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Risks of mental health outcomes in people with covid-19: cohort study

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ABSTRACT

OBJECTIVE

To estimate the risks of incident mental health disorders in survivors of the acute phase of covid-19.

DESIGN

Cohort study.

SETTING

US Department of Veterans Affairs.

PARTICIPANTS

Cohort comprising 153 848 people who survived the first 30 days of SARS-CoV-2 infection, and two control groups: a contemporary group (n=5 637 840) with no evidence of SARS-CoV-2, and a historical control group (n=5 859 251) that predated the covid-19 pandemic.

MAIN OUTCOMES MEASURES

Risks of prespecified incident mental health outcomes, calculated as hazard ratio and absolute risk difference per 1000 people at one year, with corresponding 95% confidence intervals. Predefined covariates and algorithmically selected high dimensional covariates were used to balance the covid-19 and control groups through inverse weighting.

RESULTS

The covid-19 group showed an increased risk of incident anxiety disorders (hazard ratio 1.35 (95% confidence interval 1.30 to 1.39); risk difference 11.06 (95% confidence interval 9.64 to 12.53) per 1000 people at one year), depressive disorders (1.39 (1.34 to 1.43); 15.12 (13.38 to 16.91) per 1000 people at one year), stress and adjustment disorders (1.38 (1.34 to 1.43); 13.29 (11.71 to 14.92) per 1000 people at one year), and use of antidepressants (1.55 (1.50 to 1.60); 21.59 (19.63 to 23.60) per 1000 people at one year) and benzodiazepines (1.65 (1.58 to 1.72); 10.46 (9.37 to 11.61) per 1000 people at one year). The risk of incident opioid prescriptions also increased (1.76 (1.71 to 1.81); 35.90 (33.61 to 38.25) per 1000 people at one year), opioid use disorders (1.34 (1.21 to 1.48); 0.96 (0.59 to 1.37) per 1000 people at one year), and other (non-opioid) substance use disorders (1.20 (1.15 to 1.26); 4.34 (3.22 to 5.51) per 1000 people at one year). The covid-19 group also showed an increased risk of incident neurocognitive decline (1.80 (1.72 to 1.89); 10.75 (9.65 to 11.91) per 1000 people at one year) and sleep disorders (1.41 (1.38 to 1.45); 23.80 (21.65 to 26.00) per 1000 people at one year). The risk of any incident mental health diagnosis or prescription was increased (1.60 (1.55 to 1.66); 64.38 (58.90 to 70.01) per 1000 people at one year). The risks of examined outcomes were increased even among people who were not admitted to hospital and were highest among those who were admitted to hospital during the acute phase of covid-19. Results were consistent with those in the historical control group. The risk of incident mental health disorders was consistently higher in the covid-19 group in comparisons of people with covid-19 not admitted to hospital versus those not admitted to hospital for seasonal influenza, admitted to hospital with covid-19 versus admitted to hospital with seasonal influenza, and admitted to hospital with covid-19 versus admitted to hospital for any other cause.

CONCLUSIONS

The findings suggest that people who survive the acute phase of covid-19 are at increased risk of an array of incident mental health disorders. Tackling mental health disorders among survivors of covid-19 should be a priority.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies limited to short follow-up (<6 months) and narrow selection of mental health outcomes showed that people with covid-19 might be at increased risk of anxiety and depression

A comprehensive assessment of the mental health manifestations in people with covid-19 at one year is important

WHAT THIS STUDY ADDS

People with covid-19 show increased risks of incident mental health disorders (eg, anxiety disorders, depressive disorders, stress and adjustment disorders, opioid use disorders, other (non-opioid) substance use disorders, neurocognitive decline, and sleep disorders) compared with contemporary controls without SARS-CoV-2 or historical controls before the pandemic

The risks of mental health disorders were evident even among those who were not admitted to hospital and were highest in those who were admitted to hospital for covid-19 during the acute phase of the disease

People with covid-19 showed higher risks of mental health disorders than people with seasonal influenza; people admitted to hospital for covid-19 showed increased risks of mental health disorders compared with those admitted to hospital for any other cause

Introduction

During the post-acute phase of covid-19, patients are at increased risk of developing mental health disorders.[1 2] Studies to date have been limited by narrow selection of mental health outcomes and a maximum of six months' follow-up. A comprehensive assessment of the mental health manifestations in people with covid-19 at one year has not been undertaken. Improving our understanding of the long term risk of mental health disorders in people with covid-19 can help guide strategies for care during the post-acute phase.

We extracted data from the US Department of Veterans Affairs national healthcare databases to estimate the risks of incident mental health outcomes in people who survived the acute phase of covid-19. From these data we constructed a cohort of 153 848 US

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veterans who survived the first 30 days of SARS-CoV-2 infection and two control groups—a contemporary group consisting of 5 637 840 users of the US Department of Veterans Health Care System (Veterans Health Administration) with no evidence of SARS-CoV-2 infection, and a historical control (predating the covid-19 pandemic) consisting of 5 859 251 users of the healthcare system during 2017. We followed these cohorts longitudinally to estimate the risks of a set of prespecified incident mental health outcomes in the overall cohort and according to care setting during the acute phase of the infection—that is, whether people were or were not admitted to hospital during the first 30 days of covid-19.

Methods

The study was conducted using data from the Veterans Health Administration, which operates the largest nationally integrated healthcare system in the US; it provides healthcare to veterans discharged from the US armed forces. The Veterans Health Administration provides a comprehensive medical benefits package that includes outpatient care, inpatient hospital care, mental healthcare, prescriptions, medical equipment, and prosthetics. The healthcare system operates 1255 healthcare facilities, including 170 medical centers and 1074 outpatient sites.

Cohort

Those who had used the Veterans Health Administration in 2019 (n=6 241 875) and had at least one positive covid-19 polymerase chain reaction (PCR) test result between 1 March 2020 and 15 January 2021 were selected into the covid-19 group (n=169 240). From this group we then selected those who were alive 30 days after the positive test result (n=153 848) to examine outcomes during the post-acute phase. The start of follow-up was set as the date of the positive test result in the covid-19 group; follow-up ended on 30 November 2021.

We then constructed a non-infected contemporary control group from those who used the Veterans Health Administration in 2019 (n=6 241 875). Those alive by 1 March 2020 (n=5 961 157) and not in the covid-19 group were selected into the non-infected contemporary control group (n=5 807 309). To ensure that the contemporary control group had a similar distribution of follow-up time as the covid-19 group, we randomly assigned the start of follow-up for participants in the contemporary control group following the same distribution of the date of a positive test result in the covid-19 group, so that the proportion of participants with the start of follow-up on a certain date was the same in both groups. Overall, 5 659 095 participants alive at the assigned start of follow-up and 5 637 840 of them alive 30 days after the start of follow-up were further selected as the contemporary control group; follow-up ended on 30 November 2021.

To examine the associations between covid-19 and mental health outcomes compared with a non-infected control group of people who did not experience the pandemic, we built a historical control group from participants who used the Veterans Health Administration in 2017 (n=6 461 596). Within those who were alive on 1 March 2018 (n=6 150 654), participants who were not in the covid-19 group were selected into the non-infected historical control group (n=6 008 474). To ensure that the historical control group had a similar distribution of follow-up time as the covid-19 group, we randomly assigned the start of follow-up for participants in the historical control group to have a similar distribution as the start of follow-up minus two years (730 days) in the covid-19 group. Overall, 5 875 992 participants were alive at the start of follow-up; 5 859 251 of them alive 30 days after the start of follow-up and were further selected as the historical control group. Follow-up in the historical control group ended on 30 November 2019.

The covid-19 group was further categorized into those who were not admitted to hospital (n=132 852) and those who were admitted to hospital (n=20 996) with covid-19 during the acute phase of the disease.

