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Network Analysis of Depression, Anxiety, Posttraumatic Stress Symptoms, Insomnia, Pain, and Fatigue in Clinically Stable Older Patients With Psychiatric Disorders During the COVID-19 Outbreak

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Abstract

Objectives: The Coronavirus Disease 2019 (COVID-19) pandemic has profound negative effects on the mental health of clinically stable older patients with psychiatric disorders. This study examined the influential nodes of psychiatric problems and their associations in this population using network analysis. **Methods:** Clinically stable older patients with psychiatric disorders were consecutively recruited from four major psychiatric hospitals in China from May 22 to July 15, 2020. Depressive and anxiety syndromes (depression and anxiety hereafter), insomnia, posttraumatic stress symptoms (PTSS), pain, and fatigue were measured using the Patient Health Questionnaire, General Anxiety Disorder, Insomnia Severity Index, Posttraumatic Stress Disorder Checklist - Civilian Version, and Numeric Rating Scales for pain and fatigue, respectively. **Results:** A total of 1063 participants were included. The network analysis revealed that depression was the most influential node followed by anxiety as indicated by the centrality index of strength. In contrast, the edge connecting depression and anxiety was the strongest edge, followed by the edge connecting depression and insomnia, and the edge connecting depression and fatigue as indicated by edge-weights. The network structure was invariant by gender based on the network structure invariance test (M = .14, P = .20) and global strength invariance tests (S = .08, P = .30).

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Conclusions: Attention should be paid to depression and its associations with anxiety, insomnia, and fatigue in the screening and treatment of mental health problems in clinically stable older psychiatric patients affected by the COVID-19 pandemic.

Keywords
COVID-19, older psychiatric patients, depression, network analysis

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has had profound negative effects on the mental health of clinically stable psychiatric patients who received outpatient maintenance treatment. Overall, COVID-19 has added to the burden of people with pre-existing psychiatric disorders. For example, many patients with mood and anxiety disorders experienced worse depressive and anxiety symptoms, sleep disturbances, intense suicidal ideation, and psychological distress during the pandemic,[1-3] which may be partly due to the fear of infection and the negative impact of preventive measures imposed by authorities such as mass quarantine, isolation, physical distancing, and contact tracing.[2,4-8] In China, COVID-related restrictions may create barriers to the critical psychiatric outpatient care[9] of clinically stable psychiatric patients who require long-term maintenance and follow-up care.

Due to the limited availability of primary care services in rural China, the vast majority of psychiatric patients need to travel to urban areas to access specialist care at major psychiatric hospitals or psychiatric departments in general hospitals.[10,11] The logistical difficulties involved therein increase the risk for treatment interruption and illness relapse,[12] which results in anxiety about illness recurrence in patients. Importantly, traveling to places where there is community transmission of an infectious disease inevitably increases the risk of contagion. In addition, individuals may also be under increased financial strain due to their inability to work.[13] Such burden compounds the existing psychological stress from their mental illness.

Arguably, older psychiatric patients should be prioritized because they are at greater risk of poor outcomes if infected with COVID-19 compared to other age groups.[14-17] Having greater vulnerability could elicit fear and psychological distress and as such, older people may self-restrict their daily activities and social interactions,[18] thereby aggravating their loneliness and disrupting their usual life rhythm. Furthermore, older patients often have comorbid chronic physical diseases (e.g., cardiovascular and cerebrovascular diseases and diabetes mellitus) that require long-term follow-up treatment. Greater difficulty accessing medical services due to the limited medical services during the pandemic may prevent regular treatment attendance, compromising the management of their physical diseases[19] and increasing their health worries. It is also worth noting that the mental health services and education during the COVID-19 pandemic are mostly delivered online.[20,21] However, many older psychiatric patients have limited access to broadband internet and have poor digital health literacy, thereby depriving them of the benefits.[22]

Most previous studies have investigated the mental health problems in different populations during the COVID-19 pandemic such as in psychiatric patients, general population, health professionals, and so forth. These studies covered depression and anxiety symptoms, sleep disturbances, posttraumatic stress disorder related symptoms (PTSS), and somatic symptoms.[1-3,23-25] Although the prevalence and severity of these symptoms/problems have been studied, their clustering and importance warrant further research. Since these mental health problems are frequently coexist and correlated with each other,[26-29] it is important to evaluate the significance of each problem and its interrelationships. In this study, we performed network analysis to examine the influential nodes of psychiatric problems experienced by clinically stable older patients. As previous studies showed gender differences in the pattern and clinical features of depressive and anxiety symptoms,[30,31] insomnia,[32] PTSS,[33] and somatic symptoms[34] in older adults, we also examined the network structure between genders.

Methods

Participants and Study Sites

This was a multi-center, cross-sectional study conducted in four major tertiary psychiatric settings providing maintenance treatment services (Guangji Hospital Affiliated with Soochow University in Jiangsu province, Lanzhou University Second Hospital in Gansu province, Xiamen Xianyue Hospital in Fujian province, and Beijing Anding Hospital in Beijing) between May 22 and July 15, 2020. Clinically stable older psychiatric patients and their guardians (if available) were consecutively invited to participate in this study. The inclusion criteria were the following: 1) aged 50 years and above, 2) diagnosed by a psychiatrist with any psychiatric disorder based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10); and 3) judged clinically stable by their treating psychiatrists. Following previous studies,[35,36] "clinically stable patients" were defined as patients whose dose of psychotropic medications was changed by less than 50% in the past three months. Patients who did not provide informed consent or had difficulties understanding the survey content, such as those with significant dementia, were excluded. The study protocol was approved by the ethics committees of each participating hospital. All participants and their guardians (if available) provided written informed consent.

