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Risk factors of COVID-19 in subjects with and without mental disorders

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ABSTRACT

Background: Subjects with mental disorders are at a higher risk of various pandemic, but no specific studies concerning on screening and comparing the risk factors of COVID-19 for subjects with and without mental disorders, and the role of different classes of mental disorders with respect to the COVID-19.

Methods: This study comprised 42,264 subjects with mental disorders and 431,694 subjects without. Logistic regression was used to evaluate the associations of exposure factors with COVID-19 risk. Interaction terms were employed to explore the potential interaction effect between mental disorders and each exposure factor on COVID-19 risk.

Results: Mental disorders increased 1.45-fold risk of COVID-19 compared with non-mental disorders. There were significant interaction effects between mental disorders and age, sex, ethnicity, health ratings, socioeconomic adversity, lifestyle habits or comorbidities on COVID-19 risk. Subjects with and without mental disorders shared some overlapping risk factors of COVID-19, including the non-white ethnicity, socioeconomic adversity and comorbidities. Subjects without mental disorders carried some specific risk and protective factors. Among subjects with mental disorders, the COVID-19 risk was higher in subjects with a diagnosis of organic/symptomatic mental disorders, mood disorders, and neurotic, stress-related and somatoform disorders than that of their counterparts.

Age, amount of alcohol consumption, BMI and Townsend deprivation showed non-linear increase with COVID-19 risk.

Limitations: Absence of replication.

Conclusions: Subjects with mental disorders are vulnerable populations to whom more attention should be paid. Public health guidance should focus on reducing the COVID-19 risk by advocating healthy lifestyle habits and preferential policies in populations with comorbidities.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has conveyed high rate of morbidity and mortality (Mizumoto et al., 2020; Wu and McGoogan, 2020). As of 22th August 2021, more than two hundred million infected cases and 4 million deaths have been reported worldwide (https://www.worldometers.info/coronavirus/). During the pandemic, global attention has focused on infected patients and frontline responders (Hamer et al., 2020a; Lai et al., 2020; Lu et al., 2020). Several risk factors for the COVID-19 have been reported, including older age, poor lifestyle habits (e.g., smoking, and low physical activity), pre-existing lifestyle diseases (e.g., diabetes, hypertension, and cardiovascular diseases) (Banerjee et al., 2020; Petrilli et al., 2020; Richardson et al., 2020; Simonnet et al., 2020; Tu et al., 2020) and pre-existing a diagnosis of a mental disorder (Wang et al., 2021). However, the potential risk factors among specific vulnerable populations have been largely overlooked during this pandemic.

Identification of high-risk populations or risk factors could allow timely and appropriate medical intervention and early enrollment for prevention strategy such as priority vaccinations. Subjects with mental disorders may be at a higher risk of various pandemic and have worse physical health and treatment outcomes (Rodgers et al., 2018; Sartorius, 2013; Wang et al., 2021; Yao et al., 2020). The lower life expectancy, poor general resilience, poor immune (Glaser and Kiecolt-Glaser, 2005; Minihan et al., 2020) and more susceptibility to infection (Nikolich-Zugich, 2018; Packard et al., 2011; Kelly, 2020) in subjects with mental disorders relative to general population have been widely observed. In addition, socioeconomic adversity and poor lifestyle habits...
(e.g., smoking, alcoholism and lack of physical activity) are common among subjects with mental disorders (Hailemichael et al., 2019; Jonsdottir et al., 2010; Xu et al., 2010), which were also identified as risk factors associated with development of respiratory diseases and COVID-19 (Hamer et al., 2020a, 2019; Packard et al., 2011). Although these factors might potentially suggest susceptibility towards COVID-19 infection among subjects with mental disorders (Yao et al., 2020), to our knowledge, no specific studies concerning on the risk factors of COVID-19 in this specific vulnerable population. The present cohort study aimed (1) to investigate and compare the risk factors of COVID-19 in subjects with and without mental disorders using a large sample size from the UK Biobank, and (2) to explore the role of different classes of mental disorders with respect to the COVID-19 risk.

