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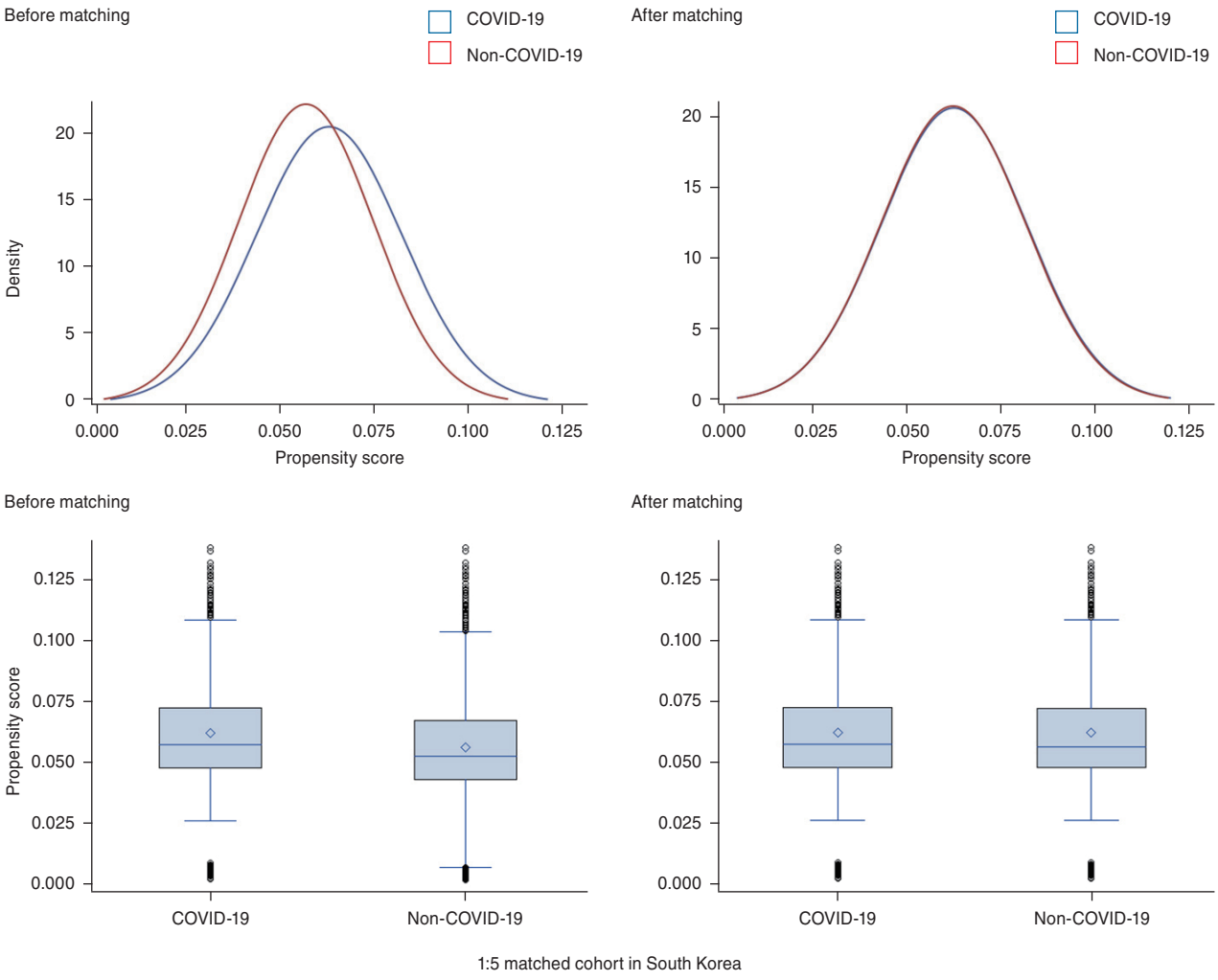
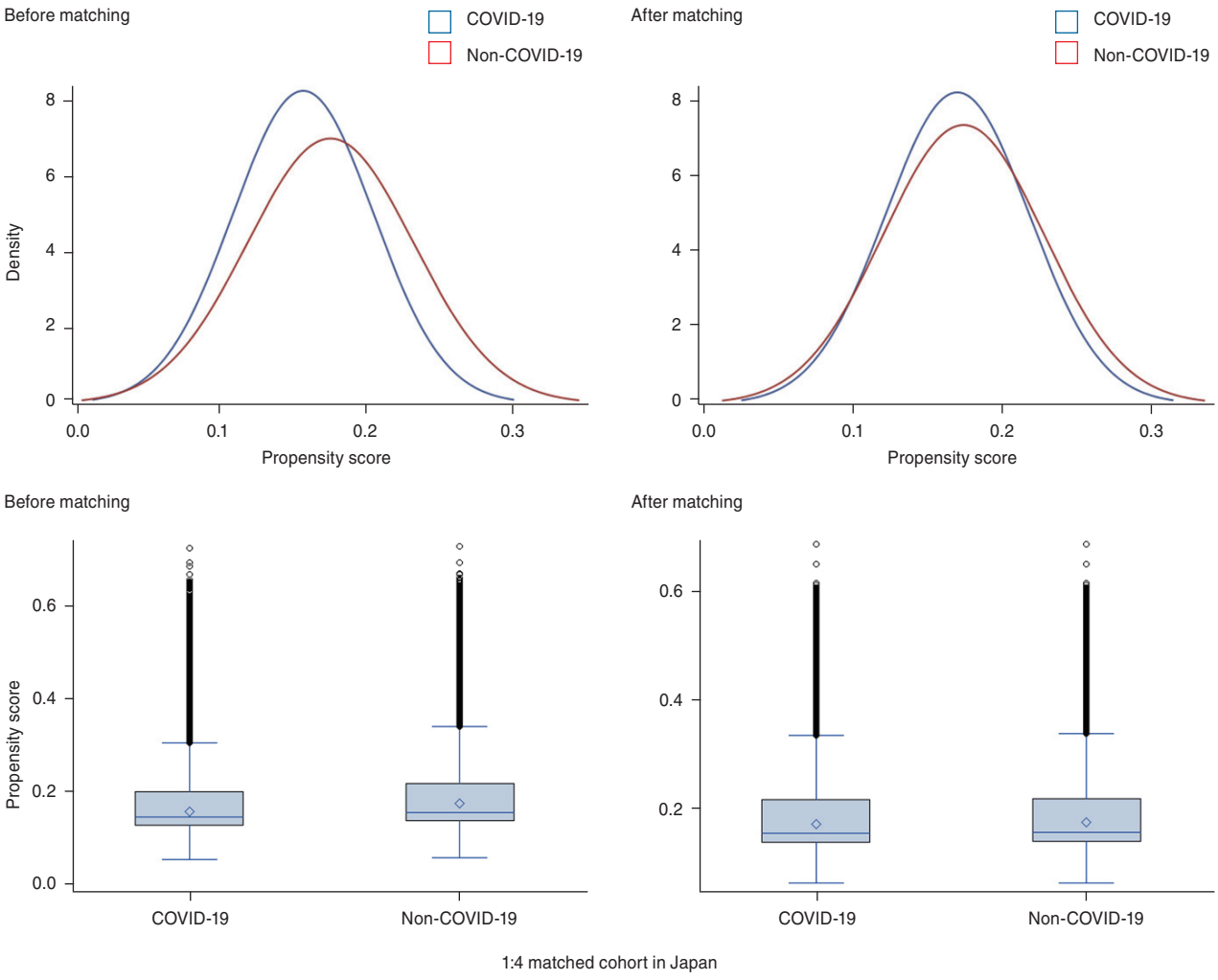
 https://doi.org/10.3350/cmh.2024.0203

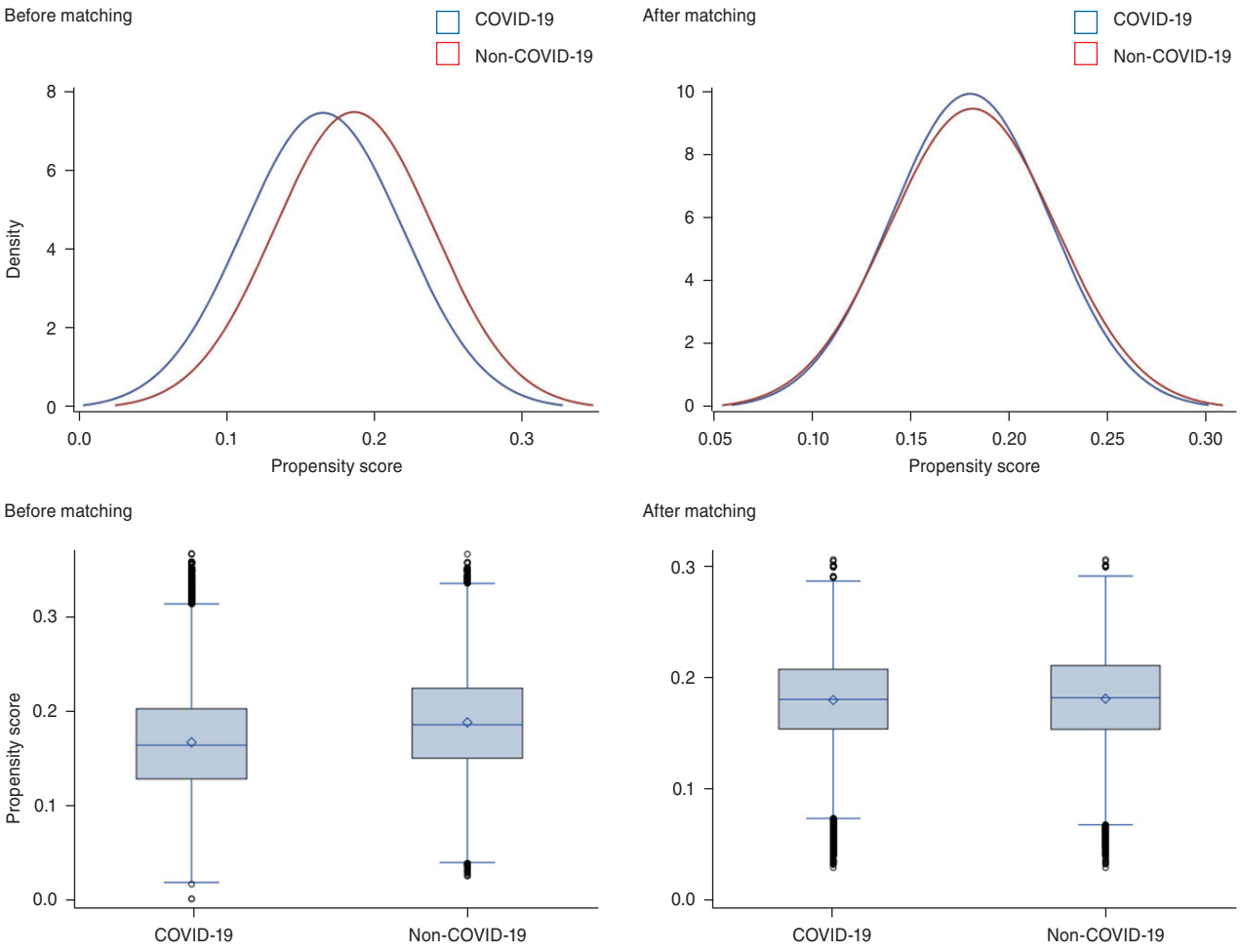


Supplementary Figure 1. Density plot and box plot for before matching and after matching in patients with COVID-19 and non- COVID-19 in discovery cohort (South Korea).



Supplementary Figure 2. Density plot and box plot for before matching and after matching in patients with COVID-19 and non- COVID-19 in validation cohort A (Japan).

 https://doi.org/10.3350/cmh.2024.0203



1:4 matched cohort in UK

Supplementary Figure 3. Density plot and box plot for before matching and after matching in patients with COVID-19 and non- COVID-19 in validation cohort B (UK).

