

Differences in the Impact of Obesity and Metabolic Unhealthiness on the Risk of Gallbladder Polyp

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Purpose: Differences in the impact of obesity and metabolic health status on the risk of gallbladder polyp (GBP) remain uncertain. Herein, we aimed to compare the risk of GBP ≥ 5 mm among individuals with different phenotypes based on obesity and metabolic health status.

Materials and Methods: A cohort of 253485 asymptomatic adults who underwent abdominal ultrasonography screening were categorized into the following four groups according to obesity and metabolic health status: 1) metabolically healthy non-obese (MHNO), 2) metabolically unhealthy and non-obese (MUNO), 3) metabolically healthy but obese (MHO), and 4) metabolically unhealthy obese (MUO).

Results: The prevalences of GBP ≥ 5 mm were 2.4%, 3.1%, 3.7%, and 4.0% in the MHNO, MUNO, MHO, and MUO groups, respectively. The multivariable-adjusted odds ratio (OR) values for prevalence of GBP ≥ 5 mm by comparing the MUNO, MHO, and MUO with the MHNO group were 1.11 [95% confidence interval (CI), 1.04–1.19], 1.30 (95% CI, 1.15–1.47), and 1.37 (95% CI, 1.28–1.45), respectively. The risk of GBP ≥ 5 mm in the MHO group was significantly higher than that in the MUNO group, but not significantly different from that in the MUO group.

Conclusion: Obesity and metabolic unhealthiness appear to be independent risk factors for the prevalence of GBP, and the impact of obesity is greater than that of metabolic unhealthiness, suggesting that maintaining both normal weight and metabolic health may help reduce the risk of GBP.

Key Words: Obesity, metabolic abnormalities, gallbladder polyp

INTRODUCTION

Gallbladder polyp (GBP), defined as a protruding lesion in the

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gallbladder mucosa, is usually found incidentally on abdominal ultrasonography (US) and represents one of the most common biliary conditions.¹ GBP is a common clinical finding and is usually a benign and harmless lesion, but its malignant potential holds clinical significance.² Although the reported malignancy rate of GBP is not high (3%–8%), gallbladder cancer (GBC) is a highly lethal malignancy, mainly because the disease is often diagnosed at an advanced stage.^{2,3} In a few cases, GBC may show polyp-like lesions; however, abdominal US, which is commonly used as an initial imaging modality for evaluating gallbladder disease, has low sensitivity for early GBC diagnosis and cannot accurately differentiate neoplastic polyps from non-neoplastic polyps.^{2,4,5} Furthermore, symptoms are nonspecific or asymptomatic in most GBPs and even in GBC cases, highlighting the clinical importance of GBP.² In recent years, the prevalence of GBP has increased in Asian countries,

including Korea.² Thus, identifying modifiable risk factors for GBP is important to prevent further increases in its incidence and subsequent complications.

Obesity is a well-established risk factor for GBC⁶⁻⁹ and has been shown to be associated with the risk of GBP.¹ Several meta-analyses have shown a positive association between increased body mass index (BMI) and the incidences of GBP¹⁰ and GBC.^{6,8} Meanwhile, obesity-related metabolic disorders, such as dyslipidemia and metabolic syndrome, may also affect GBP development.^{2,11,12} Obesity and metabolic unhealthiness frequently coexist but do not always coincide, and the magnitude of metabolic disturbances can vary among individuals with obesity.¹³ Although many individuals with obesity present with one or more metabolic abnormalities, some are metabolically healthy (MH), a subgroup that is reported to be less associated with insulin resistance.¹⁴⁻¹⁶ Conversely, a considerable proportion of non-obese individuals have also been reported with metabolic syndrome.¹⁷ These individuals may have different implications for the risk of GBP. However, to date, the differential roles of obesity and metabolic health status in relation to the risk of GBP have not been adequately assessed. In particular, it is uncertain whether metabolic unhealthiness, aside from obesity, affects the risk of GBP.

Therefore, this study aimed to compare the risk of GBP among individuals with different phenotypes based on obesity and metabolic health status in a large sample of Korean adults. Since differentiating GBP <5 mm diameter from gallstone disease is difficult and most GBPs are not neoplastic,^{4,11} we evaluated GBP risk by considering a clinically significant GBP ≥5 mm.

