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ORIGINAL RESEARCH

The Ripple Effect: Unveiling the Bidirectional Relationship Between Negative Life Events and Depressive Symptoms in Medical Cadets

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Background: Previous studies have explored the relationship between negative life events and depression, but little is known about the bidirectional relationship between negative life events and depression, particularly in specific groups of medical cadets.

Purpose: This study aimed to explore the relationship between negative life events and depressive symptoms among medical cadets during their four years of college.

Methods: An analysis of 4-wave longitudinal data collected from 2015–2018 was conducted using a cross-lagged panel network (CLPN) model to explore the complex causal relationship between negative life events and depressive symptoms in medical cadets (N=433).

Results: We found differences in negative life events and depressive symptoms among medical cadets across four network models over four years of university. Nodes A-21, A-20, A-23 and A-24, and depressive symptoms D-6 showed greater lagged effect values.

Conclusion: Our findings suggest that there is a lagged and mutually causal interaction between negative life events and depressive symptoms in medical cadets over 4 years of college, but that the predictability of negative life events is more important. However, more attention needs to be paid to the predictive role of depressive symptoms, especially those in early life which are often overlooked. Our study provides new insights into the relationship between negative life events and depressive symptoms in university students and helps to refine strategies for prevention and intervention of depression.

Keywords: depression, negative life events, CLPN, longitude relationship, vicious circle, network analysis

Introduction

Depression, one of the most prevalent mental illnesses, is characterized by physical and mental symptoms such as reduced appetite, sleep problems, persistent sadness and loss of interest, affecting approximately 5% of the world's population, and is a major contributor to disability as well as the global burden of disease.[1] In developing countries, many people with depression do not receive adequate treatment, resulting in high rates of depression prevalence and relapse. According to the Blue Book of Mental Health: Report on National Mental Health Development in China,[2] approximately 18.5% of university students are affected by depression and the rate of suicide increases significantly with the rise of depression level. Meanwhile, recent reports indicate that the prevalence of depression is on the rise.[3,4] Numerous studies have been conducted on the prevention and treatment of depression in the general population with a lot of research results,[5,6] but few studies were performed on that in Chinese military personnel, especially the military medical cadets who are more vulnerable to depression.[7,8] This may be related to the fact that military medical cadets are subjected to both heavy academic workloads and military training, resulting in a high level of depression,[7] accompanied with a high

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suicide rate[8,9] which is the main reason for non-combat attrition in the military.[10] Therefore, it is necessary to further explore the pathogenesis and prevention and intervention of depression in the military personnel.

The pathologic mechanism of depression is very complex and has not yet been fully understood.[11] The main pathogenesis includes changes in the brain, including neurotransmitter imbalance,[12] structural and functional changes in the brain,[13] dysfunction of the neuroendocrine system,[14] mitochondrial damage,[15] and abnormalities in the default network of brain patterns,[16,17] which are represented by cognitive bias in psychological activities, such as negative thinking mode,[18] process bias[19] and cognitive distortion.[20] Depression often coexists with many other diseases, such as anxiety, dementia and fear.[21,22] Given the complex pathologic mechanisms, understanding the underlying causes of depression is of great significance for the treatment of depression.[23] Although there is a general consensus that both genetic and environmental factors influence depression,[24,25] environmental factors play a more important role in the prevention and intervention of depression as genetic factors are unlikely to change on a large scale.[26,27]

Many social environmental factors influence depression,[28] making the study very challenging. In China, the study at military medical universities generally lasts four to five years for undergraduate students, making the university time a main period of transition from school to workplace.[29] Military medical students must grapple with multiple life scenarios. For example, newcomers must adjust themselves to new environment and confront interpersonal problems, and as they become seniors they may face other problems such as internship, job hunting, and complex interpersonal interactions. At the same time, the home environment of university students is also changing. For example, their parents often reach middle age at this time with more health problems,[30] and the older family members gradually pass away.[31] These changes can increase the stress levels of university students. Life stressors are one of the main causes of depression.[32,33] Depressive episodes can affect interpersonal relationships,[34] academic work[35] and quality of life,[36] with committing suicide as the worst consequence. Studies have shown that recent negative life events increase the risk and severity of depression.[37] Depressive symptoms might cause interpersonal relationship deterioration and low quality of learning and work, etc., which are the very stressful events that induce depression. This implies that negative life events and depressive symptoms are to some extent in a vicious circle, which has not been well explored. The above problems may be common among college students, but the situation is more challenging for military medical students when they are faced with these problems due to the strict management. For example, military cadets rarely take time off to be with their family members when they are sick.[38]

It is important to explore the predictive (causal) relationship between negative life events and depressive symptoms in the time dimension, and a new cross-lagged panel model can be used to address this issue.[39] In a cross-lagged panel design, two (or more) structural data are measured at two (or more) discrete time points. By calculating the regression of the set of variables from the first occasion (T1) on the set of variables from the second occasion of measurement (T2), it is possible to estimate the "cross-lagged" effect of each variable on the other variable at a given time lag (i.e., whatever the time lag between the two periods of evaluation), while controlling the autoregressive effect of each variable on itself. Cross-lagged panel models are the most appropriate when individuals have data on several structures at several discrete time points, and when the research is focused on the causal effects of these structures over time.[40] The cross-lagged panel network model is a combination of a mental network model and a cross-lagged panel model, which utilizes regularized regression estimates to identify autoregressive and cross-lagged paths that demonstrate the influence of one another in the temporal domain,[40] thus allowing us to obtain a finer degree of information.

