

Brief Communication



COVID-19 and Long-term Risk of Ischemic Heart Disease in Asthma

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ABSTRACT

Despite the importance of comorbid ischemic heart disease (IHD) in the prognosis of asthma, the long-term impact of coronavirus disease 2019 (COVID-19) on IHD in adults with asthma remains unclear. This study investigated the long-term effects of COVID-19 on the risk of IHD in individuals with asthma, particularly regarding COVID-19 severity. Using the Korean National Health Insurance Service claims database, we identified individuals with asthma who had recovered from COVID-19 between October 8, 2020, and December 31, 2021 (n = 8,011) and 1:1 propensity score-matched controls (n = 8,011). The incidence and risk of IHD were compared between the two groups. Overall, during a median follow-up of 95 days (interquartile range, 34–213 days; range, 1–448 days), which includes a median of 14 lag days, the COVID-19 cohort did not show a higher risk of IHD (hazard ratio [HR], 2.11; 95% confidence interval [CI], 0.99–4.48) compared to matched controls. However, when the severity of COVID-19 was considered, the severe COVID-19 cohort exhibited a higher risk of IHD (HR, 4.89; 95% CI, 1.86–12.84) than matched controls; in contrast, the non-severe COVID-19 cohort showed no significantly increased risk of IHD (HR, 1.64; 95% CI, 0.73–3.70). Severe COVID-19 is associated with an increased long-term risk of IHD in adults with asthma, emphasizing the importance of cardiovascular events monitoring to improve asthma treatment outcomes in the era of COVID-19.

Keywords: Asthma; COVID-19; severity; ischemic heart disease; epidemiology; risk

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There are no financial or other issues that might lead to conflict of interest.

INTRODUCTION

Ischemic heart disease (IHD) is a leading cause of death in asthmatics.^{1,2} Previous studies have established an increased risk of cardiovascular disease in asthmatics compared to those without asthma.³⁻⁵ Although the exact mechanism remains unclear, chronic activation of proinflammatory cytokines in asthma has been suggested to contribute to the development of IHD.⁶

The risk of IHD can be substantially increased during the acute phase of coronavirus disease 2019 (COVID-19) due to the systemic inflammatory response caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.⁷⁻⁹ This increased risk seems to persist even after the resolution of the infection, especially in severe cases.¹⁰ Although the impacts of COVID-19 on cardiovascular disease are well established,^{8,11} data on the long-term risk of IHD in patients with asthma, particularly concerning COVID-19 severity, are lacking.

Therefore, this study aimed to assess the long-term effects of COVID-19 on the risk of IHD in asthmatics, particularly regarding COVID-19 severity, using a nationwide cohort dataset.

MATERIALS AND METHODS

Data source

This retrospective cohort study utilized the Korean National Health Information database, encompassing health data for the entire Korean population (approximately 52 million).^{12,13} Managed by the National Health Insurance Service (NHIS), this dataset includes International Classification of Disease, Tenth Revision (ICD-10) disease diagnoses, demographics, socioeconomic factors, healthcare utilization, personal health-related habits (smoking status, alcohol consumption, daily physical activity, etc.), medical treatments, and mortality data provided by Statistics Korea.

To facilitate COVID-19 research, the Korean government provided the NHIS SARS-CoV-2 database (NHIS-2022-1-623, n = 8,463,712), which comprises the medical data of all individuals tested for SARS-CoV-2 during the pandemic.¹⁴⁻¹⁷ This database included 561,009 subjects diagnosed with COVID-19 and 7,902,703 without COVID-19 diagnosis, from October 8, 2020, to December 31, 2021, who were extracted from NHIS database using randomized stratified sampling based on age and sex.

Study population

A total of 689,395 asthmatic patients were found from January 1, 2015, to December 16, 2021 (**Fig. 1**). Asthma was defined as 3 or more prescriptions of asthma-related medications (inhaled or oral corticosteroids, bronchodilators, leukotriene receptor antagonists, and xanthine derivatives) under ICD-10 codes (J45 or J46).¹⁶⁻²¹ After excluding those under 20 years old (n = 358,880) and those without health screenings (n = 133,069) between 2019–2020, we analyzed 197,446 adults, including 13,169 with COVID-19 (COVID-19 cohort) and 184,277 without (control cohort).