Supplementary Table 1. Representative population

Category	
Disease	■ Exposure: SARS-CoV-2 infection ■ Outcome: Digestive disorders 1. Eighteen gastrointestinal diseases are defined as esophagitis; gastro-esophageal reflux disease; vascular disorder of intestine; peptic ulcer; gastritis and duodenitis; Functional dyspepsia; acute appendicitis; inflammatory bowel disease; colitis; paralytic ileus; diverticular disease; irritable bowel syndrome; functional intestinal disorders; abscess or fissure of anal regions; hemorrhoids and perianal venous thrombosis; peritonitis; and other gastrointestinal diseases. 2. Eight hepatobiliary diseases are defined as hepatic failure; chronic hepatitis; inflammatory liver diseases; cirrhosis of liver; cholelithiasis; cholecystitis and cholangitis; acute pancreatitis; and other hepato-biliary-pancreatic diseases. 3. Nine other digestive abnormalities are defined as abdominal and pelvic pain; nausea, vomiting, and dysphagia; heartburn; fecal incontinence; hepatomegaly and splenomegaly; hyperbilirubinemia; ascites; abnormal results of liver function studies; and abdominal distension and other symptoms. 4. We used appropriate ICD-10 codes for the definition of each disease.
Special considerations related to	
Sex	Sex differences are frequently observed in digestive disorders, including gastrointestinal and hepatobiliary diseases. The distribution of gut microbiota, which affects the occurrence of post-infectious digestive disorders, also varies according to sex.
Age	Older individuals are susceptible to digestive disorders due to altered function of relevant organs.
Socioeconomic status	Socioeconomic status is associated with a subset of digestive disorders, such as functional gastrointestinal disorders and liver cirrhosis.
Race and country	Digestive disorders are common across all races and ethnicities but have a different trend according to diet, cultural background, and biological factors.
Geography of urban-rural interaction	The region of residence is associated with risk of a subset of digestive disorders, such as inflammatory bowel disease and steatotic liver disease.
Other considerations	Comorbidities, such as type 2 diabetes mellitus, can affect digestive disorders, including functional gastrointestinal disorders and steatotic liver disease. Obesity, smoking, alcohol, and decreased physical activity increase the risk of developing digestive disorders.
Overall representativeness of this study	This study used the Korean nationwide cohort comprising over 10 million individuals to assess the long-term gastrointestinal and hepatobiliary outcomes and on long COVID. The risk of infected patients was compared to contemporary controls (general population). Validation with two independent cohorts, the Japanese and the UK cohorts, enhanced the robustness of our findings. This is the largest analysis to estimate a comprehensive set of gastrointestinal and hepatobiliary outcomes following COVID-19 infection.

ICD-10, International Classification of Diseases, 10th edition.

 https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 2. Definitions of diseases

Diseases	ICD-10 codes
Gastrointestinal diseases	
Esophagitis	K20
Gastro-esophageal reflux disease	K21
Vascular disorder of intestine	K55
Peptic ulcer	K25, K26, K27, and K28
Gastritis and duodenitis	K29
Functional dyspepsia	K30
Acute appendicitis	K35, K36, K37, and K38
Inflammatory bowel disease	K50 and K51
Colitis	K52
Paralytic ileus	K56
Diverticular disease	K57
Irritable bowel syndrome	K58
Functional intestinal disorders	K59
Abscess or fissure of anal regions	K60 and K61
Hemorrhoids and perianal venous thrombosis	K64
Peritonitis	K65
Other gastrointestinal diseases	K22, K31, K62, K63, K66, K92, and K90
Hepatobiliary diseases	
Hepatic failure	K72
Chronic hepatitis	K73
Inflammatory liver diseases	K75
Cirrhosis of liver	K74, I98.2, I98.3, and I86.4
Cholelithiasis	K80
Cholecystitis and cholangitis	K81 and K83
Acute pancreatitis	K85
Other hepato-biliary-pancreatic diseases	K82 and K86
Other digestive abnormalities	
Abdominal and pelvic pain	R10
Nausea, vomiting, and dysphagia	R11 and R13
Heartburn	R12
Fecal incontinence	R15
Hepatomegaly and splenomegaly	R16
Hyperbilirubinemia	R17
Ascites	R18
Abnormal results of liver function studies	R94.5
Abdominal distension and other symptoms	R14 and R19

ICD-10, International Classification of Diseases, 10th edition.

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 3. Sensitivity and subgroup analyses and justification

Sensitivity analysis (1 to 11)	Cohort	Justification
1. Incident gastrointestinal and hepatobiliary outcomes and other digestive abnormalities in SARS-CoV2 infection versus contemporary control	Discovery cohort (Korea) after 1:5 propensity score matching	- Main results - Matching covariates for the Korean (discovery) cohort are age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; and history of medication use for diabetes mellitus, dyslipidemia, and hypertension. - Adjusting covariates were selected for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; and history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).
2. Subgroup analysis of the risk of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development in patients with COVID-19, stratified by vaccination, COVID-19 severity, and strains.	Discovery cohort (Korea) after 1:5 propensity score matching	- Main results - To investigate the association of overall gastrointestinal disease, hepatobiliary disease, and other digestive abnormalities after COVID-19, stratified by vaccination status (once vs. twice or more), severity of COVID-19 (mild vs. moderate to severe), and strains (original vs. delta)

Supplementary Table 3 Continued

Sensitivity analysis (1 to 11)	Cohort	Justification
3. Attenuation time effect of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection	Discovery cohort (Korea) after 1:5 propensity score matching	- Main results - To investigate the time attenuation effect of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection
4. Subgroup analysis of the risk of several gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection	Discovery cohort (Korea) after 1:5 propensity score matching	- To investigate the association of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities after SARS-CoV-2 infection, compared with non-infected individuals. - Several gastrointestinal diseases: gastro-esophageal reflux disease; vascular disorder of intestine; peptic ulcer; gastritis and duodenitis; Functional dyspepsia; acute appendicitis; inflammatory bowel disease; colitis; paralytic ileus; diverticular disease; irritable bowel syndrome; functional intestinal disorders; abscess or fissure of anal regions; hemorrhoids and perianal venous thrombosis; peritonitis; and other gastrointestinal diseases. - Several hepatobiliary diseases: hepatic failure; chronic hepatitis; inflammatory liver diseases; cirrhosis of liver; cholelithiasis; cholecystitis and cholangitis; acute pancreatitis; and other hepato-biliary-pancreatic diseases. - Several other digestive abnormalities: abdominal and pelvic pain; nausea, vomiting, and dysphagia; heartburn; fecal incontinence; hepatomegaly and splenomegaly; hyperbilirubinemia; ascites; abnormal results of liver function studies; and abdominal distension and other symptoms.
5. Stratification analysis of the risk of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection	Discovery cohort (Korea) after 1:5 propensity score matching	- To investigate unexpected effects mediated by sex, age, household income, body mass index, region of residence, CCI score, alcohol use, aerobic physical activity, and smoking status.

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 3 Continued

Sensitivity analysis (1 to 11)	Cohort	Justification
6. Incident gastrointestinal and hepatobiliary outcomes and other digestive abnormalities in SARS-CoV2 infection versus contemporary control	Validation cohort A (Japan) after 1:4 propensity score matching	- Main results - Matching covariates for the Japanese (validation A) cohort are age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, everyday, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; and history of medication use for diabetes mellitus, dyslipidemia, and hypertension. - Adjusting covariates were selected for age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, everyday, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; and history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).
7. Attenuation time effect of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection	Validation cohort A (Japan) after 1:4 propensity score matching	- Main results - To investigate the time attenuation effect of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection

Supplementary Table 3 Continued

Sensitivity analysis (1 to 11)	Cohort	Justification
8. Subgroup analysis of the risk of several gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities SARS-CoV-2 infection	Validation cohort A (Japan) after 1:4 propensity score matching	- To investigate the association of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities after SARS-CoV-2 infection, compared with non-infected individuals. - Several gastrointestinal diseases: gastro-esophageal reflux disease; vascular disorder of intestine; peptic ulcer; gastritis and duodenitis; Functional dyspepsia; acute appendicitis; inflammatory bowel disease; colitis; paralytic ileus; diverticular disease; irritable bowel syndrome; functional intestinal disorders; abscess or fissure of anal regions; hemorrhoids and perianal venous thrombosis; peritonitis; and other gastrointestinal diseases. - Several hepatobiliary diseases: hepatic failure; chronic hepatitis; inflammatory liver diseases; cirrhosis of liver; cholelithiasis; cholecystitis and cholangitis; acute pancreatitis; and other hepato-biliary-pancreatic diseases. - Several other digestive abnormalities: abdominal and pelvic pain; nausea, vomiting, and dysphagia; heartburn; fecal incontinence; hepatomegaly and splenomegaly; hyperbilirubinemia; ascites; abnormal results of liver function studies; and abdominal distension and other symptoms.
9. Stratification analysis of the risk of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection	Validation cohort A (Japan) after 1:4 propensity score matching	- To investigate unexpected effects mediated by sex, age, body mass index, region of residence, CCI score, alcohol use, aerobic physical activity, and smoking status.

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 3 Continued

Sensitivity analysis (1 to 11)	Cohort	Justification
10. Incident gastrointestinal and hepatobiliary outcomes and other digestive abnormalities in SARS-CoV2 infection versus contemporary control	Validation cohort B (UK) after 1:4 propensity score matching	- Main results - Matching covariates for the UK (validation B) cohort are sex, household income (<£18,000, £18,000–£30,999, £31,000–£51,999, £52,000–£100,000, and >£100,000), region of residence (urban and rural), Townsend deprivation index (tertiles and unknown), ethnicity (white, mixed, Asian, black, others, and unknown), CCI score(0, 1, and ≥ 2), obesity (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown), education levels (≤10, 11-12, >12, and unknown), blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure < 90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg, and unknown), fasting blood glucose (<100, ≥100 mg/dL, and unknown), smoking status (never, former, and current smoker), alcohol consumption (drinks; <1, 1–2, 3–4, ≥5 days per week, and unknown), aerobic physical activity (low, moderate, and high), previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease, and history of medication use for diabetes mellitus, dyslipidemia, and hypertension. - Adjusting covariates were selected for sex, household income (<£18,000, £18,000–£30,999, £31,000–£51,999, £52,000–£100,000, and >£100,000), region of residence (urban and rural), Townsend deprivation index (tertiles and unknown), ethnicity (white, mixed, Asian, black, others, and unknown), CCI score(0, 1, and ≥2), obesity (normal [<25.0 kg/m2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown), education levels ≤10, 11-12, >12, and unknown), blood pressure (systolic blood pressure < 140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown), fasting blood glucose (<100, ≥100 mg/dL, and unknown), smoking status (never, former, and current smoker), alcohol consumption (drinks; <1, 1–2, 3–4, ≥5 days per week, and unknown), aerobic physical activity (low, moderate, and high), previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease, and history of medication use for diabetes mellitus, dyslipidemia, and hypertension.
11. Attenuation time effect of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection	Validation cohort B (UK) after 1:4 propensity score matching	- Main results - To investigate the time attenuation effect of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities development after SARS-CoV-2 infection

CCI, Charlson comorbidity index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Supplementary Table 4. Baseline characteristics for the full unmatched cohort of South Korea (discovery)

Characteristics	Entire discovery cohort (Korea) (n=10,027,506)
Total, n	10,027,506
Age, years, mean (SD)	48.40 (13.40)
Age, years, n (%)	
20–39	2,756,102 (27.50)
40–59	4,799,784 (47.90)
≥60	2,471,620 (24.70)
Sex, n (%)	
Male	5,026,885 (50.10)
Female	5,000,621 (49.90)
Region of residence, n (%)	
Rural	4,460,562 (44.48)
Urban	5,566,944 (55.52)

SD, standard deviation.

Supplementary Table 5. Baseline characteristics for the full unmatched cohort of Japan (validation A)

Characteristics	Entire validation cohort A (Japan) (n=12,218,680)
Total, n	12,218,680
Age, years, mean (SD)	43.50 (14.70)
Age, years, n (%)	
20–39	5,298,703 (43.40)
40–59	4,935,219 (40.40)
≥60	1,984,758 (16.20)
Sex, n (%)	
Male	6,334,565 (51.80)
Female	5,884,115 (48.20)
Insurance status, n (%)	
Insured	8,524,220 (69.8)
Dependent	3,694,460 (30.2)

SD, standard deviation.

 https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 6. Baseline characteristics for the full unmatched cohort of the UK (validation B)

Characteristics	Entire validation cohort B (UK) (n=468,617)
Total, n	468,617
Age, years, mean (SD)	71.18 (8.09)
Age, years, n (%)	
40–59	50,872 (10.86)
≥60	417,745 (89.14)
Sex, n (%)	
Male	209,472 (44.70)
Female	259,145 (55.30)
Region of residence, n (%)	
Rural	65,206 (13.90)
Urban	403,411 (86.10)

SD, standard deviation.