The life circumstances and stressful events of the university students may differ from year by year, and the relationship between these events and depressive symptoms may also vary. To further understand the changes in life events and depressive symptoms over time among medical cadets, the current study explored the longitudinal relationship of negative life events and depressive symptoms using Cross-Lagged Panel Network Models.[39] We analyzed 4-wave data from medical cadets over four years and therefore hypothesized: (1) the network of life events and depressive symptoms over four years from freshman to senior is heterogeneous, i.e., the temporal network is not replicable, and (2) negative life events and depressive symptoms are mutually predictive of each other (vicious circle).

Materials and Methods

Study Design and Procedure

We reanalyzed data from a longitudinal survey with 4 waves spaced one year apart (2015–2018), and the choice of data nodes was determined according to the research theme, which was to explore and improve the relationship between negative life events and depressive symptoms. A convenience sampling approach was used to recruit freshmen in this survey in 2015 through verbal invitations from the faculty or posters around the campus. All surveys were conducted at the midterm of the fall semester of each academic year. The survey was carried out in quiet classrooms where the students completed a series of questionnaires, including such variables as: demographic variables, depression, and negative life events. The subjects received course credit for their participation after the investigation in the fourth year. The study was approved by the Medical Ethics Committee of Army Medical University (Project No: 30970898). The study complies with the Declaration of Helsinki, and the written informed consent was obtained from all the participants. The study team protected the physical and mental health of the participants and promised to keep the data confidential to protect the rights of the participants.

Participants

A total of 505 military medical cadets in Chongqing, China, were recruited for this investigation in 2015, and they completed the baseline investigation. The students were further invited to take part in a four-year longitudinal investigation from 2015 to 2018, 433 of whom completed the four-year longitudinal survey, including 389 males and 44 females, and 72 cadets were absent during the follow-up investigation (loss rate was 14.26%). The age of participants ranged from 17 to 25 (mean = 18.93± 1.41). The majority of the participants in the study were male, as they were all from a military medical university.

Measure Tools

Negative Life Events

To collect life-stress information, the Adolescent Self-Rating Life-Events Checklist (ASLEC) was used, which was designed by Liu in 1997.[41] This scale is a retrospective self-report questionnaire that includes 27 items measuring the frequency and intensity of negative life events. In the current study, the mean Cronbach' α coefficients for the scale was 0.76, with a separate Cronbach' α coefficient of 0.81, 0.73, 0.77 and 0.72 for each wave.

Depressive Symptoms

The Patient Health Questionnaire (PHQ-9)[42] was used to assess participants' depression levels. The PHQ-9, containing 9 questions, is the most commonly used depression survey with excellent reliability and validity. In the current survey, the mean Cronbach' α coefficients for the scale was 0.80, with a separate Cronbach' α coefficient of 0.72, 0.79, 0.82 and 0.85 for each wave.

Data Analysis

The data was analyzed using Excel software and the validity of the measurement instruments was estimated using SPSS 25.0[43] for descriptive statistical analysis. To establish CLPN models, an average of 1.77% of the data was interpolated using R-package mice. The details of missing data are listed in Figure S1. Contemporaneous and cross-lagged networks were estimated and graphically visualized via R 4.0.3 (https://www.R-project.org).

Using the network analysis, the interrelationships between 27 negative life events and 9 depressive symptoms were explored. The current CLPN model is better suited to nodes fewer than 30,[39] but the number of our network nodes was slightly higher than the recommended one, totaling 36. Given the operational economy of the software and the purpose of the study, we did not discard any of these nodes because of the relatively homogeneous nature of our scale and the heterogeneity of these events, e.g., the death of a friend affects individuals differently from the death of a family member, even though many previous studies have optimized the number of nodes through a range of methods such as factor loadings, importance and theoretical underpinnings.[40,44] As suggested by Rhemtulla & van Bork,[40] the more variables are collapsed, the more composite variables are extracted from specific observable behaviours/beliefs/attitudes, and to avoid human error, we did not consider collapsing or censoring nodes, either.

First, we estimated the Graphical Gaussian Model (GGM) for the 4-wave cross-sectional data, and then used a graphical least absolute shrinkage and selection algorithm (GLASSO) to optimize the Gaussian model, combined with an extended Bayesian information criterion (EBIC), setting the hyperparameter γ to 0.5. The smaller edge connections were made to shrink to 0, forming a sparse network and avoiding false positive edges for a more robust interpretation of the network.[45] For the cross-sectional network, we considered the expected influence centrality of each model,[46] and the expected influence centrality of the bridge.[47] The nodes of the network represent the items of each variable, and the edges connecting the nodes indicate the regularized partial correlation coefficients, with thicker edges indicating stronger relationships.[45]

Finally, we estimated cross-lagged networks for the 4-wave data. We conducted analysis of the last 2 steps according to the 3-step analysis[40] by first fitting regularized regression models to estimate cross-lagged and autoregressive coefficients across time. And then, results were summarized by generating graphs and calculating summary statistics (e.g., within and outside predictions by node). We used the T1 main demographic variables “gender” and “age” as covariates in the cross-lagged network, using minimum absolute shrinkage with 10-fold cross-validation and selection operator regularization to estimate the temporal network.[40] The network structure was analyzed by the R-package glmnet, and the visualization was performed using the R-package qgraph. Higher cross-lagged predictions indicated that the latter node was more influenced by all other nodes at the early time point. In contrast, lower cross-lagged prediction values indicated that the earlier node was more influenced by all other nodes at a later time point.[40] For the temporal network, we considered 2 indicators: inExpected Influence (InEI) and outExpected Influence (OutEI). The former indicates the relative predictability, i.e., the extent to which each variable is predicted by other variables in the network; the latter indicates the relative influence of the target node, i.e., the extent to which each variable predicts other variables in the network. Clinically, OutEI can be considered a therapeutic target, while inEI an important therapeutic outcome.[48]

The accuracy and stability of edge weights were estimated using two bootstrap methods implemented in the R package bootnet.[49] First, the accuracy of the network was estimated by calculating the 95% confidence intervals (CI) for each metric using 1000 iterations of the non-parametric bootstrap method. To evaluate the dependability of the centrality index, we estimated the correlation stability (CS) coefficients by implementing case-drop bootstrapping (nboot = 1000). It is considered to be adequate if the CS coefficients are higher than 0.25, with a desirable value of 0.5 or higher.[49] And then, edge weight difference tests and centrality difference tests were performed to examine if the variations between edge weights or node centrality were statistically significant (see Epskamp et al,[39] for a detailed description of these methods).

