by reviewing the NHID linked to the Department of Statistics Korea in the NHIC. Korean medical institutions contracted by the NHIC are mandated to provide medical information to patients. As such, if gallstones were detected in asymptomatic or symptomatic patients by imaging modalities or surgical operations, medical institutions should register patients with newly identified gallstones in the NHID as having cholelithiasis with ICD-K80. We excluded all individuals who presented with ICD-K80. Of the remaining participants, participants with newly registered ICD-K80 between 2009 and 2013 were identified as cases of incident cholelithiasis.

Statistical analysis. Data are expressed as mean ± SD or median (interquartile range) for continuous variables and as percentages for categorical variables. Independent *t*-tests and χ^2 tests were used to analyze the statistical differences between baseline non-MetS and MetS. One-way ANOVA and χ^2 tests were used to analyze the statistical differences among the characteristics of the study participants at the time of enrollment in relation to the number of MetS components. The number of MetS components was as follows: 0, 1, 2, 3, and 4–5. Categories 4 (N = 22 124, 10.64%) and 5 (N = 5662, 2.72%) were combined for analysis because of the relatively small number of participants in category 5. Person-years were calculated as the sum of follow-up times, from baseline until the time of cholelithiasis diagnosis (31 December 2013).

Cox proportional hazard models were used to estimate adjusted hazard-ratios (HRs) and 95% CIs to evaluate the associations between the baseline number of MetS components and incident cholelithiasis. The Cox proportional hazard models were adjusted for multiple confounding factors. In the multivariate models, we included variables that might confound the relationship between MetS and incident cholelithiasis, including age, sex, eGFR, GGT, smoking amount, alcohol intake, and physical activity. To test the validity of the Cox proportional hazard models, we checked the proportional hazard assumption. The proportional hazard assumption was assessed using the log-minus-log survival function and was found to be graphically unviolated. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

During the 906 402.6 person-years of follow-up, 2929 (1.41%) cases of incident cholelithiasis developed between 2009 and 2013. The baseline characteristics of the study participants concerning MetS are presented in Table 1. At baseline, the mean (SD) age and BMI of study participants were 57.8 (8.7) years and 24.0 (2.9) kg/m^2, respectively. There were significant differences in all of the listed variables between the non-MetS and MetS groups, except for SCr.

Table 2 shows the baseline characteristics of the study participants according to the number of MetS components. There were clear dose–response relationships between all of the listed variables and the number of MetS components**.**

In contrast to participants without incident cholelithiasis, those with incident cholelithiasis were older (60.8 *vs* 57.8) and more likely to have a less favorable metabolic profile at baseline. As expected, all clinical variables showed statistically significant differences between groups, except for sex, diastolic BP, triglycerides, smoking status, alcohol intake, and physical activity (Table S1).

Table 3 shows the HRs and 95% CIs for cholelithiasis according to the number of MetS components. In the age-adjusted and sex-adjusted model, HRs and 95% CI for cholelithiasis comparing 1, 2, 3, and 4–5 MetS components (*vs* 0) were 1.07 (0.94–1.24), 1.24 (1.08–1.42), 1.43 (1.24–1.64); and 1.42 (1.22–1.65), respectively ($P < 0.001$). These associations remained statistically significant, even after further adjustments for covariates in the multivariate adjusted model, the adjusted HRs and 95% CI for incident cholelithiasis were 1.08 (0.93–1.24), 1.22 (1.06–1.41), 1.35 (1.17–1.57), and 1.35 (1.15–1.57), respectively ($P < 0.001$). Men and women were both significantly associated with an increased risk of incident cholelithiasis, even after adjusting for multiple covariates ($P < 0.001$).

The HRs of the individual metabolic components of incident cholelithiasis are presented in Table 4. Compared with participants without any metabolic components present, participants with low HDL cholesterol (1.39 [1.05–1.85]) had a significantly increased risk of developing cholelithiasis. However, there was no statistically significant difference in the risk of incident cholelithiasis in the presence of elevated BP (1.02 [0.85–1.23]), elevated fasting glucose (1.19 [0.91–1.38]), high triglyceride (0.93 [0.72–1.21]), or abdominal obesity (1.30 [0.98–1.72]).

