

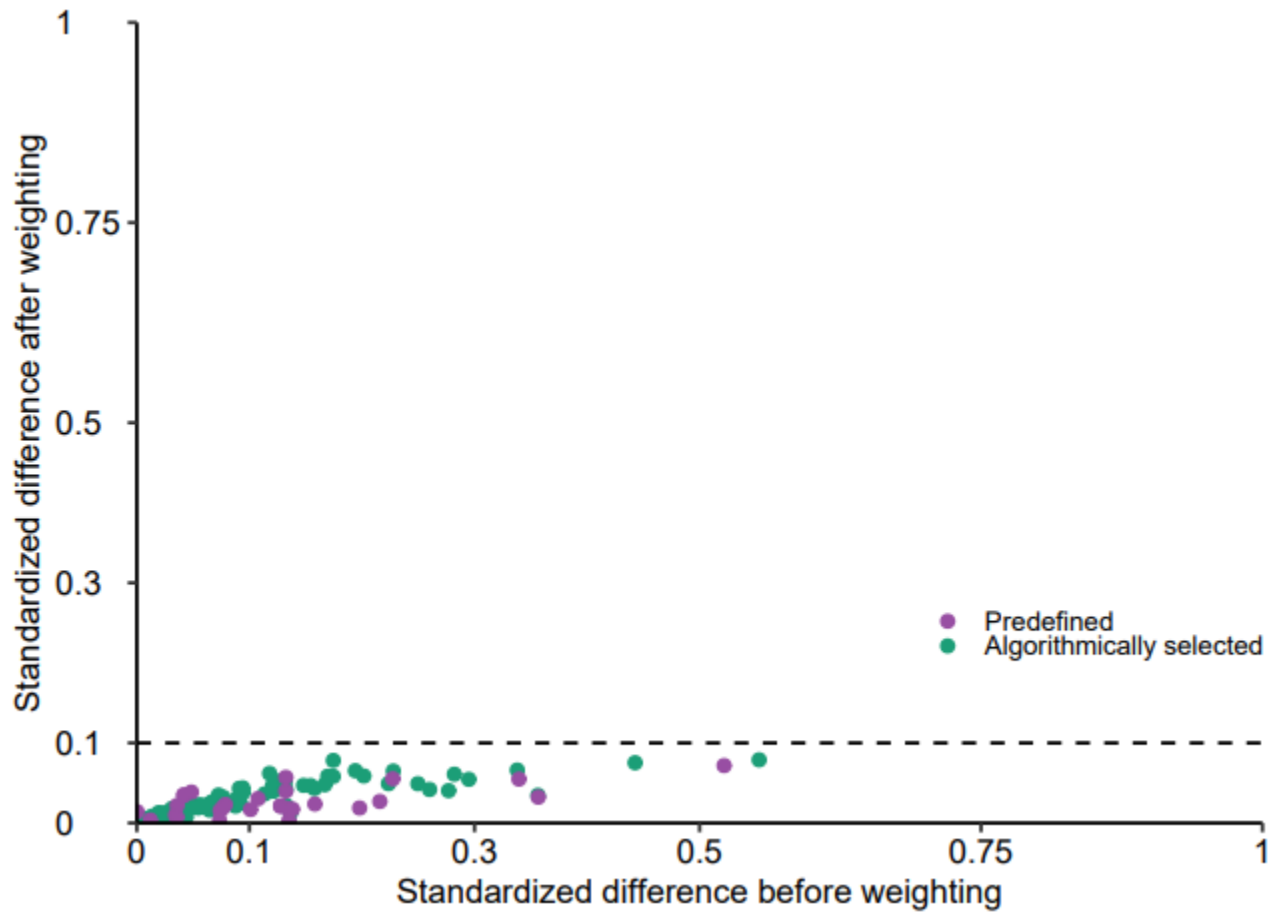
Risks of Mental Health Outcomes in people with COVID-19: cohort study

Yan Xie, Evan Xu, and Ziyad Al-Aly

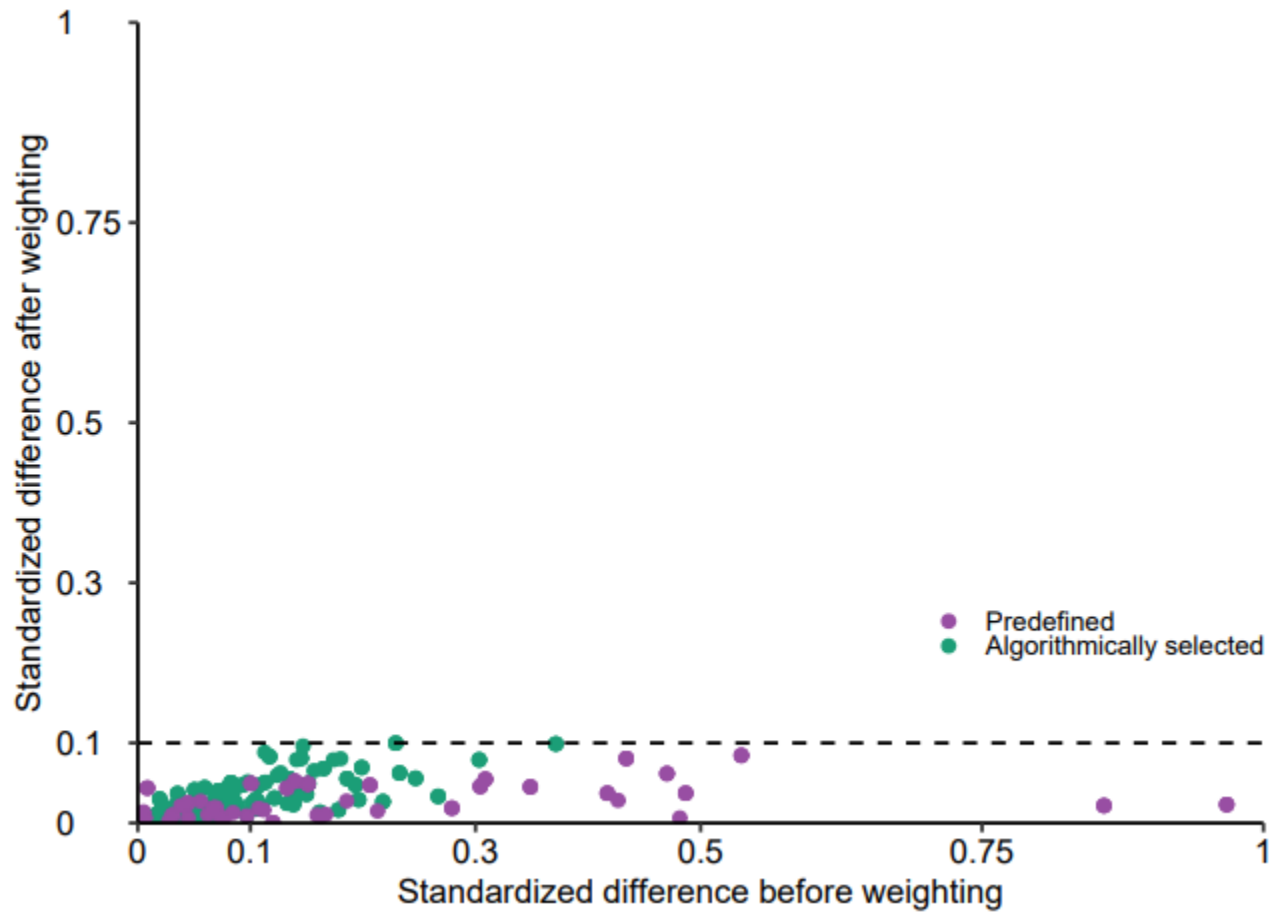
Table of Contents	Page
SUPPLEMENTARY FIGURES	3-12
Supplementary Figure S1. Standardized mean difference of predefined and algorithmically selected high dimensional variables between COVID-19 and contemporary control	3
Supplementary Figure S2. Standardized mean difference of predefined and algorithmically selected high dimensional variables by care setting of the acute infection between COVID-19 and contemporary control	4
Supplementary Figure S3. Standardized mean difference of predefined and algorithmically selected high dimensional variables between COVID-19 and historical control	5
Supplementary Figure S4. Risks of incident post-acute COVID-19 mental health outcomes compared to historical control	6
Supplementary Figure S5. Risks of incident post-acute COVID-19 mental health composite outcomes compared to historical control	7
Supplementary Figure S6. Survival probability of incident post-acute COVID-19 mental health composite outcomes compared to historical control	8
Supplementary Figure S7. Standardized mean difference of predefined and algorithmically selected high dimensional variables by care setting of the acute infection between COVID-19 and historical control	9
Supplementary Figure S8. Risks of incident post-acute COVID-19 mental health outcomes by care setting of the acute infection compared to historical control	10
Supplementary Figure S9. Risks of incident post-acute COVID-19 mental health composite outcomes by care setting of the acute infection compared to historical control	11
Supplementary Figure S10. Survival probability of incident post-acute COVID-19 mental health composite outcomes by care setting of the acute infection compared to historical control	12
SUPPLEMENTARY TABLES	13-42
Supplementary Table S1. Outcomes definition	13-14
Supplementary Table S2. Demographic and health characteristics of COVID-19, contemporary, and historical cohorts before weighting	15-16
Supplementary Table S3. Risks of incident post-acute COVID-19 mental health outcomes compared to contemporary control	17-18
Supplementary Table S4. Demographic and health characteristics of the COVID-19 and contemporary cohorts by care setting of the acute infection before weighting	19-20
Supplementary Table S5. Demographic and health characteristics of the COVID-19 and contemporary cohorts by care setting of the acute infection after weighting	21-22
Supplementary Table S6. Risks of incident post-acute COVID-19 mental health outcomes by care setting of the acute infection compared to contemporary control	23-26

Supplementary Table S7. Risks of incident post-acute COVID-19 mental health outcomes in pairwise comparison of people who were not hospitalized for COVID-19 vs those who were hospitalized for COVID-19 during the acute phase of the infection	27-28
Supplementary Table S8. Risks of incident post-acute COVID-19 mental health outcomes compared to historical control	29-30
Supplementary Table S9. Demographic and health characteristics of the COVID-19 and historical cohorts by care setting of the acute infection before weighting	31-32
Supplementary Table S10. Demographic and health characteristics of the COVID-19 and historical cohorts by care setting of the acute infection after weighting	33-34
Supplementary Table S11. Risks of incident post-acute COVID-19 mental health outcomes by care setting of the acute infection compared to historical control	35-38
Supplementary Table S12. Risks of incident composite post-acute COVID-19 mental health outcomes in comparisons involving non-hospitalized COVID-19 vs non-hospitalized seasonal influenza, hospitalized COVID-19 vs hospitalized seasonal influenza, and hospitalized COVID-19 vs hospitalized for any other cause	39
Supplementary Table S13. Sensitivity analysis for any mental health diagnosis, any mental health drug prescription, and any mental health outcome compared to contemporary and historical controls	40
Supplementary Table S14. Sensitivity analysis for any mental health diagnosis, any mental health drug prescription, and any mental health outcome by care setting of the acute infection compared to contemporary and historical controls	41
Supplementary Table S15. Positive and negative outcome controls	42

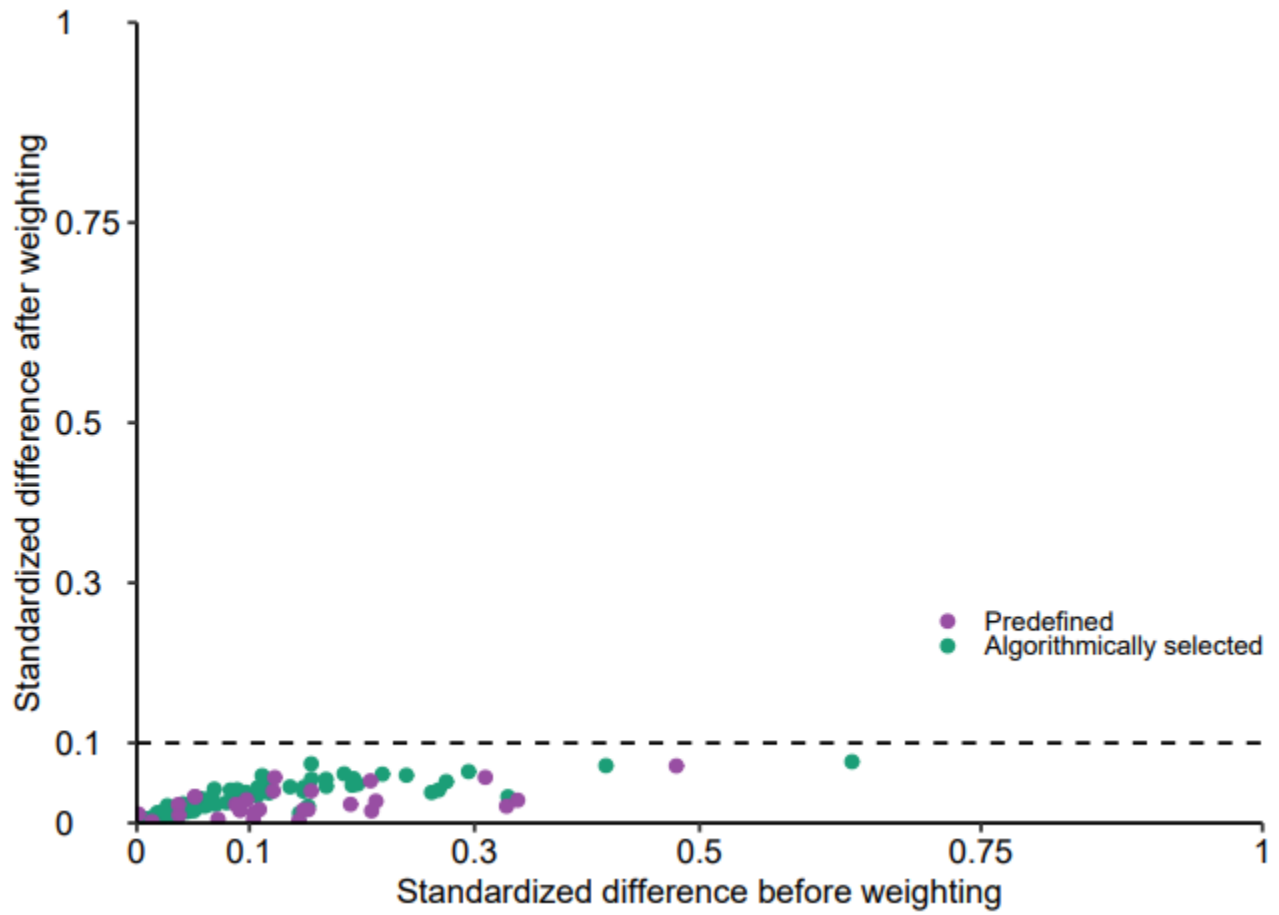
Supplementary Figure S1. Standardized mean difference of predefined and algorithmically selected high dimensional variables between COVID-19 and contemporary control standardized difference less than 0.10 is considered good balance.



