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ORIGINAL RESEARCH

Unveiling the Interplay Between Depressive Symptoms' Alleviation and Quality of Life Improvement in Major Depressive Disorder: A Network Analysis Based on Longitudinal Data

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Background: Understanding the dynamic relationship between depressive symptoms and quality of life (QOL) is essential in improving long-term outcomes for patients with Major Depressive Disorder (MDD). While previous studies often relied on cross-sectional data, there is a pressing need for stronger evidence based on longitudinal data to better inform the development of effective clinical interventions. By focusing on key depressive symptoms, such interventions have the potential to ultimately enhance QOL in individuals with MDD.

Methods: This multi-center prospective study, conducted between 2016 and 2020, enrolled outpatients and inpatients diagnosed with MDD across twelve psychiatric hospitals in China. Longitudinal data on Patient Health Questionnaire – 9 (PHQ-9) and Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) was analyzed using an Extended Bayesian Information Criterion (EBIC) graphical least absolute shrinkage and selection operator (gLASSO) network model to explore the connections between depressive symptom changes and QOL changes. Flow network was applied to investigate relationships between individual symptom changes and overall QOL score change, as well as daily functional independence.

Results: This study included 818 participants with complete data after 8-week antidepressant treatment. Apart from the overlapping items from PHQ-9 and Q-LES-Q-SF, the three edges between "mood" (delta-QLES2) and "anhedonia" (delta-DEP1), between "physical health" (delta-QLES1) and "sleep problems" (delta-DEP3), and between "physical health" (delta-QLES1) and "sad mood" (delta-DEP2) were the most strong bridges between the cluster of depressive symptoms alleviation and the cluster of QOL change. "Anhedonia" (delta-DEP1), "sad mood" (delta-DEP2) and "loss of energy" (delta-DEP4) had the highest bridge strength between the alleviations of depressive symptoms and the total score change of Q-LES-Q-SF. Anhedonia had the greatest connection with participants' satisfaction with function in daily life.

Conclusion: This study highlighted the potential for developing highly effective interventions by targeting on central symptoms, thereby to ultimately improve QOL for patients with MDD.

Keywords: network analysis, patients with MDD, acute phase treatment, depressive symptoms, quality of life

Introduction

Major Depressive Disorder (MDD) is a common mental illness characterized by persistent low mood, loss of interest, and feelings of helplessness. According to previous systematic meta-analyses, the global prevalence of MDD is approximately 4.4%-5.0%, and has become one of the leading causes of disability worldwide.[1,2] In 2019, the Chinese Mental

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Health Survey (CMHS) showed that the lifetime prevalence of MDD was about 3.4%.[3,4] MDD poses a heavy burden on patients, families, and society and has become a major public health problem that needs to be addressed urgently.[5]

In contemporary healthcare, there is a shifting emphasis towards the assessment of medium- and long-term disease outcomes, notably the Quality of Life (QOL), rather than focusing solely on symptom alleviation.[6] This shift aligns with a patient-centered approach, highlighting the importance of tailoring healthcare interventions to improve patients' overall QOL, addressing their unique needs and preferences. As healthcare continues to evolve, this emphasis on QOL will likely play a pivotal role in shaping treatment strategies and healthcare policies. While conventional pharmacotherapy and psychotherapy remain central to treating MDD, newer interventions such as esketamine, Electroconvulsive Therapy (ECT), and Transcranial Magnetic Stimulation (TMS) have shown promising results in managing MDD or treatment-resistant depression (TRD) in the long run, further highlighting the need to understand how symptom changes impact long-term quality of life outcomes in diverse patient populations.[7–9]

Network analysis, a newly emerging research methodology, is progressively gaining traction and finding broader application within the domains of psychiatry and psychology.[10–12] Unlike the traditional latent model that assumes psychiatric syndromes such as depression as an unobservable latent factor and individual depressive symptoms as independent observable manifestations of depression,[13,14] the network approach possesses the capacity to offer a visually illuminating portrayal of the intricate interdependencies that exist among individual symptoms, thereby unveiling the insightful associations that underlie psychiatric syndromes at the symptom level.[12]

Several preceding cross-sectional studies have unequivocally demonstrated the interdependent relationships between depression and QOL at the level of individual symptoms.[15–18] The findings stemming from these studies conclusively highlighted the potential for developing highly effective interventions by targeting on central symptoms, thereby to mitigate the detrimental effects of depression and ultimately to improve QOL for affected populations. Nevertheless, it is imperative to note that the aforementioned studies primarily relied on cross-sectional data, which inherently possesses limitations in capturing the dynamic changes over time of the core symptoms and their consequential impact on the improvement of QOL in patients with MDD, leaving a pronounced demand to be comprehensively explored and diligently addressed.

This study filled this research gap by using the longitudinal score changes in psychiatric scales over time as the main objects of network analysis, rather than the cross-sectional scores of psychiatric instruments. This study aims to construct the network model for the change in depressive symptoms and the change in QOL during the real-world acute-phase treatment process among patients with MDD, to explore the bridge symptoms connecting depression and QOL, and to provide stronger evidence for the potential of developing effective clinical interventions by focusing on key depressive symptoms to ultimately promote QOL in patients with MDD.