Consistent with a previous multi-wave data study,[50] we also considered the replicability of cross-period networks to demonstrate differences in negative life events and depression networks among college students over 4 years. To assess network replicability, we used the same methods to estimate replication networks of symptoms at T2 predicting T3 variables, as well as T3 to T4 predictions. Similarity between the four networks was assessed using (1) correlations between lists of edges, which provides a global measure of network similarity, (2) the percentage of individual edges in one network that replicates in another (i.e., odds ratios OR > 1 or OR < 1 across the four networks), (3) correlations of centrality indices between networks, and (4) consistency of the most central symptoms.

Results

Cross-Sectional Network

Figure 1 illustrates the cross-sectional network structure of the 4-wave data. In the T1 network, the CS coefficients of edge, EI and BridgeEI were 0.21, 0.28 and 0, respectively; in the T2 network, the CS coefficients of edge, EI and BridgeEI were 0.28, 0.44 and 0, respectively; in the T3 network, the CS coefficients were 0.36, 0.28 and 0.13, respectively; in the T4 network, the CS coefficients for edge, EI and BridgeEI were 0.59, 0.67 and 0.05, respectively,

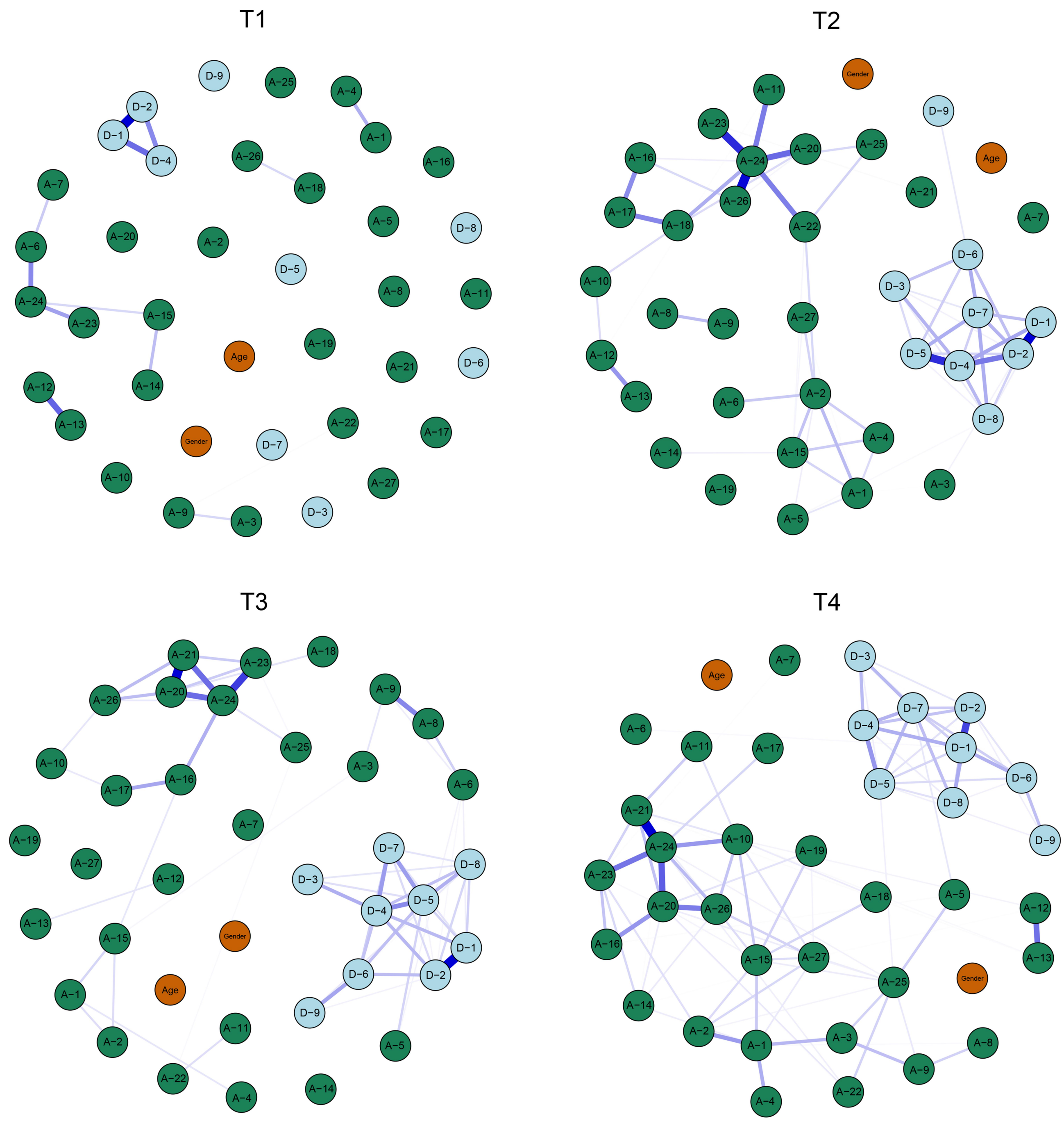

Figure 1 The cross-sectional network structure of negative life events-depression symptoms.