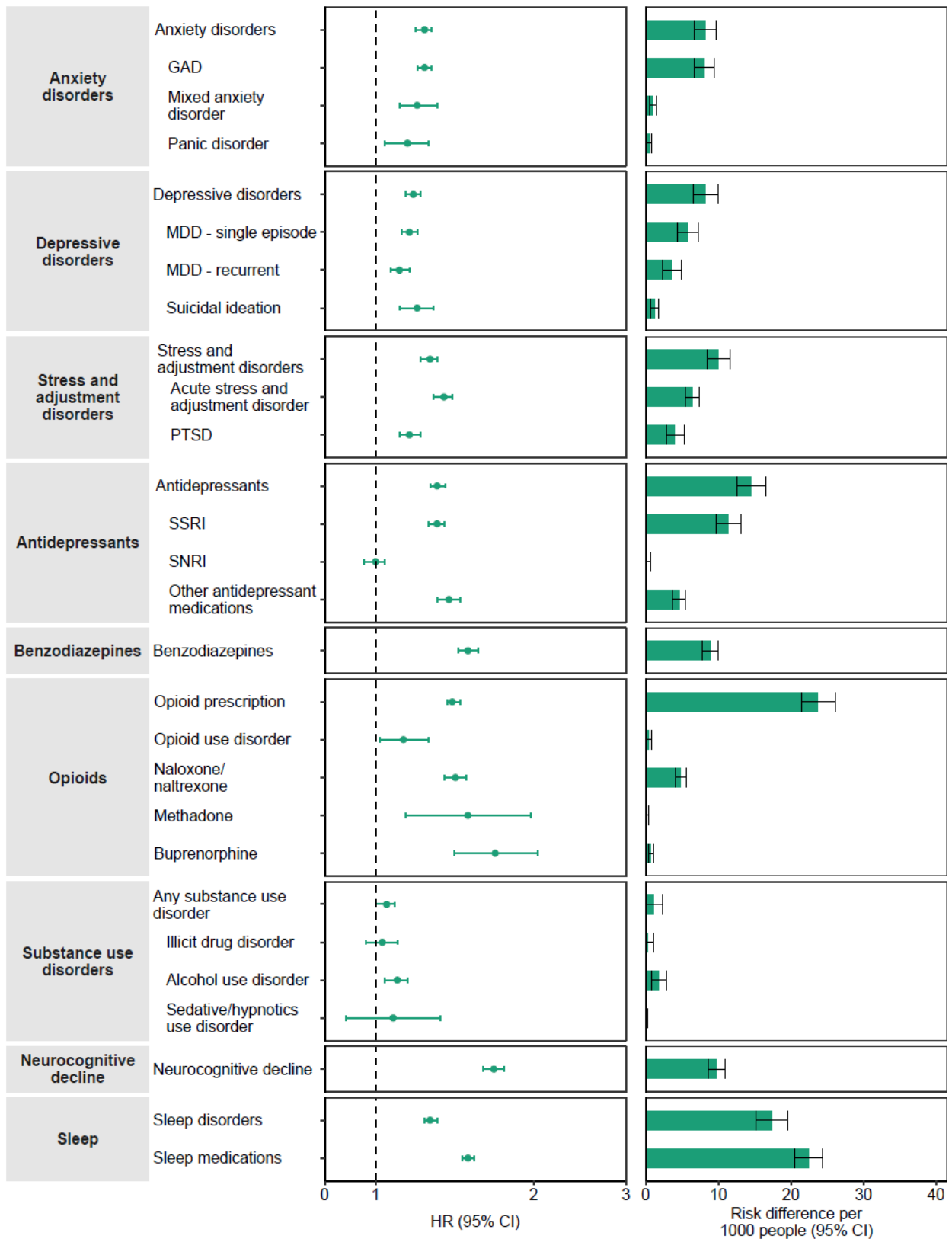
Supplementary Figure S2. Standardized mean difference of predefined and algorithmically selected high dimensional variables by care setting of the acute infection between COVID-19 and contemporary control standardized difference less than 0.10 is considered good balance.



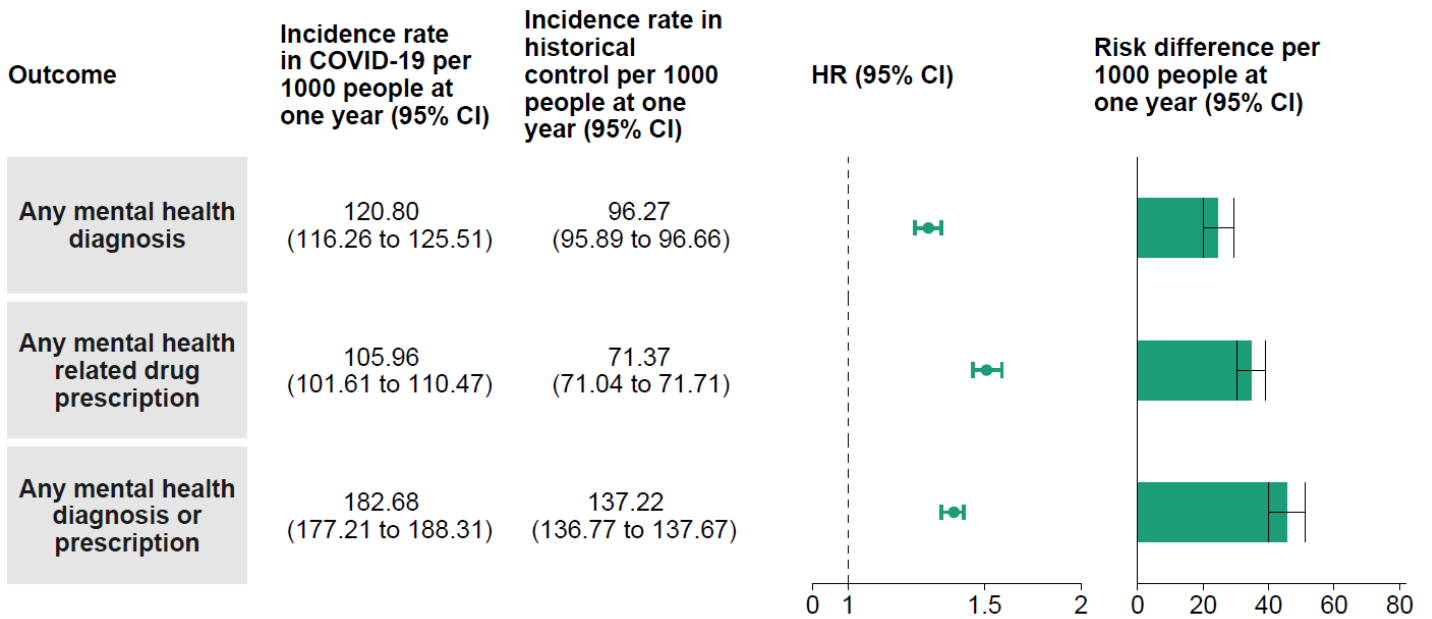
Supplementary Figure S3. Standardized mean difference of predefined and algorithmically selected high dimensional variables between COVID-19 and historical control standardized difference less than 0.10 is considered good balance.



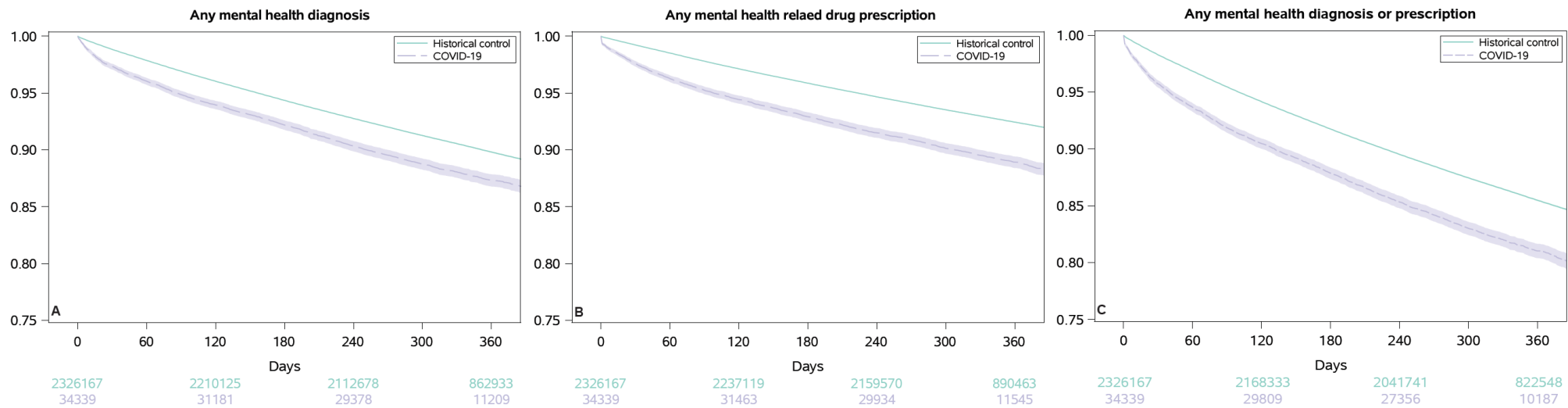
Supplementary Figure S4. Risks of incident post-acute COVID-19 mental health outcomes compared to historical control Outcomes were ascertained 30 days after the initial COVID-19 positive test result until the end of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented. The risk difference per 1000 people at one year and associated 95% confidence intervals are also shown. GAD, generalized anxiety disorder; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors.



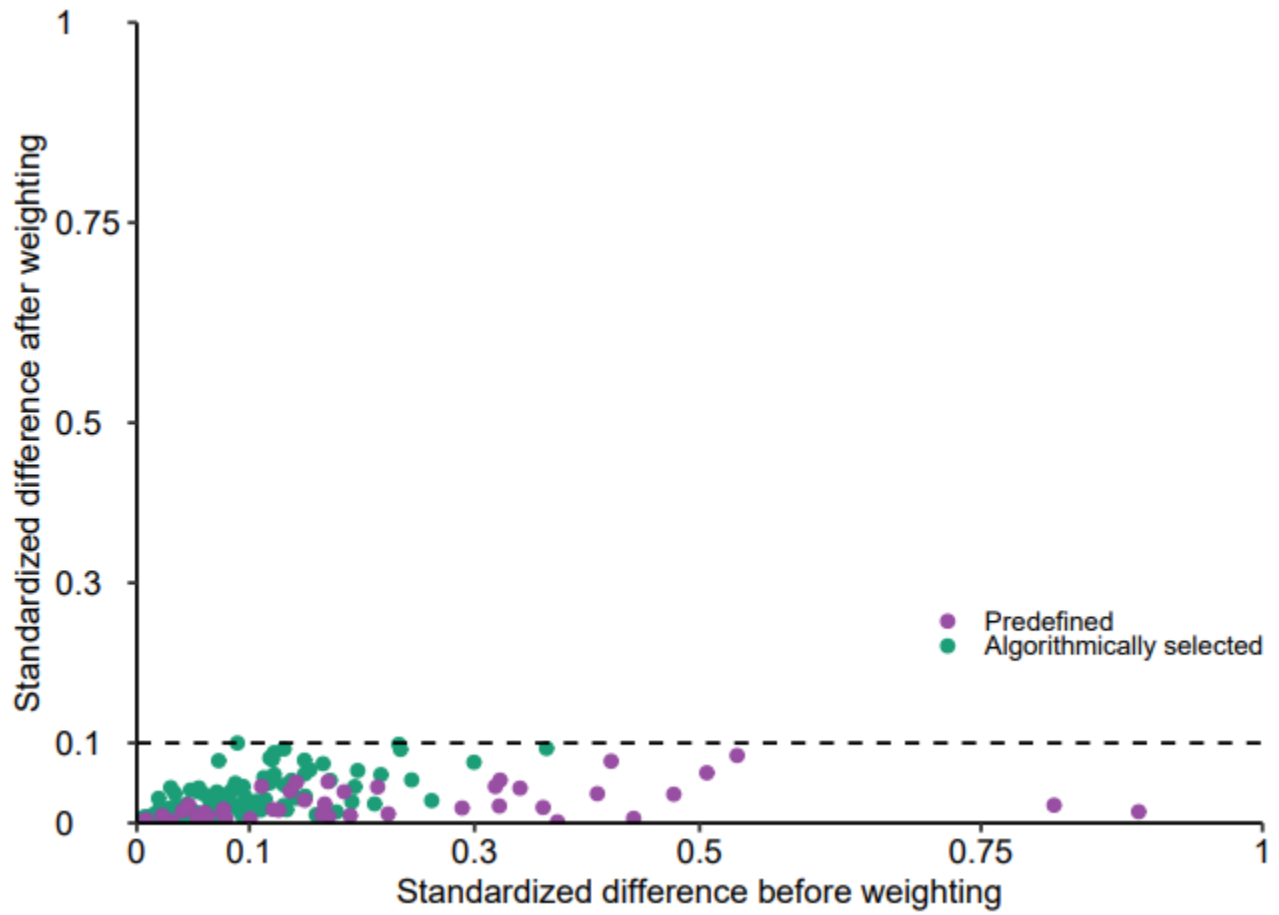
Supplementary Figure S5. Risks of incident post-acute COVID-19 mental health composite outcomes compared to historical control Composite outcomes consisted of any mental health related drug prescription, any mental health diagnosis, and any mental health diagnosis or prescription. Outcomes were ascertained 30 days after the initial COVID-19 positive test result until the end of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented. The risk difference per 1000 people at one year and associated 95% confidence intervals are also shown.



