The COVID-19 pandemic: early life adversities, mental health trajectories and health service use

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Thesis for the degree of Philosophiae Doctor

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Áföll í æsku, geðheilbrigði og aðgengi að heilbrigðisþjónustu í heimsfaraldri COVID-19

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Ágrip

Heimsfaraldur kórónaveirunnar 2019 (COVID-19) var veruleg ógn við lýðheilsu á heimsvísu, bæði hvað varðar líkamlega og andlega heilsu fólks. Rannsóknir á þróun nýgengis geðraskana hafa hingað til einkum beinst að skammtímaáhrifum heimsfaraldursins og að ákveðnum áhættuhópum (t.d. COVID-19 sjúklingum eða heilbrigðisstarfsfólki) en færri að langtímaáhrifum heimsfaraldursins á geðheilsu og aðgengi á heilbrigðisþjónustu meðal almennings. Einnig er lítið vitað um hvort sálfélagslegir áhættuþættir snemma á lífsleiðinni, svo sem áföll í æsku (t.d. andleg vanræksla og líkamlegt ofbeldi), hafi haft áhrif á alvarleika COVID-19 sjúkdómsins. Markmið þessarar doktorsritgerðar var að varpa ljósi á ofangreinda þætti, í fjórum rannsóknum.

Í fyrstu rannsókninni voru tengslin milli áfalla í æsku og alvarleika COVID-19 sjúkdómsins könnuð. Notuð voru gögn úr breska lífsýnabankanum (UK Biobank) frá 151,427 einstaklingum. Í ljós kom að einstaklingar sem höfðu orðið fyrir áföllum í æsku voru líklegri en einstaklingar án slíkrar reynslu til að leggjast inn á sjúkrahús eða deyja af völdum COVID-19, einkum tengt líkamlegri vanrækslu í æsku. Þessum tengslum milli áfalla í æsku og alvarleika COVID-19 var að hluta til miðlað af lágri félagslegri stöðu, óæskilegum lífsstílsþáttum sem og sögu um geðsjúkdóma eða aðra langvinnra sjúkdóma. Niðurstöður sýndu einnig að fjölgena áhættuskor fyrir alvarlegt COVID-19 hafði ekki áhrif á samband áfalla í æsku og alvarleika COVID-19. Þessar niðurstöður varpa enn frekara ljósi á tengsl áfalla í æsku við alvarlegar heilsufarsútkomur á fullorðinsárum og benda til þess að huga þurfi að þeim áhættuþáttum í COVID-19 og öðrum heimsfaröldrum.

Önnur rannsóknin sneri að nýgengi kvíða- og þunglyndisgreininga sem og ávísunum á samsvarandi geðlyf á fyrstu 18 mánuðum heimsfaraldursins og byggði hún á gögnum frá breska lífsýnabankanum sem samtengdur er breskum heilbrigðisgagnagrunnum (N=401,180). Í samanburði við tímabilið fyrir faraldurinn (þ.e. 2017-2019) bentu niðurstöður til aukinnar hættu á kvíða- og þunglyndisgreiningum meðal einstaklinga sem fóru í COVID-19 greiningarpróf, sérstaklega á fyrstu sex mánuðum heimsfaraldursins (þ.e. mars 2020 - september 2020). Sambærilegar niðurstöður fengust einnig hvað varðar ávísanir kvíða- eða þunglyndislyfja meðal einstaklinga sem fóru í COVID-19 greiningapróf. Aftur á móti voru einstaklingar sem fóru ekki í COVID-19 greiningarpróf í minni hættu á bæði kvíða- og þunglyndisgreiningum og ávísunum kvíða- og þunglyndislyfja á fyrstu 18 mánuðum heimsfaraldursins. Þessar niðurstöður benda til almennt lægra nýgengis þunglyndis og kvíðaraskana í heimsfaraldri COVID-19, en aukins nýgengis meðal einstaklinga með COVID-19 eða flensueinkenni sem líkjast einkennum COVID-19 sjúkdómsins.

Þriðja rannsóknin var langsniðsrannsókn sem hafði það markmið að kanna breytileika í þróun þunglyndiseinkenna í COVID-19 heimsfaraldrinum. Hún byggði á rannsókninni *Líðan þjóðar á tímum COVID-19* sem náði til 6,423 þátttakenda sem höfðu svarað spurningalista á fjórum ólíkum tímapunktum (frá apríl 2020 til febrúar 2023; 68·7% konur). Niðurstöður sýndu að meirihluti þátttakenda (83·7%) var með lága einkennabyrði þunglyndis í öllum eftirfylgnimælingum á meðan minnihluti sýndi á einhverju stigi háa einkennabyrgði: 5·3% voru alltaf með háa einkennabyrði, 5·1% voru upphaflega með háa einkennabyrgði sem lækkaði yfir tíma og 5·9% voru upphaflega með lága einkennabyrgði sem hækkaði yfir tíma. Einstaklingar sem hreyfðu sig oft (≥ 3 daga/viku) eða nutu félagslegs stuðnings frá vinum eða fjölskyldu voru líklegri að hafa lága einkennabyrði. Aftur á móti voru einstaklingar með sögu um geðraskanir, konur og einstaklingar á aldrinum18-39 ára ólíklegri til að hafa lága einkennabyrði. Þá voru vísbendingar um að einstaklingar sem á einhverjum tímapunkti í faraldrinum mældust með einkenni kvíða og þunglyndis væru einnig með aukna einkennabyrgði þunglyndis, kvíða, líkamlegra einkenna og minnisörðugleika eftir heimsfaraldurinn. Þessar niðurstöður benda til þess að meirihluti einstaklinga hafi verið við nokkuð góða andlega heilsu í heimsfaraldri COVID-19 en gefa jafnframt mikilvægar vísbendingar um áhrifaþætti geðheilbrigðis á tímum heimsfaraldurs.

Markmið fjórðu rannsóknarinnar var að kanna röskun á heilbrigðisþjónustu í COVID-19 faraldrinum á Íslandi og möguleg tengsl hennar við félags- og lýðfræðilega þætti, heilsufarssögu sem og líkamleg og sálræn einkenni. Þessir rannsókn byggði á þversniðsgögnum úr rannsókninni *Líðan þjóðar á tímum COVID-19 (*N=15,754). Heildarhlutfall þátttakenda sem greindu frá röskun á heilbrigðisþjónustu lækkaði frá desember 2020 (12·3%) til júlí 2021 (11·1%). Upplifun á röskun á heilbrigðisþjónustu var algengari meðal einstaklinga með fyrri sögu um heilsufarsvandamál samanborið við einstaklinga án slíkrar sögu, þar á meðal vegna geðraskana og langvarandi líkamlegra sjúkdóma. Upplifun á röskun á heilbrigðisþjónustu reyndist ekki algengari meðal einstaklinga sem greinst höfðu með COVID-19 samanborið við þá sem ekki höfðu greinst. Þá tengdist upplifun á röskun á heilbrigðisþjónustu á tímabilinu verri andlegri heilsu. Niðurstöður benda til þess að einstaklingar með COVID-19 hafi haft gott aðgengi að heilbrigðisþjónustu í heimsfaraldrinum en að einstaklingar með með sögu um heilsufarsvandamál hafi upplifað slíka röskun.

Samtantekið varpa þessar niðurstöður ljósi á seiglu- og berskjöldunarþætti geðheilbrigðis, aðgengi að heilbrigðisþjónustu, sem og alvarleika COVID-19 í nýafstöðnum heimsfaraldri en þær geta haft mikilvægt forvarnargildi í komandi heimsfaröldrum.

Lykilorð:

COVID 19; andleg heilsa; þunglyndi; ill meðferð í æsku; heilbrigðisþjónusta.

Abstract

The global spread of Coronavirus 2019 (COVID-19) posed significant threats to public health, and serious concerns have been raised about the adverse impact of the pandemic on population mental health. However, most existing studies have focused on mental health effects during the early stages of the pandemic or on specific high-risk groups (e.g., COVID-19 patients and healthcare workers), leading to a gap in understanding the long-term effects of the pandemic on mental health and health service use for the general population. Also, while psychological abnormality has been indicated as a risk factor in acute COVID-19 severity, little is known about the role of childhood maltreatment (e.g., emotional neglect and physical abuse), a potent risk factor of various adverse health outcomes, in severe COVID-19 outcomes. The overarching aim of the thesis was to fill the abovementioned knowledge gaps with four research studies.

In Study I, we explored the associations between the history of childhood maltreatment and COVID-19 hospitalizations and deaths, using data from the UK Biobank cohort (N=151,427). We found any childhood maltreatment was associated with 54% increased odds of COVID-19 hospitalizations and deaths compared to individuals without childhood maltreatment. The association was similar across individuals with different disease susceptibilities and was partially (50.9%) mediated by poor socioeconomic status, lifestyle, and pre-existing psychiatric or chronic medical conditions. Our results enhance the understanding of how childhood maltreatment contributes to long-term negative health outcomes and suggest that this risk factor should be considered in future pandemics.

In Study II, we assessed trends in new diagnoses of anxiety and depression as well as prescriptions of anxiolytics and antidepressants during the first 18 months of the pandemic in the UK, using data from the UK Biobank cohort (N=401,180). Compared with the pre-pandemic period (i.e., 2017-2019), we observed an increased risk of new anxiety and depression diagnoses among individuals tested for COVID-19 during the pandemic, particularly between March and September 2020. Similar results were observed for the use of psychotropic medications. In contrast, individuals who were not tested for COVID-19 had consistently lower risks of both diagnoses and prescriptions during the COVID-19 pandemic. While these findings suggest lower incidence in diagnoses of anxiety and depression in most of the population, the study suggested psychiatric vulnerabilities among individuals with confirmed or suspected COVID-19.

In Study III, we investigated the variation in depressive symptom trajectories during the COVID-19 pandemic in Iceland, using data from the Icelandic COVID-19 National Resilience Cohort (N=6,423). We found four distinct depressive symptom trajectories between April 2020 and December 2021, with the majority showing consistently low symptom burden (83·7%), while others showed symptom burden at various stages of the pandemic, including 5·3% consistently high, 5·1% initially high and 5·9% late-onset high symptom trajectories. Both protective factors (e.g., exercise, social and family support) and risk factors (e.g., history of psychiatric disorders, female sex, younger age) associated with a consistently low symptom trajectory were identified. Furthermore, compared with the consistently low symptom trajectory, we found the other trajectories were associated with significantly higher levels of depression, anxiety and somatic symptoms and compromised cognitive function during the post-pandemic period (September 2022 - February 2023). These data suggest that while most of the population maintained good mental health throughout the pandemic, there are vulnerable groups that may need particular attention in coming pandemics.

In Study IV, we examined the risk factors for perceived disruption in health service use during the COVID-19 pandemic and their association with concurrent well-being, using data from the Icelandic COVID-19 National Resilience Cohort (N=15,754). From December 2020 to July 2021, the prevalence of perceived disruption in health service use in Iceland decreased slightly, from 12·3% to 11·1%. We further found that emerging perceived disruption in health service use was associated with a rise in mental health symptoms during the COVID-19 pandemic. Although individuals diagnosed with COVID-19 did not experience a significant increase in perceived disruption, we found those with preexisting health conditions—particularly those who were female, younger, and had lower incomes—reported a greater perception of disruption in health service use during the COVID-19 pandemic. Our findings suggest adequate access to health services among patients with COVID-19 in Iceland while individuals with preexisting health conditions experienced limitations in their access to health services.

In conclusion, these studies reveal resilience and vulnerability factors of COVID-19 severity, population mental health and access to health services during the COVID-19 pandemic with considerable implications for research and prevention in future pandemics.

Keywords:

COVID-19; Mental health; Depression; Childhood maltreatment; Health service use.

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Completing this PhD thesis has been a journey filled with challenges and growth. I am deeply grateful to the many people and companions who have supported me along the way.

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Contents

List of Abbreviations

ACE	Angiotensin-Converting Enzyme
AIC	Akaike Information Criterion
a-BIC	Adjusted Bayesian Information Criterion
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Receiver Operating Curve
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
C-19 Resilience	The Icelandic COVID-19 National Resilience Cohort
CTS	Childhood Trauma Screener
EHRs	Electronic health records
EVD	Ebola Virus Disease
GAD-7	Generalized Anxiety Disorder 7 Item Questionnaire
GWAS	Genome-Wide Association Studies
HLA	Human Leukocyte Antigen
ICD-10	The International Classification of Diseases-Tenth Revision
ICU	The Intensive Care Unit
IRs	Incidence Rates
LMR-LRT	Lo—Mendel—Rubin—Likelihood Ratio Test
NAISS	National Academic Infrastructure for Supercomputing in Sweden
NBC	National Bioethics Committee

NHS	National Health Service
OR	Odds Ratio
PHE	Public Health England
PHQ-9	Patient Health Questionnaire-9
PHQ-15	Patient Health Questionnaire-15
PHS	Public Health Scotland
PROMIS-CFS	Patient-Reported Outcomes Measurement Information System Cognitive Function Scale
PRS	Polygenic Risk Score
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-Traumatic Stress Disorder
SAIL	Secure Anonymized Information Linkage
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SES	Socio-economic Status
SHAP	Shapley Additive Explanation
SIR	Standardized Incidence Ratio
SNIC	Swedish National Infrastructure for Computing
T1	Time Point 1
T2	Time Point 2
UK	United Kingdom
US	United States
UPPMAX	Uppsala Multidisciplinary Centre for Advanced Computational Science
WHO	World Health Organization
XGBoost	Extreme Gradient Boosting

List of Figures

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List of Original Papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I, II, III, IV]):

I. *History of childhood maltreatment associated with hospitalization or death due to COVID-19: a cohort study*. Wang, Y*., Ge, F*., Aspelund, T., Ask, H., Hauksdóttir, A., Hu, K., Jakobsdóttir, J., Zoega, H., Shen, Q., Whalley, H. C., Pedersen, O. B. V., Lehto, K., Andreassen, O. A., Fang, F., Song, H., Valdimarsdóttir, U. A., (2024). BMC Medicine, 22(1): 319.

II. *Trends in incident diagnoses and drug prescriptions for anxiety and depression during the COVID-19 pandemic: an 18-month follow-up study based on the UK Biobank*. Wang, Y., Ge, F., Wang, J., Yang, H., Han, X., Ying, Z., Hu, Y., Sun, Y., Qu, Y., Aspelund, T., Hauksdóttir, A., Zoega, H., Fang, F., Valdimarsdóttir, U. A. & Song, H., (2023). Translational Psychiatry, 13(1), 12.

III. *Depressive symptom trajectories among general population during the COVID-19 pandemic – a prospective cohort study (2020-2023)*. Wang, Y., Haukdóttir, A., Thordardottir, E., Ge, F., Gísladóttir, E., Jakobsdóttir, j., Ásbjörnsdóttir, K., Rúnarsdóttir, H., Unnarsdottir, A., Magnúsdóttir, I., Love, T., Kristinsson, S., Pálsson, R., Zoega, H., Fang, F., Tómasson, G., Song, H., Aspelund, T., Valdimarsdóttir, U. A., (2024). BMJ Public Health, 2024, 2(2).

IV. *Trends of perceived disruption in healthcare services during the pandemic: findings from the COVID-19 National Resilience Cohort in Iceland*. Wang, Y., Unnarsdóttir, A. B., Magnúsdóttir, I., Fang, F., Thordardottir, E. B., Rúnarsdóttir, H., Love, T. J., Kristinsson, S. Y., Pálsson, R., Jakobsdóttir, J., Zoega, H., Ásbjörnsdóttir, K. H., Song, H., Hauksdóttir, A., Aspelund, T., Valdimarsdóttir, U. A., (2024). European Journal of Public Health, 34(2), 394-401.

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Declaration of Contribution

The doctoral student, Yue Wang, designed the research for Studies I-IV, conducted the statistical analyses for each study, drafted the manuscripts, and wrote this thesis, all under the expert guidance of her supervisors, the doctoral committee, and in collaboration with the co-authors of each study.

1 Introduction

1.1 Overview of COVID-19

1.1.1 Prevalence and severity of COVID-19

The global spread of COVID-19, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has posed a significant threat to public health, leading to widespread illness and unprecedented social disruption (Cucinotta & Vanelli, 2020; García-Azorín et al., 2021; Schumacher et al., 2024). Although most COVID-19 patients develop mild symptoms, a significant minority experience critical illness requiring hospitalization and advanced medical care (Wu & McGoogan, 2020). Indeed, a report in 2020 from the Chinese Centre for Disease Control and Prevention suggested that nearly 81% of COVID-19 cases are mild, presenting with either no pneumonia or mild pneumonia, while the remaining 19% are classified as severe or critical, involving complications such as dyspnea, respiratory failure and septic shock (Wu & McGoogan, 2020). In Europe, a study from 2020 estimated that nearly 6.5% of the population would likely require hospitalization if infected with COVID-19, potentially placing a significant burden on the healthcare system (Clark et al., 2020). Moreover, a study using public surveillance data from the United States (US) reported that the mortality rate for hospitalized patients was 30.5% while the mortality rate was 0.7% for non-hospitalized patients (Tabatabai et al., 2023). Additionally, the risk of death from COVID-19 varied significantly across different SARS-CoV-2 variants. For example, a recent meta-analysis found that the case fatality rates of COVID-19 ranged from 0.7% to 4.2% across various variants, with the Omicron variant being the least fatal and the Beta variant being the most fatal (Xia et al., 2024).

1.1.2 Risk factors for severity of COVID-19

Understanding the factors that contribute to severe COVID-19 is crucial for improving treatment strategies and reducing mortality rates. Indeed, previous studies have indicated that older adults (Colnago et al., 2022), males (Docherty et al., 2020; Zaher et al., 2023), and individuals of non-White ethnicity (Siddiq et al., 2023) were at increased risk of COVID-19 hospitalizations and deaths. For example, a meta-analysis conducted in December 2020 has shown that each additional year of age was associated with a 3.4% increased risk of hospitalization and a 7.4% increased risk of death (Starke et al., 2021). Similarly, studies have shown that advanced age and male gender were significant risk factors for COVID-19 mortality during the Omicron wave, even among individuals who had received a booster vaccine (Nafilyan et al., 2022). In addition, poor socioeconomic status (Bell et al., 2023; Maher et al., 2022) and unhealthy lifestyles (Patanavanich & Glantz, 2020; Tavakol et al., 2021; Wang et al., 2024) have been identified as factors associated with increased COVID-19 disease severity. For instance, a study using UK Biobank data found that deprivation and lifestyle scores were associated with COVID-19 mortality, with the highest risks observed in the most disadvantaged groups, indicating an additive interaction between socioeconomic status and lifestyle factors (Foster et al., 2022). Moreover, nearly all chronic medical conditions, including psychotic disorders, diabetes, coronary heart diseases and cancers were associated with an increased risk of COVID-19-related hospitalization and death (Batty et al., 2020; Nafilyan et al., 2022). It is also noteworthy that a modelling study estimated that 1.7 billion people, or 22% of the global population, may be at increased risk of severe COVID-19 due to underlying health conditions (Clark et al., 2020). In terms of genetic susceptibility and severe COVID-19, emerging evidence suggested that higher expression of angiotensin-converting enzyme (ACE) polymorphisms and high-risk human leukocyte antigen (HLA) haplotypes were linked with the severity and clinical outcomes of COVID-19 (Ishak et al., 2022). Meanwhile, several lead variants (e.g., rs35731912, rs657152, and rs1405655) and candidate causal genes (e.g., LZTFL1, ABO, and NAPSA) have been identified and associated with COVID-19 hospitalization and critical illness (Cappadona et al., 2023).

1.1.3 Childhood maltreatment and COVID-19

Childhood maltreatment—including sexual, physical, emotional abuse and neglect—has been shown to have lasting negative impacts on health and has been associated with many of the risk factors linked to COVID-19 severity (Figure 1) (Bellis et al., 2019; Gao et al., 2021; Hughes et al., 2017; Jaffee et al., 2018). For instance, studies have suggested that childhood maltreatment was linked to poor socioeconomic status (Jaffee et al., 2018), unhealthy lifestyles (e.g., smoking and severe overweight) (Bellis et al., 2019), and multiple health conditions such as diabetes, cardiovascular disease, and respiratory illness (Hughes et al., 2017), all of which were associated with poor COVID-19 outcomes (Jean Y Ko et al., 2021; Rodrigues et al., 2022). Furthermore, the link between childhood adversity and adult mental health is well established (Daníelsdóttir et al., 2024; Nelson et al., 2020), and both psychological factors and psychiatric disorders have been identified as significant contributors to COVID-19-related hospitalization and death (Batty et al., 2020; Yang et al., 2020).

Additionally, childhood maltreatment has been linked to an elevated risk of infectious diseases. For instance, individuals with a history of childhood sexual abuse were at higher risk of developing respiratory infections in adulthood (Dargan et al., 2019). Case reports have also suggested possible associations between childhood abuse or neglect and fatal systemic Pseudomonas aeruginosa infection (Senati et al., 2013), meningitis (Nguefack et al., 2016), and recurrent sepsis (Rubin et al., 1986). Moreover, while vaccination has been documented as one of the most effective measures in reducing the risk of severe illness and death from COVID-19 (de Gier et al., 2023; Kerr et al., 2024), individuals with adverse childhood experiences were more likely to exhibit vaccine hesitancy and display mistrust in the government (Bellis et al., 2022), further increasing their risk for severe COVID-19 outcomes.

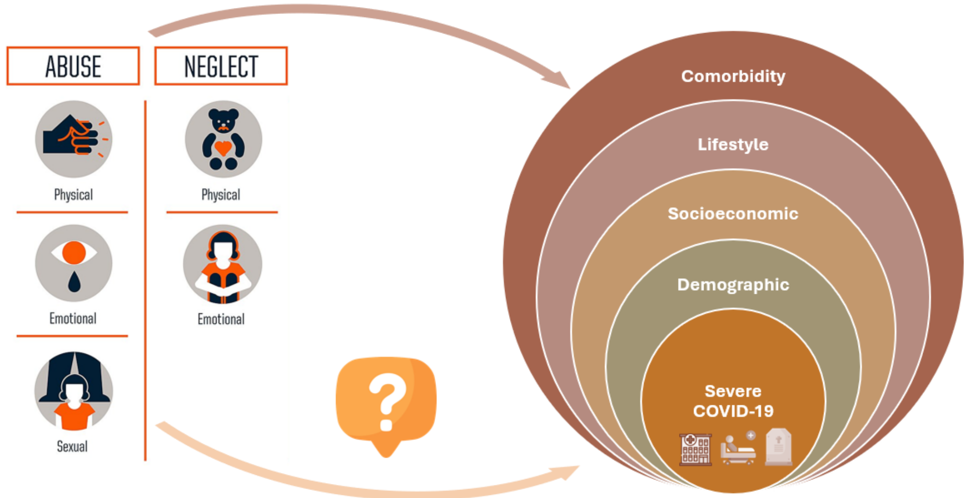


Figure 1. Risk factors for severe COVID-19 outcomes

Given the existing evidence, childhood maltreatment may be a critical risk factor for COVID-19-related morbidity and mortality. While two previous studies have explored the link between childhood maltreatment and COVID-19-related outcomes (Hanson et al., 2023; Srivastav et al., 2021), no research has yet explored how specific types or the cumulative number of childhood maltreatment experiences influence severe COVID-19 outcomes, nor have potential mediating pathways through socioeconomic factors, lifestyle, and pre-existing comorbidities been investigated.

1.2 COVID-19 and mental health

1.2.1 Previous pandemics and mental health impact

Previous epidemics and pandemics have consistently shown significant impacts on mental health of affected individuals and communities (von Lubitz & Gibson, 2023). For example, a recent meta-analysis reviewed the mental health impact of the 2002-2003 severe acute respiratory syndrome (SARS) outbreak (Chau et al., 2021), suggesting a long-lasting psychiatric morbidity among SARS survivors. Additionally, a cohort study in Hong Kong found that 30 months after the SARS outbreak, post-traumatic stress disorder (PTSD) and depressive disorders were the most prevalent long-term psychiatric conditions among SARS survivors, with a prevalence of 25.0% for PTSD and 15.6% for depressive disorders (Mak et al., 2009). A cross-sectional study on Ebola Virus Disease (EVD) survivors similarly found that nearly half of the survivors met the criteria for possible depression approximately two years after being discharged from the treatment centre

(Bah et al., 2020). Furthermore, the mental health of healthcare workers during these crises has been severely affected, leading to higher rates of stress, burnout, and psychological distress (Sanghera et al., 2020; Shah & Kuriansky, 2016). While psychological distress may decrease over time, several studies have shown that the risk of insomnia, burnout, and PTSD can persist for up to three years after the outbreak (Magill et al., 2020).

Not only do infected patients and healthcare workers experience mental health challenges, the general population also suffers from increased anxiety, depression, and even higher suicide rates during outbreaks (Delanerolle et al., 2022). Indeed, the pandemic could affect the entire population through widespread stressors such as fear of infection (Person et al., 2004), uncertainty (Afifi et al., 2012), and social restriction and disruptions (Brooks et al., 2020). Addressing the public's mental health needs could help mitigate the broader psychological impact of the crisis, yet there is a scarcity of data on its effects on the general population (Chau et al., 2021).

1.2.2 Population mental health during the COVID-19 pandemic

In comparison to previous pandemics, the COVID-19 pandemic had a far more extensive global impact, raising significant concerns about its effects on population mental health (Delanerolle et al., 2022; Vindegaard & Benros, 2020). According to a World Health Organization (WHO) report, the COVID-19 pandemic led to a 25% increase in the prevalence of anxiety and depression symptoms during the first year (WHO, 2022b). This negative impact seemed long-lasting, as a nationally representative survey of United States adults in 2022 reported 28% higher odds of experiencing poor mental health than during the early stages of the pandemic (Kim et al., 2023). Furthermore, several longitudinal studies reported evidence for that populations showed varying mental health responses or mental health trajectories over time during the pandemic (Fancourt et al., 2021; Kimhi et al., 2021; Pierce et al., 2021). For instance, a report from the Organization for Economic Cooperation and Development (OECD) found a fluctuating depression levels in European countries during the pandemic, with peaks in mental health distress often coinciding with surges in COVID-19 deaths and strict control measures (Hewlett et al., 2021). Additionally, research in England identified distinct trajectories of depression and anxiety among the general population between March 2020 and May 2021, including consistently low, moderate, and high levels of symptoms throughout the pandemic, clinically significant symptoms early in the pandemic that subsequently decreased, and clinically significant symptoms that emerged after five months of the pandemic (Saunders et al., 2024).

Compared to survey data, which typically use validated self-report questionnaires to assess mental health symptoms and reflect the population's current mental health condition or needs, electronic health records (EHRs) or hospital-setting studies offer insights into mental health service utilization during the pandemic, which provide an alternative perspective on the population's mental health care needs (or unmet needs) during the pandemic. For example, research using primary care EHRs from the UK Clinical Practice Research Datalink reported a 43% decline in recorded incident depression diagnoses in April 2020 compared to expected levels, indicating a significant drop in primary care visits for mental health concerns at the onset of the pandemic (Carr et al., 2021). Similarly, a recent study in Hong Kong found that patients newly diagnosed with depression during the pandemic utilized 11% less healthcare resources (i.e., less visit episodes or bed-days) than those diagnosed before the pandemic (Chan et al., 2024). However, these trends are not consistent across all regions. A study in Germany, analysing data from general and specialized medical practices, observed an increase in newly diagnosed anxiety disorders between March and June 2020 (Jacob et al., 2021). Additionally, fluctuations in the prescription rates of antidepressants and benzodiazepines in Canada were noted, with a temporary decline in April 2020, followed by a return to pre-pandemic levels by August of the same year. These discrepancies underscore the complex and region-specific impact of the pandemic on mental health service utilization. Moreover, as most research has focused on population mental health during the early stages of the pandemic, there is a growing need for extended follow-up studies to better understand its long-term effects.

1.2.3 Risk factors for mental health during the COVID-19 pandemic

Many factors have been identified associated with poor mental health outcomes during the COVID-19 pandemic (Figure 2). While gender inequality was well-documented prior to the pandemic, recent evidence indicates that women have faced increased household chores, childcare burdens and income losses, leading to worsened mental health during the COVID-19 pandemic (Borrescio-Higa & Valenzuela, 2021). Furthermore, factors such as younger age, poor socioeconomic status, and a history of psychiatric disorders have been identified and associated with consistently low or deteriorating mental health during the COVID-19 pandemic (Pierce et al., 2021). Studies have also shown that individuals who were single (Lei et al., 2020), unemployment (Xiong et al., 2020) or had a family member infected with COVID-19 (Lovik et al., 2023) were more likely to be affected by the COVID-19 pandemic and experienced higher levels of psychological distress compared to others during the COVID-19 pandemic.

On the other hand, multiple contextual factors, including uncertainty about the pandemic (Koçak et al., 2021), social restrictions (Brooks et al., 2020), and economic disruption (McKibbin & Fernando, 2021; Nicola et al., 2020) have been associated with poor mental health outcomes during the COVID-19 pandemic. For instance, pandemic control measures like social distancing, self-isolation, and lockdown, which limit individuals' social interactions, have the potential to induce or worsen feelings of anxiety and depression (TMGH-Global COVID-19 Collaborative, 2021). In contrast, several protective factors, such as financial security (e.g., unemployment insurance) (Donnelly & Farina, 2021), high levels of family functioning (Liu et al., 2023) and institutional trust (Li et al., 2022) have been identified and may help protect subjective well-being during the COVID-19 pandemic. However, most studies have examined these factors in isolation, without adequately considering the interactions between them. This limits our understanding of how these factors may interact or which ones are more important, highlighting a gap in the existing evidence.

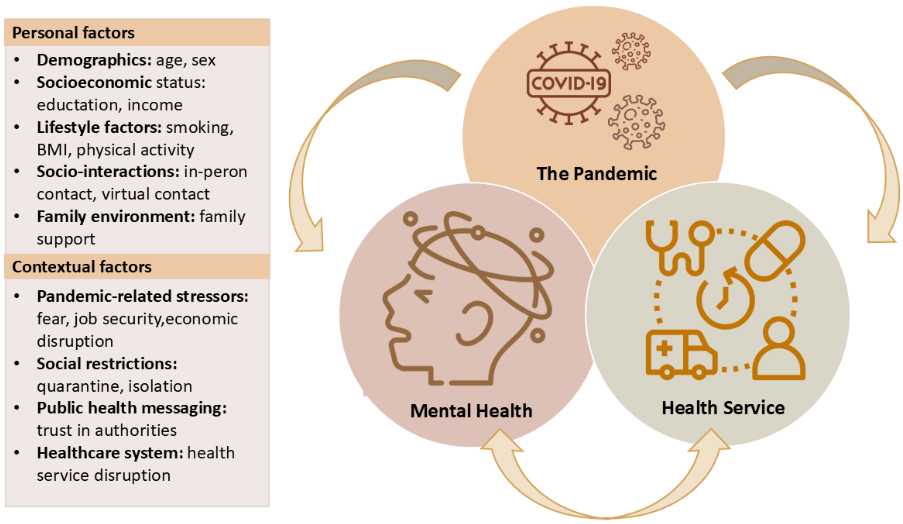


Figure 2. The COVID-19 pandemic, population mental health and health service

1.3 Health service use during the pandemic

1.3.1 Prevalence of disruption in health service use

Not only has the COVID-19 pandemic impacted population mental health, it has also caused significant backlogs and delays in the use of general health services. For example, Dilawari et al. reported that nearly half of breast cancer survivors experienced medical care disruptions during the early COVID-19 pandemic (Dilawari et al., 2021). In the US, routine care and chronic care management were the most frequently delayed health services (Ponce et al., 2023), with an estimated 32% of adults having postponed or avoided routine care by June 2020 (Czeisler et al., 2020). Similar trends were observed across Europe and around the world, and an average of 26% of health services were experiencing disruptions across the European region by 2021 (WHO, 2022a). Additionally, widespread healthcare worker shortages and the repurposing of hospital spaces to care for severe COVID-19 patients raised significant concerns about the quality of care for non-COVID patients during this unprecedented period (Huggins et al., 2023). Indeed, delays in critical treatments, such as aortic valve interventions for cardiovascular patients, can have a significant negative impact on prognosis (Raisi-Estabragh & Mamas, 2022). Notably, an 8% rise in acute cardiovascular deaths was observed during the COVID-19 pandemic in England (Wu et al., 2021).

The disruptions in health service use may have had a disproportionate impact on different socio-demographic groups during the COVID-19 pandemic (Gertz et al., 2022). Previous studies have indicated that young adults (Blundell et al., 2020), ethnic minorities (Ormiston & Williams, 2022), and low-income groups (Blundell et al., 2020) were more vulnerable to the negative impacts of health disruptions during the pandemic. However, existing evidence is limited by cross-sectional study designs and the availability of comprehensive data. More in-depth research is necessary to fully understand how and to what extent the pandemic impacted these vulnerable populations.

1.3.2 Disruption in health service use and population mental health

While it is challenging to separate the specific impact of healthcare disruptions from broader economic and social disruptions to prevent the spread of the virus, disruptions in health service use may independently further exacerbate psychological distress, particularly among patients in particular need for health services. For instance, untreated or undertreated pain and other physical symptoms have been linked to an increased risk of depression and anxiety during the pandemic (Manchikanti et al., 2021). A cross-sectional study using data from the 2020 Health and Retirement Study (HRS) also found that delays in surgery and dental care were associated with higher levels of depression among middle-aged and older adults (Luo, 2021). These disruptions may cause quality of life impairments among patients which contributes elevated psychological distress. Notably, mental health services were severely impacted, with almost 93% of countries around the world reporting disruptions to mental health services in 2020 (WHO, 2020), highlighting the significant mental health challenges faced by populations during the pandemic. Moreover, studies have shown that individuals experiencing common symptoms of anxiety and depression are more likely to avoid seeking non-COVID-19 related medical care, even when such care is necessary, further exacerbating concerns about the poor mental health outcomes in this population (Ganson et al., 2020). Similarly, compared to individuals with normal levels of mental distress, a study have found that individuals showing signs of mental distress had increased odds of delaying medical visits and missing prescription refills during the pandemic (Jalan et al., 2022). However, as most studies were conducted during the early phases of the COVID-19 pandemic, there remains limited information on trends in health service disruptions throughout the pandemic and their long-term effects on population mental health.

In summary, a comprehensive understanding of the factors contributing to both severe COVID-19 outcomes and population mental health is crucial for protecting public health throughout the pandemic and beyond. While numerous factors influencing COVID-19 severity have been extensively studied, certain critical factors—such as history of childhood maltreatment—remain insufficiently explored. Moreover, much of the existing research on the pandemic's mental health impacts has focused on the early stages of the pandemic or on specific high-risk groups. This focus has led to a significant gap in understanding how the pandemic has affected the general population over time, particularly in terms of long-term mental health consequences and disruptions in health service use. Addressing these research gaps is essential not only for understanding the full scope of the pandemic's impact but also for informing the development of targeted interventions that may mitigate the effects of COVID-19 on both physical and mental health.

2 Aims

The overarching aim of this thesis was to better understand the role of psychosocial factors in COVID-19 severity and to explore the long-term effects of the pandemic on population mental health and health service use. The four specific aims were the following:

2.1 Study I: To determine the associations between history of childhood maltreatment and severe COVID-19 outcomes

Using data from the UK Biobank, the objective of this study was to investigate the association between history of childhood maltreatment and COVID-19 hospitalizations and deaths, and further examine the potential mechanisms and the role of disease susceptibility in this association.

2.2 Study II: To determine trends in new diagnoses and drug prescriptions for anxiety and depression during the COVID-19 pandemic in the UK

Using data from the UK Biobank, the objective of this study was to assess trends in new diagnoses of anxiety and depression and new prescriptions of anxiolytics and antidepressants between March 2020 and August 2021.

2.3 Study III: To determine depressive symptom trajectories in the Icelandic population during the COVID-19 pandemic

Using data from the COVID-19 National Resilience Cohort, the objective of this study was to investigate varying depressive symptom trajectories during the COVID-19 pandemic in Iceland and further identify determinants of each trajectory and their long-term sequelae over a total of three-year follow-up (i.e., from April 2020 to February 2023).

2.4 Study IV: To determine trends of health services disruption in Iceland during the COVID-19 pandemic

Using data from the COVID-19 National Resilience Cohort, the objective of this study was to examine trends in perceived disruption in health service use during the COVID-19 pandemic and to further explore how these perceived disruptions are related to sociodemographic factors, preexisting health conditions, and concurrent well-being.

3 Materials and Methods

In this thesis, we used data from the UK Biobank for Studies I and II, and data from the Icelandic COVID-19 National Resilience (C-19 Resilience) Cohort for Studies III and IV. We performed different kinds of study designs and statistical analyses in the included four studies (Table 1).

Table 1. Summary of the materials and methods used in each study

Study	Study Design	Measures	Statistical methods
I	Cohort study	• Self-report questionnaires • National health registers	• Binomial logistic regression • Causal mediation analysis
II	Longitudinal study	• National health registers	• Standardization
III	Mixed study • Cross-sectional study • Cohort study	• Self-report questionnaires	• Latent growth mixture model • Extreme gradient boosting model • Generalized linear regression • k-Nearest Neighbour Imputation
IV	Mixed study • Cross-sectional study • Cohort study	• Self-report questionnaires	• Poisson regression • Generalized linear regression • Multiple imputation

3.1 Data Sources

3.1.1 Study setting

This thesis use data from both the United Kingdom and Iceland.

On January 31, 2020, the first confirmed cases of COVID-19 were reported in England, and the number of cases rapidly increased across the UK in the following months. In response to the escalating health crisis, the UK government implemented a range of measures aimed at reducing the spread of the virus, including social distancing, self-isolation, and a series of lockdowns (Appendix 1). Specifically, on March 23, 2020, the UK government announced the first nationwide lockdown, instructing people to stay at home except for essential activities and limited exceptions. The lockdown was gradually eased in the following weeks, but similar restrictions were reintroduced in late 2020 and early 2021 as COVID-19 cases surged again. According to the UK government, the UK experienced three significant waves of the pandemic between 2020 and 2021, and the crude COVID-19-related death rates ranged from 4.48 per 1,000 person-years during the first wave (March—May 2020) to 0.64 per 1,000 person-years in the third wave (May—December 2021) (Nab et al., 2023). A substantial decrease in COVID-19-related death rates during the third wave was observed among groups prioritized for the primary SARS-CoV-2 vaccination. Moreover, with the success of the UK's vaccine and booster rollout by February 2022—where 85% of the population received a second dose and 66% received a booster or third dose—the UK government introduced the "Living with COVID-19"plan (GOV.DK, 2022a), and all COVID-19 travel restrictions were further lifted on March 18, 2022 (GOV.UK, 2022b).

Iceland confirmed its first cases of COVID-19 on February 28, 2020, and promptly implemented gathering restrictions, school closures, and large-scale testing of the general population to limit the spread of the virus in the country (Government of Iceland, 2020a). In contrast to the strict lockdowns in the UK, Iceland never utilized such strict measures but implemented social restrictions in March 2020, limiting social gatherings to 20 people and school closing and remote learning. Then in October 2020 and mid of 2021, similar restrictions were imposed, but all loosened within several weeks. By the end of 2021, Iceland had recorded 37 COVID-19-related deaths, with a mortality rate of 5.6 per 100,000 people, which was relatively low compared to other European countries, such as the UK, where the COVID-19 mortality rate was 131.1 per 100,000 people (H. Wang et al., 2022). Iceland began its COVID-19 vaccination campaign in early 2021, and by April 2022, 82% of the eligible population had been fully vaccinated (Yelena, 2022). On February 25, 2022, all COVID-19-related public restrictions, both domestically and at the border, were lifted, marking Iceland's transition out of the COVID-19 pandemic (Government of Iceland, 2022).

3.1.2 UK Biobank

In the years 2006-2010 (i.e., baseline), the UK Biobank recruited more than 500,000 middle-aged individuals (aged 40—69 years) in the UK and collected data on demographic factors, socioeconomic status, lifestyle factors, and genetic information (Bycroft et al., 2018). Between 2016 and 2017, 157,366 out of 339,092 participants who had consented to future contact were invited and responded to an online mental health follow-up, which included a retrospective assessment of childhood maltreatment. Health-related outcomes were periodically collected for UK Biobank participants through linkage with various national health registries (Table 2). To support COVID-19-related research, primary care data—including clinical information and prescriptions—were made available to approved researchers between 2020 and 2021, covering most UK Biobank participants. Additionally, COVID-19 test result for all UK Biobank participants were accessible through linkage with Public Health Scotland (PHS), Public Health England (PHE), and the Secure Anonymised Information Linkage (SAIL) databank. Compared to the general UK population, the UK Biobank participants were more likely to be older, female, live in less socioeconomically deprived areas, and report fewer health conditions at baseline (Fry et al., 2017).

Table 2. Data availability: the UK Biobank and linkage to national registers

Register	Country	Period of data available	
Hospital inpatient data	England	1997 onwards	30/09/2021

Register	Country	Period of data available	
	Scotland	1981 onwards	31/07/2021
	Wales	1991 onwards	28/02/2018
Death data	England & Wales	2006 onwards	30/09/2021
	Scotland	2006 onwards	31/10/2021
Primary care data - for COVID-19 research	England	1938 onwards	31/08/2021
COVID-19 test results	England	16/03/2020	30/09/2021
	Scotland	16/03/2020	31/08/2021
	Wales	16/03/2020	31/08/2021

3.1.3 The C-19 Resilience Cohort

The C-19 Resilience Cohort was established in April 2020 and was eligible for all Icelandic-speaking adults (aged ≥ 18 years) in Iceland (Unnarsdóttir et al., 2021). Participants were recruited through media outreach and invitations to those involved in other ongoing cohort studies in Iceland (Directorate of Health, 2023; Rögnvaldsson et al., 2021; The SAGA cohort, 2023). A total of 23,960 participants were enrolled between April 2020 and May 2021 (i.e., baseline), and three waves of follow-up were completed by February 2023 (Figure 3). Since all domestic and border restrictions due to COVID-19 were lifted as of February 25, 2022 (Government of Iceland, 2022), we categorized the first three assessments as pandemic assessments and the latest follow-up as a post-pandemic assessment. At each assessment wave, participants were invited to complete a series of online questionnaires, providing information on demographics, socioeconomic status, lifestyle, preexisting health conditions, COVID-19 illness, and pandemic-related disruptions (Unnarsdóttir et al., 2021).

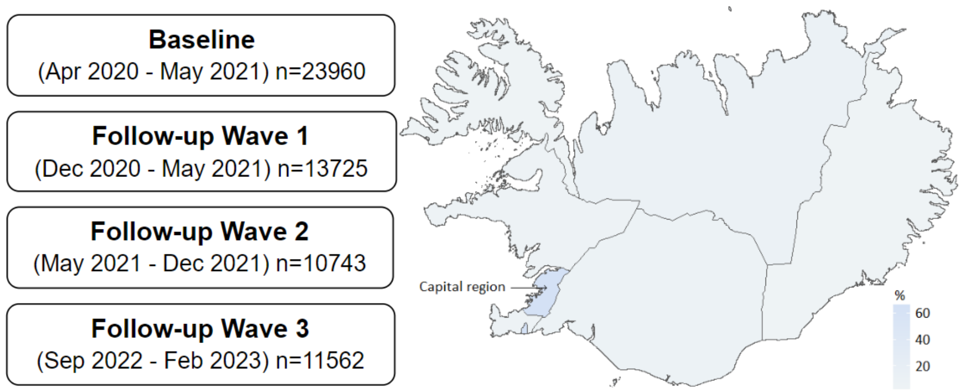


Figure 3. Data collection timeline

Compared to the Icelandic general population, C-19 Resilience participants were more likely to be older, female, residents of the capital area, and to have a higher level of education (Figure 4).

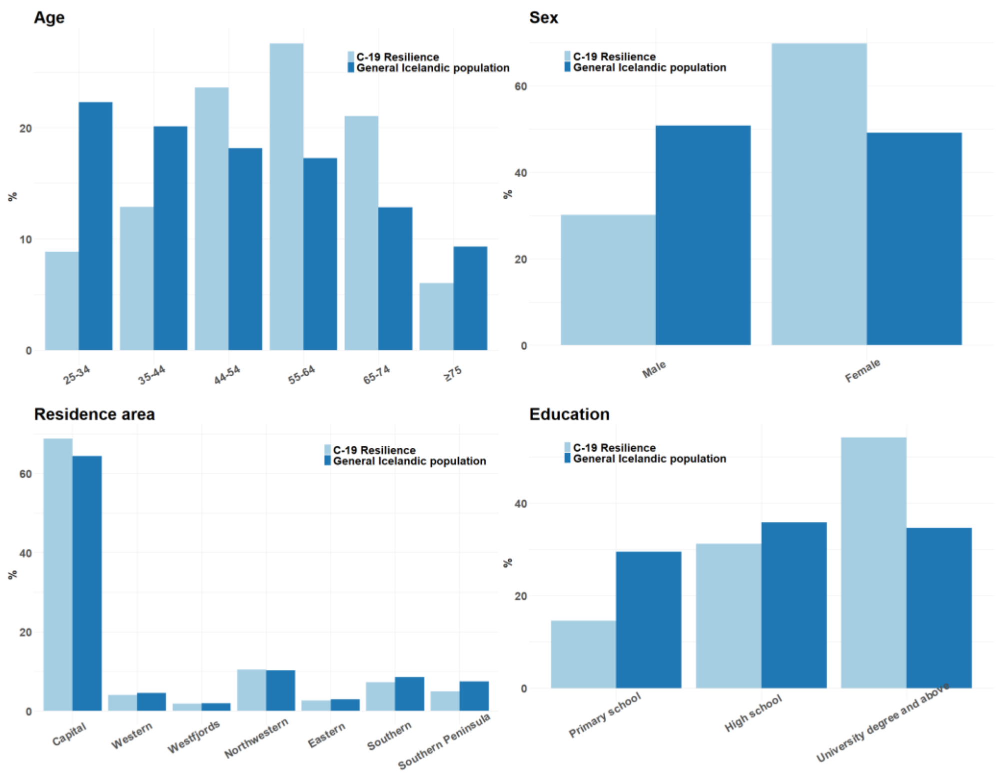


Figure 4. Comparison of socio-demographic factors between C-19 resilience participants and the general Icelandic population

Note, this figure was adapted from Table S1 in Wang et al. European Journal of Public Health (2024).

3.2 Study design and methods

3.2.1 Study I

3.2.1.1 Participants and study design

In Study I, we performed a cohort study and included 151,427 participants from UK Biobank who provided information on their history of childhood maltreatment and were alive as of January 31, 2020, namely the first confirmed COVID-19 cases reported in the UK (Dunn et al., 2024). Considering the data availability, we restricted the studied pandemic period to between January 31, 2020, and October 31, 2021. We first examined the association between the history of childhood maltreatment and COVID-19 hospitalizations and deaths. We then included 117,793 White British participants with eligible genotyping data to investigate the potential impact of genetic risk for severe COVID-19 outcomes on the observed associations (Figure 5).

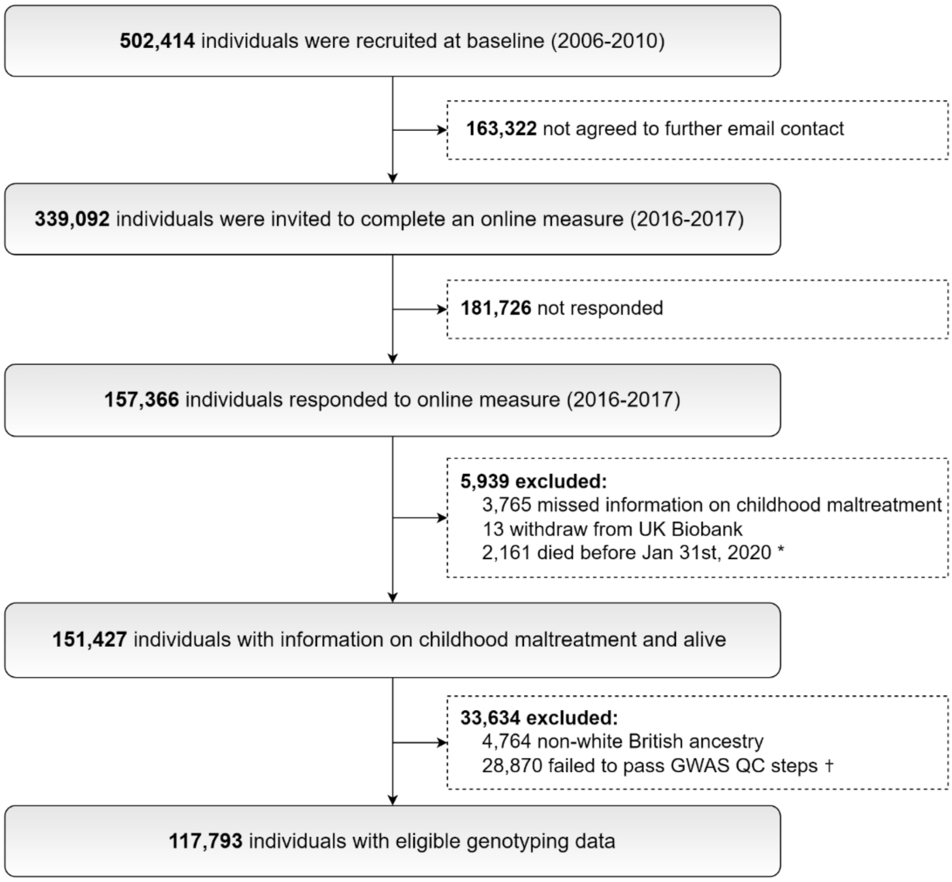


Figure 5. Flow-chart of the analytical sample for study I

Note, * First confirmed COVID-19 cases in the UK. † Individuals with a genotyping rate below 98%, abnormal heterozygosity levels, or a kinship coefficient above 0.0884 were excluded. This figure was adapted from Figure S1 in Wang et al. BMC Medicine (2024).