Among the COVID-19 cohort, we excluded 2,036 who recovered after December 31, 2021 (due to a lack of available follow-up data), 189 who died before the index date, 2,570 with pre-existing IHD before the index date, and 363 matched to excluded controls, resulting in 8,011 subjects in the COVID-19 cohort.

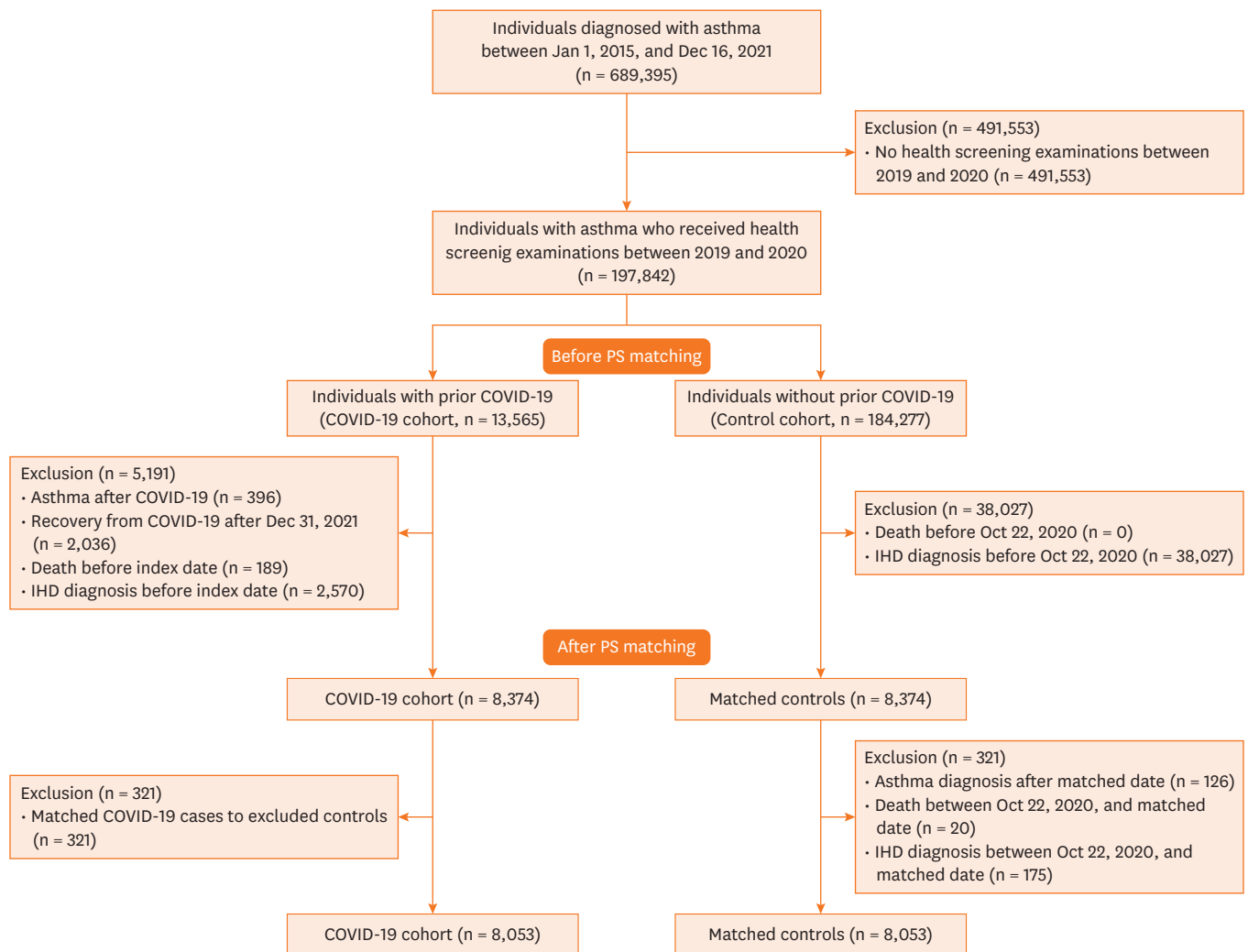


Fig. 1. Flow chart of the study population. COVID-19, coronavirus disease 2019; IHD, ischemic heart disease.

