Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Genetic and environmental influences on networks of depression, anxiety, and post-traumatic stress symptoms

Jonathan Coleman

jonathan.coleman@kcl.ac.uk

King's College London https://orcid.org/0000-0002-6759-0944

Jacob Knyspel

Institute of Psychiatry, Psychology & Neuroscience, King's College London https://orcid.org/0000-0001-5600-4826

Chloe Wong

King's College London https://orcid.org/0000-0003-4886-8506

Article

Keywords:

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11484197/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: There is **NO** Competing Interest.

Genetic and environmental influences on networks of depression, anxiety, and post-traumatic stress symptoms

Jacob Knyspel[1], Chloe C.Y. Wong[1,2], Jonathan R.I. Coleman[1,2]

[1] Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, UK

[2] National Institute for Health and Care Research Biomedical Research Centre: Maudsley, South London and Maudsley National Health Service Foundation Trust, UK

Abstract

Network analysis is a popular method for assessing the comorbidity of psychiatric symptoms. Studies have reported inconsistent group differences in symptom networks based on risk factors such as sex and trauma exposure. We conducted the most comprehensive study of group differences in symptom networks to date, analysing nine depression, six anxiety, and three PTSD symptoms in the UK Biobank (N=130,519). We tested group differences based on four polygenic scores and eight demographic/environmental risk factors, using thirteen network comparison metrics. Feelings of worthlessness were the leading bridge symptom, suggesting a central role in explaining or predicting comorbidity. We found significant group differences for eleven risk factors, with sex and childhood trauma showing the broadest patterns. Group differences were greater for symptom relationships within than across conditions. We find broad associations between risk factors and networks of internalising symptoms, which may help foster greater understanding of psychiatric risk and group specific interventions.

Main

Depression, anxiety, and post-traumatic stress disorder (PTSD) are common internalising psychiatric conditions that contribute substantially to the global burden of mental ill-health. In 2019, an estimated 280 million people experienced depressive disorders and 301 million experienced anxiety disorders, corresponding to point prevalences of approximately 3.4% and 3.8% respectively[1]. PTSD is also common following exposure to traumatic events: data from the World Mental Health Surveys indicate a 12-month prevalence of approximately 2.8% among individuals exposed to trauma[2]. These conditions are also highly comorbid. Around 80% of people with PTSD meet criteria for at least one other psychiatric condition[3], with meta-analytic research estimating that 52% also meet criteria for major depressive disorder alone[4]. In the World Mental Health Surveys, 46% of people with lifetime depression also reported a lifetime anxiety disorder, which under the DSM-IV included PTSD[5]. Several studies have estimated that over half of people with a lifetime anxiety disorder also have lifetime depression[6,7]. Comorbidity is clinically important, as the presence of multiple conditions is often associated with greater symptom severity, persistence and functional impairment than the presence of a single disorder[5,7]. Individuals with comorbid PTSD and depression, for example, show greater social, occupational, and cognitive impairment and poorer prognosis than those with PTSD alone[8]. Comorbidity also presents an important challenge for psychiatric research, raising questions about the genetic, environmental, and symptom-level mechanisms that give rise to the co-occurrence of psychiatric conditions. Understanding these mechanisms has therefore become an important focus of research seeking to explain the considerable overlap between depression, anxiety, and PTSD.

Network analysis has become a popular method for assessing relationships among the symptoms of depression, anxiety and PTSD, often with a focus on comorbidity[9]. Rather than

looking at broad diagnostic categories, network analysis focuses on specific symptoms and the pairwise associations among them[10,11]. Symptoms are represented as nodes and their associations as edges. In a partial correlation network, an edge describes the association between two symptoms conditional on the remaining symptoms. Network analyses complement network theories of psychopathology, which view psychiatric conditions as complex systems in which symptoms may causally influence or regulate one another, rather than as manifestations of underlying latent domains[12]. These theories have become especially popular when it comes to internalising conditions[13,14], for which direct causal influences among symptoms might seem particularly intuitive (e.g. nightmares causing loss of sleep and resultant difficulty concentrating[15]). Network analyses do not provide direct evidence for network theories of psychopathology, as these theories typically rely on specific causal assumptions that network analyses do not often meet[16]. Instead, they provide primarily exploratory insight into the observed relationships among symptoms within a given sample. Still, interest in network analysis and interest in network theories have fuelled one another over time, and it is common to see discussion of one with reference to the other.

Depression is a common subject of symptom-level research using network analysis[9]. A systematic review of 58 depression networks from 23 samples identified several highly robust symptom associations, with the most replicable being between the cardinal depression symptoms of depressed mood and anhedonia[17]. Reviews have also identified depressed mood, low energy, and feelings of worthlessness as frequently central symptoms (i.e., symptoms with high relative importance based on their associations), although there has been considerable heterogeneity in which symptoms have ranked highest in centrality across networks[16,17]. This heterogeneity raises concerns about the replicability of key findings from network models, which remains the subject of considerable debate[18,19]. Meta-analytic research has therefore proved invaluable in evaluating networks of internalising symptoms. A

random-effects meta-analysis of PTSD symptom networks across 52 samples (N=29,561) identified a high degree of cross-sample heterogeneity in network estimates[20], reflected by notable differences in reported symptom centrality rankings[21]. The meta-analysed PTSD network did not identify any particular symptoms that were clearly most central. A recent meta-analysis of anxiety symptom (GAD-7) networks across 61 samples (N=303,151) also identified a high degree of heterogeneity, although minimal differences were found in meta-analysed networks between clinical and community samples. The meta-analysed anxiety network identified uncontrollable worry as the most central symptom.

When symptoms of multiple conditions (e.g. depression, anxiety) are examined together, network analysis can provide useful insight into comorbidity at the symptom level[22], by highlighting which pairs of symptoms seem to be particularly related across diagnostic boundaries. Symptoms identified as important in terms of their associations with the symptoms of other conditions are commonly referred to as bridge symptoms, and such importance can be assessed through the use of dedicated bridge centrality statistics[23]. Many studies have applied network analysis to the symptoms of depression, anxiety, and/or PTSD simultaneously, although these have differed notably in bridge symptoms identified[24,25]. A systematic review of combined depression and anxiety networks by Cai and colleagues found that restlessness, depressed mood and psychomotor problems frequently ranked highly in bridge centrality, although across 12 samples, seven different symptoms emerged as the single highest ranking[24], again suggestive of notable between-sample heterogeneity.

Combined networks of depression, anxiety, and PTSD symptoms have been assessed in a broad range of different samples, including trauma exposed adults[26,27], men receiving treatment for domestic violence[28], treatment seeking veterans[29], postpartum women[30], and adults during the COVID-19 pandemic[31]. These studies, which have also differed in specific symptoms examined and network estimation methods used, have again varied in findings. In

their study of 591 treatment seeking veterans, Baker and colleagues explicitly tested bridge centrality among depression, anxiety, and PTSD symptoms, identifying negative emotion and sleep problems as the two highest ranking and generalised worry as the lowest ranking[29]. Bridge symptoms might be particularly useful for theorising how and when comorbidity occurs[22], and perhaps for predicting comorbidity risk based on the presence of these symptoms. A study of 909 trauma exposed adults found that depression and PTSD symptoms identified as bridge symptoms were not necessarily those which overlap in DSM-IV diagnostic criteria[32]. This suggests that network analysis can provide important insight into the nature of psychiatric comorbidity beyond the symptom overlap encoded in existing diagnostic classifications.

Many researchers have investigated whether certain factors might influence group differences in the structure of symptom networks. This has included many of the typical risk factors for psychiatric conditions (e.g., sex, trauma exposure)[33–35] but also factors such as diagnostic status[36,37] and treatment[38]. The intention here has been to assess whether these factors can associate not just with the presence or severity of symptoms, but the relationships among them. The Network Comparison Test[39] has become the most widely adopted method for assessing group differences in network structure. In this method, group labels are permuted to evaluate differences in global strength (the sum of absolute edge values), the maximum difference between edges, and differences in individual edges. The first two of these, global strength difference and maximum edge difference, are considered global metrics, meaning they provide network-level tests of structural differences rather than tests of specific associations. Alternative methods for assessing group differences have included the use of multigroup models[40], moderated network models[41], and Bayesian methods[42,43].

Studies examining group differences in network structure among internalising symptoms have produced mixed results. A few studies have identified differences in

depression symptom connectivity based on lifetime or current diagnostic status[36,37,44], although other studies have not[45]. A study of 515 adults identified greater connectivity among those with persistent depression symptoms two years later[46], suggesting a potential prognostic association. However, a later study of 465 adolescents did not conceptually replicate this association[47]. Findings have also been mixed regarding risk factors for internalising problems. Sex differences in symptom networks have frequently been studied, although null findings have outnumbered positive findings for anxiety[48], depression[35,49,50], and PTSD[51–53]. Yang and colleagues found the network structure of depression symptoms to differ by genetic risk, childhood trauma, and comorbid anxiety among 115,609 adults in the UK Biobank[34]. However, in two clinical cohort studies, one including 5,784 women with recurrent depression[33] and one including 9,713 people with lifetime depression[35], symptom network structure was not found to differ significantly based on genetic/familial risk or adversity.