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 7. Baseline characteristics for 1:4 propensity score-matched cohort in validation cohort A (Japan) among the full unmatched cohort (total n=12,218,680)

Matching covariates	1:4 propensity score-matched validation cohort A			
	Total (n=2,654,945)	COVID-19 (n=602,058)	Non-COVID-19 (n=2,052,887)	SMD[a]
Mean age (SD), y	43.26 (8.21)	42.76 (11.55)	43.47 (11.66)	0.061
Age, n (%)				0.042
20–39 y	1,053,227 (39.67)	246,602 (40.96)	806,625 (39.29)	
40–59 y	1,385,832 (52.20)	305,510 (50.74)	1,080,322 (52.62)	
≥60 y	215,886 (8.13)	49,946 (8.30)	165,940 (8.08)	
Sex, n (%)				0.003
Male	1,703,350 (64.16)	385,578 (64.04)	1,317,772 (64.19)	
Female	951,595 (35.84)	216,480 (35.96)	735,115 (35.81)	
Insurance status, n (%)				0.006
Insured	2,402,700 (90.50)	545,634 (90.63)	1,857,066 (90.46)	
Dependent	252,245 (9.50)	56,424 (9.37)	195,821 (9.54)	
Medical history, n (%)				
Cardiovascular disease	157,551 (5.93)	37,358 (6.21)	120,193 (5.85)	0.015
Chronic kidney disease	82,976 (3.13)	20,148 (3.35)	62,828 (3.06)	0.016
Chronic obstructive pulmonary disease	7005 (0.26)	1795 (0.30)	5210 (0.25)	0.009
Medication use for diabetes	50,131 (1.89)	12,341 (2.05)	37,790 (1.84)	0.015
Medication use for hyperlipidemia	176,788 (6.66)	41,562 (6.90)	135,226 (6.59)	0.013
Medication use for hypertension	130,622 (4.92)	30,712 (5.10)	99,910 (4.87)	0.011
Charlson Comorbidity Index score, n (%)				0.142
0	2,627,813 (98.98)	590,734 (98.12)	2,037,079 (99.23)	
1	10,544 (0.40)	4387 (0.73)	6157 (0.30)	
≥2	16,588 (0.62)	6937 (1.15)	9651 (0.47)	
Body mass index, n (%)				0.142
Normal (<25.0 kg/m^2)	1,930,062 (72.7)	435,940 (72.41)	1,494,122 (72.78)	
Overweight (25–0-29.9 kg/m^2)	560,878 (21.13)	127,685 (21.21)	433,193 (21.1)	
Obese (≥30.0 kg/m^2)	160,163 (6.03)	37,533 (6.23)	122,630 (5.97)	
Unknown	3842 (0.14)	900 (0.15)	2942 (0.14)	
Blood pressure, n (%)				<0.001
SBP <140 mmHg and DBP <90 mmHg	2,317,374 (87.29)	525,966 (87.36)	1,791,408 (87.26)	
SBP ≥140mmHg or DBP ≥90 mmHg	151,301 (5.70)	33,882 (5.63)	117,419 (5.72)	

Supplementary Table 7. Continued

Matching covariates	1:4 propensity score-matched validation cohort A			
	Total (n=2,654,945)	COVID-19 (n=602,058)	Non-COVID-19 (n=2,052,887)	SMD[a]
Unknown	186,270 (7.02)	42,210 (7.01)	144,060 (7.02)	
Serum total cholesterol, n (%)				0.065
<200 mg/dL	1,235,176 (46.52)	283,717 (47.12)	951,459 (46.35)	
200–240 mg/dL	955,030 (35.97)	214,756 (35.67)	740,274 (36.06)	
≥240 mg/dL	408,647 (15.39)	91,573 (15.21)	317,074 (15.45)	
Unknown	56,092 (2.11)	12,012 (2.00)	44,080 (2.15)	
Fasting blood glucose, n (%)				<0.001
<100 mg/dL	1,723,459 (64.92)	390,325 (64.83)	1,333,134 (64.94)	
≥100 mg/dL	500,267 (18.84)	113,365 (18.83)	386,902 (18.85)	
Unknown	431,219 (16.24)	98,368 (16.34)	332,851 (16.21)	
Glomerular filtration rate, n (%)				0.021
<60 mL/min/1.73 m^2	8233 (0.31)	2265 (0.38)	5968 (0.29)	
60 to 89 mL/min/1.73 m^2	224,487 (8.46)	51,098 (8.49)	173,389 (8.45)	
≥90 mL/min/1.73 m^2	1,447,998 (54.54)	330,730 (54.93)	1,117,268 (54.42)	
Unknown	974,227 (36.69)	217,965 (8.21)	756,262 (28.49)	
Smoking status, n (%)				<0.001
Current smoker	616,760 (23.23)	139,295 (23.14)	477,465 (23.26)	
Non-smoker	1,934,872 (72.88)	438,772 (72.88)	1,496,100 (72.88)	
Unknown	103,313 (3.89)	23,991 (3.98)	79322 (3.86)	
Alcohol consumption, n (%)				<0.001
Everyday	526,830 (19.84)	119,232 (19.80)	407,598 (19.85)	
Sometimes	894,688 (33.70)	204,854 (34.03)	689,834 (33.60)	
Rarely	1,035,781 (39.01)	232,799 (38.67)	802,982 (39.11)	
Unknown	197,646 (7.44)	45,173 (7.50)	152,473 (7.43)	
Aerobic physical activity, n (%)				0.039
Sufficient	542,733 (20.44)	121,295 (20.15)	421,438 (20.53)	
Insufficient	1,860,916 (70.09)	423,431 (70.33)	1,437,485 (70.02)	
Unknown	251,296 (9.47)	57,332 (9.52)	193,964 (9.45)	
Unmatched covariates[b]				
Hospital admissions in the year before index date, n (%)				0.221

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 7. Continued

Matching covariates	1:4 propensity score-matched validation cohort A			
	Total (n=2,654,945)	COVID-19 (n=602,058)	Non-COVID-19 (n=2,052,887)	SMD[a]
0	2,555,385 (96.25)	554,496 (92.1)	2,000,539 (97.45)	
1	2920 (0.11)	1204 (0.20)	1642 (0.08)	
≥2	96,640 (3.64)	46,358 (7.70)	50,706 (2.47)	
Outpatient contacts in the year before index date, n (%)				0.471
0	153,986 (5.80)	241 (0.04)	153,351 (7.47)	
1–4	55,223 (2.08)	1325 (0.22)	53,786 (2.62)	
≥5	2,445,469 (92.11)	600,552 (99.75)	1,845,750 (89.91)	

DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; SMD, standardized mean difference.
[a]SMD <0.1 indicates no significant imbalance. All SMDs were <0.100 in the propensity score–matched cohorts, except for Charlson Comorbidity Index score and Body mass index.
[b]Unmatched covariates were included as adjustment factors in statistical analyses.

Supplementary Table 8. Baseline characteristics for 1:4 propensity score-matched cohort in validation cohort B (UK) among the full unmatched cohort (total n=468,617)

Matching covariates	1:4 propensity score-matched validation cohort B			
	Total (n=322,920)	COVID-19 (n=75,814)	Non-COVID-19 (n=247,106)	SMD[a]
Mean age (SD), y	71.08 (7.87)	71.33 (7.58)	71.00 (7.95)	0.042
Age, n (%)				0.025
20–39 y	31,139 (9.64)	6911 (9.12)	24,228 (9.80)	
40–59 y	291,781 (90.36)	68,903 (90.88)	222,878 (90.2)	
≥60 y				0.033
Sex, n (%)	189,893 (58.80)	45,510 (60.03)	144,383 (58.43)	
Male	133,027 (41.20)	30,304 (39.97)	102,723 (41.57)	
Female				0.012
Region of residence, n (%)	274,532 (85.02)	64,209 (84.69)	210,323 (85.11)	
Urban	48,388 (14.98)	11,605 (15.31)	36,783 (14.89)	
Rural				<0.001
Medical history, n (%)				
Cardiovascular disease	30,408 (9.42)	7623 (10.05)	22,785 (9.22)	0.028
Chronic kidney disease	13,348 (4.13)	3826 (5.05)	9522 (3.85)	0.058
Chronic obstructive pulmonary disease	7532 (2.33)	2126 (2.80)	5406 (2.19)	0.040
Medication use for diabetes	470 (0.15)	136 (0.18)	334 (0.14)	0.011
Medication use for hyperlipidemia	9831 (3.04)	2407 (3.17)	7424 (3.00)	0.010
Medication use for hypertension	27,711 (8.58)	6593 (8.70)	21,118 (8.55)	0.005
Charlson Comorbidity Index score, n (%)				0.082
0	312,331 (96.72)	72,469 (95.59)	239,862 (97.07)	
1	5958 (1.85)	1833 (2.42)	4125 (1.67)	
≥2	4631 (1.43)	1512 (1.99)	3119 (1.26)	
Household income, n (%)				
Level1 (<£18,000)	52,794 (16.35)	9938 (13.11)	42,856 (17.34)	
Level2 (£18,000–£30,999)	69,401 (21.49)	15,932 (21.01)	53,469 (21.64)	
Level3 (£31,000–£51,999)	76,292 (23.63)	18,962 (25.01)	57,330 (23.20)	
Level4 (£52,000–£100,000)	62,639 (19.40)	16,878 (22.26)	45,761 (18.52)	
Level5 (>£100,000)	17,091 (5.29)	5118 (6.75)	11,973 (4.85)	
Unknown	44,703 (13.84)	8986 (11.85)	35,717 (14.45)	
Mean Townsend deprivation index (SD)	-1.65 (2.90)	-1.73 (2.82)	-1.63 (2.92)	0.036

https://doi.org/10.3350/cmh.2024.0203
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https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 8. Continued

Matching covariates	1:4 propensity score-matched validation cohort B			
	Total (n=322,920)	COVID-19 (n=75,814)	Non-COVID-19 (n=247,106)	SMD[a]
Tertiles of Townsend deprivation index, n (%)				0.024
T1 (last deprived)	117,691 (36.45)	28,157 (37.14)	89,534 (36.23)	
T2	111,665 (34.58)	25,971 (34.26)	85,694 (34.68)	
T3 (most deprived)	93,326 (28.9)	21,623 (28.52)	71,703 (29.02)	
Unknown	238 (0.07)	63 (0.08)	175 (0.07)	
Ethnicity, n (%)				<0.001
White	311,086 (96.34)	73,042 (96.34)	238,044 (96.33)	
Mixed	2488 (0.77)	604 (0.80)	1884 (0.76)	
Asian	3803 (1.18)	883 (1.16)	2920 (1.18)	
Black	2708 (0.84)	581 (0.77)	2127 (0.86)	
Others	1788 (0.55)	437 (0.58)	1351 (0.55)	
Unknown	1047 (0.32)	267 (0.35)	780 (0.32)	
Education levels, years, n (%)				0.142
≤10	146 (0.05)	37 (0.05)	109 (0.04)	
11–12	9072 (2.81)	2311 (3.05)	6761 (2.74)	
>12	311,711 (96.53)	72,981 (96.26)	238,730 (96.61)	
Unknown	1991 (0.62)	485 (0.64)	1506 (0.61)	
Body mass index, n (%)				0.042
Normal (<25.0 kg/m^2)	120,325 (37.26)	29,366 (38.73)	90,959 (36.81)	
Overweight (25.0–29.9 kg/m^2)	137,658 (42.63)	31,604 (41.69)	106,054 (42.92)	
Obese (≥30.0 kg/m^2)	64,061 (19.84)	14,632 (19.30)	49,429 (20.00)	
Unknown	876 (0.27)	212 (0.28)	664 (0.27)	
Blood pressure, n (%)				<0.001
SBP <140 mmHg and DBP <90 mmHg	132 (0.04)	40 (0.05)	92 (0.04)	
SBP ≥140 mmHg or DBP ≥90 mmHg	305,833 (94.71)	71,856 (94.78)	233,977 (94.69)	
Unknown	16,955 (5.25)	3918 (5.17)	13,037 (5.28)	
Fasting blood glucose, n (%)				0.030
<100 mg/dL	240,598 (74.51)	56,287 (74.24)	184,311 (74.59)	
≥100 mg/dL	39,084 (12.10)	9339 (12.32)	29,745 (12.04)	
Unknown	43,238 (13.39)	10,188 (13.44)	33,050 (13.37)	

Supplementary Table 8. Continued

Matching covariates	1:4 propensity score-matched validation cohort B			
	Total (n=322,920)	COVID-19 (n=75,814)	Non-COVID-19 (n=247,106)	SMD[a]
Smoking status, n (%)				<0.001
Current smoker	186,905 (57.88)	43,900 (57.9)	143,005 (57.87)	
Non-smoker	135,283 (41.89)	31,719 (41.84)	103,564 (41.91)	
Unknown	732 (0.23)	195 (0.26)	537 (0.22)	
Alcoholic drinks, n (%)				0.029
Every day	51,262 (15.87)	11,719 (15.46)	39,543 (16.00)	
Sometimes	119,950 (37.15)	27,777 (36.64)	92,173 (37.3)	
Rarely	151,377 (46.88)	36,246 (47.81)	115,131 (46.59)	
Unknown	331 (0.10)	72 (0.09)	259 (0.10)	
Aerobic physical activity, n (%)				0.022
Sufficient	101,454 (31.42)	24,230 (31.96)	77,224 (31.25)	
Insufficient	219,310 (67.91)	51,103 (67.41)	168,207 (68.07)	
Unknown	2156 (0.67)	481 (0.63)	1675 (0.68)	

DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; SMD, standardized mean difference.
[a]SMD <0.1 indicates no significant imbalance. All SMDs were <0.100 in the propensity score–matched cohorts, except for education levels.