2. Materials and methods

2.1. Subjects

A total of 502,505 participants from 22 centers across England, Scotland, and Wales in the UK Biobank were recruited between March 2006 and December 2010. During the available follow-up period, the participants who died before 31-November 2019 were removed (n = 28,547), and the remaining participants (n = 473,958) were grouped into subjects with and without mental disorders. The diagnosis of mental disorder was assessed by International Classification of Diseases, v10 (ICD10) term from UK Biobank data category 41,270 (Fig. 1). Ethical approval was obtained from the North West Multi-center Research Ethics Committee (REC reference: 16/NW/0274).

2.2. Categories of mental disorders

Mental disorders comprise ten categories (Supplementary Methods), including the organic disorders (symptomatic disorders and mental disorders) (ICD-10 codes F00-F09); psychoactive substance use-related mental and behavioral disorders (codes F10-F19); schizophrenia, schizotypal and delusional disorders (codes F20-F29); mood [affective] disorders (codes F30-F39); neurotic, stress-related and somatoform disorders (codes F40-F48); behavioral syndromes associated with physiological disturbances and physical factors (codes F50-F59); disorders of adult personality and behavior (codes F60-F69); mental retardation (codes F70-F79); disorders of psychological development (codes F80-F89); and behavioral and emotional disorders with onset usually occurring in childhood and adolescence (codes F90-F99).

2.3. Primary outcomes

Confirmed COVID-19 test results included the specimen date, specimen type (locations/methods used to generate samples), laboratory, origin (inpatient or not) and outcome of confirmed COVID-19 (positive or negative). Confirmed COVID-19 infection was defined as at least one positive test result. We updated the outcome of COVID-19 test results from the UK Biobank on 26th July 2021. Duplicate data were removed by selecting the latest positive test results. Participants who did not report COVID-19 test results were deemed to have negative COVID-19
### Table 1
Characteristics of participants with and without mental disorders who suffer and not suffer from COVID-19 in UK Biobank.

| Characteristics                          | Mental disorders, n = 42,264 | Non-Mental disorders, n = 431,694 |
|------------------------------------------|-------------------------------|-----------------------------------|
| COVID-19 (n = 2027)                      |                               |                                   |
| Age to July 2021 (years), mean ± SD      | 66.2 ± 6.8                    | 69.2 ± 8.1***                     |
| Age categories, N (%)                    |                               |                                   |
| <60 years                                | 498(24.6)                     | 7545(18.8)***                     |
| 61–70 years                              | 670(33.1)                     | 13,036(32.4)                      |
| ≥71 years                                | 859(42.4)                     | 19,656(48.9)                      |
| Sex (male), N (%)                        | 932(46.0)                     | 18,098(45.0)                      |
| Education level (degree), N (%)          | 320(16.3)                     | 9050 (22.3)***                    |
| Usual walking pace                       | 37(9.4)                       | 9050 (22.3)***                    |
| Brisk pace                               | 520(26.3)                     | 13,176(32.4)                      |
| Overall health rating, N (%)             | 1073(53.8)                    | 19,142(48.2)                      |
| Physical activity, N (%)                 | 1070(53.2)                    | 21,387(53.7)                      |
| Usual walking pace, N (%)                | 320(16.3)                     | 9050 (22.3)***                    |
| Moderate                                 | 523(26.3)                     | 13,176(32.4)                      |
| High                                     | 535(26.3)                     | 13,176(32.4)                      |
| Chronically employed, N (%)              | 670(33.1)                     | 13,036(32.4)                      |
| Smoking (current smoker), N (%)          | 320(16.3)                     | 9050 (22.3)***                    |
| Obesity (BMI ≥30 kg/m²), N (%)           | 722(36.0)                     | 12,590(31.6)***                   |
| Exposures                                |                               |                                   |
| **p value** < 0.001 between COVID-19 and non-COVID-19 in mental disorders subgroup or non-mental disorders subgroup. The p values indicated p values of main effect of each factor and mental disorders, and interaction effect between each factor and mental disorders on risk of COVID-19 infection. |
interstitium (ICD-10 codes J85-86) and other diseases of the pleura and respiratory system (ICD-10 codes J90-99).