MATERIALS AND METHODS

Study population

The Kangbuk Samsung Health Study included a cohort of Ko-

rean males and females aged ≥18 years who underwent a comprehensive annual or biennial health examination at one of the Kangbuk Samsung Hospital Total Healthcare Center clinics in Seoul and Suwon, South Korea, as previously described.^{18,19} The study population comprised a subset of Kangbuk Samsung Health Study participants who underwent screening abdominal US between January 2011 and December 2016 (n=419058). In Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. Approximately 80% of the participants were employees of various companies and local government organizations, and their spouses and the remaining participants volunteered to register for the screening program.

To evaluate the effect of obesity and metabolic health status on the risk of GBP, we applied the following exclusion criteria at baseline (Fig. 1): participants having 1) a history of cholecystectomy, 2) incomplete data on BMI and other metabolic indices, and 3) incomplete data on other demographic factors, including smoking status and alcohol consumption. After excluding 165573 participants who met one or more of the exclusion criteria, the analyzed sample included 253485 participants.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB No. KBSMC 2023-02-023). The requirement for informed consent was waived because the study was designed to use anonymized retrospective data routinely collected during the health-screening process.

Measurements and definitions of variables

Demographic characteristics, health-related behaviors, and medical history were obtained through a standardized, self-administered questionnaire, whereas anthropometry, blood pressure (BP), and serum biochemical parameters were measured by trained staff during health examinations.^{18,19} Smoking status was categorized as never, former, or current, and the weekly frequency of moderate or vigorous physical activity was

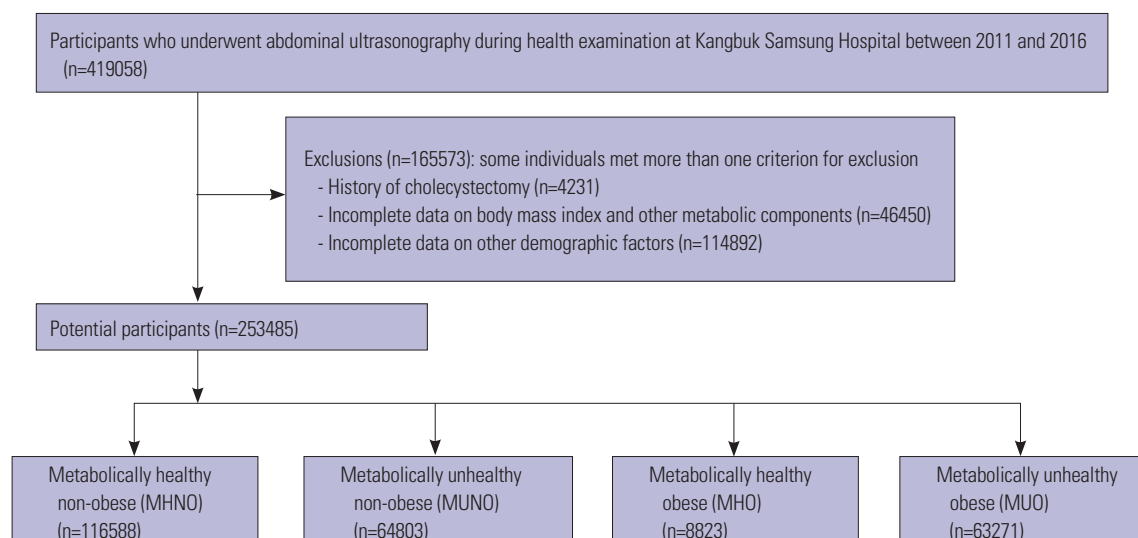


Fig. 1. Flow chart of the study population.

assessed. Physical activity was estimated using a summarized form of the Korean version of the International Physical Activity Questionnaire, which was converted to a metabolic equivalent (MET) score and classified into three categories as follows: inactive, minimally active, and health-enhancing physical activity (HEPA).²⁰ HEPA level was defined as the presence of at least one of the following: physical activity consuming over 1500 MET-minutes per week, including more than three days of vigorous activity, or physical activity consuming over 3000 MET-minutes per week.²⁰

Blood tests were performed after at least 10 hours of fasting and included lipid profiles, liver enzymes, high-sensitivity C-reactive protein, fasting blood glucose (FBG), and insulin levels. The homeostatic model assessment of insulin resistance was calculated as follows: fasting blood insulin (IU/L)×FBG (mg/dL)/405.