Methods

Study Setting and Participants

This is a post-hoc analysis of a study aiming at achieving the Optimization of Measurement-Based Care (OMBC) for MDD by establishing a comprehensive MBC framework based on all-round, continuous assessment for depression. The study protocol was published by Zhou J et al in 2022.[19] This multi-center prospective real-word study was conducted from November 9, 2016, to December 30, 2020, in twelve psychiatric hospitals or psychiatric units of general hospitals in China. Outpatients and inpatients with MDD in this study in these twelve psychiatric hospitals or units who met the following eligibility criteria were consecutively invited to participate: 1) aged 18 to 65 years; 2) diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria; 3) total score of the 17-item Hamilton Rating Score for Depression (HAMD-17) ≥14 in baseline; 4) total score of the 16-item Quick Inventory of Depressive Symptoms – Self-Report (QIDS-SR16) ≥11 in baseline; 5) able to understand the purpose of this study and the contents of the psychiatric assessments in this study. Patients with severe physical diseases and female patients in pregnancy were excluded. Patients at high risk of suicidal ideation (determined by a HAMD-17 item-3 score ≥ 3 points) were excluded from this study. Patients were excluded if they had used antidepressants continuously for more than 7 days in the most recent 14 days before screening.

After screening, participants were prescribed with one of the following seven antidepressants for 12-week medical treatment: escitalopram, citalopram, paroxetine, fluvoxamine, sertraline, mirtazapine or fluoxetine. The choice and dose of the antidepressant treatments were determined by the clinical judgement of psychiatrists. Psychiatrists could choose aripiprazole as an augmentation therapy depending on the patient's condition. The participants were randomly assigned to the Measurement-Based Care (MBC) group and treatment as usual (TAU) group at a ratio of 2:1.[19] Although the actual number of recruited participants exceeded the target sample in study protocol, sample attrition occurred during the follow-up period.[19,20] Given that the network model analysis requires complete data for each node, and to balance the consideration of symptom recovery with the need for a robust sample size to support our conclusion, we opted to analyze the complete dataset from baseline to week 8 for this post-hoc analysis.

The protocol of this study was reviewed and approved by the Institutional Review Board (IRB) of all the participating centers, including Beijing Anding Hospital, Guangdong Mental Health Center, the First Affiliated Hospital of Harbin Medical University, the First Affiliated Hospital of Hebei Medical University, West China Hospital of Sichuan University, the First Affiliated Hospital of Kunming Medical University, Nanjing Brain Hospital Affiliated to Nanjing Medical University, the First Psychiatric Hospital of Harbin, Tongji Hospital of Tongji University, the First Hospital of Shanxi Medical University, Shenzhen Mental Health Center, and the Fourth Military Medical University of People's Liberation Army. Written informed consent was obtained from all participants before screening and all the other study procedures. This study was conducted following ethical principles for medical research involving human subjects in compliance with the Declaration of Helsinki.

Data Collection and Assessments Tools

Socio-demographic data including age, sex, education level, residence area (urban or rural), marital status and employment status of the participants were collected.

Severity of depressive symptoms was assessed using the validated Chinese version of the Patient Health Questionnaire – 9 (PHQ-9). The PHQ-9 consists of nine items, each rated on a frequency scale from 0 (not at all) to 3 (almost every day).[21,22] Higher PHQ-9 scores represent more severe depression.[23] The psychometric properties of the PHQ-9 had been proved to be reliable in Chinese populations.[24,25]

Overall quality of life (QOL) was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF). Q-LES-Q-SF consisted of 16 self-report items, of which only the first 14 items yield a total score.[26] The last two items are stand-alone items that measures perceived satisfaction on medication and overall life, respectively. Every item in Q-LES-Q-SF ranges from 1 (very poor satisfaction) to 5 (very good satisfaction). The Chinese version of the Q-LES-Q-SF has been validated and widely used in Chinese population.[27–29]

Data Analyses

An extended Bayesian Information Criterion (EBIC) model graphical least absolute shrinkage and selection operator (gLASSO) network model was constructed to explore the interconnective relationships between the changes in depressive symptoms and the changes in the first 14 item of Q-LES-Q-SF from baseline to week 8. In the network structure, the score change in each individual symptom was a "node", and connections between the score changes in symptoms were "edges". The centrality of the score change in each symptom was measured using strength and bridge strength. Strength is the sum of the absolute weights of the edges connecting a certain node to all the other nodes.[30] Bridge strength is the sum of the absolute weights of all the edges connecting a certain node to all the other nodes from the other cluster.[31,32] The size of a node represented the strength of the score change in a particular symptom. The thickness of each edge represented the strength of the association between two nodes. The color of an edge reflected the direction of the association with green edges indicating positive associations and red edges indicating negative associations between nodes.

Network stability was examined via the correlation stability coefficient (CS-C) using a case-dropping 1000-time bootstrap method.[33,34] The CS-C quantifies the maximum proportion of cases that can be dropped at random to retain, with 95% certainty, a correlation coefficient (r) of at least 0.7 between the centralities of the original network and the subsample network.[35] Preferably, a CS-C exceeds 0.5, with a minimum value requirement of 0.25.[35]

A flow network was applied to investigate relationships between the score change in each individual depressive symptoms and Q-LES-Q-SF total score among the patients with MDD. To verify the results of the network analyses, generalized linear models were applied to explore the impact of the score change in each individual depressive symptom on the change in Q-LES-Q-SF total score while adjusting age and sex.

Network comparison tests (NCT) with Holm's correction for multiple comparisons were employed to investigate whether variations in socio-demographic factors (sex and age group, categorized using the median-split method) and clinical features (first episode or relapse, receiving TAU or MBC) led to significant differences to the EBIC gLASSO network model.

To explore the impact of depressive symptom recovery on the functional independence, a flow network was adopted on the changes in PHQ-9 scores and the 8th item from Q-LES-Q-SF (satisfactory level on ability to function in daily life).