Discussion

Our findings suggest that Korean participants with MetS had a significantly increased risk of incident cholelithiasis, even after adjusting for covariates. Previous studies have shown trends consistent with the results of this study. Several cross-sectional studies have reported that MetS is significantly associated with gallstone disease.[13–16] In addition, the statistically significant overall odds ratios (ORs) of MetS for gallstone disease ranged from 1.42 to 3.20. However, few longitudinal studies have investigated the association between MetS and the incidence of cholelithiasis.[12,17]

Table 1 Baseline characteristics of study participants according to the presence of MetS (*N* = 207 850)

Characteristic	Overall	Non-MetS (*N* = 136 516)	MetS (*N* = 71 334)	*P*-value*
Person-year (total)	906 402.6	595 184.2	311 218.4	
Person-year (average)	4.36 ± (0.51)	4.36 ± (0.49)	4.36 ± (0.55)	
Age (years)	57.8 ± (8.7)	56.7 ± (8.3)	60.0 ± (9.0)	< 0.001
Sex				< 0.001
Male (%)	117 539 (56.5)	80 222 (58.8)	37 317 (52.3)	
Female (%)	90 311 (43.5)	56 294 (41.2)	34 017 (47.7)	
BMI (kg/m^2)	24.0 ± (2.9)	23.2 ± (2.6)	25.6 ± (2.8)	< 0.001
WC (cm)	82.0 ± (8.1)	79.6 ± (7.4)	86.8 ± (7.5)	< 0.001
Systolic BP (mmHg)	125.3 ± (15.2)	122.1 ± (14.5)	131.4 ± (14.7)	< 0.001
Diastolic BP (mmHg)	77.7 ± (9.9)	76.1 ± (9.6)	80.8 ± (9.8)	< 0.001
Total cholesterol (mmol/L)	5.19 ± (0.97)	5.14 ± (0.92)	5.27 ± (1.05)	< 0.001
Triglyceride (mmol/L)	1.33 (0.94–1.93)	1.14 (0.84–1.53)	1.92 (1.37–2.60)	< 0.001
HDL cholesterol (mmol/L)	1.44 ± (0.84)	1.51 ± (0.85)	1.29 ± (0.77)	< 0.001
LDL cholesterol (mmol/L)	3.07 ± (1.01)	3.09 ± (0.97)	3.03 ± (1.08)	< 0.001
Fasting blood glucose (mmol/L)	5.59 ± (1.40)	5.29 ± (1.09)	6.16 ± (1.73)	< 0.001
SCr (μmol/L)	101.9 ± (131.9)	102.1 ± (131.9)	101.5 ± (131.8)	0.389
eGFR (mL/min per 1.73 m^2)	80.8 ± (20.2)	82.0 ± (20.0)	78.5 ± (20.3)	< 0.001
AST (U/L)	24 (20–29)	23 (20–28)	25 (20–31)	< 0.001
ALT (U/L)	21 (16–29)	20 (15–27)	24 (18–34)	< 0.001
GGT (U/L)	25 (17–41)	23 (16–37)	30 (19–51)	< 0.001
Smoking amount (pack-year)	7.8 ± (13.8)	7.7 ± (13.5)	8.0 ± (14.5)	0.003
Smoking status (%)				< 0.001
Never smoker	62.8	61.8	64.6	
Former smoker	18.3	18.6	17.8	
Current smoker	18.9	19.6	17.6	
Alcohol intake (%)	14.6	14.4	15.1	< 0.001
Physical activity (%)	16.8	17.3	16.0	< 0.001
Development of cholelithiasis (%)	2929 (1.41)	1695 (1.24)	1234 (1.73)	< 0.001

Data are presented as mean (standard deviation), median (interquartile range), or percentage.