Obesity was defined as a BMI ≥ 25 kg/m², which is the proposed cutoff value for obesity diagnosis in Asian populations.²¹ The cutoff values of waist circumference, as per the proposed criteria for the Korean population, to define abdominal obesity were ≥ 90 cm and ≥ 85 cm for male and female, respectively.^{22,23}

Metabolic syndrome was defined as having three or more of the following five metabolic abnormalities used in the National Cholesterol Education Program and Adult Treatment Panel-III (NCEP ATP-III) criteria: abdominal obesity (waist circumference ≥ 90 cm in male and ≥ 85 cm in female, the proposed cutoff values for Asians),²⁴ elevated FBG levels (≥ 100 mg/dL) or use of glucose-lowering medications, elevated BP (≥ 130 mm Hg systolic, ≥ 85 mm Hg diastolic), use of antihypertensive drugs, elevated triglyceride levels (≥ 150 mg/dL) or use of lipid-lowering agents, and reduced high-density lipoprotein cholesterol levels (<40 mg/dL in male and <50 mg/dL in female).²⁵ MH was defined as the absence of any of the five metabolic criteria, whereas metabolically unhealthy (MU) was defined as having one or more of the five metabolic criteria.

The study participants were categorized into four groups according to obesity and metabolic health status as follows: 1) MH non-obese (MHNO) as a reference, 2) MU and non-obese (MUNO), 3) MH but obese (MHO), and 4) MU obese (MUO).

Diagnosis of GBP

After at least 10 hours of fasting, GBP was assessed using abdominal US, which was performed using a 3.5-MHz transducer (LOGIQ 9; General Electric, Madison, WI, USA) by experienced radiologists who were unaware of the study aims and were blinded to the clinical information. According to the standard radiologic criteria, GBP was diagnosed when the lesion was an immobile mucosal lesion protruding into the GB lumen attached to the GB wall without posterior acoustic shadowing.²⁶ For analysis, the endpoint was incident GBP ≥ 5 mm in size.

Statistical analyses

The baseline characteristics of the four groups are presented according to obesity and metabolic health status (MHNO, MUNO, MHO, and MUO). The primary outcome was the prevalence of GBP (≥ 5 mm in size). The baseline characteristics and the prevalence of GBP ≥ 5 mm among the four groups were compared using the chi-square test and one-way analysis of variance for categorical and continuous variables, respectively.

Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for prevalence of GBP ≥ 5 mm in comparison with the corresponding values from the reference exposure groups using multivariate logistic regression analysis. The multivariable model was adjusted for confounders, including age, sex, smoking status (never, former, or current), alcohol consumption (0, <20 , or ≥ 20 g/day), physical activity (inactive, minimally active, or HEPA), education level (<12 or ≥ 12 years), and the presence or absence of hepatitis B virus surface antigen.

All reported *p* values were two-tailed, and *p* < 0.05 was considered statistically significant. All statistical analyses were conducted with SPSS version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Table 1 shows the baseline characteristics according to obesity and metabolic status. At baseline, the average age of the 253485 participants was 38.1 years (standard deviation, 9.3), and the proportion of male participants was 57.6%. The prevalences of MHNO, MUNO, MHO, and MUO were 46.0%, 25.6%, 3.5%, and 25.0%, respectively. The MH group, including MHNO and MHO, tended to be younger than the MU group, whereas the obese groups, including those with MHO and MUO, tended to have more current smokers or individuals with HEPA levels of physical activity than the non-obese groups. The prevalences of GBP ≥ 5 mm in the MHNO, MUNO, MHO, and MUO groups were 2.4%, 3.1%, 3.7%, and 4.0%, respectively.