3.2.1.2 Measures

The history of childhood maltreatment was assessed using validated Childhood Trauma Screener (CTS) (Grabe et al., 2012; Witt et al., 2022), and we created three types of exposure variables:

a) Any childhood maltreatment (yes or no).
b) The number of childhood maltreatment types (0, 1, 2 or ≥3).
c) Five binary variables (yes or no), each indicating the presence of a specific type of childhood maltreatment (i.e., emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse).

Severe COVID-19 outcomes were defined as cases where participants had a primary diagnosis of COVID-19 in hospital inpatient data (the International Classification of

Diseases-Tenth Revision [ICD-10]: U07.1 or U07.2), or where COVID-19 was listed as the cause of death in death registries. The secondary outcomes of interest were COVID-19 diagnosis and COVID-19 vaccination. COVID-19 diagnosis was determined from test records in the PHS, PHE, and SAIL databanks, and was categorized as tested positive, tested negative, or not tested for COVID-19. COVID-19 vaccination status was determined based on whether the participant had received the first dose of a COVID-19 vaccine and was categorized as yes or no.

Polygenic risk score (PRS) for severe COVID-19 outcomes was calculated based on Genome-Wide Association Studies (GWAS) summary statistics from the COVID-19 Host Genetics Initiative (Version 5, https://www.covid19hg.org/), which included very severe respiratory confirmed COVID-19 cases (i.e., laboratory confirmed SARS-CoV-2 infection AND hospitalized for COVID-19 AND (death OR respiratory support), n=4,792) and a control population of European ancestry without UK Biobank and 23andMe participants (n=1,054,664).

Confounders were selected on the basis of previous findings (Aldridge et al., 2020; Chandan et al., 2020; Docherty et al., 2020; Elkin, 2020) and a directed acyclic graph (Figure 6), including birth year, sex, ethnicity and recruitment region.

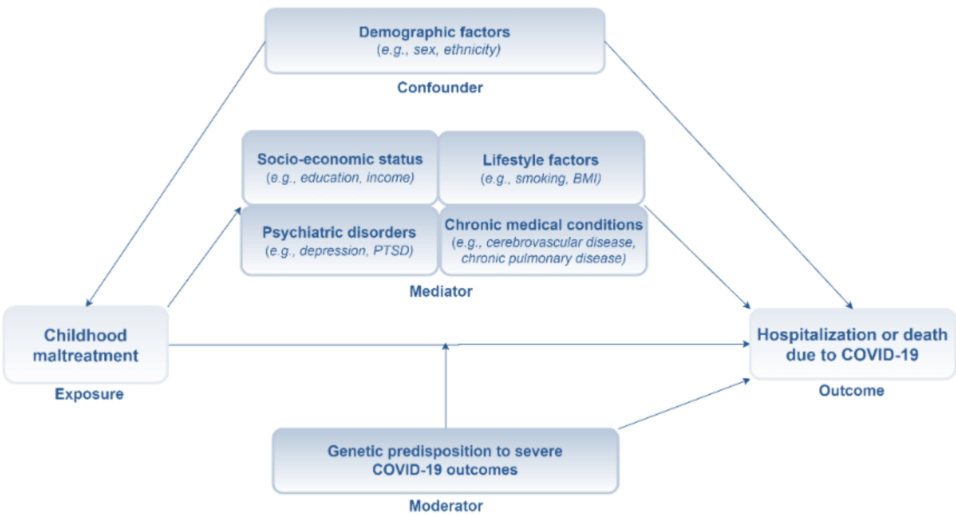


Figure 6. Proposed causal model of the relationship between the history of childhood maltreatment and COVID-19 hospitalizations and deaths

Note, this figure was adapted from Figure 1 in Wang et al. BMC Medicine (2024).

Likewise, four mediator clusters were selected (Hughes et al., 2017; Jaffee et al., 2018; Jean Y Ko et al., 2021; Macpherson et al., 2021; Topitzes et al., 2010).

a) Socioeconomic status (M1), including Townsend deprivation index, annual household income and college education.
b) Lifestyle factors (M2), including smoking status and body mass index [BMI].
c) Pre-pandemic chronic medical conditions (M3, measured by Charlson Comorbidity Index [CCI]≥1]). More details about CCI please refer to Paper I, Additional file 2, Table S3.
d) Pre-pandemic psychiatric disorders (M4, measured by the diagnosis of psychiatric disorders in hospital inpatient data, ICD-10: F10-F99).

3.2.1.3 Statistical analysis

We first described participant characteristics by history of childhood maltreatment. We used binomial logistic regression to examine the associations between history of childhood maltreatment and COVID-19 hospitalizations and deaths. We constructed five models, where the basic model was adjusted for demographic factors only, and then, in a stepwise manner, the other four models were additionally adjusted for the mediator clusters (M1-M4).

We then conducted a regression-based causal mediation analysis using CMAverse package in R (Shi et al., 2021) to estimate the proportion of mediation effect attributed by each individual mediator cluster (M1-M4) as well as all of them combined. Specifically, the outcome variable was regressed on the main exposure variable (i.e., any childhood maltreatment), the studied mediators, and confounders using a binomial logistic regression model. Each mediator was regressed on the exposure variable and confounders using either binomial (e.g., pre-pandemic chronic medical conditions) or multinomial (e.g., smoking status) logistic regression models. The results from the outcome and mediator models were combined to estimate the proportion mediated by each considered mediation factor and all combined (Valeri & VanderWeele, 2013; VanderWeele & Vansteelandt, 2014).

We ran analyses for each of the five types of childhood maltreatment to assess their individual impacts on the outcome. Furthermore, we conducted analyses stratified by tertiles of the PRS for severe COVID-19 outcomes to examine the role of genetic susceptibility in the association between history of childhood maltreatment and COVID-19 hospitalizations and deaths.

We performed secondary analyses to examine the association between history of childhood maltreatment and COVID-19 diagnosis as well as COVID-19 vaccination. Additionally, we performed two sensitivity analyses to assess the robustness of our findings. First, we limited the sample to individuals diagnosed with COVID-19 and repeated the analysis. Then, we conducted separate analyses for COVID-19 hospitalizations and deaths to determine whether there were any differences between these two indicators of severe COVID-19 outcomes.

3.2.2 Study II

3.2.2.1 Participants and study design

In Study II, we performed a longitudinal study and constructed two incident cohorts (Figure 7). Given the data availability of the linked health registers, we defined the study period between March 16, 2020 (i.e., baseline; results of COVID-19 testing were available) and August 31, 2021. First, we constructed an incident diagnosis cohort including 308,400 participants who were free of anxiety and depression at baseline. Similarly, we constructed another incident prescription cohort of 213,757 participants who were free of anxiolytic and antidepressant prescriptions at baseline. We followed each participant from baseline until the occurrence of any outcomes of interest, death, or until August 31, 2021. For comparison, we used the three years preceding the pandemic as the reference pre-pandemic period (i.e., 2017-2019).

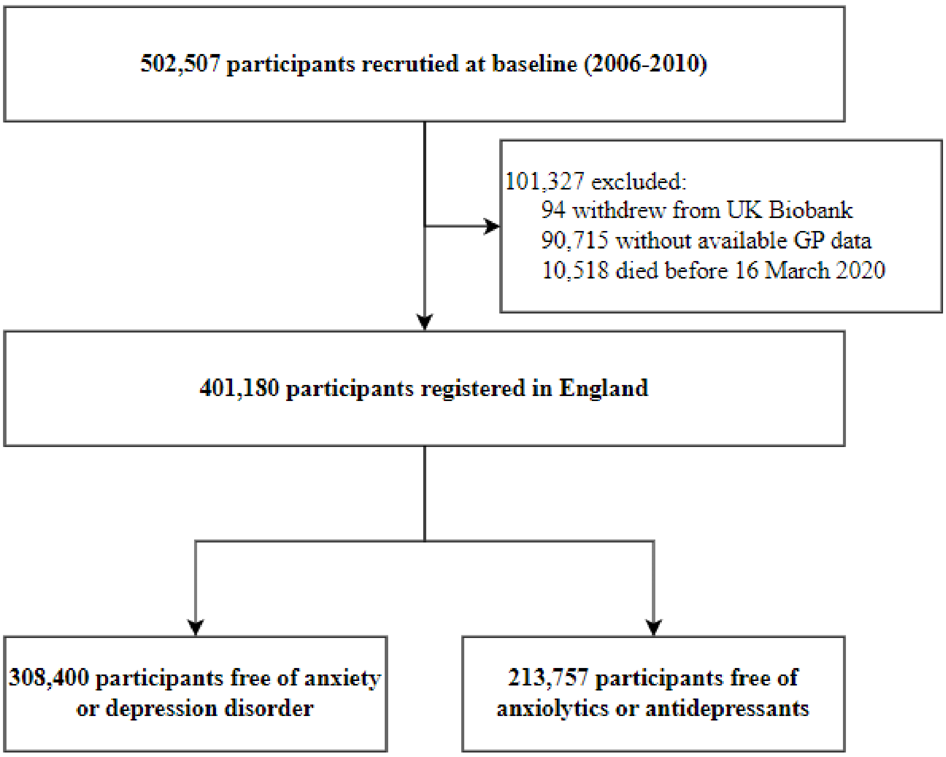


Figure 7. Flow-chart of the analytical sample for study II

Note, this figure was adapted from Figure 1 in Wang et al. Transl Psychiatry (2023).

3.2.2.2 Measures

In Study II, the outcomes of interest were the new diagnoses of anxiety (ICD-10: F40-F41) and depression (ICD-10: F32-F33) as well as prescriptions of anxiolytics (Anatomical

Therapeutic Chemical [ATC]: N05B) and antidepressants (ATC: N06A). Diagnoses of anxiety and depression were derived from hospital inpatient records and primary care records. Prescription information was obtained from primary care prescription records. Pandemic exposure status was determined by COVID-19 test results, which were obtained through linkage with the PHS, PHE, and SAIL databanks, and categorized in a time-varying manner as not tested, tested negative, or tested positive (Figure 8).

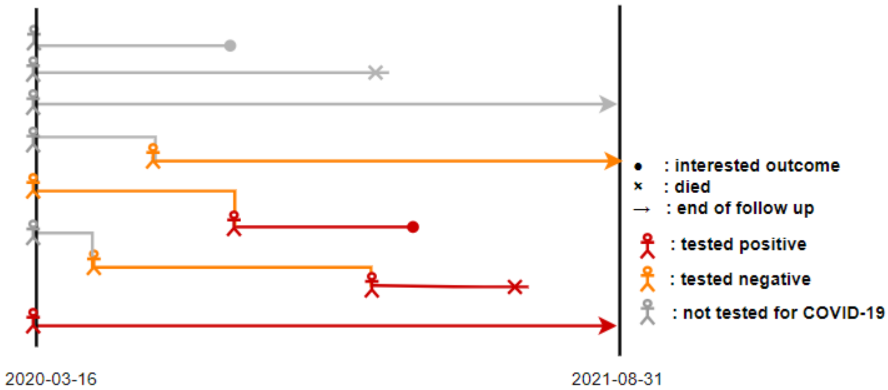


Figure 8. Illustration of a time-varying pandemic exposure status definition

3.2.2.3 Statistical analyses

We first described participant characteristics by each incident cohort. Next, we calculated the crude incidence rates (IRs) for anxiety or depression diagnoses and respective psychotropic medication prescriptions during the pandemic period. The incidence rate was calculated by dividing the number of observed outcomes by the total person-years at risk. To assess whether the observed incident cases during the COVID-19 pandemic increased compared to the pre-pandemic period, we calculated age and sex standardized incidence ratios (SIRs) using indirect standardization method (Figure 9; epitools package in R) (Anderson & Rosenberg, 1998; Aragon et al., 2017). Moreover, we stratified the analyses by COVID-19 testing results to investigate the impact of pandemic exposure status on incident psychiatric morbidity. Additionally, we calculated the SIRs by month to account for potential seasonal variations.

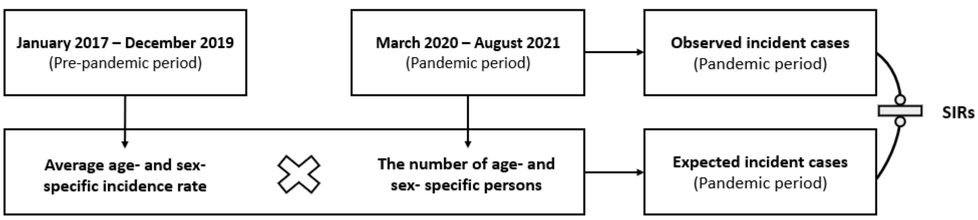


Figure 9. Calculation of age and sex standardized incidence ratios

We performed three sensitivity analyses to test the robustness of the findings. First, we restricted the sample to individuals without chronic medical conditions (indicated by a CCI<1) to minimize the potential confounding effects of pre-existing health conditions on the outcomes. Second, we redefined the pandemic period starting from May 18, 2020, when COVID-19 testing became accessible to anyone with symptoms in the UK (Dunn et al., 2024). Third, we conducted separate analyses for anxiety and depression as well as for anxiolytics and antidepressants to determine if differences existed between these outcomes.

3.2.3 Study III

3.2.3.1 Participants and study design

In Study III, we performed a mixed study design and included 6,423 participants with four consecutive sets of data on depressive symptoms in the analysis (Figure 10). We first conducted a cross-sectional study using the first three assessments during the pandemic—baseline, follow-up wave 1, and follow-up wave 2—to examine variations in depressive symptom trajectories and their determinants. Then, we performed a cohort study to investigate the relationship between these depressive symptom trajectories and post-pandemic health outcomes at follow-up wave 3, including depressive symptoms, anxiety, somatic symptoms, and cognitive problems.

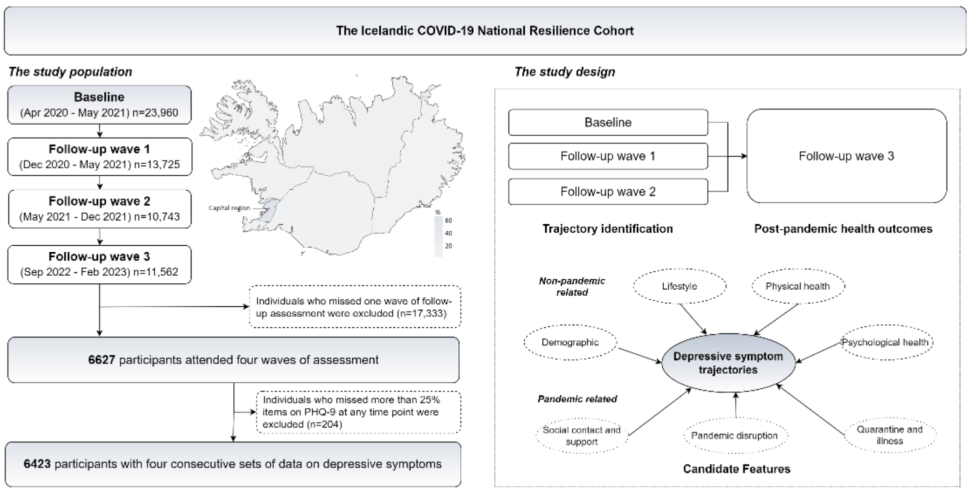


Figure 10. Flow-chart of the analytical sample for study III

Note, this figure was adapted from Figure 1 in Wang et al. BMJ Public Health (2024).

3.2.3.2 Measures

Four validated self-report psychological instruments were used to assess depressive symptoms and post-pandemic health outcomes, including Patient Health Questionnaire-9 (PHQ-9) (Levis et al., 2019), Generalized Anxiety Disorder 7 item questionnaire (GAD-

7) (Spitzer et al., 2006), Patient Health Questionnaire-15 (PHQ-15) (Kocalevent et al., 2013), and Patient-Reported Outcomes Measurement Information System Cognitive Function Scale (PROMIS-CFS) (Iverson et al., 2021). Specifically, the PHQ-9 is a measure with 9 Likert-type items that assess the frequency of depressive symptoms over the previous 2 weeks, with scores ranging from 0 to 27. The GAD-7 is a 7-item Likert scale that measures the severity of anxiety symptoms over the past 2 weeks, with scores ranging from 0 to 21. The PHQ-15 is a 15-item Likert scale that assesses somatic symptom severity and screens for the potential presence of somatoform disorders in adults, with scores ranging from 0 to 30. The PROMIS-CFS is a set of person-cantered measures that evaluates and monitors health status (Iverson et al., 2021), including a subscale with 8 items for cognitive function, with scores ranging from 0 to 40.

37 factors with potential relevance to depressive symptom trajectories during the pandemic were assessed. More details about the measuring and scoring rules please refer to Paper III, Supplementary Materials, sTable 2.

a) Demographic factors, including age, sex, sexual orientation, residence area, relationship status, education, and childcare burden (Cook et al., 2021; Pierce et al., 2021; Sevilla & Smith, 2020).
b) Lifestyle factors, including exercise level at baseline, change in exercise levels during the pandemic, and smoking status (Cook et al., 2021; Giuntella et al., 2021; Steptoe & Di Gessa, 2021).
c) Physical and psychological health factors, including BMI, chronic medical conditions, mobility/hearing/visual impairment, and history of psychiatric disorders (Castro-de-Araujo et al., 2022; Luppino et al., 2010; Na & Yang, 2022).
d) Pandemic-related social contact and support factors, including in-person contact, change in frequency of in-person contact, virtual contact, change in frequency of virtual contact, perceived family support, change in family support, perceived social support, change in social support, trust in Icelandic health authorities, and change in trust (Li & Xu, 2022; Ozbay et al., 2007; Sommerlad et al., 2022).
e) Quarantine- and COVID-19-related factors, including quarantine, COVID-19 testing and diagnosis, bedridden due to COVID-19, family/friends diagnosed with COVID-19, family/friends admitted to a hospital, family/friends admitted to the intensive care unit (ICU), and COVID-19 vaccination status (Brooks et al., 2020; Lovik et al., 2023; Magnúsdóttir et al., 2022; Nguyen, 2021).
f) Pandemic disruption-related factors, including financial difficulties, change in financial difficulties, difficulty in obtaining necessities, change in difficulty in obtaining necessities, disruption of necessary services, and change in disruption of necessary services during the pandemic (Fu et al., 2023)

3.2.3.3 Statistical analyses

We first examined the demographic characteristics of the study population. We then constructed latent growth mixture models using GMM in Mplus (Muthén & Muthén, 2012) to explore variations in depressive symptom trajectories during the pandemic. We fitted the model from one to seven latent classes and selected the optimal model based on fit statistics, including Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-size-adjusted BIC (aBIC), the Lo–Mendel–Rubin–likelihood ratio test (LMR–LRT), and the relative entropy value (Van De Schoot et al., 2017). We also took into consideration whether each trajectory group had a sufficient number of individuals, ensuring that each group comprised more than 5.0% of the total sample (Van De Schoot et al., 2017).

Participants were then categorized into probable groups based on the selection of the optimal model. To identify the most important factors for each trajectory group, we constructed an extreme gradient boosting (XGBoost) model using the Scikit-learn package in Python and calculated the mean absolute SHapley Additive exPlanation (SHAP) values to rank the importance of the factors. XGBoost is a scalable, distributed gradient-boosted decision tree algorithm designed for efficient model exploration (Chen & Guestrin, 2016). It incorporates regularization techniques to mitigate overfitting and for these reasons sometimes preferred over traditional methods as it makes no assumptions about the data and is capable of capturing complex data relationships. The mean absolute SHAP value quantifies the magnitude and direction of a factor's contribution to the model (Lundberg et al., 2018). Specifically, factors with high positive mean absolute SHAP values have a high positive impact on the prediction.

We split the data into 70% for training and 30% for testing. We assessed the model's performance by calculating the optimal Youden index (i.e., max [sensitivity + specificity - 1]; ranging from 0 to 1) and the area under the receiver operating curve (AUC; ranging from 0.5 to 1), with higher values indicating better model performance (Huang & Ling, 2005; Perkins & Schisterman, 2006; Schisterman et al., 2005; Youden, 1950).

Furthermore, we performed generalized linear regression analyses using stats package in R (Team, 2021) to explore the associations between depressive symptom trajectories and post-pandemic health outcomes, adjusted for age at baseline, sex, education, relationship status, smoking status, BMI, chronic medical conditions, and history of psychiatric disorders.

We performed single imputation for individuals with less than 25% of items missing for each psychological assessment instruments. Since menstrual cramps are only applicable to female under 60 years of age (Daan & Fauser, 2015), we assigned a value of 0 for this item from the PHQ-15 for males and for females older than 60 years. Missing data for 37 factors potentially relevant to depressive symptoms were imputed using k-Nearest Neighbour Imputation (k=10) (Templ et al., 2022).

3.2.4 Study IV

3.2.4.1 Participants and study design

In Study IV, we performed a mixed study design and included 15,754 participants who provided information on their perceived health service use status during the COVID-19 pandemic (Figure 11). Data on perceived health service use was collected at two assessment periods: Time Point 1 (T1): from December 2020 to February 2021 and Time Point 2 (T2): from May 2021 to July 2021. We first conducted a cross-sectional study to investigate associations between socio-demographic factors, health indicators and pre-existing conditions, and perceived disruptions in health service use. Among the 7,848 participants who responded at both T1 and T2, we performed a cohort study and investigate the associations between the duration of perceived disruptions in health service use and changes in mental health symptoms.

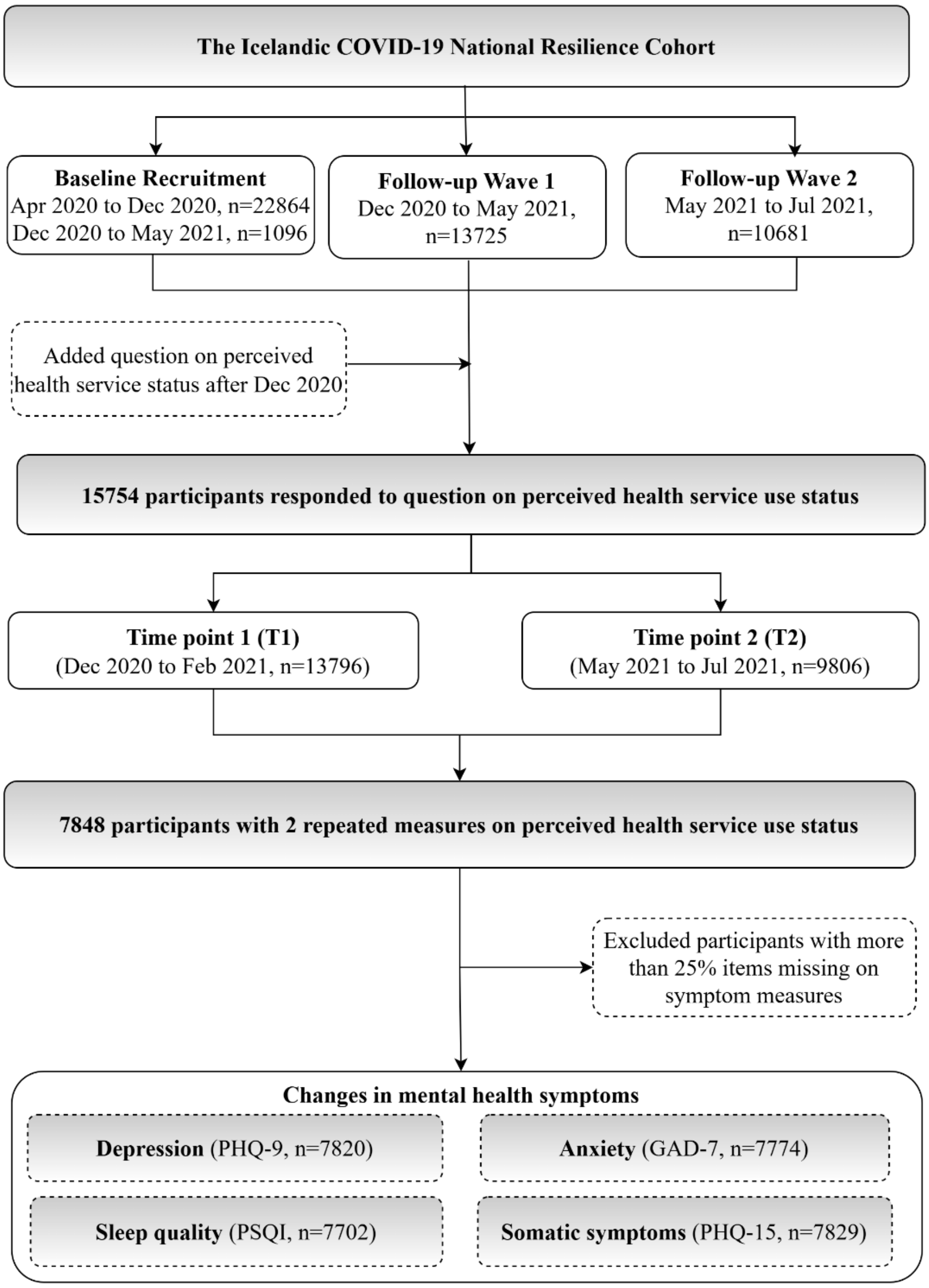


Figure 11. Flow-chart of the analytical sample for study IV

Note, this figure was adapted from Figure S1 in Wang et al. European Journal of Public Health (2024).

3.2.4.2 Measures

We used one question to assess perceived health service use status: 'During the COVID-19 epidemic, have you experienced any inconvenience caused by limited health services?' and created two types of variables.

a) A binary variable indicated perceived disruption at each time point (Yes or No).

b) A cumulative variable combining responses from both time points indicated the duration of perceived disruption ('Neither perceived at T1 nor T2,' 'Perceived at T1 only,' 'Perceived at T2 only,' and 'Perceived at both T1 and T2').

We assessed socio-demographic factors, health indicators, and pre-existing conditions at T1, and collected COVID-19-related factors at both T1 and T2. The included variables are as follows:

a) Socio-demographic factors, including age, sex, sexual orientation, residence area, highest education completed, and monthly income before tax.
b) Health indicators and pre-existing health conditions, including smoking status, BMI, history of psychiatric disorders, and chronic medical conditions.
c) COVID-19-related factors, including history of quarantine, history of COVID-19 testing and diagnosis, and history of being bedridden due to COVID-19.

We used the PHQ-9 (Kroenke et al., 2001), GAD-7 (Spitzer et al., 2006) and PHQ-15 (Kocalevent et al., 2013) to assess symptoms of depression, anxiety and somatoform disorders, respectively, at both T1 and T2. In addition, one single item from the validated Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the overall sleep quality during the pandemic (Buysse et al., 1989), with response options including 'very good', 'fairly good', 'fairly bad', and 'very bad'.

3.2.4.3 Statistical analyses

We first examined the demographic characteristics of the study population. Then the crude prevalence of perceived disruption in health service use was estimated. We fitted the modified Poisson regression models using geepack package in R (Højsgaard et al., 2006) to investigate associations between socio-demographic factors, health indicators and conditions, and perceived disruption in health service use. To account for the intra-individual correlation across repeated measures, we incorporated a classical sandwich estimator with an exchangeable working correlation structure into the model (Hu et al., 1998; Zou & Donner, 2013).

In all models, we adjusted for the response month. We additionally adjusted for socio-demographic factors when exploring the association between health indicators and pre-existing health conditions and perceived disruption in health service use. We further introduced a product term into the model to assess the interaction between socio-demographic factors and pre-existing health conditions. Moreover, for individuals with two repeated measures on health service use status, we performed generalized linear regression models to examine the association between the duration of perceived health service disruption and changes in mental health symptoms between T1 and T2.

Missing data for socio-demographic factors and health indicators and conditions were handled using predictive mean matching multiple imputation (m=20) (Mazza et al., 2015; Van Buuren, 2018). Similarly, we performed imputation for individuals who had less than 25% of items missing for each symptom measure.

3.3 Ethical considerations

Data for the UK Biobank were collected following written informed consent from each participant, with ethical approval granted by the NHS National Research Ethics Service (REC reference: 16/NW/0274). Additionally, Study I used the UK Biobank resource under application 76517 and was approved by the Swedish Ethical Review Authority (DNR: 2022-01516-01). Study II was conducted under application 54803 and was authorized by the Biomedical Research Ethics Committee of West China Hospital (No. 2020.661). The computations and data handling were partly enabled by resources provided by the National Academic Infrastructure for Supercomputing in Sweden (NAISS) and the Swedish National Infrastructure for Computing (SNIC) at Uppsala Multidisciplinary Centre for Advanced Computational Science (UPPMAX).

The C-19 Resilience Cohort collected all data after obtaining electronic informed consent from each participant. The Studies III and IV was approved by the National Bioethics Committee (NBC 2020-073) and the Data Protection Authority in Iceland.

4 Results

4.1 Study I

Of 151,427 participants included in Study I, 56.5% were female, and the mean (standard deviation, SD) age was 67.7 (7.72) years at the start of the pandemic. Compared to those who did not experience childhood maltreatment, participants who did experience childhood maltreatment generally had lower levels of education and household income. Moreover, they were more likely to be younger, female, overweight, and to have pre-pandemic chronic medical conditions and psychiatric disorders.

As presented in **Table 3**, any childhood maltreatment was associated with 54% increased odds of COVID-19 hospitalizations and deaths compared to individuals without childhood maltreatment in the basic model (odds ratio [OR]=1.54 [95%CI 1.31-1.81]). Although remaining statistically significant, the association between any childhood maltreatment and COVID-19 hospitalizations and deaths was attenuated when studied mediator clusters were included in the models (Model 2-5). Additionally, the analyses of five types of childhood maltreatment showed that physical neglect had the strongest association with COVID-19 hospitalizations and deaths (data not shown, please refer to Paper I, Figure 2).

A dose-response association was identified between the number of childhood maltreatment types and COVID-19 hospitalizations and deaths (Model 1: ORs 1.33-2.32; $p_{\text{for trend}} < 0.01$).

Table 3. Association between the history of childhood maltreatment and COVID-19 hospitalizations and deaths (OR and 95% CI)

	Case/N (%)	Model 1	Model 2	Model 3	Model 4	Model 5
Any childhood maltreatment						
No	**345/100986 (0.34)**	**Ref.**	**Ref.**	**Ref.**	**Ref.**	**Ref.**
Yes	**261/50441 (0.52)**	**1.54 (1.31-1.81)**	**1.42 (1.21-1.68)**	**1.33 (1.12-1.56)**	**1.28 (1.08-1.51)**	**1.26 (1.07-1.48)**
Number of childhood maltreatment types						
0	**345/100986 (0.34)**	**Ref.**	**Ref.**	**Ref.**	**Ref.**	**Ref.**
1	**141/30819 (0.46)**	**1.33 (1.09-1.62)**	**1.27 (1.04-1.54)**	**1.22 (1.00-1.48)**	**1.20 (0.98-1.46)**	**1.19 (0.97-1.44)**
2	**62/11586 (0.54)**	**1.62 (1.22-2.10)**	**1.47 (1.11-1.91)**	**1.34 (1.01-1.75)**	**1.29 (0.97-1.68)**	**1.27 (0.95-1.65)**

	Case/N (%)	Model 1	Model 2	Model 3	Model 4	Model 5
≥3	**58/8036 (0.72)**	**2.32 (1.73-3.05)**	**2.00 (1.49-2.63)**	**1.69 (1.26-2.24)**	**1.56 (1.16-2.06)**	**1.50 (1.11-1.98)**

Note, ref: reference. Model 1: adjusted for demographic factors; Model 2: M1+adjusted for socioeconomic status; Model 3: M2+adjusted for lifestyle factors; Model 4: M3+adjusted for pre-pandemic chronic medical conditions; Model 5: Model 4+adjusted for pre-pandemic psychiatric disorders. This table was adapted from Table 2 in Wang et al. BMC Medicine (2024).

Moreover, the mediation analysis indicated that the studied mediator clusters accounted for 50.9% of the association between childhood maltreatment and COVID-19 hospitalizations and deaths. Separately, 27.8% of the association was mediated through lifestyle factors, followed by 20.5% through socio-economic factors, 17.4% through pre-pandemic chronic medical conditions, and 16.6% through psychiatric disorders.

The stratification analysis suggested the associations between childhood maltreatment and COVID-19 hospitalizations and deaths were similar across individuals with low, intermediate, and high genetic risk for severe COVID-19 outcomes ($p_{\text{for difference}} > 0.05$; data not shown, please refer to Paper I, Figure 4).

In the secondary analysis (Table 4), any childhood maltreatment was associated with 21% increased odds of being unvaccinated for COVID-19 compared with those unexposed individuals (Model 1: 1.21 [1.13-1.29]), and the association remained statistically significant when additionally adjusted for potential mediator clusters (Models 2-5). In contrast, any childhood maltreatment was weekly associated with a COVID-19 diagnosis (Model 1: 1.06 [1.01-1.12]), and the association attenuated to null when additionally adjusted for potential mediator clusters.

Table 4. Association between history of childhood maltreatment and COVID-19 diagnosis and vaccination (OR and 95% CI)

	Case/N (%)	Model 1	Model 2	Model 3	Model 4	Model 5
Outcome: COVID-19 diagnosis						
Exposure: any childhood maltreatment						
No	5362/35050 (15.30)	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	2994/18028 (16.61)	1.06 (1.01-1.12)	1.02 (0.97-1.08)	1.01 (0.96-1.07)	1.02 (0.97-1.07)	1.02 (0.97-1.07)
Exposure: number of childhood maltreatment types						
0	5362/35050 (15.30)	Ref.	Ref.	Ref.	Ref.	Ref.
1	1735/10873 (15.96)	1.03 (0.97-1.10)	1.01 (0.95-1.07)	1.00 (0.94-1.06)	1.00 (0.94-1.07)	1.01 (0.95-1.07)
2	714/4209 (16.96)	1.08 (0.99-1.18)	1.04 (0.95-1.13)	1.02 (0.94-1.12)	1.03 (0.94-1.12)	1.03 (0.94-1.13)
≥3	545/2946 (18.50)	1.14 (1.03-1.26)	1.07 (0.97-1.18)	1.05 (0.94-1.16)	1.05 (0.95-1.17)	1.06 (0.96-1.18)
Outcome: being unvaccinated for COVID-19						
Exposure: any childhood maltreatment						
No	2544/71830 (3.54)	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1606/34921 (4.60)	1.21 (1.13-1.29)	1.18 (1.10-1.26)	1.21 (1.13-1.29)	1.22 (1.14-1.31)	1.23 (1.15-1.32)
Exposure: number of childhood maltreatment types						
0	2544/71830 (3.54)	Ref.	Ref.	Ref.	Ref.	Ref.
1	907/21539 (4.21)	1.16 (1.07-1.26)	1.14 (1.05-1.24)	1.16 (1.07-1.26)	1.16 (1.07-1.26)	1.17 (1.08-1.27)
2	381/7973 (4.78)	1.23 (1.10-1.38)	1.20 (1.06-1.34)	1.23 (1.10-1.38)	1.25 (1.11-1.41)	1.27 (1.13-1.42)
≥3	318/5409 (5.88)	1.38 (1.21-1.56)	1.30 (1.14-1.48)	1.36 (1.20-1.55)	1.40 (1.23-1.59)	1.43 (1.25-1.62)

Note: Ref, reference. Model 1: adjusted for demographic factors; Model 2: Model 1+adjusted for socioeconomic status; Model 3: Model 2+adjusted for lifestyle factors; Model 4: Model 3+adjusted for pre-pandemic chronic medical conditions; Model 5: Model 4+adjusted for pre-pandemic psychiatric disorders. This table was adapted from Table 2 and Table S9 in Wang et al. BMC Medicine (2024).

In the sensitivity analyses, we obtained largely comparable results when restricted our analysis to individuals with a COVID-19 diagnosis, or after separating hospitalization and death due to COVID-19 as individual outcomes (data not shown, please refer to Paper I, Additional file 2: Table S4 and Table S8).

4.2 Study II

Of the 308,400 participants included in the incident diagnoses cohort, 52.1% were female, and the mean (SD) age was 68.2 (8.1) years at the start of the pandemic. During the 18-month follow-up period, 4,439 individuals were newly diagnosed with anxiety or depression, with an incidence rate of 9.7 per 1,000 person-years. For participants who tested positive for COVID-19, the incidence rate of anxiety or depression during the pandemic was nearly two-fold higher compared to the pre-pandemic period (SIR = 2.03 [95%CI 1.76–2.34]). For those who tested negative for COVID-19, the incidence rate was nearly three-fold higher during the pandemic compared to the pre-pandemic period (3.05 [2.88–3.22]). Conversely, the incidence rate of anxiety or depression was nearly 30% lower during the pandemic for participants who were not tested for COVID-19 when compared to the pre-pandemic period (0.70 [0.67–0.72]).

In the analysis of period-specific newly diagnosed cases of anxiety and depression, we found the incidence rates sharply increased between March 2020 and September 2020 for those tested for COVID-19 (tested positive: SIRs 2.33–9.38, tested negative: SIRs 3.61–7.05; Figure 12) and then gradually declined in the following months, though remained elevated compared to the pre-pandemic period. In contrast, consistently lower incidence rates were observed among those who were not tested for COVID-19 throughout the entire 18-month follow-up.

In the analysis of new prescription for anxiolytics and antidepressants, we observed largely comparable risk patterns. Overall, compared to the pre-pandemic period, the incidence rate of anxiolytic or antidepressant prescriptions was 50% higher during the pandemic period among those who were tested for COVID-19 (tested positive: 1.41 [1.22-1.62]; tested negative: 1.56 [1.47-1.67]). While nearly 30% lower for participants who were not tested for COVID-19 (0.70 [0.68-0.72]) during the COVID-19 pandemic period.

The results remained robust even after restricting the analysis to participants without pre-existing severe somatic diseases and redefining the start of the pandemic period to May 18, 2020 (data not shown, please refer to Paper II, Supplementary Figures S5-8). Similar risk patterns were also observed when separate analysing anxiety and depression, as well as anxiolytics and antidepressants as individual outcomes (data not shown, please refer to Paper II, Supplementary Figures S3-4).

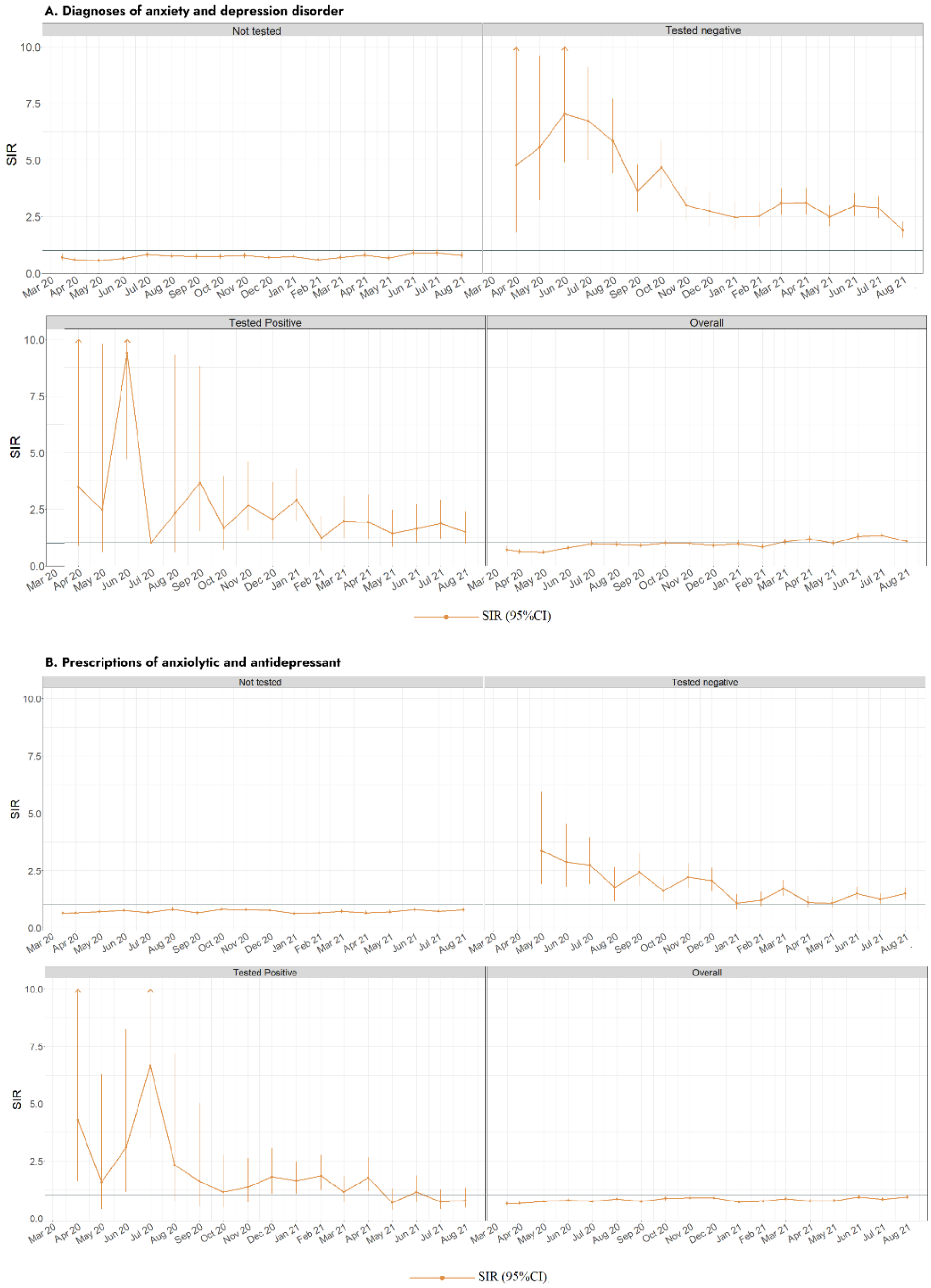


Figure 12. New diagnoses of anxiety and depression disorder (A) and new prescriptions of anxiolytic and antidepressant (B) during the COVID-19 pandemic

Note, this figure was adapted from Figure 2 and Figure 3 in Wang et al. Transl Psychiatry (2023).

4.3 Study III

Of the 6,423 participants included in Study III, 68.7% were female, with a mean (SD) age of 57.0 (13.0) years at baseline. By fitting models with data from three pandemic assessments, we identified four distinct trajectories of depressive symptoms. Most participants (83.7%) exhibited consistently low symptom burden, while others showed symptom burden at various stages of the pandemic, including 5·3% consistently high, 5·1% initially high but decreasing and 5·9% initially low but late-onset high symptom trajectories (Figure 13).

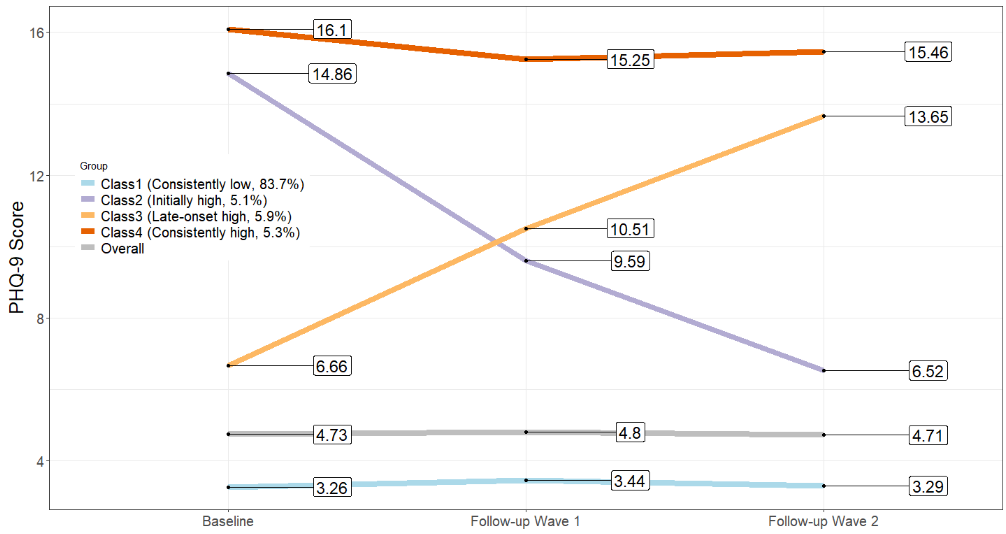


Figure 13. Four class-specific depressive symptom trajectories during the COVID-19 pandemic in Iceland

Note, this figure was adapted from Figure 2 in Wang et al. BMJ Public Health (2024).

As presented in Figure 14 and Appendix 2, individuals with a consistently low symptom trajectory were more likely to be men, older (aged ≥ 60 years), and frequent exercisers (≥ 3 days per week). By contrast, individuals with a consistently high symptom trajectory were more likely to have a history of psychiatric disorders, financial difficulties, and to be female and younger (aged < 40 years).

Compared to individuals in the consistently low symptom trajectory group, those in the initially high but decreasing symptom trajectory group were more likely to have a history of psychiatric disorders, be female, single or widowed, and have tested negative for COVID-19. In contrast, individuals in the initially low but late-onset high symptom trajectory group were more likely to have pre-existing psychiatric disorders, childcare burden, and to be female or have tested negative for COVID-19.

Additionally, a decrease in social support during the pandemic was associated with the initially low but late-onset high symptom trajectory, whereas an increase in family and social support during the pandemic was associated with the initially high but decreasing symptom trajectory.

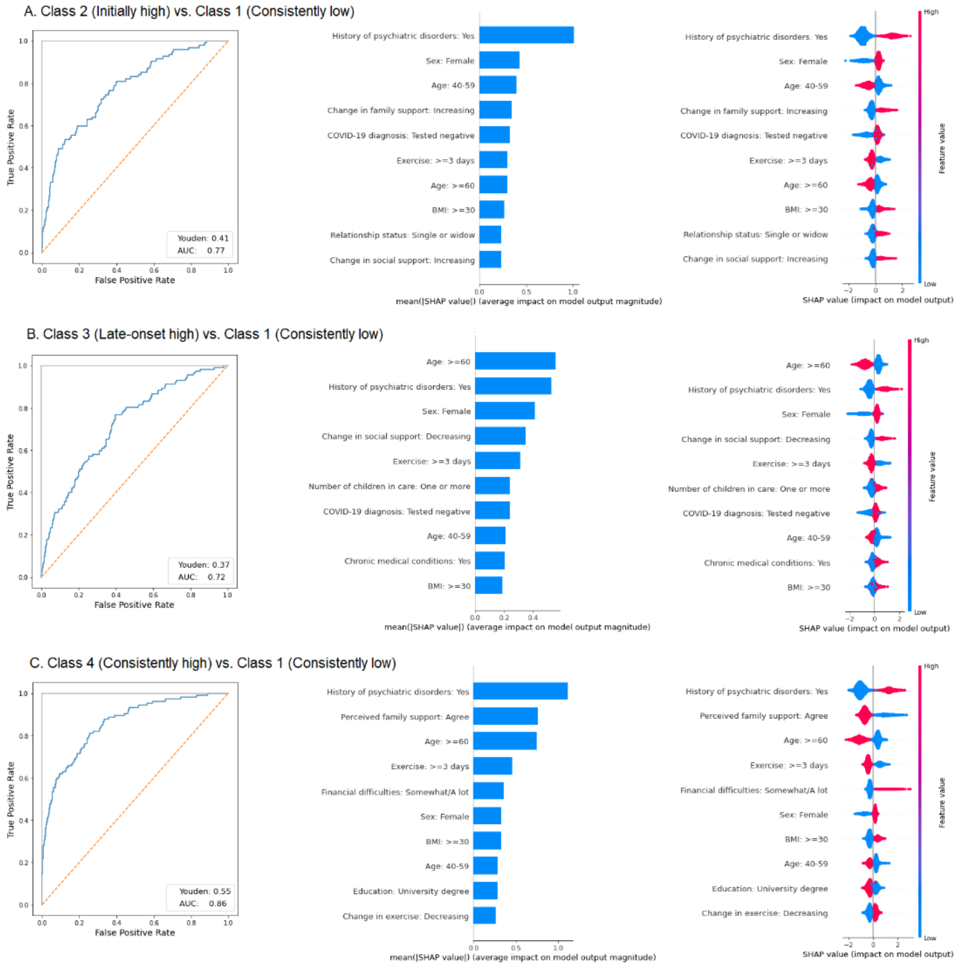


Figure 14. Model performance and 10 most important factors

Note, this figure was adapted from Figure 3 in Wang et al. BMJ Public Health (2024).

In the analysis of post-pandemic health outcomes, we found that symptom trajectories characterized by initially high, late-onset high, and consistently high levels during the pandemic were associated with greater depressive (βs 0.78 – 1.86), anxiety (βs 0.63 – 1.55), and somatic symptoms (βs 0.56 – 1.23), as well as cognitive problems (βs 0.64 – 1.37) in the post-pandemic period (data not shown, please refer to Paper III, Figure 4).

4.4 Study IV

Of the 15,754 participants included in Study IV, 68.7% were female, and the mean (SD) age was 54.8 (13.9) years. The crude prevalence of perceived disruption in health service use slightly decreased from 12.3 per 100 persons in December 2020 to 11.1 per 100 persons in July 2021 (p<0.01).