Notes: Blue edges represent positive correlations. The thicker and darker colors of the edge reflect a stronger correlation, and vice versa. Cut value = 0.05. T1 to T4 represents a network of 4 waves of data. The green circles represent life events, the light blue circles represent depressive symptoms, and the orange circles represent covariates gender and age. The text of nodes can be seen in Figure 4.

and all of the CS coefficients for bridgeEI were below the recommended critical values (Figures S2 and S3);.[45,49] We therefore only interpreted the edge and EI values.

We found that the network was relatively sparsely connected for T1 (the number of edge connections was 14), while the connection density of the network gradually increased as time passed (the number of edge connections was 62 for T2, 61 for T3 and 90 for T4). The most strongly connected nodes were D-1 - D-2 and A-12 - A-13 in the T1 network; D-1 - D-2 and A-24 - A-26 in the T2 network; D-1 - D-2 and A-20 - A-21 in the T3 network; A-21 - A-24 and D-1 - D-2 in the

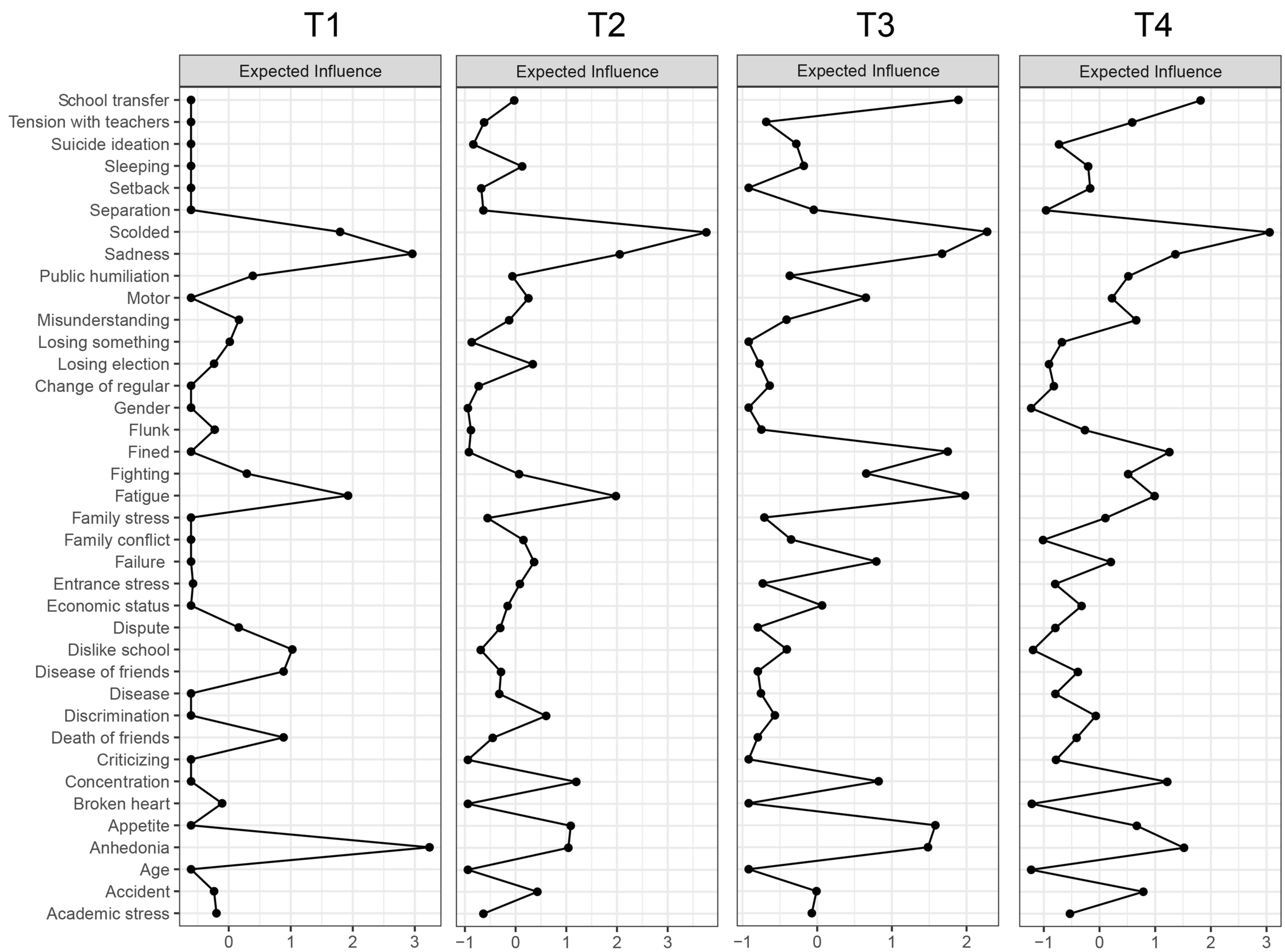

Figure 2 The centrality of expected influence of 4-wave cross-sectional networks (z-score).

T4 network (Figure 1). The nodes with the highest EI values were D-1 and D-2 in the T1 network; A-24, D-1 and D-4 in the T2 network; A-24 and D-4 in the T3 network; A-24 and A-20 in the T4 network (Figure 2).

