Supplementary Method

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1. Symptom data

1a. Depression (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Item	UKB field ID	Included?	Label
Poor appetite or overeating.	20511	Yes	D1
Trouble concentrating on things, such as reading the newspaper or watching television.	20508	Yes	D2
Feeling bad about yourself or that you are a failure or have let yourself or your family down.	20507	Yes	D3
Feeling down, depressed, or hopeless.	20510	Yes	D4
Little interest or pleasure in doing things.	20514	Yes	D5
Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	20518	Yes	D6
Trouble falling or staying asleep or sleeping too much.	20517	Yes	D7
Thoughts that you would be better off dead or of hurting yourself in some way.	20513	Yes	D8
Feeling tired or having little energy.	20519	Yes	D9

Note. Response options for all items were as follows: “Not at all”, “Several days”, “More than half the days”, “Nearly every day”.

1b. Anxiety (GAD-7)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Item	UKB field ID	Included?	Label
Becoming easily annoyed or irritable.	20505	Yes	A1
Feeling afraid as if something awful might happen.	20512	Yes	A2
Feeling nervous, anxious or on edge.	20506	Yes	A3
Not being able to stop or control worrying.	20509	Yes	A4
Trouble relaxing.	20515	Yes	A5
Worrying too much about different things.	20520	Yes	A6
Being so restless that it is hard to sit still.	20516	No - redundant due to overlap with D6	

Note. Response options for all items were as follows: "Not at all", "Several days", "More than half the days", "Nearly every day". Symptom redundancy due to overlap was assessed using the goldbricker() function from the "networktools" *R* package[1].

1c. Post-traumatic stress disorder (PCL)

Next is a list of problems and complaints that people sometimes have in response to such extremely stressful experiences. Please indicate how much you have been bothered by that problem in the past month:

Item	UKB field ID	Included?	Label
Avoiding activities or situations because they reminded you of a stressful experience.	20495	Yes	P1
Repeated, disturbing memories, thoughts, or images of a stressful experience.	20497	Yes	P2
Feeling very upset when something reminded you of a stressful experience.	20498	Yes	P3
Feeling distant or cut off from other people.	20496	No - gated item	
Feeling irritable or having angry outbursts.	20494	No - gated item	

Note. Response options for all items were as follows: "Not at all", "A little bit", "Moderately", "Quite a bit", "Extremely". Gated items were excluded to avoid logical dependencies among symptoms.

1d. Symptom data processing

To reduce bias when testing associations between polygenic scores and symptoms, we residualized symptoms on genotyping batch [UKB field 22000] and six genomic principal components [UKB field 22009]. As symptom data were ordinal, we ran ordinal logistic regression models using the "MASS" *R* package[2] and estimated surrogate residuals using the "sure" *R* package[3]. These residuals were then used for network analyses.

2. Risk factor data and definitions

2a. Sex

We used sex reported at UK Biobank baseline [UKB field 31]. This was acquired primarily from NHS records at recruitment, but in some cases was updated by the participant during the initial assessment visit. In total there were 57,054 male and 73,465 female participants with symptom data.

2b. Childhood trauma exposure

We derived childhood trauma exposure from responses to the Childhood Trauma Screener[4] [UKB fields 20487-20491]. This screener includes single-item descriptions of five potentially traumatic experiences in childhood (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect). Participants were asked to report how true each of these descriptions was to their childhood, with response options ranging from "never true" to "very often true". We considered participants childhood trauma exposed if they met exposure cutoffs for any item (see below), which were adopted from previous literature[5]. This resulted in 28,761 childhood trauma exposed and 101,758 unexposed participants.

When I was growing up…

	Never	Rarely	Sometimes	Often	Very Often
I felt loved. [20489]	Exposed				
People in my family hit me so hard that it left me with bruises or marks. [20488]			Exposed		
I felt that someone in my family hated me. [20487]			Exposed		
Someone molested me (sexually). [20490]		Exposed			
There was someone to take me to the doctor if I needed it. [20491]	Exposed				

2c. Adulthood trauma exposure

We derived adulthood trauma exposure from responses to a brief six-item checklist [UKB fields 20526-20531]. Participants were asked to report whether they had ever experienced six potentially traumatic experiences (serious accident, serious illness, sexual assault, violent crime, war exposure, witnessing death). We considered participants adulthood trauma exposed if they responded yes to any item (within the last 12 months or otherwise). This resulted in 65,579 adulthood trauma exposed and 64,940 unexposed participants.