For matched controls, we performed a 1:1 propensity score (PS) matching between 8,374 COVID-19 and 146,250 non-COVID-19 subjects, resulting in 8,374 matched controls. After excluding subjects diagnosed with asthma after the index date (matched date) (n = 143), those who died before the index date (n = 27), and those with pre-existing IHD (n = 193), 8,011 populations remained as matched controls.

The index date was the recovery date for COVID-19 patients and the matching date for controls. Recovery was defined as 14 days post-diagnosis for outpatients, 14 days post-diagnosis for hospitalized patients discharged within 14 days, or the discharge date for those hospitalized over 14 days. Both cohorts were followed until IHD diagnosis, death, or December 31, 2021, whichever came first.

The Institutional Review Board of Hanyang University Hospital approved the study protocol (No. 2023-10-039), with informed consent waived due to anonymized patient records.

Study exposure: COVID-19

The exposure in our study was COVID-19, defined by the laboratory diagnosis of SARS-CoV-2 infection: a positive result through real-time polymerase chain reaction testing of nasal or pharyngeal swab samples from individuals with ICD-10 code for SARS-CoV-2 infection (U071).^{14,17}

Severe COVID-19 was defined as the presence of one of the following treatments during hospitalization for COVID-19^{14,17}: 1) oxygen therapy, 2) intensive care unit admission, 3) mechanical ventilation treatment, or 4) extracorporeal membrane oxygenation.

Primary outcome: IHD

The primary outcome was IHD, defined as ICD-10 claims for I20–I25 requiring hospitalization.^{22,23}

Covariates

Demographic characteristics, socioeconomic variables, and comorbidities were collected from the database. Body mass index (BMI) was defined as weight (kg) divided by the square of height (m²) and classified using Asian categories¹⁹: underweight (<18.5 kg/m²), normal (18.5–22.9 kg/m²), overweight (23.0–24.9 kg/m²), obese (25–29.9 kg/m²), and highly obese (≥30 kg/m²). Smoking status (never, ex-, and current smokers) and alcohol consumption (none, 1–2/week, 3–4/week, almost every day) were determined by self-reported questionnaires. Regular physical activity was defined as: 1) walking ≥ 30 min/day, 5 times/week, 2) moderate activity ≥ 30 minutes, 5 times/week, or 3) vigorous activity ≥ 20 minutes, 3 times/week.^{19,24} Income status was categorized as high (upper 30%), low (lower 30% and medical aid recipients), and middle income for the remaining.^{23,25} Residential areas were classified as rural, middle/small-sized cities, and metropolitan cities. Comorbidities were identified using ICD-10 codes over the previous 3 years: hypertension (I10–I13, and I15), diabetes mellitus (E10–E14), chronic kidney disease (N18), dyslipidemia (E78), and chronic obstructive pulmonary disease (J431, J432, J438, J439, or J44).^{26–33} To determine the severity of asthma, asthma-related medications were classified into five categories according to some modifications of the Global Initiative for Asthma treatment recommendations as follows¹⁷: Step 1: short-acting beta-agonists or short-acting muscarinic antagonists as the primary treatment; Step 2: inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRAs), or xanthines; Step 3: ICS/long-acting beta-agonists (LABAs) alone or in combination with LTRAs or xanthines; Step 4: 1) ICS/LABAs in combination with long-acting muscarinic antagonists, LTRAs, or xanthines or 2) oral corticosteroid use for more than 90 days/year regardless of other asthma-related medications. Severe asthma exacerbation was defined as the presence of ICD-10 codes for asthma during emergency room visits or hospitalization with the concomitant systemic corticosteroids use.³⁴