Measurement Tools and Assessment

Data were collected using the WeChat-based "Questionnaire Star" application. Participants attending the outpatient departments of participating hospitals were asked to complete the assessment either using their or their guardians' smartphones. As a public health measure during the pandemic, all patients attending outpatient departments in the participating hospitals needed to register their personal health information on smartphones. Hence, all participants who took part in the survey used their or their guardians' smartphone-based application "Questionnaire Star". A research psychiatrist could help patients who had difficulties to complete the assessment.

The severity of depression and anxiety syndromes (depression and anxiety hereafter) was assessed using the Chinese version of the 9-item Patient Health Questionnaire (PHQ-9)[37,38] and the 7-item General Anxiety Disorder (GAD-7),[39,40] respectively, both of which have been well-validated and widely used in Chinese populations.[41] The total score of the PHQ-9 and the GAD-7 ranges from 0 to 27 and 0 to 21, respectively, both with a higher total score representing more severe depression or anxiety.

Severity of insomnia was evaluated with the Chinese version of Insomnia Severity Index (ISI),[42,43] which had satisfactory psychometric properties.[43] Its total score ranges from 0 to 28 and a higher total score indicates more severe insomnia. The Chinese version of Posttraumatic Stress Disorder Checklist - Civilian Version (PCL-C)[44,45] was previously shown to have satisfactory screening ability for PTSS.[45] Its total score ranges from 17 to 85 with a higher total score representing more severe PTSS.

The Numeric Rating Scale (NRS) was used to measure body pain (pain hereafter) and fatigue symptoms. The NRS is a visual analog scale with a horizontal line marked with integers from 0 to 10 at equal intervals, where "0" indicates "no suffering" and "10" indicates "unbearable suffering". The NRS for pain is regarded as one of the best tools to examine the severity of pain,[46,47] while the NRS for fatigue is also widely used in clinical studies.[48,49]

Conceptual Overview of Network Analysis

We present here the concepts and terminology of network analysis. A network is a collection of entities that are connected to each other.[50] These entities can be anything (i.e., airports, people, companies, and in this paper, psychiatric problems) that can be connected to others of the same kind. Each of these psychiatric problems constitutes a *node* that is related to other problems, and these relations are called *edges*. A cluster of these psychiatric problems can be defined as a group of meaningful related psychiatric problems that collectively define a general mental health status. A network can have one or more clusters of problems/symptoms that are not connected at all. The structure of networks can be analyzed statistically in order to reveal importance.[50]

Influential problems/symptoms occupy a more *central* position in the network while less influential ones are peripheral. Centrality can be measured in many ways, but in this study we focused on *strength* that refers to the summation of absolute weights of all edges that directly connects to a particular node as recommended previously.[51,52]

Data Analysis

Continuous and categorical variables were described as mean (standardized deviation (SD)) and frequency (percentage), respectively. The R program was used in all data analyses. The network was estimated using the Gaussian graphical model with possible spurious edges controlled using the technique of least absolute shrinkage and selection operator (LASSO), which could make estimated models more interpretable and understandable.[53] The tuning parameter related to LASSO was administered with the extended Bayesian information criterion (EBIC).[54,55] The stability of the networks was measured by centrality stability and edge-weight accuracy. The centrality stability was tested with the correlation stability coefficient (CS-coefficient) that refers to the maximum proportion of cases that could be dropped while the correlation of the centrality indices between the networks of original sample and case-dropping subsets was at least .7 with a probability of 95%.[54] The centrality index of strength was viewed as stable when the CS-coefficient was larger than .25 and preferably larger than .50 [54]. The edge-weight accuracy was calculated using nonparametric bootstrap with 1000 samples and visualized with a line diagram. Narrower bootstrapped confidence intervals (CI) of edge weights from the network of the bootstrapped sample represented more precise estimation of the edges. In addition, the bootstrapped difference test was conducted to examine whether the centrality index (strength) between two nodes or the edge-weights between two edges significantly differed. Two nodes significantly differed from each other when zero was not included in the bootstrapped CI.[56] Two edge weights significantly differed from each other when their corresponding bootstrapped CIs did not overlap.[54] The results of the bootstrapped difference test were graphically displayed with checkerboard diagrams.

In addition, the influence of gender on the network structure was estimated using the Network Comparison Tests, including the invariant global strength, the invariant network structure, and the invariant edge strength. The invariant global strength reflected the difference in overall network connectivity between male and female patients. The invariant network structure tested the overall difference between all the possible edges. When a significant difference was reported in either invariant global strength or network structure test, the invariant edge strength would be further tested to investigate the possible difference of each edge between the two gender networks.[57]

Results

Initially, 1068 patients were invited to participate in this study; of whom, 1063 met the eligibility criteria and completed the assessment. Their mean age was 62.8 (standard deviation (SD):9.4) years and 32.6% (n = 347) were males. Their mean years of education was 7.9 (SD: 4.0) years. The percentage of married patients was 90.4% (n = 961), while the percentage of those living in rural areas was 35.1% (n=373). The majority of the participants (45.6%, n = 485) had a primary psychiatric diagnosis of major depressive disorder followed by schizophrenia (6.9%, n = 73) and organic mental disorder (5.9%, n = 63) while the remaining participants suffered from other psychiatric diagnoses (41.6%, n = 442).