2.5. Statistical analysis

Continuous variables are presented as the mean ± SD, and categorical variables as a number (percentage). We used the unpaired t-tests, Mann-Whitney U test and χ² test to compare the differences between groups where appropriate.

Logistic regression was used to evaluate the associations of exposure factors with outcomes. Univariate and multivariate models were applied to evaluate the odds ratio (OR) and 95% confidence intervals (95% CIs). Four schemes were performed in the Logistic regression analysis: (1) model 1-adjusted for age, sex, education, and ethnicity; (2) model 2-further adjusted for BMI, overall health rating, employment status, able to confide, and Townsend deprivation if they were significant between groups; (3) model 3- further adjusted for lifestyle habits and medications; (4) model 4-further adjusted for prevalent diseases. Potential confounders for Logistic regression analysis should fulfill the following criteria: (1) imbalance between COVID-19 and non-COVID-19 in each of the exposures (p < 0.05), (2) correlation with primary outcomes, (3) not mediators between exposures and outcomes, and (4) no significant collinearity (correlation coefficient > 0.5) with any other exposures.

The interaction terms were employed for the overall model to explore the potential interaction effect between mental disorders and exposure factors on the risk of COVID-19. For continuous variables, a non-linearity association between each of exposure factors and the COVID-19 risk were tested using penalized cubic splines in generalized additive model (GAM). Nonlinearity was tested using likelihood ratio test comparing a model with the exposure fitted on a spline with a model assuming a non-linear exposure-outcome relationship. P-values for nonlinearity p < 0.05 suggested evidence against the linearity assumption.

All the analyses were conducted with SPSS version 24.0 and R Statistical Software version 4.0, and a two-tailed p-value < 0.05 was considered significant.

3. Results

3.1. Sample characteristics

A total of 77,217 participants reported COVID-19 test results, including 16,559 participants with positive test results and 60,658 participants with negative test results. Among the participants with positive for COVID-19, 12.2% participants (n = 2027) reported positive COVID-19. Mental disorders increased 1.45-fold risk of COVID-19 infection (OR [95% CI], 1.45 [1.38, 1.52], p < 0.001), this was significant (1.11 [1.04, 1.18], p = 0.001) even after adjusting for age, sex, education, ethnicity, BMI, overall health rating, usual walking pace, IPAQ, antidepressants, and cholesterol lowering medication, cerebrovascular disease, cardiovascular disease, respiratory disease, diabetes, and hypertension.

Compared with other three subgroups (mental disorders without COVID-19, non-mental disorders with and without COVID-19), mental disorders with positive for COVID-19 exhibited the highest proportion of the older age, male sex, poor/fair health ratings, comorbidities (e.g., lifestyle diseases) and socioeconomic adversity (Table 1). However, no differences were found in lifestyle habits between those with mental disorders with and without COVID-19.
3.2. Interaction effect

There were significant main effects of mental disorders and some potentially exposure factors, and significant interaction effects between the two items (mental disorders × exposure factors) on the COVID-19 risk (Table 1). There were significant interaction effects between mental disorders and age (interaction quadratic \( p < 0.001\), sex \( p < 0.001\), ethnicity \( p < 0.001\), health ratings \( p = 0.023\), socioeconomic adversity (employment status, \( p < 0.001\); Townsend deprivation, \( p < 0.001\), lifestyle habits (obesity, \( p = 0.001\); smoking, \( p = 0.001\), lifestyle diseases (cancer, \( p = 0.011\); diabetes, \( p = 0.032\); cerebrovascular diseases, \( p < 0.001\)) and medication use (cholesterol lowering medication, \( p < 0.001\)) on the COVID-19 risk (Table 1).