All data analyses were conducted using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and R version 4.3.1.[36] R packages used in this study were *networktools version 1.2.3, bootnet version 1.4.3, NetworkComparisonTest version 2.2.2* and *qgraph version 1.6.5*.[32,35,37,38]

Results

Socio-Demographic and Clinical Features of the Study Sample

In total, 818 patients with MDD were included in this study; of these, 555 (67.8%) were female. The mean age of the participants was 35.8±12.4 years. A majority of the participants were in the first episode of MDD (503/818; 61.5%). For the participants with recurrent MDD, they experienced an average of 2.86 MDD episodes, and the average duration of MDD was 5.61 years. About 14.2% of the participants (116/818) had a family history of mental disorders. Detailed description of the socio-demographic characteristics and clinical features of the study sample is shown in Supplementary Table 1. The changes in PHQ-9 item scores and Q-LES-Q-SF item scores from baseline to week 8 are described in Supplementary Table 2.

EBIC gLASSO Network Model

The network model for the change in PHQ-9 and change in Q-LES-Q-SF from baseline to week 8 is shown in Figure 1. All edges between depressive symptom score changes and life quality score changes were negative. Nodes within the cluster of depressive symptoms were closely interconnected with those within the cluster of life quality generally. The score changes in the 2nd item (mood), 14th item (overall sense of wellbeing), 7th item (leisure time activities) and 5th item (social relationships) in Q-LES-Q-SF had the highest strength in this network (Figure 2).

The edge between "physically getting around" (delta-QLES12) and "psychomotor signs" (delta-DEP8), the edge between "mood" (delta-QLES2) and "sad mood" (delta-DEP2), the edge between "mood" (delta-QLES2) and "anhedonia" (delta-DEP1), the edge between "physical health" (delta-QLES1) and "sleep problems" (delta-DEP3), and the edge between "physical health" (delta-QLES1) and "sad mood" (delta-DEP2) had the highest edge weights. The weighted adjacency matrix for this network model is displayed om Supplementary Table 3.

The CS-C for strength in this network model was 0.751, indicating that the strength values in this network remained stable after dropping 75.1% of the study sample (Supplementary Figure 1). The bootstrapped confidence intervals of edge weights, bootstrapped edge weight difference tests and bootstrapped node strength tests were displayed in Supplementary Figures 2–4.

Flow Network Model

The flow network model for the change in PHQ-9 and change in Q-LES-Q-SF total score from baseline to week 8 is shown in Figure 3. The score changes in "anhedonia" (delta-DEP1), "sad mood" (delta-DEP2) and "loss of energy" (delta-DEP4) had the highest bridge strength between the cluster of depressive symptoms' alleviations and the total score change of Q-LES-Q-SF (Figure 4), indicating that the symptom alleviations in these three items had the strongest connection with the improvement of QOL. The weighted adjacency matrix for this flow network model is displayed om Supplementary Table 4.

