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Association between cholelithiasis and sialolithiasis

Two longitudinal follow-up studies

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Abstract

This study aimed to evaluate the association between cholelithiasis and sialolithiasis using a national sample cohort in Korea.

The Korean National Health Insurance Service-National Sample Cohort (patients ≥20 years old) was collected from 2002 to 2013. In study I, we extracted cholelithiasis patients (n = 21,170) and 1:4 matched control I subjects (n = 84,680) and analyzed the occurrence of sialolithiasis. In study II, we extracted sialolithiasis patients (n = 761) and 1:4 matched control II subjects (n = 3044) and analyzed the occurrence of cholelithiasis. Hazard ratios (HRs) were determined using the stratified Cox proportional hazard model.

The HR for sialolithiasis was 1.49 (95% CI = 0.88–2.52) in the cholelithiasis group (P = .14), and the HR for cholelithiasis was 1.18 (95% CI = 0.53–2.59) in the sialolithiasis group (P = .69).

We did not find an association between cholelithiasis and sialolithiasis.

Abbreviations: CIs = confidence intervals, HIRA = Health Insurance Review and Assessment, HRs = hazard ratios.

Keywords: cholelithiasis, cohort studies, epidemiology, gallstone, nested case–control studies, salivary gland calculi, sialolith, sialolithiasis

1. Introduction

Cholelithiasis is the process of gallstone formation. Its prevalence is 5.5% in men and 8.6% in women in the USA[1] and 4.2% to 5.3% in Korea.[2,3] Gallstones are categorized as cholesterol stones, pigment stones, or mixed stones based on their composition. [4] The prevalence rates of stone types in Korea are 58.1% for cholesterol, 25.2% for black pigment, and 12.1% for brown pigment stones.[5] Age, ethnicity, female gender, obesity, diabetes mellitus, and Western diet are considered risk factors for cholelithiasis.[6]

Sialolithiasis is characterized by stone formation in the salivary gland. The incidence of sialolithiasis is not well documented but is 1.2% according to autopsy reports.[7] The annual incidences of sialadenitis and sialolithiasis are 2.7 to 3.2/100,000 in England.[8] We could not find the reported incidence of sialolithiasis in Korea. The etiologic factors for sialolithiasis are not evident, but tobacco smoking has been suggested as a risk factor.[9]

A previous study reported a positive association between sialolithiasis and cholelithiasis. [10] We aimed to determine whether sialolithiasis is related to cholelithiasis, despite the difference in the etiology and risk factors of the 2 diseases. To answer this question, we reviewed the PubMed and EMBASE databases for studies using the keywords "([cholelithiasis] OR [gallstone]) AND ([salivary gland calculi] OR [sialolithiasis] OR [sialolith])"; the search was limited to English-language, human-based studies published until December 2017. Two studies were found. One study reported a positive association, [10], while the other did not report an association.[11]

The purpose of this study was to evaluate the association between cholelithiasis and sialolithiasis using a national sample cohort of the Korean population. To analyze the direction of the effect between cholelithiasis and sialolithiasis, we designed 2 longitudinal follow-up studies. In 1 study, we extracted cholelithiasis patients and 1:4 matched control subjects and analyzed the occurrence of sialolithiasis; in the other study, we extracted sialolithiasis patients and 1:4 matched control subjects and analyzed the occurrence of cholelithiasis.

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2. Materials and methods

2.1. Study population and data collection

The ethics committee of Hallym University (2014-I148) approved the use of these data. The study was exempted from the need for written informed consent by the Institutional Review Board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service-National Sample Cohort (HIRA-NSC). A detailed description of these data was provided in our previous studies[12,13]. The Korean National Health Insurance Service (NHIS) selects samples directly from a database that includes the entire population to prevent non-sampling errors. Approximately 2% of the samples (representing 1 million individuals) were selected from the entire Korean population (50 million individuals). The selected data can be classified in 1476 ways (based on age [18 categories], sex [2 categories], and income level [41 categories]), and randomized stratified systematic sampling methods involving proportional allocation are used to ensure representation of the entire population. The appropriateness of the sample after data selection was verified by a prior study[18]. Details regarding the methods used to perform these procedures are provided by the National Health Insurance Sharing Service[19]. This cohort database included:

(i) personal information,
(ii) health insurance claim codes (procedures and prescriptions),
(iii) diagnostic codes determined using the International Classification of Disease-10 (ICD-10),
(iv) death records from the Korean National Statistical Office (which uses the Korean Standard Classification of Diseases),
(v) socioeconomic data (regarding residence and income), and
(vi) medical examination data for each participant from 2002 to 2013.

