Depressive symptoms, but not anxiety, predict subsequent diagnosis of Coronavirus disease 19: a national cohort study

G. Meinlschmidt[1,2,3,4] (iD), S. Guemghar[1,2], N. Roemmel[1,2], E. Battegay[1,5,6], S. Hunziker[2,7] and R. Schaefert[1,2]

[1]Department of Psychosomatic Medicine, University Hospital Basel, Basel, Switzerland; [2]Faculty of Medicine, University of Basel, Basel, Switzerland; [3]Division of Clinical Psychology and Cognitive Behavioural Therapy, International Psychoanalytic University, Berlin, Germany; [4]Division of Clinical Psychology and Epidemiology, Department of Psychology, University of Basel, Basel, Switzerland; [5]International Center for Multimorbidity and Complexity in Medicine (ICMC), University of Zurich, Zurich, Switzerland; [6]Merian Iselin Clinic, Basel, Switzerland and [7]Medical Communication/Psychosomatic Medicine, University Hospital Basel, Basel, Switzerland

Original Article

Abstract

Aims. Several diseases are linked to increased risk of Coronavirus disease 19 (COVID-19). Our aim was to investigate whether depressive and anxiety symptoms predict subsequent risk of COVID-19, as has been shown for other respiratory infections.

Methods. We based our analysis on UK Biobank participants providing prospective data to estimate temporal association between depressive and anxiety symptoms and COVID-19. We estimated whether the magnitude of these symptoms predicts subsequent diagnosis of COVID-19 in this sample. Further, we evaluated whether depressive and anxiety symptoms predicted (i) being tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and (ii) COVID-19 in those tested.

Results. Based on data from $N = 135\,102$ participants, depressive symptoms (odds ratio (OR) = 1.052; 95% confidence interval (CI) 1.017–1.086; absolute case risk: (moderately) severe depression: 493 per 100 000 *v.* minimal depression: 231 per 100 000) but not anxiety (OR = 1.009; 95% CI 0.97–1.047) predicted COVID-19. While depressive symptoms but not anxiety predicted (i) being tested for SARS-CoV-2 (OR = 1.039; 95% CI 1.029–1.05 and OR = 0.99; 95% CI 0.978–1.002), (ii) neither predicted COVID-19 in those tested (OR = 1.015; 95% CI 0.981–1.05 and OR = 1.021; 95% CI 0.981–1.061). Results remained stable after adjusting for sociodemographic characteristics, multimorbidity and behavioural factors.

Conclusions. Depressive symptoms were associated with a higher risk of COVID-19 diagnosis, irrespective of multimorbidities. Potential underlying mechanisms to be elucidated include risk behaviour, symptom perception, healthcare use, testing likelihood, viral exposure, immune function and disease progress. Our findings highlight the relevance of mental processes in the context of COVID-19.

CAMBRIDGE
UNIVERSITY PRESS

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes Coronavirus disease 19 (COVID-19) and has spread across the globe, with over 23 million confirmed cases worldwide as of 24 August 2020 (the date of the latest data available for this study; World Health Organization, 2020). The COVID-19 pandemic has impacted mortality and entire societies substantially (Petterson *et al.*, 2020; World Health Organization, 2020). Several conditions, diseases and sociodemographic factors have been associated with COVID-19 and related deaths (Richardson *et al.*, 2020; Rozenfeld *et al.*, 2020; Wang *et al.*, 2020*a*; Williamson *et al.*, 2020; Zhou *et al.*, 2020). Recent population-based, prospective studies found evidence for an association between the history of depression or anxiety and the subsequent risk of COVID-19 (Lee *et al.*, 2020; Li *et al.*, 2020*b*; Wang *et al.*, 2021; Fond *et al.*, 2021). However, the relevance of depression or anxiety to the likelihood of being tested for SARS-CoV-2, additionally to being diagnosed with COVID-19 remains unclear.

Notably, subjects with COVID-19 show increased rates of psychosocial stress, including depressive and anxiety symptoms, as well as disturbed sleep (Krishnamoorthy *et al.*, 2020; Li *et al.*, 2020*a*; Mazza *et al.*, 2020; Rogers *et al.*, 2020). However, given the cross-sectional nature of previous studies, studies need to determine the directions of these associations. Indeed, the psychosocial burden of COVID-19 and its symptoms, potentially severe or fatal disease trajectories, treatment and required isolation may trigger these symptoms. On the other hand, depression and anxiety may precede respiratory diseases (Goodwin *et al.*, 2014).

Indeed, multiple studies have shown a link between mental factors and infectious diseases, including respiratory tract infections (Goodwin *et al.*, 2003; Adam *et al.*, 2013). However, it is unknown whether symptoms of mental disorders precede and predict the subsequent risk of COVID-19.

The objective of our study was to evaluate the association of depressive symptoms and anxiety with the subsequent risk of being diagnosed with COVID-19. We hypothesised that the magnitudes of both are linked to an increased risk of COVID-19. Further, given the potential relevance of testing rates and their relation to mental disorders (van der Meer *et al.*, 2020), we estimated associations between depressive and anxiety symptoms with the likelihood of being tested for SARS-CoV-2. Scrutinising the role of mental factors for disease trajectories of COVID-19 in the UK Biobank, a large-scale study that includes prospective data may contribute to a better understanding and potentially better management of COVID-19.

