

Multidimensional symptom network and exploratory symptom- level associations with health-related quality of life among people living with HIV: a multicenter cross-sectional study

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Abstract

Background

Despite effective antiretroviral therapy, people living with HIV (PLWH) often experience multiple symptoms that may impair health-related quality of life (HRQoL). Network analysis can identify structurally important symptoms, but their centrality may not correspond to patient-reported outcomes. We constructed a multidimensional symptom network, evaluated structural stability and psychosocial moderation, and explored symptom-level associations with a study-defined overall MOS-HIV domain mean score.

Methods

This multicenter cross-sectional study recruited 474 PLWH from one tertiary hospital and four county-level general hospitals in Guangxi, China, between March and June 2025. Frequency, severity, and distress ratings for 27 symptoms were summed to generate composite symptom experience scores. Acute stress reaction, psychological resilience, and HIV-specific HRQoL were assessed using the SASRQ, CD-RISC, and MOS-HIV, respectively. A study-defined overall MOS-HIV domain mean score was used as the regression outcome. A regularized partial correlation network was estimated using EBICglasso. Node strength, bridge strength, and predictability were calculated, and bridge strength stability was evaluated using nonparametric and case-dropping bootstrap procedures. Separate moderated Gaussian graphical models evaluated the SASRQ and CD-RISC as continuous moderators. Multivariable regression used HC3-robust inference with Benjamini–Hochberg FDR correction; penalized regression summarized selection consistency across eight specifications.

Results

Uncontrollable worrying had the highest node strength (1.190), bridge strength (0.777), and predictability ($R^2=0.743$); the bridge-strength CS coefficient was 0.75. Neither the SASRQ nor the CD-RISC model retained a non-zero three-way moderation term, and their conditional networks were identical across moderator levels. The full model explained 46.0% of the variance in the overall MOS-HIV domain mean score (adjusted $R^2=0.407$). Mild heteroscedasticity was detected (Breusch–Pagan $P = 0.042$). Four symptom coefficients were nominally significant under HC3-robust inference, but none remained significant after FDR correction (minimum FDR-adjusted $P = 0.052$). Fatigue, dizziness, cough, and mouth ulcer/white patches were retained in all eight penalized-regression specifications, whereas uncontrollable worrying was not retained in any specification.

Conclusions

Network structure and exploratory HRQoL associations yielded partly different patterns of symptom importance. These findings may inform multidimensional symptom assessment and hypothesis generation but do not establish causal effects or intervention priorities.

Background

With the widespread use of antiretroviral therapy (ART), HIV infection is increasingly managed as a chronic health condition requiring long-term care rather than as a highly fatal infectious disease. For people living with HIV

(PLWH), virological suppression and extended survival remain fundamental indicators of treatment success, but they do not fully reflect the quality of long-term care. In chronic disease management, symptom burden, functional status, and health-related quality of life (HRQoL) have become important patient-reported outcomes [1–3]. Previous studies have shown that PLWH may continue to experience multidimensional symptoms, including fatigue, sleep disturbance, pain, gastrointestinal symptoms, and cognitive difficulties, even during ART. These symptoms often co-occur and may affect treatment adherence, daily functioning, and HRQoL [4, 5]. Therefore, HIV symptom management requires not only assessment of symptom burden but also identification of key symptoms within multisymptom systems and evaluation of their relevance to patient-reported outcomes.

Previous studies of symptom co-occurrence among PLWH have commonly used a symptom cluster framework. Although this framework identifies groups of co-occurring symptoms, it is less able to address two key questions: which symptoms remain conditionally associated after controlling for other symptoms, and which symptoms bridge physical, cognitive, and psychological symptom domains [6]. Symptom network analysis conceptualizes symptoms as interconnected nodes and uses edge weights to represent conditional associations between symptoms. By characterizing network structure, this approach identifies central symptoms, bridge symptoms, and node predictability [7, 8]. This approach supports multidimensional symptom assessment and generates hypotheses about potentially important symptoms for future validation in resource-limited healthcare settings.

Recent studies have applied network analysis to examine complex symptom interrelationships among PLWH. Findings suggest that central and bridge symptoms vary across infection duration, psychological symptom profiles, and depression–anxiety comorbidity, indicating heterogeneity in symptom interconnections [9–12]. However, most existing studies focus on internal network metrics, with limited attention to whether structurally important symptoms are consistent with patient-reported outcomes such as HRQoL. Highly central symptoms may reflect network connectivity but do not necessarily correspond to symptoms most strongly associated with patient outcomes. Therefore, integrating symptom network analysis with overall MOS-HIV domain mean score-based associations may clarify how structural importance differs from patient-reported outcome relevance.

Acute stress reaction and psychological resilience are important psychosocial factors in the long-term management of HIV. Previous studies have shown that HIV-related stress is associated with symptom burden, treatment adherence, and HRQoL, while psychological resilience is considered a protective factor for adaptation and better HRQoL [13–15]. However, it remains unclear whether these factors are associated only with symptom levels or whether they also alter coupling within symptom systems. The moderated network model allows examination of whether symptom associations vary across levels of continuous psychosocial variables, thereby distinguishing effects on symptom levels from potential effects on symptom network structure [16].

Accordingly, this study aimed to (1) construct a multidimensional symptom experience network encompassing physical, cognitive, and psychological symptom domains and identify central symptoms, bridge symptoms, and node predictability; (2) examine whether acute stress reaction and psychological resilience moderated symptom–symptom associations; and (3) assess the independent associations between individual symptoms and a study-defined overall MOS-HIV domain mean score and compare the evidence from network structure with HRQoL-based evidence. The analyses were intended to provide descriptive evidence for symptom assessment and future hypothesis testing among PLWH.

Methods

Setting and study sample

This multicenter cross-sectional study was conducted in Guangxi Zhuang Autonomous Region, China. The study was carried out in one tertiary hospital and four county-level general hospitals in a prefecture-level city, with recruitment conducted in both outpatient and inpatient departments. Between March and June 2025, people living with HIV (PLWH) were recruited using convenience sampling. Study size was determined by the number of eligible participants who completed the survey during the scheduled recruitment period. During the recruitment period, 493 eligible individuals were invited to participate, of whom 19 declined because of time constraints or unwillingness to participate. A total of 474 participants completed the questionnaire and were included in the final analysis. All 474 participants had complete data for variables included in the primary analyses; no imputation was performed. All study sites followed a standardized data collection protocol.