Table 2 shows the association between obesity, metabolic health status, and the risk of GBP ≥ 5 mm. In univariate analysis, individuals with obesity were associated with an increased risk of GBP ≥ 5 mm. Individuals with metabolic syndrome also had an increased risk of GBP ≥ 5 mm, and the risk increased with an increasing number of metabolic components in a dose-dependent manner. The multivariate analysis also confirmed the positive association of obesity with the risk of GBP. In addition, the positive dose-response associations of increasing number of metabolic components with the risk of GBP ≥ 5 mm were consistently observed even after adjusting for potential confounders.

In multivariate analysis adjusted for age, sex, smoking status, and other confounders, the MUNO (adjusted OR, 1.11; 95% CI, 1.04–1.19), MHO (adjusted OR, 1.30; 95% CI, 1.15–1.47), and MUO (adjusted OR, 1.37; 95% CI, 1.28–1.45) groups ex-

hibited a significantly higher risk of GBP ≥ 5 mm than the MHNO group (the reference), with the highest risk observed in the MUO group.

With the MUNO group as a reference, the risk of GBP ≥ 5 mm significantly increased in the obese group, including the MHO (adjusted OR, 1.17; 95% CI, 1.03–1.32) and MUO groups (ad-

Table 1. Baseline Characteristics According to Obesity and Metabolic Health Status (n=253485)

Characteristics	Overall (n=253485)	Metabolically healthy and obese status			
		MHNO (n=116588)	MUNO (n=64803)	MHO (n=8823)	MUO (n=63271)
Age (yr)	38.1 $\pm$ 9.3	35.5 $\pm$ 7.7	41.3 $\pm$ 10.4	36.5 $\pm$ 7.8	40.0 $\pm$ 9.4
Male sex	57.6	39.1	64.9	78.7	81.3
Current smoker	23.0	14.9	26.3	26.9	34.1
Alcohol intake ≥ 20 g/d	19.1	11.0	22.3	21.0	30.4
HEPA	16.5	15.3	16.8	21.7	17.7
High education level*	81.5	83.6	78.3	85.6	80.3
BMI (kg/m ²)	23.3 $\pm$ 3.4	21.1 $\pm$ 2.0	22.6 $\pm$ 1.8	25.9 $\pm$ 0.8	27.6 $\pm$ 2.3
Obesity [†]	28.4	0.0	0.0	100.0	100.0
Systolic BP (mm Hg)	108.9 $\pm$ 3.1	102.5 $\pm$ 9.8	112.0 $\pm$ 123.5	110.1 $\pm$ 8.8	117.5 $\pm$ 12.4
Diastolic BP (mm Hg)	69.8 $\pm$ 9.9	65.4 $\pm$ 7.4	72.4 $\pm$ 10.4	69.1 $\pm$ 7.2	75.4 $\pm$ 10.0
Glucose (mg/dL)	94.8 $\pm$ 14.7	89.0 $\pm$ 6.1	100.0 $\pm$ 17.3	91.0 $\pm$ 5.5	101.0 $\pm$ 18.9
Total cholesterol (mg/dL)	193.1 $\pm$ 34.2	185.4 $\pm$ 30.0	195.5 $\pm$ 36.2	195.2 $\pm$ 31.3	204.5 $\pm$ 36.0
LDL-C (mg/dL)	119.4 $\pm$ 32.0	109.4 $\pm$ 28.3	123.3 $\pm$ 32.4	125.2 $\pm$ 29.6	132.8 $\pm$ 32.4
HDL-C (mg/dL)	58.5 $\pm$ 15.2	66.1 $\pm$ 13.7	54.1 $\pm$ 14.4	57.4 $\pm$ 11.6	49.3 $\pm$ 11.8
Triglycerides (mg/dL)	115.5 $\pm$ 78.5	73.8 $\pm$ 26.5	132.8 $\pm$ 83.0	90.3 $\pm$ 28.8	161.9 $\pm$ 102.6
ALT (U/L)	23.7 $\pm$ 22.1	17.1 $\pm$ 15.2	23.3 $\pm$ 19.4	25.5 $\pm$ 21.5	36.1 $\pm$ 29.3
GGT (U/L)	30.0 $\pm$ 40.5	19.7 $\pm$ 18.3	36.1 $\pm$ 51.0	31.2 $\pm$ 31.5	50.6 $\pm$ 49.9
hs-CRP (mg/L)	0.1 $\pm$ 0.3	0.1 $\pm$ 0.3	0.1 $\pm$ 0.4	0.1 $\pm$ 0.4	0.2 $\pm$ 0.4
HOMA-IR	1.5 (0.8–1.8)	1.0 (0.6–1.3)	1.5 (0.9–1.9)	1.3 (0.8–1.6)	2.3 (1.3–2.7)
HBsAg	3.2	3.1	3.0	3.7	3.4
Gallbladder polyp ≥ 5 mm	3.0	2.4	3.1	3.7	4.0

ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; GGT, gamma-glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein-cholesterol; HEPA, health-enhancing physically active; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein-cholesterol; MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy and non-obese; MHO, metabolically healthy but obese; MUO, metabolically unhealthy obese.

Data are expressed as a mean $\pm$ standard deviation, median (interquartile range), or percentage.

* $\geq$ College graduate; [†]Body mass index ≥ 25 kg/m².

Table 2. Risk of Gallbladder Polyp ≥ 5 mm by Obesity and Metabolic Health Status among 253485 Participants

Risk factors	Crude OR	95% CI	p value	Multivariable-adjusted OR	95% CI	p value
BMI	1.08	1.07–1.09	<0.001	1.05	1.42–1.77	<0.001
Obesity (BMI ≥ 25 kg/m ²)	1.53	1.46–1.60	<0.001	1.29	1.23–1.36	<0.001
Metabolic syndrome*	1.42	1.33–1.51	<0.001	1.08	1.00–1.16	0.043
Number of metabolic factors [†]						
0	1 (reference)	1 (reference)		1 (reference)	1 (reference)	
1	1.31	1.23–1.38	<0.001	1.08	1.01–1.15	0.023
2	1.49	1.39–1.59	<0.001	1.12	1.04–1.21	0.004
≥ 3	1.65	1.54–1.76	<0.001	1.16	1.06–1.27	0.001
Metabolically healthy and obese status [‡]						
MHNO	1 (reference)	1 (reference)		1 (reference)	1 (reference)	
MUNO	1.29	1.22–1.37	<0.001	1.11	1.04–1.19	0.001
MHO	1.58	1.41–1.78	<0.001	1.30	1.15–1.47	<0.001
MUO	1.70	1.61–1.80	<0.001	1.37	1.28–1.45	<0.001

BMI, body mass index; CI, confidence interval; HBsAg, hepatitis B surface antigen; MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy and non-obese; MHO, metabolically healthy but obese; MUO, metabolically unhealthy obese; OR, odds ratio.

The multivariable-adjusted model was adjusted for confounders of age, sex, smoking status, alcohol intake, physical activity, educational level, presence or absence of HBsAg, and obesity or metabolic syndrome.

*Obesity was excluded, and metabolic syndrome was added for the analysis; [†]Obesity was excluded, and number of metabolic factors was added for the analysis; [‡]Obesity was excluded, and metabolically healthy and obese status was added for the analysis.

Table 3. Multivariate Analysis for Gallbladder Polyp ≥ 5 mm According to the Different Reference Groups

Metabolically healthy and obese status	Multivariable-adjusted OR (95% CI)	<i>p</i> value	Multivariable-adjusted OR (95% CI)	<i>p</i> value	Multivariable-adjusted OR (95% CI)	<i>p</i> value
MHNO	1 (reference)		0.90 (0.84–0.96)	0.001	0.77 (0.68–0.87)	<0.001
MUNO	1.11 (1.04–1.19)	0.001	1 (reference)		0.86 (0.76–0.97)	0.015
MHO	1.30 (1.15–1.47)	<0.001	1.17 (1.03–1.32)	0.015	1 (reference)	
MUO	1.37 (1.28–1.45)	<0.001	1.23 (1.15–1.31)	<0.001	1.05 (0.93–1.19)	0.442

CI, confidence interval; MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy and non-obese; MHO, metabolically healthy but obese; MUO, metabolically unhealthy obese; OR, odds ratio.