Methods

Study design and population

The present study is based on the UK Biobank, a large population-based national cohort of UK residents (Smith *et al.*, 2013). Voluntary participants were recruited between March 2006 and December 2010. Additionally, a proportion of participants were invited to repeat assessments and to answer questionnaires between 2012 and 2019. During these subsequent visits, some information that was missing at the initial assessment was collected. Further, information from the hospital inpatient data was linked to the UK Biobank dataset, cancer register, death register and primary care data. Information provided by participants at recruitment and at subsequent assessments included sociodemographic characteristics, self-reported health conditions and answers to a mental health web-based questionnaire between 2016 and 2017. We used the latter to calculate the nine-item Patient Health Questionnaire (PHQ-9) (Spitzer, 1999; Spitzer *et al.*, 2000; Kroenke *et al.*, 2001; Kroenke and Spitzer, 2002) and seven-item Generalised Anxiety Disorder (GAD-7) (Spitzer *et al.*, 2006; Löwe *et al.*, 2008; Dear *et al.*, 2011) scores where possible. Information on SARS-CoV-2 tests of UK Biobank participants was provided by Public Health England (PHE) for the period from 16 March 2020 to 24 August 2020. We included participants who were recruited in England, were alive on 31 December 2019 before the onset of the COVID-19 pandemic, and provided sufficient information on PHQ-9 and GAD-7 available so that we were able to calculate respective scores. We provide more details on the UK Biobank and the study procedures in online Supplementary material 1.

Statistical analysis

To estimate the association of depressive and anxiety symptoms with COVID-19, we conducted logistic regression analyses. For the crude models, we entered depressive and anxiety symptom scores as continuous predictor variables with COVID-19 as the main outcome. For adjusted models, we conducted a two-step adjustment scheme. As a first step, we concomitantly adjusted the analyses for *a priori* defined sociodemographic variables, acting as potential confounders: age, sex, ethnicity and deprivation index, categorised as outlined in Table 1. As a second step, we adjusted analyses for *a priori* selected physical diseases

Table 1. Descriptive statistics of UK Biobank participants included in the study

	Total N = 135 102 Frequency (%)[a]
Sociodemographic information	
Sex	
Female	76 457 (56.6%)
Male	58 645 (43.4%)
Age[b] (years)	
Median (IQR) [range]	68 (61–73) [49–83]
Age intervals[b] (years)	
49–54	11 313 (8.4%)
55–59	17 858 (13.2%)
60–64	21 973 (16.3%)
65–69	27 170 (20.1%)
70–74	33 589 (24.9%)
75–79	20 694 (15.3%)
80–83	2505 (1.9%)
Ethnicity[c]	
White	130 590 (96.7%)
Black	1059 (0.8%)
South Asian	1200 (0.9%)
Other	1836 (1.4%)
Townsend category[d]	
Least deprived <−2	75 890 (56.2%)
Average (−2, 2)	42 304 (31.3%)
Most deprived ≥2	16 740 (12.4%)
Died after 31 December 2019	502 (0.4%)
Multimorbidities	
Asthma	18 226 (13.5%)
Cancer	20 815 (15.4%)
Cerebrovascular disease	2571 (1.9%)
COPD	2907 (2.2%)
Coronary artery disease	6927 (5.1%)
Diabetes mellitus[e]	6664 (4.9%)
Hypertension	24 114 (17.8%)
Body mass index[f] (kg/m^2)	
Median (IQR) [range]	26 (24–29) [12–70]
Obesity (BMI ≥ 30)	26 465 (19.6%)
Morbid obesity (BMI ≥ 35)	7070 (5.2%)
Never smoked[g]	77 187 (57.2%)
Never drank[h]	3630 (2.7%)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a]Percentages may not add up to 100 because of rounding.
[b]Age on 1 January 2020.
[c]White includes British, Irish and any other white background. Black includes Caribbean, African and any other black background. South Asian includes Indian, Pakistani, Bangladeshi and any other south Asian background. Other includes mixed, Chinese or other ethnicities. 417 participants were missing ethnicity data.
[d]Participants were assigned a Townsend deprivation score corresponding to the output area of their residential postcode). 168 participants were missing Townsend scores.
[e]Includes diet-controlled and non-insulin-dependent diabetes.
[f]283 participants were missing BMI data.
[g]266 participants were missing smoking status data.
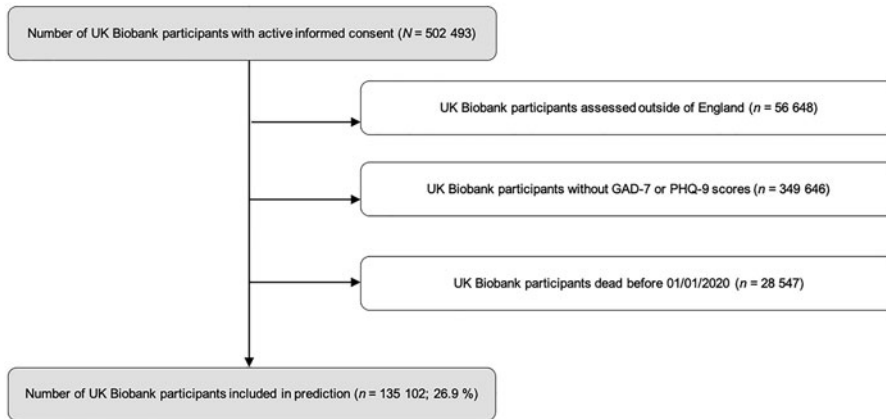[h]107 participants were missing drinking status data.

Fig. 1. Flow chart of study participants. Predictions were calculated with UKB participants assessed in England, alive on 31 December 2019 and with complete GAD-7 and PHQ-9 scores.

and behavioural risk factors (see Table 1) that have been reported elsewhere as being linked to an increased risk of COVID-19 (Wang *et al.*, 2020*a*; Zhou *et al.*, 2020). These may potentially act as confounders or mediators, given the lack of information on the timing of these physical diseases and behavioural risk factors as compared to the depressive and anxiety symptoms. For the second adjustment step, we entered first step covariates, as well as one physical disease or behavioural risk factor at a time. Next, to estimate the association between depressive and anxiety symptoms with *being tested for SARS-CoV-2*, we conducted additional logistic regression analyses. Here again, we applied the two-step adjustment scheme outlined above. Further, to estimate the association of depressive and anxiety symptoms with COVID-19 *in those being tested for SARS-CoV-2*, we conducted logistic regression analyses as outlined above, this time however restricting the analyses to participants who had been tested for SARS-CoV-2. To prevent overfitting, we adjusted for only one sociodemographic variable at a time in step 1 and omitted adjusting for step 1 covariates during step 2.