3.3. Multivariate risk factors for incident COVID-19

In the multivariate final model, the two populations shared several overlapping key independent risk factors for COVID-19 (Tables 2, 3, Figs. 2, 3). These factors included socioeconomic factors (low education level, 1.50 [1.30, 1.72] and 1.56 [1.49, 1.63] in mental disorders and non-mental disorders, respectively), non-white ethnicity (1.31 [1.06, 1.63] and 1.56 [1.49, 1.63]), and some comorbidities (respiratory disease, 1.14 [1.02, 1.27] and 1.25 [1.19, 1.32]; cerebrovascular disease, 1.74 [1.45–2.10] and 1.19 [1.02–1.38]; diabetes, 1.18 [1.00, 1.39] and 1.35 [1.24, 1.47]; hypertension, 1.13 [1.00–1.28] and 1.13 [1.07, 1.20]).

Subjects without mental disorders carry some specific protective factors contributing to a lower risk of COVID-19. These protective factors included not in paid employment status (0.84 [0.79, 0.88]) and brisk walking pace (0.92 [0.88, 0.96]).

3.4. Multivariate risk factors for mental disorder subtypes

In the multivariate final model, the organic/symptomatic mental
disorders (3.00 [2.47, 3.63]), mood [affective] disorders (1.17 [1.07, 1.27]), and neurotic, stress-related and somatoform disorders (1.18 [1.06, 1.31]) respectively predisposed to a higher risk of COVID-19 when compared with their counterparts (Table 4). However, other subgroups of mental disorders were not associated with COVID-19 risk.

3.5. Nonlinear associations

Nonlinear associations of continuous factors with COVID-19 risk are shown in Fig. 2. Subjects with and without mental disorders shared similar curve with COVID-19 risk across these factors. Age was associated with COVID-19 curvilinearly (Fig. 4A), where participants aged about 50–75 years had a gradually decreased risk of COVID-19 with increase of age and the risk was gradually increased among participants aged over 75 years (mental disorders: $R^2 = 0.69$, deviance explained = 73.4%, $p < 0.001$; non-mental disorders: $R^2 = 0.91$, deviance explained = 92.5%, $p < 0.001$). The amount of alcohol consumption had a curvilinear J-shaped correlation with risk of COVID-19 (Fig. 4B), where participants had a higher risk with the increase of amount of alcohol consumption (mental disorders: $R^2 = 0.55$, deviance explained = 56.1%, $p < 0.001$; non-mental disorders: $R^2 = 0.73$, deviance explained = 73.5%, $p < 0.001$). BMI showed a U-shaped correlation with risk of COVID-19 (Fig. 4C), where the risk was first decreased and then increased with BMI (mental disorders: $R^2 = 0.30$, deviance explained = 29.8%, $p < 0.001$; non-mental disorders: $R^2 = 0.35$, deviance explained = 34.8%, $p < 0.001$). Townsend deprivation showed curvilinear increase with risk of COVID-19 (Fig. 4D), where the risk of COVID-19 reached a threshold and was not significant increased with Townsend deprivation (mental disorders: $R^2 = 0.42$, deviance explained = 41.7%, $p < 0.001$; non-mental disorders: $R^2 = 0.50$, deviance explained = 49.4%, $p < 0.001$).

4. Discussion

In this cohort study with a large sample size in the UK Biobank, three main novel findings are worthy noting. First, subjects with mental disorders are vulnerable populations with a 1.45-fold higher risk of COVID-19 compared with subjects without mental disorders. Second, subjects with and without mental disorders shared some overlapping risk factors, including non-white ethnicity, socioeconomic adversity, and comorbidities (respiratory disease, cerebrovascular disease, diabetes, hypertension). Furthermore, subjects without mental disorders carry some specific risk factors contributing to higher risks of COVID-19 and some specific protective factors contributing to lower risks of COVID-19. Third, subgroup analysis of mental disorders showed that the organic/symptomatic mental disorders, mood [affective] disorders, and neurotic, stress-related and somatoform disorders respectively predisposed to a risk of COVID-19 infection. Fourth, the continuous variables

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**Fig. 2. Association of risk factors for COVID-19 cases with mental disorders in the final model**

Note: this figure shows the results of the final model, which is the same as the model 4 in Table 2.
of age, amount of alcohol consumption, BMI and Townsend deprivation showed non-linear correlations with risk of COVID-19.