The estimated network of the studied psychiatric problems is displayed in Figure 1. A total of 13 (86.7%) non-zero edges emerged out of all possible 15 edges. The centrality indices are displayed in Supplementary Figure 1. The CS-coefficient value indicated that the strength (CS-coefficient=.75) presented excellent stability, suggesting the ranking of nodes was trustworthy. The nonparametric bootstrapped difference test for strength revealed that the node of depression was statistically stronger than all the other psychiatric problems in the network, followed by anxiety as another statistically stronger node than others in the network (Figure 2).

Figure 3 visualizes the estimated edge-weights accuracy. The relatively narrow bootstrapped CIs indicated that the estimated edge-weights were precise. The nonparametric bootstrapped difference test for edge-weights revealed that the edge connecting depression and anxiety was the strongest and was significantly different from all the other edges. The edge connecting depression and insomnia and the edge connecting depression and fatigue were also strong and significantly different from most of other edges (Figure 4).

Figure 5 visualizes the networks of all studied psychiatric problems in male and female patients separately. The two networks visually differed in their structures. A total of 13 (86.7%) non-zero edges emerged out of all 15 potential edges in the male network, whereas the corresponding figure was 14 (93.3%) in the female network. However, Network Comparison Test did not find significant difference in the network structure invariance between the networks of female and male patients (M = .14, P = .20). The invariant edge strength was not further tested since the network structure was invariant.[57] There was also no difference on the invariance of global strength between the networks of male and female patients (S = .08, P = .30).

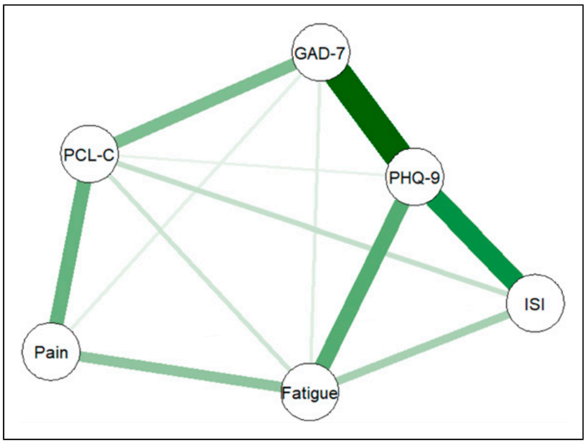

Figure 1. The network of all studied psychiatric problems. Notes: The green edges represent positive correlations. The red edges are set to represent negative correlations and no negative correlation merged in this figure. The saturation and thickness of the edges represent connection strongness of two nodes.

Discussion

To the best of our Knowledge, this was the first study that examined psychiatric problems during the COVID-19 pandemic in clinically stable older psychiatric patients using network analysis. We found that depression and anxiety were the most influential psychiatric problems in the network, followed by fatigue, PTSS, insomnia, and pain. Meanwhile, the edge connecting depression and anxiety was the most influential edge in the model, which is consistent with the findings that comorbid depression and anxiety are common in late life.[26,58,59] Additionally, anxiety seems to result in depression[60] and vice versa,[61] suggesting a bi-directional relationship between the two psychiatric syndromes. Common neuropsychological mechanisms shared by depression and anxiety (e.g., alteration of activation and connectivity of ventral cingulate and amygdala and polymorphic variation at the serotonin receptor gene) may also contribute to their co-occurrence.[62,63]

The edge connecting depression and insomnia was also influential in the network model. Comorbid insomnia is common in psychiatric patients since many psychiatric disorders and psychotropic medications can affect sleep

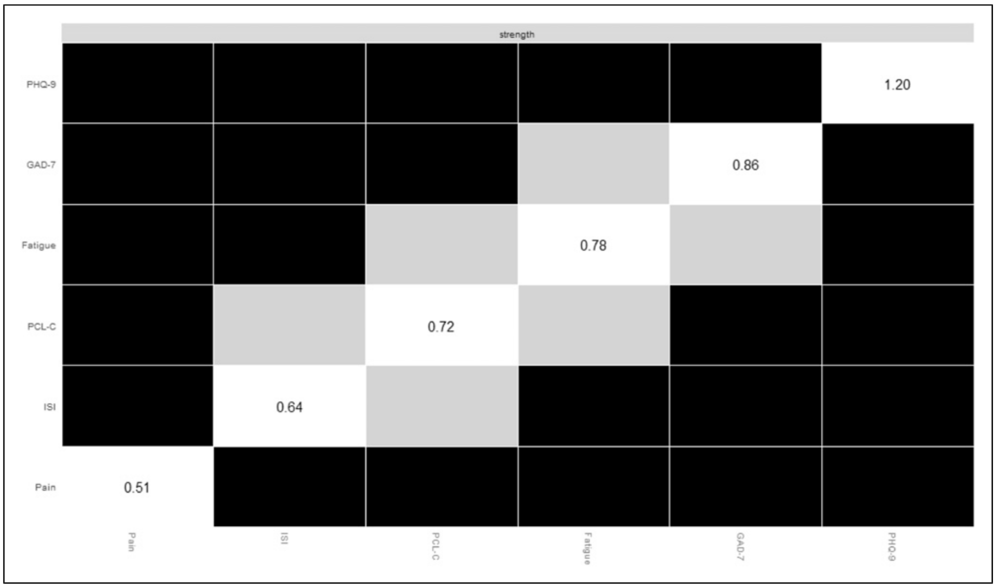

Figure 2. Nonparametric bootstrapped difference test for strength in the network of all studied psychiatric problems. Notes: Gray and black boxes represent no significant difference and significant difference between nodes separately. Values in box on the diagonal indicate the strength of each node.