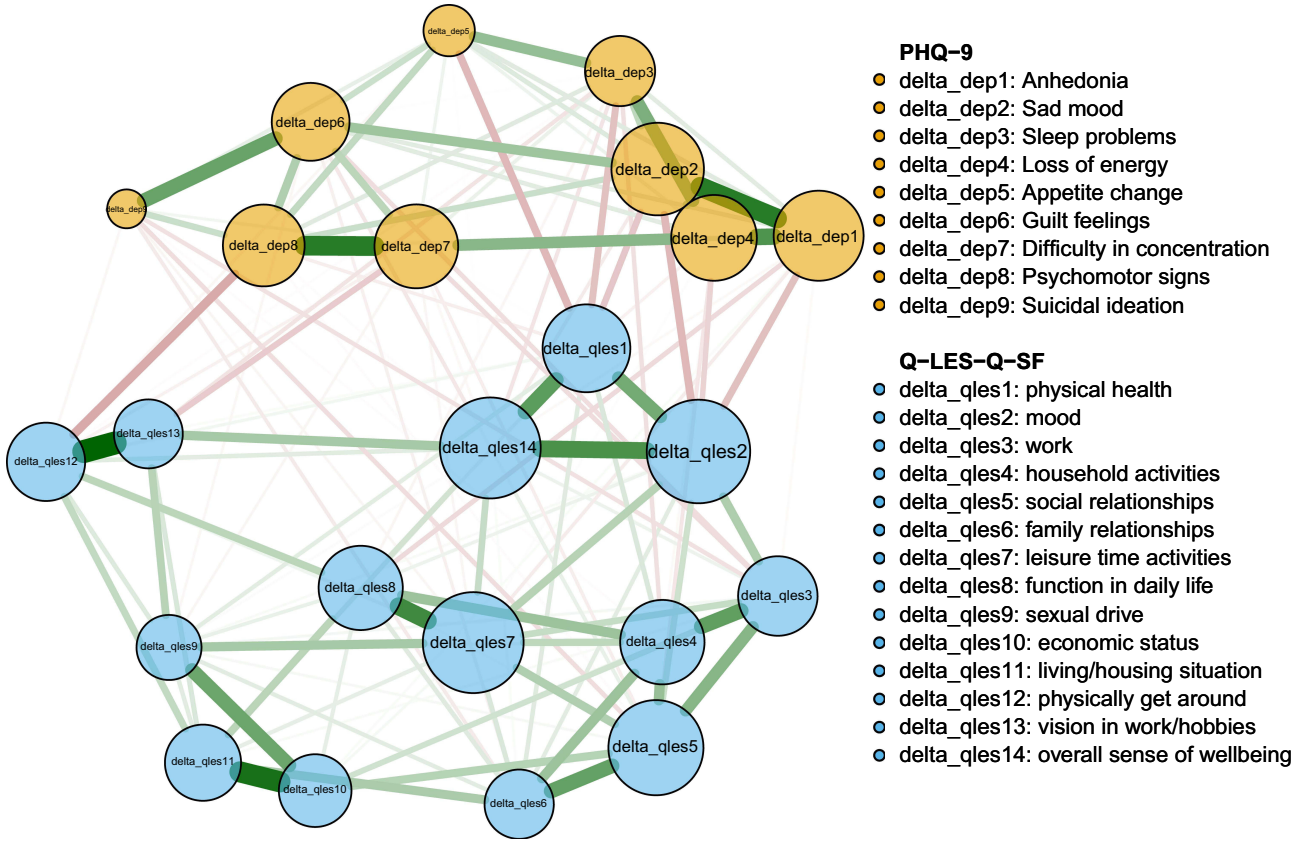

Figure 1 Network model for the change in PHQ-9 and change in Q-LES-Q-SF from baseline to week 8.
Notes: The size of each node indicates the relative level of strength. Green edges indicate positive associations; red edges indicate negative associations. Delta refers to score change from baseline to week 8.

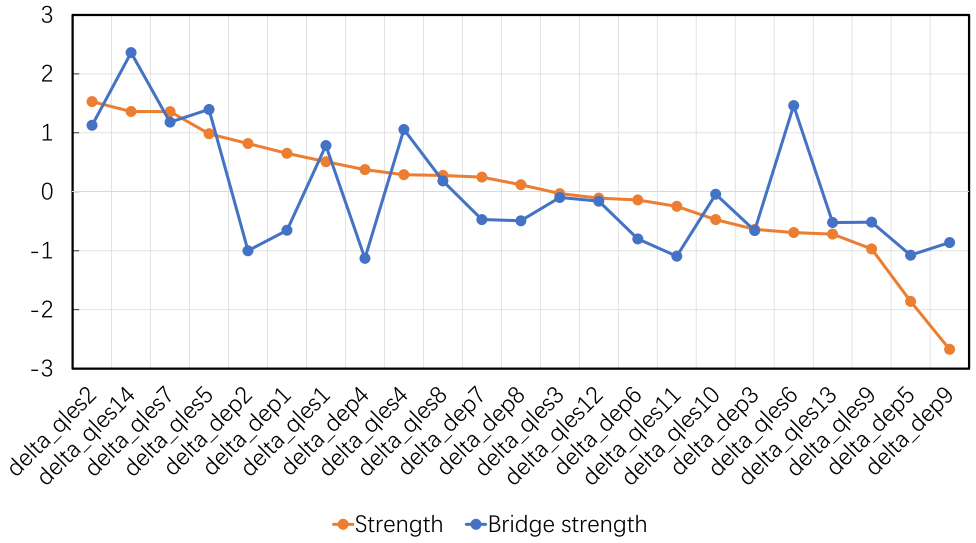

Figure 2 Strength and bridge strength of the network model for the change in PHQ-9 and change in Q-LES-Q-SF from baseline to week 8 (z-score).

The CS-C for bridge strength in this network model was 0.751, indicating that the bridge strength values in this network remained stable after dropping 75.1% of the study sample (Supplementary Figure 5). The bootstrapped confidence intervals of edge weights, bootstrapped edge weight difference tests and bootstrapped node strength tests were displayed in Supplementary Figures 6–8.