Cross-Lagged Panel Network

In the T1→T2 network, the nodes with the highest InEI values were A-9 and A-6, and the nodes with the highest OutEI values were A-2 and D-3; in the T2→T3 network, the nodes with the highest InEI values were A-16, A-2 and A-27, and the nodes with the highest OutEI values were A-23 and A-24; in the T3→T4 network, the nodes with the highest InEI values were D-7 and D-9, and the nodes with the highest OutEI values were A-20 and D-6 (Figure 3, Table S1).

Figure 4 shows the cross-lagged panel network. A total of 188 edge connections were identified in the T1→T2 network, where the strongest edges across communities were A-21->D-7, D-6->A-17, D-6->A-6; 175 edge connections were identified in the T2→T3 network, where the strongest edges across communities were A-18->D-4, A-23->D-5, A-11->D-5; 157 edge connections were identified in the T3→T4 network, where the strongest edges across communities were A-20->D-9, A-14->D-3, D-7->A-3 (Table S2, node weights OR values), where the arrows indicate cross-time effects (eg., the arrow from A-21->D-7 indicates the path from A-21 at T1 to D-7 at T2). The thickness of the arrows indicates the strength of these effects (thicker arrows indicate stronger relationships), and the color indicates the direction of the effect (blue arrows indicate positive effects). Low correlation exists between T1→T2 and T2→T3, T2→T3 and T3→T4 network edges (r = 0.037, r = 0.036, respectively).

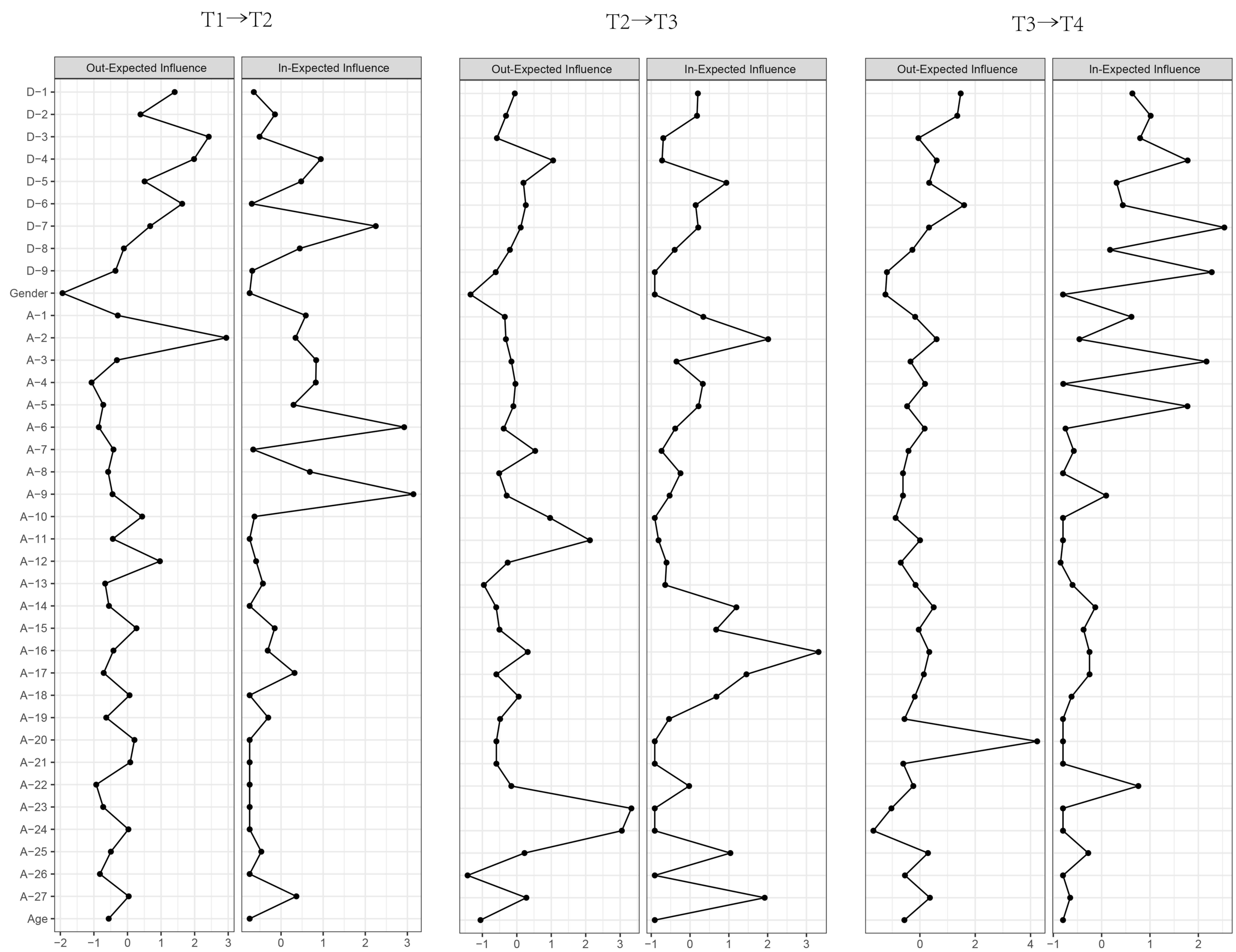

Figure 3 The centrality of in-expected influence and out-expected influence of 4-wave cross-sectional networks (z-score).

There were 41 replicable edges in T1→T2 and T2→T3 networks, accounting for 21.81% of the total number of edges in T1→T2 network and 23.43% of T2→T3 network, respectively. There were 37 replicable edges in T2→T3 and T3→T4 networks, accounting for 21.14% of the total number of edges in T2→T3 network and 23.57% of T3→T4 network, respectively.