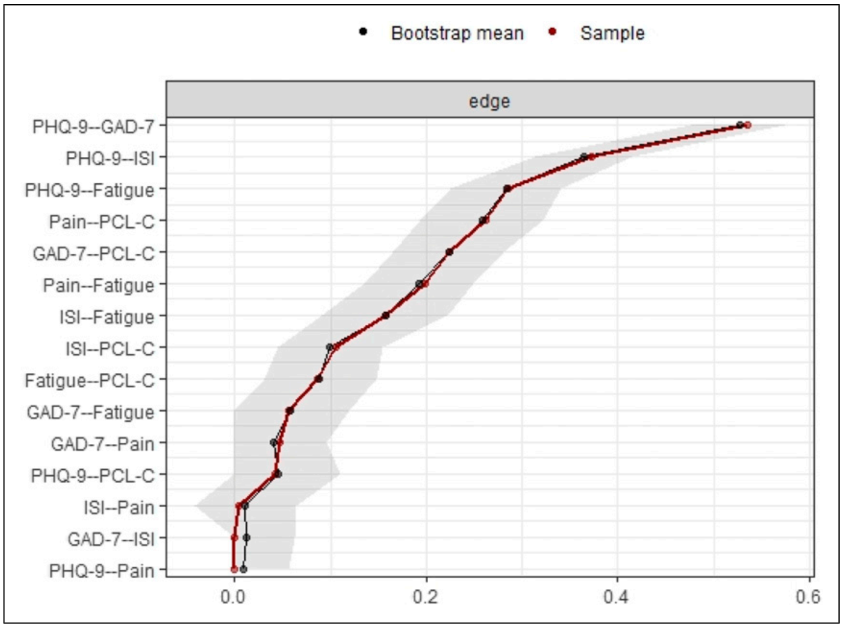

Figure 3. Edge-weights accuracy of the network of all studied psychiatric problems. Notes: The gray area represents the bootstrapped confidence intervals (CIs). The horizontal axis represents the edge-weight, while the vertical axis represents the edges between each pair of nodes.

rhythm.[64,65] The association between insomnia and depression is bidirectional. On one hand, insomnia is a risk factor for depressive disorders.[66,67] On the other hand, depressive disorders can increase the likelihood of insomnia.[68] Previous meta-analyses revealed that insomnia could significantly predict the onset of depressive episodes[67,69,70] with an odd ratio (OR) of up to 2.83 (95% CI: 1.55–5.17).[67] The association between depression and insomnia could be partly explained by the impaired emotional processing[71] and also certain common mechanisms such as alterations of arousal states[72-74] and level of inflammatory markers.[75]

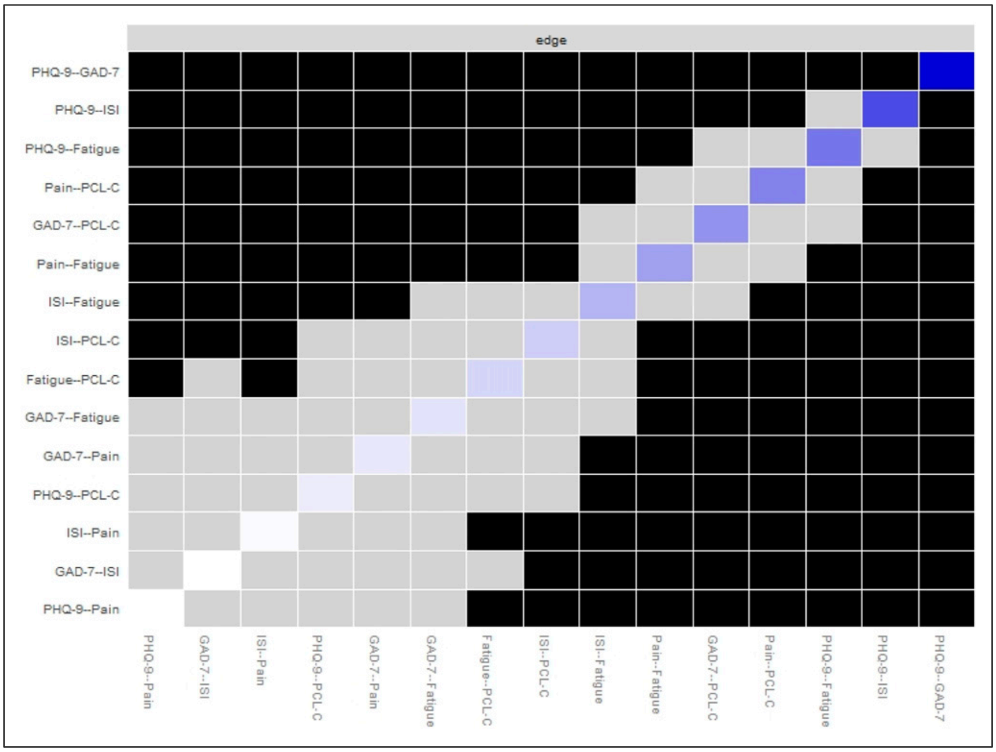

Figure 4. Nonparametric bootstrapped difference test for edge-weights in the network of all studied psychiatric problems. Notes: Gray boxes and black boxes represent non-significant difference and significant difference between two edges weights separately. The saturation of box on the diagonal represent the edge-weights with the blue box representing positive correlation between nodes. Red box was set to represent negative correlation between nodes, which did not merge in the network.