We excluded participants who did not answer all the questions in the mental health web-based questionnaire necessary to calculate GAD-7 and PHQ-9 scores. We handled missing data by conducting completer analyses, excluding participants who lacked information on ethnicity, Townsend score, body mass index, or smoking and drinking status, when adjusting for these confounders, respectively (see online Supplementary Tables 4–8 in online Supplementary material 3).

To further test for a dose–response relationship, we conducted a logistic regression analysis with depressive symptom scores as ordered categorical predictor variables and COVID-19 as the outcome.

We provided estimates with 95% confidence intervals. We performed all calculations at sciCORE (sciCORE | Center for Scientific Computing, 2020) scientific computing centre at the University of Basel, using R version 4.0.0 (R Core Team, 2020). We provide more details on statistical analyses in online Supplementary material 2.

Results

Figure 1 shows the flow chart of study participants.

Table 1 shows descriptive information on sociodemographic characteristics, multimorbidities and behavioural factors in the 135 102 UK Biobank participants on which our analyses are

based. In our sample, 3217 of these participants were tested for SARS-CoV-2. Of these, 337 tested positive.

Depressive symptoms but not anxiety symptoms predicted COVID-19 (OR = 1.052; 95% CI 1.017–1.086; $p = 0.0024$ and OR = 1.009; 95% CI 0.97–1.047; $p = 0.65$, respectively). Estimates remained stable when adjusting for potential sociodemographic confounders (OR = 1.037; 95% CI 1.002–1.072; $p = 0.034$ and OR = 1.005; 95% CI 0.965–1.044; $p = 0.82$, respectively), as well as when adjusting for individual physical diseases and behavioural factors (see online Supplementary Tables 4 and 5 in online Supplementary material 3).

Depressive symptoms but not anxiety symptoms predicted being tested for SARS-CoV-2 (OR = 1.039; 95% CI 1.029–1.05; $p < 0.0001$ and OR = 0.99; 95% CI 0.978–1.002; $p = 0.08$, respectively). Estimates remained stable when adjusting for potential sociodemographic confounders (OR = 1.042; CI 1.032–1.053; $p < 0.0001$ and OR = 0.993; CI 0.981–1.005; $p = 0.24$, respectively), as well as when additionally adjusting for individual physical diseases and behavioural factors (see online Supplementary Tables 6 and 7 in online Supplementary material 3).

Neither depressive symptoms nor anxiety symptoms predicted COVID-19 in those tested for SARS-CoV-2 in the crude models (OR = 1.015; 95% CI 0.981–1.05; $p = 0.38$ and OR = 1.021; 95% CI 0.981–1.061; $p = 0.30$, respectively) as well as in the adjusted models (see online Supplementary Table 8 in online Supplementary material 3).

Depressive symptoms have a dose–response effect on COVID-19 (OR = 1.77; 95% CI 1.16–2.55; $p = 0.0041$).

We depict the probabilities of COVID-19 in the total sample, being tested for SARS-CoV-2 in the total sample, and COVID-19 in those tested, stratified by depressive symptom and anxiety symptom severity categories in Fig. 2. Additionally, we estimated the unadjusted absolute risks (AR) and risk differences (RD) expressed as the number of cases per 100 000 subjects (see Table 2).