**P*-value following *t*-test for continuous variables and χ^2 test for categorical variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; SCr, serum creatinine; WC, waist circumference.

According to a longitudinal cohort study conducted on 18 291 urban Han Chinese participants over 6 years,[12] 873 cases of gallstones were reported, and the age-adjusted-relative-risk (RR) for incident gallstone disease associated with MetS was 1.33 (CI: 1.11–1.59) in men and 1.15 (CI: 0.77–1.71) in women. This sex difference caused by low incidence rates of MetS in women was not found in our study.[12] According to a cohort study in Copenhagen,[17] of 2848 participants, 256 participants developed gallstones, and factors that were significantly associated with gallstones were age, female sex, non-HDL cholesterol, and gallbladder polyps. BMI was associated with gallstones only in men. Furthermore, according to a systematic review with meta-analysis in the same study,[17] gallstones and MetS shared risk factors such as age, BMI, and non-HDL cholesterol, but not HDL cholesterol or triglycerides.

Most previous studies reporting an association between MetS and cholelithiasis were cross-sectional studies. In addition, previous cohort studies were relatively small and may have shown different associations in men and women. Furthermore, to our knowledge, no longitudinal study has found an association between incident cholelithiasis and the presence of each metabolic component. Therefore, a larger and more appropriate longitudinal study is required to clarify the association between MetS components and cholelithiasis.

In this study, the risk of incident cholelithiasis increased progressively with an increasing number of metabolic components. The presence of two or more metabolic components was significantly associated with an increased risk of cholelithiasis according to the multivariate adjusted model. This increasing trend was observed in both men and women. These findings suggest that MetS may play an important independent role in the incidence of cholelithiasis in both sexes. A significant increasing trend between the number of MetS components and the prevalence of gallstones has been shown in previous cross-sectional studies.[13,15] Additionally, the risk of incident gallstone disease increased with the number of MetS components in men in a Chinese cohort study.[12]

Only participants with low HDL cholesterol as a single MetS component had a significantly increased incidence of cholelithiasis compared with those with no metabolic components. The relationship between HDL cholesterol and gallstone formation remains controversial. Several studies found that HDL cholesterol levels in participants with gallstone disease were significantly lower than those without gallstone disease.[15,21–23] A Chinese study reported that participants with serum HDL cholesterol levels < 40 mg/dL

Table 2 Baseline characteristics of participants according to the number of MetS components (N = 207 850)