In your life, have you…?

Never	Yes, within the last 12 months	Yes, but not in the last 12 months

Been a victim of a sexual assault, whether by a stranger or someone you knew. [20531]	Exposed
Been attacked, mugged, robbed, or been the victim of a physically violent crime. [20529]	Exposed
Been in a serious accident that you believe to be life-threatening at the time. [20526]	Exposed
Been diagnosed with a life-threatening illness. [20528]	Exposed
Been involved in combat or exposed to a war-zone (either in the military or as a civilian). [20527]	Exposed
Witnessed a sudden violent death (e.g. murder, suicide, aftermath of an accident). [20530]	Exposed

2d. Intimate partner violence exposure

We derived intimate partner violence (IPV) exposure from responses to a brief four-item checklist [UKB fields 20521-20524]. Participants were presented with descriptions of partner violence and confiding relationships and asked to report how true each of these were to their lives, with response options ranging from "never true" to "very often true". We considered participants IPV exposed if they met exposure cutoffs for any item (see below). This resulted in 50,859 IPV exposed and 79,660 unexposed participants.

Since I was sixteen…

	Never	Rarely	Sometimes	Often	Very Often
I have been in a confiding relationship. [20522]	Exposed				
A partner or ex-partner deliberately hit me or used violence in any other way. [20523]			Exposed		
A partner or ex-partner repeatedly belittled me to the extent that I felt worthless. [20521]			Exposed		

A partner or ex-partner sexually interfered with me or forced me to have sex against my wishes. [20524]	Exposed

2e. Longstanding illness/disability

We derived longstanding illness/disability from a single self-report question ("Do you have any long-standing illness, disability or infirmity?") asked to participants during in-person assessment visits [UKB field 2188]. We considered participants to have longstanding illness/disability if they responded yes to this question in any assessment visit they had prior to completing symptom questionnaires. Assessment visits which took place after participants completed the symptom questionnaires were excluded. In total we identified 43,793 participants with and 86,726 without self-reported longstanding illness/disability.

2f. Obesity

We derived obesity status from BMI measurements taken during in-person assessment visits [UKB field 21001]. In accordance with NICE guidelines, we considered participants to have obesity if they met a BMI cutoff of $\geq$30 kg/m^2 in any assessment visit they had prior to completing symptom questionnaires. Assessment visits which took place after participants completed the symptom questionnaires were excluded. In total we identified 27,288 participants with and 103,231 participants without obesity.

2g. Vitamin D deficiency

We derived vitamin D deficiency from blood sample measurements taken during in-person assessment visits [UKB field 30890]. In accordance with NICE guidelines, we considered participants to be vitamin D deficient if their serum vitamin D was <25 nmol/L in any assessment visit they had prior to completing symptom questionnaires. Assessment visits which took place after participants completed the symptom questionnaires were excluded. In total we identified 14,308 participants with and 109,310 participants without vitamin D deficiency.

2h. Local deprivation

Local deprivation was assessed via the Townsend index[6] [UKB field 22189], a composite index that incorporates information about employment, car ownership, home ownership, and household crowding. A greater index score indicates that a person is exposed to a greater amount of deprivation in their local area. The Townsend index of UK Biobank participants

was calculated at recruitment. We split participants based on the median value among all UK Biobank participants of European genomic ancestries (N=426,454), so that group allocation was more reflective of the broader UK Biobank cohort. This resulted in 73,462 below median and 57,057 above median participants.

2i. Polygenic scores

We calculated polygenic scores for depression, anxiety, and PTSD from imputed SNP data [UKB field 22828] using PRScs[7] and the latest European ancestry GWAS summary statistics from the Psychiatric Genomics Consortium for each condition[8–10] excluding the UK Biobank. As a negative control we also calculated polygenic scores for height using the latest European ancestry GWAS summary statistics from the GIANT consortium[11] excluding the UK Biobank. Only SNPs with imputation quality (INFO) scores >0.8 and minor allele frequencies >0.01 were included. As with the symptom data, we residualized all polygenic scores on genotyping batch [UKB field 22000] and six genomic principal components [UKB field 22009]. The PRScs parameters used are listed below. The --phi parameter was not specified and therefore learned from the data.