As presented in Table 5, those who were less likely to perceive disruption in health service use during the COVID-19 pandemic were individuals aged 60 years or older (vs. 18-39 years, prevalence ratios [PR]=0.58 [95%CI 0.53-0.64]), those with a Master's or PhD degree (vs. primary school education, 0.70 [0.62-0.79]), and individuals with a monthly income higher than €6,574 (vs. €1,972 or less, 0.45 [0.38-0.53]). By contrast, females (vs. males, 1.26 [1.16-1.37]) and sexual minorities (vs. heterosexuals, 1.52 [1.31-1.77]) were more likely to report perceived disruption in health service use during the COVID–19 pandemic.

Moreover, individuals residing in non-capital region—particularly in the Southern Peninsula and the Westfjords—had a higher prevalence of perceived disruption in health service use during the COVID-19 pandemic (10.8 - 17.1 per 100 persons) when compared to those in the capital region (9.9 per 100 persons).

In the analysis of health indicators and pre-existing conditions, those with a history of psychiatric disorders (1.59 [1.48—1.72]), who were overweight (1.48 [1.34—1.62]), and had a chronic medical condition (1.40 [1.30—1.52]) were at an increased risk of perceiving disruption in health service use compared to those without these health conditions. However, no increased risk was observed among individuals diagnosed with COVID-19 (0.99 [0.84—1.18]) when compared to those not tested individuals.

Table 5. The association between socio-demographic factors, health indicators and pre-existing conditions, and perceived disruption in health service use

	Prevalence per 100 persons (95% CI)	Prevalence ratios (95% CI)
Socio-demographic factors [a]		
Age, years		
18-39	15.6 (14.4 - 16.9)	Ref.
40-59	11.5 (10.8 - 12.1)	0.74 (0.67 - 0.81)
≥60	9.0 (8.4 - 9.6)	0.58 (0.53 - 0.64)
Sex		
Male	9.3 (8.7 - 10.1)	Ref.
Female	11.8 (11.2 - 12.3)	1.26 (1.16 - 1.37)
Sexual orientation		
Heterosexual	10.8 (10.4 - 11.3)	Ref.
Sexual minority	16.5 (14.2 - 19.1)	1.52 (1.31 - 1.77)
Residential area		
Capital region	9.9 (9.4 - 10.4)	Ref.
Non-capital region	13.4 (12.6 - 14.3)	1.35 (1.25 - 1.45)

	Prevalence per 100 persons (95% CI)	Prevalence ratios (95% CI)
Western Region	11.7 (9.8 - 13.9)	1.17 (0.98 - 1.40)
Westfjords	16.8 (13.5 - 20.6)	1.68 (1.36 - 2.09)
Northwestern Region	13.5 (12.2 - 14.9)	1.36 (1.22 - 1.51)
Eastern Region	14.2 (11.6 - 17.2)	1.42 (1.16 - 1.74)
Southern Region	10.8 (9.4 - 12.3)	1.08 (0.94 - 1.25)
Southern Peninsula	17.1 (15.0 - 19.5)	1.72 (1.50 - 1.97)
Highest education completed		
Primary school	13.1 (11.9 - 14.4)	Ref.
High school	12.3 (11.5 - 13.1)	0.94 (0.84 - 1.04)
BA/BS degree	10.3 (9.6 - 11.0)	0.79 (0.70 - 0.88)
Master's or PhD degree	9.2 (8.4 - 10.0)	0.70 (0.62 - 0.79)
Monthly income before tax, EUR		
€1,972 or less	16.5 (15.4 - 17.7)	Ref.
€1,973-3,287	12.2 (11.4 - 13.0)	0.74 (0.67 - 0.81)
€3,288-4,601 thousand	9.5 (8.7 - 10.3)	0.58 (0.52 - 0.64)
€4,602-6,574 thousand	8.0 (7.2 - 8.9)	0.48 (0.43 - 0.55)
More than €6,574	7.3 (6.3 - 8.5)	0.45 (0.38 - 0.53)
Health indicators and pre-existing health conditions [b]		
Smoking status		
Never	11.4 (10.4 - 12.6)	Ref.
Current/Previous	13.5 (12.3 - 14.8)	1.18 (1.09 - 1.27)
Body mass index, kg/m^2		
<25	10.4 (9.3 - 11.6)	Ref.
25-30	11.6 (10.4 - 12.8)	1.11 (1.01 - 1.23)
>30	15.4 (14.0 - 16.9)	1.48 (1.34 - 1.62)
History of psychiatric disorders		
No	10.3 (9.4 - 11.4)	Ref.
Yes	16.5 (15.0 - 18.1)	1.59 (1.48 - 1.72)
Chronic medical conditions (somatic only)		
No	10.9 (9.9 - 12.0)	Ref.
Yes	15.3 (13.9 - 16.8)	1.40 (1.30 - 1.52)
History of quarantine		
No	11.4 (10.4 - 12.6)	Ref.
Yes	14.2 (12.9 - 15.6)	1.25 (1.16 - 1.34)
History of COVID-19 testing and diagnosis		
Not tested	11.6 (10.5 - 12.9)	Ref.
Tested but not diagnosed	13.4 (12.2 - 14.7)	1.15 (1.07 - 1.25)
Diagnosed with COVID-19	11.5 (9.7 - 13.7)	0.99 (0.84 - 1.18)
History of being bedridden due to COVID-19		
No	12.6 (11.5 - 13.7)	Ref.
Yes	13.6 (11.2 - 16.4)	1.08 (0.90 - 1.29)

Note, Ref, reference. a. Model was adjusted for responding month; b. Model was adjusted for age, sex, sexual orientation, residential area, highest education completed, monthly income before tax and month response received. This table was adapted from Table 1 in Wang et al. European Journal of Public Health (2024).

Additionally, a significant interaction was found between age, monthly income, and history of psychiatric disorders or chronic medical conditions (p for interaction<0.05). Individuals with preexisting health conditions—particularly those who were female, younger, and had lower incomes—were at a higher risk of perceiving health service disruption during the COVID-19 pandemic (data not shown, please refer to Paper IV, Figure 2).

Furthermore, as presented in Figure 15, perceived disruption in health service use at T2 only was associated with an increase in depressive symptoms (β=0.68 [95%CI 0.27-1.08]), anxiety (0.58 [0.22-0.94]), sleep symptoms (0.06 [-0.01-0.13]) and somatic symptoms (0.41 [0.01-0.82]) between T1 and T2.

Timing and duration of perceived disruption	Changes in mental health symptoms (T2-T1), mean(SD)	ß (95%CI)
	Depression	
Neither T1 nor T2	-0.10 (3.03)	Ref.
T1 only	-0.33 (4.23)	-0.14 (-0.54 - 0.26)
T2 only	0.52 (3.73)	0.71 (0.28 - 1.15)
Both T1 and T2	-0.46 (4.15)	-0.32 (-0.74 - 0.10)
	Anxiety	
Neither T1 nor T2	-0.17 (2.77)	Ref.
T1 only	-0.32 (3.84)	-0.14 (-0.52 - 0.24)
T2 only	0.28 (3.35)	0.54 (0.16 - 0.93)
Both T1 and T2	-0.36 (3.91)	-0.21 (-0.61 - 0.20)
	Sleep quality	
Neither T1 nor T2	-0.01 (0.64)	Ref.
T1 only	-0.09 (0.68)	-0.07 (-0.14 - -0.01)
T2 only	0.03 (0.66)	0.07 (-0.01 - 0.14)
Both T1 and T2	-0.03 (0.73)	0.00 (-0.07 - 0.08)
	Somatic symptoms	
Neither T1 nor T2	0.52 (3.38)	Ref.
T1 only	0.11 (3.75)	-0.36 (-0.77 - 0.04)
T2 only	0.86 (3.73)	0.28 (-0.20 - 0.77)
Both T1 and T2	-0.09 (4.07)	-0.45 (-0.91 - 0.01)

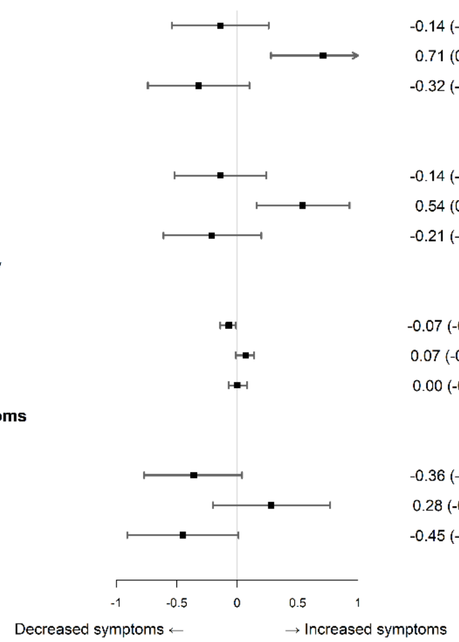


Figure 15. The association between the duration of perceived disruption in health service use and changes in mental health symptoms between T1 and T2.

Note, linear regression model was adjusted for age, sex, sexual orientation, residence area, highest education completed, monthly income before tax, smoking status, body mass index, history of psychiatric disorders, chronic medical conditions (somatic only), history of quarantine, history of COVID-19 testing and diagnosis, and history of bedridden due to COVID-19. This figure was adapted from Figure 3 in Wang et al. European Journal of Public Health (2024).

5 Discussion

5.1 Main findings

Our studies, leveraging longitudinal data from the UK Biobank and the C-19 Resilience Cohort, demonstrate the significant long-term effects of the COVID-19 pandemic on population mental health and health service use. By further analysing these datasets, we also identified key factors associated with COVID-19 severity, mental health outcomes and access to health services during the pandemic.

Specifically, in Study I, we provide robust evidence showing that exposure to childhood maltreatment is associated with increased odds of COVID-19 hospitalizations and deaths. Potential mediating pathways, including socioeconomic status, lifestyle factors, and preexisting physical and psychiatric comorbidities, were identified. While a weak association was observed for COVID-19 diagnosis, our secondary analysis further suggest that individuals exposed to childhood maltreatment were more likely to be unvaccinated for COVID-19 compared to those unexposed.

In Studies II and III, we found a significant portion of the general population demonstrated resilience during the pandemic, showing consistently low levels of depressive symptoms, with exercise, social support, and family support identified as potential protective factors. However, we observed an increase in new diagnoses of anxiety and depression, as well as prescriptions for psychotropic medications, among individuals tested for COVID-19 during the pandemic in the UK, regardless of the test result, particularly between March and September 2020. Additionally, our results found that females, younger adults, and individuals with a history of psychiatric disorders were less likely to follow consistently low levels of depressive symptoms during the pandemic in Iceland.

In Studies II and IV, we found reduced healthcare utilisation for psychiatric disorders in the UK, particularly among individuals not tested for COVID-19, along with long-term disruption in health service use during the pandemic in Iceland. While individuals diagnosed with COVID-19 did not report a notable increase in perceived health service disruptions in Iceland, those with preexisting health conditions—especially for females, young adults, and individuals with lower income—were more likely to perceive greater disruption. Furthermore, findings from Study IV indicated that emerging perceived disruption in health service use was associated with a rise in mental health symptoms during the pandemic.

5.1.1 Childhood maltreatment and COVID-19 (Study I)

Consistent with previous studies (Hanson et al., 2023; Srivastav et al., 2021), we found that a history of childhood maltreatment—including sexual, physical, and emotional abuse, as well as neglect—is associated with increased risk of COVID-19 hospitalizations and deaths. While physical neglect—defined as the lack of necessary medical care during childhood—had the strongest association with COVID-19 hospitalizations and deaths, our study expands on existing evidence by showing that each type and the number of maltreatment experiences were strongly linked to these severe outcomes.

Moreover, in line with previous research indicating that childhood maltreatment can increase the risk of health issues in adulthood through various mechanisms (Kendall-Tackett, 2002), our results suggest that nearly half of the association between a history of childhood maltreatment and severe COVID-19 outcomes can be attributed to poor socioeconomic status, unhealthy lifestyles, and pre-existing psychiatric or physical comorbidities. For example, individuals exposed to childhood maltreatment were more likely to have lower education or be unemployed in adulthood (Jaffee et al., 2018), and a population-based cohort study in Sweden further found that socio-economic risk factors, such as lower education and personal income, were associated with increased risk of death from COVID-19 (Drefahl et al., 2020). Additionally, childhood maltreatment has been related to numerous health conditions, including obesity, psychiatric disorders, diabetes, and cardiovascular disease (Bellis et al., 2019; Hughes et al., 2017), and all of which have been identified as risk factors for COVID-19-related hospitalization and in-hospital death (J. Y. Ko et al., 2021; Semenzato et al., 2021). Notably, among the four mediator clusters examined, lifestyle-related factors appeared to have the greatest impact, with 27.8% of the association mediated through these factors. However, there is a well-established link between socioeconomic status, lifestyle factors, and both psychological and physical conditions (Bahrami et al., 2020; Said et al., 2018; Stalling et al., 2022). For instance, a genome-wide association study has identified extensive polygenic overlap and shared genetic loci between BMI and major psychiatric disorders (Bahrami et al., 2020). Consequently, the proportions mediated by each cluster, as indicated by the causal mediation analysis, are likely confounded by the presence of the other mediating clusters and the findings should be interpreted with caution.

We also observed that individuals exposed to childhood maltreatment were more likely to be unvaccinated for COVID-19 compared to those who were unexposed. In line with our findings, Moffitt et al. used prospective data from a five-decade cohort study, suggesting that vaccine-hesitant and vaccine-resistant individuals were more likely to have experienced extreme adverse childhood experiences (Moffitt et al., 2022). Although the mechanisms behind this finding remain unclear, these adverse childhood experiences may lead to neglect of healthcare or mistrust of the healthcare system, potentially increasing the risk of negative health outcomes (Bellis et al., 2022; Hornor, 2014; Moffitt et al., 2022; Rokach & Clayton, 2023).

5.1.2 Mental health during the COVID-19 pandemic (Studies II and III)

Consistent with previous findings (Pierce et al., 2021; Saunders et al., 2021), our results indicated that most of the general population reported consistently low depressive symptoms during the COVID-19 pandemic. However, compared to findings of Hemi et al. in the Israeli population (Hemi et al., 2023), our results of the Icelandic population (Study III) revealed a more complex and variable pattern of mental health during the pandemic, including two groups with consistent symptomatology and two groups showing initially high or late-onset high depressive symptoms. In contrast to Pierce et al. findings in the UK population (Pierce et al., 2021), our study revealed that a larger proportion of the general population in Iceland maintained consistently low depressive symptom trajectories throughout the COVID-19 pandemic. Differences in assessment points, follow-up duration, and governmental pandemic policies may account for these discrepancies. For example, the COVID-19 stringency index—which reflects measures such as school and workplace closures, restrictions on public gatherings, and travel controls—was consistently lower in Iceland compared to the UK (Hale et al., 2021). Also, the significantly longer follow-up period in our study provides a better representation of long-term adaptation trajectory to the pandemic, rather than just capturing the acute responses during the early stages.

Furthermore, the results of Study II revealed that the impact of the pandemic on population mental health varied across time and the level of pandemic exposure. Despite a low overall incidence rate in the study population, we observed an increase in new diagnoses of anxiety and depression, as well as in prescriptions for anxiolytics and antidepressants among individuals tested for COVID-19 during the pandemic when compared to pre-pandemic years. While the most significant increase occurred at the beginning of the pandemic, elevated incidence rates persisted throughout nearly the entire 18-month follow-up (i.e., from March 2020 to August 2021). It is highly likely that individuals who were tested might have been exposed to the virus. The stress of waiting for the test results, combined with fears of a positive outcome, could have contributed to the increased psychological distress among the tested population (Li et al., 2021). Specifically, for those who tested negative, the possibility of having another similar infection, such as influenza, may be associated with increased psychological distress. In fact, previous studies have noted that patients with influenza may experience similar or even greater levels of psychiatric morbidity during the pandemic as SARS-CoV-2-positive individuals (Abel et al., 2021).

Our Study III further indicated that the COVID-19 pandemic disproportionately impacted vulnerable groups, including females, younger adults, and individuals with pre-existing psychiatric disorders. These subgroups were less likely to maintain consistently low levels of depressive symptoms during the pandemic. Several factors may explain this disproportionate impact on mental health. Indeed, there have been widespread reports of increased violence against women (Roesch et al., 2020), along with a greater burden of childcare and household responsibilities for mothers (Sevilla & Smith, 2020) during the pandemic, both of which likely contributed to the greater decline in women's mental health. For younger adults, the closure of schools and workplaces (Benzeval et al., 2020), increased feelings of loneliness (Lee et al., 2020), and economic uncertainties (Li et al., 2023) may have contributed to heightened psychological distress in this group. Additionally, individuals with preexisting psychiatric conditions appeared more vulnerable to pandemic-related stress (Sukut & Ayhan Balik, 2021), intolerance of uncertainty (Sukut & Ayhan Balik, 2021), and were at higher risk of COVID-19 infection, hospitalization, and mortality (Hassan et al., 2022). The combined burdens of psychological and physical health challenges in this population likely exacerbated their levels of psychological distress.

Importantly, we also identified several modifiable protective factors, including physical exercise, and high levels of family and social support, that may mitigate the impact of the pandemic on population mental health. Supporting our findings, a recent review indicated that engaging in physical exercise may have alleviated anxiety, sadness, and depression during the COVID-19 pandemic (Ai et al., 2021). Indeed, evidence has shown that physical exercise could reduce levels of stress hormones such as cortisol and improve sleep quality (De Nys et al., 2022), which can, in turn, enhance mental health and reduce symptoms of depression. Additionally, physical exercise could also provide opportunities for social interaction, and research by Choi et al. found that higher levels of social support, including emotional support and positive social interactions, were associated with a lower risk of depression during the pandemic (Choi et al., 2022). In line with our findings, Li et al. also found perceived support from family members was associated with positive attitudes toward social distancing and psychological well-being during the COVID-19 pandemic (Li & Xu, 2022).

5.1.3 Health service use during the pandemic (Studies II and IV)

In Study II, we observed a decrease in new psychiatric diagnoses and prescriptions in the general UK population during the COVID-19 pandemic. This decline may reflect reduced psychiatric service use among the general population during this unprecedented period. Consistent with our findings, other studies have reported reduced psychiatric emergency consultations (Balestrieri et al., 2021) and psychiatric hospital admission in other European countries (Bonello et al., 2021). In Study IV, we also found that nearly 11-12% of participants in Iceland perceived disruption in health service use during the pandemic. It is likely that some health systems prioritized COVID-19 response efforts, leading to the postponement or cancellation of other essential health services (Webb et al., 2022). Importantly, our study indicated that individuals diagnosed with COVID-19 did not report a significant increase in perceived health service disruptions, whereas those who tested negative or had preexisting health conditions were more likely to perceive such disruptions.

Moreover, we found that psychiatric patients who were older (60 years and above), female, or had lower monthly incomes were more likely to perceive disruption in health service use during the COVID-19 pandemic. Notably, several studies have indicated that these vulnerable groups faced significant health inequalities and limited access to healthcare even before the pandemic (Fiscella et al., 2000), and the pandemic might have further exacerbated these challenges (Blundell et al., 2020; Spivak et al., 2018).

Lastly, it is noteworthy that the observed reduced incident diagnoses of depression and anxiety in Study II were primarily attributable to individuals who were not tested for COVID-19. Therefore, the observed declines may not reflect reduced use of health services but could suggest a lower prevalence of psychiatric conditions in the population. Indeed, studies have suggested that the pandemic led to changes in lifestyle, such as increased time spent with family and a slower daily pace (Kowalski et al., 2022), which could have contributed to the lower prevalence of psychiatric conditions. Taken together, these findings highlight the complex and multifaceted impact of the pandemic on population mental health and health service use.

5.2 Strengths and limitations

5.2.1 Strengths

The major strength of these studies is the use of timely updated UK Biobank and C-19 Resilience Cohort data, which enabled us to investigate the long-term trends of psychiatric morbidity among the general population. Also, leveraging the wealth of information collected (e.g., socio-demographic factors and pre-pandemic and current health conditions), we were able to identify potential mechanisms underlying the association between childhood maltreatment and COVID-19 hospitalizations and deaths (Study I), and further provided an in-depth analysis of the groups most likely to be affected by the COVID-19 pandemic (Studies III and IV).

A particular advantage in Study I is that the data on history of childhood maltreatment was collected prior to the pandemic, which minimizes the risk of reverse causality. In Study II, we applied a time series analysis, which enabled us to control potential confounders that remain constant over time. The use of validated symptom assessments for mental morbidities in Studies III and IV, along with national registry data on psychiatric diagnoses and COVID-19-related information in Studies I and II, enhanced the reliability of our findings.

5.2.2 Limitations

These studies also have limitations. First, most of the data was collected through retrospective and concurrent self-reports, which may introduce recall and information biases. For example, in Study I, participants recalled their history of childhood maltreatment in middle or older age. Notably, a recent meta-analysis revealing that, on average, 52% of individuals with documented prospective evidence of maltreatment did not report it retrospectively, while 56% of those who reported maltreatment retrospectively lacked corresponding prospective evidence (Baldwin et al., 2019). This discrepancy may be explained by the fact that prospective reports, often based on health records, tend to capture only the most severe cases, whereas retrospective studies may detect a broader range of cases, including milder instances. In addition, memory biases can also contribute to this inconsistency, leading to either underreporting and overreporting of actual experiences (Baldwin et al., 2019). Furthermore, in Studies III and IV, the mental health assessments were based on self-report questionnaires (e.g., PHQ-9, GAD-7, and PHQ-15) but not clinical diagnostic interviews which might lead to information bias. Similarly, in Study IV, perceived health service status was assessed using a single self-report question that was not validated. However, this measurement error is likely to be consistent across the groups and should not significantly affect the identification of vulnerable populations.

Second, the findings of Study II regarding the increased risk of psychiatric morbidity among tested for COVID-19 population may be subject to surveillance bias. Receiving COVID-19 tests may indicate a higher level of medical care use, which could increase the likelihood of being diagnosed with or prescribed medication for existing psychiatric symptoms. However, any potential influence of this factor should remain consistent throughout the study period, whereas the changes in new diagnoses and prescriptions for anxiety and depression were, in fact, variable over time. In addition, the findings of Study III about the association between tested negative for COVID-19 and greater depressive symptom burden during the COVID-19 pandemic may be explained by the fact that individuals vulnerable to or currently experiencing psychiatric disorders were more likely to undergo COVID-19 testing than those without (van der Meer et al., 2020). Therefore, the possibility of reverse causation cannot be ruled out.

Third, considering the disruption in health service use during the pandemic, the estimated new diagnoses of anxiety and depression, as well as prescriptions for anxiolytics and antidepressants in Study II, may be underestimated. Additionally, individuals with mental illnesses, such as depression, may reduce their utilization of services due to diminished motivation, further contributing to this underestimation. Moreover, the lack of pre-pandemic data in Study III limits our ability to clearly differentiate between depressive symptoms that predated the pandemic and those that emerged during it.

Finally, there is evidence of selection bias in the UK Biobank and C-19 Resilience Cohorts, which may limit the generalizability of our findings. Specifically, compared to the general population, UK Biobank participants were more likely to be older, female, and healthier, while C-19 Resilience participants were overrepresented by older individuals, females, those with higher levels of education, and residents of the capital region.

5.3 Implications and future directions

Understanding the factors that contribute to COVID-19 severity, poor depressive symptom trajectories, and healthcare accessibility during the pandemic is crucial for enhancing population well-being and refining response strategies. Expanding on existing evidence, our findings first emphasize the need for clinicians and public health officials to recognize childhood maltreatment as a potential risk factor for COVID-19 hospitalization and death, calling for increased clinical monitoring for individuals with a history of childhood maltreatment in future pandemics. Additionally, while most of the population maintained good mental health and demonstrated resilience, females, younger adults, and individuals with pre-existing psychiatric conditions faced a higher risk of poor mental health outcomes and experienced greater disruptions in health service use during the pandemic. It is important for the public to be aware of these vulnerable groups in future similar crises, and strategies targeting those most affected should be prioritized.

Moreover, by identifying potential mediating factors—such as smoking, overweight, mental illness, and other chronic medical conditions—our findings provide possible intervention strategies to mitigate the adverse effects of childhood maltreatment on severe COVID-19 outcomes. For example, promoting healthy behaviours—such as smoking cessation, weight management, and seeking medical care for both psychological and physical conditions—could be instrumental in reducing the adverse effects of childhood maltreatment (Segal & Amos, 2023). Meanwhile, addressing vaccine hesitancy or refusal among survivors of childhood maltreatment is crucial. Indeed, both our findings and those of others (Bellis et al., 2022; Moffitt et al., 2022) indicate a higher risk of unvaccinated COVID-19 among individuals who experienced childhood maltreatment. This underscores the need for more effective health education and pro-vaccination messaging tailored to this population. In addition, our study further found that physical activity, along with family and social support, plays a critical role in maintaining psychological well-being during the COVID-19 pandemic.

Moving forward, it is important to highlight that the association between history of childhood maltreatment and COVID-19 hospitalizations and deaths remained robust, even after adjusting for studied mediator clusters and genetic risk. Further research is warranted to investigate additional unmeasured pathways and to examine potential biological mechanisms underlying this relationship. For example, childhood maltreatment has been linked to immune system dysfunction (Chen et al., 2021; Schury & Kolassa, 2012), including disruption in immune cell activation (do Prado et al., 2017) and elevated levels of proinflammatory cytokine (Carpenter et al., 2010), potentially reducing the ability to recover from COVID-19. Furthermore, in line with previous findings, our results revealed that both individuals who tested positive for COVID-19 and those who were screened but not diagnosed faced an increased risk of psychiatric disorders and medication use during the COVID-19 period. As this risk persisted throughout the 18-

month study period, it underscores the need for further research to explore the underlying factors contributing to these mental health challenges.

Notably, in Iceland, a significant portion of the population maintained good mental health throughout the pandemic, and individuals with COVID-19 had adequate access to health services. Additionally, while 11-12% of participants reported experiencing disruption in health service use, this figure is relatively low compared to the disruptions reported in other countries (Ball et al., 2020; Moynihan et al., 2021; Ojetti et al., 2020; Zhang et al., 2020). These findings may suggest effective management of the pandemic and optimal healthcare access to infected individuals in Iceland during this unprecedented period, offering valuable lessons for other nations aiming to enhance their responses to similar public health crises. According to the Icelandic government, key factors contributing to this success may include large-scale testing, effective tracing efforts, quarantining, protection of the elderly population, and the provision of remote care in the early stages of the pandemic (Government of Iceland, 2020b). Moreover, indicating by the COVID-19 stringency index (Hale et al., 2021), Iceland has indeed implemented less stringent infection-control measures during the pandemic (Figure 16), which may have resulted in a reduced impact on the daily lives of the general population, thereby supporting overall well-being. It is also important to acknowledge that Iceland's small population and public welfare healthcare system may have contributed significantly to its effective pandemic response.

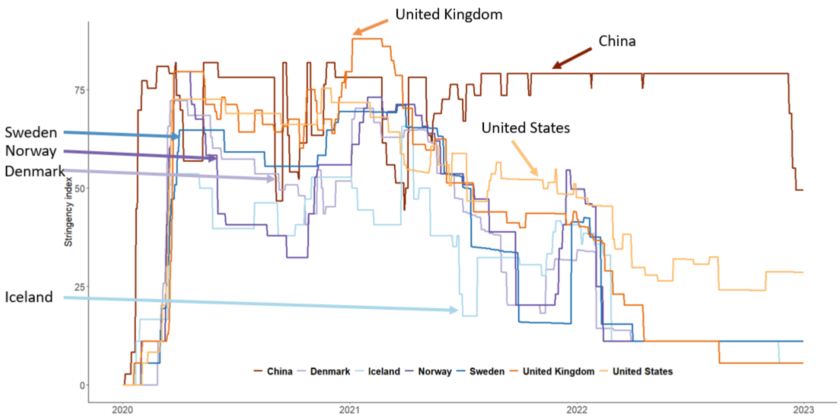


Figure 16. Variation in Government Responses to COVID-19: Stringency Index

Conversely, our findings highlight potential disruption in mental health service use during the pandemic in both Iceland and the UK, raising concerns about the worsening of symptoms in individuals with pre-existing psychiatric disorders and the emergence of new cases. To ensure more effective responses and support, health systems must be better prepared for future pandemics, particularly regarding mental health services. Notably, telehealth and digital health interventions show promise for treating mental health conditions in the context of the COVID-19 pandemic (Philippe et al., 2022) and could be recommended during similar times of crisis.

6 Conclusions

Our studies identify both resilience and vulnerability factors related to COVID-19 severity, population mental health, and access to health services during the pandemic. The findings presented in this thesis offer a comprehensive understanding of the associations between psychosocial factors and COVID-19 outcomes and provide valuable insights into the long-term effects of the pandemic on mental health and health service use (Figure 17).

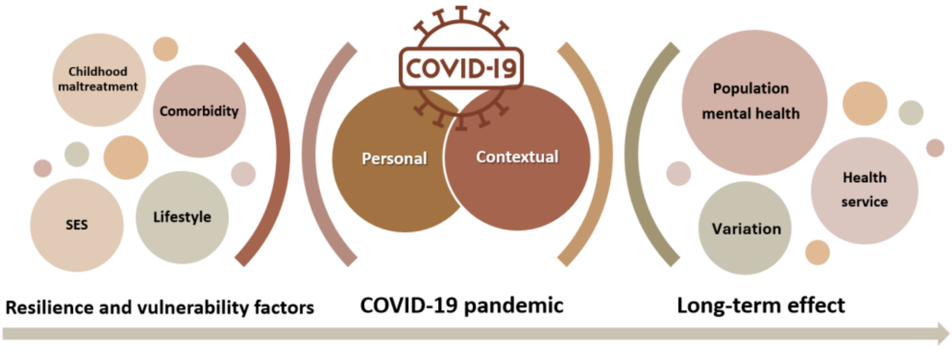


Figure 17. Main findings of the thesis

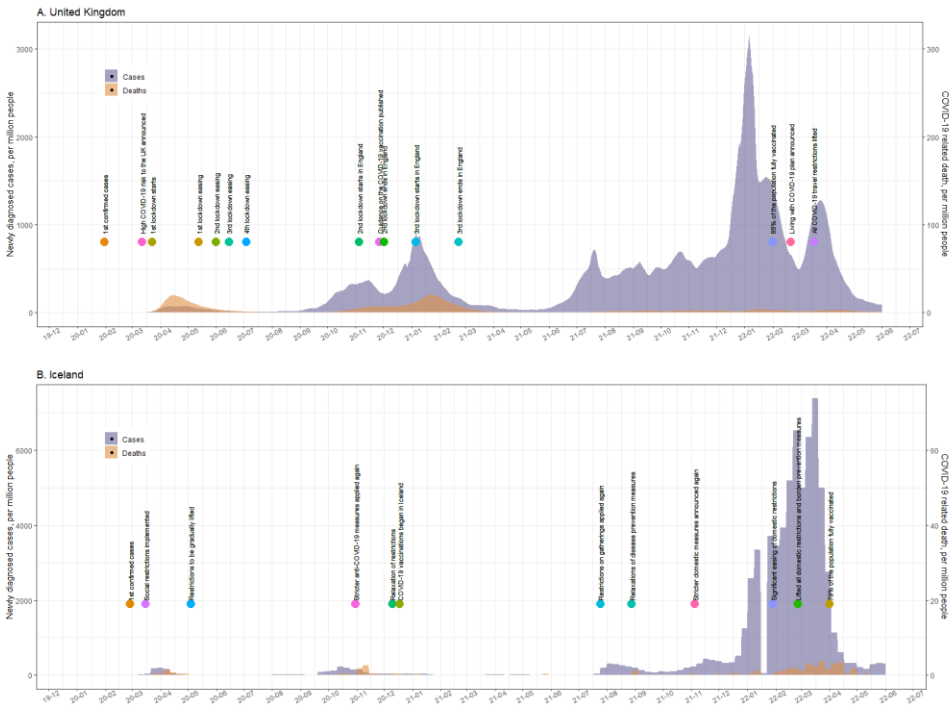
First, the results from Study I suggest that the number and types of childhood maltreatment are associated with COVID-19 hospitalizations and deaths, and the association was partially mediated by poor socioeconomic status (SES), lifestyle factors, and pre-existing health conditions. Our findings enhance the understanding of how childhood maltreatment contributes to long-term negative health outcomes and suggest that this risk factor should be considered in COVID-19 and future pandemics.

Second, the results from Study II and Study III suggest that the COVID-19 pandemic had a long-term, disproportionate impact on the mental health of certain subgroups within the general population. Although our findings indicate a lower incidence of anxiety and depression diagnoses, as well as consistently low depressive symptoms in most of the population during the pandemic, the results identified psychiatric vulnerabilities among females, younger adults, individuals with a history of psychiatric disorders, and those with confirmed or suspected COVID-19. Moreover, our findings revealed several protective factors—such as exercise, family support, and social support—that were linked to consistently low levels of depressive symptoms during the pandemic. Future interventions should prioritize the most vulnerable populations and focus on strengthening these protective factors to mitigate the negative mental health effects of future pandemics.

Third, the results from Study II and Study IV suggest a long-term reduction in healthcare utilization for psychiatric disorders, alongside disruption in health service use during the pandemic. Females and younger adults with preexisting psychiatric disorders were more likely to perceive these disruptions. Additionally, our findings indicate that emerging perceived disruption in health services use was associated with an increase in mental health symptoms. Therefore, addressing barriers to accessing health service, particularly mental health care, will be crucial for improving psychological well-being during future crises.

7 Appendix

Appendix 1. Newly Diagnosed COVID-19 Cases and Public Health Responses in the UK and Iceland.



Appendix 2. Characteristics of four distinct depressive symptom trajectories.

	Class 1 Consistently low (n=5376)	Class 2 Initial high (n=327)	Class 3 Late-onset high (n=379)	Class 4 Consistently high (n=341)	Overall (n=6423)
Age at baseline, years					
Mean (SD)	58.3 (12.6)	49.9 (13.8)	51.0 (12.9)	50.0 (13.2)	57.0 (13.0)
Median [Min, Max]	60.0 [18.0, 89.0]	51.0 [19.0, 84.0]	52.0 [18.0, 80.0]	51.0 [18.0, 81.0]	58.0 [18.0, 89.0]
Age group					
18-39	469 (8.7%)	87 (26.6%)	79 (20.8%)	76 (22.3%)	711 (11.1%)
40-59	2192 (40.8%)	148 (45.3%)	198 (52.2%)	177 (51.9%)	2715 (42.3%)
≥60	2715 (50.5%)	92 (28.1%)	102 (26.9%)	88 (25.8%)	2997 (46.7%)
Sex					
Male	1808 (33.6%)	65 (19.9%)	68 (17.9%)	57 (16.7%)	1998 (31.1%)
Female	3559 (66.2%)	262 (80.1%)	310 (81.8%)	283 (83.0%)	4414 (68.7%)
Unknown	9 (0.2%)	0 (0%)	1 (0.3%)	1 (0.3%)	11 (0.2%)
Sexual orientation					
Heterosexual	5196 (96.7%)	298 (91.1%)	348 (91.8%)	314 (92.1%)	6156 (95.8%)
Sexual minorities	156 (2.9%)	29 (8.9%)	30 (7.9%)	23 (6.7%)	238 (3.7%)
Unknown	24 (0.4%)	0 (0%)	1 (0.3%)	4 (1.2%)	29 (0.5%)
Residence area					
Not capital area	1666 (31.0%)	110 (33.6%)	136 (35.9%)	118 (34.6%)	2030 (31.6%)
In capitl area	3709 (69.0%)	217 (66.4%)	243 (64.1%)	222 (65.1%)	4391 (68.4%)
Unknown	1 (0.0%)	0 (0%)	0 (0%)	1 (0.3%)	2 (0.0%)
Relationship status					
Married or in a relationship	4103 (76.3%)	213 (65.1%)	278 (73.4%)	203 (59.5%)	4797 (74.7%)
Single or Widow	1260 (23.4%)	112 (34.3%)	98 (25.9%)	136 (39.9%)	1606 (25.0%)
Unknown	13 (0.2%)	2 (0.6%)	3 (0.8%)	2 (0.6%)	20 (0.3%)
Education					
Primary school	657 (12.2%)	49 (15.0%)	48 (12.7%)	76 (22.3%)	830 (12.9%)
High school	1607 (29.9%)	98 (30.0%)	110 (29.0%)	113 (33.1%)	1928 (30.0%)
University degree and above	3087 (57.4%)	178 (54.4%)	217 (57.3%)	147 (43.1%)	3629 (56.5%)
Unknown	25 (0.5%)	2 (0.6%)	4 (1.1%)	5 (1.5%)	36 (0.6%)
Number of children in need of care					
None	3778 (70.3%)	193 (59.0%)	213 (56.2%)	210 (61.6%)	4394 (68.4%)
One or more	1569 (29.2%)	134 (41.0%)	166 (43.8%)	131 (38.4%)	2000 (31.1%)
Unknown	29 (0.5%)	0 (0%)	0 (0%)	0 (0%)	29 (0.5%)
Exercise					
0-2 days	1370 (25.5%)	149 (45.6%)	148 (39.1%)	160 (46.9%)	1827 (28.4%)
≥3 days	3992 (74.3%)	176 (53.8%)	228 (60.2%)	175 (51.3%)	4571 (71.2%)
Unknown	14 (0.3%)	2 (0.6%)	3 (0.8%)	6 (1.8%)	25 (0.4%)
Change in exercise					
Decreasing	2508 (46.7%)	126 (38.5%)	194 (51.2%)	152 (44.6%)	2980 (46.4%)
Stable	1481 (27.5%)	91 (27.8%)	97 (25.6%)	91 (26.7%)	1760 (27.4%)
Increasing	1352 (25.1%)	108 (33.0%)	82 (21.6%)	90 (26.4%)	1632 (25.4%)
Unknown	35 (0.7%)	2 (0.6%)	6 (1.6%)	8 (2.3%)	51 (0.8%)
Smoking status					

Never	2483 (46.2%)	127 (38.8%)	166 (43.8%)	135 (39.6%)	2911 (45.3%)
Current/Previous	2863 (53.3%)	199 (60.9%)	211 (55.7%)	205 (60.1%)	3478 (54.1%)
Unknown	30 (0.6%)	1 (0.3%)	2 (0.5%)	1 (0.3%)	34 (0.5%)
Body Mass Index (kg/m²)					
≤25	1563 (29.1%)	76 (23.2%)	86 (22.7%)	67 (19.6%)	1792 (27.9%)
25-30	2147 (39.9%)	105 (32.1%)	126 (33.2%)	97 (28.4%)	2475 (38.5%)
≥30	1566 (29.1%)	139 (42.5%)	153 (40.4%)	168 (49.3%)	2026 (31.5%)
Unknown	100 (1.9%)	7 (2.1%)	14 (3.7%)	9 (2.6%)	130 (2.0%)
Chronic medical conditions					
No	2922 (54.4%)	193 (59.0%)	218 (57.5%)	167 (49.0%)	3500 (54.5%)
Yes	2428 (45.2%)	133 (40.7%)	160 (42.2%)	172 (50.4%)	2893 (45.0%)
Unknown	26 (0.5%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	30 (0.5%)
Mobility/hearing/visual impairment					
No	4837 (90.0%)	271 (82.9%)	331 (87.3%)	264 (77.4%)	5703 (88.8%)
Yes	487 (9.1%)	51 (15.6%)	42 (11.1%)	64 (18.8%)	644 (10.0%)
Unknown	52 (1.0%)	5 (1.5%)	6 (1.6%)	13 (3.8%)	76 (1.2%)
History of psychiatric disorders					
No	4241 (78.9%)	119 (36.4%)	181 (47.8%)	94 (27.6%)	4635 (72.2%)
Yes	1085 (20.2%)	205 (62.7%)	190 (50.1%)	239 (70.1%)	1719 (26.8%)
Unknown	50 (0.9%)	3 (0.9%)	8 (2.1%)	8 (2.3%)	69 (1.1%)
In-person contact					
Never	1168 (21.7%)	96 (29.4%)	109 (28.8%)	126 (37.0%)	1499 (23.3%)
Sometimes	1830 (34.0%)	121 (37.0%)	133 (35.1%)	116 (34.0%)	2200 (34.3%)
Often	2356 (43.8%)	108 (33.0%)	134 (35.4%)	95 (27.9%)	2693 (41.9%)
Unknown	22 (0.4%)	2 (0.6%)	3 (0.8%)	4 (1.2%)	31 (0.5%)
Change in in-person contact					
Decreasing	768 (14.3%)	48 (14.7%)	64 (16.9%)	53 (15.5%)	933 (14.5%)
Stable	2063 (38.4%)	134 (41.0%)	153 (40.4%)	145 (42.5%)	2495 (38.8%)
Increasing	2487 (46.3%)	137 (41.9%)	153 (40.4%)	132 (38.7%)	2909 (45.3%)
Unknown	58 (1.1%)	8 (2.4%)	9 (2.4%)	11 (3.2%)	86 (1.3%)
Virtual contact					
Never	81 (1.5%)	14 (4.3%)	8 (2.1%)	16 (4.7%)	119 (1.9%)
Sometimes	825 (15.3%)	70 (21.4%)	76 (20.1%)	87 (25.5%)	1058 (16.5%)
Often	4461 (83.0%)	242 (74.0%)	294 (77.6%)	236 (69.2%)	5233 (81.5%)
Unknown	9 (0.2%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	13 (0.2%)
Change in virtual contact					
Decreasing	1371 (25.5%)	71 (21.7%)	123 (32.5%)	99 (29.0%)	1664 (25.9%)
Stable	2935 (54.6%)	157 (48.0%)	189 (49.9%)	156 (45.7%)	3437 (53.5%)
Increasing	1029 (19.1%)	92 (28.1%)	60 (15.8%)	79 (23.2%)	1260 (19.6%)
Unknown	41 (0.8%)	7 (2.1%)	7 (1.8%)	7 (2.1%)	62 (1.0%)
Perceived family support					
Disagree	456 (8.5%)	65 (19.9%)	52 (13.7%)	96 (28.2%)	669 (10.4%)
Neutral	482 (9.0%)	73 (22.3%)	60 (15.8%)	87 (25.5%)	702 (10.9%)
Agree	4409 (82.0%)	184 (56.3%)	264 (69.7%)	154 (45.2%)	5011 (78.0%)
Unknown	29 (0.5%)	5 (1.5%)	3 (0.8%)	4 (1.2%)	41 (0.6%)

Change in family support					
Decreasing	1203 (22.4%)	62 (19.0%)	143 (37.7%)	103 (30.2%)	1511 (23.5%)
Stable	3016 (56.1%)	127 (38.8%)	159 (42.0%)	135 (39.6%)	3437 (53.5%)
Increasing	1070 (19.9%)	127 (38.8%)	66 (17.4%)	88 (25.8%)	1351 (21.0%)
Unknown	87 (1.6%)	11 (3.4%)	11 (2.9%)	15 (4.4%)	124 (1.9%)
Perceived social support (comfort; etc.)					
Disagree	442 (8.2%)	52 (15.9%)	49 (12.9%)	79 (23.2%)	622 (9.7%)
Neutral	454 (8.4%)	41 (12.5%)	43 (11.3%)	59 (17.3%)	597 (9.3%)
Agree	4440 (82.6%)	232 (70.9%)	284 (74.9%)	198 (58.1%)	5154 (80.2%)
Unknown	40 (0.7%)	2 (0.6%)	3 (0.8%)	5 (1.5%)	50 (0.8%)
Change in social support (comfort; etc.)					
Decreasing	1003 (18.7%)	55 (16.8%)	132 (34.8%)	84 (24.6%)	1274 (19.8%)
Stable	3265 (60.7%)	158 (48.3%)	161 (42.5%)	160 (46.9%)	3744 (58.3%)
Increasing	1003 (18.7%)	103 (31.5%)	75 (19.8%)	85 (24.9%)	1266 (19.7%)
Unknown	105 (2.0%)	11 (3.4%)	11 (2.9%)	12 (3.5%)	139 (2.2%)
Trust in Icelandic health authorities					
Little	33 (0.6%)	7 (2.1%)	9 (2.4%)	11 (3.2%)	60 (0.9%)
Somewhat	133 (2.5%)	18 (5.5%)	18 (4.7%)	31 (9.1%)	200 (3.1%)
A lot	5198 (96.7%)	300 (91.7%)	350 (92.3%)	298 (87.4%)	6146 (95.7%)
Unknown	12 (0.2%)	2 (0.6%)	2 (0.5%)	1 (0.3%)	17 (0.3%)
Change in trust					
Decreasing	2148 (40.0%)	141 (43.1%)	194 (51.2%)	155 (45.5%)	2638 (41.1%)
Stable	2938 (54.7%)	158 (48.3%)	156 (41.2%)	141 (41.3%)	3393 (52.8%)
Increasing	238 (4.4%)	18 (5.5%)	19 (5.0%)	36 (10.6%)	311 (4.8%)
Unknown	52 (1.0%)	10 (3.1%)	10 (2.6%)	9 (2.6%)	81 (1.3%)
Quarantine					
No	2454 (45.6%)	113 (34.6%)	161 (42.5%)	114 (33.4%)	2842 (44.2%)
Yes	2922 (54.4%)	214 (65.4%)	218 (57.5%)	227 (66.6%)	3581 (55.8%)
COVID-19 testing and diagnosis					
Not tested	1785 (33.2%)	67 (20.5%)	99 (26.1%)	90 (26.4%)	2041 (31.8%)
Tested Negative	3422 (63.7%)	248 (75.8%)	261 (68.9%)	238 (69.8%)	4169 (64.9%)
Tested Positive	169 (3.1%)	12 (3.7%)	19 (5.0%)	13 (3.8%)	213 (3.3%)
Bedridden due to COVID-19					
No	5245 (97.6%)	317 (96.9%)	361 (95.3%)	331 (97.1%)	6254 (97.4%)
Yes	131 (2.4%)	10 (3.1%)	18 (4.7%)	10 (2.9%)	169 (2.6%)
Family/friends diagnosed with COVID-19					
No	3567 (66.4%)	194 (59.3%)	241 (63.6%)	217 (63.6%)	4219 (65.7%)
Yes	1809 (33.6%)	133 (40.7%)	138 (36.4%)	124 (36.4%)	2204 (34.3%)
Family/friends admitted to a hospital					
No	5029 (93.5%)	297 (90.8%)	341 (90.0%)	304 (89.1%)	5971 (93.0%)
Yes	347 (6.5%)	30 (9.2%)	38 (10.0%)	37 (10.9%)	452 (7.0%)

Family/friends admitted ICU					
No	5223 (97.2%)	316 (96.6%)	365 (96.3%)	315 (92.4%)	6219 (96.8%)
Yes	153 (2.8%)	11 (3.4%)	14 (3.7%)	26 (7.6%)	204 (3.2%)
Vaccination status					
No	526 (9.8%)	52 (15.9%)	57 (15.0%)	47 (13.8%)	682 (10.6%)
Yes	4811 (89.5%)	269 (82.3%)	315 (83.1%)	289 (84.8%)	5684 (88.5%)
Unknown	39 (0.7%)	6 (1.8%)	7 (1.8%)	5 (1.5%)	57 (0.9%)
Financial difficulties					
Little	4983 (92.7%)	244 (74.6%)	316 (83.4%)	214 (62.8%)	5757 (89.6%)
Somewhat	243 (4.5%)	44 (13.5%)	40 (10.6%)	57 (16.7%)	384 (6.0%)
A lot	140 (2.6%)	37 (11.3%)	21 (5.5%)	65 (19.1%)	263 (4.1%)
Unknown	10 (0.2%)	2 (0.6%)	2 (0.5%)	5 (1.5%)	19 (0.3%)
Change in financial difficulties					
Decreasing	448 (8.3%)	64 (19.6%)	42 (11.1%)	71 (20.8%)	625 (9.7%)
Stable	4505 (83.8%)	199 (60.9%)	265 (69.9%)	178 (52.2%)	5147 (80.1%)
Increasing	377 (7.0%)	57 (17.4%)	65 (17.2%)	80 (23.5%)	579 (9.0%)
Unknown	46 (0.9%)	7 (2.1%)	7 (1.8%)	12 (3.5%)	72 (1.1%)
Difficulty obtaining necessities					
Little	5170 (96.2%)	294 (89.9%)	350 (92.3%)	270 (79.2%)	6084 (94.7%)
Somewhat	152 (2.8%)	18 (5.5%)	19 (5.0%)	37 (10.9%)	226 (3.5%)
A lot	47 (0.9%)	14 (4.3%)	9 (2.4%)	33 (9.7%)	103 (1.6%)
Unknown	7 (0.1%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	10 (0.2%)
Change in difficulty obtaining necessities					
Decreasing	501 (9.3%)	58 (17.7%)	67 (17.7%)	84 (24.6%)	710 (11.1%)
Stable	4560 (84.8%)	224 (68.5%)	261 (68.9%)	183 (53.7%)	5228 (81.4%)
Increasing	277 (5.2%)	39 (11.9%)	46 (12.1%)	69 (20.2%)	431 (6.7%)
Unknown	38 (0.7%)	6 (1.8%)	5 (1.3%)	5 (1.5%)	54 (0.8%)
Disruption of necessary services					
Little	5129 (95.4%)	291 (89.0%)	349 (92.1%)	281 (82.4%)	6050 (94.2%)
Somewhat	163 (3.0%)	21 (6.4%)	19 (5.0%)	23 (6.7%)	226 (3.5%)
A lot	72 (1.3%)	14 (4.3%)	8 (2.1%)	33 (9.7%)	127 (2.0%)
Unknown	12 (0.2%)	1 (0.3%)	3 (0.8%)	4 (1.2%)	20 (0.3%)
Change in disruption of necessary services					
Decreasing	372 (6.9%)	39 (11.9%)	35 (9.2%)	61 (17.9%)	507 (7.9%)
Stable	4765 (88.6%)	265 (81.0%)	319 (84.2%)	245 (71.8%)	5594 (87.1%)
Increasing	187 (3.5%)	14 (4.3%)	17 (4.5%)	24 (7.0%)	242 (3.8%)
Unknown	52 (1.0%)	9 (2.8%)	8 (2.1%)	11 (3.2%)	80 (1.2%)

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RESEARCH ARTICLE

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History of childhood maltreatment associated with hospitalization or death due to COVID-19: a cohort study

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Abstract

Background Childhood maltreatment (CM) has been indicated in adverse health outcomes across the lifespan, including severe infection-related outcomes. Yet, data are scarce on the potential role of CM in severe COVID-19-related outcomes as well as on mechanisms underlying this association.