Several studies have assessed group differences in combined networks of depression, anxiety, and/or PTSD symptoms, providing insight into group differences in comorbidity at the symptom level. Sex differences in combined networks of depression, anxiety, and/or PTSD symptoms have been identified in clinical and community samples[31,54–56]. This has suggested that sex differences in network structure might be more apparent in terms of symptom relationships across conditions than within conditions. Peel and colleagues found there to be greater connectivity in combined networks of depression and anxiety symptoms among self-reporters of adulthood trauma in the UK Biobank. However, this was not the case for childhood trauma and did not replicate in the more clinically severe Genetic Links to Anxiety and Depression cohort[57]. Two studies have identified differences in networks of depression and anxiety symptoms before and after the COVID-19 pandemic[58,59], albeit according to different metrics. Shi and colleagues tested group differences in combined

networks of depression and PTSD symptoms associated with mild traumatic brain injury in 2,797 military veterans, although did not identify any differences[60]. Within a postpartum context, Wang and colleagues tested group differences in depression, anxiety, and stress symptom networks associated with pain in a sample of 1,153 postpartum women[30] but found no significant differences in global network structure, although some symptom centralities differed. Overall, findings regarding group differences in network structure have been mixed and null findings have been common. Discrepancies in findings between studies can plausibly be attributed to a wide range of methodological factors, including differences in sampling, group definitions, symptom measurement, sample size, and statistical methods. Which of these contribute most to differences in findings from group network comparisons is currently unclear.

Identifying reproducible group differences in network structure could help to explain heterogeneity in symptom co-occurrence and generate hypotheses about which relationships warrant closer investigation in particular groups. This in turn could help to refine our understanding of symptom presentations and inform more personalised clinical practice by identifying potential treatment targets[61]. Detectability of group differences in network structure depends on group sizes, effect magnitudes, and estimation choices, and non-significant tests of group differences do not establish network invariance[41]. It is plausible that many studies have been underpowered to detect small group differences in network structure (and power analyses have been rare), although the practical importance of small group differences is also questionable. Most studies have focused on single group differences at a time, which makes systematic comparison of group differences across risk factors challenging. Such systematic comparison is warranted; just as researchers might be interested in understanding which risk factors associate most strongly with symptom severity, so too

might researchers be interested in understanding which risk factors associate most strongly with symptom network structure.

Our aim with this study was to examine associations of a broad range of genetic and environmental/demographic risk factors with the network structure of depression, anxiety, and post-traumatic stress symptoms in a large population-based sample. We used data from 130,519 participants in the UK Biobank[62,63], a population-scale resource drawn from over 500,000 volunteers aged 40–69 in the United Kingdom. We examined a total of eight environmental/demographic risk factors (sex, childhood trauma, adulthood trauma, intimate partner violence, longstanding illness, obesity, vitamin D deficiency, and local deprivation) and four genetic risk factors (polygenic scores for depression, anxiety, PTSD, and height). These were selected because they have strong evidence for associations with internalising mental health problems from umbrella reviews[64–67] (except the polygenic score for height, which was included as a negative control). We used a permutation testing approach to assess group differences in network structure, building upon previous research using this approach[39] by accommodating a wider range of network comparison metrics and differentiating between network comparisons at the within-cluster and between-cluster (bridge) levels.

Results

Symptom descriptives

We analysed a total of 18 self-reported internalising symptoms: nine depression (Patient Health Questionnaire-9; PHQ-9), six anxiety (General Anxiety Disorder-7; GAD-7), and three PTSD (abbreviated PTSD Checklist; PCL). Symptom-level descriptive statistics are reported in Supplementary Table 1. The three most commonly endorsed symptoms were low energy (50.5%), sleep problems (49.3%), and being upset by reminders of stressful experiences (37.9%). All symptoms had positive correlations ranging from .197 to .793 (Supplementary Table 2).

Symptom networks

We estimated sample-wide symptom networks using four methods: non-convex Atan regularisation, Lasso regularisation, alpha level pruning, and a saturated network. The first three methods, which produce sparse networks, varied notably in network density (Atan = 43.8%, Lasso = 71.2%, pruning = 75.8%). The estimated edge matrices from each method are reported in Supplementary Tables 3–6. Here we focus on the Atan regularised model, which is displayed in Figure 1. Among estimated non-zero edges, 40 (59.7%) were within-cluster edges and 27 (40.3%) were bridge edges. Within-cluster edges were stronger than bridge edges on average (median = .129 vs .052). Non-zero edges were stronger within the PTSD cluster (median = .335) than depression (median = .119) or anxiety (median = .148), likely due to the inclusion of only three closely related PTSD symptoms. The three strongest edges were between cardinal symptoms of depression (depressed mood – anhedonia), anxiety (generalized worry – uncontrollable worry), and PTSD (reexperiencing – upset by reminders).

Figure 1 approximately here

We calculated symptom centrality statistics (strength, closeness, betweenness), including centrality statistics based specifically on within-cluster and bridge edges. These centrality statistics are displayed in Figure 2 and reported in full in Supplementary Table 7 (alongside those from the other estimation methods). The most central symptoms varied across statistics, with depressed mood having the greatest strength, trouble concentrating having the greatest closeness, and trouble relaxing having the greatest betweenness. We found that symptoms varied in their relative centrality when separating within-cluster and bridge edges. Spearman rank correlations between the two were -.492 for strength and -.104 for betweenness, indicating that symptoms with greater within-cluster centrality tended to have lower bridge centrality, particularly for strength. The strength of appetite problems, anhedonia, and suicidal ideation was driven almost entirely by connections with other depression symptoms, whereas the strength of other symptoms reflected a mixture of within-cluster and bridge connections.

Figure 2 approximately here

To assess centrality at the edge level, we calculated edge betweenness, which is reported in Supplementary Table 8 (alongside the other estimation methods). The edges with the greatest betweenness values were depressed mood – anhedonia and trouble relaxing – trouble concentrating, indicating that these edges were particularly important for bridging the gap between many symptoms. We also derived a maximum spanning tree (MST) from the network, reducing it to the minimum number of edges required to connect all symptoms while preferentially retaining the strongest edges. This MST is displayed in Figure 3. Among depression symptoms, feelings of worthlessness appeared particularly central in the MST for connecting cognitive/affective (e.g. depressed mood) and somatic (appetite problems, sleep problems, low energy) symptoms. Depression and anxiety symptoms were connected through a single edge (trouble concentrating – trouble relaxing), as were PTSD and anxiety symptoms

(reexperiencing – foreboding), illustrating the importance of these bridge connections. Depression and PTSD symptoms were connected only indirectly in the MST through the anxiety cluster.

Figure 3 approximately here

We ran bootstrapping with 10,000 iterations to estimate edge inclusion probabilities, which signify the stability of individual edges under repeated estimations. In total, 80.6% of non-zero edges had probabilities ≥0.98, indicating high stability. The corresponding proportions were 87.2% for Lasso and 81.0% for pruning. For all edge inclusion probability values, see Supplementary Tables 3–5.

Group comparisons

We examined group differences in network structure associated with 12 risk factors, which are briefly outlined in Table 1. We quantified these group differences based on seven network comparison metrics (see Method for list), three of which were additionally broken down into within-cluster and bridge versions (like symptom centrality), and we used permutation testing with 10,000 iterations to generate p-values. The results of all group comparisons from each network estimation method are reported in Supplementary Table 9. Here we again focus on the Atan regularised models, the significant results from which are presented in Table 2. For estimated networks stratified by risk factors, see Supplementary Tables 10–21.

Table 1 approximately here

Table 2 approximately here

All risk factors except vitamin D deficiency were associated with statistically significant group differences in network structure according to at least one metric, after FDR

correction (156 tests, $q < .05$). Among risk factors, sex was associated with the greatest number of significant group differences (11 out of 13 metrics) and had the largest group difference z-scores among risk factors for 7 metrics. This was closely followed by childhood trauma exposure (10 out of 13 significant), which had the largest z-scores for 3 metrics. Polygenic scores for depression, anxiety, and PTSD all had at least 5 significant group differences, meaning that both environmental and genetic risk factors were associated with group differences in network structure. The polygenic score for height, despite being included as a negative control, was also associated with a significant Jensen-Shannon distance and edge distance. Among network comparison metrics, Jensen-Shannon distance was the most often significant. Global strength differences and edge distances indicated that many risk factors were associated with differences in overall and pairwise symptom connectivity, while node strength distances indicated variability in the relative importance of symptoms. Only sex and childhood trauma were associated with significant group differences in network density, with slightly denser networks among male participants (+7.8%) and participants exposed to childhood trauma (+5.2%). Similarly, only sex and longstanding illness/disability were associated with significant spectral distances, suggesting that differences in higher-order network topology were observed for certain risk factors, but that this was rare.

Group differences based on within-cluster edges were more often significant and had consistently greater z-score values than those based on bridge edges. This meant that symptom connections within clusters were generally more variable than symptom connections across clusters. Based on group specific network estimates (Supplementary Tables 10–21), the greatest variability generally appeared to occur among depression symptoms, with the anxiety and PTSD clusters being more stable across groups. Obesity, local deprivation, and the polygenic scores for depression and anxiety were all associated with significant group differences at the within-cluster level but not the bridge level. Among

the three psychiatric polygenic scores, only the PTSD score was associated with any significant bridge metrics. Consistent with this, group differences in symptom bridge strength were greater on average for the PTSD polygenic score (median difference = .016) than depression (.011) or anxiety (.010) scores. These differences were small and spread out across many symptoms, meaning that no single symptom appeared to explain this unique finding for the PTSD polygenic score.