Eligibility criteria included: (1) confirmed HIV infection; (2) age ≥ 18 years; and (3) ability to understand the study procedures and provide informed consent. Exclusion criteria were: (1) presence of severe comorbid conditions such as malignant tumors; and (2) severe cognitive impairment or other conditions preventing completion of the questionnaire.

This study was approved by the Ethics Committee of The People's Hospital of Laibin (KYLX2021-08), and the approval remained valid throughout the 2025 data-collection period. All participants provided written informed consent prior to participation.

Measurements

A study-specific demographic and clinical questionnaire designed by the research team was used to collect information on sex, age, educational level, annual income, marital status, and number of comorbid chronic diseases. These variables were used to describe sample characteristics and were included as predefined covariates in the regression models for the overall MOS-HIV domain mean score.

Symptom experience was assessed using the Chinese version of the Self-Report Symptom Scale [12, 17]. The scale includes 27 symptom items and assesses symptom frequency, severity, and distress over the previous two weeks. In this study, each dimension was scored on a 0–4 scale. The three dimension-specific scores were summed to generate a composite symptom experience score for each symptom, ranging from 0 to 12, with higher scores indicating greater overall burden for that symptom. The 27 composite symptom experience scores were used as nodes in the symptom network analysis.

Acute stress reaction was measured using the Chinese version of the Stanford Acute Stress Reaction Questionnaire (SASRQ) [18]. Although the SASRQ was originally developed to assess acute stress reactions, long-term HIV infection and its associated treatment burden, stigma, disclosure concerns, and illness uncertainty were conceptualized in this study as an ongoing illness-related stress context. The SASRQ was therefore used to characterize stress-reaction symptoms within this context rather than to diagnose acute stress disorder. The instrument consists of 30 items rated on a 6-point Likert scale (0 = never experienced, 5 = always experienced), with total scores ranging from 0 to 150. Higher scores indicate a stronger acute stress reaction. The total SASRQ score was treated as a continuous moderator in the moderated network model. Cronbach's α in this sample was 0.982.

Psychological resilience was measured using the Connor–Davidson Resilience Scale (CD-RISC) [19]. The Chinese version of the CD-RISC has been psychometrically validated in Chinese populations [20]. The scale consists of 25 items rated on a 5-point Likert scale (0–4), with total scores ranging from 0 to 100. Higher scores indicate greater psychological resilience. The total CD-RISC score was treated as a continuous moderator in the moderated network model. Cronbach's α in this sample was 0.974.

Health-related quality of life (HRQoL) was assessed using the Medical Outcomes Study HIV Health Survey (MOS-HIV) [21]. The MOS-HIV is an HIV-specific HRQoL instrument comprising 10 domains, and its Chinese version has been validated among PLWH in China [22]. Domain scores were calculated according to the instrument scoring rules and transformed to 0–100 scales. The health-transition item was excluded. We calculated a study-defined overall MOS-HIV domain mean score as the unweighted mean of the 10 domain scores. Higher scores indicate better HIV-specific HRQoL. This score was z-standardized for subsequent regression analyses. Cronbach's α in this sample was 0.901.

Data collection

Potential participants were screened by trained research staff in outpatient waiting areas and inpatient wards. Eligible individuals were informed of the study purpose and survey procedures. After providing written informed consent, participants completed the questionnaires independently; trained research staff provided neutral clarification only when necessary. All research staff received standardized training before data collection.

Completed questionnaires were checked on site. When missing responses or apparent logical inconsistencies were identified, participants were asked to complete or correct the relevant items at the time of collection. Data were entered independently by two researchers and cross-checked for accuracy.

Statistical analysis

All statistical analyses were performed using R software (version 4.6.1; R Foundation for Statistical Computing). Network analyses were conducted using the qgraph, bootnet, networktools, and mgm packages [7, 8, 16, 23–25]. Regression and penalized regression analyses were performed using the car and glmnet packages [26]. Regression diagnostics and HC3 heteroscedasticity-consistent inference used the lmtest and sandwich packages. All tests were two-sided. For symptom coefficients, unadjusted $P < 0.05$ denoted nominal significance, whereas Benjamini–Hochberg FDR-adjusted $P < 0.05$ was the multiplicity-corrected criterion; $P < 0.05$ was used for other inferential and diagnostic tests.

The 27 composite symptom experience scores were used as nodes in the symptom network. Before network estimation, the data were checked for missing values, outliers, and zero-variance nodes. Conditional associations between symptoms were estimated using a Gaussian graphical model (GGM). Because the composite symptom experience scores were skewed, a Spearman correlation matrix was used as the input, and the network was estimated using EBICglasso regularization [8, 24]. The extended Bayesian information criterion (EBIC) tuning parameter γ was set to 0.50 for the primary network. In the network, edges represent regularized partial correlations retained between two symptoms after controlling for all other symptoms in the network. Larger absolute edge weights indicate stronger conditional associations. The network plot was displayed using the spring layout [23].

To identify key symptoms, node strength, bridge strength, and node predictability were calculated. Node strength was defined as the sum of the absolute edge weights connected to a given node and was used to quantify the overall connectivity of that symptom within the network. Bridge strength was calculated based on the predefined physical, cognitive, and psychological symptom domains and was used to identify bridge symptoms connecting different symptom domains [7]. Node predictability was derived from the primary EBICglasso precision matrix. The nodewise regression coefficients implied by this matrix were applied to rank-standardized symptom scores, and in-sample R^2 quantified the proportion of observed variance reproduced by the remaining network nodes [8].

Network accuracy and stability were evaluated using bootstrap procedures. Edge-weight accuracy was assessed by estimating 95% confidence intervals for edge weights using nonparametric bootstrap with 1,000 resamples. Node-strength stability was evaluated using case-dropping bootstrap and reported using the correlation stability coefficient (CS coefficient). Bridge-strength stability was additionally assessed using 1,000 nonparametric bootstrap resamples and 1,000 case-dropping resamples distributed across case-drop proportions from 10% to 75%; the bridge-strength CS coefficient was defined as the maximum drop proportion at which at least 95% of correlations with the original bridge-strength vector were ≥ 0.70 . To assess the robustness of network estimation, we compared edge weights, global strength, and the number of non-zero edges between networks estimated with EBIC $\gamma = 0.50$ and $\gamma = 0.25$. In addition, a more conservative sparse network was estimated using EBICglasso with `threshold=TRUE`.