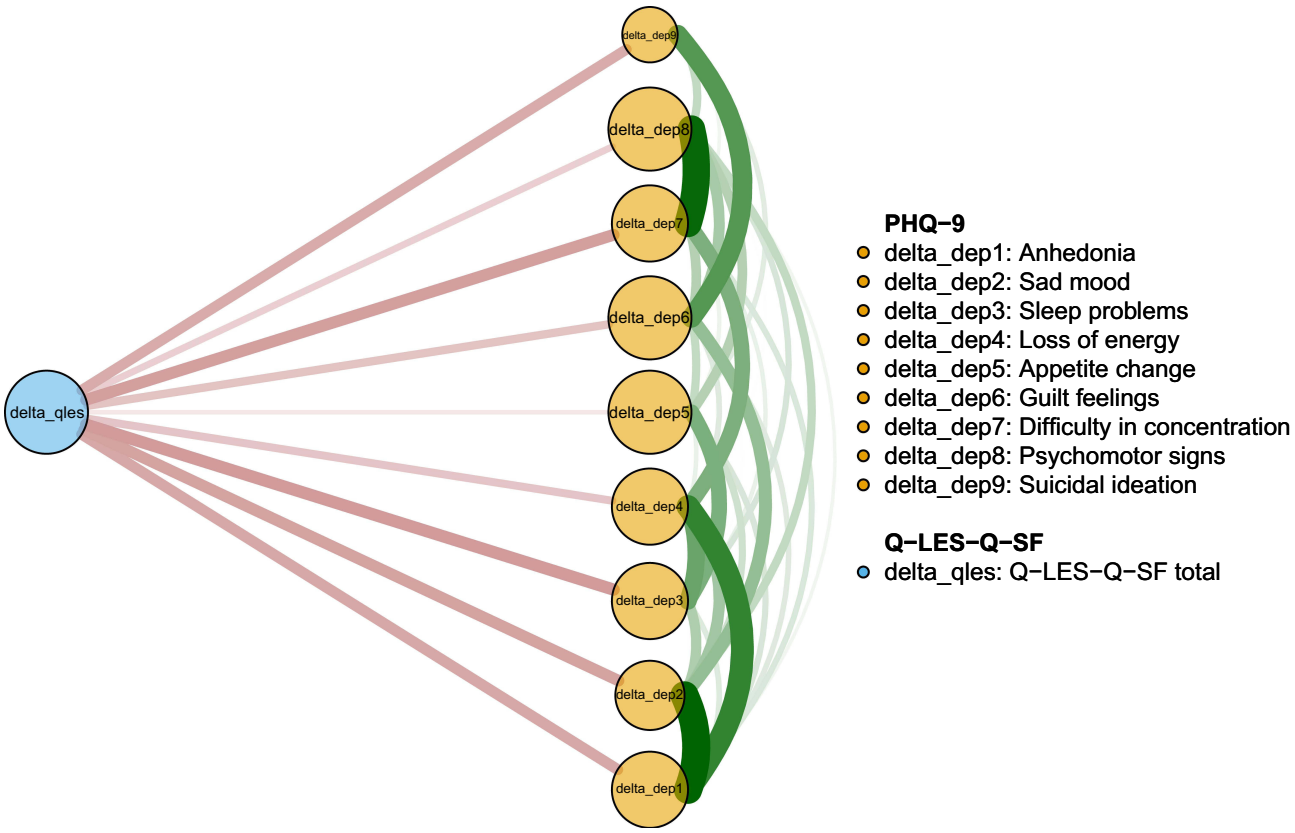

Figure 3 Flow network model for the change in PHQ-9 and change in Q-LES-Q-SF total score from baseline to week 8.
Notes: The size of each node indicates the relative level of strength. Green edges indicate positive associations; red edges indicate negative associations. Delta refers to score change from baseline to week 8.

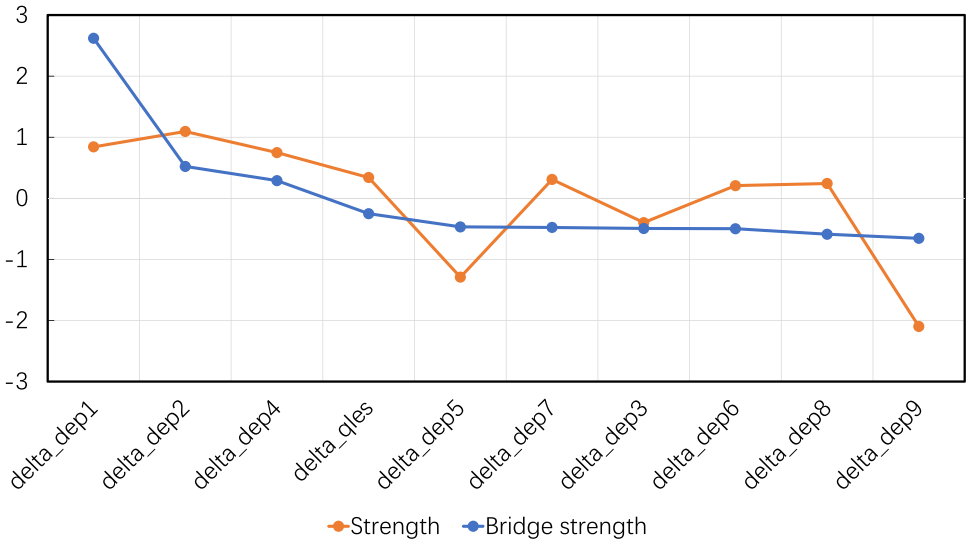

Figure 4 Strength and bridge strength of the network model for the change in PHQ-9 and change in Q-LES-Q-SF total score from baseline to week 8 (z-score).

The Impact of the Alleviations in Each Depressive Symptom on the Improvement of QOL

The results of generalized linear models showed that the alleviations in all the nine depressive symptoms had significant impact on the improvement of QOL after adjusting for age and sex. Anhedonia (DEP-1), sad mood (DEP-2) and loss of

energy (DEP-4) had the highest r-square values and lowest Akaike Information Criterion (AIC) values, which is consistent with the finding from the flow network model (Supplementary Table 5).

Subgroup Analyses Based on Socio-Demographic Factors and Clinical Features

Comparisons of networks based on sex, age groups (split by the median age), episode status (first episode or relapse), and treatment type (TAU or MBC) are displayed in Figure 5. The invariance tests on network structure, global strength, and edge weights showed that those network features were consistent between subgroups based on sex, episode status, and treatment type, with the exception of age group. The network invariance test showed that the network structure was statistically different between younger and older participants (test statistic M=0.239, p=0.012) and the maximum difference lies in the edge between the first item (physical health) and second item (mood) from Q-LES-Q-SF. This indicates that older participants exhibit significantly stronger connections between their satisfaction in physical health and their mood status.

The Impact of the Alleviations in Each Depressive Symptom on the Functional Independence

The flow network model for the change in PHQ-9 and change in functional independence (identified as the 8th item from Q-LES-Q-SF, ie, satisfactory level on function in daily life) from baseline to week 8 is shown in Figure 6. Alleviation on anhedonia had the greatest connection with participants' satisfactory level of function in daily life. The CS-C for bridge