Methods We included 151,427 individuals in the UK Biobank who responded to questions on the history of CM in 2016 and 2017 and were alive on January 31, 2020. Binomial logistic regression models were performed to estimate the association between a history of CM and severe COVID-19 outcomes (i.e. hospitalization or death due to COVID-19), as well as COVID-19 diagnosis and vaccination as secondary outcomes. We then explored the potential mediating roles of socio-economic status, lifestyle and pre-pandemic comorbidities, and the effect modification by polygenic risk score for severe COVID-19 outcomes.

Results The mean age of the study population at the start of the pandemic was 67.7 (SD = 7.72) years, and 56.5% were female. We found the number of CM types was associated with the risk of severe COVID-19 outcomes in a graded manner ($p_{\text{for trend}} < 0.01$). Compared to individuals with no history of CM, individuals exposed to any CM were more likely to be hospitalized or die due to COVID-19 (odds ratio [OR] = 1.54 [95%CI 1.31–1.81]), particularly after physical neglect (2.04 [1.57–2.62]). Largely comparable risk patterns were observed across groups of high vs. low genetic risks for severe COVID-19 outcomes ($p_{\text{for difference}} > 0.05$). Mediation analysis revealed that 50.9% of the association between CM and severe COVID-19 outcomes was explained by suboptimal socio-economic status, lifestyle, and pre-pandemic diagnosis of psychiatric disorders or other chronic medical conditions. In contrast, any CM exposure was only weakly associated with COVID-19 diagnosis (1.06 [1.01–1.12]) while significantly associated with not being vaccinated for COVID-19 (1.21 [1.13–1.29]).

Conclusions Our results add to the growing knowledge base indicating the role of childhood maltreatment in negative health outcomes across the lifespan, including severe COVID-19-related outcomes. The identified factors underlying this association represent potential intervention targets for mitigating the harmful effects of childhood maltreatment in COVID-19 and similar future pandemics.

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Keywords COVID-19, Hospitalization, Mortality, Childhood maltreatment, Psychiatric disorders

Background

COVID-19 has spread widely around the world and has now resulted in almost 7 million deaths and 100 million hospitalizations worldwide [1, 2]. Both death and hospitalization are commonly used indicators of the severity of COVID-19 illness [3, 4]. Accumulating evidence suggests that older age [5], male sex [5], non-White ethnicity [6], and genetic predisposition [7] are significant risk factors for severe COVID-19. In addition, psychosocial factors such as socio-economic status [8] and pre-pandemic history of psychiatric disorders [9] have been indicated in severe COVID-19 outcomes. While childhood maltreatment is one of the strongest risk factors for both low socioeconomic status [10] and psychiatric disorders in adulthood [11], less is known about its role in COVID-19-related outcomes.

Childhood maltreatment, such as sexual, physical and emotional abuse, or neglect, is common worldwide, affecting 42.2% of children and adolescents in Europe and 58.4% in North America [12]. Previous studies have demonstrated the role of childhood maltreatment in multiple adverse health outcomes across the lifespan, including psychiatric disorders, cardiovascular diseases, cancers, and some infectious diseases [13–17]. Childhood maltreatment might impact COVID-19-related morbidity and mortality outcomes through social, behavioural, emotional, and biological pathways [18, 19]. Indeed, individuals exposed to childhood maltreatment have been reported to have lower socio-economic status (educational attainment and income) in adulthood [10], more likely to have suboptimal health behaviours (e.g. smoking) [20] and immune function [21], and to be at higher risk of obesity [12], cardiovascular disease [22], psychiatric disorders [11], and other chronic diseases in adulthood [13], all of which are associated with severe COVID-19 outcomes [23].

While two previous studies have reported a suggestive link between the history of childhood maltreatment and severe COVID-19 outcomes [24, 25], no study has yet examined the role of specific childhood maltreatment types on severe COVID-19 outcomes nor attempted to disentangle potential underlying mechanisms of this association. Moreover, the role of genetic predisposition to COVID-19-related morbidity and mortality [26] in the association between childhood maltreatment and severe COVID-19-related outcomes remains unknown. Indeed, addressing these knowledge gaps is imperative for health policy and interventions targeting the reduction of potential maltreatment-related negative outcomes in COVID-19 and similar pandemics. Therefore, leveraging the large population-based UK Biobank cohort with pre-pandemic data on childhood maltreatment, we aimed to comprehensively explore the associations between the number and types of childhood maltreatment and severe COVID-19 outcomes, as well as elucidate the mechanisms underlying this association.

Methods

Study population and design

We used data from the UK Biobank cohort, which recruited more than 500,000 participants aged 40–69 years from England, Scotland, and Wales between 2006 and 2010. At baseline, participants answered questions on demographic, socio-economic, lifestyle, and health-related factors and provided biological samples for genetic studies [27]. Then, 339,092 participants who agreed to be contacted again were invited to complete online mental health questionnaires during 2016 and 2017, including a retrospective measure of childhood maltreatment. Of the invited participants, 46.4% ($n=157{,}366$) responded to this online measure. Despite those respondents being of higher average socio-economic status, the reported mental health problems are comparable to the population prevalence estimates for the corresponding age group [28].

Health-related outcomes (e.g. diagnosis, hospitalization, and death) for the participants were obtained periodically through linkage with multiple national datasets. Specifically, hospital inpatient data were obtained from Hospital Episode Statistics for England (from 1997 to September 30, 2021), the Scottish Morbidity Record for Scotland (from 1981 to July 31, 2021), and the Patient Episode Database for Wales (from 1998 to February 28, 2018). Mortality data were obtained from National Health Service (NHS) Digital for England as well as Wales (from 2006 to September 30, 2021) and NHS Central Register for Scotland (from 2006 to October 31, 2021). Records of COVID-19 test results (by RT-PCR of nose/throat swab samples) were obtained through linkage to Public Health England (i.e. PHE, from March 16, 2020, to September 30, 2021), Public Health Scotland (i.e. PHS, from March 16, 2020, to August 31, 2021), and the Secure Anonymised Information Linkage (SAIL) databank (from March 16, 2020, to August 31, 2021). Additionally, information on the COVID-19 vaccination status was collected for participants of the COVID-19 Self-Test Antibody study (from February 2021 to July 2021). Details of the COVID-19 Self-Test Antibody study are described elsewhere [29, 30].

In the present retrospective cohort study, we included 151,427 participants with information on childhood maltreatment who were alive on January 31, 2020 (i.e. first confirmed COVID-19 cases in the UK) in the analysis. When exploring the potential effect modification by genetic predisposition to severe COVID-19 outcomes, we restricted the analytic sample to only White-British participants considering the variations in genetic predisposition across populations with different ancestries [31, 32]. We excluded participants of non-White British ancestry (n = 14,079) or without eligible genotyping data (i.e. genotyping rate < 99%, abnormal heterozygosity level, or kinship coefficient > 0.0884, n = 19,555) [33], leaving 117,793 participants in this analysis. Additional file 1: Fig. S1 shows the details of the study profile.

History of childhood maltreatment

The history of childhood maltreatment was measured using the validated Childhood Trauma Screener (CTS) [34, 35]. It consists of five items assessing whether and how often individuals were exposed to the following types of maltreatment during childhood: sexual abuse, physical neglect, physical abuse, emotional neglect, and emotional abuse, with response options ranging from '0' (never true) to '4' (very often true). Weak correlations were observed among pairs of childhood maltreatment types (Additional file 1: Fig. S2). The questions and threshold values to define each type of childhood maltreatment are based on previous published studies [22, 36] and are shown in Additional file 2: Table S1. In our study, we generated three types of exposure variables: (1) a binary variable indicating any childhood maltreatment, coded as '0' (no) or '1' (yes); (2) a cumulative variable indicating the number of childhood maltreatment types (range from 0 to 5), which was coded as '0', '1', '2', or '≥ 3' childhood maltreatment types according to the distribution of the entire study sample (Additional file 1: Fig. S3); and (3) five binary variables for each type of childhood maltreatment, coded as '0' (no) or '1' (yes).

COVID-19 outcomes

The main outcome of interest was severe COVID-19 outcomes during the study period (i.e. from January 31, 2020, to October 31, 2021). Specifically, participants with a primary diagnosis (i.e. main condition treated or investigated) as COVID-19 (ICD-10, U07.1 or U07.2) in hospital inpatient data or with a cause of death recorded as COVID-19 in death registries were defined as having severe COVID-19 outcomes. A secondary outcome of interest was COVID-19 diagnosis (i.e. tested positive for COVID-19 vs. tested negative for COVID-19), which was determined through records of COVID-19 test results in the PHE, PHS, and SAIL databanks from March 16, 2020, to September 30, 2021. Another secondary outcome of interest was COVID-19 vaccination, based on responses to the question 'Have you received a first dose of a COVID-19 vaccine?'.

Genetic predisposition to severe COVID-19 outcomes

We assessed the genetic predisposition to severe COVID-19 outcomes by calculating the polygenic risk score (PRS) for COVID-19 hospitalization or death according to summary statistics (version 5) from the COVID-19 Host Genetics Initiative large-scale GWAS including critically ill COVID-19 patients (n = 4,792) and the control population (n = 1,054,664) among individuals with European ancestry after excluding UK Biobank and 23andMe participants [32]. We calculated the PRS using the clumping + thresholding approach [37] under 10 p-value thresholds (i.e. 5×10^{-8}, 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, 1×10^{-4}, 1×10^{-3}, 0.005, 0.01, 0.05, and 0.1) and validated the association between PRS and severe COVID-19 outcomes in our dataset by fitting logistic regression models adjusting for birth year, sex, genotyping array, and top ten ancestry principal components. We selected the PRS with the highest Nagelkerke R^2 for further analyses (i.e. p threshold = 5.00×10^{-8}; odds ratio = 1.21, 95% CI 1.11–1.32; Nagelkerke R^2 = 2.01%; Additional file 2: Table S2). To avoid inflated type I error from overfitting, we additionally performed a principal component (PC) analysis on the set of the 10 PRSs and used the first PRS-PC for sensitivity analyses [38]. In our dataset, the first PRS-PC for severe COVID-19 outcomes showed a strong association with the severe COVID-19 outcome phenotype (odds ratio = 1.22, 95% CI 1.11–1.33; Nagelkerke R^2 = 2.01%). More information about the PRS-PC analysis is shown in Additional file 1: Fig. S4.

Covariates

We considered birth year (< 1950, 1950–1959 or ≥ 1960), sex (female or male), ethnicity (White [British, Irish, and any other White background], non-White [mixed, Asian or Asian British, Black or Black British, Chinese, and others], or unknown) and recruitment region (Scotland, England, or Wales) as potential confounders due to previously reported associations to both primary exposure [39, 40] and outcome [5, 6, 41] (Fig. 1). Also, based on previous findings [10–13, 20, 23], we selected four variable clusters as potential mediators: (1) socioeconomic status (i.e. Townsend deprivation index [TDI, lower than median, higher than median, or unknown], annual household income [≤ £18,000, £18,000–£30,999, £31,000–£51,999, £52,000–£100,000, ≥ £100,000, or unknown], and college education [no, yes, or unknown]);

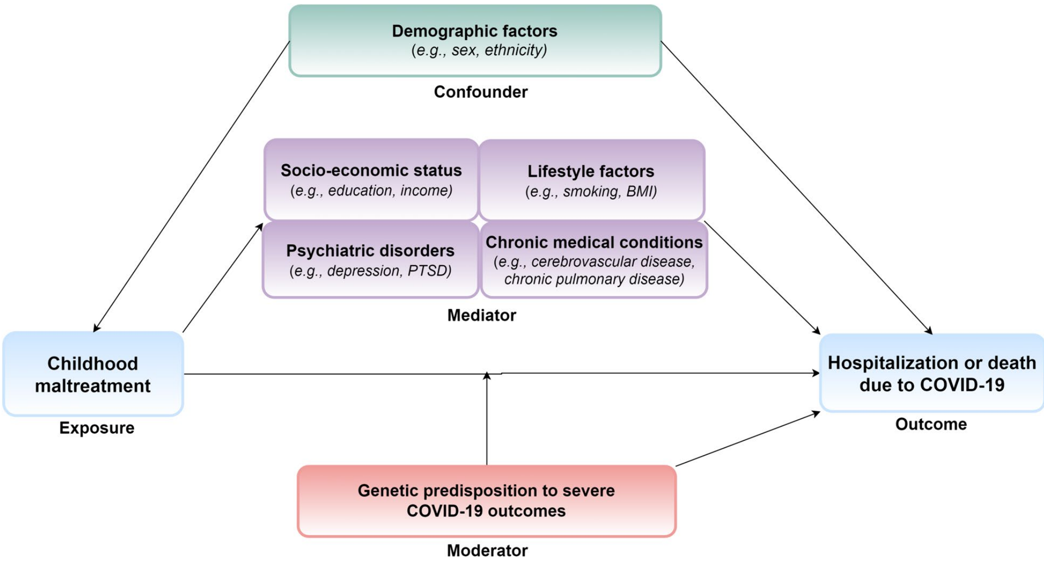

Fig. 1 Proposed causal model with alternative pathways of how childhood maltreatment could influence severe COVID-19 outcomes (i.e. hospitalization or death due to COVID-19), taking into account the availability of data

(2) lifestyle factors (i.e. smoking status [never, previous, current, or unknown] and body mass index [BMI, < 25 kg/m^2, 25–29.9 kg/m^2, ≥ 30 kg/m^2, or unknown]); (3) pre-pandemic chronic medical conditions (no or yes); and (4) pre-pandemic psychiatric disorders (no or yes).

Specifically, TDI was calculated based on the postcode of participants' address, representing the deprivation at a population level [42]. BMI was calculated using kilogrammes (kg) divided by the square of height in metres (m^2) using anthropometric data measured at the assessment centre at baseline. We calculated the Charlson Comorbidity Index (CCI) based on Deyo's coding algorithm [43] using hospital inpatient data (before January 31, 2020), and patients with a CCI ≥ 1 were considered to have pre-pandemic chronic medical conditions. Additional file 2: Table S3 provides more details about the diseases included in the calculation of the CCI. We defined pre-pandemic psychiatric disorders as any diagnosis of psychiatric disorders (ICD-10, F10–F99) in hospital inpatient data before January 31, 2020.

Statistical analysis

We first compared the characteristics of participants by the history of childhood maltreatment using ANOVAs for continuous data and chi-square tests for categorical data. We then performed binomial logistic regression to estimate the association between a history of childhood maltreatment and severe COVID-19 outcomes, as well as COVID-19 diagnosis and COVID-19 vaccination (i.e. secondary outcomes), with the estimates reported as odds ratios (ORs) and 95% confidence intervals (CIs). The basic model (model 1) was adjusted for demographic factors (i.e. birth year, sex, ethnicity, and recruitment region). In a stepwise approach, the four variable clusters of mediators were additionally adjusted to examine whether and to what extent the ORs between childhood maltreatment and severe COVID-19 outcomes were attenuated (models 2–5). We then conducted a regression-based causal mediation analysis using the CMAverse package in R [44–46] to estimate the proportion of mediation effect by the four variable clusters of mediators individually (M1–M4) and combined (M5). Specifically, the outcomes were regressed by the primary exposure variable (i.e. any childhood maltreatment), specific variable cluster of mediators, and demographic factors in a binomial logistic regression model. Each mediator was then regressed by exposure and demographic factors in either binomial (e.g. pre-pandemic psychiatric disorders) or multinomial (e.g. BMI) logistic regression models. The results of the outcome and mediator models were then combined to calculate the proportion of mediation.

To determine the association of specific types of childhood maltreatment with severe COVID-19 outcomes, we ran separate analyses for each of the five childhood maltreatment types. Furthermore, to examine the potential effect modification by genetic predisposition, we stratified our main analyses of the association between childhood maltreatment (both as a binary variable and a cumulative variable) and severe COVID-19 by tertile of the PRS or the first PRS-PC for severe COVID-19 outcomes (i.e. low, < 1st tertile; intermediate, 1st to 2nd tertile; high, > 2nd tertile). The differences between the groups were tested by introducing interaction terms (i.e. childhood maltreatment × PRS for severe COVID-19 outcomes) in the logistic regression adjusted for birth year, sex, ethnicity, and recruitment region. We then obtained *p*-values to indicate the statistical significance of the interaction terms through the Wald test.

In sensitivity analyses, we first restricted the analysis of the association between childhood maltreatment and severe COVID-19 outcomes to individuals with COVID-19 diagnosis—a population effectively at risk of severe COVID-19-related outcomes. Then, to address the potential impact of COVID-19 vaccination, which started on December 8, 2020, in the UK [47], we reran the main analysis by redefining the study period from January 31, 2020, to December 8, 2020 (i.e. before vaccination roll out). Additionally, given the difference in data coverage across registries (e.g. hospital inpatient data and death registries) and recruitment regions (i.e. England, Scotland, and Wales), we repeated the main analysis by excluding participants registered in Wales as well as by redefining the study period from January 31, 2020, to July 31, 2021. Moreover, instead of using cut-off scores for the measure of childhood maltreatment, we repeated our main analysis using the total CTS score (ranging from 0 to 20), to capture the full range of variability in the severity of childhood maltreatment. Finally, as our primary outcome was hospitalization or death due to COVID-19 as a combined indicator of severe COVID-19, we performed a sensitivity analysis for hospitalization and death due to COVID-19, separately, to determine if there were any differences between these two outcomes.

The regression function for each analysis was shown in the Additional file 3. All analyses were completed using R (version 4.0) and Plink (version 1.9), and a two-tailed test with $p < 0.05$ was considered statistically significant.

Results

Of 151,427 participants included in the present study, 56.5% were female, and the mean (SD) age at the start of the pandemic was 67.7 (7.72) years. Nearly one-third ($n = 50{,}441$) of the participants reported at least one type of childhood maltreatment, and emotional neglect (22.2%) was the most commonly reported type, while physical neglect (5.6%) was the least commonly reported type (Additional file 2: Table S1). Compared with unexposed individuals, those who were exposed to childhood maltreatment tended to have a lower level of education and annual household income ($p < 0.001$). They were also more likely to be younger, female, non-White ethnicity, recruited from England, have high BMI (i.e. ≥ 30 kg/m^2), and with pre-pandemic chronic medical conditions as well as psychiatric disorders ($p < 0.001$; Table 1).

A total of 606 individuals were hospitalized ($n = 542$) and/or died ($n = 155$) as a result of COVID-19 during the study period. We observed increased odds of severe COVID-19 outcomes among patients exposed to any childhood maltreatment (OR = 1.54 [95% CI 1.31–1.81]; Table 2) when compared with unexposed individuals in the basic model (model 1). The association was amplified in a graded manner by the cumulative number of childhood maltreatment types ($p_{\text{for trend}} < 0.01$). Specifically, those who experienced three or more childhood maltreatment types had the highest odds of severe COVID-19 outcomes (2.32 [1.73–3.05]), followed by those who experienced two (1.62 [1.22–2.10]) or one (1.33 [1.09–1.62]) type. The inclusion of potential mediators in the models attenuated the magnitude of the association, although ORs remained statistically significantly higher than one in the fully adjusted model (model 5) among individuals with any childhood maltreatment (1.26 [1.07–1.48]) and those who experienced three or more types of childhood maltreatment (1.50 [1.11–1.98]). Of the five types of childhood maltreatment, physical neglect yielded the strongest association with severe COVID-19 outcomes in the basic model (model 1, 2.04 [1.57–2.62]; Fig. 2) as well as in the model adjusted for all variable clusters of mediators (model 5, 1.52 [1.16–1.96]), although the differences between the groups were not statistically significant ($p_{\text{for difference}} > 0.05$).

The majority of the association between childhood maltreatment and severe COVID-19 outcomes was mediated through lifestyle factors (27.8%; Fig. 3), followed by socioeconomic factors (20.5%), pre-pandemic chronic medical conditions (17.4%), and psychiatric disorders (16.6%). In total, 50.9% of the association was mediated by all studied mediators and ranged from 49.5% (after physical neglect) to 79.0% (after sexual abuse) across different types of childhood maltreatment.

We obtained largely comparable results when stratified by tertiles of PRS for severe COVID-19 outcomes ($p_{\text{for difference}} > 0.05$; Fig. 4). Specifically, exposure to any childhood maltreatment (low genetic risk, 1.88 [1.30–2.69]; intermediate genetic risk, 1.41 [1.01–1.95]; high genetic risk, 1.55 [1.14–2.09]) and three or more types of childhood maltreatment (low genetic risk, 2.68 [1.29–5.00]; intermediate genetic risk, 2.14 [1.11–3.78]; high genetic risk, 3.11 [1.84–4.98]) were both consistently associated with significantly increased odds of severe COVID-19 outcomes, regardless of PRS for severe COVID-19 outcomes. We observed similar results when stratifying by

Table 1 Characteristics of the study population

	History of childhood maltreatment		Overall (n = 151,427)
	No (n = 100,986)	Yes (n = 50,441)	
Age at the measure of childhood maltreatment			
Mean (SD)	64.1 (7.69)	63.3 (7.75)	63.8 (7.72)
Median [min, max]	65.0 [46.0, 81.0]	64.0 [46.0, 80.0]	65.0 [46.0, 81.0]
Age at the start of the pandemic (i.e. 2020)			
Mean (SD)	68.0 (7.69)	67.2 (7.75)	67.7 (7.72)
Median [min, max]	69.0 [50.0, 84.0]	68.0 [50.0, 84.0]	69.0 [50.0, 84.0]
Birth year			
< 1950	44,042 (43.6%)	19,711 (39.1%)	63,753 (42.1%)
1950–1959	36,316 (36.0%)	18,997 (37.7%)	55,313 (36.5%)
≥ 1960	20,628 (20.4%)	11,733 (23.3%)	32,361 (21.4%)
Sex			
Female	55,882 (55.3%)	29,709 (58.9%)	85,591 (56.5%)
Male	45,104 (44.7%)	20,732 (41.1%)	65,836 (43.5%)
Ethnicity			
White	98,688 (97.7%)	47,975 (95.1%)	146,663 (96.9%)
British	93,211 (92.3%)	44,137 (87.5%)	137,348 (90.7%)
Irish	2044 (2.0%)	1523 (3.0%)	3567 (2.4%)
Others	3433 (3.4%)	2315 (4.6%)	5748 (3.8%)
Non-White	2013 (2.0%)	2250 (4.5%)	4263 (2.8%)
Mixed	356 (0.4%)	428 (0.8%)	784 (0.5%)
Asian or Asian British	650 (0.6%)	595 (1.2%)	1245 (0.8%)
Black or Black British	451 (0.4%)	609 (1.2%)	1060 (0.7%)
Chinese	144 (0.1%)	203 (0.4%)	347 (0.2%)
Others	412 (0.4%)	415 (0.8%)	827 (0.5%)
Unknown	285 (0.3%)	216 (0.4%)	501 (0.3%)
Recruitment region			
Scotland	7019 (7.0%)	3137 (6.2%)	10,156 (6.7%)
Wales	3771 (3.7%)	1795 (3.6%)	5566 (3.7%)
England	90,196 (89.3%)	45,509 (90.2%)	135,705 (89.6%)
Townsend deprivation index			
Lower than median (< − 2.43)	52,826 (52.3%)	22,825 (45.3%)	75,651 (50.0%)
Higher than median (≥ − 2.43)	48,041 (47.6%)	27,540 (54.6%)	75,581 (49.9%)
Unknown	119 (0.1%)	76 (0.2%)	195 (0.1%)
College education			
No	46,757 (46.3%)	24,230 (48.0%)	70,987 (46.9%)
Yes	47,047 (46.6%)	21,806 (43.2%)	68,853 (45.5%)
Unknown	7182 (7.1%)	4405 (8.7%)	11,587 (7.7%)
Annual household income			
≤ £18,000	10,924 (10.8%)	7478 (14.8%)	18,402 (12.2%)
£18,000–£30,999	20,838 (20.6%)	10,886 (21.6%)	31,724 (21.0%)
£31,000–£51,999	26,403 (26.1%)	13,223 (26.2%)	39,626 (26.2%)
£52,000-£100,000	24,926 (24.7%)	10,946 (21.7%)	35,872 (23.7%)
≥ £100,000	7812 (7.7%)	3195 (6.3%)	11,007 (7.3%)
Unknown	10,083 (10.0%)	4713 (9.3%)	14,796 (9.8%)
Smoking status			
Never	61,041 (60.4%)	26,272 (52.1%)	87,313 (57.7%)
Previous	33,519 (33.2%)	19,440 (38.5%)	52,959 (35.0%)
Current	6215 (6.2%)	4589 (9.1%)	10,804 (7.1%)

Table 1 (continued)

	History of childhood maltreatment		Overall ($n = 151{,}427$)
	No ($n = 100{,}986$)	Yes ($n = 50{,}441$)	
Unknown	211 (0.2%)	140 (0.3%)	351 (0.2%)
Body mass index, kg/m^2 [a]			
< 25	40,352 (40.0%)	18,488 (36.7%)	58,840 (38.9%)
25–29.9	41,925 (41.5%)	20,621 (40.9%)	62,546 (41.3%)
≥ 30	18,477 (18.3%)	11,191 (22.2%)	29,668 (19.6%)
Unknown	232 (0.2%)	141 (0.3%)	373 (0.2%)
Pre-pandemic chronic medical conditions [b]			
No	73,538 (72.8%)	35,050 (69.5%)	108,588 (71.7%)
Yes	27,448 (27.2%)	15,391 (30.5%)	42,839 (28.3%)
Pre-pandemic psychiatric disorders			
No	94,307 (93.4%)	44,493 (88.2%)	138,800 (91.7%)
Yes	6679 (6.6%)	5948 (11.8%)	12,627 (8.3%)

[a] The body mass index was calculated using weight kilogrammes (kg) by the square of height in metres (m^2), using anthropometric data measured at the assessment centre at baseline

[b] We calculated the Charlson Comorbidity Index using hospital inpatient data (before January 31, 2020), and patients with a CCI ≥ 1 were considered to have pre-pandemic chronic medical conditions

Table 2 Association between history of childhood maltreatment and COVID-19 outcomes (OR and 95% CI)

	Case/*N* (%)	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]
Outcome: severe COVID-19 outcomes (i.e. hospitalization or death due to COVID-19)						
Exposure: any childhood maltreatment						
No	345/100,986 (0.34)	Ref	Ref	Ref	Ref	Ref
Yes	261/50,441 (0.52)	1.54 (1.31–1.81)	1.42 (1.21–1.68)	1.33 (1.12–1.56)	1.28 (1.08–1.51)	1.26 (1.07–1.48)
Exposure: number of childhood maltreatment types						
0	345/100,986 (0.34)	Ref	Ref	Ref	Ref	Ref
1	141/30,819 (0.46)	1.33 (1.09–1.62)	1.27 (1.04–1.54)	1.22 (1.00–1.48)	1.20 (0.98–1.46)	1.19 (0.97–1.44)
2	62/11,586 (0.54)	1.62 (1.22–2.10)	1.47 (1.11–1.91)	1.34 (1.01–1.75)	1.29 (0.97–1.68)	1.27 (0.95–1.65)
≥ 3	58/8036 (0.72)	2.32 (1.73–3.05)	2.00 (1.49–2.63)	1.69 (1.26–2.24)	1.56 (1.16–2.06)	1.50 (1.11–1.98)
Outcome: COVID-19 diagnosis[f]						
Exposure: any childhood maltreatment						
No	5362/35,050 (15.30)	Ref	Ref	Ref	Ref	Ref
Yes	2994/18,028 (16.61)	1.06 (1.01–1.12)	1.02 (0.97–1.08)	1.01 (0.96–1.07)	1.02 (0.97–1.07)	1.02 (0.97–1.07)
Exposure: number of childhood maltreatment types						
0	5362/35,050 (15.30)	Ref	Ref	Ref	Ref	Ref
1	1735/10,873 (15.96)	1.03 (0.97–1.10)	1.01 (0.95–1.07)	1.00 (0.94–1.06)	1.00 (0.94–1.07)	1.01 (0.95–1.07)
2	714/4209 (16.96)	1.08 (0.99–1.18)	1.04 (0.95–1.13)	1.02 (0.94–1.12)	1.03 (0.94–1.12)	1.03 (0.94–1.13)
≥ 3	545/2946 (18.50)	1.14 (1.03–1.26)	1.07 (0.97–1.18)	1.05 (0.94–1.16)	1.05 (0.95–1.17)	1.06 (0.96–1.18)

[a] Model 1: adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region)

[b] Model 2: model 1 additionally adjusted for socio-economic status (Townsend deprivation index, college education, and annual household income)

[c] Model 3: model 2 additionally adjusted for lifestyle-related factors (smoking status and body mass index)

[d] Model 4: model 3 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥ 1, before January 31, 2020)

[e] Model 5: model 4 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10, F10–F99; before January 31, 2020)

[f] COVID-19 diagnosis was determined through records of positive COVID-19 test results in the PHE, PHS, and SAIL databanks ($n = 8356$) and compared with individuals who had records of negative COVID-19 test results ($n = 44{,}722$)

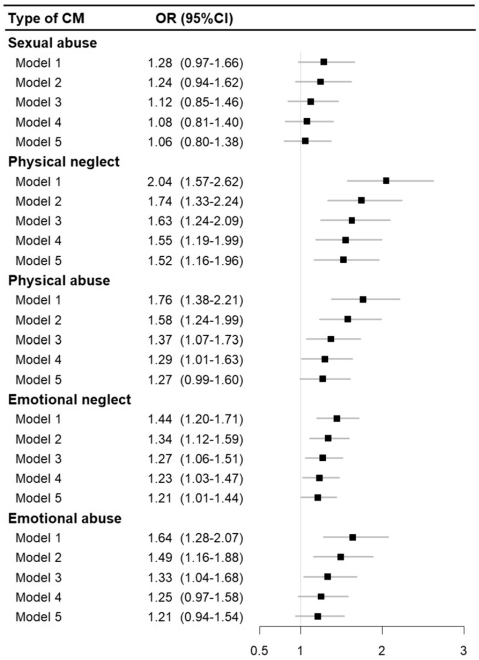

Fig. 2 Association between history of childhood maltreatment (CM) and severe COVID-19 outcomes (i.e. hospitalization or death due to COVID-19) by types of childhood maltreatment. *Note*: model 1—adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region); model 2—model 1 additionally adjusted for socio-economic factors (Townsend deprivation index, college education, and annual household income); model 3—model 2 additionally adjusted for lifestyle-related factors (smoking status and body mass index); model 4—model 3 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥ 1, before January 31, 2020); model 5—model 4 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10, F10–F99; before January 31, 2020)

the first PRS-PC for severe COVID-19 outcomes (Additional file 1: Fig. S5).

In the sensitivity analyses, we obtained largely comparable results when restricting our analysis to individuals with a COVID-19 diagnosis (Additional file 2: Table S4), redefining the study period before vaccination rollout (Additional file 2: Table S5), and excluding participants registered in Wales and redefining the study period from January 31, 2020, to July 31, 2021 (Additional file 2: Table S6). Also, we observed similar result patterns when using the total CTS score (Additional file 2: Table S7) or analysing hospitalization and death due to COVID-19 as separate outcomes (Additional file 2: Table S8).

Finally, in the secondary analyses, we found any childhood maltreatment and the number of childhood maltreatment types were both consistently associated with significantly increased odds of being unvaccinated for COVID-19 (models 1–5; Additional file 2: Table S9). By contrast, we found a weak association between any childhood maltreatment (model 1, 1.06 [1.01–1.12]) and three or more types of childhood maltreatment (model 1, 1.14 [1.03–1.26]) with COVID-19 diagnosis, which attenuated to null when adding potential mediators to the model (models 2–5; Table 2).

Discussion

The findings of this cohort study with pre-pandemic data on childhood maltreatment suggest a robust dose–response association between the number of childhood maltreatment types and severe COVID-19 outcomes. While all types of childhood maltreatment were associated with severe COVID-19 outcomes, physical neglect in childhood yielded the strongest association. The associations were partly mediated by suboptimal socio-economic status, lifestyle, and pre-pandemic psychiatric disorders or other chronic medical conditions and were not modified by genetic predisposition to severe COVID-19 outcomes.

In line with the findings of two previous studies [24, 25], our findings confirm the association between childhood maltreatment and severe COVID-19 outcomes. Our findings moreover extend the current level of evidence by showing that all types of childhood maltreatment, ranging from sexual abuse to physical neglect, are robustly associated with severe COVID-19 outcomes. In our study, physical neglect in childhood yielded the highest odds ratios of severe COVID-19-related outcomes, which is similar to the findings from previous studies on other long-term physical outcomes after childhood physical neglect, including test-identified sexually transmitted infections, diabetes, and lung disease [48, 49]. Although the mechanisms underlying this finding remain unclear, it is possible that individuals who experience physical neglect may not receive necessary medical care in childhood, leading to a lack of awareness or appropriate utilization of medical services in adulthood, thereby contributing to the increased risk of severe health consequences in adulthood [50, 51].

Importantly, our findings indicate that more than half of the association between childhood maltreatment and severe COVID-19 outcomes is mediated by suboptimal socio-economic status, lifestyle, and comorbid psychiatric or other chronic medical conditions. These results are consistent with previous findings suggesting that childhood maltreatment may increase the risk of health problems in adulthood through multiple factors, including

Models	OR (95%CI)	Mediation effect: Proportion of mediation (%)	p
Total effect			
Adjusted for demographic factors (M0)	1.54 (1.31-1.81)	-	
Direct effect			
Additionally adjusted for potential mediators, separately			
Socio-economic status (M1)	1.42 (1.34-1.66)	20.5	<0.01
Lifestyle factors (M2)	1.40 (1.34-1.65)	27.8	<0.01
Pre-pandemic chronic medical conditions (M3)	1.45 (1.35-1.64)	17.4	<0.01
Pre-pandemic psychiatric disorders (M4)	1.45 (1.35-1.63)	16.6	<0.01
All potential mediators (M5)	1.26 (1.20-1.39)	50.9	<0.01

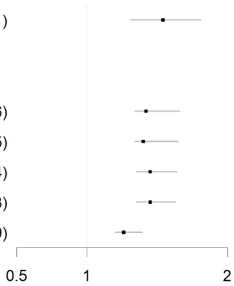

Fig. 3 Mediating roles of socioeconomic status, lifestyle, and pre-pandemic chronic medical conditions or psychiatric disorders on the associations between history of childhood maltreatment and severe COVID-19 outcomes (i.e. hospitalization or death due to COVID-19). *Note*: M0—adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region); M1—M0 and additionally adjusted for socio-economic status (Townsend deprivation index, college education, and annual household income); M2—M0 additionally adjusted for lifestyle-related factors (smoking status and body mass index); M3—M0 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥ 1, before January 31, 2020); M4—M0 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10, F10–F99; before January 31, 2020); M5—M0 additionally adjusted for socioeconomic status, lifestyle, and pre-pandemic chronic medical conditions psychiatric disorders; proportion of mediation: the proportion of the total effect that is mediated through the specified mediators

the adoption of adverse health behaviours and increased vulnerabilities to obesity and other chronic medical conditions of relevance for COVID-19 severity [13, 20, 23]. In line with previous findings [52, 53], we found that childhood maltreatment survivors were more likely to be unvaccinated against COVID-19 which may result in greater risks of severe COVID-19 outcomes [54]. Yet, in the present study, most of the severe COVID-19 outcome events occurred before the introduction of the COVID-19 vaccine, and therefore, we observed similar estimates when redefining the study period before the vaccination rollout.

We further found the history of psychiatric disorders to mediate the association between childhood maltreatment and severe COVID-19 outcomes. Indeed, there is strong evidence for the associations between childhood maltreatment and the risk of psychiatric disorders [11], coupled with our [9] and more recent findings [55] indicating a role of pre-existing psychiatric disorders in severe COVID-19 outcomes. Among the four studied variable clusters of mediators, lifestyle-related factors appear to have the strongest contribution to the association between childhood maltreatment and severe COVID-19 outcomes. However, there is an established link between lifestyle factors and socio-economic status [56], as well as multiple diseases, including cardiometabolic conditions [57] and mental disorders [58]. Therefore, the proportion mediated by each cluster of mediators, as suggested in the causal mediation analysis, is likely confounded by the other mediating clusters.

We found that the association between childhood maltreatment and severe COVID-19 outcomes remained robust after controlling for these potential mediators as well as genetic susceptibility to severe COVID-19 outcomes. Therefore, other unmeasured biological pathways, including disruption of inflammatory responses [59] and hormonal dysregulation [19], may contribute to the elevated risk of severe COVID-19 outcomes. For instance, childhood maltreatment has been associated with immune dysregulation [60, 61], such as disruption in immune cell activation [62], increased proinflammatory cytokine production [63], and accelerated telomere erosion [64], which may reduce an individual's capacity to recover from COVID-19. Indeed, recent evidence suggests that elevated IL-6 and TNF-α levels can predict disease severity and survival in patients with COVID-19 [65]. In addition, previous studies report an atypical hypothalamic–pituitary–adrenal axis stress response among childhood maltreatment survivors [66], which has been identified as a potential risk factor of severe illness in COVID-19 [67]. In contrast, increased susceptibility to COVID-19 infection is an unlikely explanation for the elevated risk of severe COVID-19-related outcomes by childhood maltreatment, as we found weak or no associations between childhood maltreatment and COVID-19 diagnosis.

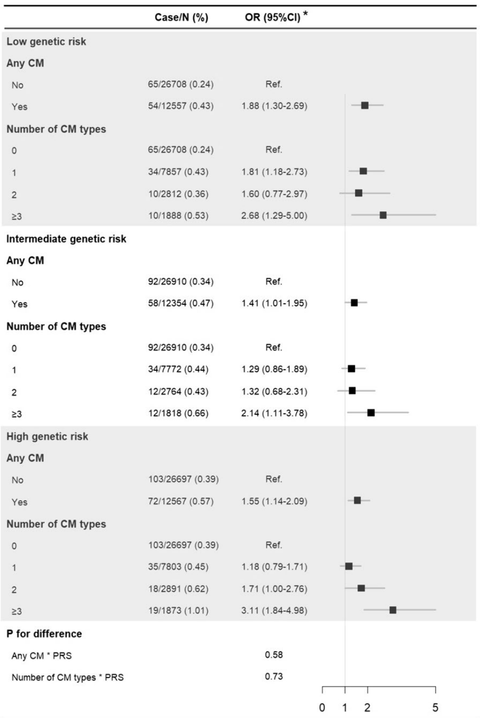

Fig. 4 Association between history of childhood maltreatment (CM) and severe COVID-19 outcomes (i.e. hospitalization or death due to COVID-19) by levels of polygenic risk score (PRS) to severe COVID-19 outcomes. *Adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region)

Strengths and limitations of this study

The major strength of our study is the use of a longitudinal study design, i.e. pre-pandemic individual data on childhood maltreatment and follow-up data on COVID-19, in a large population-based cohort. This ensures that the measures of childhood maltreatment indeed preceded any severe COVID-19 outcomes and hence minimizes the risk of reverse causality. Additionally, the primary outcome of interest was death or hospitalization with COVID-19 as the primary diagnosis, as opposed to also including secondary diagnoses in a previous study [25], reducing risks of misclassification of the outcome. Also, by utilizing severe COVID-19 events as the outcome, the influence of surveillance bias should be minor. Moreover, our consideration of genetic predisposition to severe COVID-19 outcomes and a wide range of mediators provides evidence of pathways linking childhood adversities to severe COVID-19 outcomes, with potential relevance for prevention and intervention strategies.

This study also has several limitations to be noted. First, as in most studies on childhood maltreatment, information on childhood maltreatment was recalled by participants in middle or older age rather than captured prospectively (in childhood), which may be liable to underreport [28] and biased by current mental state [68]. However, to explain the observed result pattern, such measurement error would have to be systematic in relation to later severe COVID-19 outcomes. Second, we do not have information on childhood poverty or parental socio-economic status, and several included mediators (e.g. smoking status, BMI) were only measured once at baseline and might have changed over the 10-year follow-up. Third, the incidence of COVID-19 varied across populations and geographical regions [41], yet our sensitivity analyses restricted to individuals with a COVID-19 diagnosis, excluding participants registered in Wales and confined to the study period from January 31, 2020, to July 31, 2021, suggested a minimal influence of these factors on the reported associations. Fourth, the identification of COVID-19 cases relies solely on RT-PCR testing which may lead to underestimation of the COVID-19 diagnosis. Also, the identified hospitalization or mortality rate in our study is lower than the reported rate in the UK during the same period [2]. Indeed, there is evidence of a 'healthy volunteer' selection bias of the UK participants who were more likely to live in less socioeconomically deprived areas and have lower rates of all-cause mortality [69]. In addition, most severe childhood maltreatment cases were probably not included in the cohort, possibly resulting in an underestimation of the studied association. Finally, the UK Biobank cohort is not representative of the entire UK population [69], and only approximately 30% of the UK Biobank participants were included in our analysis; thus, the generalization of our findings should be made with caution.

Conclusions

Our findings suggest that a history of childhood maltreatment, including exposure to physical and emotional neglect or abuse, is robustly associated with severe COVID-19 outcomes. This association was not modified by genetic predisposition to severe COVID-19 outcomes but partly mediated by suboptimal socio-economic status, lifestyle factors, and comorbidities. The latter constitute potential targets for clinical and public health interventions. These findings highlight the role of early life adversities in severe health consequences across the lifespan and call for increased clinical surveillance of people exposed to childhood maltreatment in COVID-19 outbreaks and future pandemics.

Abbreviations

BMI	Body mass index
CCI	Charlson Comorbidity Index
CM	Childhood maltreatment
CTS	Childhood Trauma Screener
NHS	National Health Service
PC	Principal component
PHE	Public Health England
PHS	Public Health Scotland
PRS	Polygenic risk score
SAIL	Secure Anonymised Information Linkage
TDI	Townsend deprivation index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03399-8.

Additional file 1: Fig. S1. Study profile. **Fig. S2.** Spearman rank correlation matrix for different types of childhood maltreatment. **Fig. S3.** Distribution of cumulative number of childhood maltreatment types. **Fig. S4.** Principal component on the set of the 10 polygenic risk score for severe COVID-19 outcomes. **Fig. S5.** Association between history of childhood maltreatment and severe COVID-19 outcomes, by levels of first PRS-PC to severe COVID-19 outcomes.

Additional file 2: Table S1. Participants' response to the 5 types of childhood maltreatment. **Table S2.** Associations between polygenic risk scores for severe COVID-19 outcomes. **Table S3.** Diseases used for calculating Charlson comorbidity index. **Table S4.** Association between history of childhood maltreatment and severe COVID-19 outcomes, restricted analysis to individuals with COVID-19 diagnosis. **Table S5.** Association between history of childhood maltreatment and severe COVID-19 outcomes, re-defining the study period before vaccination roll out. **Table S6.** Association between history of childhood maltreatment and severe COVID-19 outcomes, excluding participants registered in Wales as well as re-defining the study period from January 31st, 2020 to July 31st, 2021. **Table S7.** Association between total childhood trauma screener score and COVID-19 outcomes. **Table S8.** Association between any childhood maltreatment and severe COVID-19 outcomes, separating for hospitalization and death due to COVID-19. **Table S9.** Association between history of childhood maltreatment and COVID-19 vaccination.

Additional file 3. Regression function for each analysis.

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Authors' contributions

YW and UAV designed the study. YW performed the phenotypic analysis and FG performed the genotypic analysis, with supervision from UAV, TA, KH, and FF. YW, FG, and UAV drafted the manuscript. HA, AH, JJ, HZ, QS, HCW, OBVP, KL, OAA, FF, and HS provided critical feedback. All authors contributed to the data interpretation. All authors read and approved the final manuscript.

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Availability of data and materials

Data from the UK Biobank (http://www.ukbiobank.ac.uk/) are available to all researchers upon making an application.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics review authority (2022–01516-01) in Sweden. The UK Biobank has approval from the North West Multi-Centre Research Ethics Committee as a Research Tissue Bank approval (11/NW/0382).

Consent for publication

Not applicable.

Competing interests

OAA is a consultant to cortechs.ai and received a speaker's honorarium from Lundbeck, Sunovion, and Janssen. All other authors declare that they have no competing interests.

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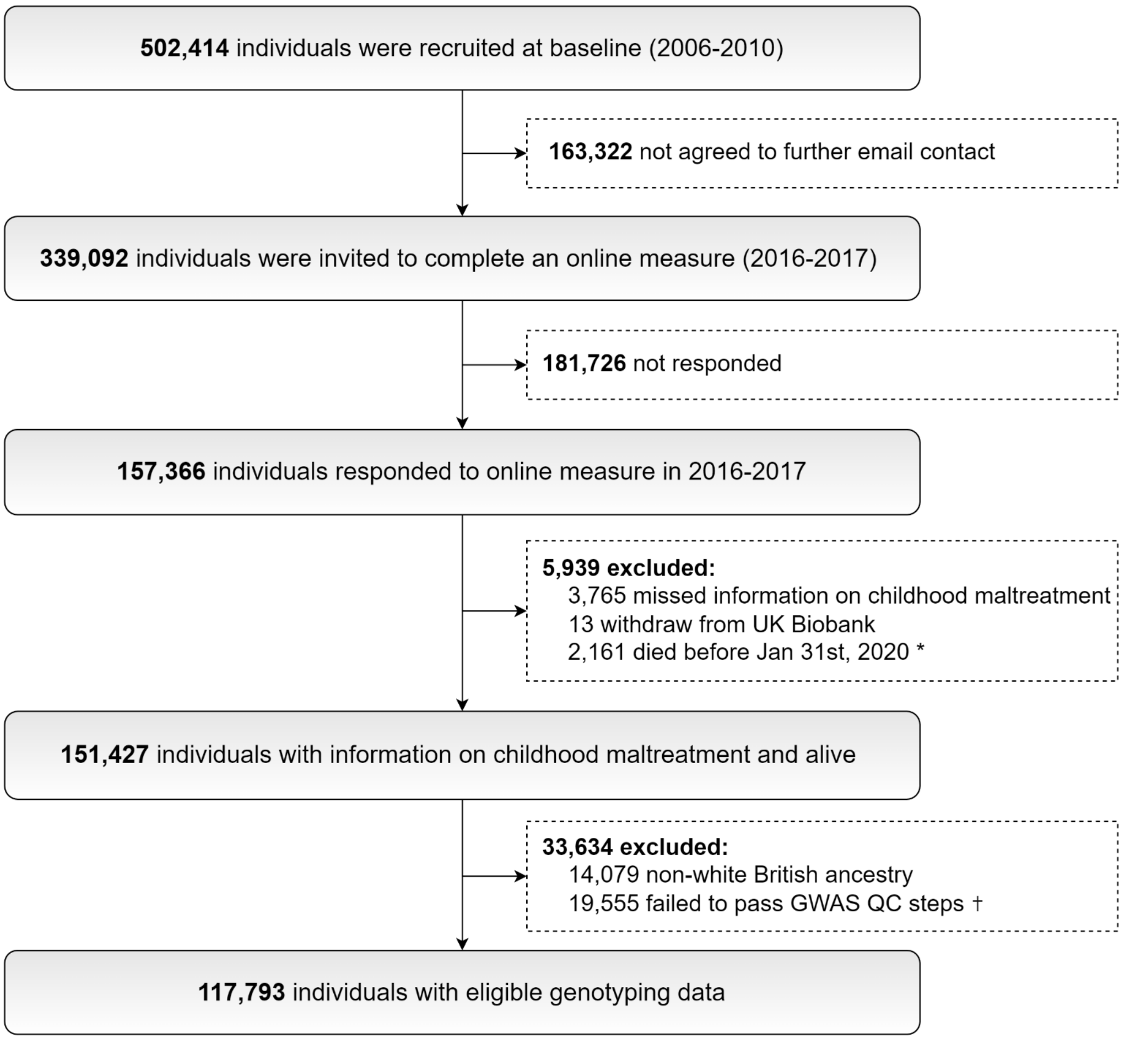
Publisher's Note

Additional file 1

Fig. S1 Study profile.



* 1st confirmed COVID-19 cases in the UK

† We excluded individuals having genotyping rate <98%, with abnormal heterozygosity level or a kinship coefficient >0.0884.

Fig. S2 Spearman rank correlation matrix for different types of childhood maltreatment.