Discussion

Results of our population-based study, using prospective and self-report data provide evidence that the magnitude of depressive but not of anxiety symptoms years before the COVID-19 pandemic predicts being tested for SARS-CoV-2 and COVID-19 diagnosis. These results remained stable after adjusting for potential confounders including other comorbidities. In those tested for SARS-CoV-2, there were no further associations of depressive
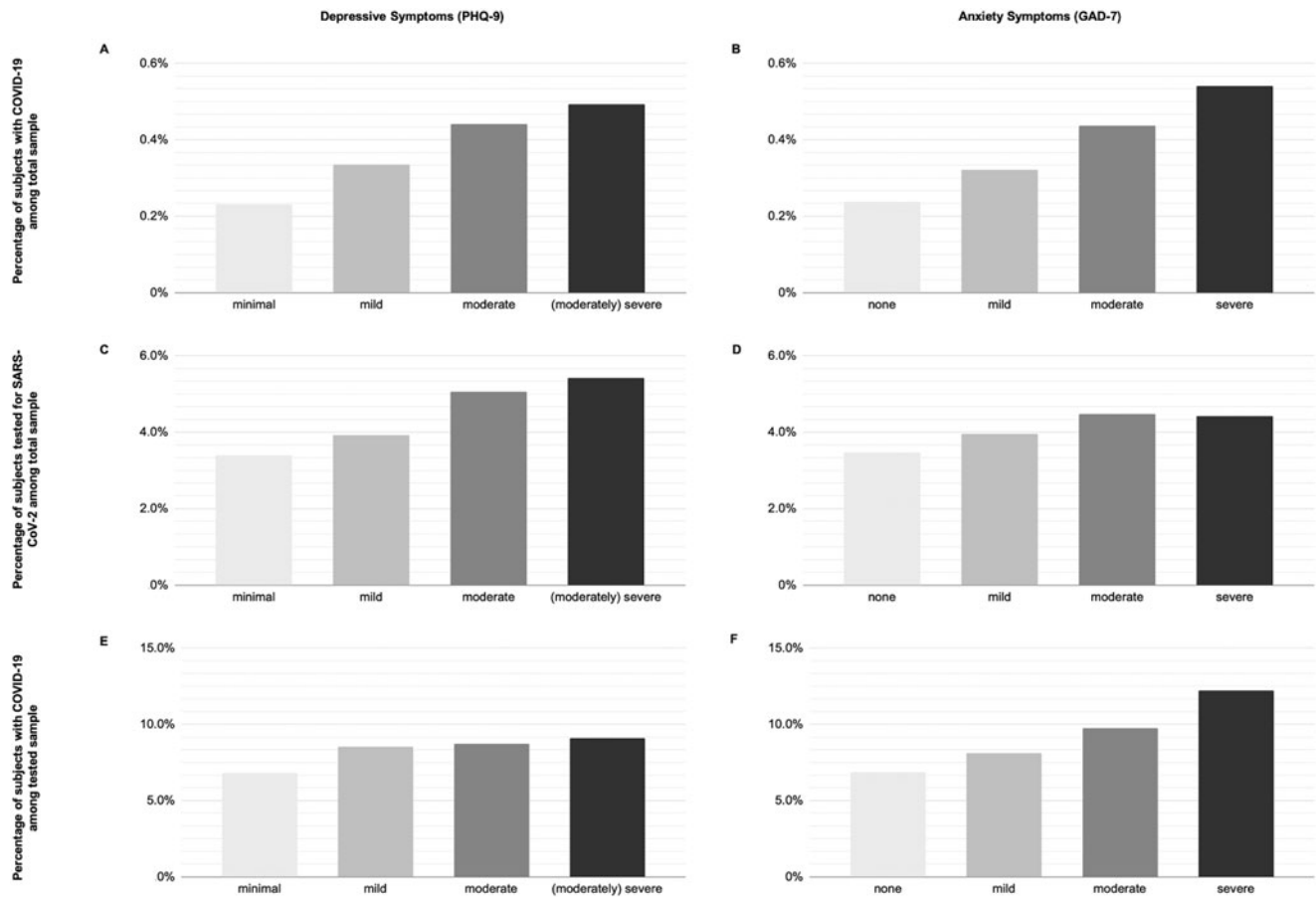
Fig. 2. Percentage of study participants with COVID-19. (A and B) Percentage of subjects with COVID-19 in the total sample stratified by depressive symptoms (A) and general anxiety disorder (B). (C and D) Percentage of subjects tested for SARS-CoV-2 in the total sample stratified by depressive symptoms (C) and general anxiety disorder (D). (E and F) Percentage of subjects with COVID-19 in the tested sample stratified by depressive symptoms (E) and general anxiety disorder (F). *PHQ-9 score:* 0–4, minimal; 5–9, mild; 10–14, moderate; 15–27, (moderately) severe. *GAD-7 score:* 0–4, none; 5–9, mild; 10–14, moderate; 15–21, severe. COVID-19, Coronavirus disease 19; GAD-7 scale, Generalised Anxiety Disorder 7-item scale; PHQ-9, Patient Health Questionnaire Depression 9-item scale; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Unadjusted absolute risks and risk differences with and without depression and anxiety of COVID-19 and being tested for SARS-CoV-2, in cases per 100 000 subjects[a]

	Depressive symptoms			Anxiety symptoms		
	Minimal	(Moderately) severe	(Moderately) severe – minimal	None	Severe	Severe – none
	AR	AR	RD	AR	AR	RD
COVID-19 in total sample	231	493	262	238	541	303
Being tested for SARS-CoV-2	3395	5419	2024	3464	4425	961
COVID-19 in tested sample	6805	9091	2286	6864	12 222	5358

AR, absolute risk; COVID-19, Coronavirus disease 19; RD, risk difference; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Number of subjects rounded to the nearest digit.

symptoms or anxiety with COVID-19. Notably, the magnitude of association between depressive symptoms and COVID-19 was comparable to associations between physical diseases and COVID-19, and remained stable after adjusting for multiple morbidities, known to predict risk of COVID-19. This is in line with previous population-based studies drawing on prospective data that found evidence for an association between the history of

depression or anxiety and COVID-19 (Lee *et al.*, 2020; Li *et al.*, 2020*b*; Wang *et al.*, 2021; Fond *et al.*, 2021).

Our findings strongly support our hypothesis that the magnitude of depressive symptom severity precedes and predicts an increased risk of subsequently being diagnosed with COVID-19. To our surprise, symptoms of anxiety were not associated with the risk of subsequently being diagnosed with COVID-19 beyond

depressive symptoms. Notably, by using population-based prospective data, allowing dose–response estimates, we extend, substantiate and specify evidence based on health records (Wang *et al.*, 2020*a*, 2021). This indicates that being diagnosed with a mental disorder is linked to an increased risk of being diagnosed with COVID-19 (Taquet *et al.*, 2021).

Our findings are in line with previous own (Adam *et al.*, 2013) and others' studies (Goodwin *et al.*, 2014) that indicate a link between symptoms of mental disorders and an increased risk of respiratory diseases, such as the common cold. Interestingly, seropositivity for other coronaviruses has been associated with a history of mood disorders (Okusaga *et al.*, 2011). Our findings show that depressive symptoms predict the risk independently of previously described mental conditions, such as nicotine use, indicative of tobacco use disorder (Gülsen *et al.*, 2020; Reddy *et al.*, 2021).

Several potential mechanisms may explain our main finding of depressive symptoms predicting the risk of a confirmed COVID-19 diagnosis.