The multivariable-adjusted model was adjusted for confounders of age, sex, smoking status, alcohol intake, physical activity, educational level, and presence or absence of hepatitis B virus surface antigen.

justed OR, 1.23; 95% CI, 1.15–1.31), while the risk decreased significantly in the MHNO group (adjusted OR, 0.90; 95% CI, 0.84–0.96) (Table 3). In contrast, with the MHO group as a reference, the risk of GBP ≥ 5 mm significantly decreased in the non-obese group, including the MUNO group (adjusted OR, 0.86; 95% CI, 0.76–0.97), while the risk of the MUO group (adjusted OR, 1.05; 95% CI, 0.93–1.19) was not significantly different from that of the MHO group.

DISCUSSION

In this study, we compared the risk of GBP according to different phenotypes of obesity and metabolic health status in a large-scale cohort study of young and middle-aged Korean adults. Compared to the MHNO group, the risk of GBP was significantly increased in individuals with obesity, metabolic unhealthiness, or both (MUNO, MHO, and MUO groups), and the MUO group had the highest risk of GBP. In particular, comparing the effects of obesity and metabolic unhealthiness on the risk of GBP, we noted that the MHO group had a significantly increased risk of GBP, compared to that in the MUNO group, with no significant difference from the MUO group, which had the highest risk of GBP. Meanwhile, the MUNO group had a significantly decreased risk of GBP, compared to the MUO group. Our results indicate that metabolic unhealthiness and obesity are independent risk factors for the prevalence of GBP and further suggest that obesity may have a greater impact on the risk of GBP than metabolic unhealthiness.

The risk factors for GBP have not been established, despite their clinical importance.²⁷ To date, there have been many studies on the risk factors of GBP, but the results have been inconsistent. Recent studies have reported that metabolic syndrome is associated with an increased risk of GBP.^{12,28} A study by Lim, et al.¹² including 1523 healthy screening subjects showed a 2.5-fold increased risk of GBP in individuals with metabolic syndrome. A cohort study comprising 23827 healthy participants also reported that metabolic syndrome was a significant risk factor for GBP (adjusted OR, 1.414; 95% CI, 1.046–1.912), suggesting that the prevalence of GBP has increased with the recent increase in metabolic syndrome.²⁸ In agreement

with these findings, our large-scale cohort study confirmed that metabolic syndrome independently increases the risk of GBP ≥ 5 mm. Our study also showed that the risk of GBP increased linearly with an increasing number of metabolic components, displaying a clear dose-response relationship.

Another possible contributing factor to the development of GBP is obesity, which has long been a major public health problem worldwide and is increasing in prevalence.²⁸ However, despite the established relationship between obesity and increased BMI with increased incidence and mortality of GBC,^{6–8,29} there have been conflicting results regarding the association between obesity or increased BMI and GBP.^{1,2,4,9,10,12,27,28,30–32} Some studies have shown a significantly increased risk of GBP in obese or overweight individuals,^{1,4,9,28} whereas other studies have suggested weak or null associations.^{2,12,27,30–32} Although the reason for the inconsistent results regarding the association between obesity or elevated BMI and GBP is uncertain, the limited sample sizes of the previous studies may have played a role in this inconsistency. Additionally, unmeasured confounding conditions linked to obesity could affect the development of GBP and contribute to the discrepancy among findings. Indeed, metabolic disorders associated with obesity have been implicated in the development of GBP, with the extent of metabolic abnormalities varying among individuals with obesity. However, most studies examining the risk of GBP have not separated the effects of obesity and metabolic abnormalities, both of which are likely to contribute to the development of GBP. Accumulating evidence suggests that obesity can be categorized into distinct phenotypes based on the presence or absence of metabolic disorders, such as hypertension, diabetes, and dyslipidemia.^{33–35} These phenotypes are known to be clinically relevant, and individuals with different obesity and metabolic health statuses are likely to involve different risks for developing GBP. In the present study, obesity was identified as an independent and significant risk factor for a higher prevalence of GBP regardless of metabolic health status. The presence of metabolic unhealthiness also independently increased the risk of GBP, particularly in the absence of obesity. However, this influence of metabolic unhealthiness may not surpass the impact of obesity on GBP risk, suggesting that obesity potentially has a greater effect on the risk of GBP than metabolic unhealth-

iness. Although obesity and metabolic abnormalities are highly correlated and may have confounded the results, our findings revealed that both obesity and metabolic unhealthiness independently contribute to the prevalence of GBP, with obesity having a greater effect on GBP risk. Unfortunately, the exact biological mechanisms underlying these findings are not fully understood. Further mechanistic studies are required to thoroughly elucidate the exact pathogenesis of GBP and to assess the relative magnitude of the impact that GBP risk factors exert.