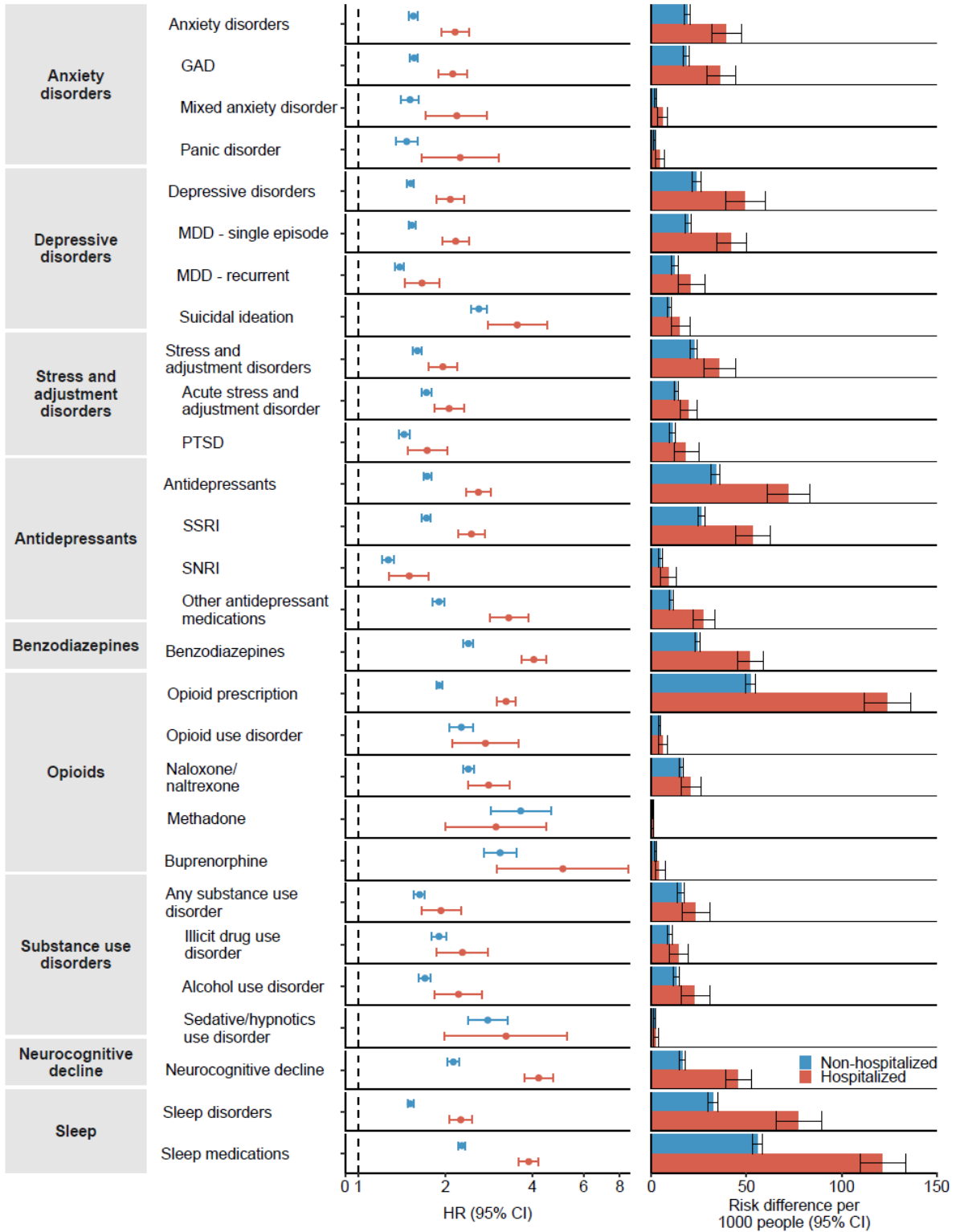
Supplementary Figure S6. Survival probability of incident post-acute COVID-19 mental health composite outcomes compared to historical control a: any mental health diagnosis; b: any mental health related drug prescription; c: any mental health diagnosis or prescription.. Outcomes were ascertained 30 days after the initial COVID-19 positive test result until the end of follow-up. Shaded areas are 95% confidence intervals.



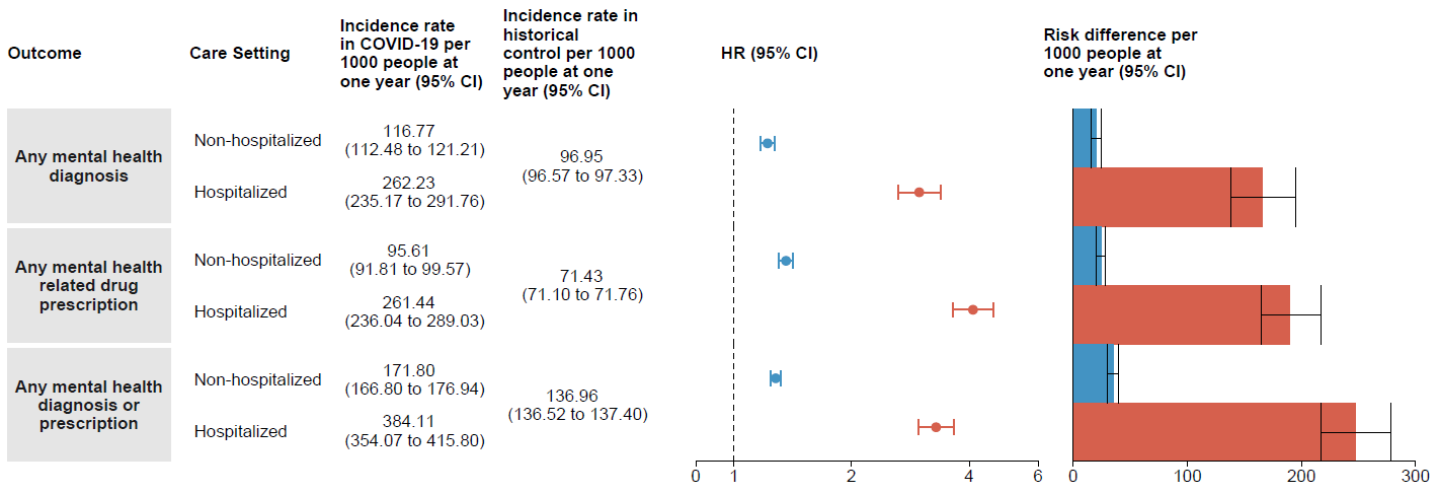
Supplementary Figure S7. Standardized mean difference of predefined and algorithmically selected high dimensional variables by care setting of the acute infection between COVID-19 and historical control standardized difference less than 0.10 is considered good balance



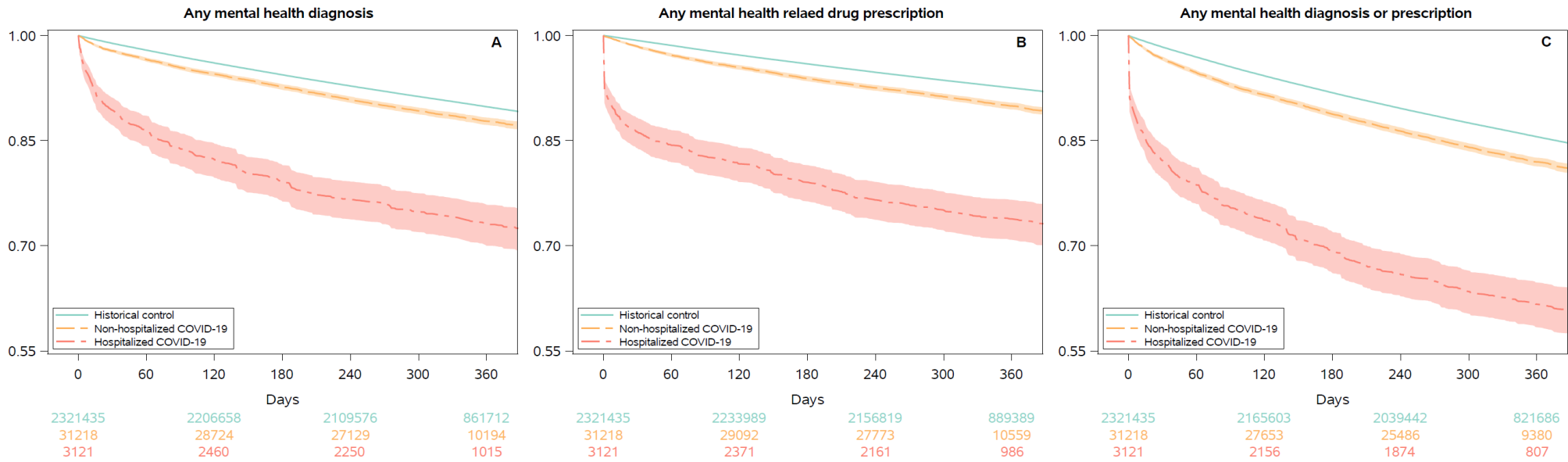
Supplementary Figure S8. Risks of incident post-acute COVID-19 mental health outcomes by care setting of the acute infection compared to historical control Risks were assessed in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (blue), and individuals hospitalized for COVID-19 (red) during the acute phase (first 30 days) of COVID-19. The historical control group served as the referent category. Outcomes were ascertained 30 days after the initial COVID-19 positive test result until the end of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented. The risk difference per 1000 people at one year and related 95% confidence intervals were also presented. GAD, generalized anxiety disorder; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors.



Supplementary Figure S9. Risks of incident post-acute COVID-19 mental health composite outcomes by care setting of the acute infection compared to historical control Composite outcomes consisted of any mental health related drug prescription, any mental health diagnosis, and any mental health diagnosis or prescription. Risks were assessed in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (blue), and individuals hospitalized for COVID-19 (red) during the acute phase (first 30 days) of COVID-19. The historical control group served as the referent category. Outcomes were ascertained 30 days after the initial COVID-19 positive test result until the end of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented. The risk difference per 1000 people at one year and associated 95% confidence intervals are also shown.



Supplementary Figure S10. Survival probability of incident post-acute COVID-19 mental health composite outcomes by care setting of the acute infection compared to historical control. a: b: any mental health diagnosis; any mental health related drug prescription; c: any mental health diagnosis or prescription. Outcomes were ascertained 30 days after the initial COVID-19 positive test result until the end of follow-up. Shaded areas are 95% confidence intervals.



Supplementary Table S1. Outcomes definition

Outcome	Definition type	Definition
Anxiety, depressive and stress disorders		
Anxiety disorders	Composite	All anxiety related codes (GAD, Mixed stress disorder and Panic disorder)
GAD	ICD10	F41.1, F41.9
Mixed stress disorder	ICD10	F41.3, F41.8
Panic disorder	ICD10	F41.0
Depressive disorders	Composite	All depression related codes (MDD – single episode, MDD - recurrent and suicidal ideation)
MDD - single episode	ICD10	F32
MDD - recurrent	ICD10	F33
Suicidal ideation	ICD10	R45.851
Stress and adjustment disorders	Composite	All stress related codes (Acute stress and adjustment disorders and PTSD)
Acute stress and adjustment disorders	ICD10	F43.0, F43.2
PTSD	ICD10	F43.1
Antidepressants	Composite	Any SSRI, SNRI, other antidepressant medication
SSRI	Medication	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, trazodone
SNRI	Medication	Desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine
Other antidepressant medications	Medication	Desipramine, doxepin, bupropion, amoxapine, maprotiline, mianserin, mirtazapine, sepiptiline
Benzodiazepines	Medication	Alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam, quazepam, lometazepam, tetrazepam
Opioids		
Opioid prescription	Medication	Codeine, dihydroetorphine, ethylmorphine, etorphine, hydrocodone, hydromorphone, metopon, morphine, opium, oxycodone, oxymorphone, alfentanil, alphaprodine, bezitramide, dextropropoxyphene, carfentanil, dihydrocodeine, diphenoxylate, fentanyl, levorphanol, oliceridine, phenazocine, remifentanil, sufentanil, tapentadol, meperidine, pentazocine, paregoric, tramadol, butorphanol, nalbuphine
Opioid use disorder	ICD10	F11
Naloxone or naltrexone	Medication	Naloxone, naltrexone
Methadone	Medication	Methadone
Buprenorphine	Medication	Buprenorphine
Substance use disorders		

Any substance use disorder	Composite	All substance use disorder codes (Illicit drug use disorder, alcohol use disorder and sedative/hypnotics use disorder)
Illicit drug use disorder	ICD10	F12, F14, F15, F16, F18, F19
Alcohol use disorder	ICD10	F10
Sedative/hypnotics use disorder	ICD10	F13
Neurocognitive decline	ICD10	R41.1, R41.2, R41.3, F01, F02, F03, F04, F44.0, G30, G31, G45.4
Sleep		
Sleep disorder	ICD10	F51, G47
Sleep medications	Medication	Trazodone, zolpidem, temazepam, eszopiclone, amitriptyline, lorazepam, doxepin, suvorexant, triazolam, diphenhydramine, flurazepam, estazolam, ramelteon, zaleplon, doxylamine, quazepam, chloral hydrate, lemborexant, lavender, melatonin, valerian, tryptophan
Composite endpoints		
Any mental health diagnosis	Composite	Any ICD code listed above
Any mental health related drug prescription	Composite	Any prescription drug listed above
Any mental health diagnosis or prescription	Composite	Any ICD code or prescription drug listed above
GAD, Generalized Anxiety Disorder; ICD, International Classification of Diseases; MDD, Major Depressive Disorder; PTSD, Post Traumatic Stress Disorder; SSRI, Selective Serotonin Reuptake Inhibitors; SNRI, Serotonin-Norepinephrine Reuptake Inhibitor.		