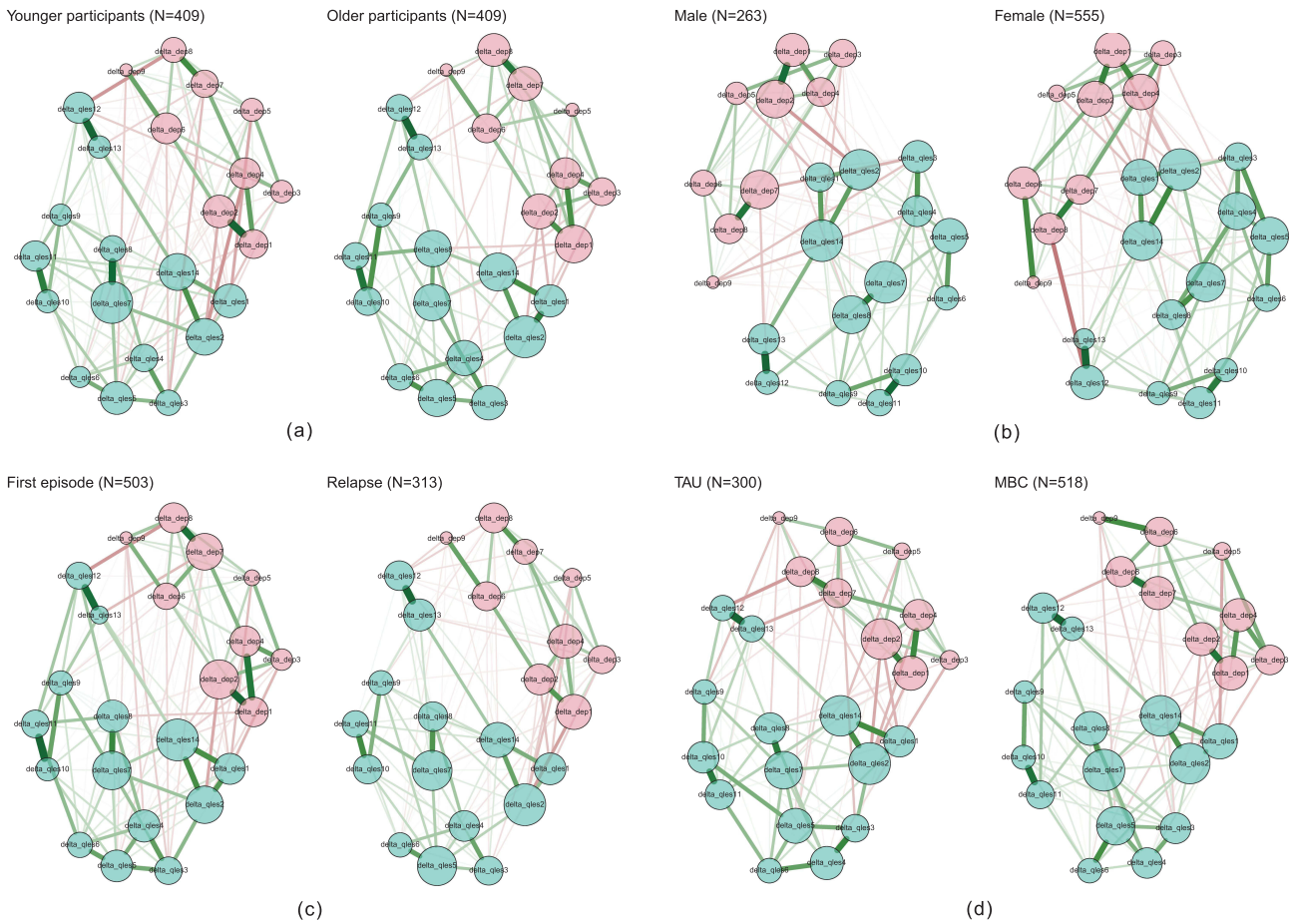

Figure 5 Network comparisons based on subgroups by socio-demographic factors and clinical features.
Notes: (**a**) subgroup analysis based on age (categorized by median of age: 33.004 years old); (**b**) subgroup analysis based on sex; (**c**) subgroup analysis based on episode status; (**d**) subgroup analysis based on treatment type. Delta refers to score change from baseline to week 8.