The CS coefficients of edge, InEI, OutEI and BridgeEI in the T1→T2 network were 0, 0, 0.36 and 0, respectively, and the stability of edge, InEI and BridgeEI were below the recommended critical values. The edge, InEI, OutEI and BridgeEI in the T2→T3 network were 0, 0, 0.36 and 0, respectively, and the stability of InEI, outEI and BridgeEI was also lower than the recommended critical values. The CS coefficients for edge, InEI, OutEI and BridgeEI in the T3→T4 network were 0.36, 0.36, 0.36 and 0, respectively, and the stability of edge and bridgeEI was lower than the recommended values (Figures S4 and S5).[45,49]

Figure 5 shows the total cross-lagged results. In the T1→T2 network, A-21, A-2 had the greatest impact on depressive symptoms, and D-6 had the greatest impact on negative events. In the T2→T3 network, A-23, A-24 and A-11 had the greatest impact on depressive symptoms. In the T3→T4 network, A-20 had the greatest impact on depressive symptoms. All the nodes mentioned above had low predictability and high influence.[49] Predictability refers to the proportion of variance of a given T2 node in the T1 variables, and the influence refers to the impact of T1 nodes on T2 variables, which did not include the autoregressive effects of a given node or the influence of nodes with the same cluster,[51,52] and so on for other nodes.

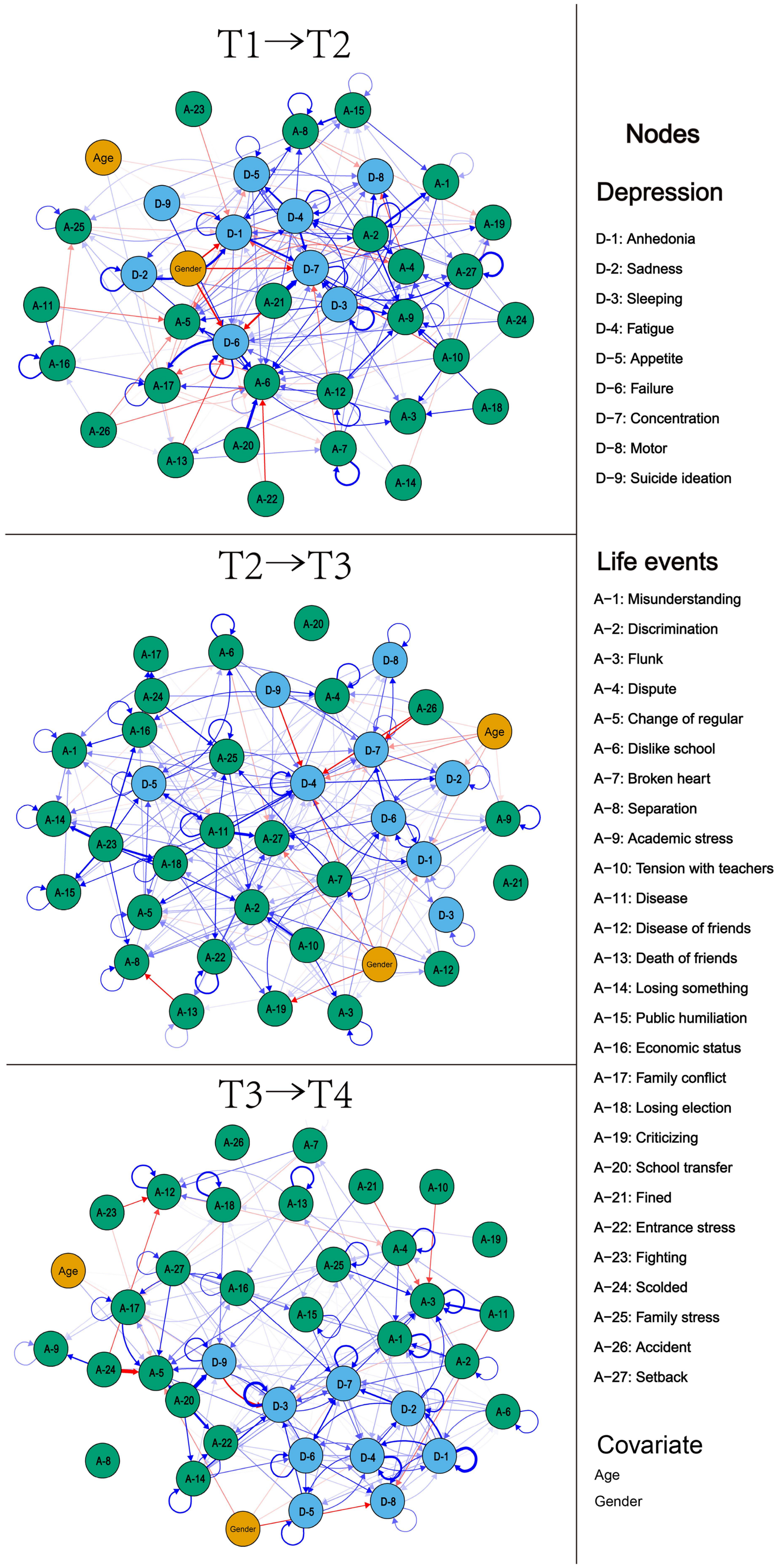

Figure 4 The cross-lagged panel networks of negative life events and depression symptoms.

Notes: Arrows represent unique longitudinal relationships. Blue edges indicate positive correlations, and red edges are negative correlations. The thicker and darker colors of the edge reflect a stronger correlation, and vice versa. The green circles represent life events, the light blue circles represent depressive symptoms, and the orange circles represent covariates gender and age.