Discussion

Our aim with this study was to explore the influence of a broad range of genetic and environmental risk factors, selected from umbrella reviews of risk factors for internalising mental health problems, on the network structure of depression, anxiety, and post-traumatic stress symptoms. Through comprehensive analyses of 12 risk factors in a sample of over 130,000 UK Biobank participants, we identified many significant group differences in network structure across multiple complementary metrics. In total, 11 of the 12 risk factors we examined had at least one significant group comparison after correction for multiple testing, with sex and childhood trauma showing the broadest patterns of differences across metrics. We identified group differences based on polygenic scores for depression, anxiety, and PTSD, highlighting associations with both environmental and genetic risk. We found that group comparisons within symptom clusters were more often significant than comparisons between clusters, with obesity, local deprivation, and the polygenic scores for depression and anxiety producing only within-cluster group differences. Overall, our results suggest that associations between risk factors and symptom connectivity are widespread.

Our estimated networks were broadly consistent with those from previous research on internalising symptoms. We identified a clear clustering pattern of depression, anxiety, and PTSD, with notable bridge symptoms connecting these clusters. Feelings of worthlessness emerged as the most prominent bridge symptom, ranking second highest in bridge strength and betweenness and highest in bridge closeness. Other notable bridge symptoms included irritability, trouble relaxing, and depressed mood. This is partly consistent with several studies that have found depressed mood and trouble relaxing to have strong bridge centrality in joint depression/anxiety networks[24]. A prior network analysis of depression, anxiety, and PTSD symptoms by Baker and colleagues found sleep problems to rank highest in bridge centrality among the symptoms we also analysed[29]. This was not replicated in our study,

where sleep problems ranked no higher than sixth in any bridge centrality statistic. Our comparisons of different network estimation methods are consistent with prior research. Through simulations we conducted (see Method), we estimated that Lasso regularisation would result in worse specificity than Atan regularisation given our sample size and network size. This aligns with previous research comparing these particular estimators[68] and provides useful evidence that non-convex regularisation penalties might be preferrable in a psychological network context.

Our group comparisons build upon a literature in which associations between risk factors for internalising symptoms and symptom network structure have been mixed. Two prior studies have examined group differences in internalising symptom networks in the UK Biobank cohort: Peel and colleagues examined depression and anxiety symptoms in 11,120 participants with clinically relevant symptomology[69]; Yang and colleagues examined depression symptoms in 115,609 participants without clinical selection[34]. These two studies are the closest parallels to our own study. Our finding that self-reported childhood and adulthood trauma exposure associated with network structure is consistent with the findings of these studies, although it should be noted that Peel and colleagues only found convincing evidence for an association with adulthood trauma specifically. Like Yang and colleagues, we identified an association between genetic risk and network structure, although we also found strong sex differences across many metrics, which they did not. Discrepancies in findings here could plausibly be due to the inclusion of PTSD symptoms in our analyses, differences in sampling approach (clinical selection versus whole UK Biobank cohort), and differences in estimation methods. That quite similar analyses from the same overarching data source can produce different findings might suggest that group differences in network structure are highly sensitive.

Among all risk factors, we found that sex was associated with the broadest range of group differences in network structure. As discussed previously, findings regarding sex differences in network structure have been mixed. Significant sex differences have more often been identified in joint networks of multiple internalising conditions[54–56] than networks of single conditions[48–53]. One possible this has raised is that sex differences are more pronounced for bridge relationships than those within conditions. However, as with all the other risk factors we investigated, we found that sex differences were stronger for within-cluster metrics than bridge metrics, which does not support this hypothesis. The three edges with the greatest sex differences were all found within the depression cluster (appetite – low energy, worthlessness – depressed mood, anhedonia – depressed mood). Our results therefore do not provide a clear explanation as to why sex differences have varied between these studies, beyond typical sources of between-study heterogeneity. Childhood trauma exposure was associated with the second broadest range of group differences in network structure, again primarily within-cluster differences. A study of 5,942 adults found that networks of depression, anxiety, and PTSD symptoms can differ based on the type of childhood trauma exposure[26] (emotional vs physical vs sexual abuse). There are many features of childhood trauma exposure that could potentially explain these differences, including developmental timing, chronicity, and physical harm to name a few. Additional research examining the role of these features in explaining symptom network differences would thus be worthwhile.

We found that polygenic scores for internalising conditions produced significant group differences according to several metrics, which broadly suggests an association between genetic risk and symptom network structure. We also identified certain differences between polygenic scores. Among the psychiatric polygenic scores, only the PTSD score was associated with significant group differences in bridge metrics. Based on the group specific networks we estimated (Supplementary Table 20), there were not any standout bridge

symptoms/edges that could readily explain these group differences; instead, small group differences accumulated across many edges. Still, this suggests a potential point of departure between polygenic scores for conditions that are otherwise highly genetically correlated[70]. More research is needed to replicate and explain this finding. Ebrahimi and colleagues recently outlined a conceptual framework for examining associations between genetic risk and psychiatric symptom networks[71]. Currently, studies of these associations have been limited to polygenic scores, and so moving forward more precise analyses would be worthwhile, whether at the pathway, gene, or even variant level. Although height polygenic scores were included as a negative control, they were also associated with group differences in symptom network structure, including edge distance and Jensen-Shannon distance. This could reflect pleiotropic genetic influences on height and mental health, residual population stratification, or selection effects, and some caution is therefore warranted when interpreting associations with psychiatric polygenic scores as condition-specific. Alternatively, it could suggest that edge distance and Jensen-Shannon distance are highly sensitive to small associations with symptom severity or network structure that are not necessarily meaningful.

Our findings suggest broad associations between risk factors for psychiatric problems and the connectivity of symptoms, which is a key component of several contemporary theories of psychopathology, including network theories and dynamical systems theories[72]. However, it remains largely unclear what it can mean from a theoretical perspective for a risk factor to associate with symptom connectivity, rather than symptom presence or severity. Future research should seek to further elucidate mechanisms through which risk factors such as trauma exposure or genetics might causally influence symptom connectivity, particularly if this goes beyond simply increasing severity of highly connected symptoms. For example, risk factor exposure might plausibly influence the tendency of particular symptoms to reinforce one another, which could be a within-person dynamic phenomenon[71,72]. This would help to

explain findings that even among people who share overall severity, symptom associations can differ markedly[73]. Intensive longitudinal analyses will be instrumental for investigating possibilities such as this[74], beyond what cross-sectional network analyses can provide. The strength of theories of psychopathology can be evaluated based on their ability to explain the core features of psychiatric conditions[13], and our findings suggest that one of the features that should be explained is the association between risk factors and symptom connectivity.

In addition to theoretical implications, our findings have certain clinical implications. Prediction of clinical outcomes may be improved by incorporating information from findings about group specific symptom networks. As just one example, our finding that feelings of worthlessness had strong bridge centrality suggests that people with depression who express feelings of worthlessness might be at particularly high risk of comorbid anxiety or PTSD symptoms. This is consistent with a longitudinal study of 606 adolescents by Liu and colleagues, which found that feelings of worthlessness played a pivotal role in bridging depression symptoms (namely suicidal ideation) and anxiety symptoms[75]. Other studies have also found feelings of worthlessness to have a central role among comorbid anxiety and/or PTSD symptoms[27,28], although these did not separate within-cluster and bridge centrality. Our findings also suggest that this increased risk of comorbid symptoms in the presence of feelings of worthlessness might be even stronger among people exposed to intimate partner violence (among other risk factors), as bridge centrality was greater in this group. Future research testing whether comorbidity incidence is predicted most strongly by certain symptoms in certain groups would be useful to explore this implication further. Simulated contagion models have suggested that targeting bridge symptoms might be a useful approach to reducing comorbidity incidence[61]. Treatment approaches informed by which specific symptoms are especially central within certain groups might be worth exploring, although generalising group specific findings to within-person dynamics remains a serious challenge in

research[76]. Researchers have also urged caution about interpreting common centrality statistics from cross-sectional networks as indicators of intervention importance[77,78], with simulations suggesting that intervention importance might be better identified through idiographic networks[79], which require intensive longitudinal data[80]. Considerably more research is therefore needed before insights from network analysis could reasonably be implemented in clinical practice.

Our study has several key strengths. Based on the plenitude of data available in the UK Biobank, we investigated a total of 12 risk factors. This allowed for a systematic within-sample comparison among risk factors, which is not possible when studies are limited to a single risk factor such as sex. We selected risk factors based on evidence from umbrella reviews[64–67], ensuring they were highly relevant. The considerable size of the UK Biobank sample also meant that even the smallest group examined (people with vitamin D deficiency) included over 10,000 participants. We adopted seven distinct network comparison metrics for our analyses, three of which (global strength difference, edge distance, node strength distance) we further broke down into within-cluster and bridge versions. Some of these metrics, such as edge distance[81,82] and spectral distance[83], have received little attention in prior mental health research and are not readily provided by existing software such as the "NetworkComparisonTest" *R* package[39]. We found that these metrics provided useful insight into changes in network structure that might be unique to certain risk factors (e.g. spectral distance based on sex and longstanding illness/disability), showing that adopting these metrics can be worthwhile.