Characteristic	Number of MetS components					
	0 (N = 28 127)	1 (N = 51 543)	2 (N = 56 846)	3 (N = 43 548)	4–5 (N = 27 786)	P for trend*
Person-year (total)	122 848.9	224 854.4	247 480.9	189 821.7	121 396.7	
Person-year (average)	4.37 ± (0.43)	4.36 ± (0.47)	4.35 ± (0.52)	4.35 ± (0.54)	4.36 ± (0.56)	
Age (years)	54.3 ± (6.9)	56.5 ± (8.2)	58.0 ± (8.6)	59.4 ± (8.8)	61.0 ± (9.1)	< 0.001
Sex						< 0.001
Male (%)	15 400 (54.7)	30 572 (59.3)	34 250 (60.3)	24 633 (56.6)	12 684 (45.6)	
Female (%)	12 727 (45.3)	20 971 (40.7)	22 596 (39.7)	18 915 (43.4)	15 102 (54.4)	
BMI (kg/m^2)	22.1 ± (2.2)	22.9 ± (2.4)	23.9 ± (2.6)	25.1 ± (2.8)	26.3 ± (2.8)	< 0.001
WC (cm)	75.8 ± (6.5)	78.8 ± (6.9)	82.1 ± (7.2)	85.4 ± (7.4)	88.8 ± (7.2)	< 0.001
Systolic BP (mmHg)	112.6 ± (9.1)	121.7 ± (14.0)	127.2 ± (14.6)	130.5 ± (14.7)	132.7 ± (14.6)	< 0.001
Diastolic BP (mmHg)	70.8 ± (7.2)	76.0 ± (9.4)	78.9 ± (9.8)	80.5 ± (9.8)	81.3 ± (9.8)	< 0.001
Total cholesterol (mmol/L)	5.04 ± (0.83)	5.12 ± (0.92)	5.22 ± (0.97)	5.28 ± (1.04)	5.27 ± (1.06)	< 0.001
Triglyceride (mmol/L)	0.94 (0.71–1.22)	1.10 (0.81–1.44)	1.34 (0.97–1.85)	1.76 (1.22–2.37)	2.17 (1.73–2.90)	< 0.001
HDL cholesterol (mmol/L)	1.59 ± (0.70)	1.53 ± (0.84)	1.46 ± (0.93)	1.35 ± (0.83)	1.18 ± (0.68)	< 0.001
LDL cholesterol (mmol/L)	3.04 ± (0.91)	3.09 ± (0.97)	3.11 ± (1.01)	3.07 ± (0.08)	3.00 ± (0.08)	< 0.001
Fasting blood glucose (mmol/L)	4.87 ± (0.41)	5.19 ± (0.92)	5.59 ± (1.34)	5.98 ± (1.61)	6.44 ± (1.86)	< 0.001
SCr (umol/L)	98.6 ± (125.7)	100.9 ± (130.3)	104.8 ± (136.2)	102.4 ± (136.3)	100.2 ± (124.5)	0.050
eGFR (mL/min per 1.73 m^2)	84.2 ± (19.5)	82.4 ± (19.7)	80.5 ± (20.4)	79.3 ± (20.2)	77.4 ± (20.4)	< 0.001
AST (U/L)	23 (19–27)	23 (20–28)	24 (20–29)	24 (20–30)	25 (21–31)	< 0.001
ALT (U/L)	18 (14–24)	19 (15–26)	21 (16–29)	23 (17–32)	25 (18–35)	< 0.001
GGT (U/L)	19 (14–29)	22 (16–35)	26 (17–43)	29 (19–50)	30 (20–52)	< 0.001
Smoking amount (pack-year)	6.7 ± (12.2)	7.8 ± (13.4)	8.3 ± (14.1)	8.4 ± (14.6)	7.3 ± (13.4)	< 0.001
Smoking status						< 0.001
Never smoker	64.6	61.6	60.6	62.1	68.5	
Former smoker	16.3	18.6	19.8	19.1	16.0	
Current smoker	19.1	19.8	19.6	18.8	15.5	
Alcohol intake (%)	11.5	14.2	16.1	16.4	12.9	< 0.001
Physical activity (%)	16.6	17.4	17.4	16.4	15.4	< 0.001
Development of cholelithiasis (%)	281 (1.00)	606 (1.18)	808 (1.42)	744 (1.71)	490 (1.76)	< 0.001

Data are presented as mean (standard deviation), median (interquartile range), or percentage.

*P-value following ANOVA for continuous variables and χ^2 test for categorical variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; MetS, metabolic syndrome; LDL, low-density lipoprotein; SCr, serum creatinine; WC, waist circumference.

Table 3 Hazard-ratios and 95% confidence intervals for the incidence of cholelithiasis according to the number MetS components