--a=1
--b=0.5
--n_iter=1000
--n_burnin=500
--thin=5
--beta_std=False
--write_psi=False
--write_pst=False

For each polygenic score, we split participants based on the median value among all UK Biobank participants of European genomic ancestries (N=426,454), so that group allocation was more reflective of the broader UK Biobank cohort. Group sizes were as follows:

Polygenic score	**N below median**	**N above median**
Depression	69,229	61,290
Anxiety	68,278	62,241
PTSD	69,406	61,113
Height	62,999	67,520

3. Network comparison metrics

3a. Global strength difference

The global strength of a network is calculated as the sum of all its absolute edge values, $\sum_{i=1}^{p}\sum_{j=1}^{p}|w_{ij}|$, where w is an edge value and p is the number of nodes in the network. The absolute difference between two global strength values quantifies a difference in total connectivity. It does not identify which individual edges differ. This metric is described by van Borkulo and colleagues (2023)[12], who term it the *S* metric.

$$\mathcal{D}_{Global\ Strength} = \left|\sum_{i=1}^{p}\sum_{j=1}^{p}|w_{ij}^{A}| - \sum_{i=1}^{p}\sum_{j=1}^{p}|w_{ij}^{B}|\right|$$

3b. Edge distance

Following Ulitzsch and colleagues (2023)[13], edge distance is calculated here as the Frobenius distance between the edge matrices of two networks, $\boldsymbol{W}_A$ and $\boldsymbol{W}_B$, scaled by the number of nodes. It reflects the extent to which there is overall variability in edge values between networks. This variability can be due to few edges with large group differences or many edges with small differences. Ulitzsch and colleagues term the inverse of this metric the *network similarity metric* (s_F).

$$\mathcal{D}_{Edge} = \sqrt{2/p}\,\|\boldsymbol{W}_A - \boldsymbol{W}_B\|_F = \sqrt{2/p}\,\sqrt{\sum_{i=1}^{p}\sum_{j=1}^{p}\left(w_{ij}^{A} - w_{ij}^{B}\right)^2}$$

3c. Node strength distance

The strength of a given node is calculated as the sum of its absolute edge values with other nodes, $\sum_{j=1}^{p}|w_{ij}|$. It is the most commonly used centrality statistic in psychometric network analysis. Node strength distance is calculated here as the Euclidean distance between the node strength vectors from two networks. It quantifies differences in the magnitudes of node strengths between networks. This need not imply a change in their rank order.

$$\mathcal{D}_{Node\ Strength} = \sqrt{\sum_{i=1}^{p}\left(\sum_{j=1}^{p}|w_{ij}^{A}| - \sum_{j=1}^{p}|w_{ij}^{B}|\right)^2}$$

3d. Maximum edge difference

Maximum edge difference is calculated as the maximum absolute difference in edge values between two networks. Rather than reflecting overall variability in edge values (see edge distance), it reflects the most extreme case of variation in edge values. This metric is described by van Borkulo and colleagues (2023)[12], who term it the *M* metric.

$$\mathcal{D}_{Maximum\ edge} = \max_{i,j} \left| w_{ij}^{A} - w_{ij}^{B} \right|$$

3e. Density difference

The density of a network is the proportion of non-zero edges. The absolute difference between two density values reflects the extent to which there is variability in how many nodes are connected, regardless of connection strength (unlike global strength distance).

$$\mathcal{D}_{Density} = \frac{1}{p(p-1)} \left| \sum_{i=1}^{p} \sum_{j=1}^{p} \mathbf{1}\left[w_{ij}^{A} \neq 0 \right] - \sum_{i=1}^{p} \sum_{j=1}^{p} \mathbf{1}\left[w_{ij}^{B} \neq 0 \right] \right|$$

3f. Jensen-Shannon distance

Jensen-Shannon distance is calculated here as the square root of the symmetrised Kullback-Leibler divergence (KL) between the precision matrices of two networks, $\boldsymbol{\Theta}_A$ and $\boldsymbol{\Theta}_B$. It broadly reflects how much information would be lost if the estimated network from one group were used to represent the data from the other group. This metric is described in a Bayesian context by Williams and colleagues (2020)[14] and is available via the "EGAnet" *R* package[15].