Supplementary Table S2. Demographic and health characteristics of COVID-19, contemporary, and historical cohorts before weighting

Baseline Characteristics	COVID-19 (N= 153,848)	Contemporary control (N= 5,637,840)	Historical control (N= 5,859,251)	Absolute standardized difference – COVID-19 and Contemporary control[‡]	Absolute standardized difference – COVID-19 and Historical control[‡]
Age, mean (std), yr	61.42 (15.64)	63.46 (16.23)	62.90 (16.48)	0.13	0.09
Race, no. (%)					
White	109048 (70.88)	4328964 (76.78)	4532214 (77.35)	0.13	0.15
Black	37125 (24.13)	1042115 (18.48)	1051756 (17.95)	0.14	0.15
Other	7675 (4.99)	266761 (4.73)	275281 (4.70)	0.01	0.01
Sex, no. (%)					
Male	136991 (89.04)	5091671 (90.31)	5308669 (90.60)	0.04	0.05
Female	16857 (10.96)	546169 (9.69)	550582 (9.40)	0.04	0.05
BMI category, no. (%), kg/m²					
Underweight/Normal	22204 (14.43)	1098871 (19.49)	1162589 (19.84)	0.14	0.14
Overweight	48848 (31.75)	2059802 (36.54)	2150870 (36.71)	0.10	0.10
Obese	82796 (53.82)	2479167 (43.97)	2545792 (43.45)	0.20	0.21
Smoking status, no. (%)					
Never	69110 (44.92)	2396999 (42.52)	3084307 (52.64)	0.05	0.15
Former	61140 (39.74)	2031674 (36.04)	1441327 (24.60)	0.08	0.33
Current	23598 (15.34)	1209167 (21.45)	1333617 (22.76)	0.16	0.19
Area Deprivation Index*, mean (std)	55.33 (18.59)	54.65 (19.05)	54.63 (19.13)	0.04	0.04
Clinical Characteristics					
Outpatient encounter[†], no. (%)					
Zero or one	30728 (19.97)	2450637 (43.47)	2430247 (41.48)	0.52	0.48
Two	44739 (29.08)	1618327 (28.70)	1622153 (27.69)	0.01	0.03
Three or more	78381 (50.95)	1568876 (27.83)	1806851 (30.84)	0.49	0.42
Long-term care, no. (%)	6108 (3.97)	33591 (0.60)	47737 (0.81)	0.23	0.21
eGFR, mean (std), ml/min/1.73m²	77.92 (22.65)	78.69 (20.54)	79.48 (20.47)	0.04	0.07

Systolic blood pressure, mean (std), mmHg	132.65 (11.74)	132.65 (12.29)	132.63 (12.63)	0.00	0.00
Diastolic blood pressure, mean (std), mmHg	78.32 (7.41)	77.77 (7.54)	77.53 (7.91)	0.07	0.10
Cancer, no. (%)	12525 (8.14)	344905 (6.12)	345677 (5.90)	0.08	0.09
Cerebrovascular disease, no. (%)	10410 (6.77)	242864 (4.31)	264761 (4.52)	0.11	0.10
Cardiovascular disease, no. (%)	26629 (17.31)	710353 (12.60)	760021 (12.97)	0.13	0.12
Chronic kidney disease, no. (%)	30020 (19.51)	939555 (16.67)	901567 (15.39)	0.07	0.11
Chronic lung disease, no. (%)	23479 (15.26)	609676 (10.81)	651653 (11.12)	0.13	0.12
Diabetes mellitus type 2, no. (%)	49423 (32.12)	1271812 (22.56)	1330212 (22.70)	0.22	0.21
Rheumatoid arthritis, no. (%)	1878 (1.22)	49122 (0.87)	49375 (0.84)	0.03	0.04

*. Area Deprivation Index is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.

†. Data collected within one year of cohort enrollment.

‡. Standardized difference less than 0.10 is considered good balance.

std, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Supplementary Table S3. Risks of incident post-acute COVID-19 mental health outcomes compared to contemporary control

Outcome*	Hazard ratio [†] (95% CI)	Rate per 1000 people at one year (95% CI) [†]		Risk difference per 1000 people at one year (95% CI) [†]
		COVID-19	Contemporary control	
Anxiety, depressive and stress disorders				
Anxiety disorders	1.35 (1.30 to 1.39)	43.70 (42.28 to 45.17)	32.64 (32.49 to 32.79)	11.06 (9.64 to 12.53)
GAD	1.34 (1.30 to 1.39)	41.93 (40.55 to 43.36)	31.37 (31.22 to 31.52)	10.56 (9.18 to 11.99)
Mixed stress disorder	1.41 (1.30 to 1.54)	5.68 (5.23 to 6.17)	4.02 (3.97 to 4.07)	1.66 (1.21 to 2.15)
Panic disorder	1.28 (1.17 to 1.41)	3.82 (3.47 to 4.20)	2.98 (2.93 to 3.02)	0.84 (0.49 to 1.22)
Depressive disorders	1.39 (1.34 to 1.43)	55.50 (53.76 to 57.29)	40.38 (40.20 to 40.55)	15.12 (13.38 to 16.91)
MDD - single episode	1.42 (1.37 to 1.47)	43.21 (41.83 to 44.63)	30.68 (30.54 to 30.83)	12.53 (11.15 to 13.95)
MDD - recurrent	1.29 (1.24 to 1.34)	35.57 (34.29 to 36.90)	27.71 (27.57 to 27.86)	7.86 (6.58 to 9.18)
Suicidal ideation	1.46 (1.35 to 1.57)	7.21 (6.69 to 7.77)	4.96 (4.90 to 5.01)	2.25 (1.73 to 2.81)
Stress and adjustment disorders	1.38 (1.34 to 1.43)	48.83 (47.25 to 50.46)	35.54 (35.37 to 35.71)	13.29 (11.71 to 14.92)
Acute stress and adjustment disorders	1.48 (1.42 to 1.54)	25.06 (24.08 to 26.07)	17.00 (16.90 to 17.11)	8.05 (7.08 to 9.07)
PTSD	1.30 (1.24 to 1.36)	29.00 (27.79 to 30.26)	22.40 (22.27 to 22.53)	6.60 (5.39 to 7.85)
Antidepressants	1.55 (1.50 to 1.60)	62.49 (60.54 to 64.51)	40.91 (40.72 to 41.09)	21.59 (19.63 to 23.60)
SSRI	1.54 (1.49 to 1.60)	49.54 (47.88 to 51.25)	32.41 (32.25 to 32.57)	17.13 (15.47 to 18.84)
SNRI	1.22 (1.17 to 1.28)	17.82 (17.03 to 18.64)	14.59 (14.49 to 14.69)	3.23 (2.45 to 4.06)
Other antidepressant medications	1.56 (1.48 to 1.64)	16.74 (15.90 to 17.61)	10.76 (10.67 to 10.84)	5.98 (5.14 to 6.86)
Benzodiazepines	1.65 (1.58 to 1.72)	26.76 (25.67 to 27.90)	16.30 (16.19 to 16.40)	10.46 (9.37 to 11.61)
Opioids				

Opioid prescription	1.76 (1.71 to 1.81)	85.06 (82.77 to 87.41)	49.16 (48.96 to 49.36)	35.90 (33.61 to 38.25)
Opioid use disorder	1.34 (1.21 to 1.48)	3.82 (3.44 to 4.23)	2.86 (2.82 to 2.90)	0.96 (0.59 to 1.37)
Naloxone or naltrexone	1.23 (1.18 to 1.29)	16.44 (15.69 to 17.23)	13.37 (13.27 to 13.46)	3.08 (2.32 to 3.86)
Methadone	1.94 (1.47 to 2.56)	0.57 (0.43 to 0.75)	0.29 (0.28 to 0.31)	0.27 (0.14 to 0.46)
Buprenorphine	1.34 (1.12 to 1.62)	1.76 (1.46 to 2.11)	1.31 (1.28 to 1.34)	0.45 (0.15 to 0.80)
Other substance use disorders				
Any substance use disorder†	1.20 (1.15 to 1.26)	26.01 (24.89 to 27.18)	21.67 (21.54 to 21.79)	4.34 (3.22 to 5.51)
Illicit drug use disorder	1.24 (1.16 to 1.32)	11.11 (10.41 to 11.86)	8.99 (8.91 to 9.07)	2.12 (1.42 to 2.87)
Alcohol use disorder	1.29 (1.22 to 1.35)	20.87 (19.88 to 21.92)	16.27 (16.16 to 16.38)	4.60 (3.61 to 5.65)
Sedative/hypnotics use disorder	1.40 (1.14 to 1.72)	0.99 (0.80 to 1.22)	0.71 (0.69 to 0.73)	0.28 (0.10 to 0.51)
Neurocognitive decline	1.80 (1.72 to 1.89)	24.34 (23.23 to 25.50)	13.58 (13.49 to 13.68)	10.75 (9.65 to 11.91)
Sleep				
Sleep disorders	1.41 (1.38 to 1.45)	84.05 (81.90 to 86.25)	60.25 (60.03 to 60.48)	23.80 (21.65 to 26.00)
Sleep medications	1.63 (1.58 to 1.67)	68.63 (66.77 to 70.54)	42.76 (42.58 to 42.94)	25.87 (24.01 to 27.78)
Composite endpoints				
Any mental health diagnosis	1.46 (1.40 to 1.52)	120.80 (116.26 to 125.51)	84.33 (83.97 to 84.69)	36.48 (31.93 to 41.19)
Any mental health related drug prescription	1.86 (1.78 to 1.95)	105.96 (101.61 to 110.47)	58.36 (58.05 to 58.66)	47.60 (43.26 to 52.12)
Any mental health diagnosis or prescription	1.60 (1.55 to 1.66)	182.68 (177.21 to 188.31)	118.30 (117.88 to 118.72)	64.38 (58.90 to 70.01)

*. Outcomes were ascertained from 30 days after the initial positive COVID-19 test result until end of follow up.

†. Adjustment through inverse probability weighting using predefined and algorithmically selected high-dimensional variables.

‡. Any substance use disorder is defined as any illicit drug use disorder, alcohol use disorder, or sedative/hypnotics use disorder (opioid use disorder was not included in this outcome).

CI, confidence interval; GAD, Generalized anxiety disorder; MDD, Major depressive disorder; PTSD, Post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor.

Supplementary Table S4. Demographic and health characteristics of the COVID-19 and contemporary cohorts by care setting of the acute infection before weighting

Baseline Characteristics	Non-hospitalized (N=132,852)	Hospitalized (N=20,996)	Contemporary control (N=5,605,762)	Absolute standardized difference - Non- hospitalized and Contemporary control[‡]	Absolute standardized difference - Hospitalized and Contemporary control[‡]	Absolute standardized difference – Non- hospitalized and Hospitalized[‡]
Age, mean (std), yr	63.35 (16.21)	65.37 (14.98)	63.01 (16.43)	0.20	0.35	0.58
Race, no. (%)						
White	95859 (72.16)	13189 (62.82)	4306463 (76.82)	0.11	0.31	0.20
Black	30519 (22.97)	6606 (31.46)	1034045 (18.45)	0.11	0.30	0.19
Other	6474 (4.87)	1201 (5.72)	265254 (4.73)	0.01	0.04	0.04
Sex, no. (%)						
Male	117190 (88.21)	19801 (94.31)	5061672 (90.29)	0.07	0.15	0.22
Female	15662 (11.79)	1195 (5.69)	544090 (9.71)	0.07	0.15	0.22
BMI category, no. (%), kg/m²						
Underweight/ Normal	17864 (13.45)	4340 (20.67)	1089825 (19.44)	0.16	0.03	0.19
Overweight	42480 (31.98)	6368 (30.33)	2049722 (36.57)	0.10	0.13	0.04
Obese	72508 (54.58)	10288 (49.00)	2466215 (43.99)	0.21	0.10	0.11
Smoking status, no. (%)						
Never	60256 (45.36)	8854 (42.17)	2387392 (42.59)	0.06	0.01	0.06
Former	52348 (39.4)	8792 (41.88)	2019899 (36.03)	0.07	0.12	0.05
Current	20248 (15.24)	3350 (15.96)	1198471 (21.38)	0.16	0.14	0.02
Area Deprivation Index*, mean (std)	54.81 (19.09)	55.18 (19.24)	54.64 (19.07)	0.05	0.08	0.13
Clinical Characteristics						
Outpatient encounter[†], no. (%)						
Zero or one	28850 (21.72)	1878 (8.95)	2448367 (43.68)	0.48	0.86	0.36
Two	40546 (30.52)	4193 (19.97)	1613114 (28.78)	0.04	0.21	0.24
Three or more	63456 (47.76)	14925 (71.09)	1544281 (27.55)	0.43	0.97	0.49

Long-term care, no. (%)	3992 (3.01)	2116 (10.08)	31442 (0.56)	0.19	0.43	0.29
eGFR, mean (std), ml/min/1.73m²	78.94 (20.52)	77.36 (20.27)	79.16 (20.56)	0.04	0.46	0.49
Systolic blood pressure, mean (std), mmHg	132.71 (12.48)	133.15 (12.54)	132.61 (12.47)	0.02	0.15	0.18
Diastolic blood pressure, mean (std), mmHg	77.65 (7.75)	77.64 (7.79)	77.67 (7.73)	0.10	0.10	0.21
Cancer, no. (%)	9498 (7.15)	3027 (14.42)	338756 (6.04)	0.04	0.28	0.24
Cerebrovascular disease, no. (%)	7431 (5.59)	2979 (14.19)	238182 (4.25)	0.06	0.35	0.29
Cardiovascular disease, no. (%)	19879 (14.96)	6750 (32.15)	698678 (12.46)	0.07	0.49	0.41
Chronic kidney disease, no. (%)	22286 (16.78)	7734 (36.84)	929931 (16.59)	0.00	0.47	0.46
Chronic lung disease, no. (%)	17890 (13.47)	5589 (26.62)	600369 (10.71)	0.08	0.42	0.33
Diabetes mellitus type 2, no. (%)	39531 (29.76)	9892 (47.11)	1258431 (22.45)	0.17	0.54	0.36
Rheumatoid arthritis, no. (%)	1516 (1.14)	362 (1.72)	48580 (0.87)	0.03	0.08	0.05

*.Area Deprivation Index is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.