	Person-year	Incidence cases	Incidence density (per 10 000 person-year)	Hazard-ratios (95% Confidence Interval)					
				Total (*N* = 207 850)		Men (*N* = 117 539)		Women (*N* = 90 311)	
				Age and sex-adjusted	Multivariate adjusted model	Age and sex-adjusted	Multivariate adjusted model	Age and sex-adjusted	Multivariate adjusted model
Number of MetS components									
0	122 848.9	281	22.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	224 854.4	606	26.9	1.07 (0.94–1.24)	1.08 (0.93–1.24)	1.02 (0.85–1.22)	1.00 (0.83–1.20)	1.18 (0.94–1.49)	1.22 (0.96–1.54)
2	247 480.9	808	32.6	1.24 (1.08–1.42)	1.22 (1.06–1.41)	1.15 (0.97–1.37)	1.11 (0.93–1.33)	1.44 (1.15–1.80)	1.47 (1.17–1.85)
3	189 821.7	744	39.2	1.43 (1.24–1.64)	1.35 (1.17–1.57)	1.31 (1.09–1.56)	1.19 (0.99–1.43)	1.73 (1.38–2.16)	1.74 (1.38–2.19)
4–5	121 396.7	490	40.4	1.42 (1.22–1.65)	1.35 (1.15–1.57)	1.51 (1.24–1.84)	1.38 (1.13–1.69)	1.50 (1.19–1.90)	1.50 (1.17–1.91)
P for trend				< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Age				1.03 (1.03–1.04)	1.03 (1.03–1.04)	1.04 (1.04–1.05)	1.044 (1.039–1.050)	1.02 (1.01–1.03)	1.022 (1.015–1.029)
Sex (female *vs* male)				0.84 (0.78–0.91)	0.93 (0.85–1.01)				
eGFR					1.001 (0.999–1.003)		1.001 (0.999–1.004)		1.000 (0.997–1.003)
GGT					1.002 (1.002–1.003)		1.002 (1.001–1.002)		1.003 (1.003–1.004)
Smoking amount					1.003 (1.001–1.006)		1.003 (1.000–1.006)		1.014 (0.997–1.030)
Alcohol intake					1.154 (1.028–1.294)		1.112 (0.987–1.253)		1.609 (1.007–2.571)
Physical activity					0.958 (0.868–1.056)		0.962 (0.850–1.088)		0.982 (0.836–1.153)

Multivariate adjusted model, adjusting for age, sex, eGFR, GGT, smoking amount (pack-year), alcohol intake, and physical activity.
eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; MetS, metabolic syndrome.

Table 4 Hazard-ratios and 95% confidence intervals for incidence of cholelithiasis according to the presence of each metabolic component

	Number of subjects	Incidence cases (%)	Hazard-ratios (95% Confidence Interval)	
			Age and sex-adjusted	Multivariate adjusted model
Whole cohort	207 850	2929 (1.41)		
Subjects with no metabolic component	28 127	281 (1.00)	1.00 (reference)	1.00 (reference)
Elevated BP alone	21 639	261 (1.21)	1.03 (0.87–1.23)	1.02 (0.85–1.23)
Elevated fasting glucose alone	11 397	136 (1.19)	1.13 (0.92–1.39)	1.12 (0.91–1.38)
Low HDL cholesterol alone	4858	63 (1.30)	1.36 (1.03–1.80)	1.39 (1.05–1.85)
High triglycerides alone	8099	79 (0.98)	0.95 (0.73–1.23)	0.93 (0.72–1.21)
Abdominal obesity alone	5550	67 (1.21)	1.28 (0.97–1.69)	1.30 (0.98–1.72)

Multivariate adjusted model, adjusting for age, sex, eGFR, GGT, smoking amount (pack-year), alcohol intake, and physical activity.
Elevated BP: systolic and diastolic BP ≥ 130/85 mmHg and previously diagnosed hypertension, elevated fasting glucose: fasting glucose ≥ 5.55 mmol/L and previously diagnosed diabetes mellitus, high triglycerides: triglyceride ≥ 1.695 mmol/L and previously diagnosed dyslipidemia, low HDL-cholesterol: HDL-cholesterol < 1.036 mmol/Lin men and < 1.295 mmol/L in women, abdominal obesity: waist circumference ≥ 90 cm in men and ≥ 85 cm in women.
BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; HDL, high-density cholesterol; MetS, metabolic syndrome.

have a 1.93-fold increased risk of biliary stones, and those with levels < 30 mg/dL have a 4.23-fold increased risk.[21] In a Mexican study, the multivariate-adjusted OR for gallstone disease associated with low HDL cholesterol was 2.32 (CI: 1.05–5.11).[13] In addition, in age-adjusted logistic regression analyses, low HDL cholesterol levels were significantly associated with the risk of gallstone formation in premenopausal women in Korea.[24] However, some studies found no significant association between HDL cholesterol and gallstone disease.[17,25,26]