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 9. The propensity-score-matched analysis of HR (95% CI) of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities events following COVID-19 diagnosis of patients in discovery cohort (South Korea)

	Events, n (%)	Incidence rate[a]	HR (95% CI)	
			Model 1[b]	Model 2[c]
Gastrointestinal diseases				
Non-infected	5,328 (1.38)	39.9	1.0 (reference)	1.0 (reference)
Patients with COVID-19	1,407 (1.56)	46.3	1.15 (1.09 to 1.22)*	1.12 (1.05 to 1.20)*
Esophagitis				
Non-infected	12 (0.00)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	2 (0.00)	0.1	0.73 (0.16 to 3.28)	0.69 (0.15 to 3.21)
Gastro-esophageal reflux disease				
Non-infected	948 (0.25)	7.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	301 (0.33)	9.8	1.38 (1.21 to 1.57)*	1.36 (1.18 to 1.56)*
Vascular disorder of intestine				
Non-infected	11 (0.00)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	0 (0.00)	0.0	NA	NA
Peptic ulcer				
Non-infected	389 (0.10)	2.9	1.0 (reference)	1.0 (reference)
Patients with COVID-19	92 (0.10)	3.0	1.02 (0.82 to 1.29)	1.06 (0.83 to 1.34)
Gastritis and duodenitis				
Non-infected	2,693 (0.70)	20.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	667 (0.74)	21.7	1.08 (0.99 to 1.17)	1.21 (1.10 to 1.32)*
Functional dyspepsia				
Non-infected	585 (0.15)	4.3	1.0 (reference)	1.0 (reference)
Patients with COVID-19	157 (0.17)	5.1	1.17 (0.98 to 1.40)	1.21 (1.00 to 1.47)*
Acute appendicitis				
Non-infected	98 (0.03)	0.7	1.0 (reference)	1.0 (reference)
Patients with COVID-19	28 (0.03)	0.9	1.25 (0.82 to 1.91)	0.49 (0.30 to 0.79)
Inflammatory bowel disease				
Non-infected	8 (0.00)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	3 (0.00)	0.1	1.66 (0.44 to 6.25)	0.88 (0.19 to 4.01)
Colitis				
Non-infected	52 (0.01)	0.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	5 (0.01)	0.2	0.42 (0.17 to 1.04)	0.50 (0.19 to 1.28)

Supplementary Table 9. Continued

	Events, n (%)	Incidence rate[a]	HR (95% CI)	
			Model 1[b]	Model 2[c]
Paralytic ileus				
Non-infected	11 (0.00)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	2 (0.00)	0.1	0.78 (0.17 to 3.51)	0.35 (0.07 to 1.77)
Diverticular disease				
Non-infected	29 (0.01)	0.2	1.0 (reference)	1.0 (reference)
Patients with COVID-19	6 (0.01)	0.2	0.90 (0.38 to 2.18)	0.39 (0.15 to 1.00)
Irritable bowel syndrome				
Non-infected	203 (0.05)	1.5	1.0 (reference)	1.0 (reference)
Patients with COVID-19	51 (0.06)	1.6	1.09 (0.80 to 1.49)	1.03 (0.74 to 1.43)
Functional intestinal disorders				
Non-infected	314 (0.08)	2.3	1.0 (reference)	1.0 (reference)
Patients with COVID-19	99 (0.11)	3.2	1.37 (1.09 to 1.72)*	1.22 (0.96 to 1.56)
Abscess or fissure of anal regions				
Non-infected	179 (0.05)	1.3	1.0 (reference)	1.0 (reference)
Patients with COVID-19	41 (0.05)	1.3	1.02 (0.72 to 1.43)	0.36 (0.25 to 0.53)*
Hemorrhoids and perianal venous thrombosis				
Non-infected	349 (0.09)	2.6	1.0 (reference)	1.0 (reference)
Patients with COVID-19	100 (0.11)	3.2	1.26 (1.01 to 1.57)*	0.57 (0.45 to 0.74)*
Peritonitis				
Non-infected	8 (0.00)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	0 (0.00)	0.0	NA	NA
Other gastrointestinal diseases				
Non-infected	8 (0.00)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	2 (0.00)	0.1	1.09 (0.23 to 5.11)	0.96 (0.20 to 4.65)
Hepatobiliary diseases				
Non-infected	539 (0.14)	4.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	166 (0.18)	5.4	1.34 (1.13 to 1.60)*	1.11 (0.92 to 1.33)
He patic failure				
Non-infected	0 (0.00)	0.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	1 (0.00)	0.0	NA	NA

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 9. Continued

	Events, n (%)	Incidence rate[a]	HR (95% CI)	
			Model 1[b]	Model 2[c]
Chronic hepatitis				
Non-infected	76 (0.02)	0.6	1.0 (reference)	1.0 (reference)
Patients with COVID-19	25 (0.03)	0.8	1.43 (0.91 to 2.25)	1.36 (0.85 to 2.18)
Inflammatory liver diseases				
Non-infected	206 (0.05)	1.5	1.0 (reference)	1.0 (reference)
Patients with COVID-19	83 (0.09)	2.7	1.75 (1.36 to 2.26)*	1.73 (1.31 to 2.26)*
Cirrhosis of liver				
Non-infected	46 (0.01)	0.3	1.0 (reference)	1.0 (reference)
Patients with COVID-19	5 (0.01)	0.2	0.47 (0.19 to 1.19)	0.37 (0.15 to 0.95)*
Cholelithiasis				
Non-infected	137 (0.04)	1.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	32 (0.04)	1.0	1.01 (0.69 to 1.49)	0.67 (0.45 to 1.00)
Cholecystitis and cholangitis				
Non-infected	37 (0.01)	0.3	1.0 (reference)	1.0 (reference)
Patients with COVID-19	6 (0.01)	0.2	0.71 (0.30 to 1.68)	0.39 (0.16 to 0.99)*
Acute pancreatitis				
Non-infected	19 (0.00)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	3 (0.00)	0.1	0.69 (0.21 to 2.34)	0.47 (0.13 to 1.65)
Other hepato-biliary-pancreatic diseases				
Non-infected	60 (0.02)	0.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	15 (0.02)	0.5	1.09 (0.62 to 1.92)	0.82 (0.45 to 1.49)
Other digestive abnormalities				
Non-infected	11,079 (2.86)	83.8	1.0 (reference)	1.0 (reference)
Patients with COVID-19	2,678 (2.96)	88.9	1.05 (1.01 to 1.10)	1.00 (0.95 to 1.04)
Abdominal and pelvic pain				
Non-infected	7,375 (1.91)	55.3	1.0 (reference)	1.0 (reference)
Patients with COVID-19	1,614 (1.79)	53.0	0.95 (0.90 to 1.01)	0.89 (0.84 to 0.94)
Nausea, vomiting, and dysphagia				
Non-infected	2,274 (0.59)	16.8	1.0 (reference)	1.0 (reference)
Patients with COVID-19	736 (0.81)	23.9	1.41 (1.30 to 1.54)*	1.28 (1.17 to 1.40)*

Supplementary Table 9. Continued

	Events, n (%)	Incidence rate[a]	HR (95% CI)	
			Model 1[b]	Model 2[c]
Heartburn				
Non-infected	1,670 (0.43)	12.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	379 (0.42)	12.3	0.99 (0.88 to 1.11)	1.02 (0.91 to 1.15)
Fecal incontinence				
Non-infected	16 (0.00)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	7 (0.01)	0.2	1.88 (0.78 to 4.58)	1.84 (0.71 to 4.79)
Hepatomegaly and splenomegaly				
Non-infected	5 (0.00)	0.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	2 (0.00)	0.1	1.74 (0.34 to 8.95)	1.43 (0.25 to 8.06)
Hyperbilirubinemia				
Non-infected	56 (0.01)	0.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	8 (0.01)	0.3	0.62 (0.30 to 1.31)	0.57 (0.27 to 1.22)
Ascites				
Non-infected	20 (0.01)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	3 (0.00)	0.1	0.65 (0.19 to 2.18)	0.55 (0.16 to 1.89)
Abnormal results of liver function studies				
Non-infected	0 (0.00)	0.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	0 (0.00)	0.0	NA	NA
Abdominal distension and other symptoms				
Non-infected	139 (0.04)	1.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	40 (0.04)	1.3	1.25 (0.88 to 1.78)	1.30 (0.89 to 1.89)

CCI, Charlson Comorbidity index; CI, confidence interval; HR, hazard ratio.
The data in asterisk indicate significant differences (P<0.05).
[a]Incidence rate expressed as per 1,000 person-years.
[b]Model 1: Adjusted for age (20–39, 40–59, and ≥60 years) and sex.
[c]Model 2 (discovery): Adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 10. The propensity-score-matched analysis of HR (95% CI) of gastrointestinal diseases, hepatobiliary diseases, and other digestive abnormalities events following COVID-19 diagnosis of patients in validation cohort A (Japan)

	Events, n (%)	Incidence rate[a]	HR (95% CI)	
			Model 1[b]	Model 2[c]
Gastrointestinal diseases				
Esophagitis				
Non-infected	228 (0.01)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	139 (0.02)	0.3	2.14 (1.73 to 2.64)*	1.99 (1.61 to 2.46)*
Gastro-esophageal reflux disease				
Non-infected	30,097 (1.47)	18.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	18,201 (3.02)	38.3	2.14 (2.10 to 2.18)*	2.08 (2.05 to 2.12)*
Vascular disorder of intestine				
Non-infected	732 (0.04)	0.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	361 (0.06)	0.7	1.73 (1.52 to 1.96)*	1.64 (1.45 to 1.87)*
Peptic ulcer				
Non-infected	18,860 (0.92)	11.2	1.0 (reference)	1.0 (reference)
Patients with COVID-19	10,954 (1.82)	22.8	2.04 (2.00 to 2.09)*	1.97 (1.92 to 2.02)*
Gastritis and duodenitis				
Non-infected	66,141 (3.22)	40.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	29,903 (4.97)	63.9	1.60 (1.57 to 1.62)*	1.59 (1.56 to 1.61)*
Functional dyspepsia				
Non-infected	1226 (0.06)	0.7	1.0 (reference)	1.0 (reference)
Patients with COVID-19	561 (0.09)	1.2	1.60 (1.45 to 1.77)*	1.57 (1.42 to 1.74)*
Acute appendicitis				
Non-infected	2575 (0.13)	1.5	1.0 (reference)	1.0 (reference)
Patients with COVID-19	1907 (0.32)	3.9	2.57 (2.42 to 2.72)*	2.52 (2.38 to 2.68)*
Inflammatory bowel disease				
Non-infected	1440 (0.07)	0.9	1.0 (reference)	1.0 (reference)
Patients with COVID-19	717 (0.12)	1.5	1.72 (1.58 to 1.89)*	1.68 (1.53 to 1.84)*
Colitis				
Non-infected	2665 (0.13)	1.6	1.0 (reference)	1.0 (reference)
Patients with COVID-19	1674 (0.28)	3.4	2.19 (2.06 to 2.33)*	2.13 (2.00 to 2.26)*
Paralytic ileus				
Non-infected	4034 (0.20)	2.4	1.0 (reference)	1.0 (reference)

Supplementary Table 10. Continued

	Events, n (%)	Incidence rate[a]	HR (95% CI)	
			Model 1[b]	Model 2[c]
Patients with COVID-19	2501 (0.42)	5.2	2.17 (2.06 to 2.28)*	2.07 (1.97 to 2.18)*
Diverticular disease				
Non-infected	3191 (0.16)	1.9	1.0 (reference)	1.0 (reference)
Patients with COVID-19	1668 (0.28)	3.4	1.84 (1.73 to 1.95)*	1.77 (1.67 to 1.88)*
Irritable bowel syndrome				
Non-infected	6436 (0.31)	3.8	1.0 (reference)	1.0 (reference)
Patients with COVID-19	3164 (0.53)	6.5	1.71 (1.64 to 1.78)*	1.68 (1.61 to 1.76)*
Functional intestinal disorders				
Non-infected	21,613 (1.05)	12.9	1.0 (reference)	1.0 (reference)
Patients with COVID-19	13,391 (2.22)	28.0.	2.18 (2.13 to 2.23)*	2.06 (2.02 to 2.11)*
Abscess or fissure of anal regions				
Non-infected	4065 (0.20)	2.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	1896 (0.31)	3.9	1.61 (1.53 to 1.70)*	1.56 (1.47 to 1.64)*
Hemorrhoids and perianal venous thrombosis				
Non-infected	15,015 (0.73)	8.9	1.0 (reference)	1.0 (reference)
Patients with COVID-19	6638 (1.10)	13.7	1.54 (1.50 to 1.59)*	1.50 (1.46 to 1.54)*
Peritonitis				
Non-infected	1096 (0.05)	0.6	1.0 (reference)	1.0 (reference)
Patients with COVID-19	903 (0.15)	1.9	2.88 (2.63 to 3.14)*	2.65 (2.43 to 2.90)*
Other gastrointestinal diseases				
Non-infected	25,982 (1.27)	15.5	1.0 (reference)	1.0 (reference)
Patients with COVID-19	10,988 (1.83)	22.9	1.49 (1.46 to 1.52)*	1.43 (1.40 to 1.47)*
Hepatobiliary diseases				
Hepatic failure				
Non-infected	321 (0.02)	0.2	1.0 (reference)	1.0 (reference)
Patients with COVID-19	295 (0.05)	0.6	3.23 (2.75 to 3.78)*	2.90 (2.47 to 3.40)*
Chronic hepatitis				
Non-infected	4596 (0.22)	2.7	1.0 (reference)	1.0 (reference)
Patients with COVID-19	2024 (0.34)	4.2	1.54 (1.46 to 1.62)*	1.49 (1.42 to 1.57)*