Statistical analysis

Using a 1:1 greedy nearest-neighbor algorithm, we performed PS matching between the COVID-19 and control cohorts based on age, sex, BMI, smoking status, alcohol consumption, regular physical activity, economic status, residential area, asthma severity stratified by asthma-related medications, history of severe asthma exacerbation in the previous year, and comorbidities (hypertension, diabetes mellitus, chronic kidney disease, dyslipidemia, and chronic obstructive pulmonary disease). PSs were derived using logistic regression with these covariates. Covariate balance was examined using the standardized mean difference (SMD), with SMD > 0.1 indicating imbalance.

Results were presented as number (%) for categorical variables and as mean ± standard deviation, median (interquartile range; IQR), or range for continuous variables. The incidence rates of IHD were determined by dividing the number of IHD events by the total follow-up period (expressed per 10,000 person-years [PY]). We used the χ^2 test for categorical variables and Student's *t*-tests for continuous variables. A cumulative incidence plot compared IHD incidence, with significant differences assessed using the log-rank test. Cox proportional hazards regression evaluated IHD hazards in the COVID-19 cohort versus controls. A 2-sided $P < 0.05$ was considered significant. All the statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

Table 1 presents the baseline characteristics of the study population. Each group consisted of 8,053 individuals with a mean age of 56 years, approximately 60% of whom were females. The baseline characteristics of the study populations were well-balanced after PS matching (all SMDs < 0.1).

COVID-19 and long-term risk of IHD in asthma

During a median follow-up of 95 days (IQR, 34–213 days; range, 1–448 days), including a median of 14 days of lag period, 0.26% (21/8,053) of the COVID-19 cohort developed IHD, whereas 0.24% (19/8,053) of the matched controls did. The cumulative incidence rate analyses did not show a significant difference between the COVID-19 cohort and the matched controls ($P = 0.075$) (**Fig. 2**). In line with the result, risk of IHD was not statistically different between the COVID-19 cohort and matched controls (**Table 2**).

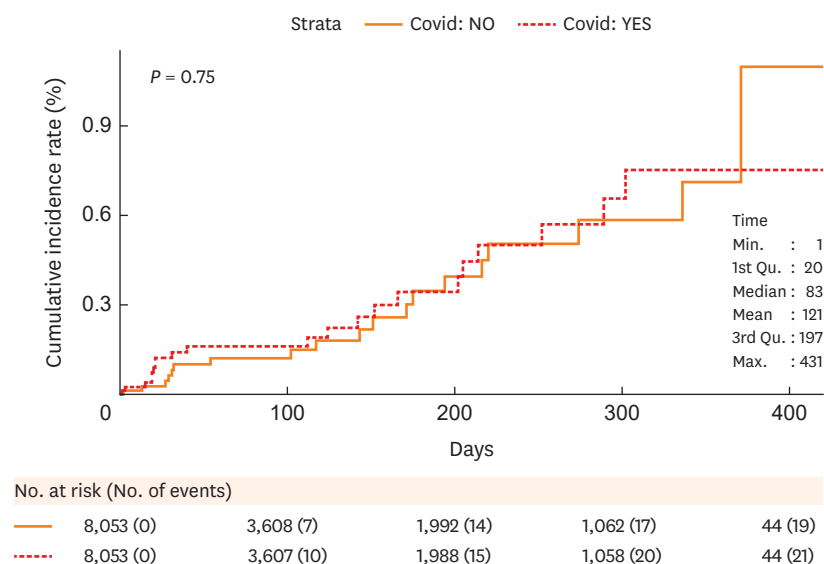


Fig. 2. Cumulative incidence of IHD in the COVID-19 cohort versus matched controls. Zero indicates the index date (date of recovery from COVID-19 in the COVID-19 cohort and matched date in matched controls). IHD, ischemic heart disease; COVID-19, coronavirus disease 2019.