Because a 13-digit resident registration number is used to identify all Korean citizens from birth to death, exact population statistics can be determined using this database. Enrollment in the NHIS is mandatory for all Koreans. All Korean hospitals and clinics use this 13-digit number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from 1 location to another. Moreover, without exception, all medical treatments in Korea can be tracked using the HIRA system. In Korea, submission of a notice of death to an administrative entity is legally required before a funeral can be held. Cause (s) of death and date of death are recorded by medical doctors on a death certificate.

2.2. Participant selection

Of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were diagnosed with cholelithiasis (ICD-10: K80). Among these participants, those who visited clinics for this condition ≥2 times were selected (n = 21,501).

Sialolithiasis was diagnosed based on the ICD-10 code K115. Among the diagnosed cases, participants who visited clinics for this condition ≥ 2 times were selected. During the period from 2002 through 2013, 973 cases of sialolithiasis were selected.

2.3. Study I

The cholelithiasis group was matched 1:4 with participants (control group I) who were not diagnosed with cholelithiasis from 2002 through 2013. The control group was selected from the total population (n = 1,104,190). Matching was performed for age group, sex, income group, region of residence, and past medical history (hypertension, diabetes, and dyslipidemia). To prevent selection bias when selecting the matched participants, the control I participants were first sorted using a random number order and were then selected from top to bottom. We set the index date as the date of diagnosis of cholelithiasis. It was assumed that the matched control participants were involved at the same time as the cholelithiasis participants (index date). Therefore, control I patients who died before the index date were excluded. Participants with a history of sialolithiasis before the index date were excluded from both the cholelithiasis and control groups. In the cholelithiasis group, 14 participants were excluded. The cholelithiasis patients for whom we could not identify sufficient matching participants were excluded (n = 93). We also excluded participants younger than 20 years of age (n = 224). Finally, 1:4 matching resulted in the inclusion of 21,170 cholelithiasis patients and 84,680 control I participants (Fig. 1A). The participants were

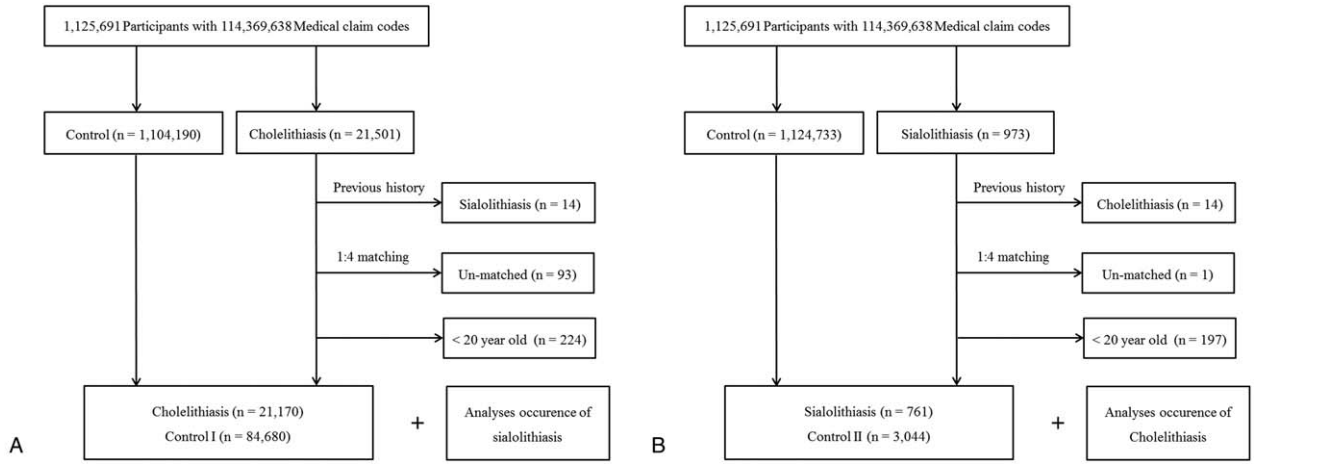

Figure 1. A schematic illustration of the participant selection process used in the present study. (A) Of a total of 1,125,691 participants, 21,170 cholelithiasis patients were matched with 84,680 control I participants for age group, sex, income group, region of residence, and past medical history. (B) Of a total of 1,125,691 participants, 761 sialolithiasis patients were matched with 3044 control II participants for age group, sex, income group, region of residence, and past medical history.

followed up to event (occurrence of sialolithiasis), death date, or the last follow-up date (December 31, 2013).