Our study suggests that mental disorders posed a higher risk in predisposing to COVID-19 infection. Mental disorders have been reported to be associated with a higher risk of developing respiratory diseases (Seminog and Goldacre, 2013). Subjects with mental disorders had lower awareness of personal protection and a higher risk of COVID-19 (Muruganandam et al., 2020; Wang et al., 2021; Yao et al.,

![Fig. 3. Association of risk factors for COVID-19 cases without mental disorders in the final model](image-url)

Note: this figure shows the results of the final model, which is the same as the model 4 in Table 3.
mental disorders. The exact reasons for these unexpected findings were unclear. The association between lifestyle factors and risk of respiratory infection among subjects with mental disorders has been less studied.

Our findings also suggest that we should pay specific attention to subjects who have a diagnosis of organic/symptomatic mental disorders (mainly presented as dementia, and brain damage and dysfunction), mood [affective] disorders and neurotic, stress-related or somatoform disorders among subjects with mental disorders, which respectively showed a higher risk of COVID-19. Subjects with mood [affective] disorders or dementia who have a higher risk of COVID-19 have been reported (2020b; Ho et al., 2020).

The major strengths of this study are the prospective large UK population-based cohort and a focus on the subgroup analyses among the population with mental disorders. However, there are several limitations that should be addressed. First, the UK Biobank has a restricted age range (48–85 years in 2021), and therefore did not represent the general population have been reported (2020b; Ho et al., 2020).

However, the association between the lifestyle practices or lifestyle diseases and the COVID-19 risk were not found among subjects with mental disorders. The exact reasons for these unexpected findings were unclear. The association between lifestyle factors and risk of respiratory disease, diabetes, and hypertension.

2020), worse health outcomes, and poor overall resilience compared with subjects without mental disorders, which may also increase exposure and susceptibility to COVID-19 for those subjects with mental disorders.

Age has been suggested to be a risk factor of COVID-19 (Pan et al., 2020). However, some studies from UK Biobank did not find an association of age with the risk of COVID-19 (Khawaja et al., 2020; Rai-si-Estabragh et al., 2020). We speculated that a curvilinear association of age with COVID-19 may explain this discrepancy. Our study draws the trajectory of COVID-19 risk with age among subjects with and without mental disorders, and found different curvilinear associations between age and the risk of COVID-19 in the two groups. The immune system of older adults possesses numerous age-related changes, which is called immune senescence (Nikolich-Zugich, 2018). We speculated that the higher risk before 65 years old may be associated with a higher exposure due to daily work, and increased risk of COVID-19 with age after 75 years old may be associated with immune senescence, poor physical health and more comorbidities. Subjects with mental disorders exhibited worse physical health and immune system, and lower awareness of infection precautions than those without mental disorders, which may explain the earlier immune senescence in subjects with mental disorders compared with subjects without mental disorders.

Unhealthy lifestyle behaviors and lifestyle diseases were considered primary intervention target for reducing the gap in physical health between subjects with and without mental disorders (Scott and Happell, 2011). Our study demonstrated that subjects without mental disorders were more likely to be affected by unhealthy lifestyle behaviors and lifestyle diseases in predisposing to future COVID-19 infection. Consistent findings of increased COVID-19 risk of unhealthy lifestyle behaviors in the general population have been reported (2020b; Ho et al., 2020). However, the association between the lifestyle practices or lifestyle diseases and the COVID-19 risk were not found among subjects with mental disorders. The exact reasons for these unexpected findings were unclear. The association between lifestyle factors and risk of respiratory