Moderated network models were used to examine whether acute stress reaction and psychological resilience moderated symptom–symptom associations [16, 25]. The total SASRQ and CD-RISC scores were standardized and entered separately into pairwise Gaussian mgm models containing 28 variables (27 symptoms plus one moderator; $k = 2$), with moderator-specific three-way interaction terms enabled (moderators = 28). Models used EBIC selection (`lambdaGam = 0.50`), the AND regularization rule, internal scaling, and conditioning at -1 SD, the mean, and $+1$ SD. The number of retained non-zero three-way moderation terms, global strength, the number of non-zero pairwise edges, and edge-weight patterns were compared across moderator levels.

A multivariable linear regression model was fitted using the z score of the study-defined overall MOS-HIV domain mean score as the primary outcome; this model was the primary inferential model. The model included all 27 z-standardized composite symptom experience scores and was adjusted for sex, age, educational level, annual income, marital status, and number of comorbid chronic diseases. Regression coefficients were reported with HC3 heteroscedasticity-consistent 95% confidence intervals and P values. For symptom variables, β represents the expected change in the outcome, in standard deviation units, associated with a one-standard-deviation increase in the composite symptom experience score. Diagnostics included the adjusted generalized variance inflation factor [$\text{GVIF}^{(1/(2 \times \text{df}))}$], the Breusch–Pagan test, the Ramsey RESET test, and observation-level flags using $|\text{studentized residual}| > 3$, $\text{leverage} > 2p/n$, and Cook's distance $> 4/n$. Given the simultaneous testing of 27 symptom variables, HC3-robust P values for symptom variables were adjusted using the Benjamini–Hochberg FDR procedure. Sensitivity models combined sparse education and comorbidity categories and separately refitted the model after excluding observations with Cook's distance $> 4/n$. Crude symptom–outcome associations were additionally estimated in 27 separate single-symptom linear regression models using z-standardized symptom and outcome scores; HC3-robust 95% confidence intervals and P values were reported, and Benjamini–Hochberg correction was applied across the 27 crude symptom coefficients.

LASSO and Elastic Net penalized regression were used as robustness analyses to summarize symptom-selection consistency across eight analytical specifications for the study-defined overall MOS-HIV domain mean score [26,

27]. Before model fitting, the study-defined overall MOS-HIV domain mean score calculated according to the instrument scoring rules was further converted to a z score as the outcome, and the 27 composite symptom experience scores were z-standardized as symptom variables. Two sets of models were constructed. The adjusted models included the 27 symptom variables and the predefined covariates; covariates were forced to remain in the models and were not penalized, whereas penalized selection was applied only to symptom variables. The symptom-only models included only the 27 symptom variables and were used as exploratory sensitivity analyses.

For LASSO regression, α was set to 1; for Elastic Net regression, α was set to 0.5. The penalty parameter λ was selected using 10-fold cross-validation, with mean squared error (MSE) as the optimization criterion. Symptom variables retained under both $\lambda_{\min}$ and λ_{1se} were recorded. Because continuous variables had been z-standardized before model fitting, internal standardization was not performed during model fitting. In total, eight variable-selection results were obtained based on two model sets, two penalized regression methods, and two λ selection criteria. The selection frequency of each symptom was calculated to summarize consistency across the eight analytical specifications.

To integrate evidence across analytic layers, symptom burden, network metrics, the HC3-robust full-model results, FDR-corrected results, and penalized-regression selection frequencies were summarized in an integrated evidence table. Symptoms were included if they were retained in at least six of eight penalized-regression specifications or had an HC3-robust nominal $P < 0.05$ in the full model. Rows were ordered by penalized selection frequency in descending order and then by HC3-robust P value in ascending order. These inclusion and ordering rules were used only for transparent presentation and were not used to generate a score, make additional statistical inferences, or develop a prediction model.

Results

Baseline characteristics

The analysis included 474 PLWH. Of the 493 eligible individuals invited to participate, 19 declined because of time constraints or unwillingness to participate, yielding a participation rate of 96.1%. Most participants were male (60.13%), members of an ethnic minority group (82.91%), rural residents (93.04%), and educated to junior middle school level or below (90.93%). Participants aged 45–59 years and ≥ 60 years accounted for 41.14% and 34.60% of the sample, respectively. Median (Q1, Q3) scores were 39.0 (28.0, 62.0) for the SASRQ, 56.0 (46.0, 69.0) for the CD-RISC, and 63.0 (54.6, 69.1) for the overall MOS-HIV domain mean score. The median total composite symptom burden was 14.0 (2.0, 55.0) (Table 1).

Table 1
Baseline characteristics of participants

Variable	Result
Age group	
≤ 44 years	115 (24.26)
45–59 years	195 (41.14)
≥ 60 years	164 (34.60)
Sex	
Male	285 (60.13)
Female	189 (39.87)
Ethnicity	
Han	81 (17.09)
Ethnic minority	393 (82.91)
Educational level	
Junior middle school or below	431 (90.93)
Senior high school or technical secondary school	31 (6.54)
College or above	12 (2.53)
Place of residence	
Urban, county, or township	33 (6.96)
Rural	441 (93.04)
Annual income (CNY)	
< 10,000	270 (56.96)
10,000–30,000	135 (28.48)
30,000–50,000	47 (9.92)
> 50,000	22 (4.64)
Payment method for medical expenses	
Urban medical insurance	55 (11.60)
New Rural Cooperative Medical Scheme	404 (85.23)
Self-pay or other	15 (3.16)
Number of hobbies	
None	279 (58.86)
Note. Categorical variables are presented as n (%); continuous variables are presented as median (Q1, Q3).	

Variable	Result
Age group	
1–2	122 (25.74)
3–5	70 (14.77)
≥ 6	3 (0.63)
Personality type	
Introverted	107 (22.57)
Neutral	278 (58.65)
Extroverted	89 (18.78)
Number of comorbid chronic diseases	
None	258 (54.43)
1–2	151 (31.86)
3–5	61 (12.87)
≥ 6	4 (0.84)
Religious belief	
No	458 (96.62)
Yes	16 (3.38)
Family relationships	
Harmonious	300 (63.29)
Fair	161 (33.97)
Unsatisfactory	13 (2.74)
Marital status	
Unmarried	84 (17.72)
Married	281 (59.28)
Cohabiting	56 (11.81)
Divorced	24 (5.06)
Widowed	29 (6.12)
Occupation	
Worker	23 (4.85)
Farmer	367 (77.43)
Note. Categorical variables are presented as n (%); continuous variables are presented as median (Q1, Q3).	