†.Data collected within one year before cohort enrollment.

‡. Standardized difference less than 0.10 is considered good balance.

std, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Supplementary Table S5. Demographic and health characteristics of the COVID-19 and contemporary control by care setting of the acute infection after weighting

Baseline Characteristics	Non-hospitalized (N=132,852)	Hospitalized (N=20,996)	Contemporary control (N=5,605,762)	Absolute standardized difference - Non- hospitalized and Contemporary control[‡]	Absolute standardized difference - Hospitalized and Contemporary control[‡]	Absolute standardized difference – Non- hospitalized and Hospitalized[‡]
Age, mean (std), yr	63.34 (16.29)	64.12 (15.84)	63.02 (16.43)	0.02	0.02	0.00
Race, no. (%)						
White	100828 (75.90)	15603 (74.31)	4297770 (76.67)	0.02	0.05	0.04
Black	25547 (19.23)	4284 (20.41)	1042391 (18.60)	0.02	0.05	0.03
Other	6477 (4.88)	1109 (5.28)	265657 (4.74)	0.01	0.02	0.02
Sex, no. (%)						
Male	119168 (89.70)	19245 (91.66)	5059761 (90.26)	0.02	0.05	0.07
Female	13684 (10.30)	1751 (8.34)	546001 (9.74)	0.02	0.05	0.07
BMI category, no. (%), kg/m²						
Underweight/ Normal	25251 (19.01)	3978 (18.95)	1082977 (19.32)	0.01	0.01	0.00
Overweight	47812 (35.99)	7209 (34.34)	2041731 (36.42)	0.01	0.04	0.03
Obese	59789 (45.00)	9808 (46.72)	2481054 (44.26)	0.01	0.05	0.03
Smoking status, no. (%)						
Never	54875 (41.31)	8502 (40.49)	2390633 (42.65)	0.03	0.05	0.02
Former	49240 (37.06)	7582 (36.11)	2025474 (36.13)	0.02	0.00	0.02
Current	28737 (21.63)	4912 (23.4)	1189711 (21.22)	0.01	0.05	0.04
Area Deprivation Index*, mean (std)	54.81 (19.08)	55.33 (19.28)	54.64 (19.07)	0.02	0.01	0.02
Clinical Characteristics						
Outpatient encounter[†], no. (%)						
Zero or one	56752 (42.72)	9261 (44.11)	2412384 (43.03)	0.01	0.02	0.03
Two	36982 (27.84)	5603 (26.69)	1614684 (28.80)	0.02	0.05	0.03
Three or more	39118 (29.45)	6132 (29.21)	1578695 (28.16)	0.03	0.02	0.01

Long-term care, no. (%)	1186 (0.89)	311 (1.48)	36550 (0.65)	0.03	0.08	0.05
eGFR, mean (std), ml/min/1.73m²	78.92 (20.52)	78.39 (20.43)	79.15 (20.56)	0.00	0.01	0.01
Systolic blood pressure, mean (std), mmHg	132.71 (12.51)	133.11 (12.78)	132.61 (12.47)	0.01	0.04	0.05
Diastolic blood pressure, mean (std), mmHg	77.62 (7.75)	77.85 (8.11)	77.67 (7.73)	0.00	0.06	0.05
Cancer, no. (%)	8307 (6.25)	1376 (6.55)	341951 (6.10)	0.01	0.02	0.01
Cerebrovascular disease, no. (%)	6021 (4.53)	1109 (5.28)	242001 (4.32)	0.01	0.04	0.03
Cardiovascular disease, no. (%)	17154 (12.91)	2909 (13.86)	706046 (12.60)	0.01	0.04	0.03
Chronic kidney disease, no. (%)	22837 (17.19)	3996 (19.03)	934256 (16.67)	0.01	0.06	0.05
Chronic lung disease, no. (%)	14929 (11.24)	2523 (12.02)	607328 (10.83)	0.01	0.04	0.02
Diabetes mellitus type 2, no. (%)	30771 (23.16)	5529 (26.33)	1272844 (22.71)	0.01	0.08	0.07
Rheumatoid arthritis, no. (%)	1193 (0.90)	173 (0.82)	49106 (0.88)	0.00	0.01	0.01

*.Area Deprivation Index is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.

†.Data collected within one year before cohort enrollment.

‡. Standardized difference less than 0.10 is considered good balance.

std, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Supplementary Table S6. Risks of incident post-acute COVID-19 mental health outcomes by care setting of the acute infection compared to contemporary control

Outcome*	Care setting†	Hazard ratio (95% CI) ‡	Rate per 1000 people at one year (95% CI) ‡		Risk difference per 1000 people at one year (95% CI) ‡
			COVID-19	Contemporary control	
Anxiety to depressive to and stress disorders					
Anxiety disorder	Non-hospitalized	1.69 (1.64 to 1.74)	54.18 (52.53 to 55.88)	32.45 (32.30 to 32.61)	21.73 (20.08 to 23.42)
	Hospitalized	2.34 (2.10 to 2.62)	74.41 (66.93 to 82.69)		41.96 (34.48 to 50.23)
GAD	Non-hospitalized	1.68 (1.63 to 1.74)	51.92 (50.34 to 53.56)	31.19 (31.04 to 31.34)	20.73 (19.14 to 22.37)
	Hospitalized	2.28 (2.04 to 2.56)	69.83 (62.66 to 77.78)		38.63 (31.47 to 46.59)
Mixed stress disorder	Non-hospitalized	1.76 (1.64 to 1.90)	7.11 (6.61 to 7.65)	4.04 (3.99 to 4.09)	3.07 (2.57 to 3.60)
	Hospitalized	2.56 (2.00 to 3.26)	10.29 (8.07 to 13.12)		6.25 (4.03 to 9.08)
Panic disorder	Non-hospitalized	1.64 (1.51 to 1.79)	4.77 (4.38 to 5.20)	2.91 (2.86 to 2.95)	1.87 (1.47 to 2.30)
	Hospitalized	2.52 (1.85 to 3.42)	7.30 (5.38 to 9.90)		4.39 (2.47 to 6.99)
Depressive disorders	Non-hospitalized	1.77 (1.72 to 1.83)	71.37 (69.20 to 73.61)	40.92 (40.74 to 41.10)	30.45 (28.28 to 32.69)
	Hospitalized	2.43 (2.17 to 2.73)	96.67 (86.67 to 107.74)		55.75 (45.76 to 66.83)
MDD - single episode	Non-hospitalized	1.87 (1.81 to 1.93)	56.56 (54.89 to 58.27)	30.64 (30.49 to 30.79)	25.91 (24.25 to 27.63)
	Hospitalized	2.64 (2.38 to 2.94)	79.01 (71.41 to 87.39)		48.37 (40.76 to 56.75)
MDD - recurrent	Non-hospitalized	1.60 (1.54 to 1.66)	44.39 (42.81 to 46.03)	27.95 (27.81 to 28.10)	16.44 (14.86 to 18.08)
	Hospitalized	1.91 (1.67 to 2.19)	52.72 (46.18 to 60.14)		24.76 (18.23 to 32.19)
Suicidal ideation	Non-hospitalized	3.14 (2.94 to 3.34)	15.37 (14.43 to 16.37)	4.92 (4.87 to 4.98)	10.44 (9.50 to 11.44)
	Hospitalized	4.26 (3.37 to 5.39)	20.80 (16.47 to 26.24)		15.87 (11.55 to 21.32)

Stress and adjustment disorder	Non-hospitalized	1.74 (1.68 to 1.80)	60.90 (58.98 to 62.88)	35.50 (35.33 to 35.67)	25.40 (23.48 to 27.38)
	Hospitalized	2.13 (1.90 to 2.40)	74.26 (66.46 to 82.94)		38.76 (30.97 to 47.44)
Acute stress and adjustment disorders	Non-hospitalized	1.89 (1.82 to 1.96)	31.75 (30.58 to 32.95)	16.96 (16.86 to 17.07)	14.78 (13.62 to 15.99)
	Hospitalized	2.26 (2.00 to 2.55)	37.87 (33.62 to 42.65)		20.91 (16.66 to 25.69)
PTSD	Non-hospitalized	1.61 (1.54 to 1.68)	35.90 (34.42 to 37.44)	22.52 (22.39 to 22.65)	13.38 (11.90 to 14.92)
	Hospitalized	1.93 (1.65 to 2.25)	42.94 (36.86 to 50.01)		20.43 (14.34 to 27.50)
Antidepressants	Non-hospitalized	2.04 (1.97 to 2.10)	81.71 (79.30 to 84.19)	41.01 (40.82 to 41.19)	40.70 (38.29 to 43.18)
	Hospitalized	3.05 (2.76 to 3.36)	119.75 (109.14 to 131.31)		78.74 (68.13 to 90.31)
SSRI	Non-hospitalized	2.02 (1.96 to 2.09)	64.40 (62.41 to 66.46)	32.36 (32.20 to 32.52)	32.04 (30.04 to 34.10)
	Hospitalized	2.90 (2.61 to 3.22)	90.99 (82.24 to 100.61)		58.63 (49.88 to 68.25)
SNRI	Non-hospitalized	1.56 (1.49 to 1.63)	22.63 (21.65 to 23.66)	14.59 (14.49 to 14.69)	8.04 (7.05 to 9.07)
	Hospitalized	1.84 (1.57 to 2.15)	26.69 (22.86 to 31.15)		12.10 (8.26 to 16.56)
Other antidepressant medications	Non-hospitalized	2.13 (2.04 to 2.24)	22.74 (21.70 to 23.82)	10.72 (10.64 to 10.81)	12.01 (10.98 to 13.10)
	Hospitalized	3.71 (3.19 to 4.33)	39.25 (33.79 to 45.57)		28.52 (23.06 to 34.84)
Benzodiazepines	Non-hospitalized	2.62 (2.52 to 2.72)	41.92 (40.42 to 43.46)	16.21 (16.11 to 16.31)	25.71 (24.21 to 27.25)
	Hospitalized	4.41 (3.98 to 4.88)	69.50 (62.97 to 76.68)		53.29 (46.76 to 60.47)
Opioids					
Opioid Prescription	Non-hospitalized	2.39 (2.33 to 2.45)	113.04 (110.40 to 115.74)	48.97 (48.77 to 49.16)	64.07 (61.43 to 66.77)
	Hospitalized	4.07 (3.79 to 4.38)	184.88 (173.14 to 197.32)		135.91 (124.17 to 148.35)
Opioid use disorder	Non-hospitalized	2.65 (2.42 to 2.91)	7.50 (6.84 to 8.22)	2.83 (2.79 to 2.87)	4.67 (4.01 to 5.39)
	Hospitalized	3.21 (2.48 to 4.16)	9.06 (6.99 to 11.73)		6.23 (4.16 to 8.90)

Naloxone or naltrexone	Non-hospitalized	2.06 (1.98 to 2.16)	26.95 (25.82 to 28.13)	13.15 (13.06 to 13.24)	13.80 (12.67 to 14.98)
	Hospitalized	2.43 (2.05 to 2.88)	31.66 (26.82 to 37.35)		18.51 (13.68 to 24.21)
Methadone	Non-hospitalized	4.51 (3.54 to 5.75)	1.32 (1.03 to 1.68)	0.29 (0.28 to 0.31)	1.03 (0.74 to 1.39)
	Hospitalized	3.71 (2.48 to 5.54)	1.08 (0.72 to 1.62)		0.79 (0.43 to 1.33)
Buprenorphine	Non-hospitalized	2.41 (2.12 to 2.75)	3.02 (2.65 to 3.44)	1.25 (1.22 to 1.28)	1.77 (1.39 to 2.19)
	Hospitalized	3.97 (2.35 to 6.70)	4.96 (2.94 to 8.36)		3.71 (1.69 to 7.11)
Substance use disorders					
Any substance use disorder [§]	Non-hospitalized	1.87 (1.79 to 1.95)	40.73 (39.02 to 42.50)	22.03 (21.91 to 22.16)	18.69 (16.99 to 20.47)
	Hospitalized	2.21 (1.90 to 2.59)	48.13 (41.34 to 55.99)		26.09 (19.31 to 33.96)
Illicit drug use disorder	Non-hospitalized	2.26 (2.13 to 2.40)	20.60 (19.43 to 21.84)	9.16 (9.09 to 9.24)	11.44 (10.27 to 12.67)
	Hospitalized	2.73 (2.23 to 3.34)	24.80 (20.31 to 30.27)		15.64 (11.15 to 21.10)
Alcohol use disorder	Non-hospitalized	1.98 (1.89 to 2.08)	31.99 (30.52 to 33.53)	16.29 (16.19 to 16.40)	15.70 (14.23 to 17.24)
	Hospitalized	2.59 (2.15 to 3.12)	41.58 (34.62 to 49.89)		25.29 (18.33 to 33.60)
Sedative/Hypnotics use disorder	Non-hospitalized	3.57 (3.05 to 4.18)	2.52 (2.16 to 2.95)	0.71 (0.69 to 0.73)	1.81 (1.45 to 2.24)
	Hospitalized	4.13 (2.54 to 6.70)	2.91 (1.79 to 4.73)		2.21 (1.09 to 4.02)
Neurocognitive decline	Non-hospitalized	2.28 (2.18 to 2.38)	30.92 (29.57 to 32.32)	13.70 (13.61 to 13.79)	17.22 (15.87 to 18.62)
	Hospitalized	4.49 (4.00 to 5.03)	60.04 (53.71 to 67.10)		46.34 (40.01 to 53.40)
Sleep					
Sleep disorders	Non-hospitalized	1.68 (1.63 to 1.72)	98.45 (96.08 to 100.88)	59.98 (59.75 to 60.20)	38.47 (36.10 to 40.90)
	Hospitalized	2.50 (2.28 to 2.74)	143.31 (131.68 to 155.88)		83.33 (71.70 to 95.90)
Sleep medications	Non-hospitalized	2.46 (2.40 to 2.53)	102.06 (99.52 to 104.67)		59.29 (56.75 to 61.90)

	Hospitalized	4.20 (3.88 to 4.54)	167.68 (156.06 to 180.06)	42.77 (42.59 to 42.95)	124.91 (113.29 to 137.30)
Composite endpoints					
Any mental health diagnosis	Non-hospitalized	1.40 (1.35 to 1.46)	116.77 (112.48 to 121.21)	84.88 (84.53 to 85.24)	31.89 (27.60 to 36.33)
	Hospitalized	3.43 (3.02 to 3.89)	262.23 (235.17 to 291.76)		177.34 (150.29 to 206.87)
Any mental health related drug prescription	Non-hospitalized	1.66 (1.60 to 1.74)	95.61 (91.81 to 99.57)	58.58 (58.28 to 58.88)	37.03 (33.22 to 40.99)
	Hospitalized	5.02 (4.46 to 5.65)	261.44 (236.04 to 289.03)		202.86 (177.45 to 230.45)
Any mental health diagnosis or prescription	Non-hospitalized	1.50 (1.45 to 1.55)	171.80 (166.80 to 176.94)	118.28 (117.86 to 118.69)	53.52 (48.52 to 58.66)
	Hospitalized	3.85 (3.47 to 4.27)	384.11 (354.07 to 415.80)		265.84 (235.79 to 297.53)

*. Outcomes were ascertained from day 30 after the initial positive COVID-19 test result until end of follow up.