Table 1. Baseline characteristics of the study subjects

Characteristics	COVID-19 cohort (n = 8,053)	Matched controls (n = 8,053)	SMD
Age (yr)			0.031
≤ 29	373 (4.6)	390 (4.8)	
30–39	810 (10.1)	869 (10.8)	
40–49	1,463 (18.2)	1,421 (17.6)	
50–59	1,538 (19.1)	1,490 (18.5)	
60–69	2,285 (28.4)	2,301 (28.6)	
≥ 70	1,584 (19.7)	1,582 (19.6)	
Sex, male	3,121 (38.8)	3,101 (38.5)	0.005
BMI (kg/m ²)			0.041
Low (< 18.5)	200 (2.5)	205 (2.5)	
Normal (18.5–22.9)	2,399 (29.8)	2,461 (30.6)	
Overweight (23.0–24.9)	1,890 (23.5)	1,936 (24.0)	
Obese (25.0–29.9)	2,864 (35.6)	2,712 (33.7)	
Highly obese (≥ 30)	700 (8.7)	739 (9.2)	
Smoking status			0.021
Never-smoker	5,772 (71.7)	5,837 (72.5)	
Ex-smoker	1,412 (17.5)	1,395 (17.3)	
Current smoker	869 (10.8)	821 (10.2)	
Alcohol consumption			0.027
None	5,470 (67.9)	5,559 (69.0)	
1–2 times/week	1,726 (21.4)	1,680 (20.9)	
3–4 times/week	609 (7.6)	591 (7.3)	
Almost everyday	248 (3.1)	223 (2.8)	
Regular physical activity*	2,216 (27.5)	2,161 (26.8)	0.015
Income status†			0.041
Low	1,609 (20.0)	1,689 (21.0)	
Middle	3,984 (49.5)	3,821 (47.4)	
High	2,460 (30.5)	2,543 (31.6)	
Residential area			0.007
Metropolitan cities	6,302 (78.3)	6,300 (78.2)	
Middle- and small-sized cities	1,435 (17.8)	1,446 (18.0)	
Rural areas	316 (3.9)	307 (3.8)	
Asthma severity			0.013
Step 1 treatment	377 (4.7)	368 (4.6)	
Step 2 treatment	4,337 (53.9)	4,390 (54.5)	
Step 3 treatment	2,402 (29.8)	2,367 (29.4)	
Step 4 treatment	937 (11.6)	928 (11.5)	
Severe exacerbation in the prior year			0.023
No	7,650 (95.0)	7,609 (94.5)	
Once	291 (3.6)	319 (4.0)	
Twice or more	112 (1.4)	125 (1.6)	
Comorbidities			
Hypertension	2,272 (28.2)	2,276 (28.3)	0.001
Diabetes mellitus	1,160 (14.4)	1,146 (14.2)	0.005
Chronic kidney disease	61 (0.8)	55 (0.7)	0.009
Dyslipidemia	1,515 (18.8)	1,557 (19.3)	0.013
Chronic obstructive pulmonary disease	391 (4.9)	372 (4.6)	0.011

Data are presented as numbers (percentages).

COVID-19, coronavirus disease 2019; SMD, standardized mean difference; BMI, body mass index.

*Regular physical activity was defined as one of the following: 1) ≥ 30 minutes of walking at least 5 times per week, 2) ≥ 30 minutes of moderate physical activity at least 5 times per week, or 3) ≥ 20 minutes of vigorous physical activity at least 3 times per week.

†Income status was divided into the highest 30% (high), lowest 30% (low), and rest (middle).

Table 2. Impact of COVID-19 on risk of ischemic heart disease

IHD	No. at risk	No. of incident cases of IHD	Incidence per 10,000 PY	HR (95% CI)
Matched controls	8,053	19	71.10	Reference
COVID-19 cohort	8,053	21	78.71	1.11 (0.60–2.06)
Non-severe COVID-19	7,044	14	61.58	0.86 (0.43–1.72)
Severe COVID-19	1,009	7	177.76	2.54 (1.07–6.05)

COVID-19, coronavirus disease 2019; IHD, ischemic heart disease; PY, person-years; HR, hazard ratio; CI, confidence interval.