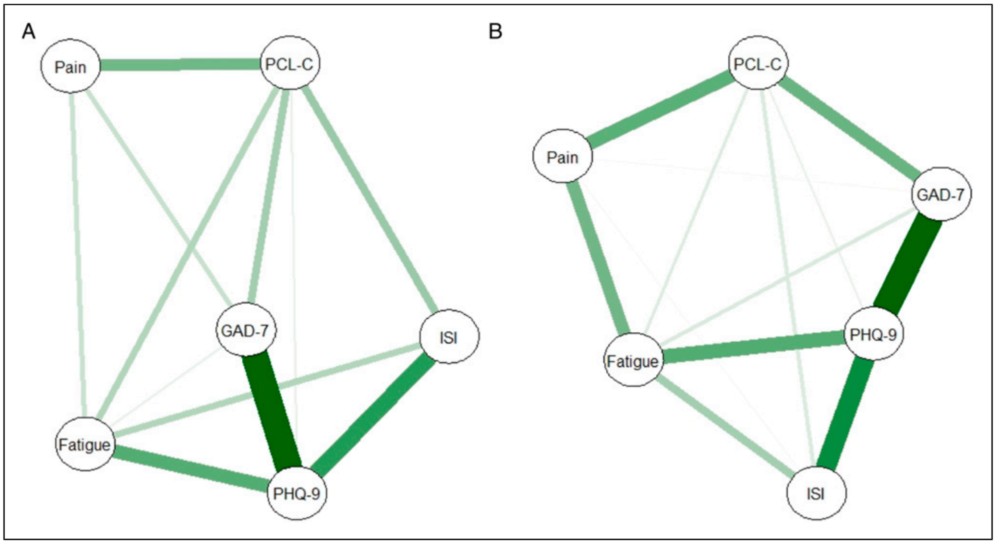

Figure 5. The networks of all studied psychiatric problems in female and male patients. Notes: The green edges represent positive correlations. The red edges are set to represent negative correlations and no negative correlation merged in this figure. The saturation and thickness of the edges represent connection strongness of two nodes.

The edge connecting depression and fatigue is also among the major edges in the network. Fatigue and depression commonly co-occur.[76-78] According to the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V),[79] fatigue is one of the key features of major depressive disorder. Previous studies found that patients with fatigue in primary care were more likely to have lifetime depressive disorders than those without[80] while those with either fatigue or depression had a two-fold increase in the risk for the co-occurrence of fatigue and depression.[81] Further, longitudinal studies found that a history of unexplained fatigue was significantly associated with increased risk of new onset of major depression in community-dwelling adults (Risk ratio (RR)=28.4, 95%CI: 11.7–68.0).[82] The co-occurring fatigue and depression may be due to shared underlying genetical mechanisms.[83,84] In addition, impaired immune function commonly found in depression and fatigue could also partly explain their association.[85,86]

This study did not find gender difference in network structure and global strength of included psychiatric problems, which indicates that the distribution and pairwise associations of these problems were similar across both genders. Gender may have an effect on the pattern and clinical presentations of certain psychiatric problems in older adults; for instance, previous studies found that females usually presented more severe or comparable depressive/anxiety symptoms,[2,87-89] insomnia,[87,89] and PTSS[87] compared to males during the COVID-19 pandemic. However, the gender difference was not found in the invariable pairwise associations measured by network analysis. It is possible that the gender difference in network analysis may be partly masked by the negative impact of the pandemic on mental health, as both genders may be equally affected by public health measures and fears about the pandemic and related consequences.

The strengths of this study include the large sample size, multicenter study design, and use of network analysis. However, several methodological limitations need to be addressed. First, the casual and dynamic relationships between the studied psychiatric problems could not be examined due to the cross-sectional study design. Second, this study only included clinically stable older patients with psychiatric disorder, which limits the generalization of the results to other psychiatric patients with different clinical status (e.g., acute illness status) or age groups. Third, only self-report assessment instruments were used which may result in recall bias.

In conclusion, the most influential psychiatric problem in clinically stable older psychiatric patients during the COVID-19 pandemic was depression. The association between depression and anxiety, insomnia, and fatigue symptoms should be addressed when developing screening and interventions for clinical stable older psychiatric patients affected by the COVID-19 pandemic.

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Contributors

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Declaration of Conflicting Interests

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Availability of Data and Materials

The Clinical Research Ethics Committee of participating hospitals that approved the study prohibits the authors from making the research dataset of clinical studies publicly available. Readers and all interested researchers may contact Dr. YT Xiang (Email address: xyutly@gmail.com) for details. Dr. Xiang could apply to the Clinical Research Ethics Committee of participating hospitals for the release of the data.

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Supplemental material

Supplemental material for this article is available online.

References

1. Hao F, Tan W, Jiang L, et al. Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. *Brain Behav Immun*. 2020;87:100-106.
2. González-Blanco L, Santo FD, García-Álvarez L, et al. COVID-19 lockdown in people with severe mental disorders in Spain: Do they have a specific psychological reaction compared with other mental disorders and healthy controls? *Schizophr Res*. 2020;223:192-198.