We constructed additional control (comparison) groups including participants with a seasonal influenza positive test result between 1 October 2017 and 29 February 2020 and were alive 30 days after the positive test result (n=72 207). This cohort was then categorized into those who were not admitted to hospital in the first 30 days after the positive test result (n=60 283) and those who were admitted to hospital in the first 30 days after the positive test result (n=11 924). Follow-up time was assigned to match the distribution of the follow-up time in the relevant covid-19 comparison group.

We also constructed a cohort including those who were admitted to hospital for any cause between 1 October 2017 and 29 February 2020 and were alive 30 days after the hospital stay (n=786 676). Follow-up time was assigned to match the distribution of the follow-up time in the relevant covid-19 comparison group.

Data sources

Data used in this study were obtained from the Veteran Affairs Corporate Data Warehouse.[3-7] Within this data warehouse, the patient data domain provided demographic information; the outpatient encounters domain and inpatient encounters domain provided clinical information, including diagnoses and procedures; the outpatient pharmacy and bar code medication administration domains provided pharmacy records; and the laboratory results domain provided laboratory test information. Information on covid-19 was obtained from the Veteran Affairs covid-19 shared data resource. Additionally, as a summary contextual measure we used the area deprivation index—a composite measure of income, education, employment, and housing in the participants' residential locations.[8]

Prespecified outcomes

The outcomes were prespecified based on our previous work on the systematic characterization of the post-

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acute sequelae of SARS-CoV-2 infection, and several other studies.[1 2 9-15] Outcomes based on ICD-10 codes (international classification of diseases, 10th revision) were anxiety disorders (generalized anxiety disorder, mixed anxiety disorder, and panic disorder), depressive disorders (major depressive disorder—single episode, recurrent major depressive disorder, and suicidal ideation), stress disorders (acute stress and adjustment disorder and post-traumatic stress disorder), opioid use disorder, substance use disorder (illicit drug use disorder, alcohol use disorder, and sedative or hypnotics use disorder), neurocognitive decline, and sleep disorders. Outcomes based on prescription records included antidepressant drugs (selective serotonin reuptake inhibitors, serotonin-noradrenaline (norepinephrine) reuptake inhibitors, other antidepressants), benzodiazepines, opioids, naloxone and naltrexone, methadone, buprenorphine, and drugs to aid sleep. Supplementary table 1 details the outcome definitions. Incidence of each mental health outcome was assessed after 30 days of a positive SARS-CoV-2 test result in those without a history of the outcome in the two years before the start of follow-up. We also specified three composite outcomes of any mental health diagnosis, any mental health related drug prescription, and any mental health diagnosis or drug prescription, and we examined the incidence of these composite outcomes in those without any mental health diagnosis or drug prescription within two years before the start of follow-up.

Covariates

In this study we used both predefined and algorithmically selected high dimensional covariates assessed within one year before the start of follow-up. Predefined covariates were selected based on previous knowledge.[1 10 13-15] The predefined covariates included age; race (white people, black people, and other); sex; area deprivation index; body mass index; smoking status (current, former, and never smoker); and healthcare utilization measures, including number of outpatient encounters, history of hospital admission, and use of long term care. The battery of predefined covariates also included comorbidities such as cancer, chronic kidney disease, chronic lung disease, dementia, diabetes mellitus, dysautonomia, hyperlipidemia, and hypertension. Additionally, we adjusted for estimated glomerular filtration rate and systolic and diastolic blood pressure. Missing values (0.80% of body mass index, 0.97% of blood pressure, and 5.39% of estimated glomerular filtration rate in covid-19 group) were imputed based on mean predicted value conditional on age, race, sex, and group assignment. Continuous variables were transformed into restricted cubic spline functions to account for potential non-linear associations with the group assignment.

To further optimize adjustment of potential confounders, we algorithmically selected high dimensional covariates from several data domains, including diagnoses, drugs, and laboratory tests.[16] We classified all patient encounters, prescriptions, and laboratory data into 540 diagnostic categories, 543 drug classes, and 62 laboratory tests. We further selected those variables that occurred in at least 100 participants within each group. The univariate relative risk between each variable and group assignment was then estimated; the top 100 variables with the strongest association were then used as the high dimensional covariates.[17] The high dimensional covariates selection process was conducted independently for the examination of each outcome, and also conducted independently for each comparison.

Statistical analyses

Baseline characteristics of the covid-19, contemporary, and historical non-infected control groups are presented as means (standard deviations) and numbers (percentages) as appropriate. Standardized mean differences between groups are also described.

Associations between covid-19 and incident mental health disorders were estimated through weighted survival analyses adjusting for both predefined and algorithmically selected high dimensional covariates. To examine the risk of each incident outcome, we constructed a subcohort of participants with no history of the outcome being examined (ie, participants with a history of major depressive disorders were removed from the analyses examining the risk of incident major depressive disorders). In each subcohort, we built logistic regressions to estimate the propensity score of each group (covid-19, contemporary control, and historical control) belonging to the target population of users of the Veterans Health Administration in 2019, utilizing both predefined and algorithmically selected high dimensional covariates. We then computed the inverse probability weights for each participant as the probability of belonging to the target population divided by the probability of being in the observed population. To examine the success of weighting we assessed the standardized mean differences for covariates in the weighted population.[18] Cause specific hazard models were then used with the inverse probability weights, and when death was considered as a competing risk. We report two measures of risk: the adjusted hazard ratios during follow-up and the adjusted risk difference per 1000 people at one year based on the difference between the estimated incidence rate in the covid-19 group and control groups at one year.

To examine the association between covid-19 and mental health disorders by care setting of the acute infection, we conducted analyses in the covid-19 group categorized into two mutually exclusive groups as not admitted to hospital or admitted to hospital for covid-19 during the acute phase of the infection (the first 30 days after a positive test result). We estimated propensity score and inverse probability weights separately for each care setting. Cause specific hazard models were then conducted in the inverse probability weighted cohort to estimate hazard ratios, event rates, and risk differences.

We additionally conducted several comparative analyses: not admitted to hospital for covid-19 versus

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not admitted to hospital for seasonal influenza; admitted to hospital for covid-19 versus admitted to hospital for seasonal influenza; and admitted to hospital for covid-19 versus admitted to hospital for any other cause. Analyses within people admitted to hospital were additionally adjusted for intensive care unit admission and length of hospital stay. Admission to hospital was defined as being admitted to hospital for a condition related to the infection and was ascertained in the first 30 days after the positive test result (covid-19 or seasonal influenza). Comparisons were conducted based on cause specific hazard model, balancing through overlap weighting generated from both predefined and algorithmically selected high dimensional covariates.[19]

To test the robustness of our findings, we performed four sensitivity analyses. Firstly, we expanded our inclusion of high dimensional covariates to adjust for the top 300 variables with the strongest association with group assignment (instead of top 100 in the primary analyses). Secondly, we examined the associations without application of the high dimensional variable selection algorithm by using only predefined covariates to construct the inverse probability weights. Thirdly, we alternatively applied the doubly robust approach (in lieu of the inverse weighting approach used in the primary analyses), where we additionally adjusted for covariates in the weighted survival models.[20] Finally, we additionally adjusted for the number of outpatient visits and number of hospital admissions during the follow-up as time varying variables.

To further test the rigor of our approach, we first tested fatigue (a cardinal feature of post-acute sequelae of SARS-CoV-2 infection) as a positive outcome control to assess whether our approach would reproduce known associations. We then tested a battery of negative outcome controls where no previous knowledge suggests an association is expected.[21] The successful application of both positive and negative controls might lessen concern about the presence of spurious biases related to the cohort construction, study design, covariate selection, analytic approach, outcome ascertainment, residual confounding, and other sources of latent biases.

Robust sandwich variance estimators were applied to adjust for the variance after application of weighting. Statistical significance was determined by a 95% confidence interval that excluded 1 for ratios and 0 for rates. Analyses were conducted using SAS Enterprise Guide version 8.2 (SAS Institute, Cary, NC), and results were visualized using R version 4.05.