Variable	Result
Age group	
Administrative worker	2 (0.42)
Service industry	19 (4.01)
Intellectual/professional	5 (1.05)
Other	58 (12.24)
History of trauma	
Yes	13 (2.74)
No	461 (97.26)
Family or personal medical history	
Yes	34 (7.17)
No	440 (92.83)
SASRQ total score, median (Q1, Q3)	39.0 (28.0, 62.0)
CD-RISC total score, median (Q1, Q3)	56.0 (46.0, 69.0)
Overall MOS-HIV domain mean score, median (Q1, Q3)	63.0 (54.6, 69.1)
Total composite symptom burden, median (Q1, Q3)	14.0 (2.0, 55.0)
Note. Categorical variables are presented as n (%); continuous variables are presented as median (Q1, Q3).	

Distribution of composite symptom experience scores and scale scores

The total composite symptom burden had a mean of 36.36 ± 47.43 and a median (Q1, Q3) of 14.0 (2.0, 55.0), with a markedly right-skewed distribution. The overall MOS-HIV domain mean score had a mean of 61.56 ± 10.99 , a median (Q1, Q3) of 63.0 (54.6, 69.1), and a range of 18.6–85.0. The highest mean composite symptom experience scores were observed for fatigue (2.62 ± 2.78), sleep disturbance (1.87 ± 2.56), dizziness (1.75 ± 2.53), feeling nervous/anxious (1.66 ± 2.46), and appetite loss (1.62 ± 2.66).

Overall structure of the composite symptom experience network

The primary regularized partial correlation network contained 179 non-zero edges, had a global strength of 12.971, and included no isolated nodes (Fig. 1). Most retained edges were positive. The largest absolute edge weights were observed for dizziness–headache (0.417), difficulty concentrating–slowed reaction (0.413), muscle/joint ache–hand/foot numbness or pain (0.390), fatigue–dizziness (0.284), and uncontrollable worrying–feeling nervous/anxious (0.279).

Central symptoms, bridge symptoms, and node predictability

Uncontrollable worrying had the highest node strength (1.190), followed by dizziness (1.170), fever/chills/night sweats (1.102), nausea/vomiting (1.098), and muscle/joint ache (1.092). The 10 highest-ranking nodes included symptoms from all three domains. Uncontrollable worrying also had the highest bridge strength (0.777), followed by little interest in doing things (0.620), difficulty concentrating (0.483), becoming confused (0.470), and feeling down/depressed/hopeless (0.461). Table 2 presents the 10 highest-ranking symptoms for node strength and bridge strength; Figs. 2 and 3 present the corresponding rankings.

Table 2 Top symptoms by node strength and bridge strength				
Rank	Symptoms with high node strength	Node strength	Symptoms with high bridge strength	Bridge strength
1	Uncontrollable worrying	1.190	Uncontrollable worrying	0.777
2	Dizziness	1.170	Little interest in doing things	0.620
3	Fever/chills/night sweats	1.102	Difficulty concentrating	0.483
4	Nausea/vomiting	1.098	Becoming confused	0.470
5	Muscle/joint ache	1.092	Feeling down/depressed/hopeless	0.461
6	Difficulty concentrating	1.076	Difficulty understanding/reasoning	0.434
7	Hand/foot numbness or pain	1.066	Feeling nervous/anxious	0.400
8	Feeling nervous/anxious	1.048	Memory loss/forgetfulness	0.293
9	Little interest in doing things	1.038	Slowed reaction	0.292
10	Memory loss/forgetfulness	1.032	Weight loss/wasting	0.265
Note. Node strength is the sum of the absolute edge weights connected to a node. Bridge strength quantifies the extent to which a node connects different symptom domains.				

Mean node predictability was 0.611 (range, 0.394–0.743). The highest R² values were observed for uncontrollable worrying (0.743), difficulty concentrating (0.733), slowed reaction (0.714), dizziness (0.710), and feeling nervous/anxious (0.704) (Fig. 4).

Network accuracy, stability, and robustness analyses

Bootstrap 95% confidence intervals were relatively narrow for most of the stronger edges (Fig. 5). In the case-dropping bootstrap analysis, the CS coefficient was 0.595 for node strength (Fig. 6) and 0.75 for bridge strength. Uncontrollable worrying ranked among the top three bridge nodes in 99.8% of the 1,000 nonparametric bridge bootstrap resamples, supporting the stability of its bridge prominence. Detailed case-dropping and nonparametric bridge-strength results are provided in Additional file 1: Supplementary Tables S2A and S2B.

Networks estimated with EBIC $\gamma = 0.50$ and $\gamma = 0.25$ were identical, with Spearman $r = 1.000$, global strength = 12.971, and 179 non-zero edges in both models. With threshold=TRUE, the network contained 45 non-zero edges and had a global strength of 8.531; its edge-weight correlation with the primary network was 0.605 (Table 3; Fig. 7).

Table 3
Network sensitivity and moderated-network analyses

Analysis	Edge-weight correlation	Global strength	Number of non-zero edges	Result
EBIC $\gamma = 0.50$ vs $\gamma = 0.25$	1.000	12.971 / 12.971	179 / 179	Identical edge weights, global strength, and number of non-zero edges
EBIC $\gamma = 0.50$ vs threshold=TRUE	0.605	12.971 / 8.531	179 / 45	45 non-zero edges; edge-weight correlation with the primary network, $r = 0.605$
SASRQ moderated network	1.000	7.892	51	Global strength, number of non-zero edges, and edge-weight pattern were unchanged across moderator levels
CD-RISC moderated network	1.000	7.703	49	Global strength, number of non-zero edges, and edge-weight pattern were unchanged across moderator levels
Note. For the EBIC γ sensitivity analyses, global strength and the number of non-zero edges are reported as primary network/comparison network. For the moderated networks, the reported values were identical at low (-1 SD), mean, and high ($+1$ SD) moderator levels.				

Moderated network analysis of acute stress reaction and psychological resilience

Neither moderated network model retained a non-zero three-way moderation term. For the SASRQ total score, the identical conditional networks at -1 SD, the mean, and $+1$ SD each had a global strength of 7.892 and 51 non-zero pairwise edges. The corresponding CD-RISC networks were also identical and each had a global strength of 7.703 and 49 non-zero pairwise edges (Table 3; Fig. 8).