### Table 4

**Association of subgroup of mental disorders with COVID-19 risk.**

| Variables | COVID-19, N (%) | None- COVID-19, N (%) | p value | model 1 OR (95%CI) | p value | model 2 OR (95%CI) | p value | model 3 OR (95%CI) | p value | model 4 OR (95%CI) | p value |
|-----------|------------------|-----------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|
| Organic and symptomatic mental disorders | 194 (1.2) | 1626 | <0.001 | 4.01 (3.43–4.68) | <0.001 | 3.70 (3.16–4.33) | <0.001 | 3.54 (2.93–4.28) | <0.001 | 3.00 (2.47–3.63) | <0.001 |
| Mental and behavioral disorders due to psychoactive substance use | 893 (5.4) | 18,643 | <0.001 | 1.21 (1.13–1.30) | <0.001 | 1.09 (1.01–1.17) | 0.021 | 1.08 (1.00–1.18) | 0.064 | 0.99 (0.91–1.07) | 0.74 |
| Schizophrenia, schizotypal and delusional disorders | 56 (0.3) | 1165 | 0.037 | 1.01 (0.76–1.34) | 0.95 | 0.75 (0.55–1.02) | 0.065 | 0.77 (0.55–1.09) | 0.15 | 0.73 (0.51-1.03) | 0.001 |
| Mood [affective] disorders | 912 (5.5) | 16,396 | <0.001 | 1.48 (1.38–1.59) | <0.001 | 1.31 (1.22–1.41) | <0.001 | 1.28 (1.17–1.40) | <0.001 | 1.17 (1.07–1.27) | 0.003 |
| Neurotic, stress-related and somatoform disorders | 573 (3.5) | 10,704 | <0.001 | 1.48 | <0.001 | 1.34 | <0.001 | 1.28 | <0.001 | 1.18 | 0.003 |
| Behavioral syndromes associated with physiological disturbances and physical factors | 33 (0.2) | 562 (0.1) | 0.006 | 1.54 (1.07–2.20) | 0.019 | 1.33 (0.91–1.94) | 0.14 | 1.22 (0.79–1.90) | 0.38 | 1.12 | 0.62 |
| Disorders of adult personality and behavior | 30 (0.2) | 482 (0.1) | 0.004 | 1.36 (0.93–1.99) | 0.11 | 1.11 (0.76–1.64) | 0.59 | 1.03 (0.65–1.63) | 0.89 | 0.94 (0.59–1.48) | 0.77 |
| Mental retardation | 6 (0.0) | 70 (0.0) | 0.037 | 1.71 (0.68–4.26) | 0.25 | 0.87 (0.27–2.78) | 0.81 | 0.48 (0.07–3.54) | 0.47 | 0.41 (0.06–2.98) | 0.38 |
| Disorders of psychological development | 25 (0.2) | 362 (0.1) | 0.001 | 1.55 (1.00–2.39) | 0.049 | 1.20 (0.75–1.91) | 0.45 | 1.49 (0.88–2.54) | 0.14 | 1.26 | 0.4 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence, and unspecified mental disorder | 22 (0.1) | 273 (0.1) | <0.001 | 2.07 (1.33–3.20) | 0.001 | 1.68 (1.06–2.66) | 0.027 | 1.60 (0.92–2.76) | 0.095 | 1.50 (0.86–2.59) | 0.15 |

Model 1 Analyses were adjusted for age, sex, education, and ethnicity.
Model 2 Analyses were further adjusted for BMI, overall health rating, and Townsend deprivation.
Model 3 Analyses were further adjusted for usual walking pace, IPAQ, antidepressants, and cholesterol lowering medication.
Model 4 Analyses were further adjusted for cerebrovascular disease, cardiovascular disease, respiratory disease, diabetes, and hypertension.

Model 1 Analyses were adjusted for age, sex, education, and ethnicity. Model 2 Analyses were further adjusted for BMI, overall health rating, and Townsend deprivation. Model 3 Analyses were further adjusted for usual walking pace, IPAQ, antidepressants, and cholesterol lowering medication. Model 4 Analyses were further adjusted for cerebrovascular disease, cardiovascular disease, respiratory disease, diabetes, and hypertension.

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comorbidities.

**Role of the funding source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had final responsibility for the decision to submit for publication.
Data availability

The data that support the findings of this study are available from the UK Biobank team.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author statement

X.J. D and Y.W had the idea for and designed this study, had full access to all the data in this study, take responsibility for the integrity of the data and the accuracy of the data analysis, and critically revised the manuscript for important intellectual content and gave final approval for the version to be published. X.J. D drafted the paper and did the analysis. Y. W, L R, Y. S, and W. T takes responsibility for double check of the data analysis. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately resolved.

Declaration of Competing Interest

We declare no competing interests.

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