Patient and public involvement

The general topic of this research was inspired by the community of patients with long covid whose admirable advocacy served as an inspiration to pursue this area of research.

Results

Figure 1 shows the selection of the study cohort. The study population comprised 153 848 participants in the covid-19 group, 5 637 840 in the contemporary control group, and 5 859 251 in the historical control group. Median follow-up was, respectively, 377 days (interquartile range 347-469 days), 378 (348-471) days, and 378 (347-470) days. Person years of follow-up were 172 091 in the covid-19 group, 6 317 461 in the contemporary control group, and 6 563 236 in the historical control group, corresponding to a total of 13 052 788 person years of follow-up. Table 1 shows the demographic and health characteristics of the three study groups after weighting, and supplementary table S2 shows the data before weighting.

Risks of incident mental health disorders

Covid-19 group versus contemporary control group

Assessment of standardized mean differences after inverse probability weighting suggested that the covariates were well balanced between the covid-19 group and contemporary control group (supplementary figure S1). Figure 2 and supplementary table S3 provide the risks of incident mental health disorders in these groups.

Anxiety, depression, and stress disorders—people who survived the first 30 days of covid-19 showed an increased risk of incident anxiety disorders (hazard ratio 1.35 (95% confidence interval 1.30 to 1.39); risk difference 11.06 (95% confidence interval 9.64 to 12.53) per 1000 people at one year), depressive disorders (1.39 (1.34 to 1.43); 15.12 (13.38 to 16.91) per 1000 people at one year), and stress and adjustment disorders (1.38 (1.34 to 1.43); 13.29 (11.71 to 14.92) per 1000 people at one year). This was coupled with an increased risk of incident use of antidepressants (1.55 (1.50 to 1.60); 21.59 (19.63 to 23.60) per 1000 people at one year) and benzodiazepines (1.65 (1.58 to 1.72); 10.46 (9.37 to 11.61) per 1000 people at one year).

Opioids—The risk of incident opioid prescriptions was increased (1.76 (1.71 to 1.81); 35.90 (33.61 to 38.25) per 1000 people at one year). This was coupled with an increased risk of opioid use disorders (1.34 (1.21 to 1.48); 0.96 (0.59 to 1.37) per 1000 people at one year) and incident use of naloxone or naltrexone (1.23 (1.18 to 1.29); 3.08 (2.32 to 3.86) per 1000 people at one year), buprenorphine (1.34 (1.12 to 1.62); 0.45 (0.15 to 0.80) per 1000 people at one year), and methadone (1.94 (1.47 to 2.56); 0.27 (0.14 to 0.46) per 1000 people at one year).

Any substance use disorders—These included increased risk of illicit drug use (1.24 (1.16 to 1.32); 2.12 (1.42 to 2.87) per 1000 people at one year), alcohol use disorders (1.29 (1.22 to 1.35); 4.60 (3.61 to 5.65) per 1000 people at one year), and sedative or hypnotic use disorders (1.40 (1.14 to 1.72); 0.28 (0.10 to 0.51) per 1000 people at one year). The risk of any (non-opioid) substance use disorders was 1.20 (1.15 to 1.26); 4.34 (3.22 to 5.51) per 1000 people at one year.

Neurocognitive decline—The risk of incident neurocognitive decline was increased (1.80 (1.72 to 1.89); 10.75 (9.65 to 11.91) per 1000 people at one year).

Sleep—The risk of incident sleep disorders was increased (1.41 (1.38 to 1.45); 23.80 (21.65 to 26.00)

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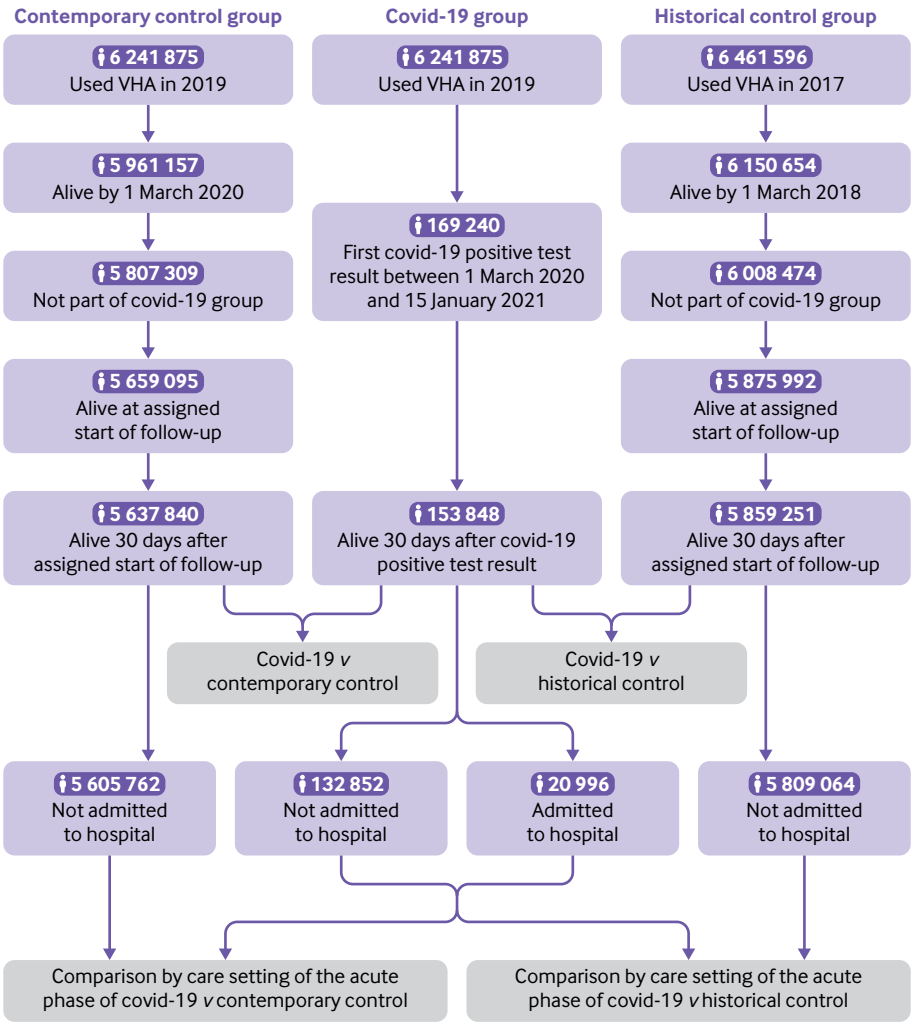

Fig 1 | Flowchart showing selection of cohort. VHA=Veterans Health Administration

per 1000 people at one year) as was the risk of incident use of sleep medications (1.63 (1.58 to 1.67); 25.87 (24.01 to 27.78) per 1000 people at one year).

Composite endpoints—The risk of any incident mental health diagnosis was 1.46 (1.40 to 1.52); 36.48 (31.93 to 41.19) per 1000 people at one year), any incident mental health related drug prescription was 1.86 (1.78 to 1.95); 47.60 (43.26 to 52.12) per 1000 people at one year), and any incident mental health diagnosis or prescription was 1.60 (1.55 to 1.66); 64.38 (58.90 to 70.01) per 1000 people at one year; fig 3). Figure 4 presents the adjusted survival probabilities of the composite endpoints across time.