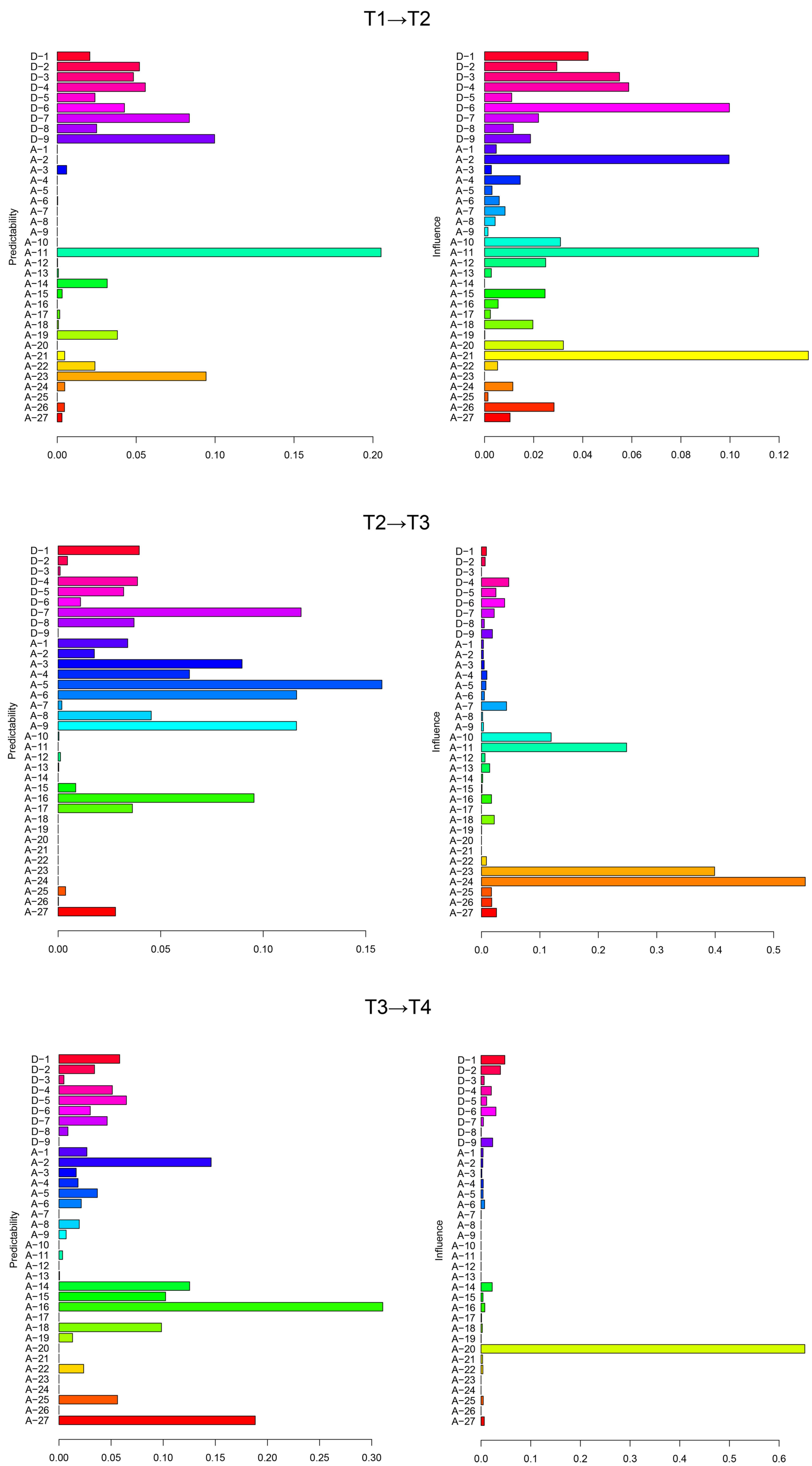

Figure 5 Predictability and influence of cross-lagged panel networks.

Notes: A larger value of the horizontal coordinate means greater centrality. The color is only used as a distinction of nodes with no other implication.

Discussion

Cadets serve as the major reserve combat power of the military. To promote research on this particular group, this study used cross-lagged panel network models to estimate the longitudinal relationship between negative life events and depressive symptoms in medical cadets. Directional estimation using 4-wave longitudinal data complicated the relationship in the time dimension, with negative life events and depressive symptoms among university students becoming progressively more strongly related over time. Multi-wave (≥3 waves) longitudinal data can extend the interrelationship between variables, as in the 2-wave study,[53] eg., T1 negative life events predict T2 depressive symptoms, while T2 depressive symptoms predict T3 negative life events. Modeling the temporal relationship between negative life events and depressive symptoms provides an opportunity to improve the understanding of the pathogenesis of depression and thus facilitate the prevention and intervention.

This study found that the dense connection of the contemporaneous networks of negative life events and depressive symptoms among medical cadets during their university years became stronger with increasing grade levels, and the number of edges in the temporal network was higher than that in the contemporaneous network. This implies that there is a delay in the relationship between negative life events and depressive symptoms; in other words, negative life events and depressive symptoms in the freshman year are more predictive than those in the sophomore year. This delay may explain the higher prevalence of depression among the sophomore (36.7%) compared with the freshmen (26.7%),[54] as well as the increase in depression prevalence with grade.[55] Our study extends the results of many previous studies using cross-sectional survey data,[56] which often examined the undirected relationship between negative life events and depressive symptoms,[57] or used structural equation modeling (SEM) which also typically only included negative life events as predictive variables for depression.[58]