†. Based on care received within the first 30 days after a positive COVID-19 test result.

‡. Adjustment through inverse probability weighting using predefined variables and algorithmically selected high-dimensional variables.

§. Any substance use disorder is defined as any illicit drug use disorder, alcohol use disorder, or sedative/hypnotics use disorder (opioid use disorder was not included in this outcome).

CI, confidence interval; GAD, Generalized anxiety disorder; MDD, Major depressive disorder; PTSD, Post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor.

Supplementary Table S7. Risks of incident post-acute COVID-19 mental health outcomes in pairwise comparison of people who were not hospitalized for COVID-19 vs those who were hospitalized for COVID-19 during the acute phase of the infection

Outcome*	Hazard ratio (95% CI) [†]	Rate per 1000 people at one year (95% CI) [†]		Risk difference per 1000 people at one year (95% CI) [†]
		COVID-19	Contemporary control	
Anxiety, depressive and stress disorders				
Anxiety disorders	1.39 (1.24 to 1.56)	74.41 (66.93 to 82.69)	54.18 (52.53 to 55.88)	20.23 (12.75 to 28.51)
GAD	1.36 (1.21 to 1.53)	69.83 (62.66 to 77.78)	51.92 (50.34 to 53.56)	17.90 (10.73 to 25.86)
Mixed stress disorder	1.45 (1.12 to 1.87)	10.29 (8.07 to 13.12)	7.11 (6.61 to 7.65)	3.18 (0.96 to 6.01)
Panic disorder	1.53 (1.11 to 2.10)	7.30 (5.38 to 9.90)	4.77 (4.38 to 5.20)	2.53 (0.60 to 5.13)
Depressive disorders	1.37 (1.22 to 1.55)	96.67 (86.67 to 107.74)	71.37 (69.20 to 73.61)	25.30 (15.30 to 36.37)
MDD - single episode	1.41 (1.27 to 1.58)	79.01 (71.41 to 87.39)	56.56 (54.89 to 58.27)	22.45 (14.85 to 30.83)
MDD - recurrent	1.19 (1.04 to 1.37)	52.72 (46.18 to 60.14)	44.39 (42.81 to 46.03)	8.32 (1.79 to 15.75)
Suicidal ideation	1.36 (1.06 to 1.73)	20.80 (16.47 to 26.24)	15.37 (14.43 to 16.37)	5.43 (1.11 to 10.87)
Stress and adjustment disorders	1.23 (1.09 to 1.38)	74.26 (66.46 to 82.94)	60.90 (58.98 to 62.88)	13.37 (5.57 to 22.04)
Acute stress and adjustment disorders	1.20 (1.05 to 1.36)	37.87 (33.62 to 42.65)	31.75 (30.58 to 32.95)	6.13 (1.88 to 10.91)
PTSD	1.20 (1.02 to 1.41)	42.94 (36.86 to 50.01)	35.90 (34.42 to 37.44)	7.05 (0.96 to 14.12)
Antidepressants	1.50 (1.35 to 1.66)	119.75 (109.14 to 131.31)	81.71 (79.30 to 84.19)	38.04 (27.43 to 49.61)
SSRI	1.43 (1.28 to 1.60)	90.99 (82.24 to 100.61)	64.40 (62.41 to 66.46)	26.59 (17.84 to 36.21)
SNRI	1.18 (1.00 to 1.39)	26.69 (22.86 to 31.15)	22.63 (21.65 to 23.66)	4.06 (0.22 to 8.52)
Other antidepressant medications	1.74 (1.48 to 2.04)	39.25 (33.79 to 45.57)	22.74 (21.70 to 23.82)	16.51 (11.05 to 22.83)
Benzodiazepines	1.68 (1.51 to 1.88)	69.50 (62.97 to 76.68)	41.92 (40.42 to 43.46)	27.58 (21.05 to 34.76)

Opioids				
Opioid prescription	1.70 (1.58 to 1.84)	184.88 (173.14 to 197.32)	113.04 (110.40 to 115.74)	71.84 (60.10 to 84.28)
Opioid use disorder	1.21 (0.92 to 1.59)	9.06 (6.99 to 11.73)	7.50 (6.84 to 8.22)	1.56 (-0.50 to 4.23)
Naloxone or naltrexone	1.18 (0.99 to 1.40)	31.66 (26.82 to 37.35)	26.95 (25.82 to 28.13)	4.71 (-0.12 to 10.41)
Methadone	0.82 (0.52 to 1.31)	1.08 (0.72 to 1.62)	1.32 (1.03 to 1.68)	-0.23 (-0.59 to 0.30)
Buprenorphine	1.65 (0.96 to 2.82)	4.96 (2.94 to 8.36)	3.02 (2.65 to 3.44)	1.94 (-0.07 to 5.34)
Substance use disorders				
Any substance use disorder‡	1.19 (1.01 to 1.39)	48.13 (41.34 to 55.99)	40.73 (39.02 to 42.50)	7.40 (0.61 to 15.26)
Illicit drug use disorder	1.21 (0.98 to 1.49)	24.80 (20.31 to 30.27)	20.60 (19.43 to 21.84)	4.20 (-0.29 to 9.67)
Alcohol use disorder	1.31 (1.08 to 1.58)	41.58 (34.62 to 49.89)	31.99 (30.52 to 33.53)	9.58 (2.63 to 17.90)
Sedative/hypnotics use disorder	1.16 (0.69 to 1.93)	2.91 (1.79 to 4.73)	2.52 (2.16 to 2.95)	0.39 (-0.73 to 2.21)
Neurocognitive decline				
	1.97 (1.74 to 2.23)	60.04 (53.71 to 67.10)	30.92 (29.57 to 32.32)	29.13 (22.79 to 36.18)
Sleep				
Sleep disorder	1.49 (1.36 to 1.64)	143.31 (131.68 to 155.88)	98.45 (96.08 to 100.88)	44.86 (33.23 to 57.43)
Sleep medications	1.70 (1.57 to 1.85)	167.68 (156.06 to 180.06)	102.06 (99.52 to 104.67)	65.62 (54.00 to 78.00)
Composite endpoints				
Any mental health diagnosis	2.45 (2.15 to 2.80)	262.23 (235.17 to 291.76)	116.77 (112.48 to 121.21)	145.46 (118.40 to 174.99)
Any mental health related drug prescription	3.02 (2.66 to 3.42)	261.44 (236.04 to 289.03)	95.61 (91.81 to 99.57)	165.83 (140.42 to 193.41)
Any mental health diagnosis or prescription	2.57 (2.31 to 2.87)	384.11 (354.07 to 415.80)	171.80 (166.80 to 176.94)	212.31 (182.27 to 244.00)
*. Outcomes were ascertained from 30 days after the initial positive COVID-19 test result until end of follow up.				
†. Adjustment through inverse probability weighting using predefined and algorithmically selected high-dimensional variables.				
‡. Any substance use disorder is defined as any illicit drug use disorder, alcohol use disorder, or sedative/hypnotics use disorder (opiod use disorder was not included in this outcome).				
CI, confidence interval; GAD, Generalized anxiety disorder; MDD, Major depressive disorder; PTSD, Post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor.				

Supplementary Table S8. Risks of incident post-acute COVID-19 mental health outcomes compared to historical control

Outcome*	Hazard ratio (95% CI) [†]	Rate per 1000 people at one year (95% CI) [†]		Risk difference per 1000 people at one year (95% CI) [†]
		COVID-19	Historical control	
Anxiety, depressive, and stress disorders				
Anxiety disorders	1.24 (1.19 to 1.28)	43.70 (42.28 to 45.17)	35.52 (35.36 to 35.68)	8.19 (6.77 to 9.66)
GAD	1.24 (1.20 to 1.28)	41.93 (40.55 to 43.36)	33.91 (33.76 to 34.07)	8.02 (6.64 to 9.45)
Mixed stress disorder	1.20 (1.11 to 1.31)	5.68 (5.23 to 6.17)	4.71 (4.66 to 4.77)	0.96 (0.51 to 1.45)
Panic disorder	1.15 (1.04 to 1.26)	3.82 (3.47 to 4.20)	3.33 (3.28 to 3.37)	0.49 (0.14 to 0.87)
Depressive disorders	1.18 (1.14 to 1.22)	55.50 (53.76 to 57.29)	47.24 (47.05 to 47.44)	8.25 (6.52 to 10.04)
MDD - single episode	1.16 (1.12 to 1.20)	43.21 (41.83 to 44.63)	37.42 (37.25 to 37.58)	5.79 (4.41 to 7.22)
MDD - recurrent	1.11 (1.07 to 1.16)	35.57 (34.29 to 36.90)	31.98 (31.82 to 32.13)	3.60 (2.32 to 4.92)
Suicidal ideation	1.20 (1.11 to 1.29)	7.21 (6.69 to 7.77)	6.01 (5.94 to 6.07)	1.20 (0.69 to 1.76)
Stress and adjustment disorders	1.27 (1.22 to 1.31)	48.83 (47.25 to 50.46)	38.78 (38.61 to 38.96)	10.05 (8.47 to 11.68)
Acute stress and adjustment disorders	1.35 (1.29 to 1.40)	25.06 (24.08 to 26.07)	18.65 (18.54 to 18.76)	6.40 (5.43 to 7.42)
PTSD	1.16 (1.11 to 1.22)	29.00 (27.79 to 30.26)	24.96 (24.83 to 25.10)	4.03 (2.83 to 5.29)
Antidepressants	1.31 (1.27 to 1.36)	62.49 (60.54 to 64.51)	47.92 (47.72 to 48.13)	14.57 (12.61 to 16.59)
SSRI	1.31 (1.26 to 1.35)	49.54 (47.88 to 51.25)	38.16 (37.98 to 38.33)	11.38 (9.72 to 13.09)
SNRI	1.00 (0.95 to 1.04)	17.82 (17.03 to 18.64)	17.90 (17.78 to 18.01)	-0.07 (-0.86 to 0.75)
Other antidepressant medications	1.38 (1.31 to 1.45)	16.74 (15.90 to 17.61)	12.15 (12.06 to 12.24)	4.59 (3.75 to 5.47)
Benzodiazepines	1.50 (1.44 to 1.57)	26.76 (25.67 to 27.90)	17.89 (17.78 to 18.00)	8.87 (7.77 to 10.01)
Opioids				

Opioid prescription	1.40 (1.37 to 1.45)	85.06 (82.77 to 87.41)	61.32 (61.10 to 61.54)	23.74 (21.45 to 26.09)
Opioid use disorder	1.13 (1.02 to 1.26)	3.82 (3.44 to 4.23)	3.36 (3.32 to 3.41)	0.45 (0.08 to 0.86)
Naloxone or naltrexone	1.42 (1.35 to 1.49)	16.44 (15.69 to 17.23)	11.61 (11.52 to 11.70)	4.83 (4.08 to 5.62)
Methadone	1.50 (1.14 to 1.98)	0.57 (0.43 to 0.75)	0.38 (0.36 to 0.39)	0.19 (0.05 to 0.37)
Buprenorphine	1.69 (1.41 to 2.04)	1.76 (1.46 to 2.11)	1.04 (1.01 to 1.06)	0.72 (0.42 to 1.07)
Substance use disorders				
Any substance use disorder [‡]	1.05 (1.00 to 1.09)	26.01 (24.89 to 27.18)	24.90 (24.77 to 25.03)	1.11 (-0.01 to 2.28)
Illicit drug use disorder	1.03 (0.96 to 1.10)	11.11 (10.41 to 11.86)	10.79 (10.71 to 10.88)	0.31 (-0.39 to 1.06)
Alcohol use disorder	1.10 (1.04 to 1.15)	20.87 (19.88 to 21.92)	19.06 (18.95 to 19.18)	1.81 (0.82 to 2.85)
Sedative/hypnotics use disorder	1.08 (0.88 to 1.33)	0.99 (0.80 to 1.22)	0.91 (0.89 to 0.94)	0.08 (-0.11 to 0.30)
Neurocognitive decline				
Sleep				
Sleep disorder	1.27 (1.24 to 1.31)	84.05 (81.90 to 86.25)	66.66 (66.43 to 66.90)	17.39 (15.24 to 19.58)
Sleep medications	1.50 (1.46 to 1.54)	68.63 (66.77 to 70.54)	46.24 (46.06 to 46.43)	22.39 (20.52 to 24.30)
Composite endpoints				
Any mental health diagnosis	1.27 (1.22 to 1.32)	120.80 (116.26 to 125.51)	96.27 (95.89 to 96.66)	24.53 (19.99 to 29.24)
Any mental health related drug prescription	1.51 (1.45 to 1.58)	105.96 (101.61 to 110.47)	71.37 (71.04 to 71.71)	34.58 (30.24 to 39.10)
Any mental health diagnosis or prescription	1.37 (1.32 to 1.41)	182.68 (177.21 to 188.31)	137.22 (136.77 to 137.67)	45.46 (39.99 to 51.09)
<p>*. Outcomes were ascertained from 30 days after the initial positive COVID-19 test result until end of follow up.</p> <p>†. Adjustment through inverse probability weighting using predefined and algorithmically selected high-dimensional variables.</p> <p>‡. Any substance use disorder is defined as any illicit drug use disorder, alcohol use disorder, or sedative/hypnotics use disorder (opioid use disorder was not included in this outcome).</p> <p>CI, confidence interval; GAD, Generalized anxiety disorder; MDD, Major depressive disorder; PTSD, Post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor.</p>				