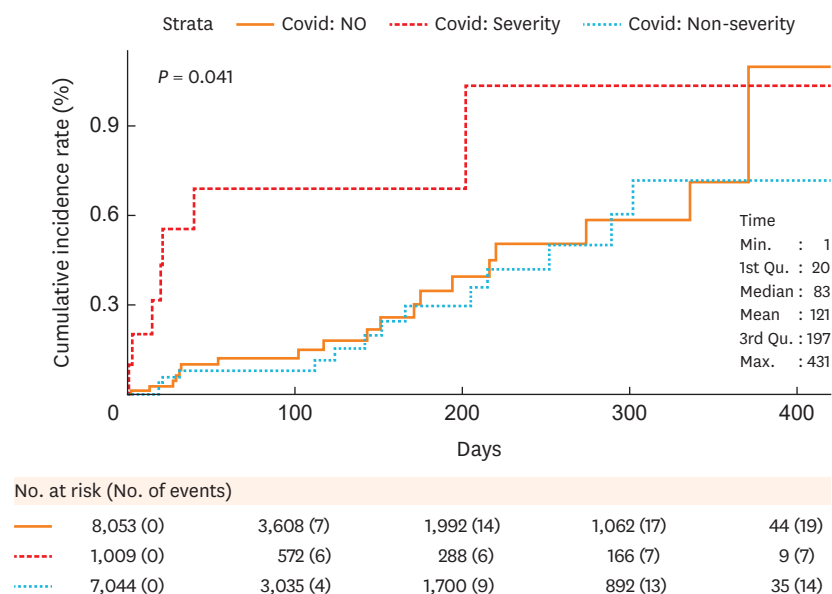


Fig. 3. Cumulative incidence of IHD in the COVID-19 cohort versus matched controls according to the infection severity. Zero indicates the index date (date of recovery from COVID-19 in the COVID-19 cohort and matched date in matched controls). IHD, ischemic heart disease; COVID-19, coronavirus disease 2019.

COVID-19 severity and long-term risk of IHD in asthma

During a median follow-up of 90 days (IQR, 34–207 days; range, 1–448 days), including a median of 14 days of lag period, 0.69% (7/1,009) of the severe COVID-19 cohort and 0.20% (14/7,044) of the non-severe COVID-19 cohort developed IHD. The severe COVID-19 cohort exhibited a higher risk of IHD (hazard ratio [HR], 2.54; 95% confidence interval [CI], 1.07–6.05) than the matched controls, whereas the non-severe COVID-19 cohort did not show a significantly increased risk of IHD (HR, 0.86; 95% CI, 0.43–1.72) (Table 2). The cumulative incidence plot showed similar results (log-rank, $P = 0.041$) (Fig. 3).

Subgroup analyses

Although not statistically significant (P for interaction > 0.05), the long-term risk of IHD in the COVID-19 cohort versus matched controls was especially higher among females, non-obese individuals, and patients without regular physical activity, who had severe COVID-19 (Table 3).

DISCUSSION

This study evaluated the association between COVID-19 severity and long-term risk of IHD in asthmatics using a large longitudinal nationwide database. Our study showed that even after the resolution of the acute phase of COVID-19, asthmatics who experienced severe COVID-19 showed a 2.54-fold higher long-term risk of IHD than matched patients with asthma. Among individuals with severe COVID-19, the risk of IHD was higher among females, non-obese individuals, and non-regular exercisers, although this was not statistically significant.

To our knowledge, this is the first study to demonstrate that severe COVID-19 persistently increases the risk of IHD in individuals with asthma even after recovery from the acute inflammatory stage. However, the exact mechanism by which COVID-19 increases the long-