This study also has several limitations. Confounding remains an issue when examining group differences in network structure, as both group differences and conditional relationships among symptoms within networks can reflect unobserved common causes, limiting causal interpretation[84]. Future research better equipped to address potential

confounding is needed, such as research using quasi-experimental designs[85,86]. Group comparisons using discordant twin pairs have found differences in networks of depression symptoms based on diagnostic status even after accounting for sources of confounding shared by twins[36,44], demonstrating the value of quasi-experimental designs in this context. More research of this kind across a broader range of risk factors could help determine whether observed group differences are consistent with causal influences of risk factors on symptom connectivity.

We investigated a broad range of risk factors for internalising mental health problems in this study, although these differed in measurement quality based on the data available in the UK Biobank. Obesity and vitamin D deficiency status were derived from physical measurements and blood tests collected during in-person assessments. This provides more systematic ascertainment and is less susceptible to healthcare-related selection bias than the use of electronic health records[87,88], although in-person assessments could have taken place several years before completion of the symptom questionnaires. The obesity or vitamin D deficiency status of participants could therefore have changed during this interval, reducing the precision of group distinctions and potentially attenuating differences in symptom network structure. The predictive performance of polygenic scores for psychiatric conditions remains modest, restricting their ability to capture individual differences in genetic risk, although this is improving as genome-wide association studies increase in sample size and methods for calculating polygenic scores develop[89,90]. Associations between polygenic scores and mental health outcomes can reflect both direct genetic effects and interplay between genetic and environmental risk[91]. Disentangling these remains a key challenge in research using polygenic scores, and caution is warranted when interpreting associations between polygenic scores and symptom network structure as reflecting direct influences of genetic risk.

The generalisability of our findings is limited by participant selection into the UK Biobank and its mental health follow-up questionnaire. Fry and colleagues have found that participants in the UK Biobank are generally healthier and less socioeconomically deprived than the broader sampling population from which they were recruited[92]. The UK Biobank also represents a specific age group (40–69 at recruitment), and it may be inappropriate to extrapolate findings to younger populations. Factors such as age, health, and socioeconomic status are relevant to the measurement of mental health outcomes and can contribute meaningfully to between study heterogeneity. Replication of group differences in independent samples is critical for strengthening our understanding of the relationships between risk factors and symptom networks. Particularly valuable moving forward would be analyses of polygenic scores and symptom networks in populations of non-European genetic ancestries, as these have been rare[33]. Our restriction to participants of European genetic ancestries, although necessary to reduce bias, limits the generalisability of our associations between genetic risk and symptom networks to other ancestry groups. This exemplifies the widely recognised need for increased diversity in research about genetic risk[93].

Overall, our study extends the body of evidence that common risk factors for internalising conditions can associate with the structure of symptom networks. We found this to be the case for many genetic and environmental risk factors, with sex and childhood trauma exposure showing the broadest patterns of associations. We found within-cluster symptom relationships to be more variable between groups than bridge relationships, suggesting that risk factors might relate more to within-condition heterogeneity than comorbidity at the symptom level. Previous findings regarding group differences in network structure have been notably heterogenous, and our findings align with those from some studies yet misalign with those from others. Future research exploring sources of heterogeneity and meta-analysing group differences in network structure is therefore needed.

Understanding associations between risk factors and networks of psychiatric symptoms has the potential to inform our theoretical understanding of symptom co-occurrence and to inform our priorities for clinical research. As we move beyond cross-sectional networks towards move intensive longitudinal and idiographic networks, this understanding should continue to increase.

Method

Sample

We analysed existing symptom and risk factor data from the UK Biobank[63], a prospective cohort that recruited more than 500,000 adults through assessment centres in England, Scotland and Wales during 2006–2010. Baseline assessments combined questionnaires, physical measurements, and biological sampling. An optional online mental health questionnaire, launched in 2016, collected information on current symptoms, lifetime psychiatric problems and adverse experiences[62]. To reduce bias when using polygenic scores, we excluded participants of non-European genetic ancestries and genetically related participants based on a shared relatedness greater than third degree (see Supplementary Method). The resulting sample included 130,519 participants with the symptom data of interest (see below), of whom 45% were male and 55% were female. For detailed information about UK Biobank demographics, we refer to Davis and colleagues[62].

Symptom data

Depression symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9)[94], anxiety symptoms using the Generalized Anxiety Disorder-7 (GAD-7) scale[95], and PTSD symptoms using five items from the abbreviated PTSD Checklist (PCL)[96]. In each of these symptom scales, participants were presented with descriptions of symptoms (e.g. "Feeling down, depressed, or hopeless") and asked to report how often each symptom had bothered them either over the last two weeks (PHQ-9, GAD-7) or over the last month (PCL), with Likert-scale responses ranging either from 1–4 (PHQ-9, GAD-7) or 1–5 (PCL). All symptom scales were administered to UK Biobank participants as part of the 2016 optional mental health follow-up questionnaire[62]. For all symptom scale items and their corresponding UK Biobank field IDs, see Supplementary Method.

We excluded two PCL items (irritability, distance from others) *a priori* because they were gated and including them would have introduced logical dependencies among the items that might bias item correlations[97]. We then used Hittner's method[98] via the "networktools" *R* package[99] to identify redundant items based on dependent zero-order correlations. We excluded one GAD-7 item (restlessness) from this, which was identified as redundant given overlap with one of the PHQ-9 items (psychomotor problems). These exclusions resulted in a total of 18 symptoms: 9 depression (PHQ-9), 6 anxiety (GAD-7) and 3 PTSD (PCL). To reduce bias when using polygenic scores, all symptoms were residualised on genotyping batch and six genomic principal components (see Supplementary Method for details).

Risk factor data

We analysed a total of 12 risk factors, selected based on umbrella reviews of risk factors for internalising conditions[64–67]. This included eight environmental/demographic factors: sex, childhood trauma, adulthood trauma, intimate partner violence, longstanding disability/illness, obesity, vitamin D deficiency, and local deprivation (Townsend index); and four polygenic scores: depression, anxiety, PTSD, and height (which was included as a negative control). For each risk factor, we derived two groups (i.e., exposed versus unexposed) for the purpose of binary group comparisons. A brief overview of each risk factor, including group sizes, is presented in Table 1. For a more detailed explanation of each risk factor, including relevant questionnaire items, UK Biobank field IDs, polygenic scoring procedure, and procedure for deriving groups, see Supplementary Method.

Symptom networks

We estimated symptom networks as Gaussian graphical models. We applied and compared four estimation methods. Our primary method was regularisation with the non-convex arctangent (Atan) penalty[100]. Like other non-convex penalties, the Atan penalty was

designed to overcome certain limitations of the Lasso penalty[101], and simulation research has found Atan regularisation to outperform graphical Lasso regularisation in a psychological network context[68]. We adopted Atan regularisation as our primary method because simulations we conducted (see Supplementary Method) suggested it would provide the best balance of specificity and sensitivity under a range of plausible network densities, given our sample size and number of symptoms. We used the "GGMncv" *R* package[102] to estimate both Atan and Lasso regularised models, applying a fixed penalty value of $\lambda = \sqrt{\log(p)/n}$, where p was the number of symptoms and n was the total sample size. We did not search for an optimal penalty value according to an information criterion because given the considerable sample size relative to number of variables, this would result in undesirably low specificity. To further improve model specificity, we applied a threshold such that values in the estimated precision matrix smaller than $\log(p(p-1)/2)/\sqrt{n}$ were constrained to zero (equivalent to the "threshold" argument of the qgraph::EBICglasso() *R* function[103]). We also estimated networks using the alpha level pruning approach outlined by Williams and Rast[104], starting with a saturated network and dropping non-significant edges based on a Bonferroni corrected alpha level of 0.01/153 = 6.54e-5. Finally, we estimated a saturated network in which all edges were non-zero. All networks were estimated from Spearman correlation matrices. For the three sparse network estimation methods (Atan, Lasso, pruning), we estimated edge inclusion probabilities using non-parametric bootstrapping with 10,000 iterations. These probabilities equal the proportions of bootstrap iterations in which an edge is estimated as non-zero. We applied a highly conservative cutoff of ≥0.98 to signify strong edge stability across iterations.

We calculated symptom centrality statistics using the "qgraph" *R* package[103], including strength, closeness, and betweenness centrality. For an explanation and critical discussion of these statistics, we refer to Bringmann and colleagues[105]. In addition, we

calculated centrality statistics based specifically on within-cluster edges (e.g. D1–D2) and bridge edges (e.g. D1–A1, also known as bridge centrality[23]). This allowed us to assess the centrality of symptoms both within their respective clusters and in terms of their relationships with symptoms from other clusters. We calculated Spearman correlations among within-cluster and bridge centrality statistics to assess the consistency of their symptom rank ordering. We estimated edge betweenness centrality[106], which signifies the tendency of an edge to exist on the shortest path between symptoms, using the "igraph" *R* package[107,108]. We estimated a maximum spanning tree (MST), also with the "igraph" package, using Prim's algorithm for weighted networks[109]. To apply Prim's algorithm to partial correlation networks, edges must be converted to distances such that smaller values correspond greater partial correlations, as the algorithm seeks to minimise distance values. In accordance with Letina and colleagues[110], we calculated distances as $d = \sqrt{2(1-r)}$, where r is a partial correlation value.