2.4. Study II

The sialolithiasis patients were matched 1:4 with participants (control group II) who were not diagnosed with sialolithiasis from 2002 through 2013. The control group was selected from the total population (n = 1,124,733). Matching was performed for age group, sex, income group, region of residence, and past medical histories (hypertension, diabetes, and dyslipidemia). To prevent selection bias while selecting the matched participants, the control II participants were sorted using another random number order and were then selected from top to bottom. We set the index date as the date of diagnosis of sialolithiasis. It was assumed that the matched control participants were involved at the same time as each of the sialolithiasis patients (index date). Therefore, the control II patients who died before the index date were excluded. The participants with a history of cholelithiasis before the index date were excluded from both the sialolithiasis and control groups. In the sialolithiasis group, 14 participants were excluded. Sialolithiasis patients for whom we could not identify sufficient matching participants were excluded (n = 1). Finally, 1:4 matching resulted in the inclusion of 761 sialolithiasis patients and 3044 control participants (Fig. 1B). The participants were followed up to event (occurrence of cholelithiasis), death date, or the last follow-up date (December 31, 2013).

2.5. Variables

The age groups were classified using 5-year intervals: 20 to 24, 25 to 29, 30 to 34, . . . , and 85+ years old. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (1 health assistance class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 11 classes (class 1 [lowest income]-11 [highest income]). The region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The past medical histories of the participants were evaluated using ICD-10 codes. For accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were verified if the participants were treated ≥2 times.

2.6. Statistical analyses

The chi-square test was used to compare the rates of the general characteristics between the cholelithiasis and control I groups and between the sialolithiasis and control II groups.

In study I, the stratified Cox proportional hazard model was used to analyze the hazard ratio (HR) of cholelithiasis (the independent variable) with sialolithiasis (the dependent variable). Additionally, we analyzed HRs for the limited period of 6 months after the occurrence of cholelithiasis.

In study II, another Cox-proportional hazard model was used to analyze the HR of sialolithiasis (the independent variable) with cholelithiasis (the dependent variable). Furthermore, we analyzed HRs for the limited period of 6 months after the occurrence of sialolithiasis.

In these analyses, age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia were stratified, and 95% confidence intervals (CIs) were calculated. A Kaplan–Meier (KM) curve was presented. In this study, we censored the participant if they had sialolithiasis (study I), cholelithiasis (study II), or died during follow-up. The last follow-up was December 31, 2013.

For the subgroup analyses, we divided the participants according to age and sex in study I (20–39 years, 40–59 years, and 60+ years; men and women). We did not perform subgroup analyses in study II due to the relatively small number of participants.

Two-tailed analyses were conducted, and *P* values less than .05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

3. Results

3.1. Study I

The rate of sialolithiasis was not higher in the cholelithiasis group (0.06% [10/21,151]) than in the control I group (0.09% [51/84,680], $P = .14$, Table 1). The general characteristics (age, sex, income, region of residence, and hypertension, diabetes, and dyslipidemia history) of the participants were the same due to the matching procedure ($P = 1.000$). The mean time from index date to event (sialolithiasis) was 51.3 months (standard deviation [SD] = 36.8) in the cholelithiasis group and 50.0 (SD = 36.4) in the control I group.

The HRs of sialolithiasis were 1.49 (95% CI = 0.88–2.52) in the cholelithiasis group for the total period ($P = .139$, Table 2). The KM curve showed similar results ($P = .135$, Fig. 2A). Additionally, the HRs of sialolithiasis were 1.45 (95% CI = 0.82–2.58) for the limited period of 6 months after the occurrence of cholelithiasis ($P = .20$). In the subgroup analyses performed according to age and sex, the HRs of sialolithiasis did not reach statistical significance (each $P > .05$, Table 3).