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 10. Continued

	Events, n (%)	Incidence rate[a]	HR (95% CI)	
			Model 1[b]	Model 2[c]
Inflammatory liver diseases				
Non-infected	7612 (0.37)	4.5	1.0 (reference)	1.0 (reference)
Patients with COVID-19	3611 (0.60)	7.5	1.66 (1.60 to 1.73)*	1.62 (1.56 to 1.69)*
Cirrhosis of liver				
Non-infected	7391 (0.36)	4.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	3509 (0.58)	7.2	1.66 (1.60 to 1.73)*	1.62 (1.56 to 1.69)*
Cholelithiasis				
Non-infected	7718 (0.38)	4.6	1.0 (reference)	1.0 (reference)
Patients with COVID-19	3630 (0.6)	7.5	1.65 (1.59 to 1.72)*	1.60 (1.54 to 1.67)*
Cholecystitis and cholangitis				
Non-infected	2412 (0.12)	1.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	1430 (0.24)	2.9	2.07 (1.94 to 2.21)*	2.01 (1.88 to 2.14)*
Acute pancreatitis				
Non-infected	8070 (0.39)	4.8	1.0 (reference)	1.0 (reference)
Patients with COVID-19	4424 (0.73)	9.1	1.92 (1.85 to 1.99)*	1.87 (1.81 to 1.94)*
Other hepato-biliary-pancreatic diseases				
Non-infected	5803 (0.28)	3.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	2525 (0.42)	5.2	1.53 (1.46 to 1.60)*	1.50 (1.43 to 1.57)*
Other digestive abnormalities				
Abdominal and pelvic pain				
Non-infected	15,540 (0.76)	9.2	1.0 (reference)	1.0 (reference)
Patients with COVID-19	8507 (1.41)	17.7	1.91 (1.86 to 1.96)*	1.89 (1.84 to 1.94)*
Nausea, vomiting, and dysphagia				
Non-infected	14,084 (0.69)	8.4	1.0 (reference)	1.0 (reference)
Patients with COVID-19	10,753 (1.79)	22.4	2.67 (2.61 to 2.74)*	2.58 (2.51 to 2.64)*
Heartburn				
Non-infected	234 (0.01)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	144 (0.02)	0.3	2.15 (1.75 to 2.65)*	2.13 (1.73 to 2.62)*
Fecal incontinence				
Non-infected	13 (0.00063)	0.0076	1.0 (reference)	1.0 (reference)

Supplementary Table 10. Continued

	Events, n (%)	Incidence rate[a]	HR (95% CI)	
			Model 1[b]	Model 2[c]
Patients with COVID-19	7 (0.0012)	0.014	1.90 (0.76 to 4.75)	1.75 (0.69 to 4.41)
Hepatomegaly and splenomegaly				
Non-infected	348 (0.02)	0.2	1.0 (reference)	1.0 (reference)
Patients with COVID-19	206 (0.03)	0.4	2.06 (1.73 to 2.45)*	2.01 (1.69 to 2.39)*
Hyperbilirubinemia				
Non-infected	252 (0.01)	0.1	1.0 (reference)	1.0 (reference)
Patients with COVID-19	127 (0.02)	0.3	1.76 (1.42 to 2.18)*	1.67 (1.35 to 2.08)*
Ascites				
Non-infected	356 (0.02)	0.2	1.0 (reference)	1.0 (reference)
Patients with COVID-19	330 (0.05)	0.7	3.24 (2.79 to 3.77)*	2.91 (2.50 to 3.39)*
Abnormal results of liver function studies				
Non-infected	1354 (0.07)	0.8	1.0 (reference)	1.0 (reference)
Patients with COVID-19	584 (0.10)	1.2	1.50 (1.36 to 1.65)*	1.48 (1.35 to 1.64)*
Abdominal distension and other symptoms				
Non-infected	11,784 (0.57)	7.0	1.0 (reference)	1.0 (reference)
Patients with COVID-19	6204 (1.03)	12.8	1.85 (1.79 to 1.91)*	1.79 (1.74 to 1.85)*

CCI, Charlson Comorbidity index; CI, confidence interval; HR, hazard ratio.
The data in asterisk indicate significant differences (P<0.05).
[a]Incidence rate expressed as per 1,000 person-years.
[b]Model 1: Adjusted for age (20–39, 40–59, and ≥60 years) and sex.
[c]Model 2 (validation A): Adjusted for age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, everyday, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 11. The HR with 95% CI for the long-term sequelae risk of incident gastrointestinal, hepatobiliary diseases, and other digestive abnormalities following COVID-19 diagnosis of patients in the propensity score-matched cohorts in South Korea (discovery), Japan (validation A), using alternative cohort specifications

Cohort	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Gastrointestinal diseases					
Discovery	Non-infected	4845 (0.86)	25.6	1.0 (reference)	1.0 (reference)
Discovery	Patients with COVID-19	1133 (0.96)	28.7	1.39 (1.30 to 1.49)*	1.34 (1.25 to 1.43)*
Validation A	Non-infected	46,719 (1.97)	24.6	1.0 (reference)	1.0 (reference)
Validation A	Patients with COVID-19	24,677 (3.59)	46.4	1.92 (1.89 to 1.95)*	1.57 (1.54 to 1.59)*
Hepatobiliary diseases					
Discovery	Non-infected	470 (0.08)	2.5	1.0 (reference)	1.0 (reference)
Discovery	Patients with COVID-19	127 (0.11)	3.2	1.51 (1.24 to 1.84)*	1.46 (1.19 to 1.78)*
Validation A	Non-infected	5944 (0.25)	3.0	1.0 (reference)	1.0 (reference)
Validation A	Patients with COVID-19	3062 (0.45)	5.6	1.86 (1.78 to 1.94)*	1.57 (1.51 to 1.65)*
Other digestive abnormalities					
Discovery	Non-infected	1167 (0.21)	6.2	1.0 (reference)	1.0 (reference)
Discovery	Patients with COVID-19	224 (0.19)	5.6	1.12 (0.97 to 1.30)	1.08 (0.94 to 1.25)
Validation A	Non-infected	6259 (0.26)	3.0	1.0 (reference)	1.0 (reference)
Validation A	Patients with COVID-19	4852 (0.71)	8.8	2.78 (2.67 to 2.88)*	2.26 (2.17 to 2.34)*

CI, confidence interval; HR, hazard ratio.

The data in asterisk indicate significant differences (P<0.05).

[a]Incidence rate expressed as per 1,000 person-years.

[b]Model 1: Adjusted for age and sex.

[c]Model 2 (discovery): Adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

[c]Model 2 (validation A): Adjusted for age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, everyday, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

Supplementary Table 12. Time attenuation effect on the development of gastrointestinal, hepatobiliary diseases, and other digestive abnormalities after SARS-CoV-2 infection in the propensity score-matched cohorts in South Korea (discovery), Japan (validation A), using alternative cohort specifications (model 2 adjusted HR with 95% CI)

Time	HR (95% CI)[a]	
	Discovery cohort	Validation A cohort
Gastrointestinal diseases		
<3 months	1.19 (1.07 to 1.31)*	2.15 (2.10 to 2.21)*
3–6 months	1.56 (1.39 to 1.75)*	1.38 (1.34 to 1.42)*
≥6 months	1.24 (1.09 to 1.42)*	1.26 (1.23 to 1.29)*
Hepatobiliary diseases		
<3 months	1.57 (1.16 to 2.11)*	1.99 (1.83 to 2.15)*
3–6 months	1.28 (0.91 to 1.81)	1.43 (1.31 to 1.55)*
≥6 months	1.39 (0.90 to 2.14)	1.42 (1.32 to 1.52)*
Other digestive abnormalities		
<3 months	1.28 (1.04 to 1.57)*	3.38 (3.16 to 3.62)*
3–6 months	0.95 (0.72 to 1.25)	2.01 (1.86 to 2.16)*
≥6 months	0.87 (0.64 to 1.19)	1.78 (1.68 to 1.89)*

CI, confidence interval; HR, hazard ratio.

The data in asterisk indicate significant differences ($P<0.05$).

[a]Discovery: Adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

[a]Validation A: Adjusted for age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, every day, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 13. Stratification analysis for the long-term risk of incident gastrointestinal diseases following COVID-19 diagnosis in the propensity score-matched cohorts of discovery cohort (South Korea)

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Male					
	None	2,996 (1.33)	38.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	791 (1.52)	45.0	1.17 (1.08 to 1.26)*	1.09 (1.00 to 1.18)*
Female					
	None	2,332 (1.45)	42.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	616 (1.61)	48.2	1.13 (1.04 to 1.24)*	1.16 (1.05 to 1.27)*
Age 20–39 years					
	None	1,421 (1.02)	29.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	374 (1.18)	34.7	1.18 (1.05 to 1.32)*	1.09 (0.96 to 1.24)
Age 40–59 years					
	None	2,583 (1.51)	42.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	656 (1.65)	46.7	1.11 (1.02 to 1.21)*	1.07 (0.97 to 1.17)
Age ≥60 years					
	None	1,324 (1.75)	56.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	377 (1.97)	68.0	1.21 (1.08 to 1.36)*	1.20 (1.06 to 1.35)*
Low income					
	None	2,262 (1.40)	40.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	590 (1.57)	46.6	1.14 (1.04 to 1.25)*	1.15 (1.04 to 1.27)*
Middle income					
	None	2,003 (1.31)	38.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	532 (1.50)	45.0	1.16 (1.06 to 1.28)*	1.12 (1.01 to 1.24)*
High income					
	None	1,063 (1.46)	41.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	285 (1.66)	48.5	1.16 (1.02 to 1.32)*	1.08 (0.94 to 1.24)
Rural residence					
	None	2,780 (1.36)	40.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	760 (1.59)	49.0	1.19 (1.10 to 1.29)*	1.16 (1.07 to 1.27)*
Urban residence					
	None	2,548 (1.40)	39.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	647 (1.52)	43.6	1.11 (1.02 to 1.21)*	1.08 (0.98 to 1.19)

Supplementary Table 13. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
CCI score, 0					
	None	4,426 (1.25)	36.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,179 (1.45)	43.7	1.18 (1.11 to 1.26)*	1.11 (1.03 to 1.19)*
CCI score, 1					
	None	658 (2.66)	64.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	161 (2.51)	63.4	0.98 (0.83 to 1.17)	0.96 (0.81 to 1.15)
CCI scores, ≥2					
	None	244 (2.80)	75.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	67 (2.50)	77.1	1.02 (0.78 to 1.34)	1.11 (0.84 to 1.46)
BMI, <18.5 kg/m^2					
	None	125 (1.11)	33.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	37 (1.35)	42.2	1.22 (0.85 to 1.76)	1.39 (0.92 to 2.11)
BMI, 18.5–23.0 kg/m^2					
	None	1,691 (1.29)	38.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	439 (1.45)	43.7	1.14 (1.03 to 1.27)*	1.11 (0.99 to 1.25)
BMI, 23.0–25.0 kg/m^2					
	None	1,194 (1.34)	38.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	330 (1.59)	47.4	1.21 (1.07 to 1.37)*	1.25 (1.10 to 1.43)*
BMI, ≥25.0 kg/m^2					
	None	2,318 (1.49)	42.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	599 (1.64)	48.0	1.12 (1.03 to 1.23)*	1.05 (0.96 to 1.16)
Drinker					
	None	2,297 (1.32)	38.3	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	598 (1.48)	43.7	1.13 (1.04 to 1.24)*	1.08 (0.98 to 1.19)
Non-drinker					
	None	3,026 (1.42)	41.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	807 (1.61)	48.4	1.17 (1.08 to 1.26)*	1.16 (1.07 to 1.26)*
Sufficient physical activity					
	None	2,646 (1.41)	40.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	717 (1.64)	48.2	1.18 (1.09 to 1.29)*	1.16 (1.06 to 1.27)*

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 13. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Insufficient physical activity					
	None	2,675 (1.35)	39.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	686 (1.47)	44.3	1.12 (1.03 to 1.22)*	1.08 (0.99 to 1.19)
Smoker					
	None	1,969 (1.39)	40.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	511 (1.55)	46.4	1.14 (1.03 to 1.25)*	1.07 (0.96 to 1.19)
Non-smoker					
	None	3,353 (1.37)	39.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	895 (1.56)	46.3	1.16 (1.08 to 1.25)*	1.16 (1.07 to 1.25)*

BMI, body mass index; CCI, Charlson Comorbidity index; CI, confidence interval; HR, hazard ratio.
The data in asterisk indicate significant differences (P<0.05).
[a]Incidence rate expressed as per 1,000 person-years.
[b]Model 1: Adjusted for age (20–39, 40–59, and ≥60 years) and sex.
[c]Model 2 (discovery): Adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥ 30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

Supplementary Table 14. Stratification analysis for the long-term risk of incident hepatobiliary diseases following COVID-19 diagnosis in the propensity score-matched cohorts of discovery cohort (South Korea)