	Emotional abuse	Physical abuse	Emotional neglect	Sexual abuse
Physical abuse	**0.37**			
Emotional neglect	**-0.38**	**-0.29**		
Sexual abuse	**0.17**	**0.16**	**-0.14**	
Physical neglect	**-0.18**	**-0.14**	**0.33**	**-0.10**

Fig. S3 Distribution of cumulative number of childhood maltreatment types**.**

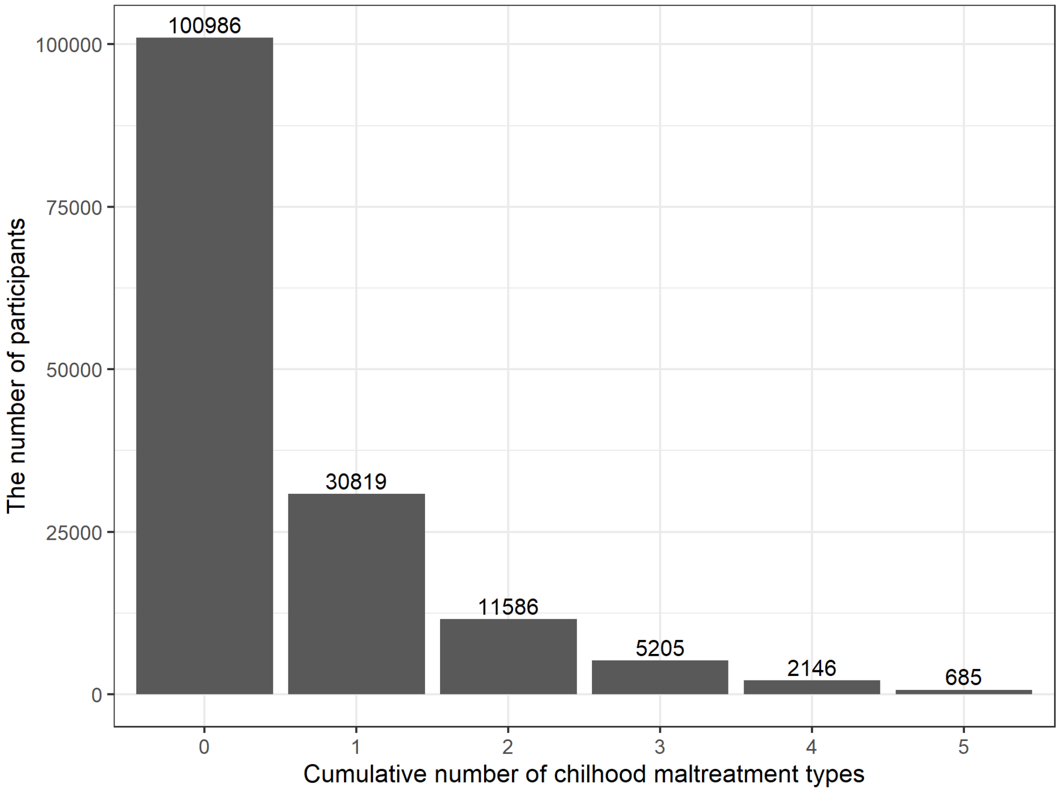
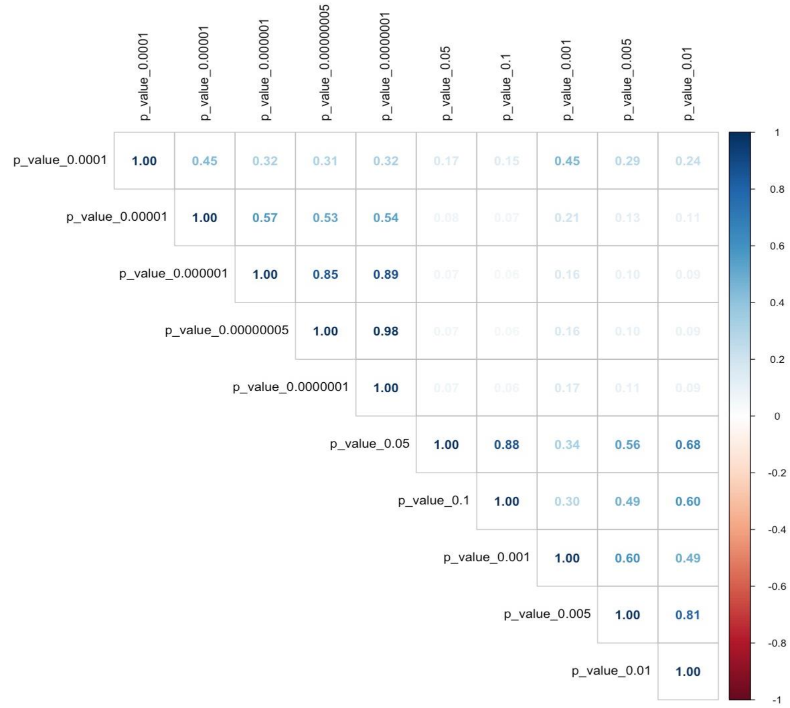
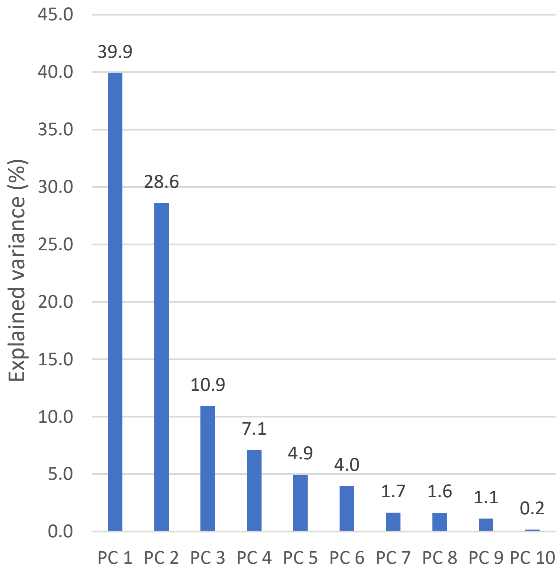


Fig. S4 Principal component (PC) on the set of the 10 polygenic risk score (PRS) for severe COVID-19 outcomes.

A. Correlation of the PRS based on different p-value thresholds in the studied sample (n=117,793).



B. Percentage explained variance by each PRS-PC.



C. The loadings in the first PRS-PC at each threshold.

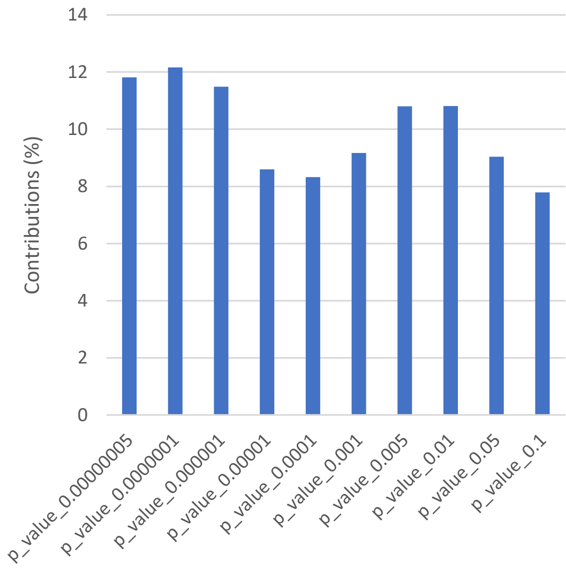
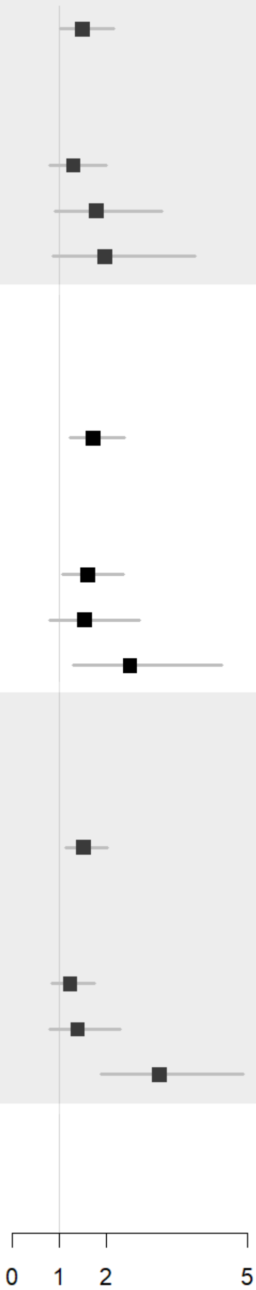


Fig. S5 Association between history of childhood maltreatment (CM) and severe COVID-19 outcomes (i.e., hospitalization or death due to COVID-19), by levels of first PRS-PC to severe COVID-19 outcomes.

	Case/N (%)	OR (95%CI) *
Low genetic risk		
Any CM		
No	70/26909 (0.26)	Ref.
Yes	46/12356 (0.37)	1.49 (1.02-2.16)
Number of CM types		
0	70/26909 (0.26)	Ref.
1	26/7787 (0.33)	1.30 (0.81-2.01)
2	12/2766 (0.43)	1.78 (0.92-3.17)
≥3	8/1803 (0.44)	1.97 (0.87-3.88)
Intermediate genetic risk		
Any CM		
No	80/26811 (0.30)	Ref.
Yes	61/12453 (0.49)	1.72 (1.22-2.39)
Number of CM types		
0	80/26811 (0.30)	Ref.
1	37/7767 (0.48)	1.61 (1.08-2.37)
2	12/2806 (0.43)	1.54 (0.79-2.71)
≥3	12/1880 (0.64)	2.50 (1.29-4.44)
High genetic risk		
Any CM		
No	110/26595 (0.41)	Ref.
Yes	77/12669 (0.61)	1.52 (1.13-2.03)
Number of CM types		
0	110/26595 (0.41)	Ref.
1	40/7878 (0.51)	1.23 (0.85-1.75)
2	16/2895 (0.55)	1.39 (0.79-2.29)
≥3	21/1896 (1.11)	3.12 (1.89-4.90)
P for difference		
Any CM * PRS-PC		0.82
Number of CM types * PRS-PC		0.83



* Adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region).

Additional file 2

Table S1 Participants' response to the 5 types of childhood maltreatment.

N (%)	Never true	Rarely true	Sometimes true	Often true	Very often true
Physical abuse: People in my family hit me so hard that it left me with bruises or marks	123020 (81.2)	16233 (10.7)	10009 (6.6)	1316 (0.9)	849 (0.6)
Emotional abuse: I felt that someone in my family hated me	128080 (84.6)	9203 (6.1)	9895 (6.5)	2322 (1.5)	1927 (1.3)
Sexual abuse: Someone molested me (sexually)	138151 (91.2)	7017 (4.6)	4854 (3.2)	766 (0.5)	639 (0.4)
Physical neglect: There was someone to take me to the doctor if I needed it	3216 (2.1)	1200 (0.8)	4051 (2.7)	15975 (10.6)	126985 (83.9)
Emotional neglect: I felt loved	2141 (1.4)	6940 (4.6)	24473 (16.2)	38482 (25.4)	79391 (52.4)

Note, red fonts indicate the responses that are categorized as exposed to childhood maltreatment.

Table S2 Associations between polygenic risk scores (PRS, calculated using Clumping + Thresholding approach) for severe COVID-19 outcomes (i.e., hospitalization or death due to COVID-19) at different p value thresholds.

P threshold	OR (95%CI)	Nagelkerke R^2 (%)	p	Number of SNPs
5.00×10^{-08}	1.21 (1.11-1.32)	2.01	<0.01	8
1.00×10^{-07}	1.21 (1.11-1.32)	2.00	<0.01	9
1.00×10^{-06}	1.19 (1.08-1.30)	1.94	<0.01	12
1.00×10^{-05}	1.11 (1.01-1.22)	1.79	0.02	37
1.00×10^{-04}	1.07 (0.98-1.18)	1.74	0.14	184
0.001	1.08 (0.98-1.18)	1.74	0.11	1225
0.005	1.10 (1.00-1.21)	1.77	0.05	4855
0.01	1.10 (1.00-1.20)	1.77	0.05	8854
0.05	1.12 (1.02-1.23)	1.80	0.02	34226
0.1	1.13 (1.03-1.24)	1.82	0.01	59893

Note, GWAS summary statistics for COVID-19 hospitalization were obtained from https://www.covid19hg.org/results/r5/. Odds ratio and 95% confidence interval were estimated by logistic regression models, adjusting for birth year, sex, genotyping array, and top 10 ancestry principal components.

Table S3 Diseases used for calculating Charlson comorbidity index.

Disease	ICD-10 code
Myocardial infarction	I21, I22, I252
Congestive heart failure	I110, I130, I132, I50
Peripheral vascular disease	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, R02, Z958, Z959
Cerebrovascular disease	I60-I69, G45, G46
Dementia	F00, F01, F02, F03, F051, G30, G311
Chronic pulmonary disease	J40-J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J70, J841, J920, J961, J982
Connective tissue disease	M05, M06, M30, M315, M32, M33, M34, M351, M353, M360
Ulcer disease	K25, K26, K27, K28
Mild liver disease	B18, K700, K701, K702, K703, K709, K713, K714, K715, K717, K73, K74, K760, K762, K763, K764, K768, K769,
Diabetes mellitus	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149,
Hemiplegia	G041, G114, G801, G802, G81, G82, G839, G830, G831, G832, G833, G834
Moderate/severe renal disease	I120, I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N18, N19, N250, Z940, Z992
Diabetes mellitus with chronic complications	E102, E103, E104, E105, E107, E112-E115, E122-E125, E132- E135, E142- E145, E117, E127, E137, E147
Any tumor	C00-C14, C15-C26, C30-C34, C37-C41, C43, C45-C49, C50-C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C76, C97
Leukemia	C91, C92, C93, C94, C95
Lymphoma	C81, C82, C83, C84, C85, C88, C90, C96
Moderate/severe liver disease	I85, K704, K72, K766
Metastatic solid tumor	C77, C78, C79, C80
AIDS	B20, B21, B22, B23, B24

Table S4 Association between history of childhood maltreatment and severe COVID-19 outcomes (i.e., hospitalization or death due to COVID-19; OR and 95%CI), restricted analysis to individuals with COVID-19 diagnosis (n=8356)

	Case/N (%)	Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 4 [d]	Model 5 [e]
Outcome: severe COVID-19 outcomes (i.e., Hospitalization or death due to COVID-19)						
Exposure: any childhood maltreatment						
No	339/5362 (6.32)	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	254/2994 (8.48)	1.44 (1.21-1.72)	1.39 (1.16-1.65)	1.29 (1.08-1.54)	1.22 (1.02-1.46)	1.20 (1.00-1.44)
Exposure: number of childhood maltreatment types						
0	339/5362 (6.32)	Ref.	Ref.	Ref.	Ref.	Ref.
1	138/1735 (7.95)	1.30 (1.05-1.60)	1.28 (1.03-1.58)	1.22 (0.98-1.51)	1.18 (0.95-1.47)	1.17 (0.94-1.45)
2	59/714 (8.26)	1.42 (1.05-1.90)	1.33 (0.98-1.78)	1.24 (0.91-1.66)	1.17 (0.85-1.57)	1.15 (0.84-1.55)
≥3	57/545 (10.46)	2.11 (1.54-2.84)	1.94 (1.41-2.63)	1.63 (1.18-2.21)	1.44 (1.04-1.98)	1.39 (1.00-1.91)

a. Model 1: adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region).
b. Model 2: Model 1 additionally adjusted for socio-economic status (Townsend deprivation index, college education, and annual household income).
c. Model 3: Model 2 additionally adjusted for lifestyle-related factors (smoking status and body mass index).
d. Model 4: Model 3 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥1, before January 31st, 2020).
e. Model 5: Model 4 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10: F10-F99; before January 31st, 2020).

Table S5 Association between history of childhood maltreatment and severe COVID-19 outcomes (i.e., hospitalization or death due to COVID-19; OR and 95%CI), re-defining the study period from January 31st, 2020 to December 8th, 2020 (i.e., before vaccination roll out).

	Case/N (%)	Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 4 [d]	Model 5 [e]
Outcome: severe COVID-19 outcomes (i.e., Hospitalization or death due to COVID-19)						
Exposure: any childhood maltreatment						
No	169/100986 (0.17)	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	132/50441 (0.26)	1.59 (1.26-2.00)	1.46 (1.16-1.84)	1.36 (1.08-1.71)	1.31 (1.04-1.65)	1.28 (1.01-1.61)
Exposure: number of childhood maltreatment types						
0	169/100986 (0.17)	Ref.	Ref.	Ref.	Ref.	Ref.
1	72/30819 (0.23)	1.39 (1.05-1.83)	1.32 (1.00-1.73)	1.27 (0.96-1.67)	1.25 (0.94-1.64)	1.23 (0.93-1.62)
2	31/11586 (0.27)	1.65 (1.10-2.38)	1.49 (0.99-2.16)	1.36 (0.90-1.97)	1.31 (0.87-1.89)	1.27 (0.85-1.84)
≥3	29/8036 (0.36)	2.37 (1.56-3.48)	2.02 (1.32-2.97)	1.69 (1.10-2.50)	1.54 (1.01-2.28)	1.45 (0.94-2.15)

a. Model 1: adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region).
b. Model 2: Model 1 additionally adjusted for socio-economic status (Townsend deprivation index, college education, and annual household income).
c. Model 3: Model 2 additionally adjusted for lifestyle-related factors (smoking status and body mass index).
d. Model 4: Model 3 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥1, before January 31st, 2020).
e. Model 5: Model 4 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10: F10-F99; before January 31st, 2020).

Table S6 Association between history of childhood maltreatment and severe COVID-19 outcomes (i.e., hospitalization or death due to COVID-19; OR and 95%CI), excluding participants registered in Wales as well as re-defining the study period from January 31st, 2020 to July 31st, 2021 (n=145,861).

	Case/N (%)	Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 4 [d]	Model 5 [e]
Outcome: severe COVID-19 outcomes (i.e., Hospitalization or death due to COVID-19)						
Exposure: any childhood maltreatment						
No	311/97215 (0.32)	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	240/48646 (0.49)	1.56 (1.31-1.85)	1.44 (1.21-1.71)	1.34 (1.13-1.59)	1.30 (1.09-1.54)	1.27 (1.07-1.51)
Exposure: number of childhood maltreatment types						
0	311/97215 (0.32)	Ref.	Ref.	Ref.	Ref.	Ref.
1	127/29668 (0.43)	1.33 (1.08-1.63)	1.27 (1.02-1.55)	1.22 (0.98-1.49)	1.19 (0.97-1.47)	1.18 (0.96-1.45)
2	56/11218 (0.50)	1.60 (1.19-2.12)	1.45 (1.08-1.92)	1.33 (0.98-1.75)	1.28 (0.95-1.69)	1.26 (0.93-1.66)
≥3	57/7760 (0.73)	2.49 (1.85-3.29)	2.14 (1.59-2.84)	1.81 (1.34-2.41)	1.67 (1.24-2.23)	1.61 (1.19-2.15)

a. Model 1: adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region).
b. Model 2: Model 1 additionally adjusted for socio-economic status (Townsend deprivation index, college education, and annual household income).
c. Model 3: Model 2 additionally adjusted for lifestyle-related factors (smoking status and body mass index).
d. Model 4: Model 3 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥1, before January 31st, 2020).
e. Model 5: Model 4 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10: F10-F99; before January 31st, 2020).

Table S7 Association between total childhood trauma screener score and COVID-19 outcomes (OR and 95% CI).

Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 4 [d]	Model 5 [e]
Exposure: total childhood trauma screener score				
Outcome: severe COVID-19 outcomes (i.e., Hospitalization or death due to COVID-19)				
1.10 (1.07-1.13)	1.08 (1.05-1.11)	1.06 (1.03-1.09)	1.05 (1.02-1.08)	1.04 (1.02-1.07)
Outcomes: COVID-19 diagnosis [f]				
1.02 (1.01-1.03)	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)

a. Model 1: adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region).

b. Model 2: Model 1 additionally adjusted for socioeconomic status (Townsend deprivation index, college education, and annual household income).

c. Model 3: Model 2 additionally adjusted for lifestyle-related factors (smoking status and body mass index).

d. Model 4: Model 3 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥1, before January 31st, 2020).

e. Model 5: Model 4 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10: F10-F99; before January 31st, 2020).

f. COVID-19 diagnosis was determined through records of positive COVID-19 test results in the PHE, PHS and SAIL databanks (n=8356) and compared with individuals who had records of negative COVID-19 test results (n=44722).

Table S8 Association between any childhood maltreatment and severe COVID-19 outcomes, separating for hospitalization and death due to COVID-19 (OR and 95%CI).

	Case/N (%)	Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 4 [d]	Model 5 [e]
Exposure: any childhood maltreatment						
Outcome: hospitalization due to COVID-19						
No	307/100986 (0.30)	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	235/50441 (0.47)	1.54 (1.30-1.83)	1.44 (1.21-1.71)	1.34 (1.12-1.59)	1.29 (1.08-1.53)	1.27 (1.06-1.51)
Outcome: death due to COVID-19						
No	90/100986 (0.09)	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	65/50441 (0.13)	1.56 (1.13-2.15)	1.43 (1.03-1.97)	1.33 (0.96-1.84)	1.28 (0.92-1.77)	1.26 (0.90-1.74)

a. Model 1: adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region).
b. Model 2: Model 1 additionally adjusted for socio-economic status (Townsend deprivation index, college education, and annual household income).
c. Model 3: Model 2 additionally adjusted for lifestyle-related factors (smoking status and body mass index).
d. Model 4: Model 3 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥1, before January 31st, 2020).
e. Model 5: Model 4 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10: F10-F99; before January 31st, 2020).

Table S9 Association between history of childhood maltreatment and COVID-19 vaccination (OR and 95% CI).

	Case/N (%)	Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 4 [d]	Model 5 [e]
Outcome: being unvaccinated for COVID-19						
Exposure: any childhood maltreatment						
No	2544/71830 (3.54)	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1606/34921 (4.60)	1.21 (1.13-1.29)	1.18 (1.10-1.26)	1.21 (1.13-1.29)	1.22 (1.14-1.31)	1.23 (1.15-1.32)
Exposure: number of childhood maltreatment types						
0	2544/71830 (3.54)	Ref.	Ref.	Ref.	Ref.	Ref.
1	907/21539 (4.21)	1.16 (1.07-1.26)	1.14 (1.05-1.24)	1.16 (1.07-1.26)	1.16 (1.07-1.26)	1.17 (1.08-1.27)
2	381/7973 (4.78)	1.23 (1.1-1.38)	1.20 (1.06-1.34)	1.23 (1.10-1.38)	1.25 (1.11-1.41)	1.27 (1.13-1.42)
≥3	318/5409 (5.88)	1.38 (1.21-1.56)	1.30 (1.14-1.48)	1.36 (1.20-1.55)	1.40 (1.23-1.59)	1.43 (1.25-1.62)

Note, information on the COVID-19 vaccination status was collected for UK Biobank participants who participated in the COVID-19 Self-Test Antibody study (from February 2021 to July 2021). In the present analysis, we included 106,751 individuals who had both information on childhood maltreatment and COVID-19 vaccine status, and alive were alive on January 31st 2020.
a. Model 1: adjusted for demographic factors (birth year, sex, ethnicity, and recruitment region).
b. Model 2: Model 1 additionally adjusted for socioeconomic status (Townsend deprivation index, college education, and annual household income).
c. Model 3: Model 2 additionally adjusted for lifestyle-related factors (smoking status and body mass index).
d. Model 4: Model 3 additionally adjusted for pre-pandemic chronic medical conditions (Charlson Comorbidity Index ≥1, before January 31st, 2020).
e. Model 5: Model 4 additionally adjusted for pre-pandemic psychiatric disorders (ICD-10: F10-F99; before January 31st, 2020).

Additional file 3

Regression function for each analysis.

Main analyses (for Table 2):

- Model 1: $Y_{\text{hospitalization or death due to COVID-19}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region.
- Model 2: $Y_{\text{hospitalization or death due to COVID-19}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income.
- Model 3: $Y_{\text{hospitalization or death due to COVID-19}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index.
- Model 4: $Y_{\text{hospitalization or death due to COVID-19}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index + pre-pandemic chronic medical conditions.
- Model 5: $Y_{\text{hospitalization or death due to COVID-19}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index + pre-pandemic chronic medical conditions + pre-pandemic psychiatric disorders.

We then replaced $X_{\text{any childhood maltreatment}}$ with $X_{\text{number of childhood maltreatment types}}$, and repeated the above analyses.

Secondary analyses (for Table 2):

- Model 1: $Y_{\text{COVID-19 diagnosis}}$~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region.
- Model 2: $Y_{\text{COVID-19 diagnosis}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income.
- Model 3: $Y_{\text{COVID-19 diagnosis}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index.
- Model 4: $Y_{\text{COVID-19 diagnosis}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index + pre-pandemic chronic medical conditions.
- Model 5: $Y_{\text{COVID-19 diagnosis}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index + pre-pandemic chronic medical conditions + pre-pandemic psychiatric disorders.

We then replaced $X_{\text{any childhood maltreatment}}$ with $X_{\text{number of childhood maltreatment types}}$, and repeated the above analyses.

Secondary analyses (for Additional file 2: Table S9):

- Model 1: $Y_{\text{being unvaccinated for COVID-19}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region.
- Model 2: $Y_{\text{being unvaccinated for COVID-19}}$ ~ $X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income.

- Model 3: $Y_{\text{being unvaccinated for COVID-19}} \sim X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index.
- Model 4: $Y_{\text{being unvaccinated for COVID-19}} \sim X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index + pre-pandemic chronic medical conditions.
- Model 5: $Y_{\text{being unvaccinated for COVID-19}} \sim X_{\text{any childhood maltreatment}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index + pre-pandemic chronic medical conditions + pre-pandemic psychiatric disorders.

We then replaced $X_{\text{any childhood maltreatment}}$ with $X_{\text{number of childhood maltreatment types,}}$ and repeated the above analyses.

Subgroup analyses (for Fig. 2)

- Model 1: $Y_{\text{hospitalization or death due to COVID-19}} \sim X_{\text{sexual abuse}}$ + birth year+ sex + ethnicity + recruitment region.
- Model 2: $Y_{\text{hospitalization or death due to COVID-19}} \sim X_{\text{sexual abuse}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income.
- Model 3: $Y_{\text{hospitalization or death due to COVID-19}} \sim X_{\text{sexual abuse}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index.
- Model 4: $Y_{\text{hospitalization or death due to COVID-19}} \sim X_{\text{sexual abuse}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index + pre-pandemic chronic medical conditions.
- Model 5: $Y_{\text{hospitalization or death due to COVID-19}} \sim X_{\text{sexual abuse}}$ + birth year+ sex + ethnicity + recruitment region + Townsend deprivation index + college education + annual household income + smoking status + body mass index + pre-pandemic chronic medical conditions + pre-pandemic psychiatric disorders.

We the replaced $X_{\text{sexual abuse}}$ with $X_{\text{physical neglect}}$, $X_{\text{physical abuse}}$, $X_{\text{emotional neglect}}$, and $X_{\text{emotional abuse,}}$ respectively, and then repeated the above analyses.

Regression-based causal mediation analyses (for Fig. 3)

- M1: cmest(data, model = "rb",

  outcome = $Y_{\text{hospitalization or death due to COVID-19}}$,

  exposure = $X_{\text{any childhood maltreatment}}$,

  mediator = c (Townsend deprivation index, college education, annual household income),

  basec = c (birth year, sex, ethnicity, recruitment region), # confounder

  mreg = list("multinomial","multinomial","multinomial"), yreg = "logistic",

  astar = 0, a = 1, mval = list('lower','Yes','Greater than 100,000'), yval=list(1),

  estimation = "imputation", inference = "bootstrap", nboot = 10).

- M2: cmest(data, model = "rb",

  outcome = $Y_{\text{hospitalization or death due to COVID-19}}$,

  exposure = $X_{\text{any childhood maltreatment}}$,

  mediator = c (smoking status, body mass index),

  basec = c (birth year, sex, ethnicity, recruitment region), # confounder

  mreg = list("multinomial","multinomial"), yreg = "logistic",

  astar = 0, a = 1, mval = list('Never','Normal weight'), yval=list(1),

  estimation = "imputation", inference = "bootstrap", nboot = 10).

- M3: cmest(data, model = "rb",

  outcome = $Y_{\text{hospitalization or death due to COVID-19}}$,

  exposure = $X_{\text{any childhood maltreatment}}$,

  mediator = pre-pandemic chronic medical conditions,

  basec = c (birth year, sex, ethnicity, recruitment region), # confounder

  mreg ="logistic", yreg = "logistic",

  astar = 0, a = 1, mval = list('No'), yval=list(1),

  estimation = "imputation", inference = "bootstrap", nboot = 10).

- M4: cmest(data, model = "rb",

  outcome = $Y_{\text{hospitalization or death due to COVID-19}}$,

  exposure = $X_{\text{any childhood maltreatment}}$,

  mediator = pre-pandemic psychiatric disorders,

  basec = c (birth year, sex, ethnicity, recruitment region), # confounder

  mreg ="logistic", yreg = "logistic",

  astar = 0, a = 1, mval = list('No'), yval=list(1),

  estimation = "imputation", inference = "bootstrap", nboot = 10).

- M5: cmest(data, model = "rb",

  outcome = $Y_{\text{hospitalization or death due to COVID-19}}$,

  exposure = $X_{\text{any childhood maltreatment}}$,

  mediator = c (Townsend deprivation index, college education, annual household income, smoking status, body mass index, pre-pandemic chronic medical conditions, pre-pandemic psychiatric disorders),

  basec = c (birth year, sex, ethnicity, recruitment region), # confounder

  mreg = list("multinomial", "multinomial","multinomial", "multinomial", "multinomial", "logistic", "logistic"),

  yreg = "logistic",

astar = 0, a = 1, mval = list('lower','Yes','Greater than 100,000','Never','Normal weight','No','No'),

yval=list(1),

estimation = "imputation", inference = "bootstrap", nboot = 10).

Modification analyses (for Fig. 4)

- $Y_{\text{hospitalization or death due to COVID-19}}$ ~ $X_{\text{any childhood maltreatment}}$ * $\text{Moderator}_{\text{polygenic risk score (PRS) for COVID-19 hospitalization or death}}$ + birth year+ sex + ethnicity + recruitment region.
- $Y_{\text{hospitalization or death due to COVID-19}}$ ~ $X_{\text{number of childhood maltreatment types}}$ * $\text{Moderator}_{\text{polygenic risk score (PRS) for COVID-19 hospitalization or death}}$ + birth year+ sex + ethnicity + recruitment region.

Paper II

Paper II

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ARTICLE OPEN

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Trends in incident diagnoses and drug prescriptions for anxiety and depression during the COVID-19 pandemic: an 18-month follow-up study based on the UK Biobank

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Serious concerns have been raised about the negative effects of the COVID-19 pandemic on population psychological well-being. However, limited data exist on the long-term effects of the pandemic on incident psychiatric morbidities among individuals with varying exposure to the pandemic. Leveraging prospective data from the community-based UK Biobank cohort, we included 308,400 participants free of diagnosis of anxiety or depression, as well as 213,757 participants free of anxiolytics or antidepressants prescriptions, to explore the trends in incident diagnoses and drug prescriptions for anxiety and depression from 16 March 2020 to 31 August 2021, compared to the pre-pandemic period (i.e., 1 January 2017 to 31 December 2019) and across populations with different exposure statuses (i.e., not tested for COVID-19, tested negative and tested positive). The age- and sex-standardized incidence ratios (SIRs) were calculated by month which indicated an increase in incident diagnoses of anxiety or depression among individuals who were tested for COVID-19 (tested negative: SIR 3.05 [95% confidence interval 2.88–3.22]; tested positive: 2.03 [1.76–2.34]), especially during the first six months of the pandemic (i.e., March-September 2020). Similar increases were also observed for incident prescriptions of anxiolytics or antidepressants (tested negative: 1.56 [1.47–1.67]; tested positive: 1.41 [1.22–1.62]). In contrast, individuals not tested for COVID-19 had consistently lower incidence rates of both diagnoses of anxiety or depression (0.70 [0.67–0.72]) and prescriptions of respective psychotropic medications (0.70 [0.68–0.72]) during the pandemic period. These data suggest a distinct rise in health care needs for anxiety and depression among individuals tested for COVID-19, regardless of the test result, in contrast to a reduction in health care consumption for these disorders among individuals not tested for and, presumably, not directly exposed to the disease.

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INTRODUCTION

The coronavirus disease (COVID-19) pandemic continues to be a world-wide public health threat [1, 2]. Serious concerns have been raised about the negative effects of the pandemic on population psychological well-being, including new-onset psychiatric symptoms and disorders in people without preexisting problems [3, 4]. Indeed, a Canadian online survey reported that the proportion of generalized anxiety disorder and depression increased by 12% and 29%, respectively, during the pandemic [4]. Based on representative primary care data, Jacob et al. also found an increase in the number of patients newly diagnosed with anxiety disorder between March and June 2020 in Germany [5]. However, a significant reduction in first diagnoses of depression and anxiety between March and September 2020 was observed in UK, especially for adults of working age [6]. Likewise, psychiatric emergency consultations were also dramatically decreased across all psychiatric disorders during the lockdown (i.e., March-April 2020) in Paris and suburbs [7]. In terms of dispensing rate for antidepressants, a study in Canada showed a temporary reduction in April 2020 which then returned to the pre-pandemic levels by August 2020 [8].

Notably, previous studies have also suggested varying effects of the pandemic on population mental health across time [9] and degree of pandemic exposure [10–12]. For example, several countries have reported fluctuating levels of anxiety and depression across and between the different pandemic "waves" (i.e., according to numbers of COVID-19 cases, hospitalizations, and deaths) [13]. Based on cross-sectional data collected at the beginning of the pandemic, a study in China reported that clinical symptoms of anxiety and depression was predominately increased among patients with COVID-19 infection, compared to individuals under quarantine or the general public [11]. In the UK, Abel et al. observed an increased risk of fatigue, sleep problems, and psychotropic medication use among patients with negative COVID-19 test result, in contrast to matched controls in the general population [12]. Altogether, those findings indicated that

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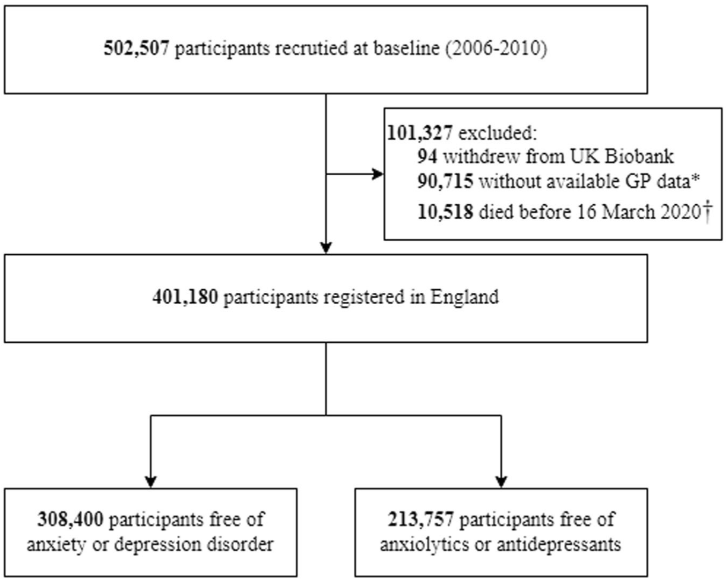

Fig. 1 Flow chart of the COVID-19 pandemic exposure population. * The primary care data were only available for participants registered in England and registered at a practice using TPP or EMIS as their data system supplier. † Considering the results of COVID-19 tests was available in England through linkage to Public Health England database since 16 March 2020 onwards, thus, we defined the pandemic period start from 16 March 2020.

patients who sought or received COVID-19 test may, irrespective of the test results, be at a higher exposure level of the pandemic (i.e., close to infected individuals or experiencing COVID-19 like symptoms) and thereby suffer a higher psychological burden.

Yet, limited data exist on the long-term effects of the pandemic on incident psychiatric disorders among individuals with varying exposure to the pandemic (e.g., COVID diagnosis), with careful control of potential confounding including seasonal effects. To this end, we leveraged routinely collected administrative data from the UK Biobank to assess trends in incident diagnoses of common psychiatric disorders – anxiety and depression – and prescriptions of respective psychotropic medications (i.e., anxiolytics and antidepressants) during the first 18 months of the pandemic, by history of COVID-19 testing (not tested, tested negative, and tested positive) as an indicator of pandemic exposure.

METHODS

Study population and design

The UK Biobank is a population-based cohort study that recruited 502,507 men and women aged 40–69 years from England, Scotland, and Wales between 2006 and 2010, accounting for 5.5% of the UK population. Health-related outcomes of the participants are obtained regularly through linkage to multiple datasets [14]. Specifically, hospital inpatient data are obtained from Hospital Episode Statistics (HES) for England, Scottish Morbidity Record for Scotland, and Patient Episode Database for Wales. Mortality data are obtained from National Health Service (NHS) Digital and NHS Central Register. The hospital inpatient data (available since 1997) and mortality data (available since 2006) in England are currently updated to 30 September 2021. Furthermore, to facilitate COVID-19 related research, the UK Biobank also provided records of COVID-19 test results (by RT-PCR of nose/throat swab samples, available from 16 March 2020 to 30 September 2021) through linkage to Public Health England (PHE) [15], as well as updated primary care data obtained from two major general practice (GP) data system suppliers (EMIS and TPP) for approximately 450,000 UK Biobank participants in England (available from 1938 onward to 31 August 2021) [16]. More details about the UK Biobank are described elsewhere [17].

In this study, the outcomes of interest are incident diagnoses of anxiety and depression as well as prescriptions of the respective psychotropic medications during the COVID-19 pandemic. As the World Health Organization (WHO) declared the COVID-19 as a pandemic on 11 March 2020 and given the availability of COVID-19 related data in the UK Biobank, we defined the pandemic exposure period from 16 March 2020 to 31 August 2021. After excluding participants who withdrew from the UK Biobank ($n = 94$), had no available primary care data ($n = 90{,}715$), or died before 16 March 2020 ($n = 10{,}518$), we included 401,180 participants registered in England in the study (Fig. 1). Among these participants, we first constructed a cohort for the analysis of incident diagnoses of depression or anxiety, including 308,400 participants who were free of anxiety (International Classification of Diseases, Tenth Revision (ICD-10), F40-F41) and depression (ICD-10, F32-F33), as of 16 March 2020, to examine the trend of incident diagnoses of these psychiatric disorders during the COVID-19 pandemic. Then, to study the trend of incident prescriptions of respective psychotropic medications (i.e., anxiolytics and antidepressants), we constructed another cohort including 213,757 participants who were free of prescription of these medications on 16 March 2020. We followed up those participants from baseline (i.e., 16 March 2020) until the occurrence of any outcomes of interest, death, or the end of followup (i.e., 31 August 2021). In comparison, we used the three preceding years before the pandemic (i.e., from 1 January 2017 to 31 December 2019) as the reference pre-pandemic period. Supplementary Fig. S1 shows the flow chart of the pre-pandemic population selection.

The UK Biobank collected all data after written informed consent obtained from each participant and the study has full ethical approval from the NHS National Research Ethics Service (16/NW/0274). This present study was also approved by the biomedical research ethics committee of West China Hospital (2020.661).

Ascertainment of anxiety, depression, and psychotropic medications

Diagnoses of anxiety and depression were retrieved from the UK Biobank hospital inpatient data (according to ICD-10 codes) [18] and primary care data (according to SNOMED CT, local EMIS codes, Clinical Terms Version 3, and Local TPP codes) [19]. The diagnoses of psychiatric

Table 1. Characteristics of the pandemic cohort.

	Incident diagnoses of psychiatric disorder analysis		Incident prescriptions of psychotropic medication analysis	
	Tested for COVID-19 (*n* = 86,529)	**Total (*n* = 308,400)**	**Tested for COVID-19 (*n* = 56,025)**	**Total (*n* = 213,757)**
Mean Age at study period	68.6 (8.2)	68.2 (8.1)	68.2 (8.3)	67.9 (8.1)
Age at study period				
Lower than median (<69 years)	38,652 (44.7%)	143,434 (46.5%)	26,095 (46.6%)	102,662 (48.0%)
Higher than median (≥69 years)	47,877 (55.3%)	164,966 (53.5%)	29,930 (53.4%)	111,095 (52.0%)
Sex				
Female	43,407 (50.2%)	160,555 (52.1%)	25,248 (45.1%)	102,014 (47.7%)
Male	43,122 (49.8%)	147,845 (47.9%)	30,777 (54.9%)	111,743 (52.3%)
Townsend deprivation index				
Lower than median (<−2.15)	43,348 (50.1%)	157,725 (51.1%)	28,266 (50.5%)	110,227 (51.6%)
Higher than median (≥−2.15)	43,069 (49.8%)	150,315 (48.7%)	27,690 (49.4%)	103,262 (48.3%)
Unknown	112 (0.1%)	360 (0.1%)	69 (0.1%)	268 (0.1%)
Ethnicity				
White	80,465 (93.0%)	287,622 (93.3%)	52,204 (93.2%)	199,806 (93.5%)
Mixed	548 (0.6%)	1860 (0.6%)	368 (0.7%)	1280 (0.6%)
Black	2304 (2.7%)	8203 (2.7%)	1407 (2.5%)	5455 (2.6%)
Asian	1834 (2.1%)	5974 (1.9%)	1156 (2.1%)	3996 (1.9%)
Other	935 (1.1%)	3042 (1.0%)	592 (1.1%)	2045 (1.0%)
Unknown	452 (0.5%)	1699 (0.6%)	298 (0.5%)	1175 (0.5%)
Annual Income				
≤£ 18,000	14,624 (16.9%)	51,482 (16.7%)	8408 (15.0%)	32,427 (15.2%)
£ 18,000–£ 30,999	17,945 (20.7%)	65,657 (21.3%)	11,330 (20.2%)	44,882 (21.0%)
£ 31,000–£ 51,999	19,402 (22.4%)	70,671 (22.9%)	13,062 (23.3%)	50,497 (23.6%)
£ 52,000–£ 100,000	16,131 (18.6%)	57,775 (18.7%)	11,506 (20.5%)	43,253 (20.2%)
≥£ 100,000	5378 (6.2%)	16,337 (5.3%)	4085 (7.3%)	12,838 (6.0%)
Unknown	13,049 (15.1%)	46,478 (15.1%)	7634 (13.6%)	29,860 (14.0%)
College education				
Without	42,749 (49.4%)	152,771 (49.5%)	27,123 (48.4%)	103,999 (48.7%)
With	28,081 (32.5%)	102,532 (33.2%)	20,346 (36.3%)	77,723 (36.4%)
Unknown	15,699 (18.1%)	53,097 (17.2%)	8556 (15.3%)	32,035 (15.0%)
Body mass index, kg/m^2[a]				
<18.5	318 (0.4%)	1379 (0.4%)	206 (0.4%)	1007 (0.5%)
18.5–24.9	26,402 (30.5%)	101,551 (32.9%)	17,858 (31.9%)	73,030 (34.2%)
25–29.9	37,425 (43.3%)	133,261 (43.2%)	24,543 (43.8%)	93,138 (43.6%)
≥30	21,866 (25.3%)	70,586 (22.9%)	13,087 (23.4%)	45,538 (21.3%)
Unknown	518 (0.6%)	1623 (0.5%)	331 (0.6%)	1044 (0.5%)
Charlson comorbidity index[b]				
0	48,638 (56.2%)	205,458 (66.6%)	33,683 (60.1%)	149,850 (70.1%)
≥1	37,891 (43.8%)	102,942 (33.4%)	22,342 (39.9%)	63,907 (29.9%)

[a]The Body mass index was calculated using weight kilograms (kg) by the square of height in meters (m^2).
[b]The Charlson comorbidity index was calculated based on the UK Biobank inpatient hospital data.

disorders from HES in England have been validated, indicating a positive predictive value of up to 75% for depression and <60% for anxiety [20]. Prescription of psychotropic medications was ascertained through mapping the UK Biobank prescription codes (i.e., dm+d and local EMIS codes) to their corresponding active ingredients using dm+d XML Transformation Tool and UK Biobank Data-Coding 7678 resource [19]. The active ingredients were then matched to the WHO Atomical Therapeutic Chemical (ATC) classification system [21], and the ingredients (e.g., doxepin, esketamine) with more than one matched ATC codes were discarded as it is difficult to disentangle therapeutic targets. We extracted information (i.e., prescription code and date) about anxiolytics (N05B) and antidepressants (N06A) in the analysis. Supplementary Table S1 provides a list of the active ingredients and their corresponding ATC codes used in this study.

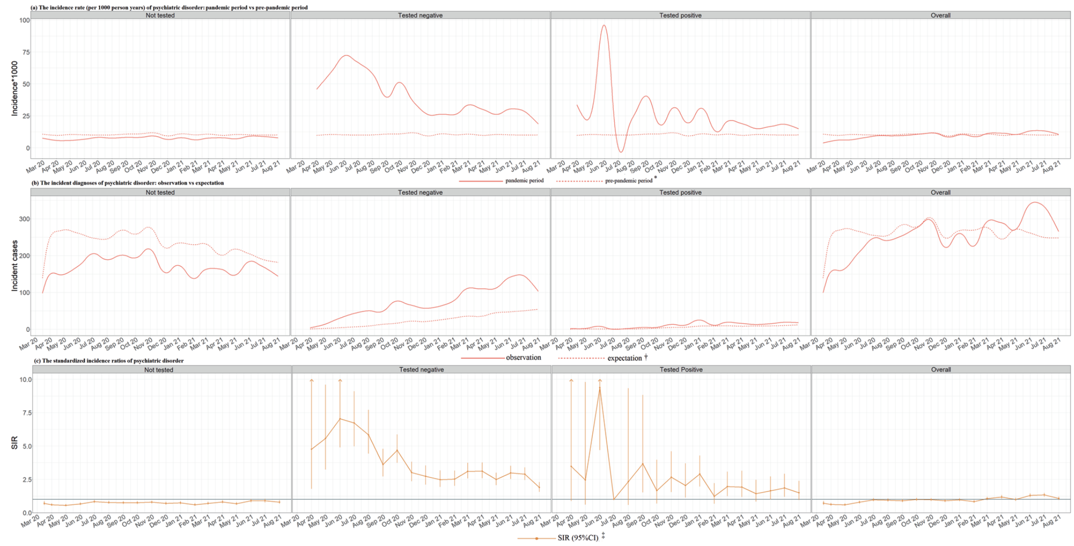

Fig. 2 Period specific incident diagnoses of anxiety and depression disorder. Note, IR incidence rate, SIR standardized incidence ratio. * Three preceding years as the pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019). † The expectation was calculated by multiplying the number of persons by the average month-specific, sex-specific, and age-specific (1-year strata) incidence rate derived from pre-pandemic period. ‡ The standardized incidence ratio was calculated by comparing the number of observed incident cases with the expectation.

Stratification by history of COVID-19 testing

Accounting for the reported variations in psychological implications of COVID-19 pandemic among populations with different exposure level, we categorized the participants into three pandemic exposure groups, using the history COVID-19 testig as an indicator (i.e., not tested, tested negative, and tested positive). As the testing status could change over time, the categorization was done in a time-varying manner, namely that all participants were in the "not tested" group on 16 March 2020, while those with a record of negative test result in PHE were moved to the "tested negative" group on the date of the corresponding COVID-19 test. Further, individuals not tested or tested negative could move to "tested positive" group on the date of a positive test result as recorded in PHE, or the date of a COVID-19 diagnosis (ICD-10 codes, U07.1 and U07.2) as documented in the UK Biobank inpatient hospital data, if any. Although the UK Biobank population is not representative of the entire UK population, we found largely similar trend in the daily number of COVID-19 cases in the study cohort as that in the whole England (i.e., publicly announced number of cases, Supplementary Fig. S2) [22].

Statistical analysis

We first calculated the crude incidence rates (IRs, dividing the number of outcomes by accumulated person-years at risk) of the incident diagnoses of anxiety or depression as well as prescriptions of psychotropic medications during the pandemic period, respectively. We then calculated the IRs by history of COVID-19 testing (i.e., not tested, tested negative, and tested positive). The comparison between the pandemic and pre-pandemic periods was achieved by applying indirect standardization method to calculate the standardized incidence ratios (SIRs, standardized by age and sex) and their 95% confidence intervals (95%CIs). As psychological well-being may be influenced by seasonal variation, we further calculated the monthly SIRs during the 18-month pandemic period, using the average month-, sex-, and age-specific incidence rate of the studied outcomes from the pre-pandemic period as reference.

Moreover, we performed separate analyses for anxiety and depression as well as for anxiolytics and antidepressants. In addition, to test the robustness of our results to severe somatic conditions, we repeated all analyses after excluding participants with severe somatic diseases (i.e., those included in Charlson comorbidity index calculation, see Supplementary Table S2) on 16 March 2020. We also conducted a sensitivity analysis by re-defining the pandemic period as 18 May 2020 (i.e., when COVID-19 test was available to everyone with symptoms in the UK) [23] to 31 August 2021.

RESULTS

Among the 308,400 participants of the cohort for incident diagnoses of anxiety or depression (mean age = 68.2, 47.9% male) (Table 1), 4 439 received their first diagnosis of anxiety or depression during the pandemic period, corresponding to an IR of 9.7 per 1000 person-years. The IR was 7.5, 33.2, and 21.3 per 1000 person-years for participants who had not been tested, had tested negative, and tested positive for COVID-19, respectively. When compared with the IR of the pre-pandemic period (10.4 per 1000 person-years), we observed a decrease in incident diagnoses of anxiety or depression among participants not tested for COVID-19 (SIR 0.70 [95% CI 0.67–0.72]), but an increase in incident diagnoses of anxiety or depression among participants tested for COVID-19, irrespective of test result (tested negative: 3.05 [2.88–3.22]; tested positive: 2.03 [1.76–2.34]). Among the 213 757 participants included in the cohort of incident prescriptions of psychotropic medications (mean age = 67.9, 52.3% male) (Table 1), we observed largely similar risk patterns. For instance, there was a decrease in incident medication prescriptions among those not tested (0.70 [0.68–0.72]), but an increase in incident medication prescriptions among those tested for COVID-19 (tested negative: 1.56 [1.47–1.67]; tested positive: 1.41 [1.22–1.62]) during the pandemic period, compared with the pre-pandemic period.