$$\boldsymbol{M} = \frac{1}{2}(\boldsymbol{\Theta}_A + \boldsymbol{\Theta}_B)$$

$$\mathcal{D}_{Jensen-Shannon} = \sqrt{\frac{1}{2} KL(\boldsymbol{\Theta}_A \parallel \boldsymbol{M}) + \frac{1}{2} KL(\boldsymbol{\Theta}_B \parallel \boldsymbol{M})}$$

3g. Spectral distance

Spectral distance is calculated here as the Euclidean distance between the sorted eigenvalues of the normalized signed Laplacian matrices, $\boldsymbol{\mathcal{L}}_A$ and $\boldsymbol{\mathcal{L}}_B$, of two networks. The signed Laplacian matrix of a given network is equivalent to the negative of its edge matrix, $-\boldsymbol{W}$, combined with its signed degree matrix, $\boldsymbol{D}$, a diagonal matrix of node strength values. This matrix is normalized such that its diagonal values equal one.

$$\boldsymbol{D}_{ii} = \sum_{j=1}^{p} \left| w_{ij} \right|, \qquad \boldsymbol{D}_{ij} = 0 \text{ for } i \neq j$$

$$\boldsymbol{\mathcal{L}} = \boldsymbol{I} - \boldsymbol{D}^{-1/2}\boldsymbol{W}\boldsymbol{D}^{-1/2}$$

$$\mathcal{D}_{Spectral}(\boldsymbol{\mathcal{L}}_A, \boldsymbol{\mathcal{L}}_B) = \sqrt{\sum_{i=1}^{p} \left(\lambda_i^{\boldsymbol{\mathcal{L}}_A} - \lambda_i^{\boldsymbol{\mathcal{L}}_B}\right)^2}$$

A brief example is provided below.

Edge matrix

$$\begin{bmatrix} 0 & 0.2 & 0.4 \\ 0.2 & 0 & 0.1 \\ 0.4 & 0.1 & 0 \end{bmatrix}$$

Signed Laplacian

$$\begin{bmatrix} 0.6 & -0.2 & -0.4 \\ -0.2 & 0.3 & -0.1 \\ -0.4 & -0.1 & 0.5 \end{bmatrix}$$

Normalized Laplacian

$$\begin{bmatrix} 1 & -0.47 & -0.73 \\ -0.47 & 1 & -0.26 \\ -0.73 & -0.26 & 1 \end{bmatrix}$$

Eigenvalues

$$[1.77 \quad 1.23 \quad 0.00]$$

The spectral distance between two networks can reflect differences in higher order topology and edge organisation. However, two networks can technically have distinct edge matrices yet have zero spectral distance (i.e., be co-spectral). This metric and several variations are described by Wills and Meyer (2020)[16] and Wilson and Zhu (2008)[17].

3h. Within-cluster and bridge metrics

A within-cluster distance metric is any network distance metric that considers only edges among nodes of the same pre-defined cluster (e.g. A1—A2). Conversely, a between-cluster (or bridge) distance metric is any metric that considers only edges among nodes of different clusters (e.g. A1—D1). These metrics therefore reflect the extent to which structural differences between two networks occur at the within-cluster and bridge levels. In this project, we calculated within-cluster and bridge equivalents to global strength difference, edge distance, and node strength distance.

4. Network estimation simulations

We conducted simulations to estimate the expected sensitivity and specificity of each of our sparse network estimation methods (Atan, LASSO, pruning) under a range of plausible network densities (0.2 to 0.6), given our sample size (N=130,519) and number of symptoms (18). We simulated random networks (100 per density) with 90% positive partial correlations ranging from 0.025 to 0.4. We concluded from these simulations that Atan regularisation would provide the best balance of sensitivity and specificity. For information about each network estimation method, see the Method section of main manuscript.

Density	Method	Median Sensitivity	Median Specificity
0.2	Atan regularisation	.977	1.000
	LASSO regularisation	1.000	1.000
	Alpha level pruning	1.000	1.000
0.3	Atan regularisation	.988	1.000
	LASSO regularisation	1.000	1.000
	Alpha level pruning	1.000	1.000
0.4	Atan regularisation	1.000	1.000
	LASSO regularisation	1.000	.978
	Alpha level pruning	1.000	1.000
0.5	Atan regularisation	1.000	1.000
	LASSO regularisation	1.000	.929
	Alpha level pruning	1.000	.971
0.6	Atan regularisation	1.000	1.000
	LASSO regularisation	1.000	.803
	Alpha level pruning	1.000	.912

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