The prevalence of depression would be increasingly high if there is a vicious cycle of negative life events and depressive symptoms. Interestingly, however, the prevalence of depression typically ranges from 9.3% to 55.9%.[59] This might be attributed to the dissolution of certain aspects of this vicious cycle. Taking the death of a family member as an example, the cadets will be no longer faced with such negative life events after the death of a certain number of family members and therefore the consequent effects will disappear, thus affecting the whole cycle. In the current study, for example, A-21 (being fined) is the most important predictive variable in the T1→T2 network, but not in the T2→T3 and T3→T4 networks. These altered life events influence the cadets' health levels.[60]

Overall, for the cross-lagged results, negative life events had a major influence (including A-21 in the T1→T2 network, A-23 and A-24 in the T2→T3 network, and A-20 in the T3→T4 network), indicating that they had the greatest impact on other nodes in the network. This is in line with other studies that have used negative life events as predictive variables.[37,55] However, we found that depressive symptoms were equally influential in the network, for example, D-6 in the T1→T2 network. In fact, our results showed that depressive symptoms of the T1-T2 network had a large lagging effect on subsequent symptoms, while the effects of depressive symptoms of the T2→T3 and T3→T4 networks were relatively small. The role of depressive symptoms as a predictor for negative life events is often overlooked, and our evidence suggests that attention should be paid to the interaction between negative life events and depressive symptoms, especially to depressive symptoms during the freshman year, which is consistent with previous views.[61] However, we do not know whether this lagging effect is present in teenagers, especially during adolescence when the prevalence of depression rises sharply.[62]

In addition, differences were found in the effects of gender on negative life events and depressive symptoms at different stages of the network. The T1 stage had the greatest impact on the T2 stage, and the impact of gender decreased over time. In the early stages, gender mainly affected depressive symptoms, such as D-1 and D-6, while in the later stages, gender began to affect negative life events, such as A-19 and A-27 in T2 → T3 network, and A-5 in T3 → T4 network. We believe that this gender difference is mainly a different response between males and females when faced with these events, such as the response after being criticized or punished (A-19).[63] Previous cross-sectional studies have reported that with the progress of depression, the impact of life events on depression is minimal, while the impact of gender remains significant.[64] In contrast, our study demonstrated that the impact of gender on depression gradually decreased. Considering that previous studies were cross-sectional surveys, the time effect may have been overlooked.

However, due to the limited sample size of this study, further investigations are needed to determine the specific impact of gender on depression.

This study explored the cross-lagged effects of negative life events and depressive symptoms in military medical cadets over a 4-year period. A cross-lagged network model was used to estimate a network of 4-wave longitudinal data, which can help us to identify the direction of the relationship and understand the temporal relationships of these nodes. Since the previous research was focused on cross-sectional data,[57] a growing number of researchers are now advocating the modeling of longitudinal networks.[50,65,66] Our study is an extension of the longitudinal network model, and provides recommendations for prevention and intervention of negative life events and depression among military medical cadets. In addition, the study examined the interaction between the stressor and the disease from a unique perspective, aiming to emphasize that attention should be paid to the influence of the mental illness on the causative factors in order to better understand the underlying mechanisms. Finally, we suggest that school administrators should develop appropriate management systems. For example, a mental health assessment should be conducted for all new college students and a mental health profile should be created. Immediate intervention should be provided for early and prominent psychological symptoms, especially the "D-6 (failure)" of college freshmen. Students' sense of failure can cause a series of negative reactions, such as stigma or labeling,[67] which can affect the subsequent college life. Interventions using supportive counseling programs can improve this situation.[68]

However, this study has several limitations. First, the current sample recruited from a single university is homogeneous, and the sample size is small (433 medical cadets), resulting in some of the indicators in the network not meeting the relevant recommended criteria.[49] Second, although gender and age were chosen as covariates, there are many factors that influence depression which we did not control. This may have influenced the results, especially when the sample size was small. In addition, depressive symptoms and negative life events were evaluated for different durations. In particular, depressive symptoms were evaluated based on subjective rating of participants in the past 2 weeks, which may have been influenced by the individual's mood rather than objective symptoms (as assessed by a psychiatrist). Therefore, in future studies, the main influencing factors should be controlled, the time range for measurement should be balanced, and the sample size should be expanded. Since the stability of some results in this study was lower than the recommended value, the interpretation of the results should be taken discreetly. Finally, our cross-lagged network included a total of 36 nodes, which is higher than the 30 nodes suggested by Epskamp,[39] which may increase the computational difficulty of the software. In conclusion, our study provides new insights into the complex relationship between negative life events and depression in medical cadets, but a large sample of evidence is needed to support this.

Conclusion

This study used a cross-lagged panel network model to estimate the complex longitudinal relationship between negative life events and depressive symptoms over 4 years among military medical cadets. We found that the network models differed across the 4 years and that the interaction of nodal variables was delayed. Furthermore, the evidence for a causal interaction between negative life events and depressive symptoms was extended. Therefore, for interventions targeting depression in medical cadets, attention should be paid to temporal effects as well as dual prevention and interventions of negative life events and depressive symptoms. In particular, A-21, A-20, A-23 and A-24, as well as D-6 showed greater external influence values, implying that these nodes play a very important role in the depression and lives of military medical cadets. Future studies should focus on the correlation between early negative life events and depressive symptoms, particularly in adolescence with large samples.

Abbreviations

PHQ-9, Patient Health Questionnaire; ASLEC, Adolescent self-rating life events checklist; CI, Confidence interval; CS, Correlation stability; GGM, Gaussian graphical model; LASSO, Least Absolute Shrinkage and Selection Operator; EBIC, extended Bayesian information criterion; inEI, in Expected Influence; outEI, out expected Influence; T1, times one, one year; OR, odds ratios.

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Disclosure

The authors report no conflicts of interest in this work.

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