Associations between network symptoms and the overall MOS-HIV domain mean score

The full multivariable model explained 46.0% of the variance in the z-standardized overall MOS-HIV domain mean score ($R^2=0.460$; adjusted $R^2=0.407$), and the maximum adjusted GVIF [$GVIF^{(1/(2 \times df))}$] was 2.498. The Breusch–Pagan test indicated mild heteroscedasticity ($\chi^2=59.071$, $df = 42$, $P = 0.042$), whereas the Ramsey RESET test did not indicate functional-form misspecification ($F = 1.257$, $df = 2$ and 429 , $P = 0.285$); HC3-robust inference was therefore used. Four observations had $|studentized\ residual| > 3$, 56 had $leverage > 2p/n$, and 48 had Cook's distance $> 4/n$. Fatigue ($\beta = -0.167$, HC3-robust 95% CI -0.327 to -0.007 , $P = 0.040$) and mouth ulcer/white patches ($\beta = -0.165$, 95% CI -0.318 to -0.012 , $P = 0.035$) had nominal inverse associations. Blurred vision ($\beta = 0.209$, 95% CI 0.078 to 0.341 , $P = 0.002$) and rash/itching ($\beta = 0.166$, 95% CI 0.038 to 0.294 , $P = 0.011$) had nominal positive coefficients despite negative bivariate correlations. No symptom coefficient remained significant after FDR correction; the smallest adjusted P value was 0.052 for blurred vision. High school or technical secondary school education was associated with a higher score than junior high school education or below ($\beta = 0.456$, 95% CI 0.126 to 0.785 , $P = 0.007$). The four nominal symptom coefficients retained the same directions after sparse categories were combined and after the 48 observations with Cook's distance $> 4/n$ were excluded. In the Cook-exclusion model ($n = 426$), coefficient magnitudes changed, as did the set of coefficients meeting the FDR threshold; therefore, the full-

sample HC3 model remained the primary basis for inference (Table 4; Fig. 9; Additional file 1: Supplementary Tables S3A and S3B). In the separate crude models, all 27 symptom scores were inversely associated with the outcome after FDR correction; these unadjusted estimates are reported in Additional file 1: Supplementary Table S4.

Table 4
Multivariable associations with the overall MOS-HIV domain mean score

Variable	β	95% CI	P value	FDR-adjusted P value
Fatigue (z score)	-0.167	-0.327, -0.007	0.040	0.272
Dizziness (z score)	-0.149	-0.319, 0.020	0.084	0.378
Headache (z score)	-0.062	-0.244, 0.119	0.499	0.926
Fever/chills/night sweats (z score)	-0.001	-0.146, 0.145	0.994	0.994
Cough (z score)	-0.115	-0.240, 0.010	0.072	0.378
Sleep disturbance (z score)	-0.019	-0.165, 0.127	0.799	0.983
Blurred vision (z score)	0.209	0.078, 0.341	0.002	0.052
Rash/itching (z score)	0.166	0.038, 0.294	0.011	0.148
Mouth ulcer/white patches (z score)	-0.165	-0.318, -0.012	0.035	0.272
Muscle/joint ache (z score)	-0.076	-0.261, 0.110	0.422	0.877
Hand/foot numbness or pain (z score)	0.036	-0.150, 0.223	0.702	0.983
Appetite loss (z score)	0.047	-0.107, 0.201	0.548	0.926
Bloating/abdominal pain/diarrhea (z score)	0.011	-0.140, 0.161	0.890	0.983
Nausea/vomiting (z score)	-0.080	-0.234, 0.074	0.309	0.759
Weight gain/fat accumulation (lipodystrophy) (z score)	0.095	-0.051, 0.240	0.202	0.611
Weight loss/wasting (z score)	-0.046	-0.196, 0.104	0.549	0.926

Note. β denotes a regression coefficient. For z-standardized symptom variables, β is the expected change in the outcome, in standard deviation units, for a one-standard-deviation increase in the symptom variable; for categorical covariates, β is the adjusted difference in outcome standard-deviation units relative to the reference category shown in parentheses. The model included all 27 z-standardized composite symptom experience scores and the prespecified covariates. Model $R^2=0.460$; adjusted $R^2=0.407$; maximum adjusted GVIF [$GVIF^{1/(2 \times df)}$] = 2.498. Confidence intervals and P values are based on HC3 heteroscedasticity-consistent standard errors. Unadjusted $P < 0.05$ denotes nominal significance for symptom coefficients; FDR adjustment used the Benjamini–Hochberg procedure across all 27 symptom variables.

Variable	β	95% CI	P value	FDR-adjusted P value
Low sex drive (z score)	-0.027	-0.180, 0.126	0.725	0.983
Hair loss (z score)	-0.098	-0.245, 0.049	0.193	0.611
Difficulty concentrating (z score)	0.016	-0.181, 0.212	0.874	0.983
Slowed reaction (z score)	-0.102	-0.279, 0.075	0.258	0.698
Memory loss/forgetfulness (z score)	0.028	-0.146, 0.202	0.753	0.983
Difficulty understanding/reasoning (z score)	0.010	-0.161, 0.180	0.910	0.983
Becoming confused (z score)	0.026	-0.127, 0.178	0.740	0.983
Uncontrollable worrying (z score)	0.006	-0.211, 0.223	0.958	0.994
Feeling nervous/anxious (z score)	-0.098	-0.306, 0.110	0.355	0.798
Little interest in doing things (z score)	-0.120	-0.305, 0.065	0.204	0.611
Feeling down/depressed/hopeless (z score)	-0.021	-0.205, 0.163	0.819	0.983
Female (ref: male)	0.048	-0.134, 0.229	0.607	--
45–59 years (ref: ≤ 44 years)	0.002	-0.209, 0.212	0.988	--
≥ 60 years (ref: ≤ 44 years)	-0.021	-0.246, 0.204	0.857	--
Senior high school or technical secondary school (ref: junior middle school or below)	0.456	0.126, 0.785	0.007	--
College or above (ref: junior middle school or below)	-0.245	-0.824, 0.334	0.406	--
CNY 10,000–30,000 (ref: $<10,000$)	0.162	-0.031, 0.354	0.099	--
Note. β denotes a regression coefficient. For z-standardized symptom variables, β is the expected change in the outcome, in standard deviation units, for a one-standard-deviation increase in the symptom variable; for categorical covariates, β is the adjusted difference in outcome standard-deviation units relative to the reference category shown in parentheses. The model included all 27 z-standardized composite symptom experience scores and the prespecified covariates. Model $R^2=0.460$; adjusted $R^2=0.407$; maximum adjusted GVIF $[GVIF^{(1/(2 \times df))}] = 2.498$. Confidence intervals and P values are based on HC3 heteroscedasticity-consistent standard errors. Unadjusted $P < 0.05$ denotes nominal significance for symptom coefficients; FDR adjustment used the Benjamini–Hochberg procedure across all 27 symptom variables.				