First, depressive symptoms are commonly associated with altered behavioural patterns that may be linked to the risk of infections, including hygiene measures, physical and social activities. More specifically, depressive symptoms were associated with reduced self-reported adherence with consistent wearing of face masks and self-reported sanitizing of hands (Pan *et al.*, 2020). This in turn may increase the risk of being exposed to the SARS-CoV-2 virus and hence infections (Lin Huang *et al.*, 2014; Wang *et al.*, 2020*b*). However, reduced social activities may decrease the risk of COVID-19 infections as decreasing social interactions equally reduced the risk of infections (Wiersinga *et al.*, 2020). Second, depressive symptoms are linked to impaired immune function increasing the risk of infection (Irwin and Miller, 2007; Dubois *et al.*, 2017). Also, depressive symptoms are associated with increased levels of proinflammatory cytokines, C-reactive protein, leukocytes and neutrophil-to-lymphocyte ratio in COVID-19 patients and beyond, suggesting an increased prevalence of low-grade inflammation (Dowlati *et al.*, 2010; Osimo *et al.*, 2019; Yuan *et al.*, 2020). This may contribute to exaggerated inflammatory responses to SARS-CoV-2 and subsequent tissue damage as well as more severe disease courses (Tay *et al.*, 2020). Similarly, the immune system may senesce more quickly in subjects with mood disorder (Rizzo *et al.*, 2018), which in turn may lead to more severe disease courses and detrimental outcomes of COVID-19 (Brietzke *et al.*, 2020). Notably, a recent report indicates that antidepressants in the form of selective serotonin reuptake inhibitors may improve COVID-19 disease trajectories, highlighting the potential mechanistic relevance of depression for COVID-19 disease courses (Lenze *et al.*, 2020).

Third, some subjects with depressive symptoms may be particularly concerned, and may therefore seek testing more readily if they suspect they have COVID-19; or they may seek access to healthcare as soon as they perceive symptoms, due to a heightened sensitivity to physical symptoms. Similarly, medical professionals may tend to test these subjects more frequently, leading to higher propensity of detecting SARS-CoV-2 infections. This is reflected by our finding that depressive symptoms are associated with higher likelihood of being tested. This is in line with previous reports that a clinical diagnosis of a mental disorder is associated with an increased likelihood of being tested for COVID-19 (van der Meer *et al.*, 2020). Interestingly, our findings do not support the hypotheses that anxiety – beyond depression – is linked to an increased likelihood of being tested for SARS-CoV-2 or to an increased risk of a diagnosis of COVID-19. This is intriguing,

because anxiety could either encourage seeking testing for reassurance or on the contrary discourage it for fear of a positive result.

Our study has important strengths. First, and most importantly, most previous studies were based on clinical diagnoses of mental disorders derived from registries or hospital health records. However, we used self-report measures of depressive and anxiety symptoms with data collected independently of hospitals or any other health services. Thereby we reduced the risk of collider bias or selection bias, also known as Berkson's bias. Collider bias may lead to spurious associations in the context of research on COVID-19 risk factors (Griffith *et al.*, 2020). However, our sample did not consist of a representative population sample tested for active infection independent of symptomatology. More precisely, if a person was tested or not dependent on government testing guidelines at that time. Hence, we cannot exclude that factors linked to testing influenced our results. Second, the self-report diagnostic measures that we used are well established with good sensitivity and specificity to detect clinically-relevant depression and anxiety (Spitzer, 1999; Spitzer *et al.*, 2000, 2006; Kroenke *et al.*, 2001; Kroenke and Spitzer, 2002; Löwe *et al.*, 2008; Dear *et al.*, 2011). This contrasts with previous studies that relied on information on mental disorders based on registry or health records. The latter are related to substantial under-diagnosing of mood and anxiety disorders (Cornelius *et al.*, 2014). However, using PHQ-9 comes with a risk of over-diagnosing the presence of major depressive disorders (Levis *et al.*, 2020). Of note, in the present study, we examined the association between depressive symptomatology (as opposed to the diagnosis of a mental disorder) and the risk of being diagnosed with COVID-19. Third, we used assessment tools that allow grading the extent and severity of depression and anxiety and thus to estimate the magnitude and dose–response of clinically relevant depression and anxiety on COVID-19. Hence, we provide evidence for a dose–response relationship, which may suggest causality (Hill, 1965; Howick *et al.*, 2009). Fourth, our analyses are based on prospective data, with information on depression and anxiety collected between July 2016 and July 2017, long before the onset of the COVID-19 pandemic. In contrast to cross-sectional studies, we provide strong evidence for temporarity, excluding the possibility of COVID-19 increasing the risk of depressive symptoms (Bo *et al.*, 2020; Cao *et al.*, 2020; Kong *et al.*, 2020; Krishnamoorthy *et al.*, 2020; Li *et al.*, 2020*c*; Mazza *et al.*, 2020; Rogers *et al.*, 2020). Fifth, we adjusted our estimates for several potential confounders, including physical diseases, assessed before the start of the COVID-19 pandemic, thereby reducing the risk of residual confounding.

Our study has several limitations. First, testing for SARS-CoV-2 was clinically and not study driven. Hence, it is difficult to untangle other factors that may affect the likelihood of being tested for COVID-19. In addition, our study might underestimate negative SARS-CoV-2 test results because not all laboratories reported these (UK Biobank, 2020). Nevertheless, the majority of laboratories reported positive as well as negative SARS-CoV-2 test results. Second, depressive and anxiety symptoms were assessed between July 2016 and July 2017, two and a half to three and a half years before the beginning of the COVID-19 pandemic. Notably, it is rather common for depressive symptoms to be stable over a period of time, particularly among adults (Musliner *et al.*, 2016). However, there is substantial heterogeneity in temporal depressive symptom patterns assessed with the PHQ-9, with a subgroup of subjects suffering from

depression characterised by fluctuating symptom intensity (Patten and Schopflocher, 2009). Hence, we cannot exclude that some subjects may have recovered from clinically relevant depressive symptoms between assessment and onset of the COVID-19 pandemic, and others may have had a new onset.