Group network comparisons

To assess group differences in network structure, we used a permutation testing approach akin to the Network Comparison Test proposed by van Borkulo and colleagues[39]. For each group comparison (i.e., risk factor), we generated 10,000 permutations in which group labels were randomly shuffled. This generated null distributions of group differences that reflect random chance, which we then compared to our observed group differences to calculate non-parametric z-scores and p-values. We adopted a total of seven global network comparison metrics, including two from the Network Comparison Test: global strength difference and maximum edge difference; and five others: edge distance[81,111], node strength distance, density difference, Jensen-Shannon distance[42], and spectral distance[83,112]. Additionally, we calculated within-cluster and bridge versions of global strength difference, edge distance and node strength distance in order to assess group differences specifically in

terms of within-cluster and bridge edges. For a more detailed description of each network comparison metric with references to relevant literature, see Supplementary Method. We conducted group comparisons with all four network estimation methods, again focusing on Atan regularisation as our primary method.

Authorship contributions

JK: Conceptualisation, formal analysis, visualization, writing – original draft, writing – review & editing. CCYW: Supervision, funding acquisition, writing – review & editing. JRIC: Conceptualisation, funding acquisition, supervision, writing – review & editing.

Data availability

Deidentified data from UK Biobank is available to bona fide researchers submitting an approved project application.

Code availability

Bespoke code underlying the primary analyses in this paper will be made available on publication at https://github.com/ColemanResearchGroup.

Acknowledgements

This research has been conducted using the UK Biobank Resource under Application Number 82087 (PI: JRI Coleman). JK is funded by a PhD studentship from the King's College London Doctoral Training Partnership in Biomedical Sciences (UKRI Ref. 2889009). CCYW and JRIC have received salary support from the National Institute for Health and Care Research (NIHR) Biomedical Research Centre: Maudsley, South London and Maudsley National Health Service (NHS) Foundation Trust and Institute of Psychiatry, Psychology, and Neuroscience, Kings College London. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the UKRI.

Ethics declarations

The UK Biobank operates inside the ethical framework of the UK Health Research Authority and was approved by the North West - Haydock Research Ethics Committee

(11/NW/0382). The UK Biobank is registered as a Research Tissue Bank (North West – Haydock Research Ethics Committee, 21/NW/0157). All data and sample applications may use this ethical clearance to conduct their research. Separate Research Ethics Committee or other ethical clearance is not required. Participants gave consent for their data to be used and can withdraw at any time, with an option to withdraw their existing data from future analysis.

Competing interests

The authors declare no relevant conflicts of interest.

References

1. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* **9**, 137–150 (2022).
2. Koenen, K. C. *et al.* Posttraumatic stress disorder in the World Mental Health Surveys. *Psychol. Med.* **47**, 2260–2274 (2017).
3. Ressler, K. J. *et al.* Post-traumatic stress disorder. *Nat. Rev. Dis. Primer* **12**, 27 (2026).
4. Rytwinski, N. K., Scur, M. D., Feeny, N. C. & Youngstrom, E. A. The Co-Occurrence of Major Depressive Disorder Among Individuals With Posttraumatic Stress Disorder: A Meta-Analysis. *J. Trauma. Stress* **26**, 299–309 (2013).
5. Kessler, R. C. *et al.* Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiol. Psychiatr. Sci.* **24**, 210–226 (2015).
6. Moffitt, T. E. *et al.* Depression and Generalized Anxiety Disorder: Cumulative and Sequential Comorbidity in a Birth Cohort Followed Prospectively to Age 32 Years. *Arch. Gen. Psychiatry* **64**, 651 (2007).
7. Kessler, R. C., DuPont, R. L., Berglund, P. & Wittchen, H.-U. Impairment in Pure and Comorbid Generalized Anxiety Disorder and Major Depression at 12 Months in Two National Surveys. *Am. J. Psychiatry* **156**, 1915–1923 (1999).
8. Flory, J. D. & Yehuda, R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues Clin. Neurosci.* **17**, 141–150 (2015).
9. Robinaugh, D. J., Hoekstra, R. H. A., Toner, E. R. & Borsboom, D. The network approach to psychopathology: a review of the literature 2008–2018 and an agenda for future research. *Psychol. Med.* **50**, 353–366 (2020).

10. Borsboom, D. *et al.* Network analysis of multivariate data in psychological science. *Nat. Rev. Methods Primer* **1**, 58 (2021).
11. Briganti, G. *et al.* Network analysis: An overview for mental health research. *Int. J. Methods Psychiatr. Res.* **33**, e2034 (2024).
12. Borsboom, D. A network theory of mental disorders. *World Psychiatry* **16**, 5–13 (2017).
13. Robinaugh, D. J. *et al.* Advancing the network theory of mental disorders: A computational model of panic disorder. *Psychol. Rev.* **131**, 1482–1508 (2024).
14. Robinaugh, D. J., Hotchkin, C. M., Wright, S. & De Ron, J. Network psychometrics and the network approach to posttraumatic stress disorder: A conceptual and methodological overview. *J. Trauma. Stress* **38**, 363–375 (2025).
15. McNally, R. J. *et al.* Mental Disorders as Causal Systems: A Network Approach to Posttraumatic Stress Disorder. *Clin. Psychol. Sci.* **3**, 836–849 (2015).
16. Huang, D., Susser, E., Rudolph, K. E. & Keyes, K. M. Depression networks: a systematic review of the network paradigm causal assumptions. *Psychol. Med.* **53**, 1665–1680 (2023).
17. Malgaroli, M., Calderon, A. & Bonanno, G. A. Networks of major depressive disorder: A systematic review. *Clin. Psychol. Rev.* **85**, 102000 (2021).
18. Neal, Z. P. *et al.* Critiques of network analysis of multivariate data in psychological science. *Nat. Rev. Methods Primer* **2**, 90 (2022).
19. Neal, Z. P. *et al.* Annotated bibliography of critiques of psychometric network analysis. Preprint at https://doi.org/10.31234/osf.io/ke6qn (2022).
20. Isvoranu, A.-M., Epskamp, S. & Cheung, M. W.-L. Network models of posttraumatic stress disorder: A meta-analysis. *J. Abnorm. Psychol.* **130**, 841–861 (2021).

21. Birkeland, M. S., Greene, T. & Spiller, T. R. The network approach to posttraumatic stress disorder: a systematic review. *Eur. J. Psychotraumatology* **11**, 1700614 (2020).
22. Cramer, A. O. J., Waldorp, L. J., Van Der Maas, H. L. J. & Borsboom, D. Comorbidity: A network perspective. *Behav. Brain Sci.* **33**, 137–150 (2010).
23. Jones, P. J., Ma, R. & McNally, R. J. Bridge Centrality: A Network Approach to Understanding Comorbidity. *Multivar. Behav. Res.* **56**, 353–367 (2021).
24. Cai, H. *et al.* A network model of depressive and anxiety symptoms: a statistical evaluation. *Mol. Psychiatry* **29**, 767–781 (2024).
25. Wichers, M., Riese, H., Hodges, T. M., Snippe, E. & Bos, F. M. A Narrative Review of Network Studies in Depression: What Different Methodological Approaches Tell Us About Depression. *Front. Psychiatry* **12**, 719490 (2021).
26. Jin, Y. *et al.* Co-occurrence of PTSD and affective symptoms in a large sample with childhood trauma subtypes: A network analysis. *Front. Public Health* **11**, 1093687 (2023).
27. Price, M., Legrand, A. C., Brier, Z. M. F. & Hébert-Dufresne, L. The symptoms at the center: Examining the comorbidity of posttraumatic stress disorder, generalized anxiety disorder, and depression with network analysis. *J. Psychiatr. Res.* **109**, 52–58 (2019).
28. Gilbar, O. Examining the boundaries between ICD-11 PTSD/CPTSD and depression and anxiety symptoms: A network analysis perspective. *J. Affect. Disord.* **262**, 429–439 (2020).
29. Baker, L. D. *et al.* Network analysis of PTSD, depression, and anxiety symptom co-occurrence among U.S. veterans seeking treatment. *Eur. J. Trauma Dissociation* **8**, 100447 (2024).
30. Wang, Y., Mao, K., Deng, J. & Gu, J. Comparison of symptoms of depression, anxiety, and stress in postpartum women with and without pain: a network analysis. *BMC Pregnancy Childbirth* **25**, 732 (2025).

31. Hu, J., Huang, Y., Westhoff, M., Ren, Q. & Hofmann, S. G. Mapping Sex Differences in Depression, Anxiety, and Co-Occurring Symptoms in Adults Under Stress: A Bayesian Network Approach. *Depress. Anxiety* **2026**, 6640438 (2026).

32. Afzali, M. H. *et al.* A network approach to the comorbidity between posttraumatic stress disorder and major depressive disorder: The role of overlapping symptoms. *J. Affect. Disord.* **208**, 490–496 (2017).

33. Van Loo, H. M. *et al.* Robust symptom networks in recurrent major depression across different levels of genetic and environmental risk. *J. Affect. Disord.* **227**, 313–322 (2018).