Covid-19 group v contemporary control group by care setting

The risks of incident mental health disorders were compared between the covid-19 group and contemporary control group by care setting of the acute phase (first 30 days) of covid-19. Within the covid-19 group, 132 852 people were not admitted to hospital and 20 996 were admitted to hospital for covid-19. Supplementary table S4 shows the demographic and health characteristics of these groups before weighting, and supplementary table S5 after weighting. Standardized mean differences suggested that covariates were well balanced (supplementary figure S2). Compared with the contemporary control group, the risks of the prespecified mental health outcomes in the covid-19 group were evident in those who were not admitted to hospital and were highest in those who were admitted to hospital during the acute phase of the disease (fig 5, fig 6, fig 7, and supplementary table S6). Among people with covid-19, a pairwise comparison of those who were not admitted to hospital versus those who were admitted to hospital for covid-19 during the acute phase of the disease suggested that those who were admitted to hospital showed a higher risk of incident mental health outcomes (supplementary table S7).

Covid-19 group v historical control group

Supplementary table S2 shows the demographic and health characteristics of the covid-19 group and historical control group before weighting, and table 1 after weighting; the characteristics of the groups were balanced after weighting (supplementary figure S3). The results suggested increased risks

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Table 1 | Baseline demographic and health characteristics of covid-19, contemporary control, and historical control groups after weighting

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*
Mean (SD) age (years)	63.06 (16.18)	63.40 (16.22)	63.32 (16.30)	0.02	0.02
Race:					
White	116 729 (75.87)	4 320 333 (76.63)	4 486 253 (76.57)	0.02	0.02
Black	29 708 (19.31)	1 050 386 (18.63)	1 093 102 (18.66)	0.02	0.02
Other	7412 (4.82)	267 121 (4.74)	279 838 (4.78)	0.00	0.00
Sex:					
Men	137 265 (89.22)	5 089 729 (90.28)	5 286 158 (90.22)	0.03	0.03
Women	16 583 (10.78)	548 111 (9.72)	573 093 (9.78)	0.03	0.03
BMI category:					
Underweight or normal	29 611 (19.25)	1 091 937 (19.37)	1 134 761 (19.37)	0.00	0.00
Overweight	54 742 (35.58)	2 051 835 (36.39)	2 121 869 (36.21)	0.02	0.01
Obese	69 495 (45.17)	2 494 011 (44.24)	2 602 562 (44.42)	0.02	0.02
Smoking status:					
Never	62 570 (40.67)	2 400 310 (42.58)	2 498 736 (42.65)	0.04	0.04
Former	57 016 (37.06)	2 037 233 (36.14)	2 112 201 (36.05)	0.02	0.02
Current	34 260 (22.27)	1 200 296 (21.29)	1 248 313 (21.31)	0.02	0.02
Mean (SD) area deprivation index†	55.09 (18.96)	54.67 (19.03)	54.65 (19.03)	0.02	0.02
Clinical characteristics					
Outpatient encounter‡:					
0 or 1	60 471 (39.31)	2 414 912 (42.83)	2 508 580 (42.81)	0.07	0.07
2	42 513 (27.63)	1 620 202 (28.74)	1 661 566 (28.36)	0.02	0.02
≥3	50 864 (33.06)	1 602 725 (28.43)	1 689 105 (28.83)	0.10	0.09
Long term care	1882 (1.22)	38 676 (0.69)	41 483 (0.71)	0.06	0.05
Mean (SD) eGFR (ml/min/1.73m^2)	78.83 (21.08)	78.67 (20.60)	78.73 (20.62)	0.01	0.00
Mean (SD) blood pressure (mm Hg):					
Systolic	132.47 (12.36)	132.65 (12.28)	132.61 (12.33)	0.01	0.01
Diastolic	77.77 (7.59)	77.79 (7.53)	77.80 (7.56)	0.00	0.00
Cancer	10 369 (6.74)	348 024 (6.17)	361 516 (6.17)	0.02	0.02
Cerebrovascular disease	7719 (5.02)	246 599 (4.37)	257 866 (4.4)	0.03	0.03
Cardiovascular disease	21 671 (14.09)	717 528 (12.73)	745 531 (12.72)	0.04	0.04
Chronic kidney disease	26 651 (17.32)	943 774 (16.74)	977 675 (16.69)	0.02	0.02
Chronic lung disease	19 662 (12.78)	616 498 (10.94)	641 061 (10.94)	0.06	0.06
Diabetes mellitus type 2	36 850 (23.95)	1 286 048 (22.81)	1 335 733 (22.80)	0.03	0.03
Rheumatoid arthritis	1502 (0.98)	49 669 (0.88)	51 679 (0.88)	0.01	0.01

SD=standard deviation; BMI=body mass index; eGFR=estimated glomerular filtration rate.
*Value ≤0.10 is considered good balance.
†Measure of socioeconomic disadvantage (from 0 to 100 representing low to high disadvantage).
‡Data collected within one year of cohort enrollment.

of the prespecified mental health outcomes in the covid-19 group compared with historical control group (supplementary table S8 and supplementary figure S4-S6)—and were consistent with those of the covid-19 group compared with contemporary control group.

Analyses were also performed by care setting of the acute phase of infection. Supplementary table S9 presents the demographic and health characteristics of the covid-19 and historical control groups before weighting, and supplementary table S10 after weighting. Characteristics of the two groups were balanced after weighting (supplementary figure S7). The risks of the prespecified mental health outcomes showed an increase according to the intensity of care during the acute phase of the infection—and were consistent with results for the covid-19 group compared with contemporary control group (supplementary table S11 and figures S8-S10).

Covid-19 *v* seasonal influenza

To better understand the increased risk of incident mental health outcomes in people with covid-19, the risk of incident composite mental health outcomes was compared between the covid-19 group and a group with seasonal influenza (n=72 207), a well characterized respiratory viral infection. In the seasonal influenza group, 60 283 were not admitted to hospital and 11 924 were admitted to hospital. This analysis was conducted in those not admitted to hospital, and, separately, in those admitted to hospital for covid-19 or for seasonal influenza (additionally adjusting for intensive care admission and length of stay during the hospital admission). Compared with seasonal influenza, covid-19 was associated with increased risk of mental health outcomes in people who both were and were not admitted to hospital (fig 8, supplementary table S12).

Hospital admissions for covid-19 *v* for any other cause

To gain a better understanding of whether the increased risk of incident mental health outcomes in people admitted to hospital for covid-19 was driven by the hospital admission itself, the risks of incident composite mental health outcomes were compared between those admitted to hospital for covid-19 and those admitted for any other cause (n=786 676),