The analysis of seasonal variation showed a lower overall risk for incident diagnoses of anxiety or depression during the pandemic period when compared to the pre-pandemic period, except in June 2021 (1.30 [1.17–1.45]) and July 2021 (1.34 [1.20–1.49]) (Fig. 2). We again obtained different results when separately analyzing by history of COVID-19 testing, with an increased incidence rate among individuals tested for COVID-19, especially during the beginning of the pandemic (i.e., March 2020 - September 2020; tested negative: SIRs 3.61–7.05, tested positive: SIRs 2.33–9.38), whereas a decreased incidence rate among those not tested during the entire 18-month period (SIRs 0.55–0.90). Similar results were obtained for incident prescriptions of anxiolytics or antidepressants (Fig. 3). There was an increase in incidence rate of these psychotropic medications during the first six months of

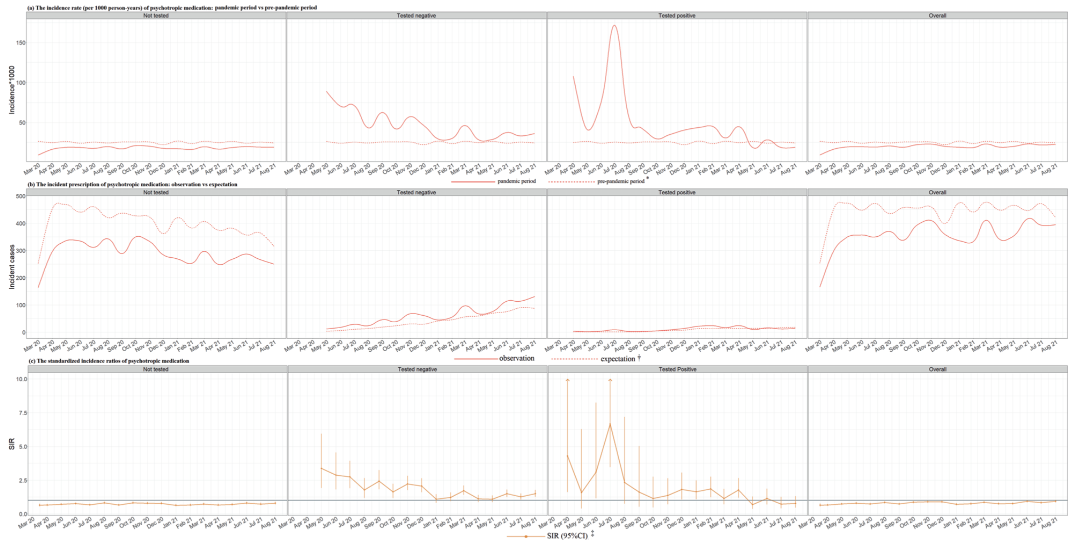

Fig. 3 Period specific incident prescription of anxiolytics and antidepressants. Note, IR incidence rate, SIR standardized incidence ratio. * Three preceding years as the pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019). † The expectation was calculated by multiplying the number of persons by the average month-specific, sex-specific, and age-specific (1-year strata) incidence rate derived from pre-pandemic period. ‡ The standardized incidence ratio was calculated by comparing the number of observed incident cases with the expectation.

the pandemic among individuals tested for COVID-19 (tested negative: SIRs 1.78–3.38; tested positive: SIRs 1.57–6.66), but a constantly lower incidence rates among those not tested for COVID-19 (SIRs 0.64–0.82).

We observed largely comparable results when analyzing anxiety and depression, as well as anxiolytics and antidepressants, separately (Supplementary Figs. S3 and S4). These findings remained robust after excluding participants with pre-existing severe somatic diseases (Supplementary Figs. S5 and S6) and after re-defining the pandemic period from 18 May 2020 (Supplementary Figs. S7 and S8).

DISCUSSION

In general, the findings of this study based on the UK Biobank indicate that individuals tested for COVID-19, irrespective of the test result, experienced a rise in the incident diagnosis of anxiety and depression as well as respective medication use, particularly at the beginning of the pandemic. In contrast, we observed a decrease in incident diagnoses of anxiety and depression as well as prescriptions of respective psychotropic medications during the pandemic in the general population not tested for COVID-19, yet with an increase beyond pre-pandemic levels in mid 2021.

The finding on lower incidence rates of anxiety and depression as well as prescriptions of psychotropic medications in the general population may reflect a decrease in general psychiatric healthcare utilization during the first 18 months of the pandemic. In line with our findings, a drop in psychiatric emergency visits and hospital admission during the pandemic has previously been reported in other European countries [24, 25]. For instance, in Italy, a 37.5% decrease in the number of psychiatric emergency consultations was observed during the lockdown (March-May 2020) and 17.9% after the lockdown period [26]. Similarly, a retrospective study in Spain suggested that the most marked reduction in admission rates during lockdown (March-June 2020) was observed for anxiety-related disorders [27]. Moreover, addition to the political restriction [23], as SARS-CoV-2 is highly infectious, people may intentionally delay or avoid seeking medical care during the unprecedented period. The findings of Czeisler et al. reported that 12% of US adults delayed or avoided emergency care and 32% avoided routine medical care [28]. Existing evidence about the trends of incident antidepressants and anxiolythics prescriptions during the pandemic is inconsistent. For instance, Antonazzo et al suggested an abrupt reduction of incident antidepressants use during the lockdown in Italy, with a following rebound during the post-lockdown period [29], while a continuing increase in new antidepressant use was observed during the first year of the pandemic in Australia [30]. Furthermore, age-group differences have been noted in the consumption of psychotropic medications, with the most significant increase found in the younger population [30, 31].

The observed decrease in incident diagnoses in the general population appeared to be mainly attributable to individuals not tested for COVID-19. Thus, it is also possible that the decrease in incident diagnoses might reflect lower prevalence of psychiatric morbidity in this population because people might have spent more time with family and friends or had slower pace of daily life during the pandemic [32]. Indeed, the protective effects of family and friends' support on depressive symptoms and PTSD symptoms are well-documented [33, 34]. Additionally, a recent study from France reported improved sleep in the general population during the pandemic which might positively affect mental health [35]. Regardless, as the effect of pandemic on population mental health is complex and profound, future research focused on both negative and positive aspects of the crisis is needed.

In contrast, the increase in incident psychiatric morbidities among individuals tested for COVID-19 may have several explanations. It is conceivable that people tested for COVID-19 might have been exposed to infected individuals or be symptomatic, and the psychological burden of suspecting to be infected may contribute to the observed increase. Testing for COVID-19 itself and waiting for the test result might also be stressful and associated with increased anxiety [36]. One study showed that more than half of patients suspected to have COVID-19 had increased psychotropic medication prescriptions [37]. Alternatively, individuals who had taken a COVID-19 test might also have temporarily reduced social contact, i.e., being quarantined or isolated, to avoid infecting others, resulting in negative impact on mental health [38]. On the other hand, studies conducted by our [39, 40] and other research groups [41] demonstrated a bidirectional association between COVID-19 and psychiatric disorders, suggesting that individuals with propensity for psychiatric disorders may be more vulnerable for COVID-19 infection and adverse outcomes. With respect to the test result, we observed a similar increased risk of anxiety and depression for individuals with both negative and positive results, which is in agreement with Abel et al.'s finding [12]. Likewise, when compared to tested negative individuals, a Danish registry study found that there was no significant increase in risk for initiation of new antidepressants among tested positive individuals [42]. However, Klaser et al reported that symptoms of anxiety and depression were slightly more prevalent among individuals tested positive compared to those tested negative for COVID-19 [43].

The most notable increase in incident diagnoses of anxiety and depression among COVID-19 tested group was found at the beginning of the pandemic. One reason for the temporary spike at the initial stage of the pandemic is the uncertainty about the virus at that timpoint [44]. Fear of being infected or infecting others may trigger psychological distress. The less or insignificantly elevated incidence rates in later periods of pandemic in this population may be attributed to population adaptation of the COVID-19 crisis [45] and the wide implementation of vaccination in the UK [46], which might have reduced stress or distress. Regardless, as the increased incidence rates persisted nearly the entire 18-month pandemic period, further research with longer follow-up is warranted to understand the continued impact of the pandemic on population mental health.

Study strengths include the use of timely updated UK Biobank primary care and PHE data, which enabled us to explore the long-term psychological consequences among individuals with different history of COVID-19 testing during the pandemic. Moreover, the application of self-comparison analysis, where the rate of incident events during the pandemic period was compared with the corresponding age- and sex-specific rate of the three preceding years in the same study population, inherently allows for the control for potential confounders that are constant over time, including genetic factors and many environmental factors that did not change greatly within the study period. In addition, we carefully considered the impact of seasonal variation through analyzing monthly SIRs.

One major concern of our study is the varying access to COVID-19 testing between groups of the study participants and during different parts of the pandemic period. We therefore performed sensitivity analyses through excluding participants with severe pre-pandemic comorbidities or re-defining pandemic period from 18 May 2020, which suggested some but limited influence of this concern. Also, regardless of test result, it is further possible that some other factors determined the likelihood of taking a COVID-19 test. For example, seeking or receiving a COVID-19 tests may indicate higher level of medical care utilization and therefore increased possibility of being diagnosed or prescribed for existing psychiatric symptoms (i.e., surveillance bias). However, the impact of such a concern, if any, should be constant throughout the whole study period, whilst the change in incident diagnoses and drug prescriptions for anxiety and depression was indeed time-varying, suggesting potential contribution of other causes, such as temporary psychological burden caused by COVID-19-related exposures or reduced social contacts. In addition, considering the overloaded healthcare system during the pandemic period, our outcome identification strategy (using diagnoses and drug prescriptions from both primary care and hospital inpatient data) is likely to only capture patients with more severe psychiatric symptoms. Conditions for individuals with less severe symptoms who did not seek medical care need to be studied in future studies. Likewise, as our identification of COVID-19 cases relies solely on RT-PCR testing (but not self-tests which became available in UK since January 2021 [47]), individuals testing positive for COVID-19 on RT-PCR are more likely represented by those have been symptomatic. Moreover, the sample size of individuals tested positive for COVID-19 was relatively small yielding insufficient precision to depict the monthly variations during the pandemic period, and the absence of data on acute COVID-19 severity prohibit the assessment of trends by varying COVID-19 severity. Also, varying mortality rates in the studied groups and the resulting competing risks may have resulted in an underestimated relative risks of psychiatric outcomes, particularly among individuals with COVID-19 [48]. Furthermore, the UK Biobank primary care data are only available for participants registered at TPP and EMIS system in England, whereas the prescriptions of psychotropic medications cannot be assumed to equal actual consumption of these medications [19]. Finally, the UK Biobank only recruited 5.5% of the UK population, mainly elderly white people, thus, our results cannot necessarily be generalized to the entire UK population or other populations.

CONCLUSION

In conclusion, the findings of this study suggest differential population mental health care utilization during the COVID-19 pandemic by level of pandemic exposure indicated by history of COVID-19 testing. Compared to the pre-pandemic period, we observed a decrease in incident diagnoses of anxiety and depression as well as prescriptions of respective psychotropic medications among individuals not tested for COVID-19, but an increase in incident psychiatric morbidity among those tested for COVID-19, irrespective of the test result, particularly at the beginning of COVID-19 pandemic.

DATA AVAILABILITY

Data from the UK Biobank (http://www.ukbiobank.ac.uk/) are available to all researchers upon making an application.

CODE AVAILABILITY

All analyses were performed in R version 4.0. Codes associated with the current submission is available and can be requested by contacting the corresponding author.

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AUTHOR CONTRIBUTIONS

UAV and HS were responsible for the study's concept and design. HY did the data and project management. YW, FG, and JW did the data cleaning and analysis. YW, UAV, and HS interpreted the data. YW, UAV, and HS drafted the manuscript. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

UAV has received grants for the current work from Nordforsk and grants outside the current work from the Icelandic Research Fund, Swedish Research Council, Swedish Cancer Society, and the European Research Council. HZ was an employee of the Centre for Big Data Research in Health at UNSW, which received a research grant from AbbVie Australia in 2020, unrelated to the current study. All other authors declare that they have no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-023-02315-7.

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Supplementary

Supplementary Tables

Table S1 Active ingredients and Anatomical Therapeutic Chemical (ATC) code of studied psychotropic medications

ATC code	Active ingredients	ATC code	Active ingredients	ATC code	Active ingredients
N05BA01	Diazepam	N06AA07	Lofepramine	N06AX01	Oxitriptan
N05BA02	Chlordiazepoxide	N06AA09	Amitriptyline	N06AX02	Tryptophan
N05BA04	Oxazepam	N06AA10	Nortriptyline	N06AX03	Mianserin
N05BA06	Lorazepam	N06AA11	Protriptyline	N06AX05	Trazodone
N05BA08	Bromazepam	N06AA16	Dosulepin	N06AX06	Nefazodone
N05BA09	Clobazam	N06AA17	Amoxapine	N06AX09	Viloxazine
N05BA11	Prazepam	N06AA21	Maprotiline	N06AX11	Mirtazapine
N05BA12	Alprazolam	N06AB03	Fluoxetine	N06AX12	Bupropion
N05BB01	Hydroxyzine	N06AB04	Citalopram	N06AX16	Venlafaxine
N05BC01	Meprobamate	N06AB05	Paroxetine	N06AX17	Milnacipran
N05BE01	Buspirone	N06AB06	Sertraline	N06AX18	Reboxetine
N06AA01	Desipramine	N06AB08	Fluvoxamine	N06AX21	Duloxetine
N06AA02	Imipramine	N06AB10	Escitalopram	N06AX22	Agomelatine
N06AA04	Clomipramine	N06AF01	Isocarboxazid	N06AX26	Vortioxetine
N06AA06	Trimipramine	N06AF03	Phenelzine	-	-

Table S2 Diseases used for calculating Charlson comorbidity index

Disease	ICD-10 code
Myocardial infarction	I21, I22, I252
Congestive heart failure	I110, I130, I132, I50
Peripheral vascular disease	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, R02, Z958, Z959
Cerebrovascular disease	I60-I69, G45, G46
Dementia	F00, F01, F02, F03, F051, G30, G311
Chronic pulmonary disease	J40-J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J70, J841, J920, J961, J982
Connective tissue disease	M05, M06, M30, M315, M32, M33, M34, M351, M353, M360
Ulcer disease	K25, K26, K27, K28
Mild liver disease	B18, K700, K701, K702, K703, K709, K713, K714, K715, K717, K73, K74, K760, K762, K763, K764, K768, K769,
Diabetes mellitus	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149,
Hemiplegia	G041, G114, G801, G802, G81, G82, G839, G830, G831, G832, G833, G834
Moderate/severe renal disease	I120, I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N18, N19, N250, Z940, Z992
Diabetes mellitus with chronic complications	E102, E103, E104, E105, E107, E112-E115, E122-E125, E132- E135, E142- E145, E117, E127, E137, E147
Any tumor	C00-C14, C15-C26, C30-C34, C37-C41, C43, C45-C49, C50-C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C76, C97
Leukemia	C91, C92, C93, C94, C95
Lymphoma	C81, C82, C83, C84, C85, C88, C90, C96
Moderate/severe liver disease	I85, K704, K72, K766
Metastatic solid tumor	C77, C78, C79, C80
AIDS	B20, B21, B22, B23, B24

Supplementary Figures

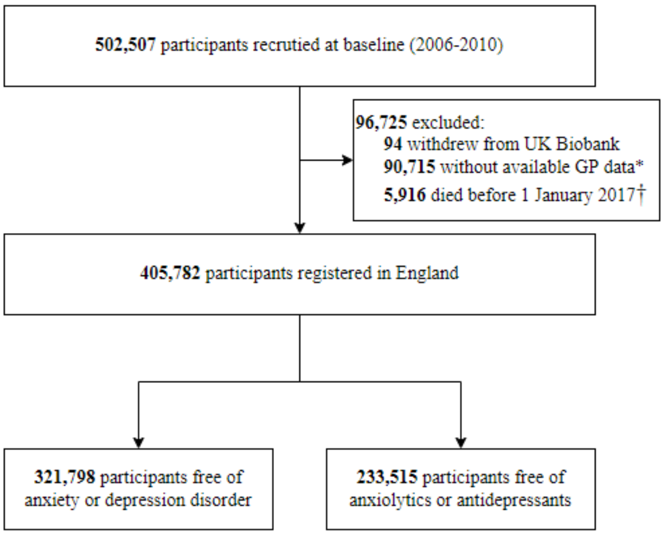

Fig. S1 Flow chart of the pre-pandemic reference population

* The primary care data were only available for participants registered in England and registered at a practice using TPP or EMIS as their data system supplier.

† Considering aging of the population, we used three preceding years as the pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019).

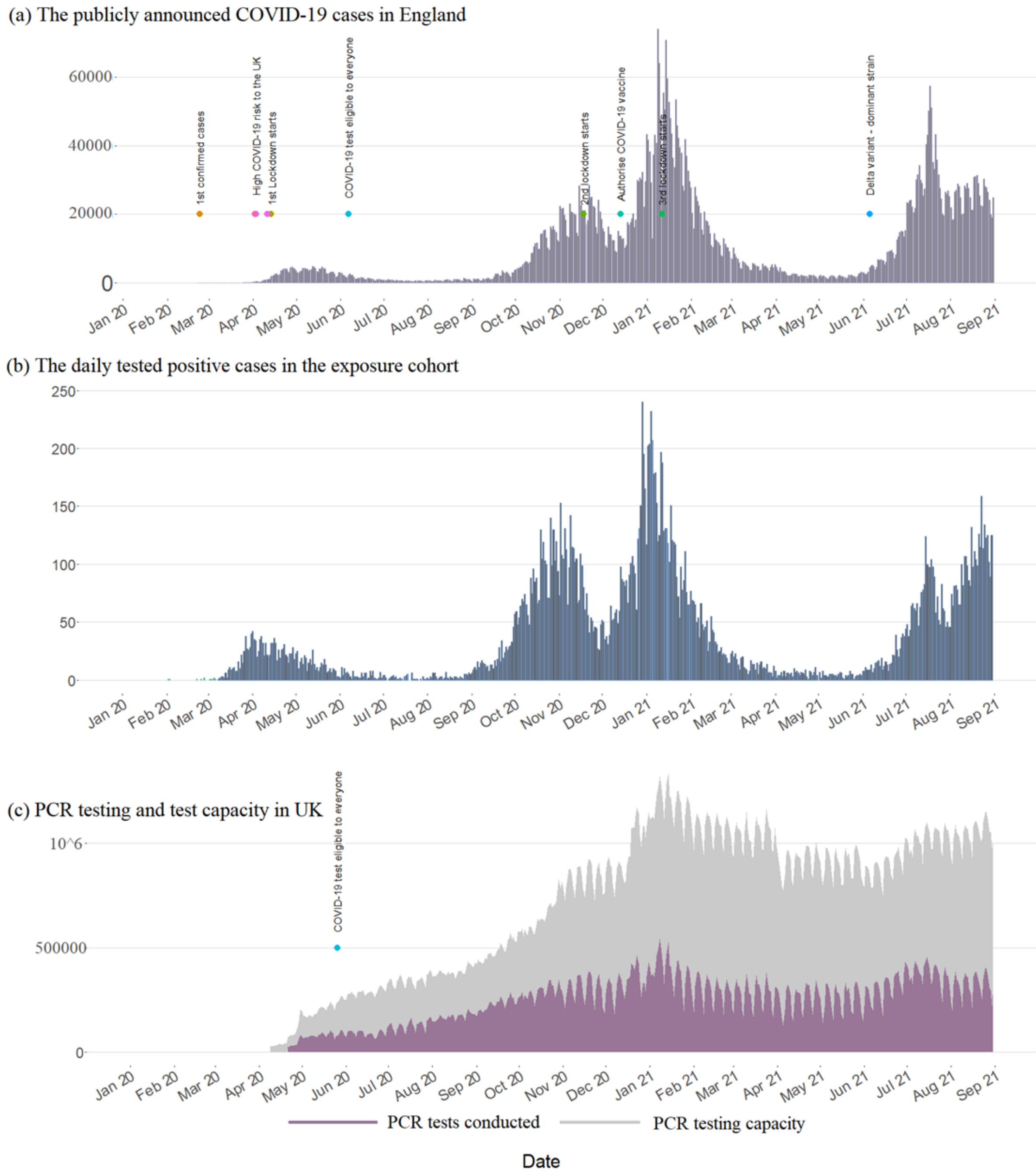

Fig. S2 The publicly announced COVID-19 cases in England and the PCR testing capacity in UK

Note, we obtained the publicly announced COVID-19 cases in England and PCR testing capacity from the official UK government website for data and insights on COVID-19 (https://coronavirus.data.gov.uk/details/cases).

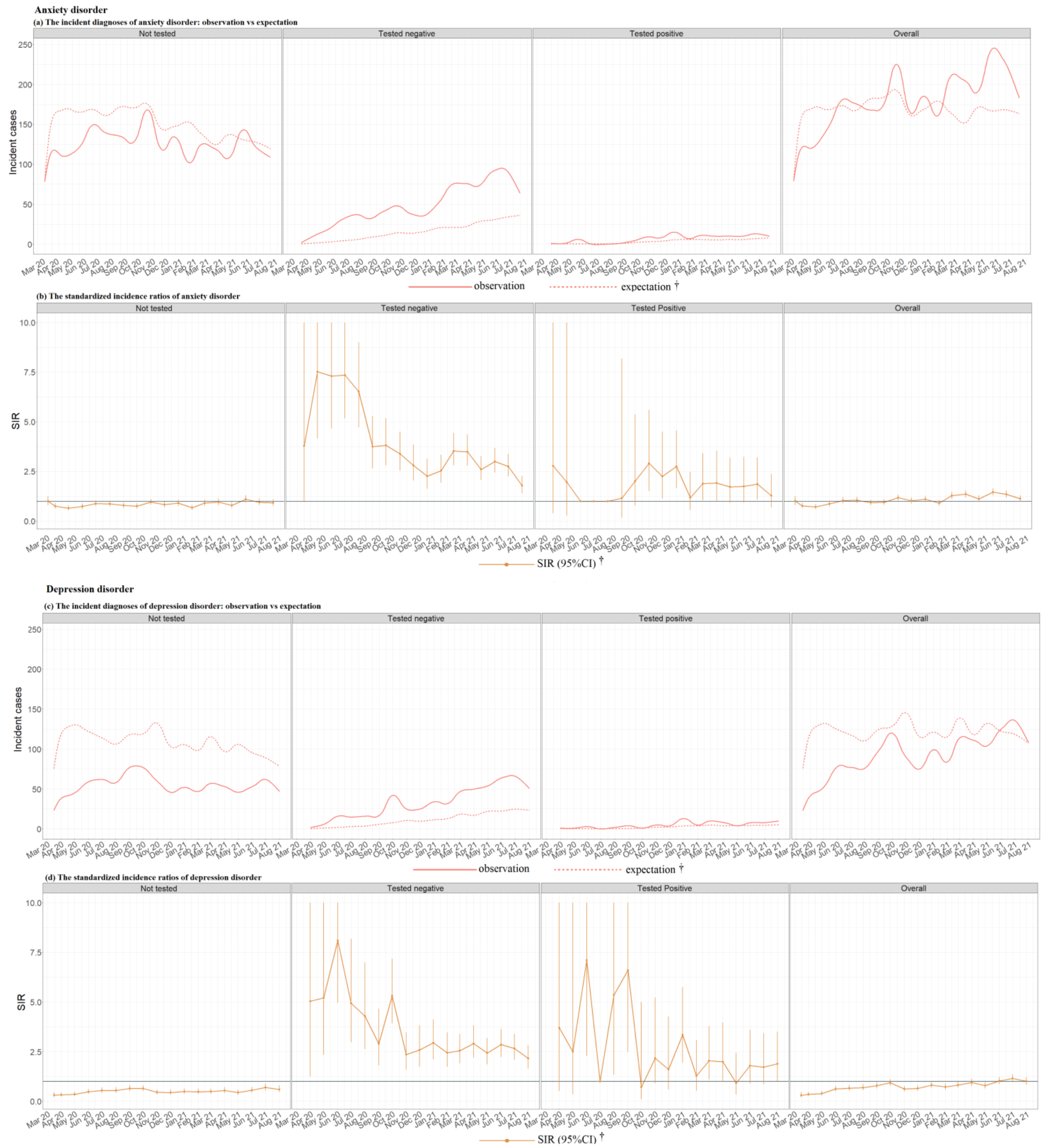

Fig. S3 Period specific incidence of anxiety and depression disorder: in subgroup analysis

* The expectation was calculated by multiplying the number of persons by the average month-specific, sex-specific, and age-specific (1-year strata) incidence rate derived from pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019).

† SIR, standardized incidence ratio. SIR was calculated by comparing the number of observed incident cases with the expectation.

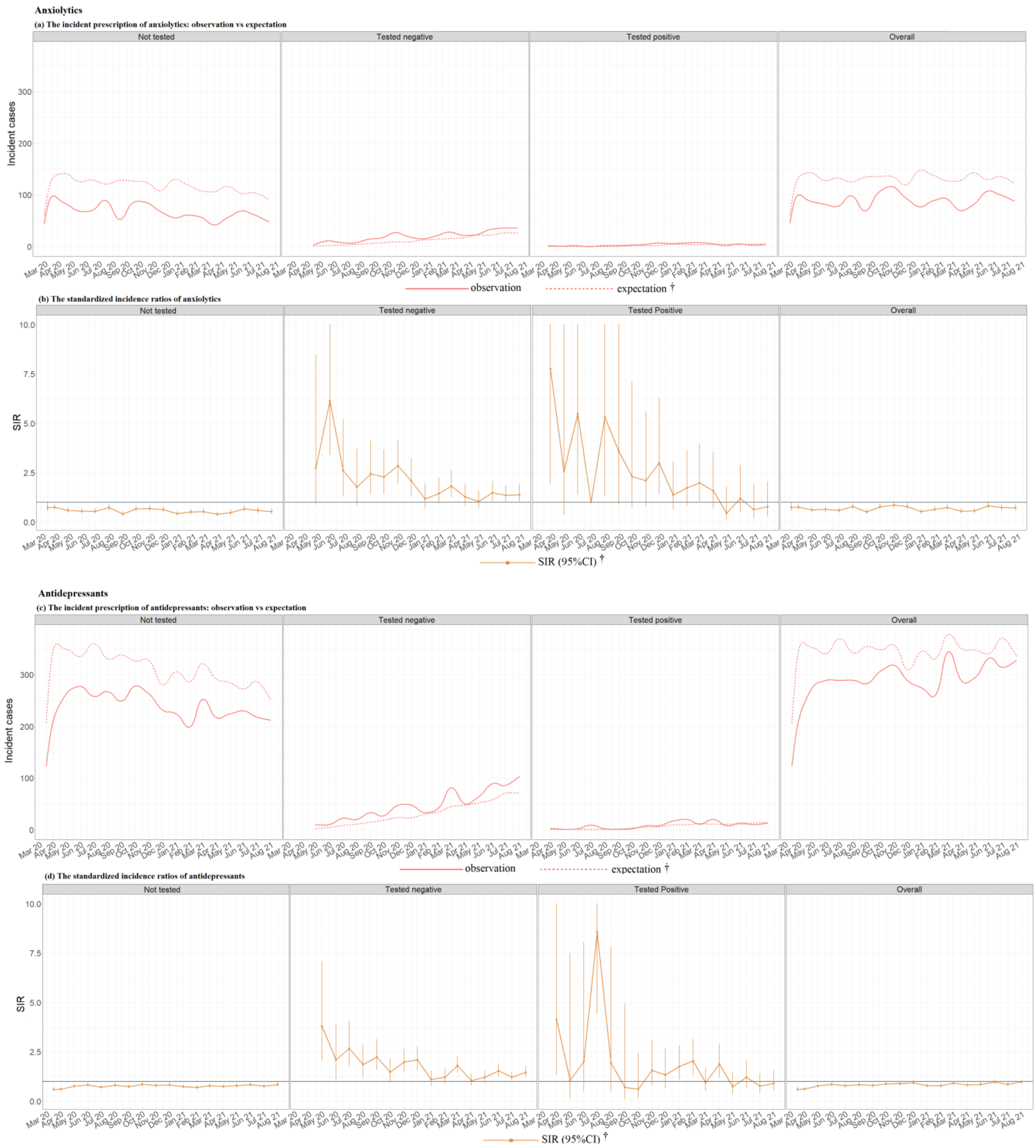

Fig. S4 Period specific incidence of anxiolytics and antidepressants prescription: in subgroup analysis

* The expectation was calculated by multiplying the number of persons by the average month-specific, sex-specific, and age-specific (1-year strata) incidence rate derived from pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019).

† SIR, standardized incidence ratio. SIR was calculated by comparing the number of observed incident cases with the expectation.

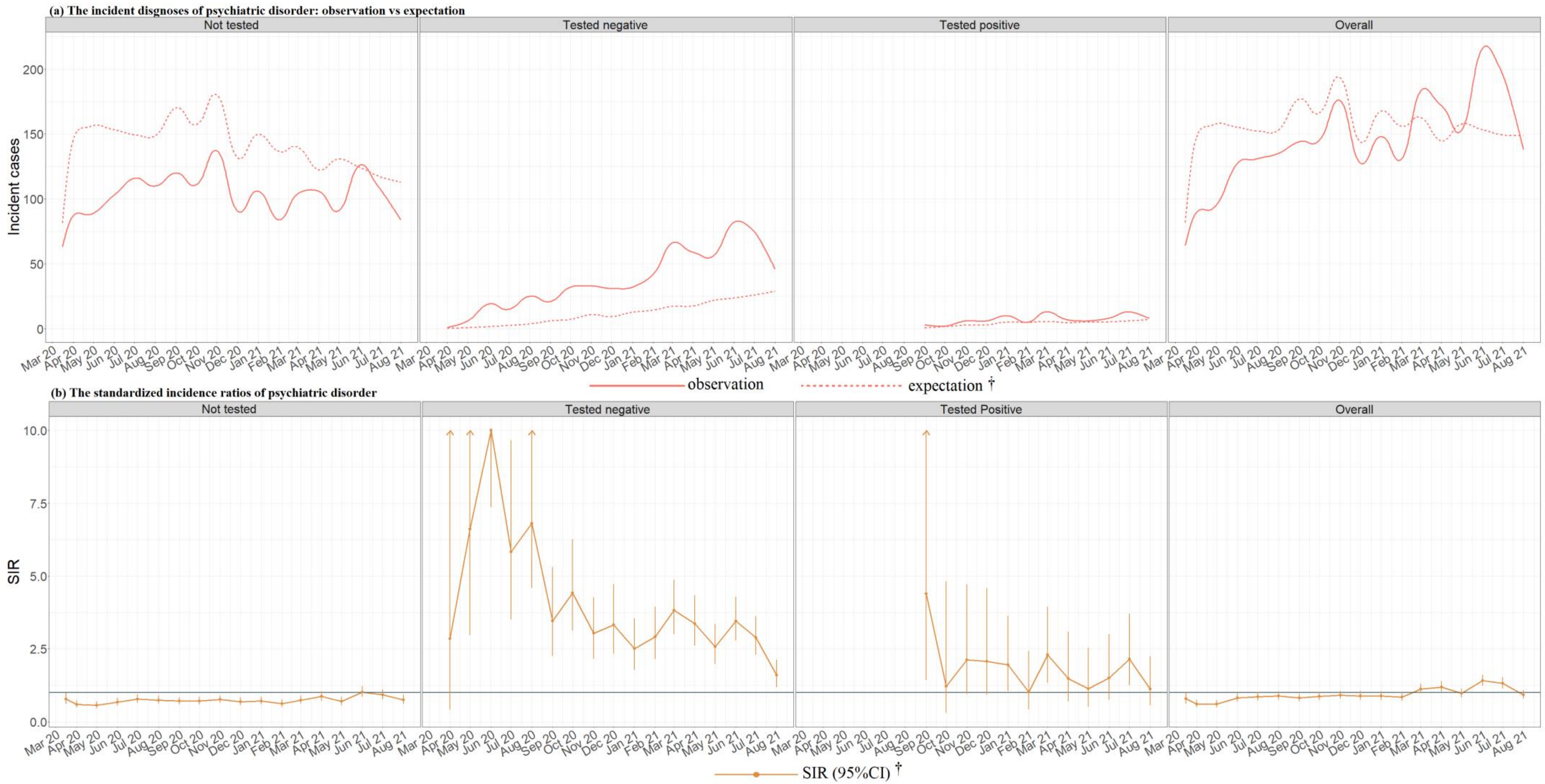

Fig. S5 Period specific incidence of anxiety and depression disorder: excluding participants with any severe somatic diseases (Charlson comorbidity index ≥1)

* The expectation was calculated by multiplying the number of persons by the average month-specific, sex-specific, and age-specific (1-year strata) incidence rate derived from pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019).

† SIR, standardized incidence ratio. SIR was calculated by comparing the number of observed incident cases with the expectatio.

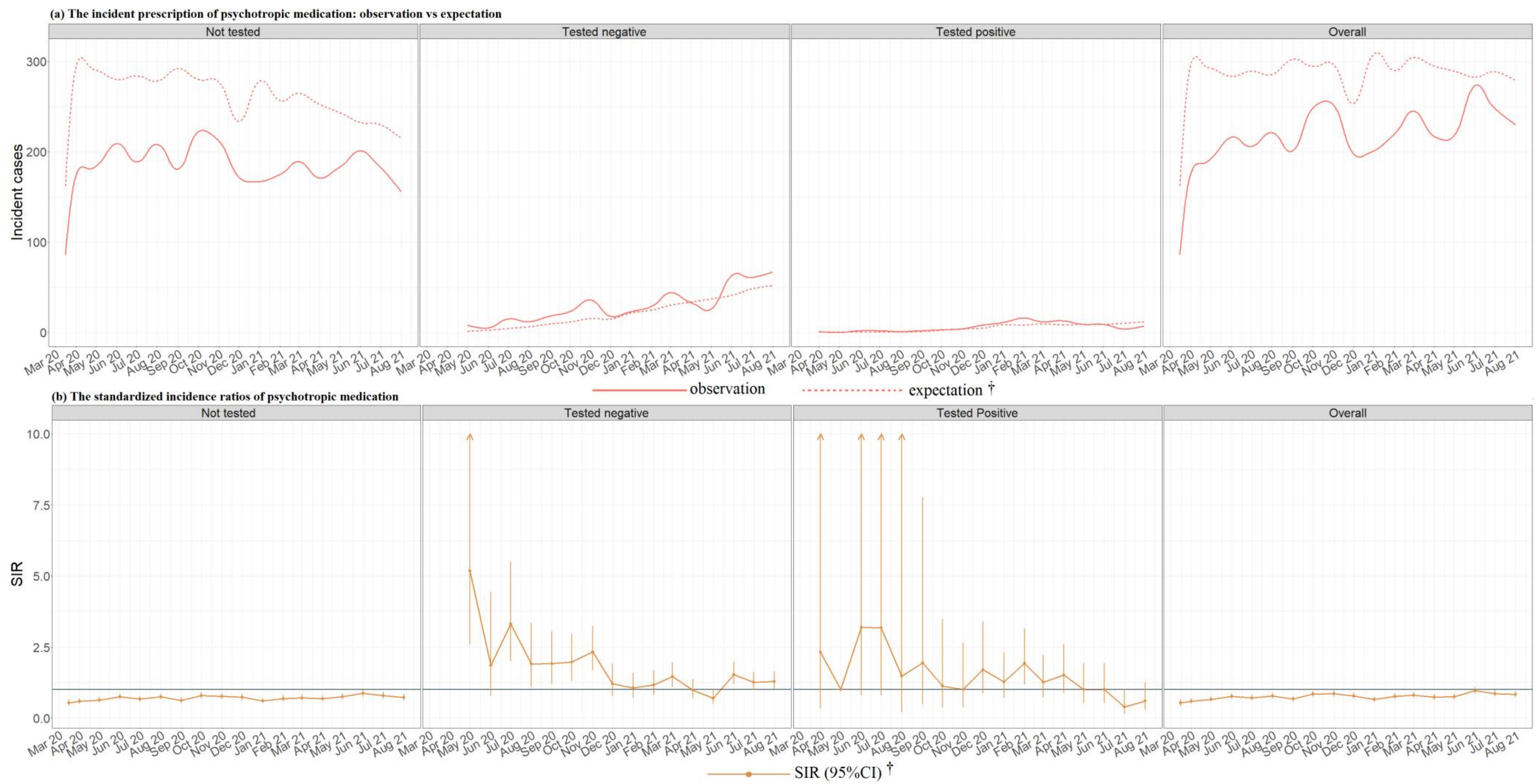

Fig. S6 Period specific incidence of anxiolytics and antidepressants prescription: excluding participants with any severe somatic diseases (Charlson comorbidity index ≥1)

* The expectation was calculated by multiplying the number of persons by the average month-specific, sex-specific, and age-specific (1-year strata) incidence rate derived from pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019).

† SIR, standardized incidence ratio. SIR was calculated by comparing the number of observed incident cases with the expectation.

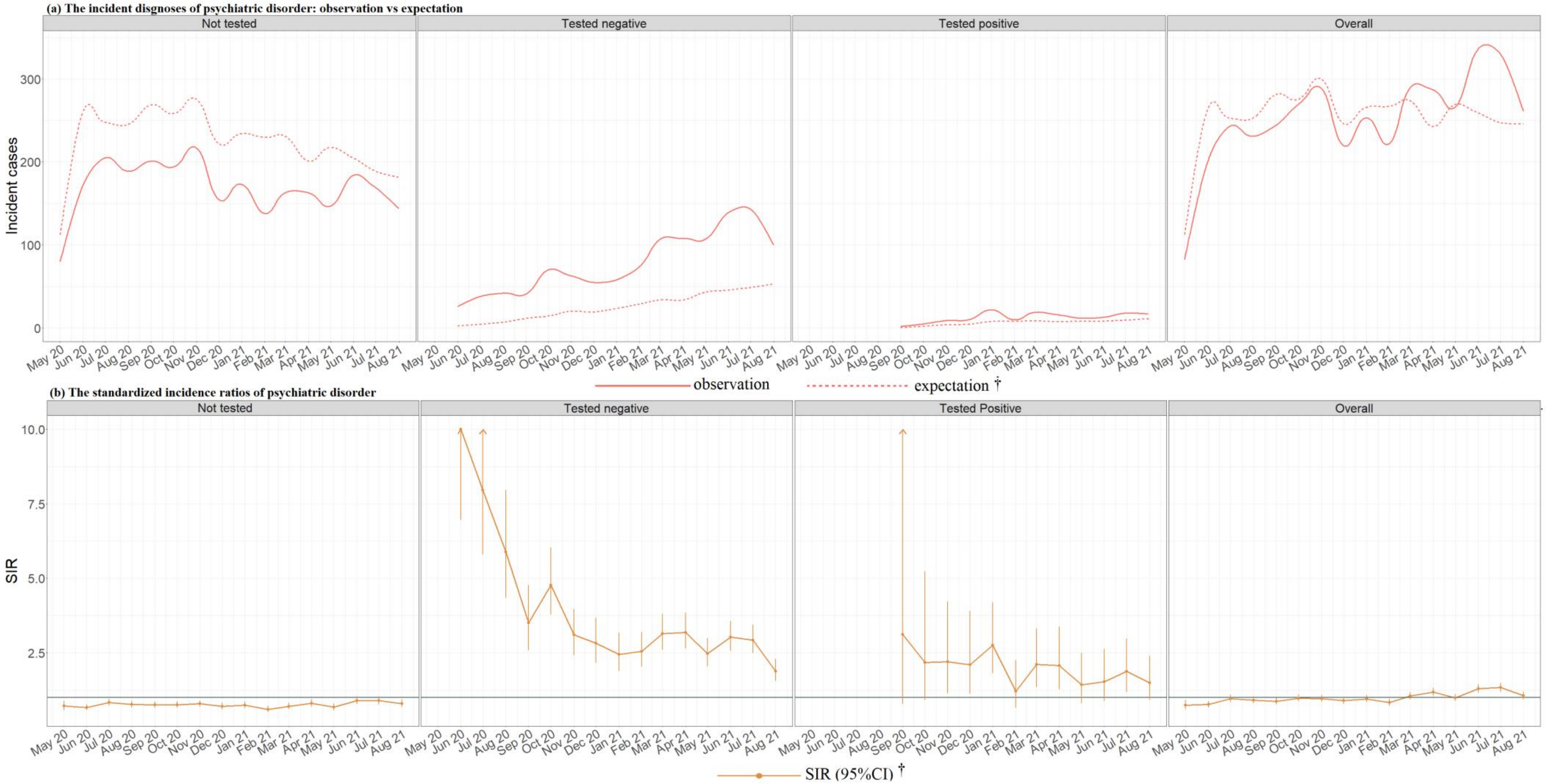

Fig. S7 Period specific incidence of anxiety and depression disorder: starting the pandemic period on 18 May 2020 (i.e, when COVID-19 test eligible to everyone with symptoms in the UK)

* The expectation was calculated by multiplying the number of persons by the average month-specific, sex-specific, and age-specific (1-year strata) incidence rate derived from pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019).

† SIR, standardized incidence ratio. SIR was calculated by comparing the number of observed incident cases with the expectation.

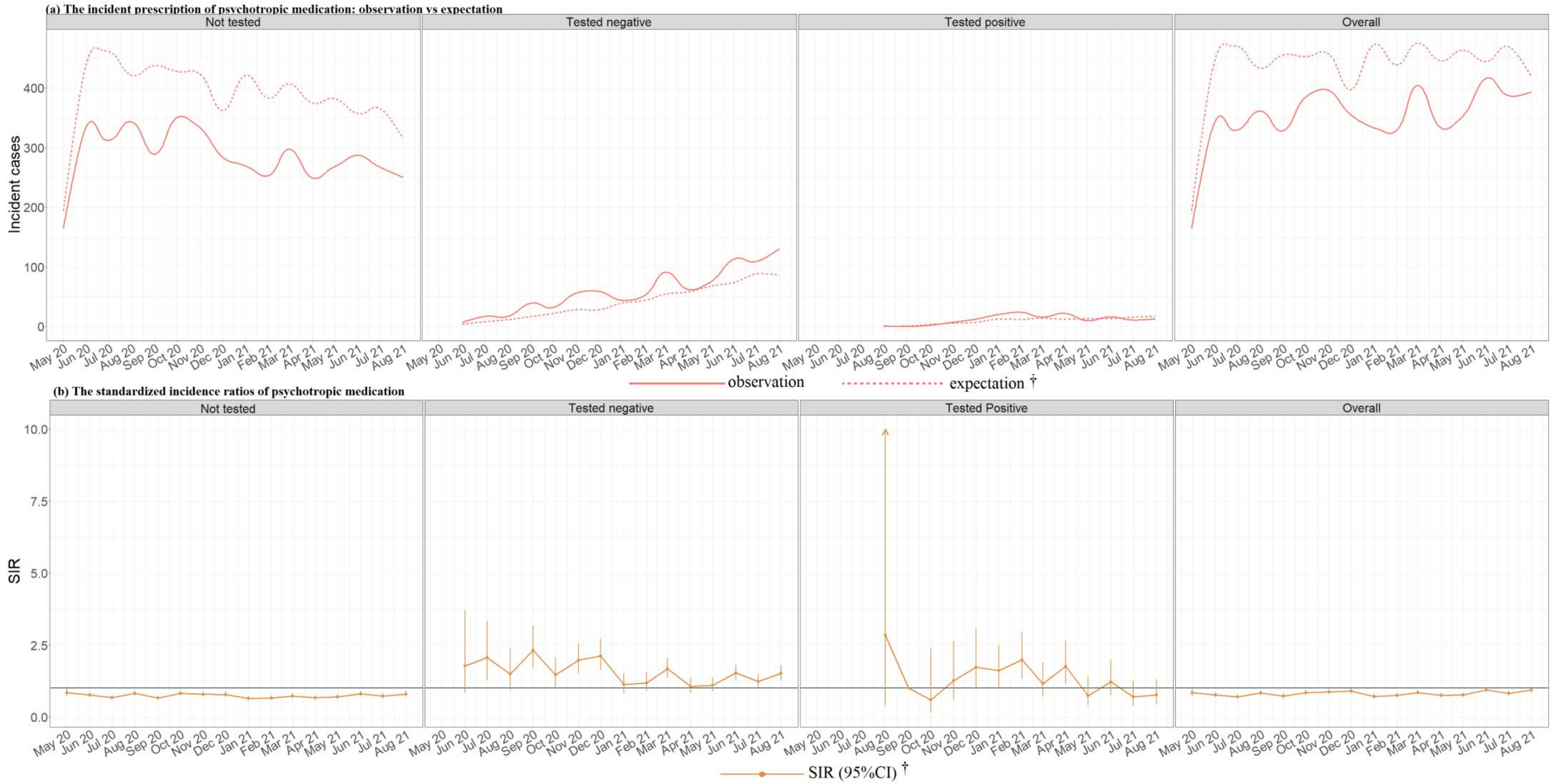

Fig. S8 Period specific incidence of anxiolytics and antidepressants prescription: starting the pandemic period on 18 May 2020 (i.e, when COVID-19 test eligible to everyone with symptoms in the UK)

* The expectation was calculated by multiplying the number of persons by the average month-specific, sex-specific, and age-specific (1-year strata) incidence rate derived from pre-pandemic period (i.e., from 1 January 2017 to 31 December 2019).

† SIR, standardized incidence ratio. SIR was calculated by comparing the number of observed incident cases with the expectation.

Paper III

Paper III

BMJ Public Health

Depressive symptom trajectories among general population during the COVID-19 pandemic in Iceland: a prospective cohort study (2020–2023)

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ABSTRACT

Introduction While changes in the prevalence of depressive symptoms during the COVID-19 pandemic have been described across populations, few studies have incorporated multidimensional variables to characterise the varying effects of the pandemic on the population's mental health.

Methods This cohort study included 6423 participants aged ≥18 years from the Icelandic COVID-19 National Resilience Cohort. Data on depressive symptoms and pandemic-related and non-pandemic-related factors were obtained during three pandemic assessment periods (baseline, follow-up wave 1 and follow-up wave 2; April 2020–December 2021), while health outcomes were obtained during the post-pandemic assessment period (follow-up wave 3; September 2022–February 2023). We used latent growth mixture models to identify variation in depressive symptom trajectories during the pandemic. We then used XGBoost models with 37 pandemic-related and non-pandemic-related factors to characterise these trajectories. Moreover, we performed linear regression to assess the association between the identified trajectories and post-pandemic health outcomes.

Results Of the included participants, we identified four depressive symptom trajectories, including consistently low (83.7%), consistently high (5.3%), initially high (5.1%) and late-onset high (5.9%) symptom trajectories. Individuals who exercised frequently (≥3 days/week) and enjoyed social and family support were more likely to experience a consistently low symptom trajectory. In contrast, individuals with a history of psychiatric disorders, women and young adults (18–39 years) were less likely to follow the consistently low symptom trajectory. Moreover, compared with the consistently low symptom trajectory, the other trajectories were associated with significantly higher levels of depressive, anxiety and somatic symptoms and cognitive problems during the post-pandemic period.

Conclusions Our results underscore the long-lasting impact of the COVID-19 pandemic on population mental health. Interventions focusing on exercise, social support and family support may mitigate the adverse mental health effects of future pandemics.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The COVID-19 pandemic had a huge impact on people's daily lives. However, most existing studies have focused on mental health responses during the early stage of the pandemic, and few studies have incorporated multidimensional variables to characterise the depressive symptom trajectories within the general population or examined their post-pandemic health outcomes.

INTRODUCTION

Mental health and well-being of the general population were severely impacted during the COVID-19 pandemic.[1] Indeed, a nationally representative survey among US adults suggested that the prevalence of depressive symptoms was more than threefold higher at the beginning of the pandemic when compared with the pre-pandemic period.[2] A recent meta-regression analysis furthermore suggested that the prevalence of depression in the general population may have increased over time during the pandemic.[3]

Yet, individuals may have experienced different mental health responses during the COVID-19 pandemic and demonstrated heterogeneous mental health trajectories over time.[4 5] For example, Batterham *et al* identified three latent depressive symptom trajectories among a representative sample of Australian adults,[6] including low or

WHAT THIS STUDY ADDS

⇒ Leveraging longitudinal data from the Icelandic COVID-19 National Resilience Cohort, our study identified four distinct depressive symptom trajectories during the pandemic period, with 83.7% of persons showing consistently low, 5.3% consistently high, 5.1% initially high and 5.9% late-onset high depressive symptom burden.

⇒ Individuals who exercised frequently (≥3 days/week) and perceived social and family support were more likely to experience a consistently low symptom trajectory during the pandemic, while those with a history of psychiatric disorders, women and young adults (18–39 years) were less likely to follow the consistently low symptom trajectory.