Variable	β	95% CI	P value	FDR-adjusted P value
CNY 30,000–50,000 (ref: <10,000)	0.030	-0.195, 0.256	0.792	--
>CNY 50,000 (ref: <10,000)	0.007	-0.400, 0.414	0.973	--
1–2 comorbidities (ref: none)	-0.019	-0.188, 0.151	0.829	--
3–5 comorbidities (ref: none)	-0.059	-0.385, 0.268	0.724	--
≥ 6 comorbidities (ref: none)	0.246	-1.086, 1.579	0.717	--
Married (ref: unmarried)	-0.037	-0.286, 0.213	0.773	--
Cohabiting (ref: unmarried)	-0.138	-0.477, 0.201	0.425	--
Divorced (ref: unmarried)	0.095	-0.333, 0.524	0.662	--
Widowed (ref: unmarried)	0.282	-0.098, 0.661	0.146	--
Note. β denotes a regression coefficient. For z-standardized symptom variables, β is the expected change in the outcome, in standard deviation units, for a one-standard-deviation increase in the symptom variable; for categorical covariates, β is the adjusted difference in outcome standard-deviation units relative to the reference category shown in parentheses. The model included all 27 z-standardized composite symptom experience scores and the prespecified covariates. Model $R^2=0.460$; adjusted $R^2=0.407$; maximum adjusted GVIF $[GVIF^{1/(2 \times df)}] = 2.498$. Confidence intervals and P values are based on HC3 heteroscedasticity-consistent standard errors. Unadjusted $P < 0.05$ denotes nominal significance for symptom coefficients; FDR adjustment used the Benjamini–Hochberg procedure across all 27 symptom variables.				

Across the eight penalized-regression specifications, fatigue, dizziness, feeling nervous/anxious, feeling down/depressed/hopeless, little interest in doing things, mouth ulcer/white patches, cough, and hair loss were retained in all eight. Headache and weight loss/wasting were retained in seven specifications, fever/chills/night sweats in five, and blurred vision and rash/itching in four. Uncontrollable worrying was not retained in any specification.

The integrated table included 12 symptoms according to the stated presentation rules (Table 5). Fatigue and mouth ulcer/white patches had nominal inverse HC3-robust associations and were retained in all eight penalized-regression specifications. Dizziness and cough were also retained in all eight specifications but were not nominally significant under HC3 inference. Blurred vision and rash/itching had nominal positive adjusted coefficients, were retained in four specifications, and contrasted with their negative bivariate correlations. No integrated-table symptom remained significant after FDR correction. Uncontrollable worrying ranked first for node strength, bridge strength, and predictability but was not associated with the outcome and was not retained in any penalized-regression specification.

Table 5
Integrated symptom evidence across analytical layers

Symptom	Mean burden	Node strength rank	Bridge strength rank	Predictability	Full-model β (HC3 P)	FDR-significant	Penalized selection frequency
Mouth ulcer/white patches	1.08	18	24	0.562	-0.165 (0.035)	No	8/8
Fatigue	2.62	25	14	0.557	-0.167 (0.040)	No	8/8
Cough	1.55	21	26	0.479	-0.115 (0.072)	No	8/8
Dizziness	1.75	2	17	0.710	-0.149 (0.084)	No	8/8
Hair loss	1.30	20	11	0.510	-0.098 (0.193)	No	8/8
Little interest in doing things	1.35	9	2	0.674	-0.120 (0.204)	No	8/8
Feeling nervous/anxious	1.66	8	7	0.704	-0.098 (0.355)	No	8/8
Feeling down/depressed/hopeless	1.49	11	5	0.688	-0.021 (0.819)	No	8/8
Headache	1.50	13	18	0.660	-0.062 (0.499)	No	7/8
Weight loss/wasting	1.20	26	10	0.530	-0.046 (0.549)	No	7/8
Blurred vision	1.28	23	20	0.509	0.209 (0.002)	No	4/8
Rash/itching	1.10	24	23	0.511	0.166 (0.011)	No	4/8

Note. Symptom burden is the mean composite symptom experience score. Node strength and bridge strength ranks were derived from the primary symptom network. Predictability is in-sample R^2 derived from the primary EBICglasso precision matrix. The full model included all 27 z-standardized composite symptom experience scores and prespecified covariates, with the z-standardized overall MOS-HIV domain mean score as the outcome; β denotes the regression coefficient for a z-standardized symptom variable, and P values are based on HC3 heteroscedasticity-consistent standard errors. FDR-significant denotes an FDR-adjusted $P < 0.05$ after Benjamini–Hochberg correction across the 27 symptom variables. Penalized selection frequency summarizes consistency across eight analytical specifications and is not a formal stability-selection probability. Symptoms were included if they were retained in at least six of eight penalized specifications or had an HC3-robust nominal $P < 0.05$. Rows were ordered by penalized selection frequency in descending order and then by HC3-robust P value in ascending order. For blurred vision and rash/itching, positive adjusted coefficients contrasted with negative bivariate Spearman correlations and may reflect suppression effects. The table is descriptive and was not used to derive a composite score, make additional inferences, or construct a prediction model.

Discussion

In this multicenter cross-sectional study of 474 PLWH, symptom importance differed according to whether it was evaluated by structural position in the network or by an exploratory association with HRQoL. Most retained edges

were positive, and uncontrollable worrying ranked highest for node strength, bridge strength, and predictability. Bridge strength showed high case-dropping stability. In the HC3-robust full model, fatigue and mouth ulcer/white patches showed nominal inverse associations, but no symptom remained significant after FDR correction. Thus, structural prominence did not necessarily correspond to robust evidence of an HRQoL association. The regression findings should be regarded as hypothesis-generating rather than as a basis for intervention prioritization.

Uncontrollable worrying was both the most central node and the strongest bridge symptom, consistent with previous network studies of psychological symptoms among PLWH [10, 11]. Its prominent position was retained when physical, cognitive, and psychological symptoms were modeled together. Disease uncertainty, long-term treatment burden, HIV-related stigma, and concerns about disclosure may sustain worry and threat monitoring in the context of chronic HIV care [28, 29]. Heightened attention to bodily sensations among individuals with anxiety or health-anxiety tendencies could partly account for the connections of uncontrollable worrying with dizziness, fatigue, pain, and gastrointestinal discomfort [30–32]. Persistent worry has also been associated with poorer attentional control and working memory, which may help explain its links with difficulty concentrating, slowed reaction, and memory loss/forgetfulness [33, 34]. Current guidelines recommend incorporating assessment of anxiety, depression, and other mental health concerns into long-term HIV care [35, 36]. In the present study, however, uncontrollable worrying was not independently associated with the overall MOS-HIV domain mean score in the full model. It was also not retained in any penalized-regression specification. In this dataset, it was therefore structurally important across symptom domains but did not indicate poorer HRQoL. The proposed mechanisms remain speculative because a cross-sectional network cannot establish temporal or causal relationships between symptoms.