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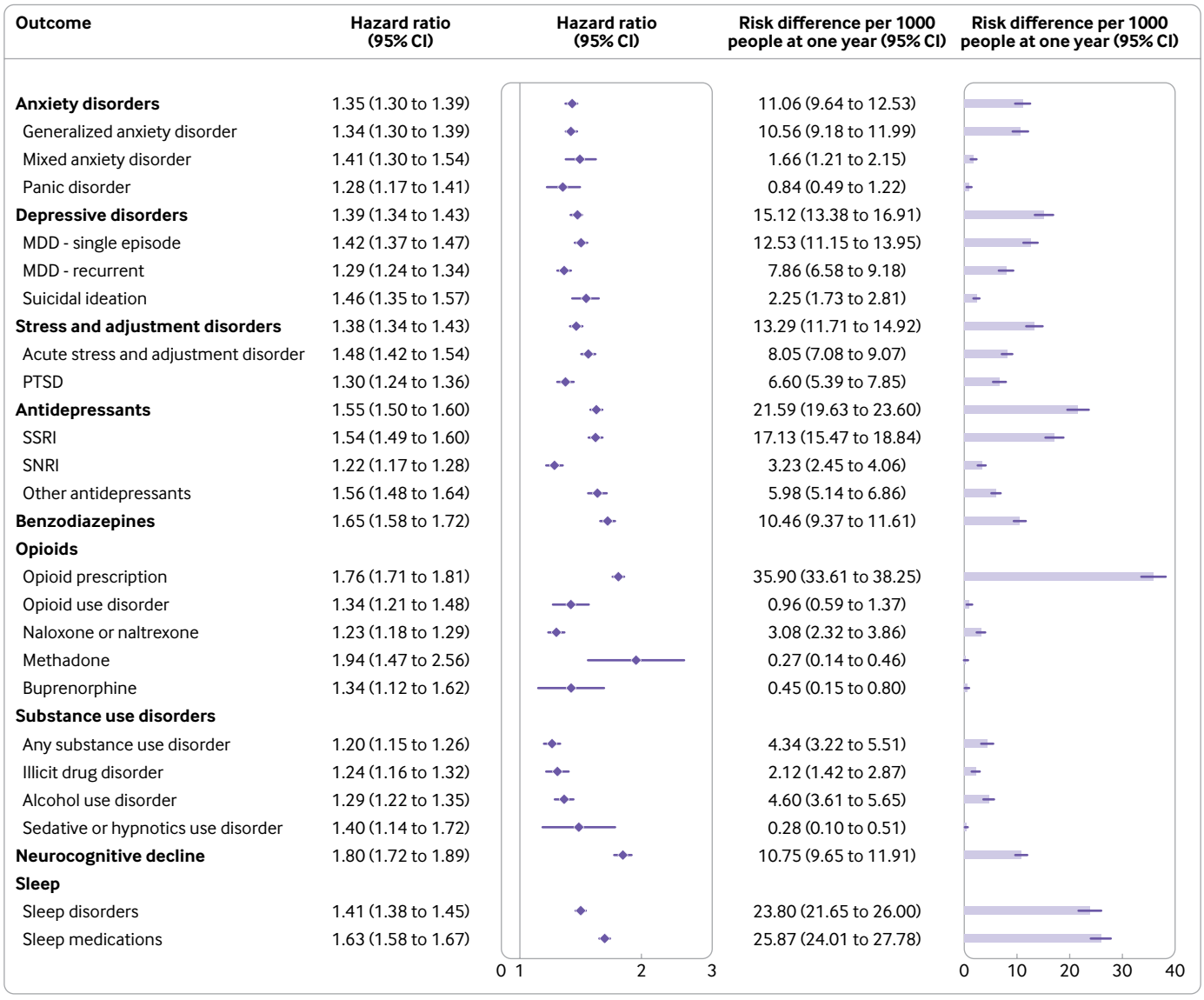

Fig 2 | Risks of incident mental health outcomes in covid-19 group during the post-acute phase compared with contemporary control group. Outcomes were ascertained 30 days after the initial SARS-CoV-2 positive test result until the end of follow-up. Hazard ratios are estimated through the follow-up and adjusted for age, race, sex, area deprivation index, body mass index, smoking status, number of outpatient encounters, history of hospital admission, use of long term care, cancer, chronic kidney disease, chronic lung disease, dementia, diabetes mellitus, dysautonomia, hyperlipidemia, hypertension, estimated glomerular filtration rate, systolic and diastolic blood pressure, and algorithmically selected high dimensional covariates. Risk differences are estimated at one year. MDD=major depressive disorder; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-noradrenaline (norepinephrine) reuptake inhibitor

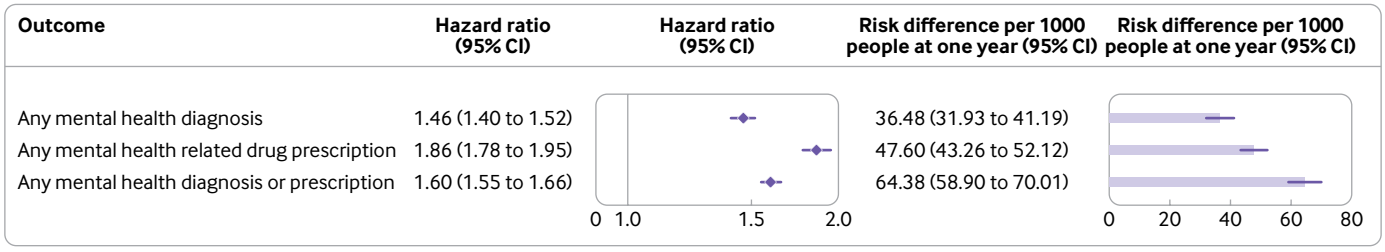

Fig 3 | Risks of incident composite mental health outcomes in covid-19 group compared with contemporary control group. Composite outcomes consisted of any mental health related drug prescription, any mental health diagnosis, and any mental health diagnosis or prescription. Outcomes were ascertained 30 days after the initial SARS-CoV-2 positive test result until end of follow-up. Hazard ratios are estimated through the follow-up and adjusted for age, race, sex, area deprivation index, body mass index, smoking status, number of outpatient encounters, history of hospital admission, use of long term care, cancer, chronic kidney disease, chronic lung disease, dementia, diabetes mellitus, dysautonomia, hyperlipidemia, hypertension, estimated glomerular filtration rate, systolic and diastolic blood pressure, and algorithmically selected high dimensional covariates. Risk differences are estimated at one year

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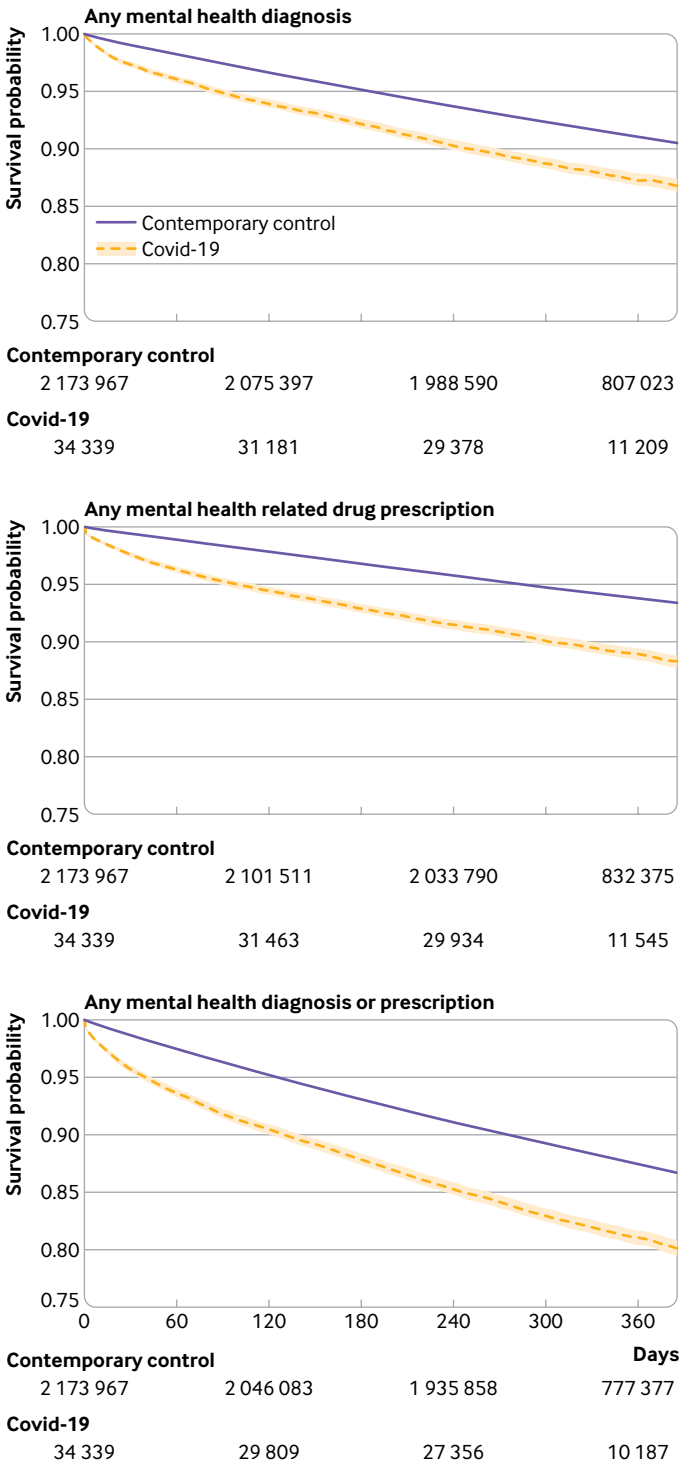

Fig 4 | Survival probability of incident composite mental health outcomes in covid-19 group compared with contemporary control group. Outcomes were ascertained 30 days after the initial SARS-CoV-2 positive test result until end of follow-up. Shaded areas are 95% confidence intervals. Numbers of participants at risk across groups are also presented

additionally adjusting for intensive care admission and length of stay during the hospital admission. People admitted to hospital for covid-19 showed a higher risk of incident mental health outcomes than people admitted to hospital for any other cause (fig 8, supplementary table S12).