34. Yang, T., Derks, E. M. & Thorp, J. G. Unravelling depression heterogeneity: Exploring the role of external risk factors in symptom network dynamics. *J. Affect. Disord.* **392**, 120112 (2026).

35. Steen, O. D., Van Borkulo, C. D. & Van Loo, H. M. Symptom networks in major depression do not diverge across sex, familial risk, and environmental risk. *J. Affect. Disord.* **294**, 227–234 (2021).

36. Moron, M., Mengel-From, J. & Semkovska, M. Monozygotic twins discordant for depression: An extended network comparison of depressive symptoms, cognitive functions and daily activities. *J. Psychiatr. Res.* **177**, 412–419 (2024).

37. Yokoyama, S. *et al.* Trace of depression: Network structure of depressive symptoms in different clinical conditions. *Eur. Psychiatry* **65**, e20 (2022).

38. Schumacher, L., Burger, J., Echterhoff, J. & Kriston, L. Methodological and statistical practices of using symptom networks to evaluate mental health interventions: A review and reflections. *Multivar. Behav. Res.* **59**, 663–676 (2024).

39. Van Borkulo, C. D. *et al.* Comparing network structures on three aspects: A permutation test. *Psychol. Methods* **28**, 1273–1285 (2023).

40. Epskamp, S. psychonetrics: Structural Equation Modeling and Confirmatory Network Analysis. 0.17.8 https://doi.org/10.32614/CRAN.package.psychonetrics (2019).
41. Haslbeck, J. M. B. Estimating group differences in network models using moderation analysis. *Behav. Res. Methods* **54**, 522–540 (2022).
42. Williams, D. R., Rast, P., Pericchi, L. R. & Mulder, J. Comparing Gaussian graphical models with the posterior predictive distribution and Bayesian model selection. *Psychol. Methods* **25**, 653–672 (2020).
43. Marsman, M., Waldorp, L. J., Sekulovski, N. & Haslbeck, J. Bayes Factor Tests for Group Differences in Ordinal and Binary Graphical Models. *Psychometrika* **90**, 1809–1842 (2025).
44. Semkovska, M. & Liefting, B. Distinct trajectories of symptoms, cognitive functions and daily activities in twins discordant for past depression. *Psychiatry Res.* **356**, 116883 (2026).
45. Hakulinen, C. *et al.* Network structure of depression symptomology in participants with and without depressive disorder: the population-based Health 2000–2011 study. *Soc. Psychiatry Psychiatr. Epidemiol.* **55**, 1273–1282 (2020).
46. Van Borkulo, C. *et al.* Association of Symptom Network Structure With the Course of Depression. *JAMA Psychiatry* **72**, 1219 (2015).
47. Schweren, L., Van Borkulo, C. D., Fried, E. & Goodyer, I. M. Assessment of Symptom Network Density as a Prognostic Marker of Treatment Response in Adolescent Depression. *JAMA Psychiatry* **75**, 98 (2018).
48. Belli, S. R., Tichelaar, M., Epskamp, S., Ebrahimi, O. V. & O'Driscoll, C. A systematic review and Meta-Analytic Gaussian Network Aggregation of anxious symptoms. *Clin. Psychol. Rev.* **127**, 102763 (2026).

49. Izquierdo, A. *et al.* Sex differences in the symptom network structure of depression: Findings from a nationwide sample of the Spanish adult population. *J. Affect. Disord.* **340**, 583–591 (2023).

50. Vetter, J. S. *et al.* Sex differences in depressive symptoms and their networks in a treatment-seeking population – a cross-sectional study. *J. Affect. Disord.* **278**, 357–364 (2021).

51. Rønning, L. *et al.* Gender differences in early posttraumatic stress disorder symptoms: a network analysis. *Eur. J. Psychotraumatology* **16**, 2448385 (2025).

52. Birkeland, M. S., Blix, I., Solberg, Ø. & Heir, T. Gender Differences in Posttraumatic Stress Symptoms after a Terrorist Attack: A Network Approach. *Front. Psychol.* **8**, 2091 (2017).

53. Gay, N. G., Wisco, B. E., Jones, E. C. & Murphy, A. D. Posttraumatic Stress Disorder Symptom Network Structures: A Comparison Between Men and Women. *J. Trauma. Stress* **33**, 96–105 (2020).

54. Wu, D., Shi, Z., Wu, C., Sun, W. & Jin, G. Sex differences in symptom network structure of depression, anxiety, and self-efficacy among people with diabetes: a network analysis. *Front. Public Health* **12**, 1368752 (2024).

55. Dong, B. *et al.* A network analysis study of anxiety, depression and loneliness among middle-aged and elderly people in Xining area. *BMC Psychol.* **13**, 931 (2025).

56. Dong, S.-W. *et al.* Sex and age differences in depression and anxiety networks among adolescents with idiopathic scoliosis: A network analysis. *World J. Psychiatry* **15**, (2025).

57. Davies, M. R. *et al.* The Genetic Links to Anxiety and Depression (GLAD) Study: Online recruitment into the largest recontactable study of depression and anxiety. *Behav. Res. Ther.* **123**, 103503 (2019).

58. Yu, J. & Mahendran, R. COVID-19 lockdown has altered the dynamics between affective symptoms and social isolation among older adults: results from a longitudinal network analysis. *Sci. Rep.* **11**, 14739 (2021).

59. Liu, T. *et al.* Comparison of networks of loneliness, depressive symptoms, and anxiety symptoms in at-risk community-dwelling older adults before and during COVID-19. *Sci. Rep.* **14**, 14737 (2024).

60. Shi, S., Almklov, E., Afari, N. & Pittman, J. O. E. Symptoms of major depressive disorder and post-traumatic stress disorder in veterans with mild traumatic brain injury: A network analysis. *PLOS ONE* **18**, e0283101 (2023).

61. Jones, P. J., Ma, R. & McNally, R. J. Bridge Centrality: A Network Approach to Understanding Comorbidity. *Multivar. Behav. Res.* **56**, 353–367 (2021).

62. Davis, K. A. S. *et al.* Mental health in UK Biobank – development, implementation and results from an online questionnaire completed by 157 366 participants: A reanalysis. *BJPsych Open* **6**, (2020).

63. Sudlow, C. *et al.* UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLOS Med.* **12**, e1001779 (2015).

64. Fullana, M. A. *et al.* Risk and protective factors for anxiety and obsessive-compulsive disorders: an umbrella review of systematic reviews and meta-analyses. *Psychol. Med.* **50**, 1300–1315 (2020).

65. Hazzard, V. M. *et al.* Identifying transdiagnostically relevant risk and protective factors for internalizing psychopathology: An umbrella review of longitudinal meta-analyses. *J. Psychiatr. Res.* **158**, 231–244 (2023).

66. Köhler, C. A. *et al.* Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies. *J. Psychiatr. Res.* **103**, 189–207 (2018).

67. Tortella-Feliu, M. *et al.* Risk factors for posttraumatic stress disorder: An umbrella review of systematic reviews and meta-analyses. *Neurosci. Biobehav. Rev.* **107**, 154–165 (2019).

68. Williams, D. R. Beyond Lasso: A Survey of Nonconvex Regularization in Gaussian Graphical Models. Preprint at https://doi.org/10.31234/osf.io/ad57p (2020).

69. Peel, A. J. *et al.* Comparison of depression and anxiety symptom networks in reporters and non-reporters of lifetime trauma in two samples of differing severity. *J. Affect. Disord. Rep.* **6**, 100201 (2021).

70. Grotzinger, A. D. *et al.* Mapping the genetic landscape across 14 psychiatric disorders. *Nature* **649**, 406–415 (2026).

71. Ebrahimi, O. V., Nivard, M. G. & Bjørndal, L. D. Towards a genetics of mental disorders as complex dynamical systems: A symptom-specific and symptom-interactive approach. Preprint at https://doi.org/10.31234/osf.io/ukcfq_v1 (2026).

72. Scheffer, M. *et al.* A Dynamical Systems View of Psychiatric Disorders—Theory: A Review. *JAMA Psychiatry* **81**, 618 (2024).

73. Ebrahimi, O. V. *et al.* Towards precision in the diagnostic profiling of patients: leveraging symptom dynamics as a clinical characterisation dimension in the assessment of major depressive disorder. *Br. J. Psychiatry* **224**, 157–163 (2024).

74. Scheffer, M. *et al.* A Dynamical Systems View of Psychiatric Disorders—Practical Implications: A Review. *JAMA Psychiatry* **81**, 624 (2024).

75. Liu, D., Yu, M., Zhang, X., Cui, J. & Yang, H. Adolescent anxiety and depression: perspectives of network analysis and longitudinal network analysis. *BMC Psychiatry* **24**, 619 (2024).

76. Fisher, A. J., Medaglia, J. D. & Jeronimus, B. F. Lack of group-to-individual generalizability is a threat to human subjects research. *Proc. Natl. Acad. Sci.* **115**, (2018).

77. Dablander, F. & Hinne, M. Node centrality measures are a poor substitute for causal inference. *Sci. Rep.* **9**, 6846 (2019).

78. Spiller, T. R. *et al.* On the validity of the centrality hypothesis in cross-sectional between-subject networks of psychopathology. *BMC Med.* **18**, 297 (2020).