Third, the vast majority of subjects tested for COVID-19 in the UK between March and May 2020 presented with severe symptoms, and were suspected of having severe disease courses. Therefore, a positive COVID-19 test in our sample may be biased by severe COVID-19 cases (Armstrong *et al.*, 2020). Our analysis may not have captured milder or asymptomatic cases of COVID-19 in the UK Biobank population. Notably, if persons with depressive symptoms and SARS-CoV-2 infection, as compared to persons without depressive symptoms but SARS-CoV-2 infection, are more likely to get tested for COVID-19, this could lead to bias away from the null with regard to an association between depressive symptoms and receiving a diagnosis of COVID-19. Even though we calculated additional prediction models in those being tested for SARS-CoV-2, there is still need for future studies to elucidate the role of symptoms of mental disorders in the context of COVID-19, including their link to testing likelihood.

We should exercise caution when it comes to generalising our results. First, the UK Biobank is not representative of the UK population because of the *healthy volunteer bias* (Fry *et al.*, 2017). However, it is one of the largest samples providing prospective data to estimate temporal associations between depressive and anxiety symptoms and subsequent COVID-19. Second, we had to exclude all UK Biobank participants outside England, because there was no information on testing for COVID-19 available for them at the time. Third, participants of the UK Biobank were between 37 and 73 years old at recruitment from March 2006 until December 2010 (Collins, 2012; Sudlow *et al.*, 2015; Ho *et al.*, 2020). Consequently, caution should be exercised in generalising our observations to subjects younger than 49 or older than 82 years of age. However, as the risk of severe or fatal courses of COVID-19 increases with age, we may have captured most of the relevant decades of life in the context of severe COVID-19 outcomes.

Our findings further substantiate the clinical relevance and weight of mental disorders, particularly depression, as a risk factor for a COVID-19 diagnosis beyond risk factors such as obesity, diabetes and cardiovascular conditions. Additionally, our results highlight the need to differentiate between the predictors of being tested for COVID-19 and the predictors of a positive test result when tested for COVID-19. Notably, this has rarely been addressed in previous studies on other risk factors for COVID-19. Future studies elucidating the role of symptoms of pre-existing mental disorders in representative samples randomly screened for COVID-19 are highly warranted. Yet, information on pre-existing symptoms would most likely be collected retrospectively, potentially inducing recall bias. In general, there is a strong need for a better understanding of the role of symptoms of mental disorders in the context of COVID-19, including how these are involved in risk behaviour, viral exposure, immune function, disease progress, symptom perception, health care use and testing likelihood. We feel strongly that depressive symptoms should be identified and addressed at early stages, for example, by incorporating collaborative care approaches (Carlo *et al.*, 2020). This could have the potential to mitigate the risk of infection or severe disease courses related to SARS-CoV-2 and other viruses.

Conclusion

Based on prospective and self-report data on the symptom severity of mental disorders in a large and nationwide sample, we provide evidence that (a) depressive symptoms but not anxiety are linked to an increased likelihood of being tested for SARS-CoV-2 and (b) depressive symptoms are associated with an increased risk of a diagnosis of COVID-19, irrespective of potential confounders. While depressive symptoms but not anxiety were linked to an increased likelihood of being tested for SARS-CoV-2, there was no such association with a COVID-19 diagnosis in those tested. This stresses the need for a better understanding of potential underlying mechanisms, including risk behaviour, viral exposure, immune function, disease progress, symptom perception, health care use and testing likelihood. Our findings highlight the relevance of mental processes in the context of COVID-19.

References

Adam Y, Meinlschmidt G and Lieb R (2013) Associations between mental disorders and the common cold in adults: a population-based cross-sectional study. *Journal of Psychosomatic Research* **74**, 69–73.

Armstrong J, Rudkin JK, Allen N, Crook DW, Wilson DJ, Wyllie DH and O'Connell AM (2020) Dynamic linkage of COVID-19 test results between Public Health England's Second Generation Surveillance System and UK Biobank. *Microbial Genomics* **6**, mgen000397.

Bo H-X, Li W, Yang Y, Wang Y, Zhang Q, Cheung T, Wu X and Xiang Y-T (2020) Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. *Psychological Medicine* **51**, 1052–1053.

Brietzke E, Magee T, Freire RCR, Gomes FA and Milev R (2020) Three insights on psychoneuroimmunology of mood disorders to be taken from the COVID-19 pandemic. *Brain, Behavior, & Immunity – Health* **5**, 100076.

Cao J, Wen M, Shi Y, Wu Y and He Q (2020) Investigation of anxiety, depression and influencing factors in patients with new coronavirus pneumonia. *Journal of Nursing* **35**, 15–17.

Carlo AD, Barnett BS and Unützer J (2020) Harnessing collaborative care to meet mental health demands in the era of COVID-19. *JAMA Psychiatry* **78**, 355–356.

Collins R (2012) What makes UK Biobank special? *The Lancet* **379**, 1173–1174.

Cornelius B, van der Klink JJL, Brouwer S and Groothoff JW (2014) Under-recognition and under-treatment of DSM-IV classified mood and anxiety disorders among disability claimants. *Disability and Rehabilitation* **36**, 1161–1168.

Dear BF, Titov N, Sunderland M, McMillan D, Anderson T, Lorian C and Robinson E (2011) Psychometric comparison of the Generalized Anxiety Disorder Scale-7 and the Penn State Worry Questionnaire for measuring response during treatment of generalised anxiety disorder. *Cognitive Behaviour Therapy* **40**, 216–227.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK and Lanctôt KL (2010) A meta-analysis of cytokines in major depression. *Biological Psychiatry* **67**, 446–457.

Dubois T, Reynaert C, Jacques D and Zdanowicz N (2017) The psycho-immunological model as a psychosomatic entity: a literature review of interactions between depression and immunity. *Psychiatria Danubina* **29** (Suppl. 3), 254–258.

Fond G, Nemani K, Etchecopar-Etchart D, Loundou A, Goff DC, Lee SW, Lancon C, Auquier P, Baumstarck K, Llorca P-M, Yon DK and Boyer L (2021) Association between mental health disorders and mortality among patients with COVID-19 in 7 countries: a systematic review and meta-analysis. *JAMA Psychiatry*. Available at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2782457 (Accessed 24 August 2021).

Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R and Allen NE (2017) Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *American Journal of Epidemiology* **186**, 1026–1034.

Goodwin RD, Jacobi F and Thefeld W (2003) Mental disorders and asthma in the community. *Archives of General Psychiatry* **60**, 1125–1130.

Goodwin RD, Scheckner B, Pena L, Feldman JM, Taha F and Lipsitz JD (2014) A 10-year prospective study of respiratory disease and depression and anxiety in adulthood. *Annals of Allergy, Asthma & Immunology* **113**, 565–570.

Griffith G, Morris TT, Tudball M, Herbert A, Mancano G, Pike L, Sharp GC, Palmer TM, Davey Smith G, Tilling K, Zuccolo L, Davies NM and Hemani G (2020) Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nature Communications* **11**, 1–12.

Gülsen A, Yigitbas BA, Uslu B, Drömann D and Kilinc O (2020) The effect of smoking on COVID-19 symptom severity: systematic review and meta-analysis. *Pulmonary Medicine* **2020**, 1–11.

Hill AB (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* **58**, 295–300.

Ho FK, Celis-Morales CA, Gray SR, Katikireddi SV, Niedzwiedz CL, Hastie C, Lyall DM, Ferguson LD, Berry C, Mackay DF, Gill JMR, Pell JP, Sattar N and Welsh PI (2020) Modifiable and non-modifiable risk factors for COVID-19: results from UK Biobank. *Epidemiology*. Available at http://medrxiv.org/lookup/doi/10.1101/2020.04.28.20083295 (Accessed 31 August 2020).

Howick J, Glasziou P and Aronson JK (2009) The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute? *Journal of the Royal Society of Medicine* **102**, 186–194.

Irwin MR and Miller AH (2007) Depressive disorders and immunity: 20 years of progress and discovery. *Brain, Behavior, and Immunity* **21**, 374–383.

Kong X, Zheng K, Tang M, Kong F, Zhou J, Diao L, Wu S, Jiao P, Su T and Dong Y (2020) Prevalence and factors associated with depression and anxiety of hospitalized patients with COVID-19. *Psychiatry and Clinical Psychology*. Available at http://medrxiv.org/lookup/doi/10.1101/2020.03.24.20043075 (Accessed 11 September 2020).

Krishnamoorthy Y, Nagarajan R, Saya GK and Menon V (2020) Prevalence of psychological morbidities among general population, healthcare workers and COVID-19 patients amidst the COVID-19 pandemic: a systematic review and meta-analysis. *Psychiatry Research* **293**, 113382.

Kroenke K and Spitzer RL (2002) The PHQ-9: a new depression diagnostic and severity measure. *Psychiatric Annals* **32**, 509–515.

Kroenke K, Spitzer RL and Williams JBW (2001) The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine* **16**, 606–613.

Lee SW, Yang JM, Moon SY, Yoo IK, Ha EK, Kim SY, Park UM, Choi S, Lee S-H, Ahn YM, Kim J-M, Koh HY and Yon DK (2020) Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. *The Lancet Psychiatry* **7**, 1025–1031.

Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, Miller JP, Yang L, Yingling M, Avidan MS and Reiersen AM (2020) Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA* **324**(22), 2292–2300. doi: https://jamanetwork.com/journals/jama/fullarticle/2773108

Levis B, Benedetti A, Ioannidis JPA, Sun Y, Negeri Z, He C, Wu Y, Krishnan A, Bhandari PM, Neupane D, Imran M, Rice DB, Riehm KE, Saadat N, Azar M, Boruff J, Cuijpers P, Gilbody S, Kloda LA, McMillan D, Patten SB, Shrier I, Ziegelstein RC, Alamri SH, Amtmann D, Ayalon L, Baradaran HR, Beraldi A, Bernstein CN, Bhana A, Bombardier CH, Carter G, Chagas MH, Chibanda D, Clover K, Conwell Y, Diez-Quevedo C, Fann JR, Fischer FH, Gholizadeh L, Gibson LJ, Green EP, Greeno CG, Hall BJ, Haroz EE, Ismail K, Jetté N, Khamseh ME, Kwan Y, Lara MA, Liu S-I, Loureiro SR, Löwe B, Marrie RA, Marsh L, McGuire A, Muramatsu K, Navarrete L, Osório FL, Petersen I, Picardi A, Pugh SL, Quinn TJ, Rooney AG, Shinn EH, Sidebottom A, Spangenberg L, Tan PLL, Taylor-Rowan M, Turner A, van Weert HC, Vöhringer PA, Wagner LI, White J, Winkley K and Thombs BD (2020) Patient Health Questionnaire-9 scores do not accurately estimate depression prevalence: individual participant data meta-analysis. *Journal of Clinical Epidemiology* **122**, 115–128.e1.

Li J, Yang Z, Qiu H, Wang Y, Jian L, Ji J and Li K (2020a) Anxiety and depression among general population in China at the peak of the COVID-19 epidemic. *World Psychiatry* **19**, 249–250.

Li L, Li F, Fortunati F and Krystal JH (2020b) Association of a prior psychiatric diagnosis with mortality among hospitalized patients with coronavirus disease 2019 (COVID-19) infection. *JAMA Network Open* **3**, e2023282.

Li W, Yang Y, Liu Z-H, Zhao Y-J, Zhang Q, Zhang L, Cheung T and Xiang Y-T (2020c) Progression of mental health services during the COVID-19 outbreak in China. *International Journal of Biological Sciences* **16**, 1732–1738.

Lin Huang GK, Stewardson AJ and Lindsay Grayson M (2014) Back to basics: hand hygiene and isolation. *Current Opinion in Infectious Diseases* **27**, 379–389.

Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W and Herzberg PY (2008) Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Medical Care* **46**, 266–274.

Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, Melloni EMT, Furlan R, Ciceri F, Rovere-Querini P and Benedetti F (2020) Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. *Brain, Behavior, and Immunity* **89**, 594–600.

Musliner KL, Munk-Olsen T, Eaton WW and Zandi PP (2016) Heterogeneity in long-term trajectories of depressive symptoms: patterns, predictors and outcomes. *Journal of Affective Disorders* **192**, 199–211.

Okusaga O, Yolken RH, Langenberg P, Lapidus M, Arling TA, Dickerson FB, Scrandis DA, Severance E, Cabassa JA, Balis T and Postolache TT (2011) Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts. *Journal of Affective Disorders* **130**, 220–225.

Osimo EF, Baxter LJ, Lewis G, Jones PB and Khandaker GM (2019) Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychological Medicine* **49**, 1958–1970.

Pan Y, Fang Y, Xin M, Dong W, Zhou L, Hou Q, Li F, Sun G, Zheng Z, Yuan J, Wang Z and He Y (2020) Self-reported compliance with personal preventive measures among Chinese factory workers at the beginning of work resumption following the COVID-19 outbreak: cross-sectional survey study. *Journal of Medical Internet Research* **22**, e22457.

Patten SB and Schopflocher D (2009) Longitudinal epidemiology of major depression as assessed by the Brief Patient Health Questionnaire (PHQ-9). *Comprehensive Psychiatry* **50**, 26–33.

Petterson S, Westfall JM and Miller BF (2020) Projected deaths of despair from COVID-19. *Well Being Trust*. Available at https://wellbeingtrust.org/wp-content/uploads/2020/05/WBT_Deaths-of-Despair_COVID-19-FINAL-FINAL.pdf (Accessed 22 October 2020).

R Core Team (2020) *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Core Team. Available at https://www.R-project.org/.

Reddy RK, Charles WN, Sklavounos A, Dutt A, Seed PT and Khajuria A (2021) The effect of smoking on COVID-19 severity: a systematic review and meta-analysis. *Journal of Medical Virology* **93**, 1045–1056.

Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M and Zanos TP (2020) Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 323, 2052–2059.

Rizzo LB, Swardfager W, Maurya PK, Graiff MZ, Pedrini M, Asevedo E, Cassinelli AC, Bauer ME, Cordeiro Q, Scott J, Brietzke E and Cogo-Moreira H (2018) An immunological age index in bipolar disorder: a confirmatory factor analysis of putative immunosenescence markers and associations with clinical characteristics. *International Journal of Methods in Psychiatric Research* **27**, e1614.

Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, Zandi MS, Lewis G and David AS (2020) Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The Lancet Psychiatry* **7**, 611–627.

Rozenfeld Y, Beam J, Maier H, Haggerson W, Boudreau K, Carlson J and Medows R (2020) A model of disparities: risk factors associated with COVID-19 infection. *International Journal for Equity in Health* **19**, 126.

sciCORE | Center for Scientific Computing (2020) Available at https://scicore.unibas.ch (Accessed 6 October 2020).

Smith DJ, Nicholl BI, Cullen B, Martin D, Ul-Haq Z, Evans J, Gill JMR, Roberts B, Gallacher J, Mackay D, Hotopf M, Deary I, Craddock N and Pell JP (2013) Prevalence and characteristics of probable major depression and bipolar disorder within UK Biobank: cross-sectional study of 172,751 participants Potash JB, ed. *PLoS ONE* **8**, e75362.

Spitzer RL (1999) Validation and utility of a self-report version of PRIME-MD the PHQ primary care study. *JAMA* **282**, 1737–1744.

Spitzer RL, Williams JBW, Kroenke K, Hornyak R and McMurray J (2000) Validity and utility of the PRIME-MD Patient Health Questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. *American Journal of Obstetrics and Gynecology* **183**, 759–769.

Spitzer RL, Kroenke K, Williams JBW and Löwe B (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine* **166**, 1092–1097.

Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T and Collins R (2015) UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Medicine* **12**, e1001779.

Taquet M, Luciano S, Geddes JR and Harrison PJ (2021) Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *The Lancet Psychiatry* **8**, 130–140.

Tay MZ, Poh CM, Rénia L, MacAry PA and Ng LFP (2020) The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews. Immunology* **20**, 363–374.

UK Biobank COVID-19 test results data (2020) Available at https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=COVID19_tests (Accessed 18 December 2020).

van der Meer D, Pinzón-Espinosa J, Lin BD, Tijdink JK, Vinkers CH, Guloksuz S and Luykx JJ (2020) Associations between psychiatric disorders, COVID-19 testing probability and COVID-19 testing results: findings from a population-based study. *British Journal of Psychiatry Open* **6**, e87.

Wang B, Li R, Lu Z and Huang Y (2020*a*) Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging* **12**, 6049–6057.

Wang J, Pan L, Tang S, Ji JS and Shi X (2020*b*) Mask use during COVID-19: a risk adjusted strategy. *Environmental Pollution* **266**, 115099.

Wang Q, Xu R and Volkow ND (2021) Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. *World Psychiatry* **20**, 124–130.

Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ and Prescott HC (2020) Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* **324**, 782.

Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L and Goldacre B (2020) Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **584**, 430–436.

World Health Organization (2020) WHO coronavirus disease (COVID-19) dashboard. Available at https://covid19.who.int/ (Accessed 22 October 2020).

Yuan B, Li W, Liu H, Cai X, Song S, Zhao J, Hu X, Li Z, Chen Y, Zhang K, Liu Z, Peng J, Wang C, Wang J and An Y (2020) Correlation between immune response and self-reported depression during convalescence from COVID-19. *Brain, Behavior, and Immunity* **88**, 39–43.

Zhou Y, Yang Q, Chi J, Dong B, Lv W, Shen L and Wang Y (2020) Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis. *International Journal of Infectious Diseases* **99**, 47–56.