Although HIV-related stress and psychological resilience have previously been associated with symptom burden, adaptation, and HRQoL among PLWH [13, 15, 37], no non-zero three-way moderation term was retained for either variable, and the conditional networks were identical across the evaluated moderator levels. Within the sensitivity limits of the penalized moderated models, this pattern may indicate that these psychosocial factors are more closely related to overall symptom severity, coping, treatment-related behaviors, or HRQoL than to the configuration of symptom–symptom associations. Total SASRQ and CD-RISC scores may also be insufficiently sensitive to context-specific influences such as HIV stigma, illness uncertainty, family support, and financial strain. Small interaction effects, limited variation in moderator values, and sensitivity to model specification cannot be excluded as alternative explanations for the null findings. Future studies using domain-specific measures, longitudinal network analysis, or ecological momentary assessment may clarify whether psychosocial factors moderate particular symptom domains, disease stages, or patient subgroups.

Fatigue and mouth ulcer/white patches showed nominal inverse HC3-robust associations and were retained in all eight penalized-regression specifications, but neither association survived FDR correction. Dizziness and cough were also retained in all eight specifications but were not nominally significant under HC3 inference. These patterns may help identify symptoms for focused assessment in future studies, but they do not establish screening performance, independent risk markers, or intervention priorities. Network centrality and exploratory HRQoL associations should therefore be interpreted as complementary descriptive evidence rather than as interchangeable criteria. All 27 symptoms had inverse crude associations, but every coefficient was attenuated in absolute magnitude and 11 changed direction after simultaneous adjustment for co-occurring symptoms and prespecified covariates, consistent with substantial shared variance among symptom scores; accordingly, primary inference rests on the adjusted model.

Blurred vision and rash/itching were negatively correlated with the overall MOS-HIV domain mean score in bivariate analyses (Spearman $\rho = -0.317$ and -0.331 , respectively) but had nominal positive HC3-robust coefficients in the full model, a direction opposite to usual clinical expectations. Because multiple correlated symptoms were entered simultaneously, these estimates may reflect suppression effects, residual confounding, or characteristics of the study sample. They should not be interpreted as evidence that blurred vision or rash/itching is protective for HRQoL, and replication in independent samples is needed.

Fatigue had the highest mean composite symptom experience score and showed a nominal inverse HC3-robust association with the overall MOS-HIV domain mean score, although the association did not survive FDR correction. Fatigue is common among PLWH and has consistently been associated with poorer perceived health and HRQoL [38, 39]. When fatigue is persistent, clinical assessment commonly considers potentially reversible contributors, including sleep disturbance, psychological symptoms, anemia, nutritional problems, comorbid chronic diseases, and ART-related adverse effects [35, 40]. Management should be guided by the factors identified rather than treating fatigue as an isolated symptom. Depending on the underlying contributors, appropriate strategies may include sleep interventions, psychological support, graded physical activity, and management of reversible physical conditions.

Dizziness had relatively high node strength and was retained in all eight penalized-regression specifications, but its full-model association was not nominally significant under HC3 inference. It therefore has network relevance, whereas its patient-reported outcome association remains uncertain. Dizziness is a non-specific symptom that may reflect several underlying conditions and may also contribute to activity limitation and fall risk. A symptom cluster study using the HIV Symptom Index found that “feeling dizzy or lightheaded” clustered with gastrointestinal symptoms [41]. Its assessment in primary HIV care may therefore include activity limitation, fall risk, blood pressure abnormalities, anemia, medication-related adverse effects, neurological symptoms, and relevant comorbidities [42]. Further assessment or referral may be warranted when dizziness is persistent or accompanied by elevated fall risk or neurological abnormalities [43].

The mouth ulcer/white patches item was not central in the symptom network but showed a nominal inverse HC3-robust association with the overall MOS-HIV domain mean score and was retained in all eight penalized-regression specifications. Thus, low network centrality does not preclude a symptom from warranting further evaluation in relation to HRQoL. Oral mucosal lesions may affect quality of life through pain, restricted eating, reduced nutritional intake, and limitations in social interaction; recent studies among PLWH have also linked these lesions to poorer oral health-related quality of life [44, 45]. This pattern supports further study of mouth ulcer/white patches in relation to symptom inquiry and oral health assessment during long-term HIV care. In resource-limited settings, its clinical usefulness for prompting assessment of oral health and HRQoL requires prospective validation.

Dizziness, cough, feeling nervous/anxious, feeling down/depressed/hopeless, little interest in doing things, and hair loss were retained in all eight penalized-regression specifications. Headache and weight loss/wasting were retained in seven specifications. Under HC3-robust inference, none of these symptoms remained statistically significant after FDR correction in the full model. These findings should therefore be regarded as exploratory rather than as evidence of stable independent associations with HRQoL. The psychological symptoms may reflect emotional distress and difficulty adapting to illness [28, 46]. Weight loss/wasting may indicate greater disease burden or functional vulnerability [47, 48], whereas hair loss may affect body image and social interaction [49]. Further research should examine whether these symptoms are related to HRQoL indirectly through psychological

distress, functional limitation, or impaired social participation and should confirm the patient-reported outcome relevance of cough and headache.

Limitations

This study has several limitations. First, the cross-sectional design precludes causal inference. Network edges represent group-level conditional associations after adjustment for other symptoms and cannot characterize the temporal ordering or within-person dynamics of symptoms. Second, participants were recruited from one prefecture-level city and county-level hospitals in Guangxi, and the sample included high proportions of rural residents, people with lower educational levels, and middle-aged or older PLWH. These sampling characteristics may limit the generalizability of the findings to urban populations and PLWH in other regions. Third, symptoms, psychosocial variables, and HRQoL were assessed using self-report scales and may be affected by recall and reporting bias. The analyses also did not fully account for clinical factors such as CD4 + T-cell count, viral load, ART regimen, duration of HIV infection, and treatment duration; residual confounding may therefore remain. In addition, mild heteroscedasticity and influential observations were present in the regression analysis, and no symptom coefficient survived FDR correction using HC3-robust inference; the symptom–HRQoL associations should therefore be interpreted as exploratory. Finally, the integrated evidence table was derived from the same sample and was intended to describe agreement and discrepancies across analytic layers rather than to establish a new scoring or selection system. Longitudinal analyses are needed to clarify the temporal ordering of symptoms, and independent samples are required to assess the reproducibility of the network and regression findings.