⇒ Compared with the consistently low symptom trajectory, initially high, late-onset high and consistently high symptom trajectories were associated with elevated post-pandemic health outcomes (ie, depressive, anxiety and somatic symptoms and cognitive problems).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study suggests that the COVID-19 pandemic has had a disproportionate impact on the general population, and strategies targeting those most affected (eg, patients with a history of psychiatric disorders, women and young adults) should be prioritised in future pandemics.

⇒ Identified modifiable protective factors, including physical exercise, family support and social support, may mitigate the impact of the pandemic on population mental health and should be recommended at similar times of crisis.

moderate symptom burden throughout the study period and initially severe followed by declining trajectories. In another sample representative of the adult UK general population,[5] five distinct mental health trajectories (measured by the 12-item General Health Questionnaire) were identified during the first 6 months of the pandemic (April–September 2020), including consistently poor, deteriorating, recovery, consistently good and consistently very good trajectories. Furthermore, these studies have suggested that younger age,[7] a history of mental illness[5 6] and COVID-19-related financial distress[6] were associated with consistently high depressive symptoms during the pandemic.

However, the findings are inconsistent, and most studies have focused on mental health responses during the early stage of the pandemic.[5–7] In addition, although previous studies have examined the role of sociodemographic factors,[8 9] lifestyle factors,[10] quarantine,[11] severity of COVID-19[12] and health service disruptions,[13] few studies have incorporated multidimensional variables to investigate and characterise the varying effects of the pandemic on population mental health. Furthermore, there is a scarcity of follow-up data to explore the long-term outcomes of these trajectories in the post-pandemic period.

To this end, leveraging longitudinal data from the Icelandic COVID-19 National Resilience (C-19 Resilience) Cohort over a period of almost 3 years (ie, from April 2020 to February 2023), we aimed to investigate the variation in depressive symptom trajectories during the COVID-19 pandemic in Iceland, and to further identify the determinants of these varying trajectories as well as the post-pandemic health outcomes associated with each trajectory.

MATERIALS AND METHODS

Study design and participants

We used data from the C-19 Resilience Cohort, which was established in April 2020 and was eligible for all Icelandic-speaking individuals aged ≥18 years in Iceland.[14] The total population in Iceland aged ≥18 years on 1 January 2020 was 273 190.[15] Recruitment of the study sample was mainly through social media and invitations to participants in existing nationwide cohort studies, including the Stress-And-Gene-Analysis cohort,[16] the Iceland Screens, Treats or Prevents Multiple Myeloma study[17] and the Health and Well-Being of Icelanders cohort.[18] In total, 23 960 persons were enrolled in the baseline assessment between April 2020 and May 2021 (8.8% of the eligible population), and three waves of follow-up were completed by February 2023 (follow-up wave 1: December 2020–May 2021; follow-up wave 2: May 2021–December 2021; follow-up wave 3: September 2022–February 2023) with the attrition rate ranging from 42.7% to 55.2% (figure 1). As the Icelandic government lifted all pandemic-related social restrictions and border prevention measures by February 2022,[19] and since 79% of Iceland's total population were fully vaccinated by April 2022,[20] we defined the baseline and the first two follow-up waves as the pandemic assessment and the third follow-up wave as the post-pandemic assessment. More COVID-19 information in Iceland is provided in online supplemental sFigure 1.

Participants were invited to complete a series of web-based questionnaires and provide information on demographics, lifestyle and general health, as well as working and life conditions at each assessment wave. In the present study, we included 6423 persons with four consecutive sets of data on depressive symptoms in the analysis. Specifically, we used the first three assessments (ie, baseline, follow-up wave 1 and follow-up wave 2) to explore the variation in depressive symptom trajectories during the pandemic and identify determinants of each trajectory. We then used the latest assessment (ie, follow-up wave 3) to investigate the long-term health outcomes of the identified trajectories after the pandemic. Though largely comparable to participants who were excluded from the study (ie, lost follow-up (n=17 333) or missed information on depressive symptom assessment (n=204)), the study sample was more likely to be older, have a higher level of education and be without childcare burden (online supplemental sTable 1).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

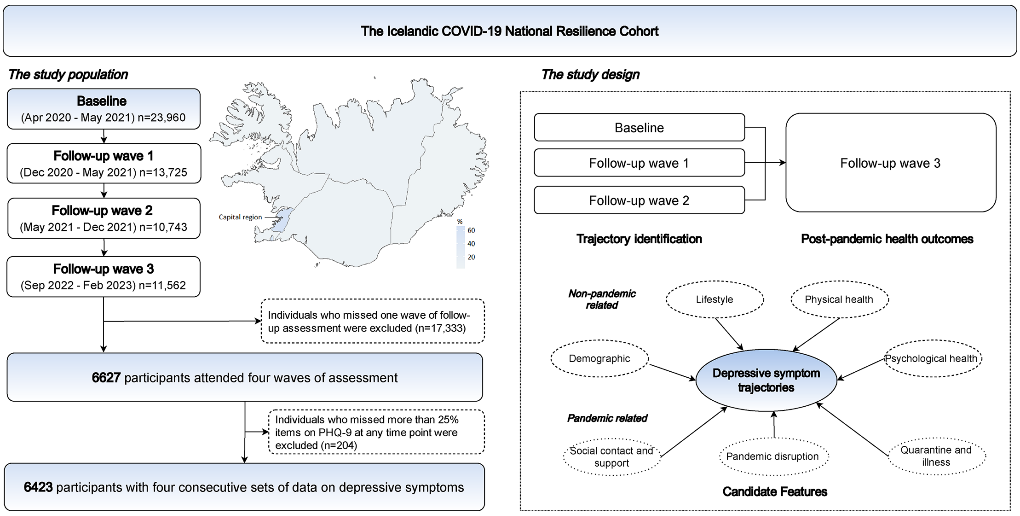

Figure 1 Flowchart outlining the selection of the study population and study design. PHQ-9, Patient Health Questionnaire-9.

Measures

Depressive symptoms

We used a validated self-report instrument, the Patient Health Questionnaire-9 item (PHQ-9),[21] to screen for depressive symptoms, over the past 2weeks. Response options in each item range from '0' (not at all) to '3' (nearly every day), and the total score ranges from 0 to 27. A threshold score of 10 or higher is considered as an indication of high depressive symptom burden.[21] For participants who responded to more than 75% of items on PHQ-9 at each assessment, we used item-level imputation by predictive mean matching to replace missing values, and then calculated the total score.

Candidate features

37 features with potential relevance to depressive symptom trajectories during the pandemic were assessed, including 7 demographic features[5 8 22] (ie, age, sex, sexual orientation, residence area, relationship status, education and childcare burden), 3 lifestyle features[8 10 23] (ie, exercise level at baseline, change in exercise habits during the pandemic and smoking status), 4 physical and psychological health features[24–27] (ie, body mass index (BMI), chronic medical conditions, mobility/hearing/visual impairment and history of psychiatric disorders), 10 pandemic-related social contact and support features[28–30] (ie, in-person contact, change in frequency of in-person contact, virtual contact, change in frequency of virtual contact, perceived family support, change in family support, perceived social support, change in social support, trust in Icelandic health authorities and change in trust in the Icelandic health authorities during the pandemic), 7 quarantine-related and COVID-19-related features[11 12 31 32] (ie, quarantine, COVID-19 testing and diagnosis, bedridden due to COVID-19, family/friends diagnosed with COVID-19, family/friends admitted to a hospital, family/friends admitted to the intensive care unit and vaccination status) and 6 pandemic disruption-related features[13 33] (ie, financial difficulties, change in financial difficulties, difficulty in obtaining necessities, change in difficulty in obtaining necessities, disruption of necessary services and change in disruption of necessary services during the pandemic).

Changes in specific features during the pandemic were derived by comparing response options from the baseline to those at follow-up wave 2, categorised as decreasing, stable or increasing. Moreover, we used K-nearest neighbour imputation (k=10) to replace missing values of the candidate features (proportions of missing values 0%–2.2%). Online supplemental sTable 2 shows more details about the measuring and scoring rules of the candidate features.

Post-pandemic health outcomes

Four validated psychological function instruments were assessed at follow-up wave 3, including depressive symptoms (PHQ-9),[21] anxiety symptoms (the Generalised Anxiety Disorder 7-item questionnaire, with a total score ranging from 0 to 21),[34] somatic symptoms (Patient Health Questionnaire-15 (PHQ-15), with a total score ranging from 0 to 30)[35] and cognitive problems (the 8-item Patient-Reported Outcomes Measurement Information System Cognitive Function Scale, with a total score ranging from 0 to 32).[36] Item-level imputation by predictive mean matching was used to replace missing items in each instrument. Specifically, considering the PHQ-15 item about menstrual cramps which only applies to women younger than 60 years, we directly imputed 0 (ie, 'Not bothered at all') for individuals who were men or older than 60 years with a missing value on this item.

Statistical analysis

We first examined the demographic features of the study population. Then, we constructed latent growth mixture models using the total score of the PHQ-9 to explore variation in depressive symptom trajectories during the pandemic. Accounting for varying months in which each person responded, we added a TSCORES term in the model to indicate variable time of measurement of depressive symptoms. We then fitted the model from one to seven latent classes. Model fit was determined using the Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-size-adjusted BIC (aBIC) and the Lo-Mendel-Rubin-likelihood ratio test (LMR-LRT).[37] The model with the lowest AIC, BIC and aBIC was preferred. Significant LMR-LRT results indicate that the specific class solution is more favourable than other classes solutions. In addition to these fit statistics, whether the number of individuals in each trajectory group was sufficient (more than 5.0%) was also considered.[37] Moreover, the entropy value was calculated to assess the model's performance, with an entropy near 1.0 indicating adequate classification of individuals. Participants were categorised into probable groups after the selection of the optimal model.

Next, we calculated the Spearman's rank correlation coefficient (r) among pairs of candidate features and excluded those with very strong correlation with other features (ie, r≥0.8). To identify the most influential features for each trajectory group, we applied the extreme gradient boosting (XGBoost) model with dummy encoding for categorical features and calculated the mean absolute SHapley Additive exPlanation (SHAP) values to rank the feature importance. XGBoost model is an effective tree boosting classifier.[38] We defined multiple tree-related hyperparameters to improve the model performance and avoid the risk of overfitting, including ntrees (number of trees), colsample_bytree (subsample ratio of columns for each tree), max-depth (maximum depth of a tree), gamma (minimum loss reduction required), minobspernode (minimum observations allowed per tree node) and eta (step size shrinkage).[38] The SHAP value can quantify the magnitude and direction (positive or negative) of the feature's contribution to a classification. Namely, a high positive SHAP value indicates a strong positive effect on the classification. To assess the performance of the model, we split the data into training (70%) and test (30%) sets. We used the training set to fit the model and the test set for assessment. Considering the imbalanced group distribution, optimal Youden index and area under the receiver operating curve (AUC) were calculated.

Furthermore, we performed linear regression analyses to explore the associations between depressive symptom trajectories and their post-pandemic health outcomes. We adjusted the analyses for age at baseline, sex, education, relationship status, smoking status, BMI, chronic medical conditions and history of psychiatric disorders, and reported standardised regression coefficients (βs) with corresponding 95% CIs.

The latent growth mixture model and XGBoost model were performed in Mplus V.8.0 and Python V.3.1, respectively. All the other analyses were conducted in R V.4.2 software.

RESULTS

Of the 6423 participants, 68.7% were women and the mean (SD) age at baseline was 57.0 (13.0) years (online supplemental sTable 1). In the entire sample, the levels of depressive symptom did not change significantly from baseline to follow-up wave 2 (p=0.16; figure 2). After fitting models with 1–7 latent classes, we identified a 4-class model as the ideal model with adequate classification of individuals (ie, significant LMR-LRT results, sufficient number of participants in each class and near 1.0 entropy; online supplemental sTable 3). From this model, we categorised participants into four distinct depressive symptom trajectories.

During a median follow-up of 13.0 months from baseline to follow-up wave 2, we found that most participants (83.7%) showed a trajectory with consistently low depressive symptoms, while 5.3% of individuals showed a trajectory with consistently high symptom burden throughout the study period. In addition, two trajectories with fluctuating depressive symptoms were identified, with 5.1% showing initially high symptom trajectory (ie, high levels of depressive symptoms at baseline which then decreased) and 5.9% showing late-onset high symptom trajectory (ie, low levels of depressive symptoms at baseline which then increased).

A strong correlation between each pair of the candidate features was not observed (online supplemental sFigure 2), and the XGBoost model achieved good performance in distinguishing consistently low symptom trajectory from other trajectories (figure 3; Youden index: 0.37–0.55; AUC: 0.72–0.86). Moreover, individuals who exercised frequently (≥3 days/week) and perceived family support at baseline were more likely to experience the consistently low symptom trajectory during the pandemic. By contrast, those with a history of psychiatric disorders, women and young adults (18–39 years) were less likely to follow consistently low symptom trajectory. In addition, individuals in the initially high symptom trajectory group were characterised by having tested negative for COVID-19 and higher weight (BMI ≥30 kg/m^2) and single, while people in the late-onset high symptom trajectory group were characterised by having childcare burden, having tested negative for COVID-19 and suffering from chronic medical conditions. Furthermore, compared with consistently low symptom trajectory group, a decrease in the level of social support during the pandemic was associated with a greater risk of showing late-onset high symptom trajectory, while an increase in family support and social support between baseline and

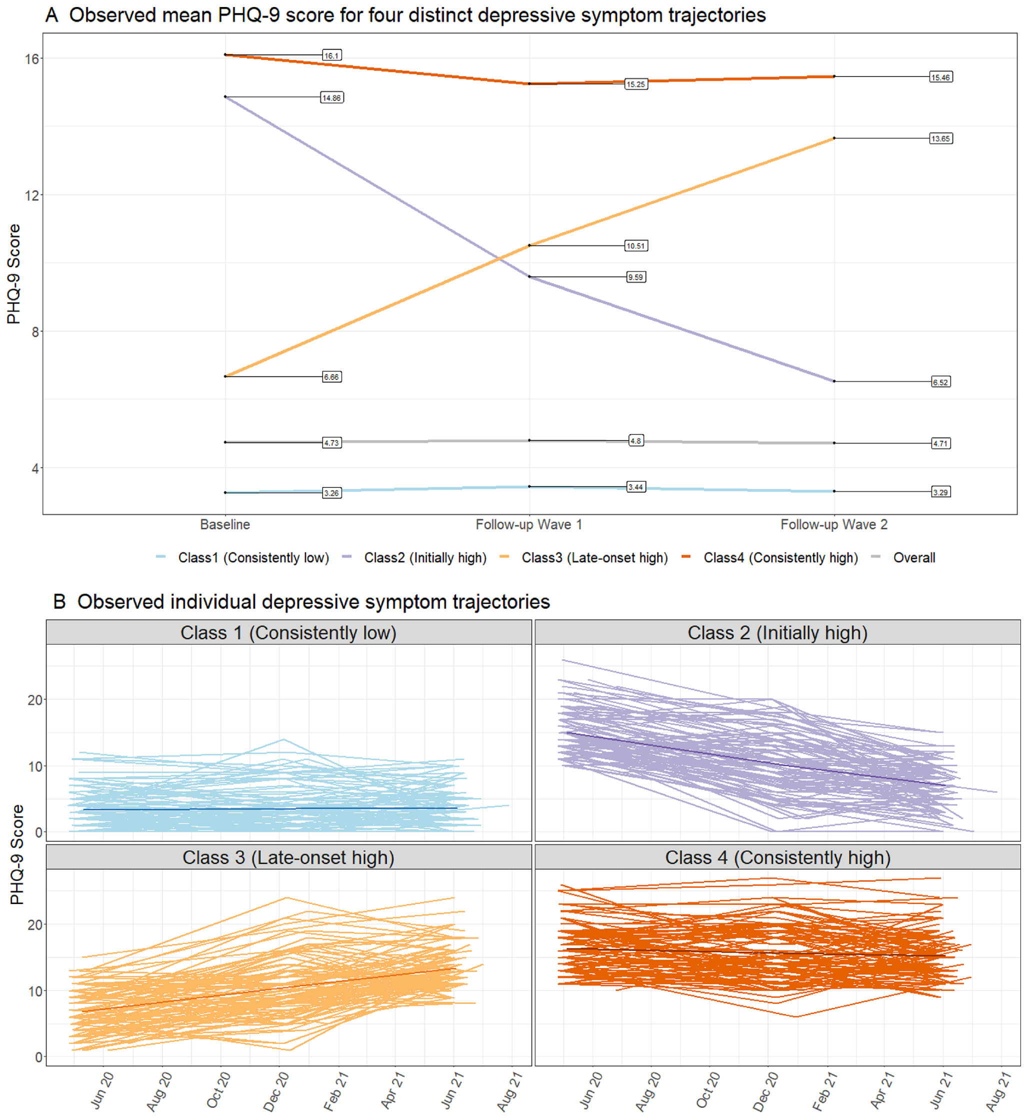

Figure 2 Four class-specific depressive symptom trajectories during the COVID-19 pandemic in Iceland. Note: For panel B, we randomly selected a subset of 100 individuals from each class to enhance the clarity of the trajectory. PHQ-9, Patient Health Questionnaire-9.

follow-up wave 2 was associated with a greater likelihood of experiencing the initially high symptom trajectory.

After a further median follow-up of 15.8 months from follow-up wave 2 to follow-up wave 3, we observed that individuals who demonstrated initially high, late-onset high and consistently high symptom trajectories during the pandemic were more likely to experience a significantly higher levels of depressive (βs 0.78–1.86, figure 4), anxiety (βs 0.63–1.55) and somatic symptoms (βs 0.56–1.23), as well as cognitive problems (βs 0.64–1.37) during the post-pandemic period, when compared with those in the consistently low symptom trajectory group.

DISCUSSION

Using a nationwide cohort, we identified four distinct depressive symptom trajectories during the COVID-19 pandemic in Iceland. Though most persons experienced a consistently low symptom trajectory, a minority (16.3%) showed trajectories with high symptom burden at the initial or late pandemic phase, or persistently. The pandemic impact on population mental health seems long-lasting as individuals with these trajectories continued to experience elevated levels of mental illness, somatic symptoms and cognitive problems during the post-pandemic period. Expanding on previous findings,

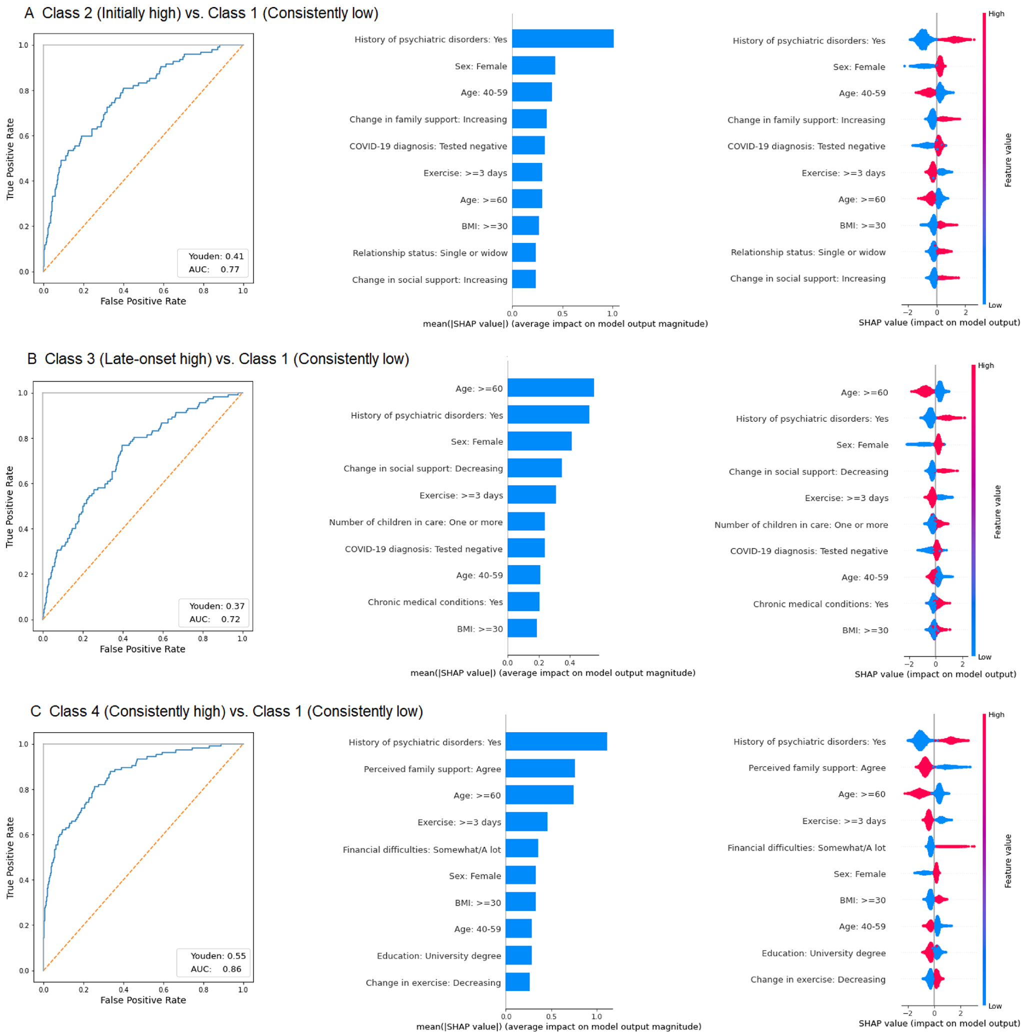

Figure 3 Model performance and 10 most influential features. Youden index, calculated as the maximum of the true positive rate minus the false positive rate. AUC, area under the curve.

we found that depressive symptoms during the pandemic were associated with a history of psychiatric disorder, being women, being younger (18–39 years) and having tested negative for COVID-19. Furthermore, we also identified several modifiable protective factors, including physical exercise, family support and social support, that may mitigate the impact of the pandemic on population mental health.

Though the main symptom trajectory in the study population was largely constant over time and good, our study identified three additional depressive symptom trajectories during the pandemic period. Compared with the findings of Hemi *et al* in the Israeli population,[7] which identified two trajectories for depression (resilient, 87% and chronic, 13%), our study indicates a varying and complex development of population mental health in Iceland during the pandemic. However, when compared with the results of a study by Pierce *et al* in the UK population,[5] we found that a high proportion of the Icelandic general population experienced consistently low symptom trajectories during the pandemic. Several reasons may account for these discrepancies, such as the difference in assessment points, length of follow-up and implemented governmental pandemic policies.[39] Also, the Icelandic population is small (total population of 400 000)[40] with close family contacts that may preserve mental health during pandemic times. Finally, the substantially longer follow-up in our study is more likely to reflect the long-term pandemic adaptation trajectories, instead of only the acute responses at the initial stage of the pandemic.

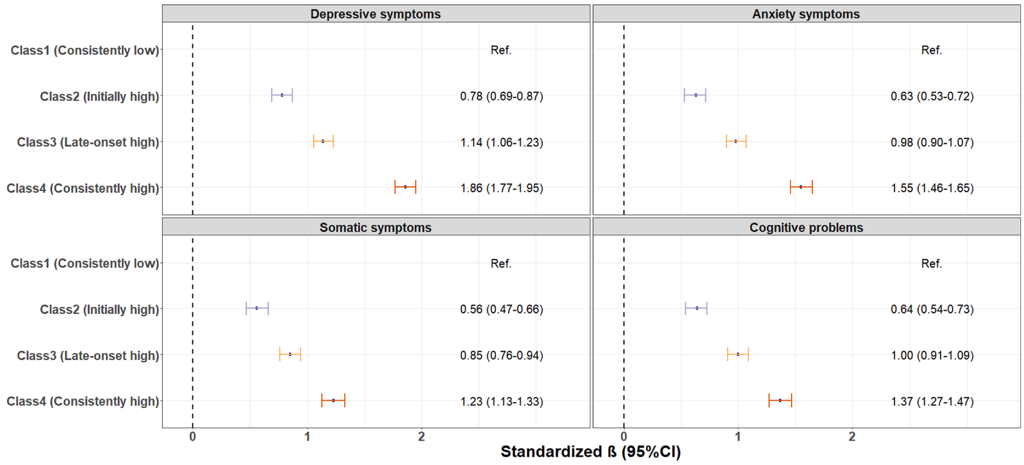

Figure 4 Multivariable-adjusted standard linear regression analyses of the association between depressive symptom trajectories and post-pandemic health outcomes (ie, depressive symptoms, anxiety symptoms, somatic symptoms and cognitive problems measured during follow-up wave 3, from September 2022 to February 2023). Model adjusted for age at baseline, sex, education level, relationship status, smoking status, BMI, chronic medical conditions and history of psychiatric disorder. BMI, body mass index.

We identified several vulnerability factors during the pandemic, including a history of psychiatric disorder, which, as in other crises[41] and situations of uncertainty,[42] may contribute to increased depressive symptoms. Also, reduced access to health services, in particular for patients with a history of psychiatric disorder, may have made these individuals more susceptible to the negative effects of the pandemic.[43] Indeed, findings from our[13] and others'[44] previous work indicate that individuals with pre-pandemic history of psychiatric disorders experienced a disruption in health services during the pandemic. Consistent with existing evidence,[5] we further found that women and young adults were more likely to experience psychological distress during the pandemic. Potential increase in domestic violence[45] and greater burden of domestic work and childcare during social gathering restriction[22] may have contributed to increased depressive symptoms burden among women during the pandemic. The mental health of young adults may have been affected by school and workplace closings and less social contact, as well as economic uncertainties (eg, job loss).[46] In addition, we found that patients with pre-existing chronic medical conditions faced an elevated risk of developing late-onset depressive symptom trajectory. A possible explanation for the delayed effects could be that individuals with chronic conditions tended to self-isolate in order to reduce their likelihood of contracting COVID-19 initially, but they may have become more vulnerable and depressed as time passes in a pandemic.

Moreover, we found that individuals who tested negative for COVID-19 were more likely to be negatively affected by the pandemic, during either the initial or late pandemic phase. Indeed, previous studies carried out by us[47] and others[48] have shown that individuals who tested negative for COVID-19 are associated with an increased risk of psychological distress, as well as receiving prescription for psychotropic medications. Patients who took a screening test but were not diagnosed with COVID-19 might have been exposed to infected individuals and therefore fear infection or have experienced severe influenza symptoms due to other causes which potentially contribute to increased levels of depressive symptoms.[48 49] It is also possible that participants susceptible to psychiatric disorders or those already suffering from such disorders were more likely to be tested for COVID-19 and therefore showed a high symptom burden of depression.[50] Thus, a reverse causation cannot be excluded. In addition, unlike previous findings,[5 51] we did not observe a link between COVID-19 infection and deterioration in mental health. The low prevalence of COVID-19 (ie, 213/6423 (3.3%)) as well as better access to healthcare for COVID-19 patients in the present study population[13] may be key factors explaining these null results. Taken together, our findings suggest that the COVID-19 pandemic has had a disproportionate impact on different groups of the general population, suggesting that strategies targeting those most affected should be prioritised in future pandemics.

By contrast, we observed that maintaining physical exercise (≥3 days/week) was associated with consistently low depressive symptom trajectories during the pandemic. In line with our findings, a recent review found that physical exercise, especially supervised exercise, was effective in reducing levels of depression during the pandemic, and that the frequency and intensity of the exercise were associated with maintenance of psychological well-being.[52] Also, the results of a study among students at the University of Pittsburgh by Giuntella *et al* suggested that the disruption in physical activity was a leading risk factor of depression during the pandemic.[10] Although barriers to increasing activity were likely present, such as the closure of gym facilities and less opportunity to exercise with others, maintaining exercise may be most beneficial in alleviating the population's psychological distress.[53] Meanwhile, the positive association between family and social support and mental health is well established.[28 29] In our study, we indeed observed that an increase in family and social support during the pandemic was associated with a decline in depressive symptoms (ie, initially high symptom trajectory), whereas a decrease in such support was linked to elevated depressive symptoms (ie, late-onset high symptom trajectory). The protective effects of these factors are important for preserving the population's mental health and should be recommended at similar times of crisis.

Strengths and limitations

A major strength of this study is the use of a large nationwide cohort to investigate the variation in depressive symptom trajectories during the COVID-19 pandemic in Iceland over a 3-year follow-up period. Moreover, leveraging the wealth of information collected, we were able to incorporate multidimensional variables to thoroughly characterise the risk and protective factors of the identified trajectories. This study also has several limitations. First, due to the lack of pre-pandemic data, our study cannot clearly differentiate between pre-existing depressive symptoms and symptoms that emerged during the pandemic. For example, it is unclear whether depressive symptoms observed at baseline are a result of the pandemic or if they were already present before the pandemic. Second, we allowed within-class variation of individuals in the latent growth mixture models; as such, the identified profiles might not represent all individuals in a specific class. Furthermore, the interpretation of the profiles is subjective, though we followed the guidelines for reporting on latent trajectory studies.[37] Third, mental health assessments were based on self-report questionnaires rather than clinical diagnostic interviews. In addition, in the setting of the COVID-19 pandemic, several items measured as depressive symptoms (eg, feeling tired, poor appetite, trouble concentrating) in the PHQ-9 instrument may be attributed to COVID-19 infection rather than depression itself. However, the low prevalence of COVID-19 in our study population may suggest a limited impact of this concern. Finally, the recruitment of the study sample was mainly through social media, and the study population was over-represented by older persons, those with higher levels of education and those without childcare burden, which may limit the generalisability of our findings.

CONCLUSIONS

The results of the current study suggest that the vast majority of the Icelandic population maintained good mental health during the COVID-19 pandemic. In addition, our results underscore the role of preexisting psychiatric disorders as a susceptibility factor for experiencing a high level of psychological distress during the pandemic. Interventions focusing on maintaining and enhancing physical exercise and social and family support can help mitigate the negative effects of future pandemics.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved. All participants provided electronic informed consent before answering the web-based questionnaire, and the study was approved by the National Bioethics Committee (NBC 2020-073) and the Data Protection Authority in Iceland. Participants gave informed consent to participate in the study before taking part.

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Supplementary Material

sTable 1 Demographic characteristics of the study population.

	Participants included in the study (n=6,423)	**Participants excluded from the study** (n=17,537)	**C-19 Resilience Cohort** (n=23,960)
Age at baseline, years			
Mean (SD)	57.0 (13.0)	53.1 (14.7)	54.1 (14.4)
Median [Min, Max]	58.0 [18.0, 89.0]	55.0 [18.0, 100]	56.0 [18.0, 100]
Age group, years			
18-39	711 (11.1%)	3367 (19.2%)	4078 (17.0%)
40-59	2715 (42.3%)	7688 (43.8%)	10403 (43.4%)
≥60	2997 (46.7%)	6482 (37.0%)	9479 (39.6%)
Sex			
Male	1998 (31.1%)	5016 (28.6%)	7014 (29.3%)
Female	4414 (68.7%)	11848 (67.6%)	16262 (67.9%)
Unknown	11 (0.2%)	673 (3.8%)	684 (2.9%)
Sexual orientation			
Heterosexual	6156 (95.8%)	16166 (92.2%)	22322 (93.2%)
Sexual minorities	238 (3.7%)	632 (3.6%)	870 (3.6%)
Unknown	29 (0.5%)	739 (4.2%)	768 (3.2%)
Residence area			
Not capital area	4391 (68.4%)	11553 (65.9%)	15944 (66.5%)
In capital area	1998 (31.1%)	5222 (29.8%)	7220 (30.1%)
Unknown	34 (0.5%)	762 (4.3%)	796 (3.3%)
Relationship status			
Married or in a relationship	4797 (74.7%)	13009 (74.2%)	17806 (74.3%)
Single or widow	1606 (25.0%)	3817 (21.8%)	5423 (22.6%)
Unknown	20 (0.3%)	711 (4.1%)	731 (3.1%)
Education			
Primary school	830 (12.9%)	2546 (14.5%)	3376 (14.1%)
High school	1928 (30.0%)	5307 (30.3%)	7235 (30.2%)
University degree	3629 (56.5%)	8930 (50.9%)	12559 (52.4%)
Unknown	36 (0.6%)	754 (4.3%)	790 (3.3%)
Childcare burden (i.e., number of children in need of care)			
None	4394 (68.4%)	10365 (59.1%)	14759 (61.6%)
One or more	2000 (31.1%)	6486 (37.0%)	8486 (35.4%)
Unknown	29 (0.5%)	686 (3.9%)	715 (3.0%)

sTable 2 Features used to identify variation in depressive symptom trajectories.

Variables	Data collection	Response options
Non-pandemic related		
Demographic		
Age at baseline (years)	Baseline	0: 18-39; 1: 40-59; 2: 60+
Sex	Baseline	0: Male; 1: Female
Sexual orientation	Baseline	0: Heterosexual; 1: Sexual minorities
Residence area	Baseline	0: Not capital area; 1: In capital area
Relationship status	Baseline	0: Married or in a relationship; 1: Single or widow
Education	Baseline	0: Primary school; 1: High school; 2: University degree
Childcare burden (i.e., number of children in need of care)	Baseline	0: None; 1: One or more
Lifestyle		
Exercise *(i.e., In the past 7 days, how many days have you engaged in vigorous exercise for a total of 30 minutes or more per day?)*	Baseline	0: 0-2 days/week; 1: ≥3 days/week
Change in exercise	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing
Smoking status	Baseline	0: Never; 1: Current/Previous
Physical and psychological health		
Body mass index (kg/m^2)	Baseline	0: ≤25; 1: 25-30; 2: ≥30
Chronic medical conditions[a]	Baseline	0: No; 1: Yes
Mobility/hearing/visual impairment	Baseline	0: No; 1: Yes
History of psychiatric disorders	Baseline	0: No; 1: Yes
Pandemic related		
Social contact and support		
In-person contact *(i.e., meet family, friends, or other people in your home or elsewhere)*	Baseline	0: Never; 1: Sometimes; 2: Often
Change in frequency of in-person contact	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing
Virtual contact *(i.e., in contact with family, friends, or other people through the phone or social media)*	Baseline	0: Never; 1: Sometimes; 2: Often
Change in frequency of virtual contact	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing
Perceived family support *(i.e., get the emotional help and support I need from my family)*	Baseline	0: Disagree; 1: Neutral; 2: Agree
Change in family support	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing
Perceived social support *(i.e., have a special person who is a real source of comfort to me)*	Baseline	0: Disagree; 1: Neutral; 2: Agree
Change in social support	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing
Trust in Icelandic health authorities	Baseline	0: Little; 1: Somewhat; 2: A lot
Change in trust	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing
Quarantine and illness		
Quarantine	Baseline; Follow-up Wave 1 & 2	0: No; 1: Yes
COVID-19 testing and diagnosis	Baseline; Follow-up Wave 1 & 2	0: No tested for COVID-19; 1: Tested negative for COVID-19 2: Tested positive for COVID-19.
Bedridden due to COVID-19	Baseline; Follow-up Wave 1 & 2	0: No; 1: Yes
Family/friends diagnosed with COVID-19	Baseline; Follow-up Wave 1 & 2	0: No; 1: Yes
Family/friends admitted to a hospital	Baseline; Follow-up Wave 1 & 2	0: No; 1: Yes
Family/friends admitted to ICU	Baseline; Follow-up Wave 1 & 2	0: No; 1: Yes
Vaccination status	Follow-up Wave 2	0: No; 1: Yes
Pandemic disruption		
Financial difficulties	Baseline	0: Little; 1: Somewhat; 2: A lot
Change in financial difficulties	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing

Difficulty obtaining necessities	Baseline	0: Little; 1: Somewhat; 2: A lot
Change in difficulty obtaining necessities	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing
Disruption of necessary services	Baseline	0: Little; 1: Somewhat; 2: A lot
Change in disruption of necessary services	Baseline; Follow-up Wave 2	0: Decreasing; 1: Stable; 2: Increasing

a. Chronic medical conditions were defined as high blood pressure, heart disease, lung disease, chronic kidney disease, cancer, diabetes, immunosuppressive state or immunosuppressive therapy.

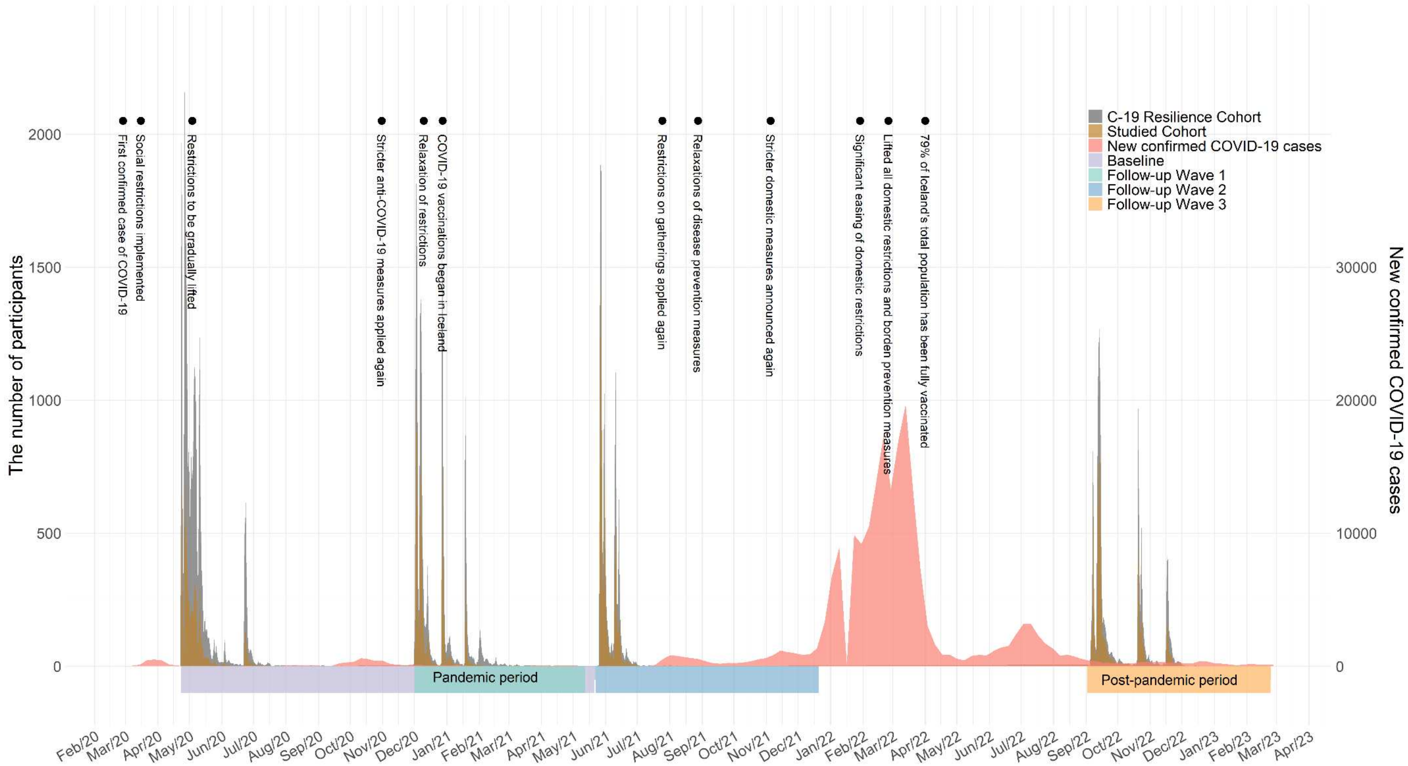
b. COVID-19 testing and diagnosis was defined according to responses to questions "Have you been tested for COVID-19?" and "Have you been diagnosed with the COVID-19?"

sTable 3 Model fit statistics for depressive symptom trajectories by different class solutions

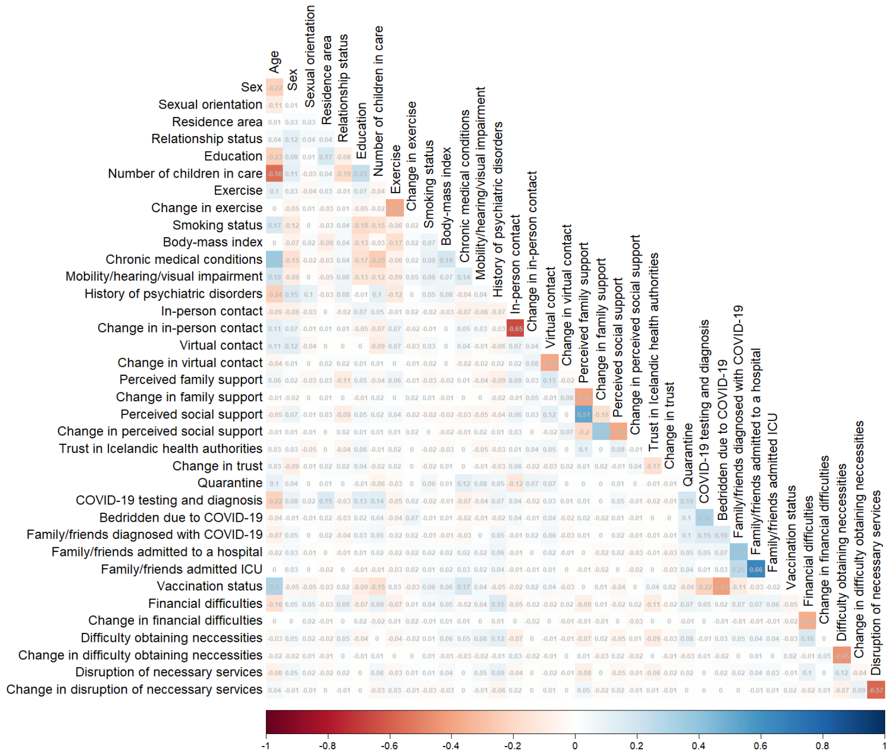
	Log-Likelihood	AIC	BIC	Adj-BIC	LMR-LRT p-value	Entropy	individuals per class						
1-class	-51242.2	102500.3	102554.5	102529.0	-	-	100.0%						
2-Class	-50283.4	100588.8	100663.3	100628.3	0.00	0.91	89.1%	10.9%					
3-Class	-49777.7	99583.4	99678.1	99633.6	0.00	0.91	85.3%	8.4%	6.3%				
4-Class	**-49439.2**	**98912.3**	**99027.4**	**98973.4**	**0.00**	**0.92**	**83.7%**	**5.9%**	**5.3%**	**5.1%**			
5-Class	-49205.6	98451.1	98586.5	98522.9	0.00	0.89	75.1%	12.8%	6.4%	3.6%	2.2%		
6-Class	-49056.4	98158.8	98314.4	98241.4	0.04	0.90	75.4%	10.9%	6.1%	3.0%	2.7%	2.0%	
7-Class	-48929.8	97911.5	98087.5	98004.9	0.05	0.87	67.2%	16.8%	4.9%	4.3%	3.6%	2.6%	0.7%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; Adj-BIC, adjusted bayesian information criterion; LMR-LRT, Lo–Mendel–Rubin–likelihood ratio test.

sFigure 1 Timeline of data collections.



sFigure 2 Spearman's rank correlation matrix of 37 candidate features



Paper IV

Paper IV

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Trends of perceived disruption in healthcare services during the pandemic: findings from the COVID-19 National Resilience Cohort in Iceland

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Background: Coronavirus disease 2019 (COVID-19) caused major disruptions in healthcare services worldwide. Yet, little is known about the association between perceived disruption in healthcare services and socio-demographic factors, pre-existing health conditions as well as concurrent physical and psychological symptoms. **Methods:** Leveraging data from the Icelandic COVID-19 National Resilience Cohort, we performed a repeated measure analysis among 15 754 participants who responded to the question on perceived disruption in healthcare services from December 2020 to July 2021, to explore its association with socio-demographic factors, health indicators and conditions. Furthermore, we performed a longitudinal analysis among 7848 participants with two repeated measures to explore the association between timing and duration of perceived disruption in healthcare services and changes in depression, anxiety, sleep quality and somatic symptoms. **Results:** The prevalence of perceived disruption in healthcare services slightly decreased over time ($P < 0.01$). Perceived disruption in healthcare services was more prevalent among individuals with pre-existing health conditions, i.e. history of psychiatric disorders (prevalence ratio = 1.59, 95% confidence interval 1.48–1.72) and chronic somatic conditions [1.40 (1.30–1.52)]. However, no increase in the prevalence of perceived disruption in healthcare services was observed among individuals diagnosed with COVID-19 [0.99 (0.84–1.18)]. Moreover, we found that emerging perceived disruption in healthcare services was associated with an increase in symptoms of mental illness during the pandemic (βs 0.06–0.68). **Conclusions:** A disruption in healthcare services during the COVID-19 pandemic was reported by vulnerable groups, while the Icelandic healthcare system managed to maintain accessible services to individuals with COVID-19.

Introduction

Backlogs and delays in healthcare services caused by the coronavirus disease 2019 (COVID-19) pandemic left millions of people without care worldwide. Indeed, nearly 93% of countries worldwide faced mental health services disruption in the early stages of the pandemic.[1] On average, 26% of healthcare services remained disrupted when the pandemic progressed across the European region in 2021.[2]

Negative effects of the disruption in healthcare services may have disproportionately affected populations across socio-demographic groups during the COVID-19 pandemic.[3] Indeed, several studies indicated that young adults,[4] ethnic minorities[5] and low-income groups[4] are more likely to suffer from the adverse effects of healthcare disruption during the pandemic. Furthermore, individuals with underlying health conditions were more likely to delay seeking health care due to fear of being infected, especially those with immunosuppressive conditions,[3] chronic somatic diseases[3] and mental disorders.[6] As these comorbidities have been associated with the risk of severe COVID-19,[7] the disruption in healthcare services could be particularly problematic for patients with pre-existing health conditions. Yet, little is known about the prevalence of perceived disruption in healthcare services during the COVID-19 pandemic period, and a more in-depth characterization of vulnerable populations affected by the pandemic is needed.

Delayed and deferred healthcare services may indeed negatively influence the mental health of those in need of services.[8–10] Moreover, a recent qualitative review indicates that people with pre-existing psychiatric disorders faced risks of relapse, further deterioration and even death during the pandemic.[11] However, to what extent deterioration of mental health is related to perceived disruption in healthcare services awaits to be further studied.

To this end, leveraging the rich data collected for the Icelandic COVID-19 National Resilience Cohort, we set out to investigate trends of perceived disruption in healthcare services during the COVID-19 pandemic period and to explore its association with socio-demographic factors, pre-existing health conditions as well as concurrent physical and psychological symptoms.

Methods

Study population and design

The Icelandic COVID-19 National Resilience (C19-resilience) cohort was established to explore the long-term impact of the COVID-19 pandemic in Iceland.[12] This nationwide study was open to all Icelandic-speaking individuals 18 years or older with an Icelandic electronic identification number. Recruitment was mainly through media and invitations to participants in ongoing cohort studies in Iceland, namely the SAGA (Stress-And-Gene-Analysis) cohort, the iStopMM (Iceland Screens, Treats or Prevents Multiple Myeloma) study, and the Health and Well-Being of Icelanders cohort (Supplementary references). In addition, all individuals in Iceland who tested positive for SARS-CoV-2 by RT-PCR through 2020 received an invitation in January and February of 2021. In total, 23 960 participants were recruited at baseline (97.1% recruited from April 2020 to December 2020) and two waves of follow-up were completed by July 2021 (Follow-up Wave 1: December 2020 to May 2021; Follow-up Wave 2: May 2021 to July 2021). The participants of the C19-resilience cohort had a similar distribution of residency to that of the general Icelandic population but were on average older and more likely to be female and have higher education compared with the general Icelandic population (Supplementary table S1).

We performed a repeated measures analysis among 15 754 participants who responded to the question on perceived disruption in healthcare services at Time point 1 (T1, from December 2020 to February 2021) or/and Time point 2 (T2, from May 2021 to July 2021), to explore its association with socio-demographic factors, health indicators and health conditions. Furthermore, we performed a longitudinal analysis among 7848 participants with two repeated measures on perceived disruption in healthcare services (i.e. those who responded at both T1 and T2) to explore the association between timing and duration of perceived disruption in healthcare services and changes in symptoms of mental illness (i.e. depression, anxiety, sleep quality and somatic symptoms). A detailed flowchart of the study population is presented in Supplementary figure S1.

All participants provided electronic informed consent before answering the web-based questionnaire. The study was approved by the National Bioethics Committee (number 20-073) and the Data Protection Authority in Iceland.

Perceived disruption in healthcare services

The question regarding perceived disruption in healthcare services during the COVID-19 pandemic was added to the questionnaire after December 2020. We used the question 'During the COVID-19 epidemic, have you experienced any inconvenience caused by limited healthcare services, e.g. delayed operations, treatments or diagnoses?' to assess perceived disruption in healthcare services, with five response options: 'no', 'rather little', 'somewhat', 'quite a lot' and 'very much'. We dichotomized the answers as 'No/rather little' and 'Yes, somewhat/quite a lot/very much'. Timing and duration of perceived disruption in healthcare services were derived by combining responses from T1 and T2 to create four categories: 'neither perceived at T1 nor T2', 'perceived at T1 only', 'perceived at T2 only' and 'perceived at both T1 and T2'.