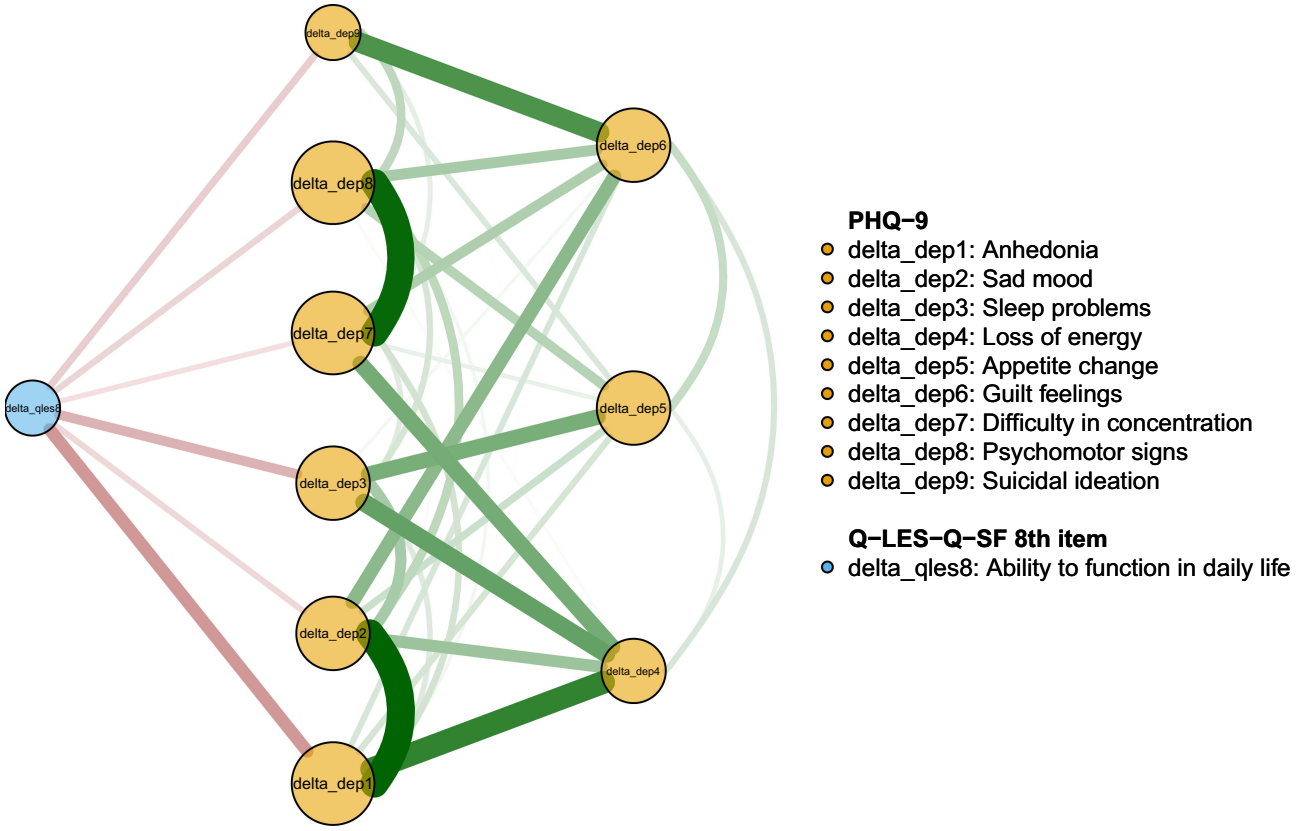

Figure 6 Flow network model for the change in PHQ-9 and change in functional Independence from baseline to week 8.
Notes: Functional independence was identified as the 8th item from Q-LES-Q-SF, ie, satisfactory level on ability to function in daily life. The size of each node indicates the relative level of strength. Green edges indicate positive associations; red edges indicate negative associations. Delta refers to score change from baseline to week 8.

strength in this network model was 0.751, indicating that the bridge strength values in this network remained stable after dropping 75.1% of the study sample (Supplementary Figure 9).

Discussion

This study found that apart from the overlapping items from PHQ-9 and Q-LES-Q-SF, the edge between "mood" (delta-QLES2) and "anhedonia" (delta-DEP1), the edge between "physical health" (delta-QLES1) and "sleep problems" (delta-DEP3), and the edge between "physical health" (delta-QLES1) and "sad mood" (delta-DEP2) were the most strong bridges between the cluster of depressive symptoms alleviation and the cluster of QOL change. "Anhedonia" (DEP-1), "sad mood" (DEP-2) and "loss of energy" (DEP-4) had the highest bridge strength between the alleviations of depressive symptoms and the total score change of Q-LES-Q-SF.

Prior research had revealed that the severities of anhedonia and sadness were highly correlated, which was consistent with the findings in our research. "Anhedonia" and "sad mood" are two required symptoms for diagnosing major depressive disorder according to DSM-IV.[11,39–42] The strong link between anhedonia and sadness could be explained by that anhedonia may prevent experiences of pleasure and interest in life and work, which may increase sadness later, given that patients with MDD usually lack the capability to complete tasks and fulfill wishes.[40] From the perspective of core symptoms of MDD, the onset of one symptom may trigger another over time.[11,43]

The coexistence of anhedonia and sad mood in the majority of MDD could also be understood from the perspective of neurobiological and neuroimaging studies.[44–47] Low dopaminergic activity has been reported in patients with MDD, as well as those with sad mood and low hedonic tone.[48] Neuro-imaging studies have reported decreased striatal activation in hedonic experience, and the prefrontal cortices play a major role in mood regulation in patients with MDD.[49,50] The pathway of mood and hedonic experience could have an up and down mutual interaction. However, there was no

correlation between sad mood and anhedonia in some patients with MDD, because of their own neuronal bases with their own circuitries.[50]

This study found that good sleep plays an essential role in physical health. Sleep problems can increase the risk of health problems such as mental health, chronic disease prevalence and mortality. The strong association between "physical health" and "sleep problems" was found in our current study, which was similar to previous studies.[51–53] This strong connection could be explained in several aspects. First of all, the theory of cognitive-emotional hyperarousal claims that sleep problems are the results of dysfunctional and abnormal excitement processes.[54–56] Second, several studies suggest that sufficient sleep may contribute to hormonal balance and impact cortisol secretion.[57,58] Deprivation of sleep may gradually change neuroendocrine systems especially the hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, associating with mental health such as depression which is highly stress-related.[58] The relationship between stress systems and sleep is complex and bidirectional.[57] This finding reminds psychiatrists to pay more attention to sleep problems so as to get a better health status and QOL for patients with MDD.

We found that "physical health" from Q-LES-Q-SF and "sad mood" from PHQ-9 had strong connection with each other, which were consistent with previous studies.[11,43] It was proved that physical health was closely linked to positive subjective wellbeing which might be a protective factor for health.[59] Depressed mood is a serious adverse factor that affects peoples' physical health. In turn, the long-term condition (LTC) could also affect emotions by complex conditions, cognitive symptoms, loss of function, reducing independence, and hinder the rehabilitation process.[60] There is growing evidence that both physical health and depression have marked lifestyle-driven components.[61–63] The mechanisms may include gut–brain axis and its effect on the modulation of inflammation and oxidative stress. Individual bioactive molecules have also been considered.[63] It is noteworthy that depression is often coexisted with chronic diseases, such as cardiovascular disease, dementia, and cancer.[64] For some individuals, chronic diseases were capable of triggering depression. For some people, chronic diseases were running alongside the depression. For some patients with depression, sad emotions may be a risk factor for developing physical illnesses.[60,64] Patients with MDD often experience somatic symptoms. They often seek their first visit to a general hospital with physical symptoms.[65–69] It provides an important implication for psychiatrists that they should not only pay attention to the patient's physical condition but also do not overlook the interaction between physical illness and depression. Our findings point to the meaningfulness to targeted therapies that address one of these bridge symptoms may improve the other symptoms. There is a need for promising interventions which ought to be developed to ensure physical and mental health.