3. Van Rheenen TE, Meyer D, Neill E, et al. Mental health status of individuals with a mood-disorder during the COVID-19 pandemic in Australia: Initial results from the COLLATE project. *J Affect Disord*. 2020;275: 69-77.
4. Xiao H, Zhang Y, Kong D, Li S, Yang N. Social capital and sleep quality in individuals who self-isolated for 14 days during the coronavirus disease 2019 (COVID-19) outbreak in January 2020 in China. *Med Sci Mon Int Med J Exp Clin Res*. 2020;26:e923921.
5. Barratt RL, Shaban R, Moyle W. Patient experience of source isolation: lessons for clinical practice. *Contemp Nurse*. 2011;39(2):180-193.
6. Ammar A, Mueller P, Trabelsi K, et al. Psychological consequences of COVID-19 home confinement: The ECLB-COVID19 multicenter study. *PLoS One*. 2020;15(11): e0240204.
7. Kılınçel Ş, Kılınçel O, Muratdağı G, Aydın A, Usta MB. Factors affecting the anxiety levels of adolescents in home-quarantine during COVID-19 pandemic in Turkey. *Asia Pac Psychiatr*. 2021;13(2):e12406.
8. Um Min Allah N, Arshad S, Mahmood H, Abbas H. The psychological impact of coronavirus outbreak in Pakistan. *Asia Pac Psychiatr*. 2020;12(4):e12409.
9. Li W, Yang Y, Liu ZH, et al. Progression of mental health services during the COVID-19 outbreak in China. *Int J Biol Sci*. 2020;16(10):1732-1738.
10. Xiang YT, Ng CH, Yu X, Wang G. Rethinking progress and challenges of mental health care in China. *World Psychiatr*. 2018;17(2):231-232.
11. Xiang YT, Yu X, Sartorius N, Ungvari GS, Chiu HF. Mental health in China: challenges and progress. *Lancet*. 2012; 17380(9855):1715-1716.
12. Chinese Society of Psychiatry. Psychiatric Hospital Branch of Chinese Hospital Association, Chinese Preventive Medicine Association SoMH, Chinese Psychiatrist Association, Psychiatry CSoN. Expert consensus on managing pathway and coping strategies for patients with mental disorders during prevention and control of infectious disease outbreak (novel coronavirus pneumonia) (in Chinese). *Chinese Journal of Psychiatry*. 2020;53:02.
13. Asmundson GJG, Paluszek MM, Landry CA, Rachor GS, McKay D, Taylor S. Do pre-existing anxiety-related and mood disorders differentially impact COVID-19 stress responses and coping? *J Anxiety Disord*. 2020;74:102271.
14. Shahid Z, Kalayanamitra R, McClafferty B, et al. COVID-19 and older adults: what we know. *J Am Geriatr Soc*. 2020; 68(5):926-929.
15. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J*. 2020;55(5):2000524.
16. Pormohammad A, Ghorbani S, Baradaran B, et al. Clinical characteristics, laboratory findings, radiographic signs and outcomes of 61,742 patients with confirmed COVID-19 infection: A systematic review and meta-analysis. *Microb Pathog*. 2020;147:104390.
17. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. *J Infect*. 2020;80(6):e14-e18.
18. Van Orden KA, Bower E, Lutz J, et al. Strategies to promote social connections among older adults during ’social distancing’ restrictions. *Am J Geriatr Psychiatr*. 2020. In press.
19. Amerio A, Aguglia A, Odone A, et al. COVID-19 pandemic impact on mental health of vulnerable populations. *Acta Biomed*. 2020;91(9-S):95-96.
20. Liu S, Yang L, Zhang C, et al. Online mental health services in China during the COVID-19 outbreak. *Lancet Psychiatr*. 2020;7(4):e17-e18.
21. Wang X, Gordon RM, Snyder EW. Comparing Chinese and US practitioners’ attitudes towards teletherapy during the COVID-19 pandemic. *Asia Pac Psychiatr*. 2021;13(1): e12440.
22. Yang Y, Li W, Zhang Q, Zhang L, Cheung T, Xiang YT. Mental health services for older adults in China during the COVID-19 outbreak. *Lancet Psychiatr*. 2020;7(4):e19.
23. Serrano-Ripoll MJ, Meneses-Echavez JF, Ricci-Cabello I, et al. Impact of viral epidemic outbreaks on mental health of healthcare workers: a rapid systematic review and meta-analysis. *J Affect Disord*. 2020;277:347-357.
24. Tan W, Hao F, McIntyre RS, et al. Is returning to work during the COVID-19 pandemic stressful? A study on immediate mental health status and psychoneuroimmunity prevention measures of Chinese workforce. *Brain Behav Immun*. 2020;87:84-92.
25. Gualano MR, Lo Moro G, Voglino G, Bert F, Siliquini R. Effects of COVID-19 lockdown on mental health and sleep disturbances in Italy. *Int J Environ Res Publ Health*. 2020; 17(13):4779.
26. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatr*. 2005;62(6):617-627.
27. Youssef N, Mostafa A, Ezzat R, Yosef M, El Kassas M. Mental health status of health-care professionals working in quarantine and non-quarantine Egyptian hospitals during the COVID-19 pandemic. *East Mediterr Health J*. 2020;26(10): 1155-1164.
28. Velly AM, Mohit S. Epidemiology of pain and relation to psychiatric disorders. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2018;87:159-167.
29. Mathias JL, Cant ML, Burke ALJ. Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis. *Sleep Med*. 2018;52:198-210.
30. Li D, Zhang DJ, Shao JJ, Qi XD, Tian L. A meta-analysis of the prevalence of depressive symptoms in Chinese older adults. *Arch Gerontol Geriatr*. 2014;58(1):1-9.
31. Holmes SE, Esterlis I, Mazure CM, et al. Trajectories of depressive and anxiety symptoms in older adults: A 6-year