Socio-demographic factors, health indicators and conditions

Information on socio-demographic factors was collected at baseline and included: age (18–39, 40–59 or ≥60 years); sex (male or female); sexual orientation [heterosexual or sexual minority (lesbian or gay, bisexual, pansexual or other)]; residence area [capital region or non-capital region (Southern Peninsula, Southern Region, Western Region, Westfjords, Northwestern Region and Eastern Region)]; highest education completed (primary school, high school, BA/BS degree or master's or PhD degree); monthly income before tax (300 thousand or less, 301–500 thousand, 501–700 thousand, 701–1000 thousand or more than a million ISK). Four health indicators or pre-existing conditions were collected at baseline, including smoking status (never or previous/current); body mass index (<25, 25–30 or >30 kg/m^2); history of psychiatric disorders (no or yes); and chronic medical conditions (defined as high blood pressure, heart disease, lung disease, chronic kidney disease, cancer, diabetes, immunosuppressive state or immunosuppressive therapy; no or yes). Data on three COVID-19-related factors were collected at the same time point as perceived disruption in healthcare services (i.e. at T1 or T2), including history of quarantine (defined according to response to the question 'Have you been in quarantine due to COVID-19'; no or yes); history of COVID-19 testing and diagnosis (defined according to response on questions 'Have you been tested for COVID-19?' and 'Have you been diagnosed with the COVID-19?'; not tested, tested but not diagnosed, or diagnosed with COVID-19) and history of being bedridden due to COVID-19 (defined according to response on question 'Were you bedridden due to the illness?'; no or yes). Participants were also able to answer 'cannot or will not answer' in response to all questions (except age), and these answers were treated as missing.

Symptoms of mental illness

Symptoms of mental illness were assessed at both T1 and T2. We used the 9-item Patient Health Questionnaire (PHQ-9) as the screening instrument for depression (total score ranging from 0 to 27)[13] and the 7-item General Anxiety Disorder (GAD-7) as the screening instrument for anxiety (total score ranging from 0 to 21).[14] One single item from the validated Pittsburgh Sleep Quality Index was used to assess sleep quality (i.e. 'during the past 2 weeks, how would you rate your sleep quality overall?'), with response options ranging from 0 (very bad) to 3 (very good).[15] The Patient Health Questionnaire-15 (PHQ-15) was used to measure somatic symptoms, with response options ranging from 0 (not bothered at all) to 2 (bothered a lot), with a total score ranging from 0 to 30.[16]

Statistical analysis

First, the crude prevalence of perceived disruption in healthcare services by the month response received (i.e. from December 2020 to July 2021) was calculated. Then, for participants who responded to the question on perceived disruption in healthcare services (i.e. at T1 or/and T2), we performed a repeated measure analysis contrasting the population average prevalence (per 100 persons) of perceived disruption in healthcare services among individuals with different socio-demographic characteristics, health indicators and conditions. Binomial logistic regression models were performed to obtain prevalence estimates of perceived disruption in healthcare services. Log-binomial Poisson regression models with robust error variance were applied to estimate prevalence ratios (PRs) with 95% confidence intervals (CIs). We used a classical sandwich estimator with exchangeable working correlation structure in the model to control for intra-individual correlation across repeated measures.[17,18] We adjusted for month response received in all models and additionally adjusted for socio-demographic factors when exploring the association between health indicators and conditions and perceived disruption in healthcare services. We further examined the role of socio-demographic factors on the association between pre-existing health conditions (i.e. history of psychiatric disorders and chronic medical conditions) and perceived disruption in healthcare services, by introducing an interaction term in the model.

In a subpopulation with two repeated measurements on perceived disruption in healthcare services (i.e. at both T1 and T2), we conducted a longitudinal analysis to investigate the association between timing and duration of perceived disruption in healthcare services (i.e. neither T1 nor T2, T1 only, T2 only and both T1 and T2) and changes in symptoms of mental illness (i.e. difference in the measure scores of T1 and T2). Generalized linear regression models were fitted to estimate effect size, β coefficients (βs) and 95% CIs. We adjusted the estimate for all socio-demographic factors, health indicators and conditions.

We used multiple imputation to replace missing items in socio-demographic factors, health indicators and conditions (proportions of missing values 0–6.0%), as well as symptom measures of mental illness, through predictive mean matching with 20 rounds of imputation.[19,20] For each symptom measure (i.e. PHQ-9, GAD-7 and PHQ-15), we imputed data for individuals who had less than 25% missing items on the scale.[19] Specifically, considering that the PHQ-15 item about menstrual cramps are only possible for women younger than 60 years,[21] we directly imputed 0 (i.e. 'Not bothered at all') for individuals who were male or older than 60 years with missing values for that item. The aforementioned analyses were conducted using the imputed dataset. To test the impact of missing data on our results, we re-ran our analyses using the complete dataset.

We conducted all statistical analyses in R (version 4.2)[22] and reported the study according to the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

Results

Of 15 754 participants responding to the question on perceived disruption in healthcare services, 68.7% were female and the mean (SD) age was 54.8 (13.9) years (Supplementary table S2). The crude monthly prevalence (per 100 persons) of perceived disruption in healthcare services decreased slightly over the study period, from 12.3 in December 2020 to 11.1 in July 2021 ($P < 0.01$; figure 1).

Differences in the prevalence of perceived disruption in healthcare services between groups with different socio-demographic characteristics and health indicators and conditions are shown in table 1. We found higher prevalence of perceived disruption in healthcare services among individuals with incomes of 300 thousand ISK or less per month (vs. more than a million ISK per month, 16.5 vs. 7.3), sexual minorities (vs. heterosexual individuals, 16.5 vs. 10.8) and primary school education (vs. Master's or PhD degree, 13.1 vs. 9.2). The prevalence of perceived disruption in healthcare services during the study period varied across geographic regions and age groups (figure 1). Young adults (i.e. aged 18–39 years) and those residing in the Northwestern Region and the Eastern Region had a relatively high prevalence of perceived disruption in healthcare services.

As for health indicators and conditions, we found that individuals with a history of psychiatric disorders [PR 1.59 (95% CI 1.48–1.72)], obesity 1.48 (1.34–1.62) and chronic medical conditions 1.40 (1.30–1.52) experienced a higher prevalence of perceived disruption in healthcare services compared with individuals without these health conditions. However, no increase in risk was observed among individuals diagnosed with COVID-19 [0.99 (0.84–1.18)], when compared with those not tested for COVID-19.

Moreover, we found that the association between history of psychiatric disorders and perceived disruption in healthcare services was significantly modified by age, residence area, level of education and monthly income ($P < 0.05$; figure 2). Specifically, the increased prevalence of perceived healthcare disruption by history of psychiatric disorders was more pronounced among young adults, individuals living in non-capital areas and those with lower education and monthly income. We also found significant interaction between age, monthly income and chronic medical conditions, indicating stronger association between chronic medical conditions and healthcare services disruption among younger and low-income individuals.

The proportion of individuals reporting that they perceived disruption at neither timepoint, at T1 only, at T2 only or at both timepoints was 83.4%, 6.3%, 4.6% and 5.7%, respectively. Compared to those who did not perceive disruption in healthcare services, results of the linear regression analysis indicated that perceived disruption in healthcare services at T2 only was positively associated with increase in symptom scores of depression [β 0.68 (95% CI 0.28–1.08)] and anxiety [0.58 (0.22–0.94)] as well as poor sleep quality [0.06 (−0.01 to 0.13)] and greater somatic symptoms [0.41 (0.01–0.82)] (figure 3). Except somatic symptoms, we did not identify statistically significant differences between perceived disruption in healthcare services at T1 only (βs −0.12 to −0.07) or at both timepoints (βs −0.23 to <−0.01) and changes in symptoms of mental illness, although all point estimates were negative.

The results of the complete case analyses were similar to those of the main analyses using multiple imputation in terms of effect size and CIs (see Supplementary table S3 and figure S2).

Discussion

The findings of this study suggest that perceived disruption in healthcare services during the COVID-19 pandemic in Iceland was most prevalent among individuals with pre-existing psychiatric and other chronic medical conditions. Building and expanding on previous findings, we also identified certain vulnerable sub-groups (e.g. younger adults, individuals with lower levels of education and those residing in non-capital areas) where history of mental illness was associated with greater rise in prevalence of perceived disruption. On the other hand, we observed no increase in prevalence of perceived disruption in healthcare services among individuals diagnosed with COVID-19, when compared with those not tested for COVID-19, indicating efficient clinical management of the groups directly affected by the pandemic.

Access to healthcare services was disrupted by the COVID-19 pandemic worldwide and the disruption remains to some extent to date in some countries.[23] A systematic review including nine studies using time-trend data reported a median reduction of 37% in healthcare utilization during the pandemic period up to May 2020.[24] In comparison with countries such as Italy,[25] China[26] and the UK,[27] the reported prevalence of perceived disruption in healthcare services was relatively low in Iceland, which may be explained by the actions of the Icelandic government which implemented less stringent infection-control measures during the pandemic (e.g. school closures, workplace closures and travel bans)[28] and the fact that we measured perceived disruption in healthcare services later than other studies (i.e. December 2020–July 2021). Indeed, measures of perceived disruption in healthcare services during the pandemic may be viewed as informative of how governments manage to respond to such crises whilst maintaining resources and capacity in the healthcare system.

Our study did not observe any increased disruption in healthcare services among individuals diagnosed with COVID-19, suggesting that the Icelandic healthcare system seems to have maintained accessible services to this patient group during the unprecedented time. However, as the healthcare resources were concentrated on managing patients with COVID-19, there is a concern that other

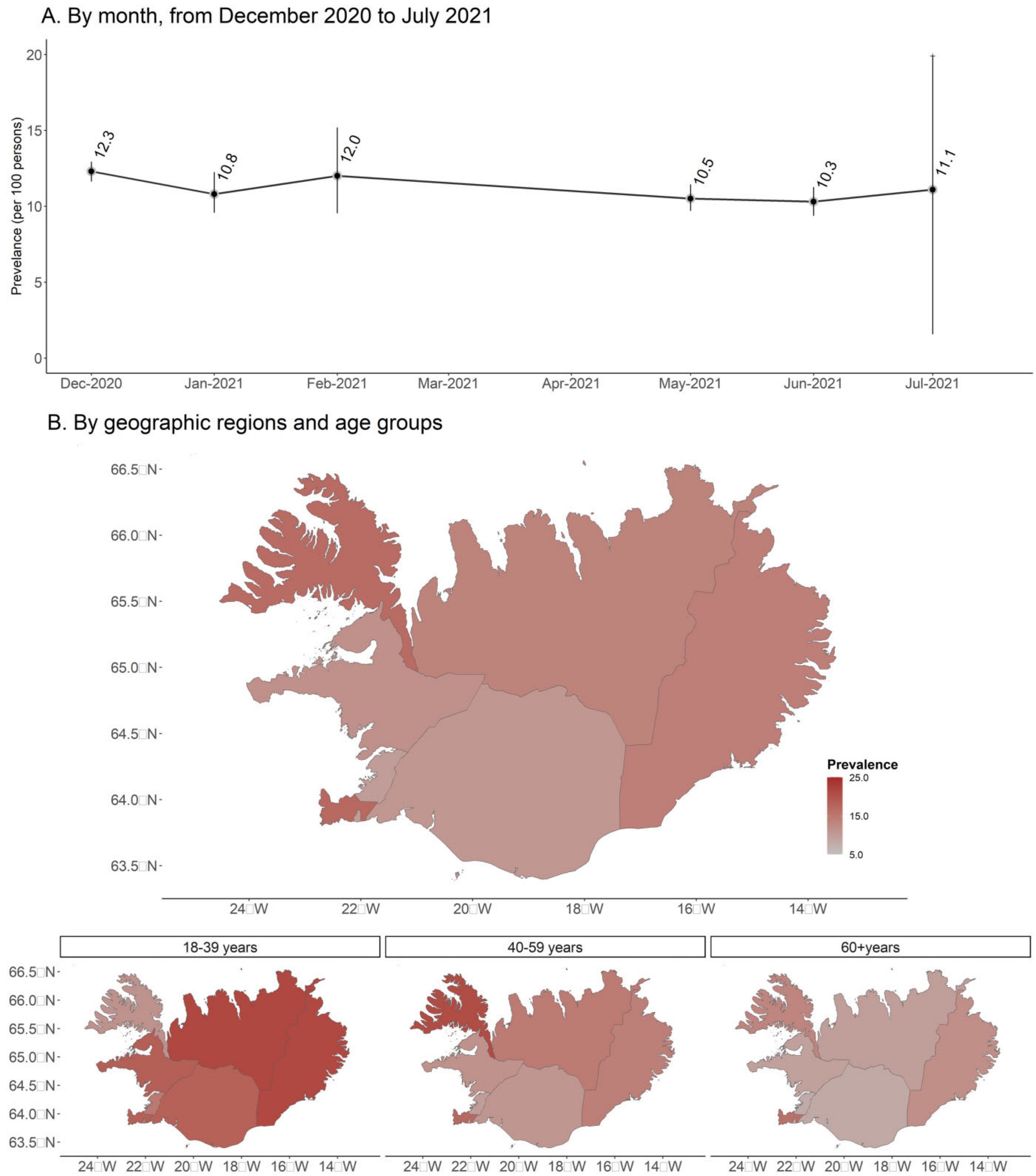

Figure 1 Prevalence (per 100 persons) of perceived disruption in healthcare services in Iceland, by month (A) and by geographic regions and age groups (B).

patients may have been neglected during the pandemic.[34] Multiple studies have indeed reported poor access to health care during the pandemic among patients with diabetes,[35] chronic kidney disease[3] and tuberculosis.[36] Of note, both the current and previous studies demonstrate a substantially higher risk of perceived disruption in healthcare services among individuals with pre-existing psychiatric disorders.[6] Due to the negative effects of lockdown as well as reduced social contact and healthcare services, patients with pre-existing psychiatric disorders experienced adverse health consequences during the pandemic.[11] For example, Robillard *et al.*[8] found increased suicidal ideation among patients who reported a reduction in the frequency of mental health appointments, when compared to patients who did not experience changes in the frequency of appointments. However, it is noteworthy that there may exist a

Table 1 Prevalence of perceived disruption in healthcare services by socio-demographic factors and pre-existing health conditions, among 15 754 participants who responded to the question on perceived disruption in healthcare services during the study period (December 2020–July 2021)

	Prevalence per 100 persons[a] (95% CI)	Prevalence ratios[b] (95% CI)
Socio-demographic factors[c]		
Age, years		
18–39	15.6 (14.4–16.9)	Ref.
40–59	11.5 (10.8–12.1)	0.74 (0.67–0.81)
≥60	9.0 (8.4–9.6)	0.58 (0.53–0.64)
Sex		
Male	9.3 (8.7–10.1)	Ref.
Female	11.8 (11.2–12.3)	1.26 (1.16–1.37)
Sexual orientation		
Heterosexual	10.8 (10.4–11.3)	Ref.
Sexual minority	16.5 (14.2–19.1)	1.52 (1.31–1.77)
Residential area		
Capital region	9.9 (9.4–10.4)	Ref.
Non-capital region	13.4 (12.6–14.3)	1.35 (1.25–1.45)
Western Region	11.7 (9.8–13.9)	1.17 (0.98–1.40)
Westfjords	16.8 (13.5–20.6)	1.68 (1.36–2.09)
Northwestern Region	13.5 (12.2–14.9)	1.36 (1.22–1.51)
Eastern Region	14.2 (11.6–17.2)	1.42 (1.16–1.74)
Southern Region	10.8 (9.4–12.3)	1.08 (0.94–1.25)
Southern Peninsula	17.1 (15.0–19.5)	1.72 (1.50–1.97)
Highest education completed		
Primary school	13.1 (11.9–14.4)	Ref.
High school	12.3 (11.5–13.1)	0.94 (0.84–1.04)
BA/BS degree	10.3 (9.6–11.0)	0.79 (0.70–0.88)
Master's or PhD degree	9.2 (8.4–10.0)	0.70 (0.62–0.79)
Monthly income before tax, ISK		
300 thousand or less	16.5 (15.4–17.7)	Ref.
301–500 thousand	12.2 (11.4–13.0)	0.74 (0.67–0.81)
501–700 thousand	9.5 (8.7–10.3)	0.58 (0.52–0.64)
701–100 thousand	8.0 (7.2–8.9)	0.48 (0.43–0.55)
More than a million	7.3 (6.3–8.5)	0.45 (0.38–0.53)
Health indicators and conditions[d]		
Smoking status		
Never	11.4 (10.4–12.6)	Ref.
Current/previous	13.5 (12.3–14.8)	1.18 (1.09–1.27)
Body mass index, kg/m^2		
<25	10.4 (9.3–11.6)	Ref.
25–30	11.6 (10.4–12.8)	1.11 (1.01–1.23)
>30	15.4 (14.0–16.9)	1.48 (1.34–1.62)
History of psychiatric disorders		
No	10.3 (9.4–11.4)	Ref.
Yes	16.5 (15.0–18.1)	1.59 (1.48–1.72)
Chronic medical conditions (somatic only)		
No	10.9 (9.9–12.0)	Ref.
Yes	15.3 (13.9–16.8)	1.40 (1.30–1.52)
History of quarantine		
No	11.4 (10.4–12.6)	Ref.
Yes	14.2 (12.9–15.6)	1.25 (1.16–1.34)
History of COVID-19 testing and diagnosis		
Not tested	11.6 (10.5–12.9)	Ref.
Tested but not diagnosed	13.4 (12.2–14.7)	1.15 (1.07–1.25)
Diagnosed with COVID-19	11.5 (9.7–13.7)	0.99 (0.84–1.18)
History of being bedridden due to COVID-19		
No	12.6 (11.5–13.7)	Ref.
Yes	13.6 (11.2–16.4)	1.08 (0.90–1.29)

a: Obtained adjusted prevalence per 100 people using binomial logistic regression.

b: Obtained adjusted prevalence ratio using log-binomial Poisson regression.

c: Adjusted for month response received (i.e. December 2020, January–February 2021, May 2021, June–July 2021).

d: Adjusted for age, sex, sexual orientation, residential area, highest education completed, monthly income before tax and month response received (i.e. December 2020, January–February 2021, May 2021, June–July 2021).

CI., confidence interval. Ref., reference.

bidirectional relationship between disruption in mental health services and mental illness, where patients suffering from suicidal ideation or depression may subjectively reduce their service utilization due to diminished motivation. Additionally, pre-existing health conditions have been associated with increased risk of COVID-19-related events (e.g. COVID-19 diagnosis, hospitalization and death).[37,38] Patients with pre-existing health conditions may therefore have been forced to self-quarantine and minimize healthcare service visits to avoid infection. These patients were battling with a double disease burden (i.e. their pre-existing health condition and

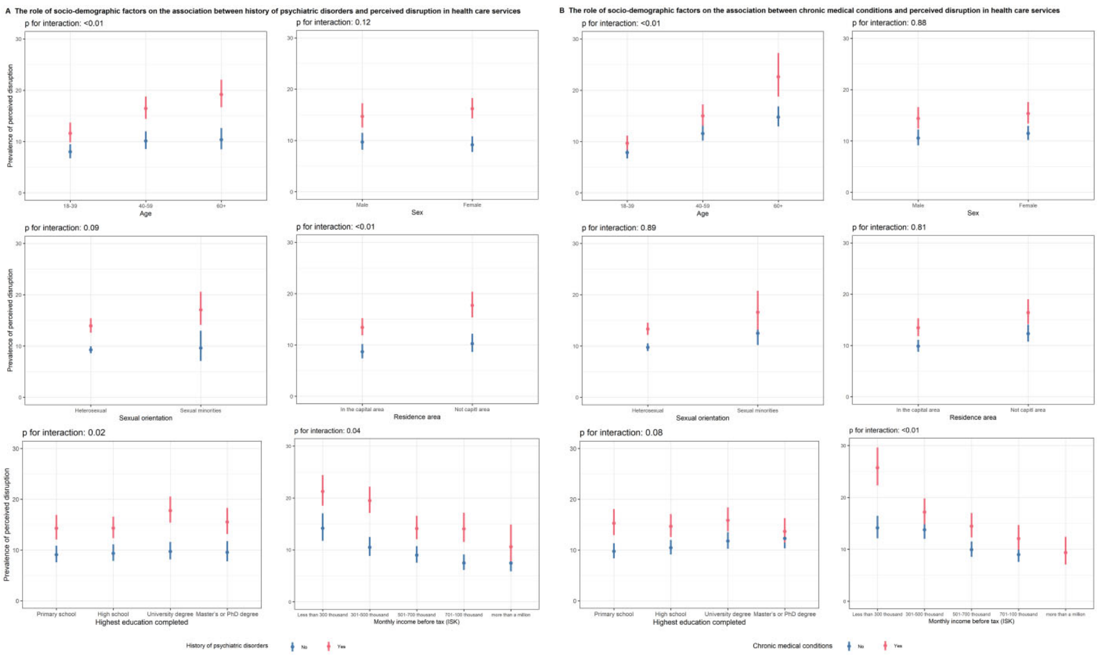

Figure 2 The role of socio-demographic factors on the association between pre-existing health conditions (i.e. history of psychiatric disorders (A) and chronic medical conditions (B)) and perceived disruption in healthcare services. *Note*: Model were adjusted for age, gender, sexual orientation, residence area, highest education completed, monthly income before tax and month response received (i.e. December 2020, January–February 2021, May 2021, June–July 2021).

added risk of severe COVID-19 outcomes) and accessible healthcare services are important for them.

In line with previous studies,[4,5] our results suggested that the negative effects of the pandemic were disproportionately distributed across social strata and pertain mainly to vulnerable groups, such as younger adults, individuals with lower levels of education and those residing in rural areas. Barriers such as financial, social and organizational factors may contribute to the reduction in healthcare utilization by these vulnerable populations.[29] A US study found that younger patients delayed seeking care largely due to financial reasons, although this may not be generalizable to countries with universal health coverage.[30] Additionally, findings from the UK suggest that young adults and those with lower levels of education were more likely to suffer job loss during the pandemic.[31] Moreover, the impact of the pandemic on perceived healthcare disruption among individuals with history of psychiatric disorders was greater among non-capital area residents than capital region residents. Shortages of non-capital healthcare personnel during the pandemic, particularly in psychiatry, may be a key factor behind these results.[32] By contrast, several studies also documented that these vulnerable groups already suffered inequalities and lower access to health care before the pandemic[33] and that the pandemic unraveled or exacerbated these disparities.[4,5]

A major strength of this study is the use of a large nationwide cohort to investigate the temporal trend of perceived disruption in healthcare services during the COVID-19 pandemic in Iceland. Furthermore, leveraging the rich data on socio-demographic factors and health conditions, we provide an in-depth characterization of the vulnerable populations who were more likely to be affected by the disruption in healthcare services during the pandemic. The study also has several limitations. First, the question on perceived disruption in healthcare services is not a validated measure and was used for the first time in this study. Thus, the study may not accurately capture perceived shortage of healthcare services or that the prevalence of perceived disruption in healthcare services was over- or underestimated. However, this measurement error should be similar across the groups, and thus would not be expected to affect the noted association between socio-demographic factors, health conditions and the prevalence of perceived disruption in healthcare services. Also, we have no data on the purpose (e.g. mental health services, dental care or cancer treatment) or type (e.g. primary care, emergency services or hospitalization) of the needed healthcare services, which limits the ability to address the research questions according to different healthcare domains. In addition, the C-19 resilience cohort is overrepresented by women, older and more educated individuals which may have influenced our results. Finally, our study is limited to an adult population in a Nordic welfare society that experienced a relatively favorable course of the pandemic, and thus limits the generalizability of our findings.

In conclusion, our findings suggest that perceived disruption in healthcare services during the COVID-19 pandemic was pronounced among individuals with pre-existing health conditions, particularly in vulnerable socio-demographic groups, such as younger adults, those with lower levels of education, living in and residing in non-capital areas. By contrast, these data suggest that the Icelandic healthcare system managed to maintain accessible services to individuals diagnosed with COVID-19.

Supplementary data

Supplementary data are available at *EURPUB* online.

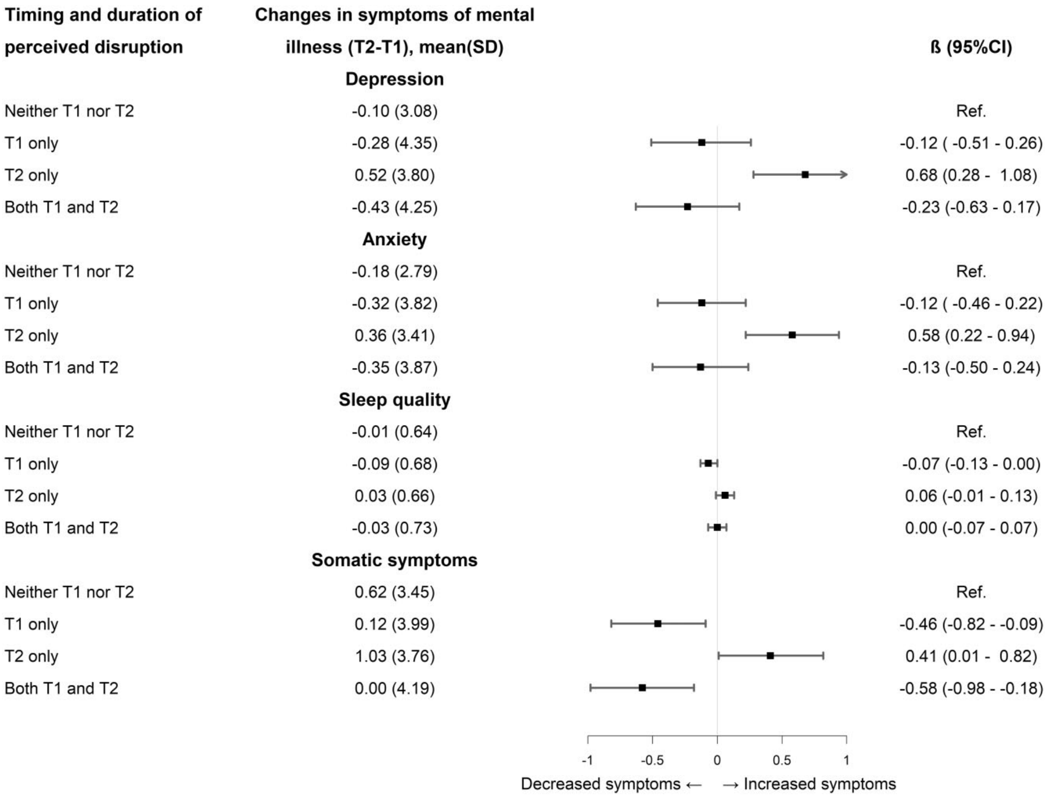

Figure 3 The association between timing and duration of perceived disruption in healthcare services and changes in symptoms of mental illness, among 7848 participants with two repeated measures. *Note*: T1, from December 2020 to February 2021; T2, from May 2021 to July 2021; changes in symptoms of mental illness was calculated by subtracting the measure score of T1 from T2 (i.e. difference in the measure scores of T1 and T2); linear regression adjusted for age, sex, sexual orientation, residence area, highest education completed, monthly income before tax, smoking status, body mass index, history of psychiatric disorders, chronic medical conditions (somatic only), history of quarantine, history of COVID-19 testing and diagnosis and history of bedridden due to COVID-19.

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Author contributions

Y.W., T.A. and U.A.V. designed the study. Y.W. did the data analyses, with support from U.A.V., T.A., A.B.U., and I.M. Y.W. and U.A.V. drafted the article, and all authors contributed to data interpretation. All authors approved the final article as submitted and agree to be accountable for all aspects of the work.

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Conflicts of interest: None declared.

Data availability

The individual-level data underlying this article were subject to ethical approval and cannot be shared publicly due to data protection laws in Iceland.

Key points

- The prevalence of perceived disruption in healthcare services in Iceland attenuated slightly during the pandemic period.
- Patients with pre-existing health conditions, particularly in vulnerable socio-demographic groups (e.g. younger adults, individuals with lower levels of education and those residing in non-capital areas), may have experienced healthcare services disruption to a greater extent than others during the pandemic.
- Individuals infected with COVID-19 did not report elevated prevalence of healthcare service disruption, indicating that the Icelandic healthcare system managed to maintain accessible services to this patient population.
- Emerging perceived disruption in healthcare services was associated with an increase in symptoms of mental illness during the pandemic.

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Supplementary Tables

Table S1 Socio-demographic characteristics of C-19 resilience participants vs. the general icelandic population

	General Icelandic Population (n=244654)	**C-19 Resilience Cohort** (n=23960)
Age group		
25-34	54513(22.3%)	2055 (8.6%)
35-44	49231(20.1%)	2996 (12.5%)
44-54	44450(18.2%)	5491 (22.9%)
55-64	42280(17.3%)	6406 (26.7%)
65-74	31447(12.9%)	4888 (20.4%)
≥75	22733(9.3%)	1403 (5.9%)
Unknown	-	721 (3.0%)
Gender		
Male	124285(50.8%)	7014 (29.3%)
Female	120369(49.2%)	16262 (67.9%)
Unknown	-	684 (2.9%)
Residence area		
Capital region	157561(64.4%)	15944 (66.5%)
Non-capital region	87093(35.6%)	7220 (30.1%)
Western Region	11031(4.5%)	943 (3.9%)
Westfjords	4771(2.0%)	417 (1.7%)
Northwestern Region	25134(10.3%)	2416 (10.1%)
Eastern Region	7167(2.9%)	614 (2.6%)
Southern Region	20921(8.6%)	1680 (7.0%)
Southern Peninsula	18069(7.4%)	1150 (4.8%)
Unknown	-	796 (3.3%)
Education		
Primary school/Basic education	72109(29.5%)	3376 (14.1%)
High school/Upper secondary education	87775(35.9%)	7235 (30.2%)
University degree and above/Tertiary education	84770(34.6%)	12559 (52.4%)
Unknown	-	790 (3.3%)

Note, data for the general Icelandic population was obtained from Statistics Iceland, and due to the data availability, the comparison was limited for participants aged 25 years and older.

Table S2 Characteristics of the study population in the Icelandic COVID-19 National Resilience Cohort, overall and stratified by perceived disruption in health care services.

	Perceived disruption in health care services				**Overall**
	T1 (December 2020 to February 2021)		**T2 (May to July 2021)**		
	No (n=12139)	**Yes (n=1657)**	**No (n=8785)**	**Yes (n=1021)**	**n=15754**
Socio-demographic factors					
Age (continuous), years					
Mean (SD)	55.2 (13.9)	51.7 (14.2)	56.2 (13.4)	53.2 (13.7)	54.8 (13.9)
Median [Min, Max]	57.0 [18.0, 93.0]	53.0 [18.0, 84.0]	58.0 [18.0, 93.0]	54.0 [18.0, 84.0]	56.0 [18.0, 93.0]
Age (category), years					
18-39	1765 (14.5%)	363 (21.9%)	1087 (12.4%)	183 (17.9%)	2408 (15.3%)
40-59	5266 (43.4%)	746 (45.0%)	3771 (42.9%)	464 (45.4%)	6886 (43.7%)
≥60	5108 (42.1%)	548 (33.1%)	3927 (44.7%)	374 (36.6%)	6460 (41.0%)
Sex					
Male	3693 (30.4%)	439 (26.5%)	2774 (31.6%)	250 (24.5%)	4710 (29.9%)
Female	8282 (68.2%)	1199 (72.4%)	5923 (67.4%)	759 (74.3%)	10816 (68.7%)
Unknown	164 (1.4%)	19 (1.1%)	88 (1.0%)	12 (1.2%)	228 (1.4%)
Sexual orientation					
Heterosexual	11519 (94.9%)	1538 (92.8%)	8355 (95.1%)	939 (92.0%)	14885 (94.5%)
Sexual minorities	424 (3.5%)	88 (5.3%)	315 (3.6%)	60 (5.9%)	589 (3.7%)
Unknown	196 (1.6%)	31 (1.9%)	115 (1.3%)	22 (2.2%)	280 (1.8%)
Residential area					
Capital region	8374 (69.0%)	1009 (60.9%)	6032 (68.7%)	632 (61.9%)	10709 (68.0%)
Non-capital region	3627 (29.9%)	632 (38.1%)	2682 (30.5%)	379 (37.1%)	4853 (30.8%)
Western Region	487 (4.0%)	70 (4.2%)	349 (4.0%)	44 (4.3%)	630 (4.0%)
Westfjords	190 (1.6%)	42 (2.5%)	152 (1.7%)	29 (2.8%)	267 (1.7%)
Northwestern Region	1214 (10.0%)	205 (12.4%)	893 (10.2%)	135 (13.2%)	1610 (10.2%)
Eastern Region	282 (2.3%)	54 (3.3%)	209 (2.4%)	30 (2.9%)	384 (2.4%)
Southern Region	874 (7.2%)	125 (7.5%)	642 (7.3%)	64 (6.3%)	1132 (7.2%)
Southern Peninsula	510 (4.2%)	126 (7.6%)	390 (4.4%)	67 (6.6%)	733 (4.7%)
Unknown	208 (1.7%)	26 (1.6%)	118 (1.3%)	20 (2.0%)	289 (1.8%)
Highest education completed					
Primary school	1556 (12.8%)	258 (15.6%)	1106 (12.6%)	154 (15.1%)	2088 (13.3%)
High school	3578 (29.5%)	560 (33.8%)	2646 (30.1%)	337 (33.0%)	4744 (30.1%)
BA/BS degree	3922 (32.3%)	478 (28.8%)	2811 (32.0%)	322 (31.5%)	5009 (31.8%)
Master's or PhD degree	2874 (23.7%)	330 (19.9%)	2110 (24.0%)	191 (18.7%)	3626 (23.0%)
Unknown	209 (1.7%)	31 (1.9%)	112 (1.3%)	17 (1.7%)	287 (1.8%)
Monthly income before tax, ISK					
300 thousand or less	1866 (15.4%)	390 (23.5%)	1278 (14.5%)	252 (24.7%)	2599 (16.5%)
301-500 thousand	3279 (27.0%)	498 (30.1%)	2385 (27.1%)	314 (30.8%)	4274 (27.1%)
501-700 thousand	3052 (25.1%)	354 (21.4%)	2206 (25.1%)	215 (21.1%)	3863 (24.5%)
701-1,000 thousand	2186 (18.0%)	212 (12.8%)	1625 (18.5%)	128 (12.5%)	2722 (17.3%)
More than a million	1062 (8.7%)	99 (6.0%)	787 (9.0%)	52 (5.1%)	1353 (8.6%)
Unknown	694 (5.7%)	104 (6.3%)	504 (5.7%)	60 (5.9%)	943 (6.0%)
Health indicators and conditions					
Smoking status					
Never	5558 (45.8%)	677 (40.9%)	3973 (45.2%)	437 (42.8%)	7085 (45.0%)
Previous /Current	6337 (52.2%)	946 (57.1%)	4658 (53.0%)	568 (55.6%)	8315 (52.8%)
Unknown	244 (2.0%)	34 (2.1%)	154 (1.8%)	16 (1.6%)	354 (2.2%)
Body mass index, kg/m^2					
<25	3475 (28.6%)	398 (24.0%)	2486 (28.3%)	234 (22.9%)	4442 (28.2%)
25-30	4700 (38.7%)	571 (34.5%)	3367 (38.3%)	326 (31.9%)	5958 (37.8%)
>30	3558 (29.3%)	637 (38.4%)	2661 (30.3%)	426 (41.7%)	4795 (30.4%)
Unknown	406 (3.3%)	51 (3.1%)	271 (3.1%)	35 (3.4%)	559 (3.5%)
History of psychiatric disorders					
No	8658 (71.3%)	918 (55.4%)	6295 (71.7%)	562 (55.0%)	10892 (69.1%)

	Perceived disruption in health care services				Overall
	T1 (December 2020 to February 2021)		T2 (May to July 2021)		
	No (n=12139)	**Yes (n=1657)**	**No (n=8785)**	**Yes (n=1021)**	**n=15754**
Yes	3180 (26.2%)	684 (41.3%)	2298 (26.2%)	431 (42.2%)	4425 (28.1%)
Unknown	301 (2.5%)	55 (3.3%)	192 (2.2%)	28 (2.7%)	437 (2.8%)
Chronic medical conditions (somatic only)					
No	6832 (56.3%)	842 (50.8%)	4834 (55.0%)	511 (50.0%)	8761 (55.6%)
Yes	5081 (41.9%)	790 (47.7%)	3817 (43.4%)	500 (49.0%)	6689 (42.5%)
Unknown	226 (1.9%)	25 (1.5%)	134 (1.5%)	10 (1.0%)	304 (1.9%)
History of quarantine					
No	7431 (61.2%)	901 (54.4%)	5217 (59.4%)	535 (52.4%)	9254 (58.7%)
Yes	4681 (38.6%)	755 (45.6%)	3553 (40.4%)	482 (47.2%)	6466 (41.0%)
Unknown	27 (0.2%)	1 (0.1%)	15 (0.2%)	4 (0.4%)	34 (0.2%)
History of COVID-19 testing and diagnosis					
Not tested	4834 (39.8%)	608 (36.7%)	2872 (32.7%)	304 (29.8%)	5365 (34.1%)
Tested but not diagnosed	6435 (53.0%)	942 (56.8%)	5434 (61.9%)	665 (65.1%)	9307 (59.1%)
Diagnosed with COVID-19	808 (6.7%)	101 (6.1%)	433 (4.9%)	48 (4.7%)	1000 (6.3%)
Unknown	62 (0.5%)	6 (0.4%)	46 (0.5%)	4 (0.4%)	82 (0.5%)
History of being bedridden due to COVID-19					
No	11596 (95.5%)	1577 (95.2%)	8437 (96.0%)	980 (96.0%)	15036 (95.4%)
Yes	493 (4.1%)	73 (4.4%)	309 (3.5%)	38 (3.7%)	647 (4.1%)
Unknown	50 (0.4%)	7 (0.4%)	39 (0.4%)	3 (0.3%)	71 (0.5%)

Table S3 Prevalence of perceived disruption in health care services by socio-demographic factors and pre-existing health conditions among participants who responded to the question on perceived disruption in health care services during the study period (December 2020 - July 2021), by complete case analysis.

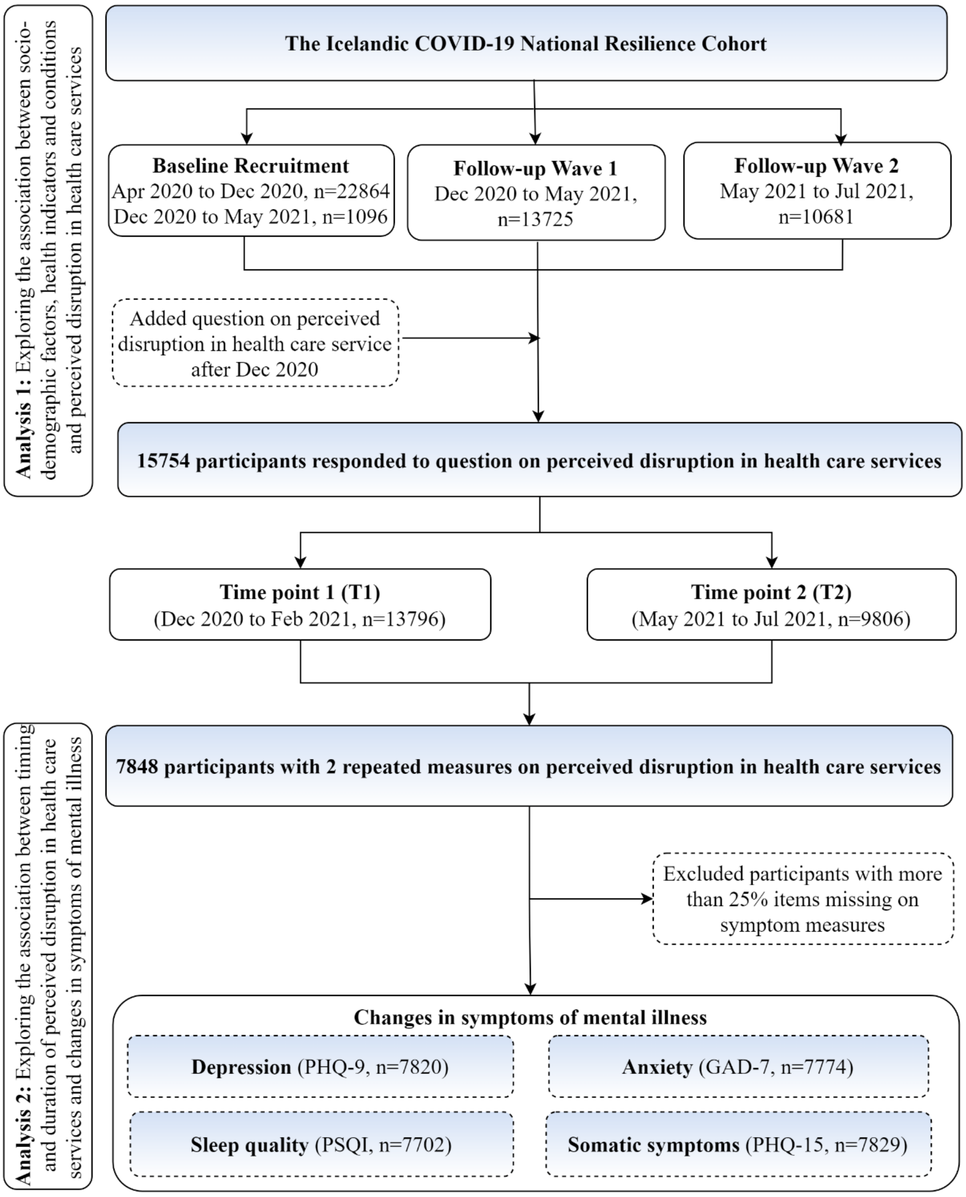
	Prevalence per 100 persons [a] (95%CI)	Prevalence ratios [b] (95%CI)
Socio-demographic factors [c]		
Age, years		
18-39	15.6 (14.4 - 16.9)	Ref.
40-59	11.5 (10.8 - 12.1)	0.74 (0.67 - 0.81)
≥60	9.0 (8.4 - 9.6)	0.58 (0.53 - 0.64)
Sex		
Male	9.3 (8.7 - 10.1)	Ref.
Female	11.8 (11.2 - 12.3)	1.26 (1.16 - 1.36)
Sexual orientation		
Heterosexual	10.8 (10.3 - 11.2)	Ref.
Sexual minorities	16.2 (13.9 - 18.8)	1.50 (1.29 - 1.75)
Residential area		
Capital region	9.9 (9.4 - 10.4)	Ref.
Non-capital region	13.4 (12.6 - 14.2)	1.35 (1.26 - 1.45)
Western Region	11.7 (9.8 - 13.9)	1.17 (0.98 - 1.40)
Westfjords	16.8 (13.5 - 20.7)	1.69 (1.36 - 2.09)
Northwestern Region	13.5 (12.2 - 14.9)	1.36 (1.22 - 1.52)
Eastern Region	14.2 (11.6 - 17.3)	1.43 (1.17 - 1.75)
Southern Region	10.8 (9.4 - 12.3)	1.08 (0.94 - 1.25)
Southern Peninsula	17.2 (15.0 - 19.5)	1.72 (1.50 - 1.97)
Highest education completed		
Primary school	13.0 (11.9 - 14.3)	Ref.
High school	12.2 (11.5 - 13.1)	0.94 (0.84 - 1.05)
BA/BS degree	10.3 (9.6 - 11.0)	0.79 (0.71 - 0.89)
Master's or PhD degree	9.2 (8.4 - 10.0)	0.71 (0.62 - 0.80)
Monthly income before tax, ISK		
300 thousand or less	16.5 (15.3 - 17.7)	Ref.
301-500 thousand	12.2 (11.3 - 13.0)	0.74 (0.67 - 0.81)
501-700 thousand	9.5 (8.7 - 10.3)	0.58 (0.52 - 0.64)
701-100 thousand	7.9 (7.2 - 8.8)	0.48 (0.43 - 0.55)
More than a million	7.3 (6.2 - 8.5)	0.44 (0.38 - 0.53)
Health indicators and conditions [d]		
Smoking status		
Never	11.0 (9.9 - 12.2)	Ref.
Current/Previous	13.3 (12.0 - 14.6)	1.20 (1.11 - 1.30)
Body mass index, kg/m^2		
<25	10.5 (9.3 - 11.8)	Ref.
25-30	11.3 (10.1 - 12.6)	1.07 (0.97 - 1.19)
>30	15.3 (13.8 - 16.9)	1.45 (1.32 - 1.59)
History of psychiatric disorders		
No	10.0 (9.1 - 11.1)	Ref.
Yes	16.1 (14.6 - 17.8)	1.60 (1.48 - 1.73)
Chronic medical conditions (somatic only)		
No	10.6 (9.6 - 11.7)	Ref.

	Prevalence per 100 persons [a] (95%CI)	Prevalence ratios [b] (95%CI)
Yes	15.0 (13.6 - 16.5)	1.41 (1.30 - 1.53)
History of quarantine		
No	11.1 (10.1 - 12.3)	Ref.
Yes	14.0 (12.6 - 15.4)	1.25 (1.16 - 1.35)
History of COVID-19 testing and diagnosis		
Not tested	11.4 (10.2 - 12.7)	Ref.
Tested but not diagnosed	13.2 (11.9 - 14.5)	1.15 (1.06 - 1.25)
Diagnosed with COVID-19	11.3 (9.4 - 13.5)	0.99 (0.83 - 1.19)
History of being bedridden due to COVID-19		
No	12.3 (11.2 - 13.5)	Ref.
Yes	13.3 (10.9 - 16.2)	1.08 (0.90 - 1.30)

a. Obtained adjusted prevalence per 100 persons using logistic regression.
b. Obtained adjusted prevalence ratio using poisson regression.
c. Adjusted for month response received (i.e., Dec 2020, Jan-Feb 2021, May 2021, Jun-Jul 2021).
d. Adjusted for age, sex, sexual orientation, residence area, highest education completed, monthly income before tax and month response received (i.e., Dec 2020, Jan-Feb 2021, May 2021, Jun-Jul 2021).

Supplementary **Figures**

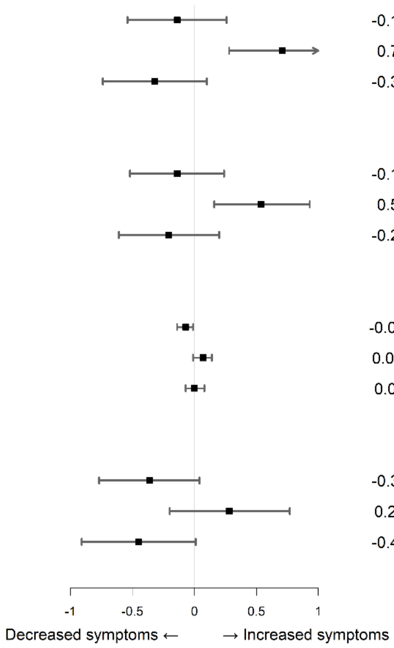
Figure S1 Flowchart of the study population.



Note, PHQ-9: Patient Health Questionnaire-9; GAD-7: General Anxiety Disorder-7; PSQI: Pittsburgh Sleep Quality Index; PHQ-15: Patient Health Questionnaire-15.

Figure S2 The association between timing and duration of perceived disruption in health care services and changes in symptoms of mental illness, among participants with two repeated measures, by complete case analysis.

Timing and duration of perceived disruption	Changes in symptoms of mental illness (T2-T1), mean(SD)	ß (95%CI)
	Depression	
Neither T1 nor T2	-0.10 (3.03)	Ref.
T1 only	-0.33 (4.23)	-0.14 (-0.54 - 0.26)
T2 only	0.52 (3.73)	0.71 (0.28 - 1.15)
Both T1 and T2	-0.46 (4.15)	-0.32 (-0.74 - 0.10)
	Anxiety	
Neither T1 nor T2	-0.17 (2.77)	Ref.
T1 only	-0.32 (3.84)	-0.14 (-0.52 - 0.24)
T2 only	0.28 (3.35)	0.54 (0.16 - 0.93)
Both T1 and T2	-0.36 (3.91)	-0.21 (-0.61 - 0.20)
	Sleep quality	
Neither T1 nor T2	-0.01 (0.64)	Ref.
T1 only	-0.09 (0.68)	-0.07 (-0.14 - -0.01)
T2 only	0.03 (0.66)	0.07 (-0.01 - 0.14)
Both T1 and T2	-0.03 (0.73)	0.00 (-0.07 - 0.08)
	Somatic symptoms	
Neither T1 nor T2	0.52 (3.38)	Ref.
T1 only	0.11 (3.75)	-0.36 (-0.77 - 0.04)
T2 only	0.86 (3.73)	0.28 (-0.20 - 0.77)
Both T1 and T2	-0.09 (4.07)	-0.45 (-0.91 - 0.01)



Note, T1, from December 2020 to February 2021; T2, from May 2021 to July 2021; Changes in symptoms of mental illness was calculated by subtracting the measure score of T1 from T2 (i.e., difference in the measure scores of T1 and T2); linear regression adjusted for age, sex, sexual orientation, residence area, highest education completed, monthly income before tax, smoking status, body mass index, history of psychiatric disorders, chronic medical conditions (somatic only), history of quarantine, history of COVID-19 testing and diagnosis and history of being bedridden due to COVID-19.

Supplementary Referenes

The SAGA (Stress-And-Gene-Analysis) cohort,[1] the iStopMM (Iceland Screens, Treats, or Prevents Multiple Myeloma) study,[2] and the Health and Well-Being of Icelanders cohort.[3]

References

1. The SAGA cohort. https://afallasaga.is/english/2023).
2. Rögnvaldsson S, Love TJ, Thorsteinsdottir S, et al. Iceland screens, treats, or prevents multiple myeloma (iStopMM): a population-based screening study for monoclonal gammopathy of undetermined significance and randomized controlled trial of follow-up strategies. *Blood Cancer Journal* 2021; **11**(5): 94.
3. Health Do. Health and wellbeing. https://island.is/en/health-and-wellbeing2023).