3.2. Study II

The rate of cholelithiasis was not higher in the sialolithiasis group (1.05% [8/761]) than in the control II group (0.88% [27/3044], Table 1). The general characteristics (age; sex; income; region of residence; and hypertension, diabetes, and dyslipidemia histories) of the participants were the same due to the matching procedure. The mean time from index date to event (cholelithiasis) was 40.8 months (SD = 31.1) for the sialolithiasis group and 55.6 (SD = 33.8) for the control II group.

The HRs of cholelithiasis were 1.18 (95% CI = 0.53–2.59) for the cholelithiasis group during the total period ($P = .69$, Table 4). The KM curve showed similar results ($P = .67$, Fig. 2B). Furthermore, the HRs of cholelithiasis were 1.11 (95% CI = 0.48–2.57) during the limited period of 6 months after the occurrence of sialolithiasis ($P = .20$).

4. Discussion

We designed 2 studies to clearly analyze the direction of the effect between cholelithiasis and sialolithiasis. In study I, we analyzed the occurrence of sialolithiasis after cholelithiasis; in study II, we analyzed the occurrence of cholelithiasis after sialolithiasis. The relationship between cholelithiasis and sialolithiasis was not

Table 1

General Characteristics of Participants.

Characteristic	Study I			Study II		
	Cholelithiasis (n, %)	Control I (n, %)	*P* value	Sialolithiasis (n, %)	Control II (n, %)	*P* value
Age, yr			1.00			1.00
20–24	292 (1.4)	1168 (1.4)		76 (10.0)	304 (10.0)	
25–29	700 (3.3)	2800 (3.3)		102 (13.4)	408 (13.4)	
30–34	1187 (5.6)	4748 (5.6)		72 (9.5)	288 (9.5)	
35–39	1553 (7.3)	6212 (7.3)		89 (11.7)	356 (11.7)	
40–44	1927 (9.1)	7708 (9.1)		83 (10.9)	332 (10.9)	
45–49	2145 (10.1)	8580 (10.1)		79 (10.4)	316 (10.4)	
50–54	2454 (11.6)	9816 (11.6)		71 (9.3)	284 (9.3)	
55–59	2247 (10.6)	8988 (10.6)		60 (7.9)	240 (7.9)	
60–64	2281 (10.8)	9124 (10.8)		42 (5.5)	168 (5.5)	
65–69	2067 (9.8)	8268 (9.8)		36 (4.7)	144 (4.7)	
70–74	1853 (8.8)	7412 (8.8)		31 (4.1)	124 (4.1)	
75–79	1294 (6.1)	5176 (6.1)		9 (1.2)	36 (1.2)	
80–84	770 (3.6)	3080 (3.6)		9 (1.2)	36 (1.2)	
85+	400 (1.9)	1600 (1.9)		2 (0.3)	8 (0.3)	
Sex			1.00			1.00
Male	10,325 (48.8)	41,300 (48.8)		357 (46.9)	1,428 (46.9)	
Female	10,845 (51.2)	43,380 (51.2)		404 (53.1)	1,616 (53.1)	
Income			1.00			1.00
1 (lowest)	639 (3.0)	2556 (3.0)		5 (0.7)	20 (0.7)	
2	1500 (7.1)	6000 (7.1)		40 (5.3)	160 (5.3)	
3	1223 (5.8)	4892 (5.8)		49 (6.4)	196 (6.4)	
4	1287 (6.1)	5148 (6.1)		53 (7.0)	212 (7.0)	
5	1491 (7.0)	5964 (7.0)		64 (8.4)	256 (8.4)	
6	1658 (7.8)	6632 (7.8)		59 (7.8)	236 (7.8)	
7	1883 (8.9)	7532 (8.9)		85 (11.2)	340 (11.2)	
8	2170 (10.3)	8680 (10.3)		76 (10.0)	304 (10.0)	
9	2543 (12.0)	10,172 (12.0)		90 (11.8)	360 (11.8)	
10	3038 (14.4)	12,152 (14.4)		116 (15.2)	464 (15.2)	
11 (highest)	3738 (17.7)	14,952 (17.7)		124 (16.3)	496 (16.3)	
Region of residence			1.00			1.00
Urban	9511 (44.9)	38,044 (44.9)		361 (47.4)	1,444 (47.4)	
Rural	11,659 (55.1)	46,636 (55.1)		400 (52.6)	1,600 (52.6)	
Hypertension	9347 (44.2)	37,388 (44.2)	1.00	205 (26.9)	820 (26.9)	1.00
Diabetes mellitus	5582 (26.4)	22,328 (26.4)	1.00	99 (13.0)	396 (13.0)	1.00
Dyslipidemia	6887 (32.5)	27,548 (32.5)	1.00	181 (23.8)	724 (23.8)	1.00
Sialolithiasis	19 (0.06)	51 (0.09)	.14	761 (100.0)	0 (0.0)	<.001*
Cholelithiasis	21,170 (100.0)	0 (0.0)	<.001*	8 (1.05)	27 (0.88)	.67