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Male					
	None	313 (1.39)	4.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	102 (1.96)	5.7	1.44 (1.15 to 1.80)*	1.18 (0.93 to 1.49)
Female					
	None	226 (1.40)	4.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	64 (1.67)	4.9	1.21 (0.92 to 1.60)	1.00 (0.75 to 1.34)
Age 20–39 years					
	None	121 (0.86)	2.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	40 (1.27)	3.7	1.48 (1.04 to 2.12)*	1.17 (0.80 to 1.73)
Age 40–59 years					
	None	273 (1.60)	4.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	98 (2.47)	6.9	1.57 (1.24 to 1.97)*	1.28 (1.00 to 1.63)*
Age ≥60 years					
	None	145 (1.91)	6.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	28 (1.46)	4.9	0.82 (0.55 to 1.22)	0.70 (0.46 to 1.06)
Low income					
	None	216 (1.34)	3.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	66 (1.75)	5.1	1.33 (1.01 to 1.75)*	1.14 (0.86 to 1.52)
Middle income					
	None	207 (1.36)	3.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	58 (1.63)	4.8	1.22 (0.91 to 1.63)	1.04 (0.76 to 1.41)
High income					
	None	116 (1.59)	4.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	42 (2.44)	7.0	1.57 (1.11 to 2.24)*	1.21 (0.83 to 1.76)
Rural residence					
	None	287 (1.41)	4.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	97 (2.03)	6.1	1.47 (1.17 to 1.85)*	1.24 (0.97 to 1.57)
Urban residence					
	None	252 (1.38)	3.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	69 (1.62)	4.6	1.19 (0.91 to 1.56)	0.97 (0.73 to 1.28)

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 14. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
CCI score, 0					
	None	364 (1.03)	3.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	125 (1.54)	4.6	1.52 (1.24 to 1.86)*	1.22 (0.98 to 1.53)
CCI score, 1					
	None	126 (5.08)	12.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	31 (4.84)	11.9	0.98 (0.66 to 1.46)	0.83 (0.56 to 1.24)
CCI scores, ≥2					
	None	49 (5.62)	14.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	10 (3.74)	11.1	0.75 (0.38 to 1.49)	0.76 (0.38 to 1.51)
BMI, <18.5 kg/m^2					
	None	10 (0.89)	2.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1 (0.36)	1.1	0.38 (0.05 to 2.98)	0.43 (0.04 to 4.12)
BMI, 18.5–23.0 kg/m^2					
	None	119 (0.91)	2.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	37 (1.22)	3.6	1.36 (0.94 to 1.97)	1.08 (0.73 to 1.59)
BMI, 23.0–25.0 kg/m^2					
	None	131 (1.47)	4.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	38 (1.83)	5.4	1.26 (0.88 to 1.81)	1.07 (0.73 to 1.56)
BMI, ≥25.0 kg/m^2					
	None	279 (1.79)	5.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	90 (2.46)	7.1	1.40 (1.10 to 1.78)*	1.15 (0.89 to 1.48)
Drinker					
	None	222 (1.28)	3.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	77 (1.91)	5.5	1.51 (1.17 to 1.96)*	1.27 (0.97 to 1.67)
Non-drinker					
	None	316 (1.48)	4.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	89 (1.78)	5.2	1.23 (0.97 to 1.55)*	1.01 (0.79 to 1.29)
Sufficient physical activity					
	None	244 (1.30)	3.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	70 (1.60)	4.6	1.25 (0.96 to 1.63)	0.96 (0.73 to 1.27)

Supplementary Table 14. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Insufficient physical activity					
	None	295 (1.49)	4.3	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	96 (2.06)	6.1	1.42 (1.12 to 1.78)*	1.22 (0.96 to 1.55)
Smoker					
	None	205 (1.45)	4.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	61 (1.85)	5.4	1.30 (0.98 to 1.73)	1.08 (0.80 to 1.47)
Non-smoker					
	None	334 (1.36)	3.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	105 (1.83)	5.3	1.36 (1.10 to 1.70)*	1.12 (0.89 to 1.41)

BMI, body mass index; CCI, Charlson Comorbidity index; CI, confidence interval; HR, hazard ratio.
The data in asterisk indicate significant differences (P<0.05).
[a]Incidence rate expressed as per 1000 person-years.
[b]Model 1: Adjusted for age (20–39, 40–59, and ≥60 years) and sex.
[c]Model 2 (discovery): Adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 15. Stratification analysis for the long-term risk of incident other digestive abnormalities following COVID-19 diagnosis in the propensity score-matched cohorts of discovery cohort (South Korea)

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Male					
	None	4,382 (1.94)	56.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,089 (2.09)	61.9	1.10 (1.03 to 1.17)*	1.04 (0.97 to 1.12)
Female					
	None	6,697 (4.15)	123.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,589 (4.15)	126.6	1.03 (0.97 to 1.08)	0.97 (0.91 to 1.02)
Age 20–39 years					
	None	4,161 (2.98)	87.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	992 (3.14)	93.2	1.06 (0.99 to 1.14)	0.99 (0.92 to 1.07)
Age 40–59 years					
	None	4,913 (2.87)	80.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,172 (2.96)	84.0	1.04 (0.98 to 1.11)	0.98 (0.91 to 1.05)
Age ≥60 years					
	None	2,005 (2.64)	85.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	514 (2.68)	92.6	1.08 (0.98 to 1.19)	1.03 (0.93 to 1.14)
Low income					
	None	4,855 (3.01)	88.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,115 (2.96)	88.8	1.00 (0.94 to 1.07)	0.94 (0.88 to 1.01)
Middle income					
	None	4,282 (2.81)	83.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,079 (3.04)	92.0	1.10 (1.03 to 1.18)*	1.05 (0.98 to 1.13)
High income					
	None	1,942 (2.66)	76.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	484 (2.81)	82.7	1.08 (0.98 to 1.19)	1.01 (0.91 to 1.12)
Rural residence					
	None	5,797 (2.84)	85.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,392 (2.92)	90.4	1.05 (0.99 to 1.11)	0.99 (0.93 to 1.05)
Urban residence					
	None	5,282 (2.89)	81.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,286 (3.02)	87.2	1.06 (1.00 to 1.13)	1.01 (0.95 to 1.08)

Supplementary Table 15. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
CCI score, 0					
	None	9,532 (2.70)	80.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	2,323 (2.86)	86.9	1.08 (1.03 to 1.13)*	1.00 (0.96 to 1.05)
CCI score, 1					
	None	1,145 (4.62)	112.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	243 (3.80)	96.0	0.84 (0.73 to 0.97)*	0.81 (0.70 to 0.93)*
CCI scores, ≥2					
	None	402 (4.61)	124.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	112 (4.19)	129.5	1.04 (0.84 to 1.28)	1.04 (0.84 to 1.29)
BMI, <18.5 kg/m^2					
	None	390 (3.47)	106.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	101 (3.68)	117.4	1.11 (0.89 to 1.39)	1.15 (0.91 to 1.45)
BMI, 18.5–23.0 kg/m^2					
	None	4,301 (3.29)	98.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,023 (3.37)	103.1	1.05 (0.98 to 1.12)	0.98 (0.91 to 1.05)
BMI, 23.0–25.0 kg/m^2					
	None	2,435 (2.75)	80.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	598 (2.88)	86.4	1.07 (0.98 to 1.17)	1.01 (0.91 to 1.11)
BMI, ≥25.0 kg/m^2					
	None	3,948 (2.54)	72.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	953 (2.61)	76.7	1.05 (0.98 to 1.12)	1.00 (0.93 to 1.08)
Drinker					
	None	4,513 (2.60)	75.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,093 (2.71)	80.3	1.05 (0.99 to 1.12)	0.99 (0.92 to 1.06)
Non-drinker					
	None	6,561 (3.08)	90.3	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,584 (3.16)	95.9	1.06 (1.00 to 1.11)	1.00 (0.94 to 1.06)
Sufficient physical activity					
	None	5,306 (2.82)	81.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,236 (2.82)	83.6	1.01 (0.95 to 1.08)	0.94 (0.88 to 1.01)

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 15. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Insufficient physical activity					
	None	5,763 (2.90)	85.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,440 (3.10)	93.9	1.09 (1.03 to 1.16)*	1.05 (0.98 to 1.11)
Smoker					
	None	2,989 (2.11)	61.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	747 (2.26)	68.0	1.09 (1.01 to 1.18)*	1.02 (0.94 to 1.11)
Non-smoker					
	None	8,086 (3.30)	96.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1,931 (3.37)	100.9	1.04 (0.99 to 1.09)	0.99 (0.94 to 1.04)

BMI, body mass index; CCI, Charlson Comorbidity index; CI, confidence interval; HR, hazard ratio.
The data in asterisk indicate significant differences (P<0.05).
[a]Incidence rate expressed as per 1,000 person-years.
[b]Model 1: Adjusted for age (20–39, 40–59, and ≥60 years) and sex.
[c]Model 2 (discovery): Adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

Supplementary Table 16. Stratification analysis for the long-term risk of incident gastrointestinal diseases following COVID-19 diagnosis in the propensity score-matched cohorts of validation cohort A (Japan)

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Male					
	None	84,275 (6.40)	82.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	42,645 (11.06)	151.0	1.84 (1.82–1.86)*	1.80 (1.78–1.82)*
Female					
	None	59,340 (8.07)	102.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	29,810 (13.77)	189.0	1.83 (1.80–1.85)*	1.80 (1.78–1.83)*
Age 20–39 years					
	None	50,935 (6.31)	79.3	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	28,325 (11.49)	153.3	1.93 (1.90–1.96)*	1.90 (1.88–1.93)*
Age 40–59 years					
	None	78,900 (7.30)	95.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	36,120 (11.82)	165.9	1.73 (1.70–1.75)*	1.69 (1.66–1.71)*
Age ≥60 years					
	None	13,780 (8.30)	100.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	8010 (16.04)	213.2	2.11 (2.05–2.16)*	2.03 (1.97–2.08)*
CCI score, 0					
	None	139,717 (6.86)	87.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	68,706 (11.63)	159.2	1.81 (1.79–1.83)*	1.81 (1.79–1.82)*
CCI score, ≥1					
	None	3898 (24.66)	288.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	3749 (33.11)	445.3	1.51 (1.45–1.58)*	1.45 (1.39–1.52)*
BMI, <25.0 kg/m^2					
	None	103,798 (6.95)	89.3	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	52,012 (11.93)	163.9	1.83 (1.81–1.85)*	1.80 (1.78–1.82)*
BMI, 25.0–29.9 kg/m^2					
	None	30,780 (7.11)	90.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	15,510 (12.15)	165.9	1.83 (1.79–1.87)*	1.78 (1.75–1.81)*

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 16. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
BMI, ≥30.0 kg/m^2					
	None	8842 (7.21)	88.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	4823 (12.85)	169.2	1.90 (1.83–1.97)*	1.84 (1.78–1.91)*
Unknown					
	None	195 (6.63)	86.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	110 (12.22)	174.3	2.01 (1.59–2.54)*	1.98 (1.56–2.51)*
Non-smoker					
	None	29,005 (6.07)	77.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	15,144 (10.87)	147.2	1.91 (1.87–1.94)*	1.86 (1.83–1.90)*
Smoker					
	None	110,039 (7.36)	94.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	54,827 (12.50)	171.4	1.82 (1.80–1.84)*	1.78 (1.76–1.80)*
Unknown					
	None	4571 (5.76)	75.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	2484 (10.35)	143.6	1.90 (1.81–2.00)*	1.87 (1.78–1.97)*
Non-drinker					
	None	29,005 (6.07)	89.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	15,144 (10.87)	160.0	1.79 (1.77–1.81)*	1.75 (1.73–1.78)*
Drinker					
	None	110,039 (7.36)	91.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	54,827 (12.50)	172.8	1.88 (1.85–1.91)*	1.84 (1.81–1.87)*
Unknown					
	None	4571 (5.76)	79.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	2484 (10.35)	155.8	1.95 (1.89–2.02)*	1.92 (1.85–1.98)*
Sufficient physical activity					
	None	28,398 (6.74)	87.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	13,874 (11.44)	157.6	1.68 (1.63–1.72)*	1.77 (1.74–1.81)*
Insufficient physical activity					
	None	103,638 (7.21)	91.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	52,309 (12.35)	168.5	1.77 (1.72–1.82)*	1.79 (1.77–1.81)*

Supplementary Table 16. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Unknown					
	None	11,579 (5.97)	77.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	6272 (10.94)	151.2	1.71 (1.59–1.84)*	1.92 (1.86–1.98)*

BMI, body mass index; CCI, Charlson Comorbidity index; CI, confidence interval; HR, hazard ratio.
The data in asterisk indicate significant differences (P<0.05).
[a]Incidence rate expressed as per 1,000 person-years.
[b]Model 1: Adjusted for age (20–39, 40–59, and ≥60 years) and sex.
[c]Model 2 (validation A): Adjusted for age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, every day, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 17. Stratification analysis for the long-term risk of incident hepatobiliary diseases following COVID-19 diagnosis in the propensity score-matched cohorts of validation cohort A (Japan)

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Male					
	None	23,059 (1.75)	21.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	10,931 (2.83)	36.1	1.68 (1.64–1.71)*	1.63 (1.60–1.67)*
Female					
	None	10,809 (1.47)	17.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	5516 (2.55)	31.8	1.80 (1.74–1.86)*	1.76 (1.70–1.81)*
Age 20–39 years					
	None	9978 (1.24)	14.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	5184 (2.10)	26.0	1.74 (1.68–1.80)*	1.71 (1.65–1.77)*
Age 40–59 years					
	None	20,131 (1.86)	23.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	9061 (2.97)	38.5	1.65 (1.61–1.69)*	1.60 (1.56–1.64)*
Age ≥60 years					
	None	3759 (2.27)	26.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	2202 (4.41)	52.8	2.03 (1.92–2.14)*	1.94 (1.84–2.05)*
CCI score, 0					
	None	32,936 (1.62)	19.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	15,406 (2.61)	33.1	1.68 (1.64–1.71)*	1.67 (1.64–1.70)*
CCI score, ≥1					
	None	932 (5.90)	58.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1041 (9.19)	98.4	1.67 (1.53–1.83)*	1.63 (1.49–1.78)*
BMI, <25.0 kg/m^2					
	None	21,738 (1.45)	17.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	10,676 (2.45)	31.0	1.74 (1.70–1.79)*	1.71 (1.67–1.75)*
BMI, 25.0–29.9 kg/m^2					
	None	8926 (2.06)	25.2	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	4174 (3.27)	41.4	1.64 (1.59–1.71)*	1.6 (1.55–1.66)*