Sensitivity analyses

Multiple sensitivity analyses were conducted to investigate the robustness of the results. The associations were examined between covid-19 and risks of any mental health related drug prescription, any mental health diagnosis, and any mental health diagnosis or drug prescription; the sensitivity analyses compared the covid-19 group with the contemporary control group and with the historical control group, and additionally compared the covid-19 group across care settings versus both control groups. Firstly, in constructing the inverse probability weighting, the number of algorithmically selected covariates and predefined covariates were expanded to 300 instead of 100. Secondly, only predefined covariates were used to construct the inverse probability weighting. Thirdly, the doubly robust method was used as an alternative modelling approach to the inverse probability weighting method used in the primary analysis. Lastly, the numbers of outpatient visits and hospital admissions during follow-up were additionally adjusted for as time varying variables. The results were found to be robust in these sensitivity analyses (supplementary tables S13 and S14).

Positive and negative outcome controls

To test whether the study's approach would reproduce established knowledge, the association between covid-19 and the risk of fatigue (a cardinal manifestation of post-acute covid-19) as a positive outcome control was examined. The results suggested that covid-19 was associated with increased risk of fatigue (supplementary table S15).

The association was then tested between covid-19 and four negative outcome controls (lichen planus, lichen simplex chronicus, melanoma in situ, and allergic eczema) where an association is not known. Consistent with a priori expectations, no statistically significant association was found between covid-19 and any of the negative outcome controls (supplementary table S15).

Discussion

In this study totaling 13 052 788 person years of follow-up of 153 848 people with covid-19, 5 637 840 people in the contemporary control group, and 5 859 251 people in the historical control group, we found that beyond the first 30 days of a positive test result for SARS-CoV-2 infection, people with covid-19 show an increased risk of incident mental health disorders, including anxiety disorders, depressive disorders, stress and adjustment disorders, opioid use disorder, other (non-opioid) substance use disorders, neurocognitive decline, and sleep disorders. The risks were evident even among those who were not admitted to hospital during the acute phase of covid-19—this group represents most people with covid-19; the risks were highest in those who were admitted to hospital during the acute phase of the disease. The results were consistent when compared with a contemporary control group without covid-19 and a historical control

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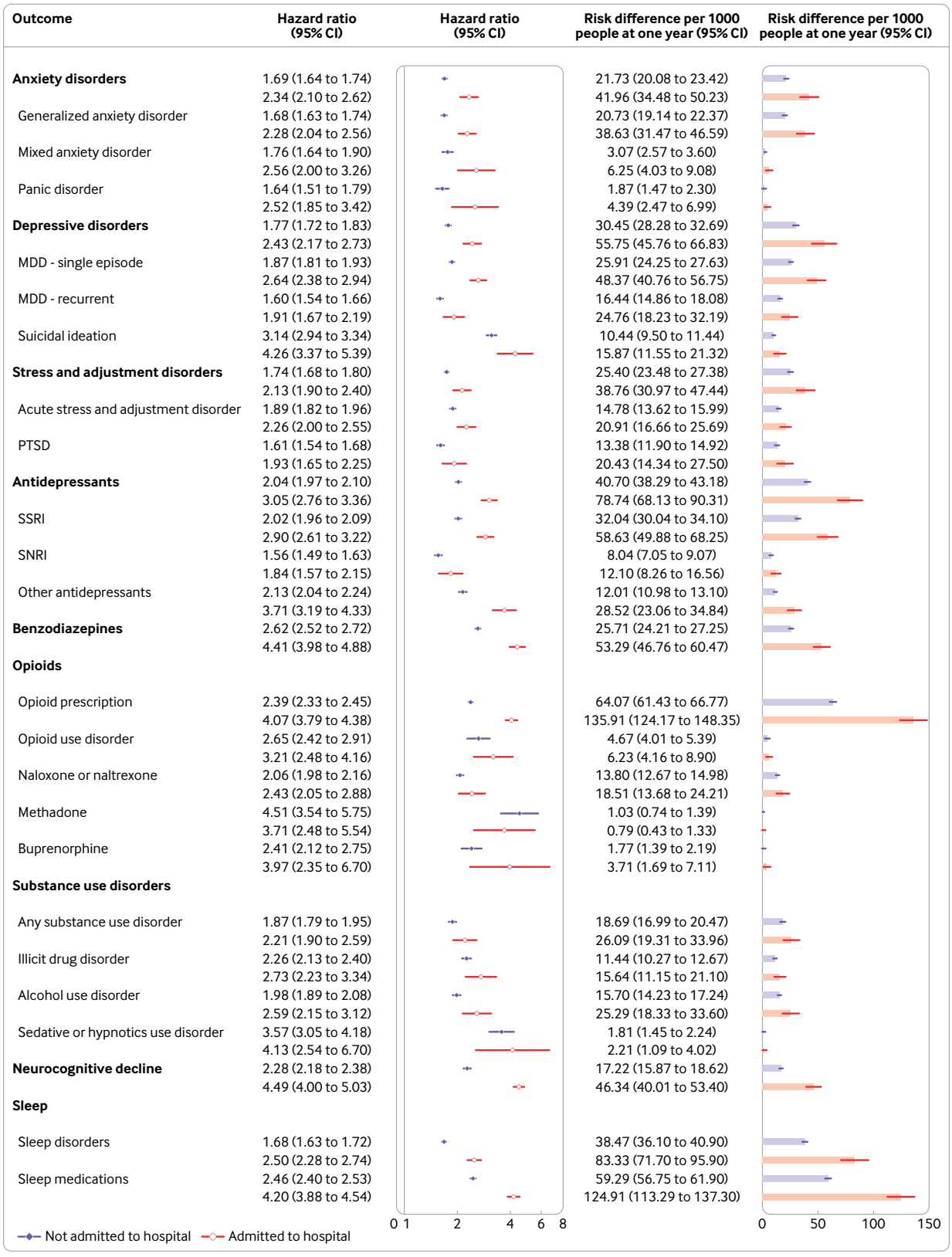

Fig 5 | Risks of incident mental health outcomes in covid-19 group compared with contemporary control group by care setting. Outcomes were ascertained 30 days after the initial SARS-CoV-2 positive test result until end of follow-up. Hazard ratios are estimated through the follow-up and adjusted for age, race, sex, area deprivation index, body mass index, smoking status, number of outpatient encounters, history of hospital admission, use of long term care, cancer, chronic kidney disease, chronic lung disease, dementia, diabetes mellitus, dysautonomia, hyperlipidemia, hypertension, estimated glomerular filtration rate, systolic and diastolic blood pressure, and algorithmically selected high dimensional covariates. Risk differences are estimated at one year. MDD=major depressive disorder; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin and noradrenaline (norepinephrine) reuptake inhibitor