* Chi-square test; significance at $P < .05$.

statistically significant in either study I or study II. In addition, we did not find significant differences in the subgroup analyses. A previous study reported the OR of cholelithiasis as 2.19 (95% CI = 1.62–2.98) in 745 sialolithiasis and 3725 control group participants, [10] while another study reported a cholelithiasis incidence of 4% in sialolithiasis patients compared to 8.2% in the general population.[11]

Table 2

Hazard ratios (95% confidence intervals) for cholelithiasis with sialolithiasis in study I.

Characteristic	Sialolithiasis	
	HR†	*P* value
Total period starting just after the occurrence of cholelithiasis		
Cholelithiasis	1.49 (0.88–2.52)	.14
Control I	1.00	
6 months after the occurrence of cholelithiasis		
Cholelithiasis	1.45 (0.82–2.58)	.20
Control I	1.00	

*Stratified Cox proportional hazard regression model; significance at $P < .05$.

† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

Although both cholelithiasis and sialolithiasis are types of stones, their etiologies are different. Gallstones are crystalline deposits in the gallbladder, [4] most of which are categorized as cholesterol (37%–86%), pigment (2%–27%), calcium (1%–17%), or mixed (4%–16%). [14,15] Imbalances between pronucleating factors and antinucleating factors in the bile result in cholelithiasis.[4] Excessive bile cholesterol, low bile salt levels, decreased gallbladder motility, and phosphatidylcholine can cause gallstones.[16] Aging, female sex, ethnicity, estrogen treatment, obesity, Western diet, low physical activity, liver cirrhosis, diabetes mellitus, and dyslipidemia are known risk factors for cholelithiasis.[6] Alcohol and smoking are controversial as risk factors for cholelithiasis.[6] Sialolithiasis is defined as calcified concretions in the salivary glands.[17] Most sialolithiasis stones contain calcium phosphates (hydroxyapatite or carbonate apatite), although some stones have organic components.[18,19]