79. Castro, D., Gysi, D., Ferreira, F., Ferreira-Santos, F. & Ferreira, T. B. Centrality measures in psychological networks: A simulation study on identifying effective treatment targets. *PLOS ONE* **19**, e0297058 (2024).

80. Mansueto, A. C., Wiers, R. W., Van Weert, J. C. M., Schouten, B. C. & Epskamp, S. Investigating the feasibility of idiographic network models. *Psychol. Methods* **28**, 1052–1068 (2023).

81. Ulitzsch, E., Khanna, S., Rhemtulla, M. & Domingue, B. W. A graph theory based similarity metric enables comparison of subpopulation psychometric networks. *Psychol. Methods* https://doi.org/10.1037/met0000625 (2023) doi:10.1037/met0000625.

82. Johal, S., Bondurant, N., Ulitzsch, E. & Rhemtulla, M. A Permutation-Based Network Invariance Test Using the Network Similarity Metric. Preprint at https://doi.org/10.31234/osf.io/p57zr_v1 (2026).

83. Wilson, R. C. & Zhu, P. A study of graph spectra for comparing graphs and trees. *Pattern Recognit.* **41**, 2833–2841 (2008).

84. Ryan, O., Bringmann, L. F. & Schuurman, N. K. The Challenge of Generating Causal Hypotheses Using Network Models. *Struct. Equ. Model. Multidiscip. J.* **29**, 953–970 (2022).

85. D'Onofrio, B. M., Lahey, B. B., Turkheimer, E. & Lichtenstein, P. Critical Need for Family-Based, Quasi-Experimental Designs in Integrating Genetic and Social Science Research. *Am. J. Public Health* **103**, S46–S55 (2013).

86. D'Onofrio, B. M., Sjölander, A., Lahey, B. B., Lichtenstein, P. & Öberg, A. S. Accounting for Confounding in Observational Studies. *Annu. Rev. Clin. Psychol.* **16**, 25–48 (2020).

87. Gianfrancesco, M. A. & Goldstein, N. D. A narrative review on the validity of electronic health record-based research in epidemiology. *BMC Med. Res. Methodol.* **21**, 234 (2021).

88. Kundu, R., Shi, X., Morrison, J., Barrett, J. & Mukherjee, B. A framework for understanding selection bias in real-world healthcare data. *J. R. Stat. Soc. Ser. A Stat. Soc.* **187**, 606–635 (2024).

89. Lewis, C. M. & Vassos, E. Polygenic Scores in Psychiatry: On the Road From Discovery to Implementation. *Am. J. Psychiatry* **179**, 800–806 (2022).

90. Plomin, R. & Von Stumm, S. Polygenic scores: prediction versus explanation. *Mol. Psychiatry* **27**, 49–52 (2022).

91. Pingault, J. *et al.* Research Review: How to interpret associations between polygenic scores, environmental risks, and phenotypes. *J. Child Psychol. Psychiatry* **63**, 1125–1139 (2022).

92. Fry, A. *et al.* Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am. J. Epidemiol.* **186**, 1026–1034 (2017).

93. Fatumo, S. *et al.* A roadmap to increase diversity in genomic studies. *Nat. Med.* **28**, 243–250 (2022).

94. Kroenke, K., Spitzer, R. L. & Williams, J. B. W. The PHQ-9: Validity of a brief depression severity measure. *J. Gen. Intern. Med.* **16**, 606–613 (2001).

95. Spitzer, R. L., Kroenke, K., Williams, J. B. W. & Löwe, B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. *Arch. Intern. Med.* **166**, 1092 (2006).

96. Lang, A. J. *et al.* Abbreviated PTSD Checklist (PCL) as a guide to clinical response. *Gen. Hosp. Psychiatry* **34**, 332–338 (2012).

97. Borsboom, D. *et al.* False alarm? A comprehensive reanalysis of "Evidence that psychopathology symptom networks have limited replicability" by Forbes, Wright, Markon, and Krueger (2017). *J. Abnorm. Psychol.* **126**, 989–999 (2017).

98. Hittner, J. B., May, K. & Silver, N. C. A Monte Carlo Evaluation of Tests for Comparing Dependent Correlations. *J. Gen. Psychol.* **130**, 149–168 (2003).

99. Jones, P. networktools: Tools for Identifying Important Nodes in Networks. 1.6.0 https://doi.org/10.32614/CRAN.package.networktools (2017).

100. Wang, Y. & Zhu, L. Variable Selection and Parameter Estimation with the Atan Regularization Method. *J. Probab. Stat.* **2016**, 1–12 (2016).

101. Tibshirani, R. Regression Shrinkage and Selection Via the Lasso. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **58**, 267–288 (1996).

102. Williams, D. R. GGMncv: Nonconvex Penalized Gaussian Graphical Models in R. Preprint at https://doi.org/10.31234/osf.io/6jz5m (2020).

103. Epskamp, S., Cramer, A. O. J., Waldorp, L. J., Schmittmann, V. D. & Borsboom, D. qgraph: Network Visualizations of Relationships in Psychometric Data. *J. Stat. Softw.* **48**, (2012).

104. Williams, D. R. & Rast, P. Back to the basics: Rethinking partial correlation network methodology. *Br. J. Math. Stat. Psychol.* **73**, 187–212 (2020).

105. Bringmann, L. F. *et al.* What do centrality measures measure in psychological networks? *J. Abnorm. Psychol.* **128**, 892–903 (2019).

106. Brandes, U. On variants of shortest-path betweenness centrality and their generic computation. *Soc. Netw.* **30**, 136–145 (2008).
107. Antonov, M. *et al.* igraph 1.0 enables fast and robust network analysis across programming languages. *PLOS One* **21**, e0355108 (2026).
108. Csárdi, G. *et al.* igraph for R: R interface of the igraph library for graph theory and network analysis. Zenodo https://doi.org/10.5281/ZENODO.7682609 (2026).
109. Prim, R. C. Shortest Connection Networks And Some Generalizations. *Bell Syst. Tech. J.* **36**, 1389–1401 (1957).
110. Letina, S., Blanken, T. F., Deserno, M. K. & Borsboom, D. Expanding Network Analysis Tools in Psychological Networks: Minimal Spanning Trees, Participation Coefficients, and Motif Analysis Applied to a Network of 26 Psychological Attributes. *Complexity* **2019**, 9424605 (2019).
111. Johal, S., Bondurant, N., Ulitzsch, E. & Rhemtulla, M. A Permutation-Based Network Invariance Test Using the Network Similarity Metric. Preprint at https://doi.org/10.31234/osf.io/p57zr_v1 (2026).
112. Wills, P. & Meyer, F. G. Metrics for graph comparison: A practitioner's guide. *PLOS ONE* **15**, e0228728 (2020).

Table 1

Overview of risk factors subject to group comparisons.

Risk factor	Brief description
Sex	Male (N=57,054) vs female (N=73,465) participants based on electronic health records or self-report.
Childhood trauma	Self-reported exposed (N=28,761) vs unexposed (N=101,758) based on five-item Childhood Trauma Screener.
Adulthood trauma	Self-reported exposed (N=65,579) vs unexposed (N=64,940) based on six-item checklist.
Intimate partner violence	Self-reported exposed (N=50,859) vs unexposed (N=79,660) based on four-item checklist.
Longstanding disability/illness	Self-reported as having (N=43,793) vs not having (N=86,726) a longstanding disability or illness.
Obesity	Screened as having (N=27,288) or not having (N=103,231) obesity based on physical measurements (BMI > 30).
Vitamin D deficiency	Screened as vitamin D deficient (N=14,308) or not deficient (N=109,310) based on blood measurements (count < 25nmol/L).
Local deprivation	Above (N=57,057) or below (N=73,462) the UKB median Townsend deprivation index.
Depression PGS	Above (N=61,290) or below (N=69,229) the UKB median depression polygenic score (excluding non-European ancestries).
Anxiety PGS	Above (N=62,241) or below (N=68,278) the UKB median anxiety polygenic score (excluding non-European ancestries).
PTSD PGS	Above (N=61,113) or below (N=69,406) the UKB median PTSD polygenic score (excluding non-European ancestries).
Height PGS	Above (N=67,520) or below (N=62,999) the UKB median height polygenic score (excluding non-European ancestries).

Note. PGS = Polygenic score; UKB = UK Biobank. For a detailed explanation of each risk factor, including relevant UKB field IDs, see Supplementary Method.