Table 3. The impact of COVID-19 on risk of IHD, subgroup analyses

Characteristics	No. at risk	No. of incident cases of IHD	Incidence per 10,000 PY	HR (95% CI)
Age (yr)				
< 59				
Matched controls	4,170	2	14.37	Ref.
Non-severe COVID-19	3,848	5	36.38	NA
Severe COVID-19	336	0	0	NA
≥ 60				
Matched controls	3,883	17	132.71	Ref.
Non-severe COVID-19	3,196	9	99.99	0.73 (0.32–1.63)
Severe COVID-19	673	7	271.78	2.00 (0.83–4.84)
Sex				
Male				
Matched controls	3,101	9	87.17	Ref.
Non-severe COVID-19	2,668	8	95.55	1.11 (0.43–2.87)
Severe COVID-19	453	2	113.41	1.34 (0.29–6.22)
Female				
Matched controls	4,952	10	60.98	Ref.
Non-severe COVID-19	4376	6	41.75	0.68 (0.25–1.88)
Severe COVID-19	556	5	229.96	3.84 (1.31–11.24)
BMI (kg/m²)				
< 23				
Matched controls	2,666	8	88.47	Ref.
Non-severe COVID-19	2,395	5	62.91	0.72 (0.24–2.20)
Severe COVID-19	204	2	250.51	2.83 (0.60–13.32)
≥ 23				
Matched controls	5,387	11	62.21	Ref.
Non-severe COVID-19	4,649	9	60.83	0.97 (0.40–2.34)
Severe COVID-19	805	5	159.26	2.66 (0.92–7.66)
Smoking status				
Never-smoker				
Matched controls	7,232	19	80.14	Ref.
Non-severe COVID-19	6,246	13	64.59	0.80 (0.40–1.62)
Severe COVID-19	938	7	189.95	2.40 (1.01–5.72)
Ever smoker				
Matched controls	821	0	0	Ref.
Non-severe COVID-19	798	1	38.24	NA
Severe COVID-19	71	0	0	NA
Alcohol consumption				
No				
Matched controls	5,559	15	81.84	Ref.
Non-severe COVID-19	4,737	9	59.59	0.72 (0.32–1.65)
Severe COVID-19	733	7	242.18	3.01 (1.23–7.39)
Yes				
Matched controls	2,494	4	47.64	Ref.
Non-severe COVID-19	2,307	5	65.45	NA
Severe COVID-19	276	0	0	NA
Regular physical activity				
No				
Matched controls	5,892	13	65.82	Ref.
Non-severe COVID-19	5,087	9	54.26	0.82 (0.35–1.92)
Severe COVID-19	750	6	210.17	3.25 (1.24–8.56)
Yes				
Matched controls	2,161	6	86.03	Ref.
Non-severe COVID-19	1,957	5	81.24	0.94 (0.29–3.09)
Severe COVID-19	259	1	92.34	1.06 (0.13–8.84)

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Table 3. (Continued) The impact of COVID-19 on risk of IHD, subgroup analyses

Characteristics	No. at risk	No. of incident cases of IHD	Incidence per 10,000 PY	HR (95% CI)
A history of severe exacerbation in the previous year				
No				
Matched controls	7,609	17	67.31	Ref.
Non-severe COVID-19	6,722	13	60.20	0.89 (0.43–1.84)
Severe COVID-19	928	5	138.80	2.11 (0.78–5.71)
Yes				
Matched controls	444	2	136.11	Ref.
Non-severe COVID-19	322	1	87.21	0.60 (0.05–6.62)
Severe COVID-19	81	2	596.11	4.04 (0.57–28.84)
Asthma severity				
Step 1 treatment				
Matched controls	368	2	166.03	Ref.
Non-severe COVID-19	331	1	85.33	NA
Severe COVID-19	46	0	0	NA
Step 2 treatment				
Matched controls	4,390	8	55.51	Ref.
Non-severe COVID-19	3,863	8	63.69	1.14 (0.43–3.05)
Severe COVID-19	474	3	158.34	2.87 (0.76–10.82)
Step 3 treatment				
Matched controls	2,367	4	49.54	Ref.
Non-severe COVID-19	2,094	4	59.26	1.19 (0.30–4.76)
Severe COVID-19	308	1	85.97	1.75 (0.20–15.65)
Step 4 treatment				
Matched controls	928	5	164.79	Ref.
Non-severe COVID-19	756	1	44.22	0.26 (0.03–2.22)
Severe COVID-19	181	3	434.70	2.58 (0.62–10.84)

COVID-19, coronavirus disease 2019; IHD, ischemic heart disease; PY, person-years; HR, hazard ratio; CI, confidence interval; Ref., reference; NA, not available.

term risk of IHD in asthmatics remains unknown. It is imperative to consider the potential mechanisms by which severe COVID-19 may worsen the long-term risk of IHD in asthmatics.