Supplementary Table 17. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
BMI, ≥30.0 kg/m^2					
	None	3164 (2.58)	30.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1578 (4.20)	51.5	1.68 (1.58–1.78)*	1.62 (1.53–1.73)*
Unknown					
	None	40 (1.36)	17.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	19 (2.11)	27.2	1.61 (0.93–2.77)	1.46 (0.83–2.55)
Non-smoker					
	None	7233 (1.51)	18.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	3650 (2.62)	33.2	1.80 (1.73–1.87)*	1.75 (1.68–1.82)*
Smoker					
	None	25536 (1.71)	20.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	12295 (2.80)	35.4	1.70 (1.66–1.73)*	1.66 (1.62–1.69)*
Unknown					
	None	1099 (1.39)	17.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	502 (2.09)	27.1	1.56 (1.40–1.73)*	1.54 (1.39–1.72)*
Non-drinker					
	None	18319 (1.67)	20.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	8729 (2.69)	34.2	1.68 (1.63–1.72)*	1.63 (1.59–1.68)*
Drinker					
	None	13399 (1.67)	20.3	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	6659 (2.86)	35.8	1.77 (1.72–1.82)*	1.72 (1.67–1.77)*
Unknown					
	None	2150 (1.41)	17.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1059 (2.34)	29.7	1.71 (1.59–1.84)*	1.69 (1.57–1.82)*
Sufficient physical activity					
	None	6731 (1.60)	19.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	3233 (2.67)	34.1	1.72 (1.65–1.80)*	1.68 (1.61–1.75)*
Insufficient physical activity					
	None	24,549 (1.71)	20.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	11,918 (2.81)	35.4	1.71 (1.67–1.75)*	1.66 (1.63–1.70)*

https://doi.org/10.3350/cmh.2024.0203

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Supplementary Table 17. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Unknown					
	None	2588 (1.33)	16.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1296 (2.26)	29.0	1.75 (1.64–1.87)*	1.72 (1.61–1.84)*

BMI, body mass index; CCI, Charlson Comorbidity index; CI, confidence interval; HR, hazard ratio.
The data in asterisk indicate significant differences (P<0.05).
[a]Incidence rate expressed as per 1000 person-years.
[b]Model 1: Adjusted for age (20–39, 40–59, and ≥60 years) and sex.
[c]Model 2 (validation A): Adjusted for age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, every day, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

Supplementary Table 18. Stratification analysis for the long-term risk of incident other digestive abnormalities following COVID-19 diagnosis in the propensity score-matched cohorts of validation cohort A (Japan)

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Male					
	None	21,655 (1.64)	20.3	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	13,219 (3.43)	43.8	2.16 (2.12–2.21)*	2.10 (2.05–2.14)*
Female					
	None	18,743 (2.55)	31.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	11,227 (5.19)	66.0	2.12 (2.07–2.17)*	2.08 (2.03–2.13)*
Age 20–39 years					
	None	15,699 (1.95)	23.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	10,272 (4.17)	52.3	2.21 (2.16–2.27)*	2.18 (2.13–2.24)*
Age 40–59 years					
	None	21,314 (1.97)	24.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	11,683 (3.82)	50.0	2.02 (1.97–2.06)*	1.96 (1.91–2.00)*
Age ≥60 years					
	None	3385 (2.04)	23.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	2491 (4.99)	60.1	2.56 (2.43–2.69)*	2.42 (2.30–2.55)*
CCI score, 0					
	None	39,137 (1.92)	23.7	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	23,029 (3.90)	49.9	2.11 (2.07–2.14)*	2.10 (2.07–2.14)*
CCI score, ≥1					
	None	1261 (7.98)	81.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1417 (12.51)	137.5	1.68 (1.55–1.81)*	1.64 (1.52–1.77)*
BMI, <25.0 kg/m^2					
	None	29,793 (1.99)	24.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	17,920 (4.11)	52.7	2.14 (2.10–2.18)*	2.09 (2.05–2.13)*
BMI, 25.0–29.9 kg/m^2					
	None	8171 (1.89)	23.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	4909 (3.84)	48.8	2.12 (2.04–2.19)*	2.05 (1.98–2.13)*

https://doi.org/10.3350/cmh.2024.0203

https://doi.org/10.3350/cmh.2024.0203

Supplementary Table 18. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
BMI, ≥30.0 kg/m^2					
	None	2376 (1.94)	22.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1581 (4.21)	51.5	2.25 (2.11–2.40)*	2.17 (2.03–2.31)*
Unknown					
	None	58 (1.97)	24.8	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	36 (4.00)	52.3	2.11 (1.39–3.20)*	1.89 (1.24–2.90)*
Non-smoker					
	None	7518 (1.57)	19.4	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	4828 (3.47)	44.1	2.28 (2.20–2.36)*	2.21 (2.13–2.29)*
Smoker					
	None	31,594 (2.11)	25.9	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	18,770 (4.28)	54.5	2.10 (2.07–2.14)*	2.05 (2.02–2.09)*
Unknown					
	None	1286 (1.62)	20.5	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	848 (3.53)	46.2	2.25 (2.06–2.45)*	2.21 (2.03–2.41)*
Non-drinker					
	None	20,535 (1.87)	23.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	12,328 (3.80)	48.7	2.11 (2.06–2.16)*	2.05 (2.01–2.10)*
Drinker					
	None	17,207 (2.14)	26.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	10,431 (4.48)	56.8	2.17 (2.12–2.23)*	2.11 (2.06–2.16)*
Unknown					
	None	2656 (1.74)	21.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	1687 (3.73)	47.9	2.22 (2.09–2.36)*	2.17 (2.05–2.31)*
Sufficient physical activity					
	None	7665 (1.82)	22.6	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	4493 (3.70)	47.7	2.11 (2.04–2.19)*	2.06 (1.98–2.14)*
Insufficient physical activity					
	None	29,472 (2.05)	25.1	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	17,890 (4.23)	53.7	2.14 (2.10–2.18)*	2.08 (2.04–2.12)*

Supplementary Table 18. Continued

	Exposure	Events, n (%)	Incidence rate[a]	HR (95% CI)	
				Model 1[b]	Model 2[c]
Unknown					
	None	3261 (1.68)	21.0	1.0 (reference)	1.0 (reference)
	Patients with COVID-19	2063 (3.60)	46.7	2.22 (2.10–2.34)*	2.18 (2.06–2.30)*

BMI, body mass index; CCI, Charlson Comorbidity index; CI, confidence interval; HR, hazard ratio.
The data in asterisk indicate significant differences (P<0.05).
[a]Incidence rate expressed as per 1,000 person-years.
[b]Model 1: Adjusted for age (20–39, 40–59, and ≥60 years) and sex.
[c]Model 2 (validation A): Adjusted for age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, every day, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

https://doi.org/10.3350/cmh.2024.0203

SUPPLEMENT METHOD

Validation cohort A in Japan

JMDC validation cohort A

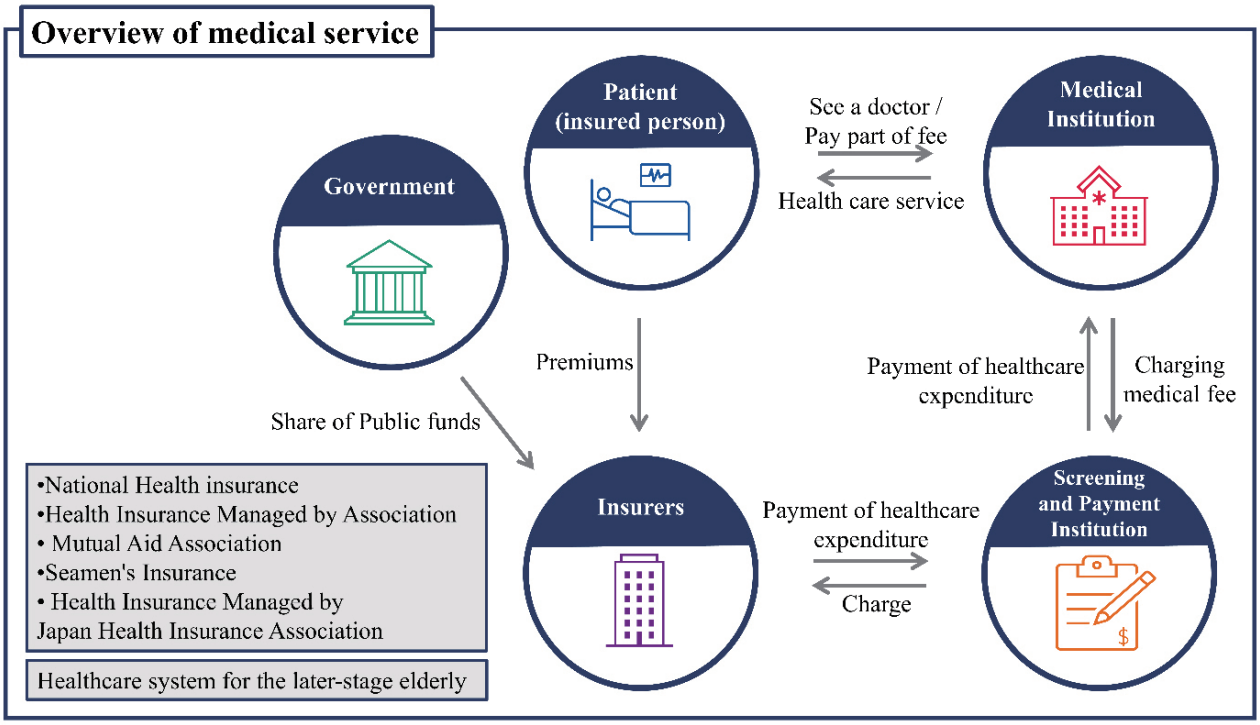
Please see this webpage (https://www.jmdc.co.jp/en/jmdc-claims-database/).

The JMDC cohort comprises 12,218,680 individuals and utilizes the same statistical methodology and coding system, ICD-10, employed in general health examinations. However, data related to SARS-CoV-2 vaccinations is not included.[1] Japan's universal insurance system provides coverage, and the JMDC collaborates with over 60 insurance providers, primarily collecting health insurance claims from employees of large Japanese corporations.[2] The database contains comprehensive patient-level data, including demographics such as age, sex, unique identifiers, and family relationships.[3] It also records detailed information on inpatient and outpatient treatments, including disease classifications based on ICD-10 codes, prescribed medications classified by the Anatomical Therapeutic Chemical class, diagnoses, therapeutic procedures, and information about medical institutions. Additionally, health checkup data, such as BMI blood pressure, medication status, clinical laboratory tests, and self-reported questionnaires on lifestyle factors like smoking, alcohol consumption, and physical activity, are included.[4]

The study sample comprised participants aged ≥20 years registered between January 1, 2018, and December 31, 2021. We excluded participants with a history of gastrointestinal disease, hepatobiliary disease, or other digestive abnormalities in the look-back period (2018–individual index data) or within 30 days of SARS-CoV-2 infection; those with insufficient information on socioeconomic status; and those with co-infection or re-infection with COVID-19 (excluded n=3,554,664).