prospective cohort study. *Int J Geriatr Psychiatr*. 2018; 33(2):405-413.
32. Wang YM, Chen HG, Song M, et al. Prevalence of insomnia and its risk factors in older individuals: a community-based study in four cities of Hebei Province, China. *Sleep Med*. 2016;19:116-122.
33. Lamoureux-Lamarche C, Vasiliadis HM. Lifetime traumatic events, health-related quality of life, and satisfaction with life in older adults. *Qual Life Res*. 2017;26(10): 2683-2692.
34. Si H, Wang C, Jin Y, et al. Prevalence, factors, and health impacts of chronic pain among community-dwelling older adults in China. *Pain Manag Nurs*. 2019;20(4):365-372.
35. Xiang YT, Weng YZ, Leung CM, Tang WK, Ungvari GS, Gerevich J. Clinical and social determinants of psychotropic drug prescription for schizophrenia outpatients in China. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2007;31(3): 756-760.
36. Lobana A, Mattoo SK, Basu D, Gupta N. Quality of life in schizophrenia in India: comparison of three approaches. *Acta Psychiatr Scand*. 2001;104(1):51-55.
37. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001; 16(9):606-613.
38. Chen M, Sheng L, Qu S. Diagnostic test of screening depressive disorder in general hospital with the Patient Health Questionnaire (in Chinese). *Chinese Mental Health*. 2015; 29(4):241-245.
39. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.
40. He X-Y, Li C-B, Qian J, Cui H-S, Wu W-Y. Reliability and validity of a generalized anxiety disorder scale in general hospital outpatients (in Chinese). *Shanghai Archives of Psychiatry*. 2010;22(4):200-203.
41. Wang W, Bian Q, Zhao Y, et al. Reliability and validity of the Chinese version of the Patient Health Questionnaire (PHQ-9) in the general population. *Gen Hosp Psychiatr*. 2014; 36(5):539-544.
42. Morin CM. *Insomnia: Psychological Assessment and Management*. New York, NY: Guilford Press; 1993.
43. Bai C, Daihong J, Chen L, Liang L, Wang C. Reliability and validity of Insomnia Severity Index in clinical insomnia patients (in Chinese). *Chinese Journal of Practical Nursing*. 2018;34(28):2182-2186.
44. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. *The PTSD Checklist (PCL): Reliability, Validity, and Diagnostic Utility*. Paper presented at. San Antonio, TX: Annual Convention of the International Society for Traumatic Stress Studies; 1993.
45. Yang X-Y, Yang H-A, Liu Q-G, Yang L-Z. The research on the reliability and validity of PCL-C and influence factors (in Chinese). *China Journal of Health Psychology*. 2007;15(1): 6-8.
46. Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Oklahoma Nurse*. 1988;33(1):8-17.
47. Li L, Liu X. Select appropriate pain intensity assessment tools for patients (in Chinese). *Chinese Journal of Practical Nursing*. 2003;19(006):50-51.
48. Zhou Y, Petpichetchian W, Kitrungrote L. Psychometric properties of pain intensity scales comparing among post-operative adult patients, elderly patients without and with mild cognitive impairment in China. *Int J Nurs Stud*. 2011; 48(4):449-457.
49. Oldenmenger WH, de Raaf PJ, de Klerk C, van der Rijt CC. Cut points on 0-10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. *J Pain Symptom Manag*. 2013;45(6):1083-1093.
50. Newman MEJ. The structure and function of complex networks. *SIAM Rev*. 2003;45(2):167-256.
51. Bringmann LF, Elmer T, Epskamp S, et al. What do centrality measures measure in psychological networks? *J Abnorm Psychol*. 2019;128(8):892-903.
52. Epskamp S, Rhemtulla M, Borsboom D. Generalized network psychometrics: Combining network and latent variable models. *Psychometrika*. 2017;82(4):904-927.
53. Friedman JH, Hastie T, Tibshirani R. Glasso: graphical lasso- estimation of Gaussian graphical models. R package version 1.8. https://CRAN.Rproject.org/package=glasso. 2014.
54. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. *Behav Res Methods*. 2018;50(1):195-212.
55. Chen J, Chen Z. Extended Bayesian information criteria for model selection with large model spaces. *Biometrika*. 2008; 95(3):759-771.
56. Chernick MR. *Bootstrap methods: A guide for practitioners and researchers*. 2nd ed., Vol 619. Hobeken, NJ: John Wiley & Sons; 2011.
57. van Borkulo C, Boschloo L, Kossakowski J, et al. *Comparing Network Structures on Three Aspects: A Permutation Test*. Preprint; 2017.
58. Beekman AT, de Beurs E, van Balkom AJ, Deeg DJ, van Dyck R, van Tilburg W. Anxiety and depression in later life: co-occurrence and communality of risk factors. *Am J Psychiatr*. 2000;157(1):89-95.
59. Schoevers RA, Deeg DJ, van Tilburg W, Beekman AT. Depression and generalized anxiety disorder: co-occurrence and longitudinal patterns in elderly patients. *Am J Geriatr Psychiatr*. 2005;13(1):31-39.
60. Hettema JM, Kuhn JW, Prescott CA, Kendler KS. The impact of generalized anxiety disorder and stressful life events on risk for major depressive episodes. *Psychol Med*. 2006;36(6):789-795.
61. Wetherell JL, Gatz M, Pedersen NL. A longitudinal analysis of anxiety and depressive symptoms. *Psychol Aging*. 2001; 16(2):187-195.