Supplementary Table S9. Demographic and health characteristics of the COVID-19 and historical control by care setting of the acute infection before weighting

Baseline Characteristics	Non-hospitalized (N= 132,852)	Hospitalized (N= 20,996)	Historical control (N= 5,809,064)	Absolute standardized difference - Non- hospitalized and Historical control[‡]	Absolute standardized difference - Hospitalized and Historical control[‡]	Absolute standardized difference – Non- hospitalized and Hospitalized[‡]
Age, mean (std), yr	63.35 (16.21)	65.37 (14.98)	63.27 (16.31)	0.16	0.39	0.58
Race, no. (%)						
White	95859 (72.16)	13189 (62.82)	4496238 (77.40)	0.12	0.32	0.20
Black	30519 (22.97)	6606 (31.46)	1039895 (17.90)	0.13	0.32	0.19
Other	6474 (4.87)	1201 (5.72)	272931 (4.70)	0.01	0.05	0.04
Sex, no. (%)						
Male	117190 (88.21)	19801 (94.31)	5261822 (90.58)	0.08	0.14	0.22
Female	15662 (11.79)	1195 (5.69)	547242 (9.42)	0.08	0.14	0.22
BMI category, no. (%), kg/m²						
Underweight/ Normal	17864 (13.45)	4340 (20.67)	1148245 (19.77)	0.17	0.02	0.19
Overweight	42480 (31.98)	6368 (30.33)	2134789 (36.75)	0.10	0.14	0.04
Obese	72508 (54.58)	10288 (49)	2526030 (43.48)	0.22	0.11	0.11
Smoking status, no. (%)						
Never	60256 (45.36)	8854 (42.17)	3066661 (52.79)	0.15	0.21	0.06
Former	52348 (39.40)	8792 (41.88)	1427443 (24.57)	0.32	0.37	0.05
Current	20248 (15.24)	3350 (15.96)	1314960 (22.64)	0.19	0.17	0.02
Area Deprivation Index*, mean (std)	54.81 (19.09)	55.18 (19.24)	54.71 (19.08)	0.05	0.08	0.13
Clinical Characteristics						
Outpatient encounter[†], no. (%)						
Zero or one	28850 (21.72)	1878 (8.95)	2426930 (41.78)	0.44	0.81	0.36
Two	40546 (30.52)	4193 (19.97)	1614322 (27.79)	0.06	0.18	0.24
Three or more	63456 (47.76)	14925 (71.09)	1767812 (30.43)	0.36	0.89	0.49

Long-term care, no. (%)	3992 (3.01)	2116 (10.08)	43458 (0.75)	0.17	0.42	0.29
eGFR, mean (std), ml/min/1.73m²	78.94 (20.52)	77.36 (20.27)	78.94 (20.58)	0.01	0.50	0.49
Systolic blood pressure, mean (std), mmHg	132.71 (12.48)	133.15 (12.54)	132.68 (12.45)	0.02	0.15	0.18
Diastolic blood pressure, mean (std), mmHg	77.65 (7.75)	77.64 (7.79)	77.66 (7.73)	0.13	0.07	0.21
Cancer, no. (%)	9498 (7.15)	3027 (14.42)	336707 (5.80)	0.06	0.29	0.24
Cerebrovascular disease, no. (%)	7431 (5.59)	2979 (14.19)	257691 (4.44)	0.05	0.34	0.29
Cardiovascular disease, no. (%)	19879 (14.96)	6750 (32.15)	742564 (12.78)	0.06	0.48	0.41
Chronic kidney disease, no. (%)	22286 (16.78)	7734 (36.84)	888016 (15.29)	0.04	0.51	0.46
Chronic lung disease, no. (%)	17890 (13.47)	5589 (26.62)	636747 (10.96)	0.08	0.41	0.33
Diabetes mellitus type 2, no. (%)	39531 (29.76)	9892 (47.11)	1310615 (22.56)	0.16	0.53	0.36
Rheumatoid arthritis, no. (%)	1516 (1.14)	362 (1.72)	48588 (0.84)	0.03	0.08	0.05

*.Area Deprivation Index is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.

†.Data collected within one year before cohort enrollment.

‡. Standardized difference less than 0.10 is considered good balance.

std, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Supplementary Table S10. Demographic and health characteristics of the COVID-19 and historical cohorts by care setting of the acute infection after weighting

Baseline Characteristics	Non-hospitalized (N= 132,852)	Hospitalized (N= 20,996)	Historical control (N= 5,809,064)	Absolute standardized difference - Non- hospitalized and Historical control[‡]	Absolute standardized difference - Hospitalized and Historical control[‡]	Absolute standardized difference – Non- hospitalized and Hospitalized[‡]
Age, mean (std), yr	63.34 (16.29)	64.12 (15.84)	63.32 (16.28)	0.02	0.02	0.00
Race, no. (%)						
White	100828 (75.90)	15603 (74.31)	4450905 (76.62)	0.02	0.05	0.04
Black	25547 (19.23)	4284 (20.41)	1080428 (18.60)	0.02	0.05	0.03
Other	6477 (4.88)	1109 (5.28)	277789 (4.78)	0.00	0.02	0.02
Sex, no. (%)						
Male	119168 (89.70)	19245 (91.66)	5240124 (90.21)	0.02	0.05	0.07
Female	13684 (10.30)	1751 (8.34)	568940 (9.79)	0.02	0.05	0.07
BMI category, no. (%), kg/m²						
Underweight/ Normal	25251 (19.01)	3978 (18.95)	1122369 (19.32)	0.01	0.01	0.00
Overweight	47812 (35.99)	7209 (34.34)	2105321 (36.24)	0.01	0.04	0.03
Obese	59789 (45)	9808 (46.72)	2581374 (44.44)	0.01	0.05	0.03
Smoking status, no. (%)						
Never	54875 (41.31)	8502 (40.49)	2481167 (42.71)	0.03	0.05	0.02
Former	49240 (37.06)	7582 (36.11)	2093645 (36.04)	0.02	0.00	0.02
Current	28737 (21.63)	4912 (23.40)	1234252 (21.25)	0.01	0.05	0.04
Area Deprivation Index*, mean (std)	54.81 (19.08)	55.33 (19.28)	54.72 (19.08)	0.02	0.01	0.02
Clinical Characteristics						
Outpatient encounter[†], no. (%)						
Zero or one	56752 (42.72)	9261 (44.11)	2498246 (43.01)	0.01	0.02	0.03
Two	36982 (27.84)	5603 (26.69)	1651517 (28.43)	0.01	0.04	0.03
Three or more	39118 (29.45)	6132 (29.21)	1659301 (28.56)	0.02	0.01	0.01

Long-term care, no. (%)	1186 (0.89)	311 (1.48)	39618 (0.68)	0.02	0.08	0.05
eGFR, mean (std), ml/min/1.73m²	78.92 (20.52)	78.39 (20.43)	78.89 (20.58)	0.00	0.01	0.01
Systolic blood pressure, mean (std), mmHg	132.71 (12.51)	133.11 (12.78)	132.69 (12.45)	0.00	0.05	0.05
Diastolic blood pressure, mean (std), mmHg	77.62 (7.75)	77.85 (8.11)	77.66 (7.73)	0.00	0.06	0.05
Cancer, no. (%)	8307 (6.25)	1376 (6.55)	354179 (6.10)	0.01	0.02	0.01
Cerebrovascular disease, no. (%)	6021 (4.53)	1109 (5.28)	252636 (4.35)	0.01	0.04	0.03
Cardiovascular disease, no. (%)	17154 (12.91)	2909 (13.86)	734150 (12.64)	0.01	0.04	0.03
Chronic kidney disease, no. (%)	22837 (17.19)	3996 (19.03)	966047 (16.63)	0.01	0.06	0.05
Chronic lung disease, no. (%)	14929 (11.24)	2523 (12.02)	630342 (10.85)	0.01	0.04	0.02
Diabetes mellitus type 2, no. (%)	30771 (23.16)	5529 (26.33)	1319122 (22.71)	0.01	0.08	0.07
Rheumatoid arthritis, no. (%)	1193 (0.90)	173 (0.82)	50887 (0.88)	0.00	0.01	0.01

*.Area Deprivation Index is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.

†.Data collected within one year before cohort enrollment.

‡. Standardized difference less than 0.10 is considered good balance.

std, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Supplementary Table S11. Risks of incident post-acute COVID-19 mental health outcomes by care setting of the acute infection compared to historical control

Outcome*	Care setting†	Hazard ratio (95% CI)‡	Rate per 1000 people at one year (95% CI)‡		Risk difference per 1000 people at one year (95% CI)‡
			COVID-19	Historical control	
Anxiety, depressive, and stress disorders					
Anxiety disorder	Non-hospitalized	1.55 (1.50 to 1.60)	54.18 (52.53 to 55.88)	35.22 (35.06 to 35.38)	18.96 (17.31 to 20.65)
	Hospitalized	2.16 (1.93 to 2.41)	74.41 (66.93 to 82.69)		39.19 (31.71 to 47.47)
GAD	Non-hospitalized	1.56 (1.51 to 1.61)	51.92 (50.34 to 53.56)	33.64 (33.48 to 33.79)	18.29 (16.70 to 19.92)
	Hospitalized	2.12 (1.89 to 2.37)	69.83 (62.66 to 77.78)		36.19 (29.02 to 44.15)
Mixed stress disorder	Non-hospitalized	1.51 (1.40 to 1.62)	7.11 (6.61 to 7.65)	4.72 (4.66 to 4.77)	2.39 (1.89 to 2.93)
	Hospitalized	2.19 (1.71 to 2.79)	10.29 (8.07 to 13.12)		5.58 (3.36 to 8.41)
Panic disorder	Non-hospitalized	1.47 (1.35 to 1.60)	4.77 (4.38 to 5.20)	3.25 (3.20 to 3.29)	1.52 (1.13 to 1.96)
	Hospitalized	2.25 (1.66 to 3.06)	7.30 (5.38 to 9.90)		4.05 (2.13 to 6.65)
Depressive disorder	Non-hospitalized	1.52 (1.47 to 1.56)	71.37 (69.20 to 73.61)	47.68 (47.49 to 47.88)	23.69 (21.52 to 25.92)
	Hospitalized	2.08 (1.86 to 2.33)	96.67 (86.67 to 107.74)		48.99 (38.99 to 60.06)
MDD - single episode	Non-hospitalized	1.53 (1.49 to 1.58)	56.56 (54.89 to 58.27)	37.22 (37.06 to 37.38)	19.33 (17.66 to 21.05)
	Hospitalized	2.17 (1.95 to 2.41)	79.01 (71.41 to 87.39)		41.79 (34.18 to 50.16)
MDD – recurrent	Non-hospitalized	1.39 (1.34 to 1.44)	44.39 (42.81 to 46.03)	32.13 (31.98 to 32.29)	12.26 (10.68 to 13.90)
	Hospitalized	1.66 (1.45 to 1.90)	52.72 (46.18 to 60.14)		20.58 (14.05 to 28.01)
Suicidal ideation	Non-hospitalized	2.61 (2.45 to 2.78)	15.37 (14.43 to 16.37)	5.92 (5.86 to 5.99)	9.44 (8.50 to 10.44)
	Hospitalized	3.54 (2.80 to 4.48)	20.80 (16.47 to 26.24)		14.87 (10.55 to 20.31)

Stress and adjustment disorder	Non-hospitalized	1.60 (1.54 to 1.65)	60.90 (58.98 to 62.88)	38.62 (38.45 to 38.80)	22.28 (20.36 to 24.25)
	Hospitalized	1.96 (1.75 to 2.20)	74.26 (66.46 to 82.94)		35.64 (27.84 to 44.32)
Acute stress and adjustment disorders	Non-hospitalized	1.72 (1.66 to 1.79)	31.75 (30.58 to 32.95)	18.54 (18.43 to 18.65)	13.21 (12.04 to 14.41)
	Hospitalized	2.06 (1.83 to 2.33)	37.87 (33.62 to 42.65)		19.33 (15.08 to 24.11)
PTSD	Non-hospitalized	1.44 (1.38 to 1.51)	35.90 (34.42 to 37.44)	25.00 (24.86 to 25.14)	10.90 (9.42 to 12.44)
	Hospitalized	1.73 (1.48 to 2.03)	42.94 (36.86 to 50.01)		17.94 (11.86 to 25.01)
Antidepressants	Non-hospitalized	1.73 (1.68 to 1.79)	81.71 (79.30 to 84.19)	47.94 (47.74 to 48.14)	33.76 (31.36 to 36.24)
	Hospitalized	2.60 (2.35 to 2.87)	119.75 (109.14 to 131.31)		71.81 (61.19 to 83.37)
SSRI	Non-hospitalized	1.72 (1.66 to 1.77)	64.40 (62.41 to 66.46)	38.03 (37.86 to 38.20)	26.37 (24.38 to 28.43)
	Hospitalized	2.46 (2.21 to 2.74)	90.99 (82.24 to 100.61)		52.96 (44.21 to 62.58)
SNRI	Non-hospitalized	1.27 (1.21 to 1.33)	22.63 (21.65 to 23.66)	17.88 (17.77 to 17.99)	4.76 (3.77 to 5.79)
	Hospitalized	1.50 (1.28 to 1.75)	26.69 (22.86 to 31.15)		8.81 (4.98 to 13.28)
Other antidepressant medications	Non-hospitalized	1.90 (1.81 to 1.99)	22.74 (21.70 to 23.82)	12.02 (11.94 to 12.11)	10.71 (9.68 to 11.80)
	Hospitalized	3.31 (2.84 to 3.86)	39.25 (33.79 to 45.57)		27.22 (21.76 to 33.54)
Benzodiazepines	Non-hospitalized	2.40 (2.31 to 2.49)	41.92 (40.42 to 43.46)	17.67 (17.56 to 17.78)	24.24 (22.75 to 25.79)
	Hospitalized	4.04 (3.65 to 4.47)	69.50 (62.97 to 76.68)		51.83 (45.29 to 59.01)
Opioid prescription	Non-hospitalized	1.90 (1.86 to 1.95)	113.04 (110.40 to 115.74)	61.05 (60.84 to 61.27)	51.98 (49.34 to 54.68)
	Hospitalized	3.24 (3.02 to 3.49)	184.88 (173.14 to 197.32)		123.82 (112.08 to 136.26)
Opioid use disorder	Non-hospitalized	2.27 (2.07 to 2.49)	7.50 (6.84 to 8.22)	3.30 (3.26 to 3.35)	4.19 (3.53 to 4.92)
	Hospitalized	2.75 (2.12 to 3.57)	9.06 (6.99 to 11.73)		5.75 (3.69 to 8.43)