The relationship between asthma and elevated cardiovascular risk is well documented.^{35,36} Both asthma and IHD involve systemic inflammatory mechanisms, with airway inflammation potentially spilling over into systemic circulation.³⁷ Atherosclerosis, the primary cause of IHD, may be further aggravated by elevated leukotriene levels, which can destabilize atherosclerotic plaques.³⁷ Patients with asthma have also shown enhanced coagulation activation, impaired anticoagulant function, and reduced fibrinolysis, all of which can precipitate acute coronary events.³⁸ Moreover, oxidative stress associated with asthma may reduce nitric oxide bioavailability, leading to endothelial dysfunction and potential acute coronary events.³⁷

The chronic inflammatory state of asthma may exacerbate these effects when combined with the atherosclerotic inflammatory response to COVID-19, amplifying cardiovascular risk.³⁹ Inadequate asthma control after COVID-19^{17,40,41} may be another risk factor for IHD development. Previous studies have established a correlation between uncontrolled asthma and adverse cardiovascular consequences.^{5,42} Considering that both asthma and COVID-19 independently increase the risk of IHD and given the additional deteriorating effect of COVID-19 on asthma control, the risk of IHD in individuals with severe COVID-19 is inevitably amplified.

This study has important clinical implications. Our results imply that prior COVID-19 infection, particularly its severity, may be associated with an increased long-term risk of IHD in asthmatics. This underscores the importance of monitoring cardiovascular events

for a better long-term prognosis of asthma during the COVID-19 endemic period. Subgroup analyses suggested that certain individuals with asthma, such as females, non-obese individuals, and non-regular exercisers, had higher risks of IHD (not statistically significant, probably due to small IHD event numbers). The higher severity of asthma, more common in females and individuals with low exercise capacity might have played a role.^{19,43} Contrary to the belief that obesity exacerbates asthma, our study found a higher long-term risk of IHD in non-obese asthmatics with COVID-19, though the reasons are not fully understood, and the relatively small study population necessitates cautious interpretation. Besides, our study results emphasize the importance of severe exacerbation history on developing IHD in asthmatics following severe COVID-19 (138.80/10,000 PY in those without exacerbations vs. 596.11/10,000 PY in those with exacerbations). As severe exacerbation history substantially increases the risk of IHD in patients with asthma following severe COVID-19, careful attention should be more paid to this population.

Our study has several limitations. First, there might be selection bias as we only included individuals who underwent health screening examinations, favoring relatively healthier individuals. Secondly, using ICD-10 codes to define the study population could lead to over- or under-diagnosis of asthma and related comorbidities. While ICD-10 codes for asthma with/without asthma-related medications are widely used to define asthma in health insurance claims databases, no study has validated these definitions.^{16,18-21,44-46} To mitigate this, we used strict diagnostic criteria requiring at least three ICD-10 codes for asthma and concurrent use of asthma-related medications. Thirdly, since our study solely focused on the association between COVID-19 and risk of IHD in patients with asthma, it is not known whether patients with asthma were more vulnerable to developing IHD compared to general population. Future studies are needed regarding this issue. Fourthly, we could not account for the continuous mutations of SARS-CoV-2, as information on SARS-CoV-2 virus was not provided. Fifthly, the small number of IHD cases limits the subgroup analyses, such as stratified analyses by asthma severity. Finally, as this study was confined to the Korean population, caution is needed when generalizing our results to other countries or ethnic groups.

In conclusion, our study found a significant increase in the occurrence and risk of IHD in individuals with asthma who experienced severe COVID-19. These findings emphasize the importance of monitoring not only asthma control but also cardiovascular complications in asthmatic patients who have had severe COVID-19 to improve long-term outcomes.

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