Table 2

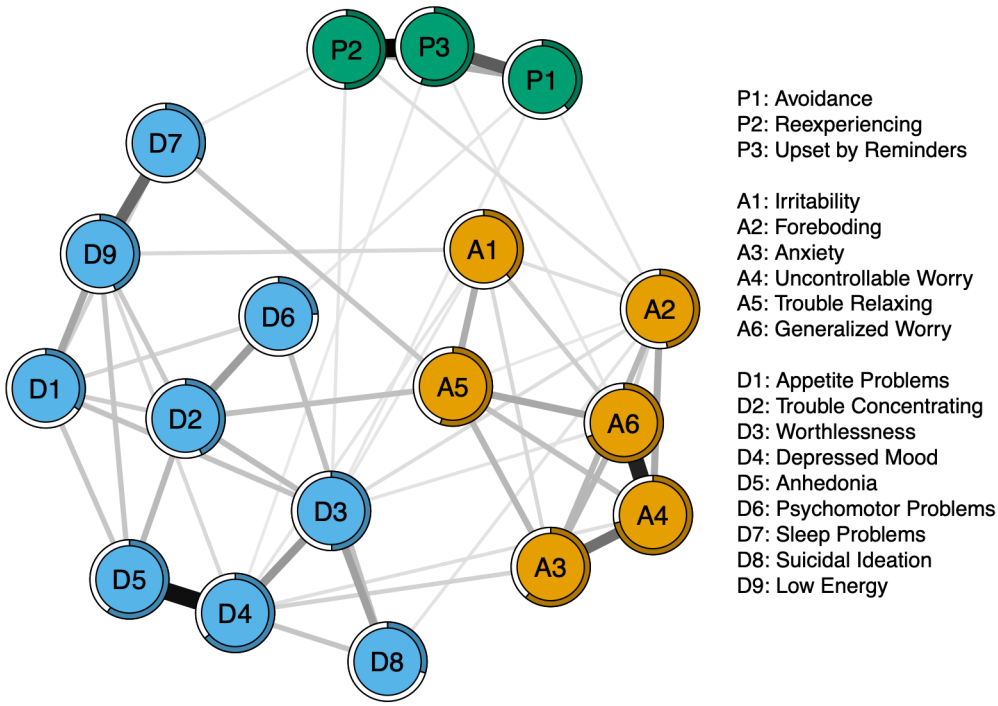
Statistical significance (FDR corrected) of group differences in network structure across risk factors.

	Global strength difference			**Edge distance**			**Node strength distance**			**Density difference**	**Maximum edge difference**	**Spectral distance**	**Jensen-Shannon distance**
	All edges	*Within cluster*	*Bridge*	*All edges*	*Within cluster*	*Bridge*	*All edges*	*Within cluster*	*Bridge*				
Sex		✓	✓*	✓*	✓*	✓*	✓	✓		✓*	✓*	✓*	✓
Childhood trauma	✓	✓*		✓	✓		✓*	✓*	✓	✓	✓		✓
Adulthood trauma	✓	✓		✓	✓	✓	✓	✓	✓*				✓
Intimate partner violence	✓*	✓		✓	✓		✓	✓	✓		✓		✓*
Longstanding disability/illness	✓	✓		✓	✓		✓	✓	✓			✓	✓
Obesity	✓	✓		✓	✓			✓			✓		✓
Vitamin D deficiency													
Local deprivation	✓	✓					✓	✓					✓
Depression PGS	✓	✓					✓	✓					✓
Anxiety PGS	✓	✓					✓	✓					✓
PTSD PGS	✓	✓				✓	✓	✓	✓				✓
Height PGS				✓	✓	✓							✓

Note. FDR = False Discovery Rate; PGS = Polygenic score. The group comparisons reported here are based on networks estimated using Atan regularisation. A tick symbol (✓) indicates that a group difference was statistically significant after FDR correction for 156 tests ($q < .05$). An asterisk (*) indicates that a group difference was the largest one observed for that metric. For metric z-scores and p-values, and for group comparisons using other network estimators, see Supplementary Table 9. Bridge edges are those among symptoms of different clusters (e.g. D1–A1). Within-cluster edges are those among symptoms of the same cluster (e.g. D1–D2). For a technical description of all metrics, see Supplementary Method.

Figure 1

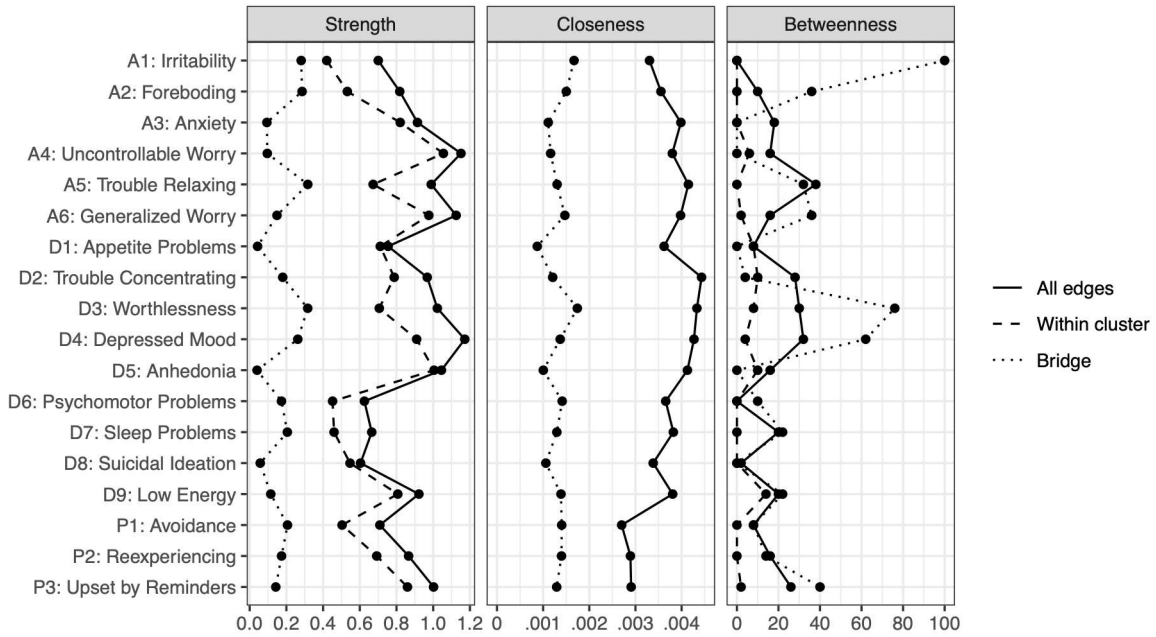
Sample-wide symptom network estimated using Atan regularisation (N=130,519)



Note. A = Anxiety; D = Depression; P = PTSD. Network layout was generated using the Fruchterman-Reingold algorithm. Only edges with bootstrapped edge inclusion probabilities ≥0.98 are displayed. Pie charts represent symptom predictability (R^2, see Supplementary Table 5). All edges are positive. For edge values and edge inclusion probabilities, see Supplementary Table 3.

Figure 2

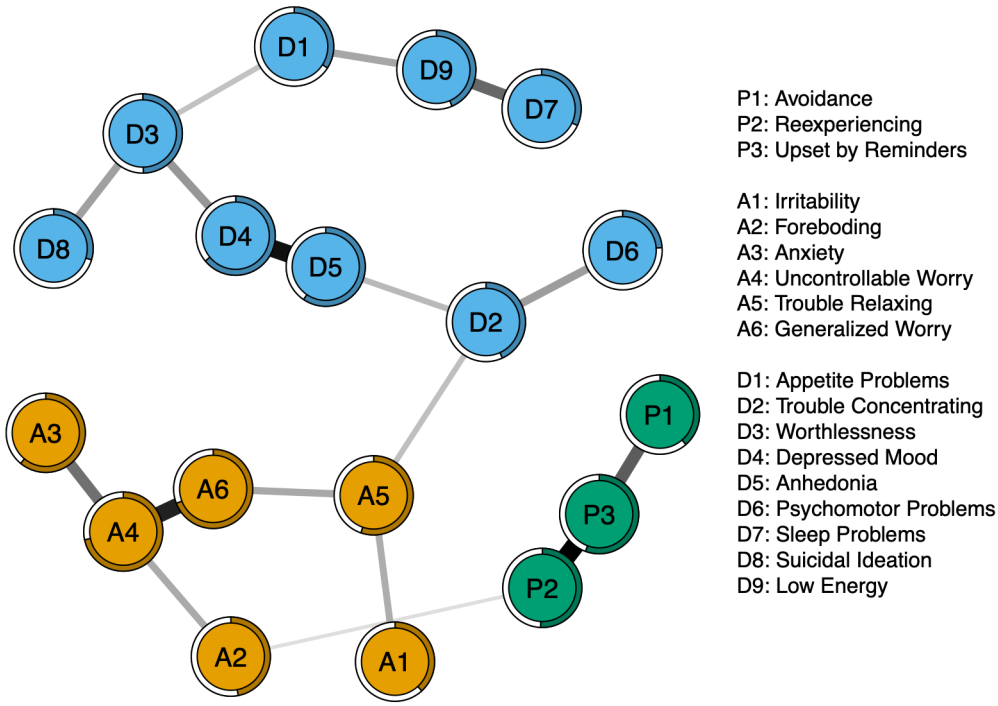
Centrality statistics calculated from the sample-wide symptom network (N=130,519)



Note. A = Anxiety; D = Depression; P = PTSD. Within-cluster edges are those among symptoms of the same cluster (e.g. D1–D2). Closeness centrality is not defined for within-cluster edges. Bridge edges are those among symptoms of different clusters (e.g. D1–A1). For all centrality statistic values, see Supplementary Table 7.

Figure 3

Maximum spanning tree estimated from sample-wide symptom network (N=130,519)



Note. A = Anxiety; D = Depression; P = PTSD. Network layout was generated using the Fruchterman-Reingold algorithm. Pie charts represent symptom predictability (R^2) calculated from the sample-wide network (see Supplementary Table 7). All edges are positive.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- nhbsupptables.xlsx
- table2.docx
- table1.docx
- nhbsuppmethod20261015.pdf