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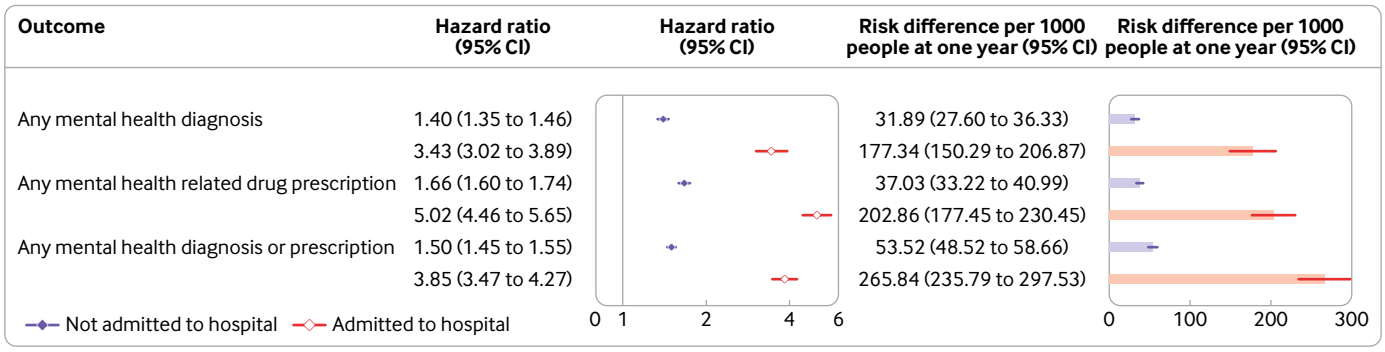

Fig 6 | Risks of incident composite mental health outcomes in covid-19 group compared with contemporary control group by care setting. Outcomes were ascertained 30 days after the initial SARS-CoV-2 positive test result until end of follow-up. Hazard ratios are estimated through the follow-up and adjusted for age, race, sex, area deprivation index, body mass index, smoking status, number of outpatient encounters, history of hospital admission, use of long term care, cancer, chronic kidney disease, chronic lung disease, dementia, diabetes mellitus, dysautonomia, hyperlipidemia, hypertension, estimated glomerular filtration rate, systolic and diastolic blood pressure, and algorithmically selected high dimensional covariates. Risk differences are estimated at one year

group that predated the pandemic. The risk of incident mental health disorders was consistently higher in the covid-19 group in comparisons of those not admitted to hospital for covid-19 versus not admitted to hospital for seasonal influenza, admitted to hospital for covid-19 versus admitted to hospital for seasonal influenza, and admitted to hospital for covid-19 versus admitted to hospital for any other cause. The findings were robust to challenge in multiple sensitivity analyses. Evaluation of positive and negative outcome controls yielded results consistent with expectations. Taken together, the findings suggest important risks of mental health disorders among people who survive the acute phase of covid-19.

Findings in relation to other studies

We evaluated the risk of mental health disorders in people with covid-19 compared with a contemporary control group that experienced the same pandemic related factors (eg, economic, social, environmental stressors) and a historical control group that predated the pandemic, which represented a baseline for people unaffected by the pandemic. Despite evidence showing that the burden of mental health disorders might have increased among the general population during the covid-19 pandemic,[22 23] our results suggested that people with covid-19 are at even higher risk of incident mental health disorders than their contemporaries without covid-19; the risk was also evident in comparisons with the historical control group. Taken together, the findings suggest enhanced vulnerability to these outcomes in people with covid-19.

We also compared the risk of mental health disorders in people with covid-19 versus seasonal influenza, a well characterized respiratory viral infection, and showed consistently increased risks associated with covid-19. This comparative assessment could help to improve our understanding of the features that differentiate post-acute covid-19 from a post-influenza viral syndrome. Furthermore, our comparative evaluation showing increased risk of mental health outcomes in people admitted to hospital for covid-19 versus those admitted to hospital for seasonal influenza and, separately, those admitted to hospital for any cause helps to disentangle the effect of hospital admission from that of covid-19 and further supports the association between covid-19 and adverse mental health outcomes.

Our findings show an increased risk of mental health disorders in people with covid-19. Evidence also suggests that people with mental health disorders are at increased risk of becoming infected with SARS-CoV-2 and having serious outcomes.[24 25] This likely suggests the putative existence of a bidirectional connection in that mental health disorders might predispose someone to covid-19 and that covid-19 itself might lead to adverse mental health manifestations. A better understanding of the interaction of mental health disorders both as risk for and sequela of covid-19 is needed.

Given the large and growing number of people with covid-19 (to date >70 million people in the US, >15 million people in the UK, and about 350 million people globally), the absolute risks of incident mental health disorders might translate into large numbers of potentially affected people around the world. Our results should be used to promote awareness of the increased risk of mental health disorders among survivors of acute covid-19 and call for the integration of mental healthcare as a core component of post-acute covid-19 care strategies. International bodies, national governments, and health systems must develop and implement strategies for early identification and treatment of affected individuals.

The mechanism or mechanisms of the increased risks of mental health disorders in people with covid-19 are not entirely clear. Several putative mechanisms are under examination, including peripheral T cell infiltration of brain parenchyma, dysregulated microglia and astrocytes, and disturbances in synaptic signaling of upper layer excitatory neurons—all these features generally overlap with disease phenotypes of genetic variants associated with impaired cognition, depression, and other neuropsychiatric

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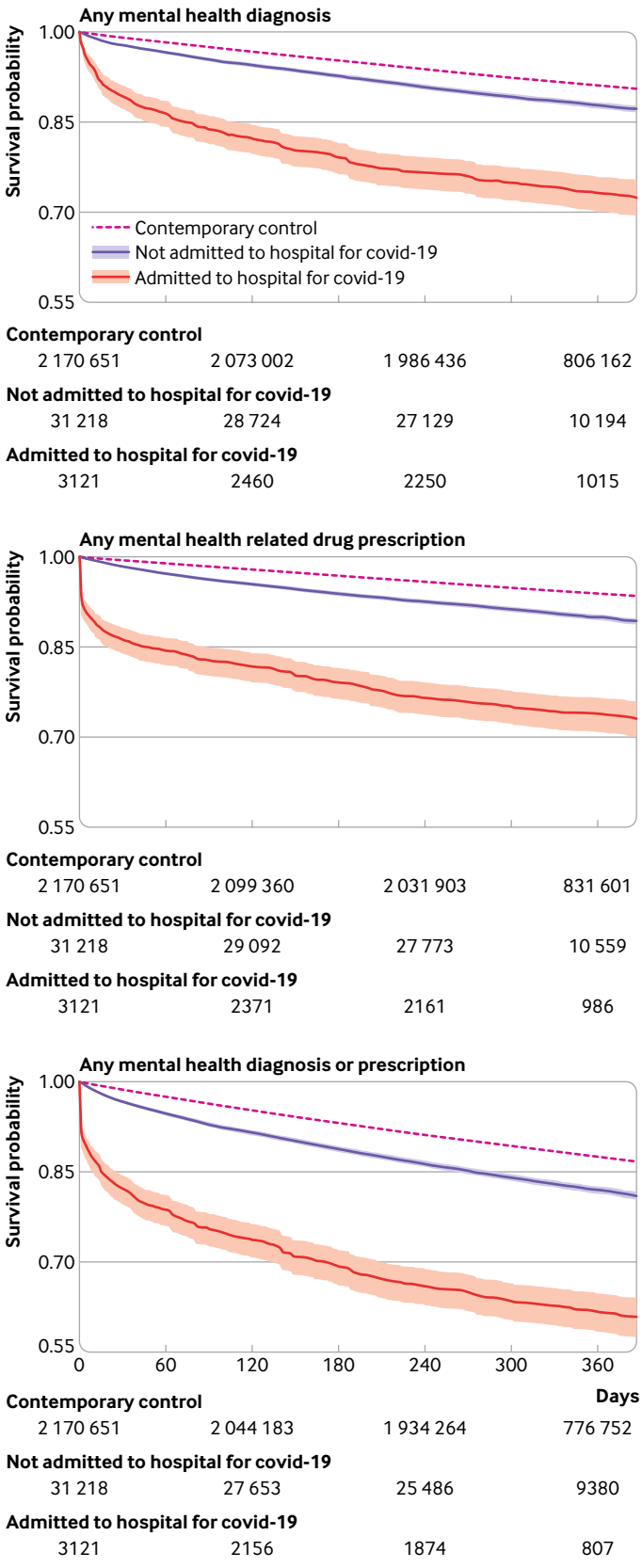