Naloxone or naltrexone	Non-hospitalized	2.40 (2.30 to 2.51)	26.95 (25.82 to 28.13)	11.33 (11.24 to 11.41)	15.62 (14.49 to 16.80)
	Hospitalized	2.82 (2.39 to 3.34)	31.66 (26.82 to 37.35)		20.33 (15.50 to 26.03)
Methadone	Non-hospitalized	3.64 (2.86 to 4.64)	1.32 (1.03 to 1.68)	0.36 (0.35 to 0.38)	0.96 (0.67 to 1.32)
	Hospitalized	2.99 (2.00 to 4.47)	1.08 (0.72 to 1.62)		0.72 (0.36 to 1.26)
Buprenorphine	Non-hospitalized	3.09 (2.71 to 3.53)	3.02 (2.65 to 3.44)	0.98 (0.95 to 1.00)	2.04 (1.67 to 2.46)
	Hospitalized	5.09 (3.02 to 8.59)	4.96 (2.94 to 8.36)		3.98 (1.97 to 7.38)
Substance use disorders					
Any substance use disorder [§]	Non-hospitalized	1.63 (1.56 to 1.70)	40.73 (39.02 to 42.50)	25.18 (25.05 to 25.31)	15.55 (13.84 to 17.32)
	Hospitalized	1.93 (1.66 to 2.26)	48.13 (41.34 to 55.99)		22.95 (16.16 to 30.81)
Illicit drug use disorder	Non-hospitalized	1.90 (1.79 to 2.01)	20.60 (19.43 to 21.84)	10.90 (10.82 to 10.99)	9.70 (8.53 to 10.93)
	Hospitalized	2.29 (1.87 to 2.80)	24.80 (20.31 to 30.27)		13.90 (9.41 to 19.36)
Alcohol use disorder	Non-hospitalized	1.70 (1.62 to 1.78)	31.99 (30.52 to 33.53)	18.99 (18.87 to 19.10)	13.01 (11.54 to 14.55)
	Hospitalized	2.22 (1.84 to 2.67)	41.58 (34.62 to 49.89)		22.59 (15.64 to 30.91)
Sedative/Hypnotics use disorder	Non-hospitalized	2.80 (2.40 to 3.27)	2.52 (2.16 to 2.95)	0.90 (0.88 to 0.92)	1.62 (1.26 to 2.05)
	Hospitalized	3.24 (1.99 to 5.26)	2.91 (1.79 to 4.73)		2.01 (0.89 to 3.83)
Neurocognitive decline	Non-hospitalized	2.13 (2.03 to 2.23)	30.92 (29.57 to 32.32)	14.64 (14.54 to 14.74)	16.27 (14.93 to 17.68)
	Hospitalized	4.20 (3.74 to 4.71)	60.04 (53.71 to 67.10)		45.40 (39.07 to 52.46)
Sleep					
Sleep disorders	Non-hospitalized	1.51 (1.48 to 1.55)	98.45 (96.08 to 100.88)	66.18 (65.95 to 66.42)	32.27 (29.89 to 34.70)
	Hospitalized	2.26 (2.06 to 2.47)	143.31 (131.68 to 155.88)		77.13 (65.50 to 89.69)
Sleep medications	Non-hospitalized	2.28 (2.22 to 2.34)	102.06 (99.52 to 104.67)		55.88 (53.33 to 58.48)

	Hospitalized	3.88 (3.59 to 4.20)	167.68 (156.06 to 180.06)	46.19 (46.00 to 46.37)	121.49 (109.88 to 133.88)
Composite endpoints					
Any mental health diagnosis	Non-hospitalized	1.22 (1.17 to 1.27)	116.77 (112.48 to 121.21)	96.95 (96.57 to 97.33)	19.82 (15.53 to 24.26)
	Hospitalized	2.98 (2.63 to 3.38)	262.23 (235.17 to 291.76)		165.28 (138.22 to 194.81)
Any mental health related drug prescription	Non-hospitalized	1.36 (1.30 to 1.42)	95.61 (91.81 to 99.57)	71.43 (71.10 to 71.76)	24.19 (20.38 to 28.14)
	Hospitalized	4.09 (3.63 to 4.60)	261.44 (236.04 to 289.03)		190.01 (164.61 to 217.60)
Any mental health diagnosis or prescription	Non-hospitalized	1.28 (1.24 to 1.32)	171.80 (166.80 to 176.94)	136.96 (136.52 to 137.40)	34.84 (29.84 to 39.98)
	Hospitalized	3.29 (2.97 to 3.65)	384.11 (354.07 to 415.80)		247.15 (217.11 to 278.84)

*. Outcomes were ascertained from day 30 after the initial positive COVID-19 test result until end of follow up.

†. Based on care received within the first 30 days after a positive COVID-19 test result.

‡. Adjustment through inverse probability weighting using predefined variables and algorithmically selected high-dimensional variables.

§. Any substance use disorder is defined as any illicit drug use disorder, alcohol use disorder, or sedative/hypnotics use disorder (opiod use disorder was not included in this outcome).

CI, confidence interval; GAD, Generalized anxiety disorder; MDD, Major depressive disorder; PTSD, Post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor.

Supplementary Table S12. Risks of incident composite post-acute COVID-19 mental health outcomes in comparisons involving non-hospitalized COVID-19 vs non-hospitalized seasonal influenza, hospitalized COVID-19 vs hospitalized seasonal influenza, and hospitalized COVID-19 vs hospitalized for any other cause

Outcome*	Hazard ratio (95% CI)		
	Non-hospitalized COVID-19 vs non-hospitalized seasonal influenza [†]	Hospitalized COVID-19 vs hospitalized seasonal influenza ^{†,‡}	Hospitalized COVID-19 vs hospitalized for other causes ^{†,‡}
Anxiety disorders	1.44 (1.22 to 1.71)	1.34 (1.13 to 1.59)	1.63 (1.48 to 1.80)
Depressive disorders	1.32 (1.12 to 1.56)	1.24 (1.06 to 1.47)	1.42 (1.29 to 1.57)
Stress and adjustment disorders	1.51 (1.27 to 1.80)	1.41 (1.17 to 1.70)	1.36 (1.22 to 1.52)
Antidepressants	1.42 (1.20 to 1.67)	1.56 (1.35 to 1.81)	1.92 (1.76 to 2.09)
Any substance use disorder[§]	1.26 (1.02 to 1.57)	1.12 (1.02 to 1.23)	1.18 (1.03 to 1.36)
Any mental health diagnosis	1.44 (1.27 to 1.64)	1.43 (1.24 to 1.65)	1.62 (1.48 to 1.76)
Any mental health related drug prescription	1.29 (1.13 to 1.48)	1.39 (1.21 to 1.59)	1.89 (1.74 to 2.05)
Any mental health diagnosis or prescription	1.27 (1.12 to 1.45)	1.45 (1.22 to 1.71)	1.86 (1.68 to 2.05)

*. Outcomes were ascertained from 30 days after the initial positive COVID-19 test result until end of follow up.

†. Adjustment through overlap weighting using predefined and algorithmically selected high-dimensional variables.

‡. Additionally adjusting for intensive care admission and length of stay during hospitalization.

§. Any substance use disorder is defined as any illicit drug use disorder, alcohol use disorder, or sedative/hypnotics use disorder (opioid use disorder was not included in this outcome).

CI, confidence interval.

Supplementary Table S13. Sensitivity analysis for any mental health related drug prescription, any mental health diagnosis, and any mental health diagnosis or prescription compared to contemporary and historical controls

Analysis	Any mental health diagnosis Hazard ratio (95% CI)*		Any mental health related drug prescription Hazard ratio (95% CI)*		Any mental health diagnosis or prescription Hazard ratio (95% CI)*	
	Contemporary	Historical	Contemporary	Historical	Contemporary	Historical
Used 300 algorithmically selected high dimensional variables	1.44 (1.38 to 1.50)	1.24 (1.19 to 1.30)	1.82 (1.74 to 1.91)	1.47 (1.40 to 1.54)	1.57 (1.52 to 1.63)	1.33 (1.29 to 1.38)
Did not use any high dimensional variables	1.56 (1.50 to 1.62)	1.37 (1.32 to 1.43)	1.95 (1.88 to 2.03)	1.61 (1.54 to 1.67)	1.69 (1.64 to 1.74)	1.46 (1.42 to 1.50)
Doubly robust	1.40 (1.35 to 1.46)	1.22 (1.17 to 1.28)	1.71 (1.64 to 1.79)	1.39 (1.33 to 1.45)	1.51 (1.46 to 1.56)	1.29 (1.24 to 1.33)
Adjusting for time updated health care utilization during follow up	1.18 (1.13 to 1.22)	1.16 (1.11 to 1.21)	1.36 (1.30 to 1.42)	1.19 (1.14 to 1.25)	1.25 (1.21 to 1.29)	1.20 (1.16 to 1.24)
*. Outcomes were ascertained from day 30 after the initial positive COVID-19 test result until end of follow up. CI, confidence interval.						

Supplementary Table S14. Sensitivity analysis for any mental health related drug prescription, any mental health diagnosis, and any mental health diagnosis or prescription by care setting of the acute infection compared to contemporary and historical controls

Analysis	Care Setting*	Any mental health diagnosis Hazard ratio (95% CI) †		Any mental health related drug prescription Hazard ratio (95% CI) †		Any mental health diagnosis or prescription Hazard ratio (95% CI) †	
		Contemporary	Historical	Contemporary	Historical	Contemporary	Historical
Used 300 algorithmically selected high dimensional variables	Non-hospitalized	1.40 (1.35 to 1.46)	1.22 (1.17 to 1.27)	1.67 (1.60 to 1.75)	1.36 (1.30 to 1.42)	1.50 (1.45 to 1.55)	1.28 (1.24 to 1.32)
	Hospitalized	3.44 (3.03 to 3.90)	2.98 (2.63 to 3.38)	5.04 (4.48 to 5.67)	4.09 (3.64 to 4.61)	3.86 (3.48 to 4.28)	3.29 (2.97 to 3.65)
Did not use any high dimensional variables	Non-hospitalized	1.40 (1.35 to 1.46)	1.24 (1.19 to 1.29)	1.67 (1.60 to 1.75)	1.38 (1.32 to 1.44)	1.50 (1.45 to 1.55)	1.30 (1.26 to 1.34)
	Hospitalized	3.43 (3.03 to 3.90)	3.03 (2.67 to 3.43)	5.04 (4.48 to 5.67)	4.16 (3.70 to 4.68)	3.86 (3.48 to 4.28)	3.34 (3.01 to 3.71)
Doubly robust	Non-hospitalized	1.34 (1.30 to 1.38)	1.19 (1.15 to 1.22)	1.53 (1.49 to 1.58)	1.29 (1.26 to 1.33)	1.49 (1.44 to 1.53)	1.27 (1.23 to 1.31)
	Hospitalized	2.69 (2.39 to 3.03)	2.38 (2.11 to 2.67)	3.65 (3.31 to 4.03)	3.07 (2.78 to 3.39)	3.47 (3.08 to 3.91)	2.97 (2.64 to 3.34)
Adjusting for time updated health care utilization during follow up	Non-hospitalized	1.30 (1.26 to 1.34)	1.08 (1.05 to 1.12)	1.44 (1.40 to 1.47)	1.08 (1.05 to 1.11)	1.42 (1.38 to 1.47)	1.14 (1.10 to 1.17)
	Hospitalized	2.13 (1.93 to 2.36)	1.78 (1.61 to 1.97)	2.65 (2.43 to 2.89)	2.00 (1.83 to 2.19)	2.69 (2.41 to 3.00)	2.15 (1.92 to 2.40)

*. Based on care received within the first 30 days after a positive COVID-19 test result .

†. Outcomes were ascertained from day 30 after the initial positive COVID-19 test result until end of follow up.

CI, confidence interval.

Supplementary Table S15. Positive and negative outcome controls

Outcome *	Hazard Ratio (95% CI)	
	Contemporary	Historical
Positive outcome control		
Fatigue	1.75 (1.71 to 1.79)	1.72 (1.68 to 1.75)
Negative outcome controls		
Lichen planus	1.04 (0.83 to 1.30)	0.98 (0.78 to 1.22)
Lichen simplex chronicus	1.08 (0.97 to 1.20)	0.99 (0.89 to 1.10)
Melanoma in situ	0.99 (0.84 to 1.18)	0.99 (0.84 to 1.17)
Allergic eczema	1.02 (0.89 to 1.17)	0.91 (0.79 to 1.04)
*. Outcomes were ascertained from day 30 after the initial positive COVID-19 test result until end of follow up. CI, confidence interval.		