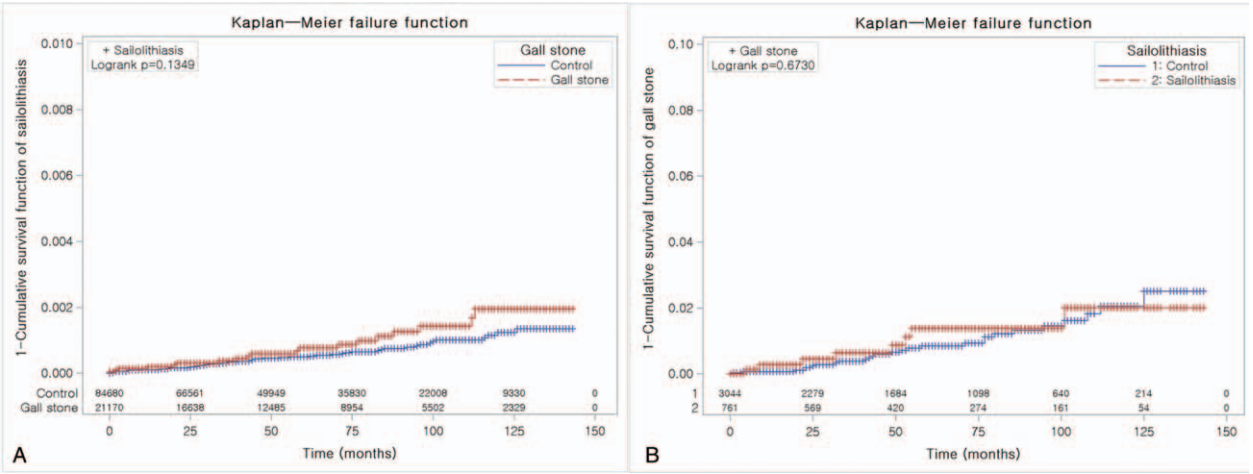

Figure 2. Kaplan–Meier curves for sialolithiasis (event) in the cholelithiasis patients and the control I group (study I) (A) and for cholelithiasis (event) in the sialolithiasis patients and the control II group (study II) (B).

Secreted microcalculi from the salivary gland, food debris, and decreased saliva flow can cause sialolithiasis.[11] Reduced concentrations of the crystallization inhibitors phytate, magnesium and citrate have been observed in patients with salivary gland stones.[20] Smoking is suggested as a risk factor for sialolithiasis because it decreases salivary amylase levels, leads to inflammation, and decreases the antimicrobial potency of saliva.[21] Therefore, we propose that these conditions are not similar, even though the calcium composition of the stones and the relevance of smoking history might suggest the possibility of a common pathophysiology.

The advantages of this study are similar to those of our previous studies in that the study used the national sample cohort.[22–24] We used a very large group representative of the nationwide population. Because NHIS data include all citizens of the nation without exception, none of the participants were missing during the follow-up periods. The control groups were randomly selected by matching for age, sex, income, region of residence, and past medical history to avoid confounding effects. Furthermore, an adjusted hazard model was used to minimize the confounders. We designed different studies to analyze the direction of the effect. Because of the possibility of overdetection, we performed additional analyses of events in the limited period of 6 months after index date in studies I and II. These results were consistent with the results for the entire period after the index date.

This study has several limitations. Despite the large number of participants (~1 million), few of the participants (n = 761) were diagnosed with sialolithiasis. Although we do not have data for sialolithiasis in Korea, the number of patients was similar to that of a report for Taiwan (n = 745) involving ~1 million participants, and this result was within the known incidence range of 1/10,000 to 1/30,000.[9] Both sialolithiasis and cholelithiasis can be asymptomatic, and our study did not include individuals who did not visit a hospital. Therefore, our study might underestimate the incidence and association between sialolithiasis and cholelithiasis. The statistical results found in our study do not deny that sialolithiasis and cholelithiasis are not associated. We only report that we did not find a statistically

Table 3

Subgroup analysis of hazard ratios (95% confidence intervals) for cholelithiasis with sialolithiasis according to age and sex in study I for the total period.

	Sialolithiasis	
Characteristic	**HR†**	***P* value**
Age <40 years (n = 18,660)		
Cholelithiasis	1.33 (0.36–4.93)	.67
Control I	1.00	
Age 40–59 years (n = 43,865)		
Cholelithiasis	1.50 (0.70–3.22)	.30
Control I	1.00	
Age ≥60 years (n = 43,325)		
Cholelithiasis	1.55 (0.65–3.72)	.32
Control I	1.00	
Men (n = 51,625)		
Cholelithiasis	1.63 (0.81–3.28)	.17
Control I	1.00	
Women (n = 54,775)		
Cholelithiasis	1.33 (0.60–2.97)	.48
Control I	1.00	

*Stratified Cox proportional hazard regression model; significance at $P < .05$.
† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

Table 4

Hazard ratios (95% confidence intervals) for sialolithiasis with cholelithiasis in study II.

	Cholelithiasis	
Characteristics	**HR†**	***P* value**
Total period after the occurrence of sialolithiasis		
Sialolithiasis	1.18 (0.53–2.59)	.69
Control II	1.00	
6 months after the occurrence of sialolithiasis		
Sialolithiasis	1.11 (0.48–2.57)	.81
Control II	1.00	

*Stratified Cox proportional hazard regression model; significance at $P < .05$.
† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

significant association based on a 95% CI. The results should be interpreted as indicating that we did not find statistical significance despite the high statistical power of our study resulting from the large number of participants. Some possible confounders, such as smoking, obesity, and medication history, might affect these associations.

We did not find any evidence regarding an association between cholelithiasis and sialolithiasis.

Author contributions

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