Study participants and individual index date

The study populations comprised patients (≥20 years of age) with SARS-CoV-2 infection. Non-infected individuals were randomly selected as controls. To reduce immortal time bias, we assigned an individual index date as the date of the first diagnosis of COVID-19 in patients with COVID-19, or as the matched date of the corresponding infected case in non-infected individuals. SARS-CoV-2 infections were confirmed through real-time reverse transcriptase polymerase chain reaction assays or antigen testing of nasal and pharyngeal swabs, following the guidelines of the



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World Health Organization.[5]

COVID-19 severity was classified based on the level of medical intervention: patients admitted to intensive care units or those who required oxygen therapy, extracorporeal membrane oxygenation, renal replacement, or cardiopulmonary resuscitation were considered to have moderate-to-severe COVID-19, while others were classified as having mild COVID-19.[6]

Exposures and outcomes

The primary outcome of the study was the development of 18 gastrointestinal diseases (esophagitis, gastroesophageal reflux disease, vascular disorder of the intestine, peptic ulcer, gastritis and duodenitis, functional dyspepsia, acute appendicitis, inflammatory bowel disease, colitis, paralytic ileus, diverticular disease, irritable bowel syndrome, functional intestinal disorders, abscess or fissure of anal regions, hemorrhoids and perianal venous thrombosis, peritonitis, and other gastrointestinal diseases), 8 hepatobiliary diseases (hepatic failure, chronic hepatitis, inflammatory liver diseases, cirrhosis of liver, cholelithiasis, cholecystitis and cholangitis, acute pancreatitis, and other hepatobiliary–pancreatic diseases), and 9 other digestive abnormalities (abdominal and pelvic pain; nausea, vomiting, and dysphagia; heartburn; fecal incontinence; hepatomegaly and splenomegaly; hyperbilirubinemia; ascites; abnormal results of liver function studies; and abdominal distension and other symptoms) at least 30 days after the index date. Outcomes were defined using ICD-10 codes.[7]

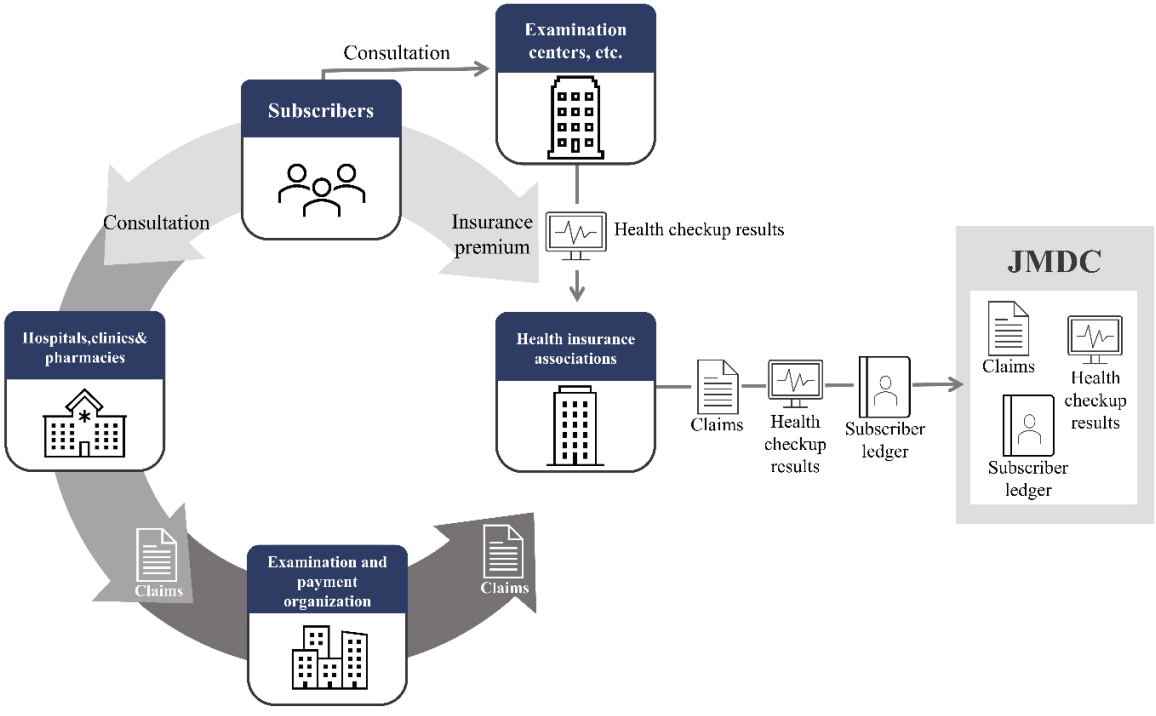
The observation period was from January 1, 2020 to December 31, 2021. Participants were followed up from the index date until the date of the primary outcomes, date of death, or December 31, 2021, whichever came first. The pre-observation period for the assessment of medical history was between 2018 and the individual index date.

Propensity score matching

To adjust for potential confounders, we used 1:4 exposure-driven propensity score matching to achieve a covariate balance across SARS-CoV-2 infected and uninfected groups. Greedy nearest-neighbor matching with random selection without replacement using a caliper of 0.001 standard deviations was implemented, and all covariates were matched.[8,9] Standardized mean differences (SMDs) below 0.1 indicate no major imbalance.

Covariates

We obtained the demographic data of the participants,



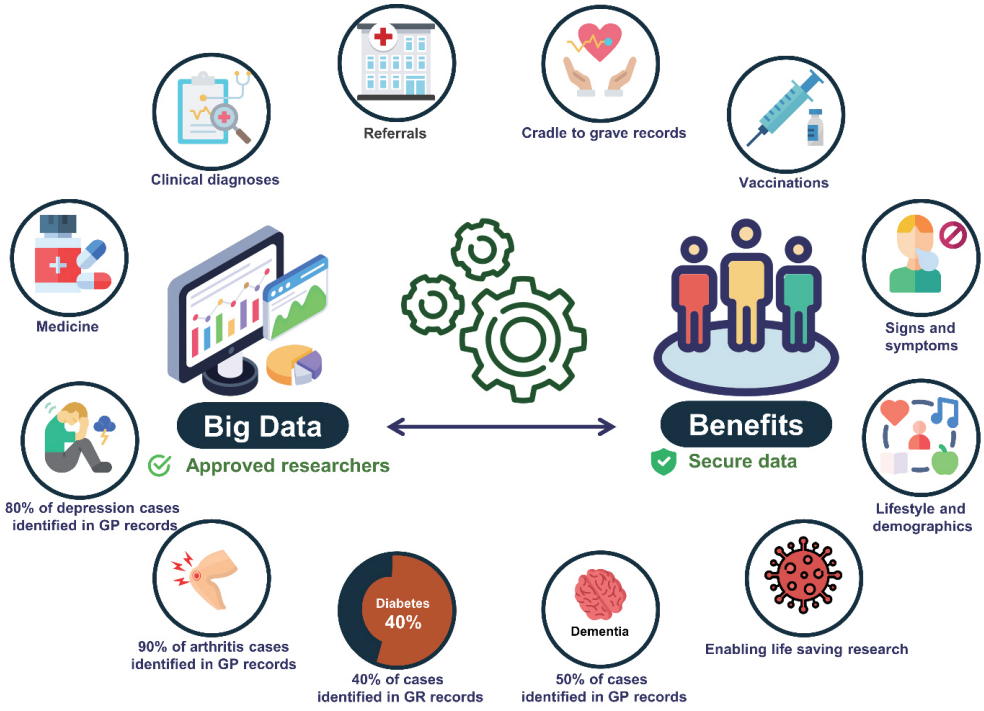
such as age (20–39, 40–59, and ≥60 years), sex, and insurance status (insured or dependent) from the insurance database. The Charlson Comorbidity Index score, history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease, and previous use of medication for diabetes, hyperlipidemia, and hypertension were obtained according to the ICD-10 code and/or results of general health checkup examination with personal medical interview. The data on the body mass index (normal range [<25.0 kg/m^2], overweight [23.0–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown), blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown), fasting blood glucose (<100, ≥100 mg/dL, and unknown), serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown), glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown), smoking status (non-smoker, current smoker, and unknown), alcoholic drinks rarely, sometimes, every day, and unknown), and aerobic physical activity (sufficient, insufficient, and unknown) were obtained from the general health examination with fasting serum samples. The national health examination data has been matched with the most recent data based on index data (2019–2021).

Validation cohort B in the UK

UKB validation cohort B

For more information, please see this webpage (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank).

The UK Biobank, an institution esteemed globally, relies on voluntary participation to furnish extensive and unique datasets for large-scale biomedical research, incorporating biomedical samples and health information.[10] Established in 2006 within the United Kingdom, this initiative has attracted a multitude of researchers who leverage participant health data and biological specimens for a wide array of medical investigations.[11] With a recruitment base exceeding 500,000 individuals nationwide, the cohort epitomizes rich diversity across age, ethnicity, sex, and geographical distribution, ensuring the generalizability of research findings to varied populations.[12] Participants have contributed an array of health-related data, encompassing health surveys, physical assessments, blood pressure measurements, and the provision of blood and urine specimens. This invaluable dataset serves as a cornerstone in research spanning diverse domains, including genomic anal-



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ysis, cardiovascular and metabolic ailments, and cancer investigation. Genomic data amassed from participants facilitate the exploration of genetic characteristics and variances, furnishing pivotal insights into genetic influences and the interplay between genes and environmental elements.[13]

Covariates

The demographic characteristics of the participants were obtained from the UK biobank database as follows: age (20–39, 40–59, and ≥60 years), sex, household income (<£18,000, £18,000–£30,999, £31,000–£51,999, £52,000–£100,000, >£100,000), and unknown), region of residence (urban and rural), townsend deprivation index (T1 [last deprived], T2, T3 [most deprived], and unknown), race (white, mixed, Asian, black, others, and unknown), Charlson Comorbidity Index score (0, 1, and ≥2), BMI (normal [<25.0 kg/m^2], overweight [25.0–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown), education levels (≤10, 11–12, >12, and unknown), blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown), fasting blood glucose (<100, ≥100 mg/dL, and unknown), smoking status (non- and current smoker, and unknown), alcohol consumption (every day, sometimes, rarely days per week, and unknown), aerobic physical activity (low, moderate, high, and unknown), previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease, and history of medication use for diabetes mellitus, dyslipidemia, and hypertension.

Adjusted model

[a]Model 1: Adjusted for age and sex.

[b]Model 2 (discovery): Adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown); smoking status (never, former, current smoker, and unknown); alcoholic drinks (<1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1-4, ≥5 times).

[c]Model 2 (validation A): Adjusted for age (20–39, 40–59, and ≥60 years); sex; CCI score (0, 1, and ≥2); body mass index (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown); serum total cholesterol (<200, 200–240, ≥240 mg/dL, and unknown); glomerular filtration rate (<60, 60–90, ≥90 mL/min/1.73 m^2, and unknown); smoking status (non- and current smoker, and unknown); alcoholic drinks (rarely, sometimes, every day, and unknown); aerobic physical activity (sufficient, insufficient, and unknown); previous history of cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease; history of medication use for diabetes mellitus, dyslipidemia, and hypertension; hospital admissions in the year before index date (0, 1, ≥2 times); and outpatient contacts in the year before index date (0, 1–4, ≥5 times).

[c]Model 2 (validation B): Adjusted for age (40–59 and ≥60 years); sex; household income (<£18,000, £18,000–£30,999, £31,000–£51,999, £52,000–£100,000, and >£100,000); region of residence (urban and rural); Townsend deprivation index (tertiles and unknown); ethnicity (white, mixed, Asian, black, others, and unknown); CCI score (0, 1, and ≥ 2); obesity (normal [<25.0 kg/m^2], overweight [25–29.9 kg/m^2], obese [≥30.0 kg/m^2], and unknown); education levels (≤10, 11–12, >12, and unknown), blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure < 90 mmHg, systolic blood pres-

sure ≥ 140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown); fasting blood glucose (<100, ≥100 mg/dL, and unknown), smoking status (never, former, and current smoker); alcohol consumption (drinks; <1, 1–2, 3–4, ≥5 days per week, and unknown); aerobic physical activity (low, moderate, and high); previous history of cardiovascular disease, chronic kidney disease, cerebrovascular disease, and chronic obstructive pulmonary disease; and history of medication use for diabetes mellitus, dyslipidemia, and hypertension.Covariates

Demographic characteristics included age (20–39, 40–59, and ≥60 years), sex, household income (low [0–39 percentile], middle [40–79 percentile], and high [80–100 percentile]), and region of residence (urban or rural). Information on body mass index (BMI; underweight [<18.5 kg/m^2], normal [18.5–22.9 kg/m^2], overweight [23.0–24.9 kg/m^2], obese [≥25.0 kg/m^2], and unknown), blood pressure (categorized as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and unknown), fasting blood glucose levels (<100, ≥100 mg/dL, and unknown), total cholesterol levels (<200, 200–239, ≥240 mg/dL, and unknown), and glomerular filtration rate (<60, 60–89, ≥90 mL/min/1.73 m^2, and unknown) were also collected. The ICD-10 codes and results of national health examinations were used to obtain information on Charlson Comorbidity Index (CCI) score, past medical history (cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease), medication for hypertension, diabetes, and hyperlipidemia, smoking status (non-, ex-, and current smoker), alcohol use (<1, 1–2, 3–4, ≥5 days per week, and unknown), and aerobic physical activity (sufficient [≥600 metabolic equivalent task scores], insufficient, and unknown).[14] Hospital admissions in the year before index date (0, 1, ≥2 times) and outpatient contacts in the year before index date (0, 1-4, ≥5 times) were obtained from the insurance database.

Subgroup analysis

Supplementary Tables 11 to 18 provide subgroup analyses of the association between post-acute phase COVID-19 and digestive disorders stratified by sex, age, sex, income level, CCI, BMI, alcohol consumption, physical activity, smoking status, region of residence, and SARS-CoV-2 strain. Generally, a consistent post-acute phase COVID-19-associated risk of gastrointestinal disease was identified across all subgroups in both the discovery and validation cohorts. The association between hepatobiliary disease and post-acute phase COVID-19 in the discovery cohort varied according to the subgroup; however, the risk was consistent regardless of alcohol consumption. The incidence of other digestive abnormalities was greater in patients with male sex, middle income, lack of sufficient physical activity, smoking, and delta-variant infections, as well as in those without comorbidities. In validation cohort A, the risk of developing hepatobiliary disease and other digestive abnormalities was consistently higher in patients with COVID-19 across all subgroups than in those without the infection.

 https://doi.org/10.3350/cmh.2024.0203

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