62. Molina E, Cervilla J, Rivera M, Torres F, Bellón JA, Moreno B, et al. Polymorphic variation at the serotonin 1-A receptor gene is associated with comorbid depression and generalized anxiety. *Psychiatr Genet*. 2011;21(4):195-201.
63. Etkin A, Schatzberg AF. Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. *Am J Psychiatr*. 2011;168(9):968-978.
64. Krystal AD. Psychiatric disorders and sleep. *Neurol Clin*. 2012;30(4):1389-1413.
65. Higuchi T, Ishigooka J, Iyo M, Hagi K. Safety and effectiveness of lurasidone for the treatment of schizophrenia in Asian patients: results of a 26-week open-label extension study. *Asia Pac Psychiatr*. 2020;12(1):e12377.
66. Jaussent I, Bouyer J, Ancelin ML, et al. Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. *Sleep*. 2011;34(8):1103-1110.
67. Hertenstein E, Feige B, Gmeiner T, et al. Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. *Sleep Med Rev*. 2019;43:96-105.
68. Sunderajan P, Gaynes BN, Wisniewski SR, et al. Insomnia in patients with depression: A STAR*D report. *CNS Spectr*. 2010;15(6):394-404.
69. Li L, Wu C, Gan Y, Qu X, Lu Z. Insomnia and the risk of depression: A meta-analysis of prospective cohort studies. *BMC Psychiatr*. 2016;16(1):375.
70. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord*. 2011;135(1-3):10-19.
71. Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep–a prefrontal amygdala disconnect. *Curr Biol*. 2007;17(20):R877-R878.
72. Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev*. 2010;14(1):19-31.
73. de Lecea L, Carter ME, Adamantidis A. Shining light on wakefulness and arousal. *Biol Psychiatr*. 2012;71(12):1046-1052.
74. Hein M, Lanquart JP, Loas G, Hubain P, Linkowski P. Similar polysomnographic pattern in primary insomnia and major depression with objective insomnia: a sign of common pathophysiology? *BMC Psychiatr*. 2017;17(1):273.
75. Krysta K, Krzystanek M, Bratek A, Krupka-Matuszczyk I. Sleep and inflammatory markers in different psychiatric disorders. *J Neural Transm*. 2017;124(1):179-186.
76. Colten HR, Altevogt BM. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington, DC: National Academies Press; 2006.
77. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med*. 2007;3(5 suppl l):S7-S10.
78. Riedel BW, Lichstein KL. Insomnia and daytime functioning. *Sleep Med Rev*. 2000;4(3):277-298.
79. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC, London, England: DSM-5)American Psychiatric Publishing; 2013.
80. Cathébras PJ, Robbins JM, Kirmayer LJ, Hayton BC. Fatigue in primary care: prevalence, psychiatric comorbidity, illness behavior, and outcome. *J Gen Intern Med*. 1992;7(3):276-286.
81. Corfield EC, Martin NG, Nyholt DR. Co-occurrence and symptomatology of fatigue and depression. *Compr Psychiatr*. 2016;71:1-10.
82. Addington AM, Gallo JJ, Ford DE, Eaton WW. Epidemiology of unexplained fatigue and major depression in the community: the Baltimore ECA follow-up, 1981-1994. *Psychol Med*. 2001;31(6):1037-1044.
83. Hansell NK, Wright MJ, Medland SE, et al. Genetic comorbidity between neuroticism, anxiety/depression and somatic distress in a population sample of adolescent and young adult twins. *Psychol Med*. 2012;42(6):1249-1260.
84. Hickie I, Kirk K, Martin N. Unique genetic and environmental determinants of prolonged fatigue: a twin study. *Psychol Med*. 1999;29(2):259-268.
85. Dimsdale JE, Dantzer R. A biological substrate for somatoform disorders: importance of pathophysiology. *Psychosom Med*. 2007;69(9):850-854.
86. ter Wolbeek M, van Doornen LJ, Kavelaars A, Tersteeg-Kamperman MD, Heijnen CJ. Fatigue, depressive symptoms, and anxiety from adolescence up to young adulthood: A longitudinal study. *Brain Behav Immun*. 2011;25(6):1249-1255.
87. Hou F, Bi F, Jiao R, Luo D, Song K. Gender differences of depression and anxiety among social media users during the COVID-19 outbreak in China:a cross-sectional study. *BMC Publ Health*. 2020;20(1):1648.
88. Mazza C, Ricci E, Biondi S, et al. A nationwide survey of psychological distress among Italian people during the COVID-19 pandemic: Immediate psychological responses and associated factors. *Int J Environ Res Publ Health*. 2020;17(9):3165.
89. Wong SYS, Zhang D, Sit RWS, et al. Impact of COVID-19 on loneliness, mental health, and health service utilisation: a prospective cohort study of older adults with multimorbidity in primary care. *Br J Gen Pract*. 2020;70(700):e817-e824.