In this study, we excluded other metabolic components and assessed the risk of cholelithiasis in participants with low HDL cholesterol alone. Thus, it was an opportunity to clarify the direct association between low HDL cholesterol and the incidence of cholelithiasis. When HDL cholesterol (involved in the transport of cholesterol to bile) decreases, hepatic bile acid synthesis is reduced, causing bile cholesterol supersaturation.[17,27] In addition, low HDL cholesterol is associated with increased hepatic insulin resistance, which increases biliary cholesterol secretion and the risk of gallstones.[12,28–30]

MetS is an insulin resistance syndrome that is closely linked to metabolic components.[1] Insulin resistance may link MetS to incident cholelithiasis. While hepatic insulin resistance increases the secretion of biliary cholesterol,[31] hyperglycemia reduces the contraction of the gall bladder through vagal-cholinergic inhibition in response to various stimuli in subjects.[32] The action of hepatic insulin resistance and hyperglycemia promotes the formation of gallbladder stones. It has been demonstrated that higher triglyceride levels lead to decreased gallbladder contraction and diminished gallbladder motility.[33] Obesity is an established risk factor for gallstones. Therefore, it is presumed that MetS and its related conditions contribute to the development of gallstones.

Cholelithiasis is one of the most common and medically costly diseases. Thus, it is clinically important to accurately identify the modifiable risk factors for cholelithiasis. Low HDL cholesterol was not only the major factor involved in increasing the prevalence of MetS in Korea[5] but also the most relevant factor with respect to the incidence of cholelithiasis among all of the metabolic components in this study. Thus, lifestyle modifications such as exercise, weight loss, polyunsaturated fat intake, and pharmacotherapy such as niacin and fibrates for increasing levels of HDL cholesterol are recommended at the national level to reduce the risk of cholelithiasis in Korea.[34] Additionally, our study suggests that patients with multiple metabolic components should be monitored for cholelithiasis.

This longitudinal cohort study has several strengths. First, we analyzed nationwide data from a large population-based sample. Thus, the information obtained for the metabolic components and the diagnosis of cholelithiasis was reliable. In addition, participants with chronic diseases associated with MetS and cholelithiasis were excluded from the analysis. Finally, we analyzed the data by dividing it into different sexes and the participants were evaluated for each metabolic component to identify its effect. This allowed us to quantify the powerful impact of each metabolic component on the HRs for cholelithiasis.

The present study has three limitations. First, this study did not identify factors such as genetic predisposition to cholelithiasis, pregnancy, corpulence, weight loss, high fat intake, and medications such as estrogen and octreotide, which can influence the development of cholelithiasis.[6,9,35] Second, our results were not evaluated from the data obtained for this research. Rather, raw data were obtained from medical examinations and related questionnaires; therefore, a collection bias may exist. Third, the study follow-up period (4.36 years) was relatively short to reveal the long-term effects of each metabolic component on cholelithiasis. Further studies should be conducted to address these limitations.

In conclusion, this study suggests that baseline MetS is independently associated with the incidence of cholelithiasis in the Korean population. Our data suggested that the more metabolic components present, the higher the risk of incident cholelithiasis in both men and women. Furthermore, our study provides strong evidence that each metabolic component may contribute to different degrees of incident cholelithiasis and that low HDL cholesterol is the most relevant factor in the incidence of cholelithiasis. Therefore, the management of metabolic components, especially HDL cholesterol, may effectively reduce the risk of gallstone formation. Further studies are needed to evaluate whether the management of metabolic components decreases the risk of incident cholelithiasis.

Acknowledgments

We used the National Health Insurance Service–National Sample Cohort database, which was obtained from the National Health Insurance Service. Our findings were not related to the National Health Insurance Service. We would like to thank Editage (http://www.editage.co.kr) for English language editing.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison between participants with and without incident cholelithiasis.