Fig 7 | Survival probability of incident composite mental health outcomes in covid-19 group compared with contemporary control group by care setting. Outcomes were ascertained 30 days after the initial SARS-CoV-2 positive test result until end of follow-up. Shaded areas are 95% confidence intervals. Numbers of participants at risk across groups are also presented

disorders.[26] Other likely mechanisms include a potential role of angiotensin converting enzyme 2 mediated neuroinflammation, and the indirect effect of a dysregulated immune response on the central nervous system.[26] Non-biologic mechanisms (eg, changes in employment, financial problems, social isolation, trauma, grief, and changes in diet and physical activity), which could have differentially impacted people with covid-19 compared with their contemporaries, might also have contributed to the increased burden of mental health disorders in people with covid-19.[27-33]

Strengths and limitations of this study

Our study has several strengths. We selected a large national cohort of people with covid-19 to estimate risks of a comprehensive set of prespecified incident mental health outcomes compared with two controls (a contemporary group with no evidence of SARS-CoV-2 infection and a historical group that predated the pandemic). In the covid-19 group we provided risk estimates for those who were and were not admitted to hospital—facilitating a better understanding of the magnitude of risk in these populations. We compared the risk of mental health outcomes in people with covid-19 versus seasonal influenza and separately for people admitted to hospital for covid-19 compared with those admitted to hospital for any other cause. We used advanced statistical methodologies and adjusted through inverse probability weighting for a battery of predefined covariates selected based on previous knowledge and 100 algorithmically selected covariates from high dimensional data domains, including diagnostic codes, prescription records, and laboratory test results. We scrutinized our results in multiple sensitivity analyses and applied positive and negative outcome controls to evaluate whether our approach would produce results consistent with pretest expectations.

Our study also has several limitations. The demographic composition of the cohort (mostly older white men) might limit the generalizability of study results. We used the vast national electronic healthcare databases of the US Department of Veterans Affairs to select our cohorts, and although we used validated outcome definitions (including diagnostic codes and prescription records) and advanced statistical methodologies to balance the study arms for a battery of predefined and algorithmically selected high dimensional variables across several data domains, we cannot completely rule out misclassification bias and residual confounding. We categorized the covid-19 group into those who were and those who were not admitted to hospital for covid-19 during the first 30 days of a positive SARS-CoV-2 test result; our approach does not account for the spectrum of disease severity among participants who were not admitted to hospital (eg, with or without symptoms of covid-19). We did not examine the severity of the mental health outcomes. Although we took care to balance the study groups by health resource utilization at baseline and conducted

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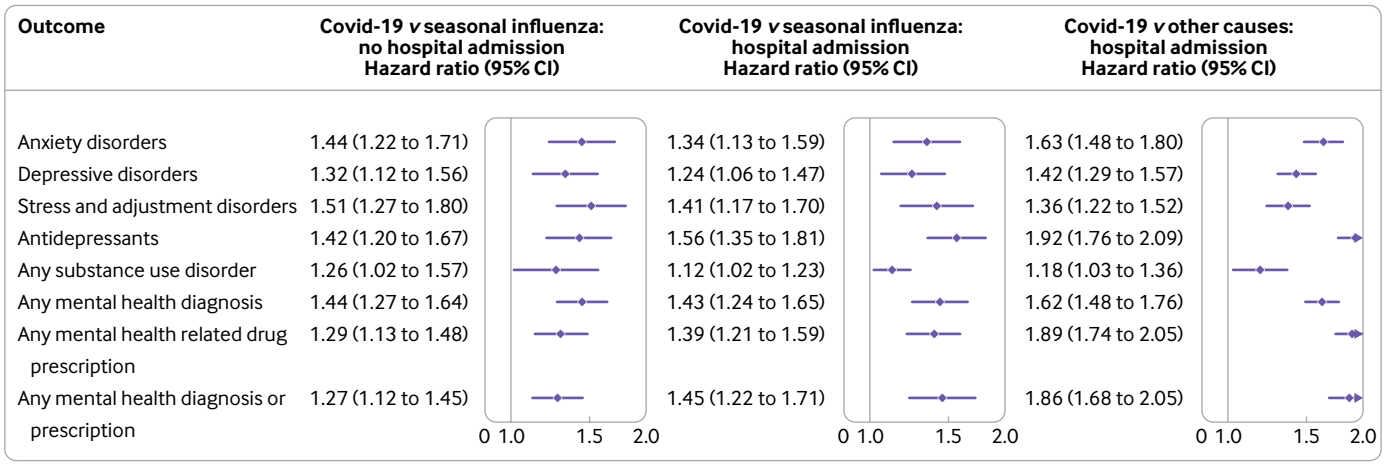

Fig 8 | Risks of incident composite mental health outcomes in people by covid-19 and seasonal influenza status and care setting. Outcomes were ascertained 30 days after enrollment of the cohort until end of follow-up. Hazard ratios adjusted for age, race, sex, area deprivation index, body mass index, smoking status, number of outpatient encounters, history of hospital admission, use of long term care, cancer, chronic kidney disease, chronic lung disease, dementia, diabetes mellitus, dysautonomia, hyperlipidemia, hypertension, estimated glomerular filtration rate, systolic and diastolic blood pressure, and algorithmically selected high dimensional covariates

sensitivity analyses to adjust for time varying health resource utilization during follow-up, we cannot completely rule out the possibility that increased attention to people with covid-19 might have resulted in greater ascertainment of mental health conditions compared with both the contemporary and historical control groups. As the pandemic continues to evolve, new variants of the virus emerge, treatment strategies of acute covid-19 improve, and vaccine uptake increases, it is likely that the epidemiology of mental health outcomes in the post-acute phase of covid-19 might also vary over time.[27]

Conclusions

Using a large national cohort of people with covid-19 and contemporary and historical controls, we found that the risks of incident mental health disorders are substantial in people with covid-19 and span several disorder categories, including anxiety, depression, stress and adjustment disorders, opioid and other substance use disorders, cognitive decline, and sleep disorders. The risks were evident even among those with covid-19 who did not require hospital admission. Tackling mental health disorders among survivors of covid-19 should be a priority.

This study used data from the Veterans Affairs covid-19 shared data resource.

Contributors: YX, EX, and ZAA conceived and designed the study. YX, EX, and ZAA analyzed and interpreted the data. ZAA drafted the manuscript. YX, EX, and ZAA critically revised the manuscript. ZAA provided administrative, technical, and material support. ZAA provided supervision and mentorship. ZAA is the guarantor. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors approved the final version of the report. The corresponding author attests that all the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted

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Competing interests: Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare support from the US Department of Veterans Affairs and the American Society of Nephrology for the submitted work. ZAA reports receiving consultation fees from Gilead Sciences and receipt of funding (unrelated to this work) from Tonix pharmaceuticals.

Ethical approval: This research project was reviewed and approved by the institutional review board of the Department of Veterans Affairs Saint Louis Health Care System.

Data sharing: All data are available through the US Department of Veterans Affairs.

The study guarantor (ZAA) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Provenance and peer review: Provenance and peer review: Not commissioned; externally peer reviewed.

Dissemination to participants and related patient and public communities: The study results will be disseminated by press release and on Twitter, and shared with patient advocacy groups.

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Supplementary information: figures S1-S10 and tables S1-S15

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