This study found that older participants exhibit significantly stronger connections between their satisfaction in physical health and their mood status. This might be due to that as people age, they tend to experience more health-related issues, such as chronic illnesses, mobility limitations, and general physical decline. These physical health challenges can significantly impact their daily life and overall well-being, making them more sensitive to their physical health status. When older adults feel physically healthy, they are more likely to experience a positive mood, whereas poor physical health can lead to feelings of frustration, sadness, or hopelessness. Meanwhile, in older adults, physical and mental health are closely interconnected.[70] Physical conditions can lead to psychological distress, and vice versa. For example, chronic pain or disability can contribute to feelings of depression or anxiety, while a positive physical health status can enhance mood and overall life satisfaction.[71,72]

This study found that anhedonia had the greatest connection with participants' satisfaction with function in daily life. Anhedonia, which is the inability to experience pleasure or interest in activities that were once enjoyable, is a core symptom of MDD.[73] It directly impacts an individual's ability to engage in and derive satisfaction from daily life activities.[74] Here are several potential explanations for this strong connection. First, anhedonia reduces motivation and the desire to participate in daily activities, including work, social interactions, and hobbies.[75] This decline in engagement naturally leads to a decreased sense of satisfaction with one's daily functioning.[76] Second, anhedonia diminishes the ability to feel pleasure, which means that even if individuals attempt to engage in daily activities, they do not experience the usual positive reinforcement that comes from these activities.[77,78] Over time, this lack of positive reinforcement can erode their overall satisfaction with life. Third, because anhedonia can lead to a lack of interest in self-care, household tasks, or professional responsibilities, it can result in reduced productivity and an overall sense of dysfunction in daily life.[77,79] This can make it difficult for individuals to meet their own or others' expectations, further decreasing their

satisfaction with daily functioning.[80] Moreover, anhedonia often leads to social withdrawal, as individuals lose interest in maintaining relationships or participating in social activities.[75,81] This isolation can negatively affect their overall quality of life and their perception of how well they are functioning in their daily lives.[82]

Depression is a multifaceted disorder that is often shaped by the socio-cultural context in which it occurs. Cultural norms and values can affect how symptoms are perceived, expressed, and managed, which in turn influences treatment outcomes. For example, in east Asian cultures, emotional distress may be more likely to manifest as physical symptoms, leading to differences in how depression is diagnosed and treated.[83,84] Additionally, access to mental health care, societal stigma, and the availability of social support vary across regions, which can further modulate the course of the disorder and the QOL of the patients.[85,86]

Given that our study was conducted within a specific cultural and geographical context, we acknowledge that the generalizability of our findings to other settings, such as rural areas or Western countries, may be limited. Therefore, while our results provide valuable insights into the treatment of MDD within the studied population, further research is needed to explore how these findings might translate to diverse populations with varying cultural backgrounds.

The strengths of this study included its multi-center prospective study design, visual depiction of depression-QOL interplays at symptom level, and focusing on symptom changes during real-world acute-phase treatment process. However, this study has several methodological limitations. First, the depression cluster in this network structure includes only the nine classical depressive symptoms. Therefore, including other facets of depressive symptoms might generate different patterns of inter-connective relationships. Second, the items from Q-LES-Q-SF have some overlaps with the items from PHQ-9, which might obscure the real connections. Third, this study focused on a specific population, ie, patients with MDD aged 18 to 65 years, excluding elderly individuals and those with chronic diseases. This approach led to a younger cohort, predominantly experiencing their first episode of depression, with fewer comorbidities. This creates a more restricted sample, which may not fully represent the broader MDD population. Given this limitation, the findings from this study may not be entirely generalizable to the entire population of individuals with MDD, particularly older adults, those with chronic, refractory, or recurrent MDD, and patients from western countries. Cultural norms, access to healthcare, and socio-economic conditions can vary significantly across different regions, potentially affecting the expression and progression of depressive symptoms. The distinct characteristics and treatment need of these groups highlight the importance of caution when extrapolating our results to more diverse patient populations. Furthermore, the recruitment model used in our study was hospital-based, focusing on patients from a psychiatric setting. This likely resulted in the inclusion of individuals with more severe depressive symptoms compared to those who might be seen in a community setting. If the study had been conducted on a community basis, the results might have differed, potentially capturing a wider range of symptom severity and demographic diversity. This could influence both the depressive symptom response and QOL outcomes observed. Further research that includes a broader range of populations, especially geriatric patients, those with chronic or recurrent MDD, and community-based samples, is essential to validate our findings and ensure that they are applicable across diverse clinical settings.

Recent advancements in rapid-acting antidepressants, such as ketamine, esketamine, and emerging psychedelic therapies like psilocybin, have shown promising results in alleviating depressive symptoms, particularly in treatment-resistant cases.[87,88] While these interventions highlight the evolving landscape of depression treatment, our study focuses on more traditional pharmacological approaches, underscoring the need for future research to explore how novel therapies might interact with or complement standard treatment modalities in enhancing quality of life outcomes.

To be conclusive, this study found that “anhedonia”, “sleep problems” and “sad mood” might be the core depressive symptoms to be targeted for promoting QOL in patients with MDD. By using the longitudinal data, this study highlighted the potential for developing highly effective interventions by targeting on central symptoms, thereby to reduce adverse effects of depression and ultimately to improve QOL for affected populations.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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