To our knowledge, this is the first and largest cohort study to compare the risk of GBP ≥ 5 mm among MHNO, MHO, MUNO, and MUO groups using high-quality, standardized clinical and laboratory indices and strict definitions of metabolic health status. Most importantly, our study is the first to differentiate the role of metabolic unhealthiness from obesity and to evaluate their individual and combined impacts on the prevalence of GBP, highlighting the contribution of both isolated and combined phenotypes.

Nevertheless, this study had some limitations. First, the study was hospital-based rather than population-based, and our findings from mostly young, middle-aged, and relatively healthy Koreans may not be generalizable to older groups or other ethnicities. However, previous epidemiologic studies have demonstrated that the highest prevalence of GBP is in the third to fifth decades of life.^{1,36} The reason for the high prevalence rate of GBP in middle-aged subjects may be that most subjects who had undergone cholecystectomy were in their 50 s and 60 s or older.² Hence, our cohort of young and middle-aged patients may be more suited to assessing the risk factors for GBP. Second, the histological classification of GBP was not considered. Predictors of GBP based on pathological classification are more accurate and reliable because differences exist in the formation and pathological processes between cholesterol and non-cholesterol GBP.³⁷ Although histological confirmation of GBP could not be obtained, our study focused only on GBP ≥ 5 mm, excluding GBP less than 5 mm in size, which may be difficult to distinguish from gallstones or is unlikely to be a neoplastic polyp in most cases. Data regarding GBP ≥ 5 mm in size may have greater clinical significance. Third, interobserver variations in the sonographic diagnoses of GBP were not assessed. However, all sonographic examinations were performed by experienced board-certified radiologists, and the same classification system, with a clear definition of GBP, was applied to all participants. Finally, this cross-sectional design did not allow the establishment of causal or temporal relationships. The presence and severity of metabolic disorders and body weight may change over time; however, most patients were assessed only once at the initial visit. Therefore, the effect of dynamic changes in metabolic health status and BMI on the risk of GBP could not be evaluated in this study. Nonetheless, the substantial sample size of this study may partially mitigate the potential influence of disease fluctuation bias. Despite these limitations, our data provide a better understanding of the distinct roles of obesity

and metabolic unhealthiness in GBP risk.

In conclusion, both obesity and metabolic unhealthiness appear to be independent risk factors for the prevalence of GBP, irrespective of individual effects on the risk, although the impact of obesity on the risk of GBP may be greater than that of metabolic unhealthiness. Given the association between obesity, metabolic unhealthiness, and GBP, patients with GBP may need to consider their metabolic health status, particularly BMI. Further large prospective studies are warranted to elucidate whether improving obesity and metabolic health status contributes to GBP regression or reduction in GBP development and its consequences.

AUTHOR CONTRIBUTIONS

Conceptualization: Nam Hee Kim and Ji Hun Kang. **Data curation:** Nam Hee Kim and Hong Joo Kim. **Formal analysis:** Nam Hee Kim and Ji Hun Kang. **Investigation:** all authors. **Methodology:** Nam Hee Kim and Ji Hun Kang. **Project administration:** all authors. **Resources:** Nam Hee Kim and Hong Joo Kim. **Software:** Nam Hee Kim and Ji Hun Kang. **Supervision:** Ji Hun Kang and Hong Joo Kim. **Validation:** all authors. **Visualization:** Nam Hee Kim and Ji Hun Kang. **Writing—original draft:** Nam Hee Kim. **Writing—review & editing:** all authors. **Approval of final manuscript:** all authors.

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