Conclusions

The composite symptom experience network among PLWH showed extensive connections across physical, cognitive, and psychological symptom domains. Uncontrollable worrying was the most prominent central and bridge symptom, and its bridge strength was stable, but its association with the overall MOS-HIV domain mean score was not supported. Fatigue and mouth ulcer/white patches showed nominal inverse HC3-robust associations and were retained in all eight penalized-regression specifications, but no symptom survived FDR correction. Neither moderated network retained a non-zero three-way moderation term. Network structure and exploratory HRQoL associations therefore captured different dimensions of symptom importance. These findings may inform multidimensional symptom assessment and future validation, but they do not establish causal effects or intervention priorities.

Abbreviations

ART

antiretroviral therapy

CD-RISC

Connor–Davidson Resilience Scale

CI

confidence interval

CS coefficient

correlation stability coefficient

EBIC

extended Bayesian information criterion

FDR

false discovery rate

GGM

Gaussian graphical model

HRQoL

health-related quality of life

LASSO

least absolute shrinkage and selection operator

MOS-HIV

Medical Outcomes Study HIV Health Survey

MSE

mean squared error

PLWH

people living with HIV

SASRQ

Stanford Acute Stress Reaction Questionnaire

SD

standard deviation

VIF

variance inflation factor

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The People's Hospital of Laibin (KYLX2021-08), and the approval remained valid throughout the 2025 data-collection period. All participants provided written informed consent before participation.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to participant confidentiality but are available from the corresponding authors on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors made substantial contributions to this study. WTH was responsible for data curation and processing, statistical analyses, interpretation of the results, and drafting the manuscript. LXW contributed to the interpretation of the results and manuscript preparation. YSL, XJQ, QMC, and QTC were responsible for participant recruitment, data collection, and data collation. LDZ and FW supervised the study and critically reviewed and revised the manuscript. WTH and LXW contributed equally to this work. All authors read and approved the final manuscript.

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Figures

Symptom network

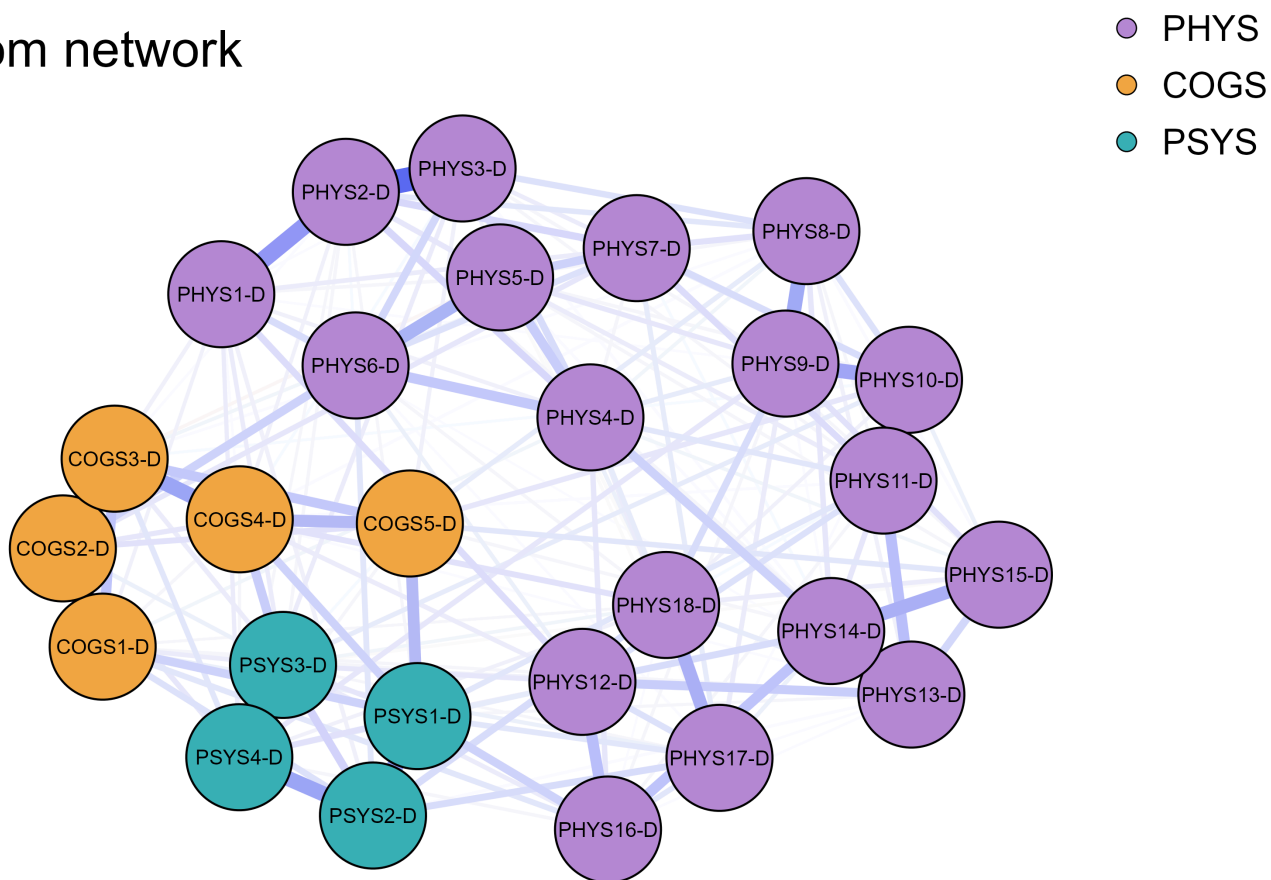


Figure 1

Composite symptom experience network among PLWH. Nodes represent composite symptom experience scores for 27 symptoms (sum of frequency, severity, and distress). Edges are non-zero regularized partial correlations retained by EBICglasso; line width is proportional to the absolute edge weight. Node colors identify physical (PHYS), cognitive (COGS), and psychological (PSYS) symptom domains. Abbreviated node labels are defined in Additional file 1: Supplementary Table S1.

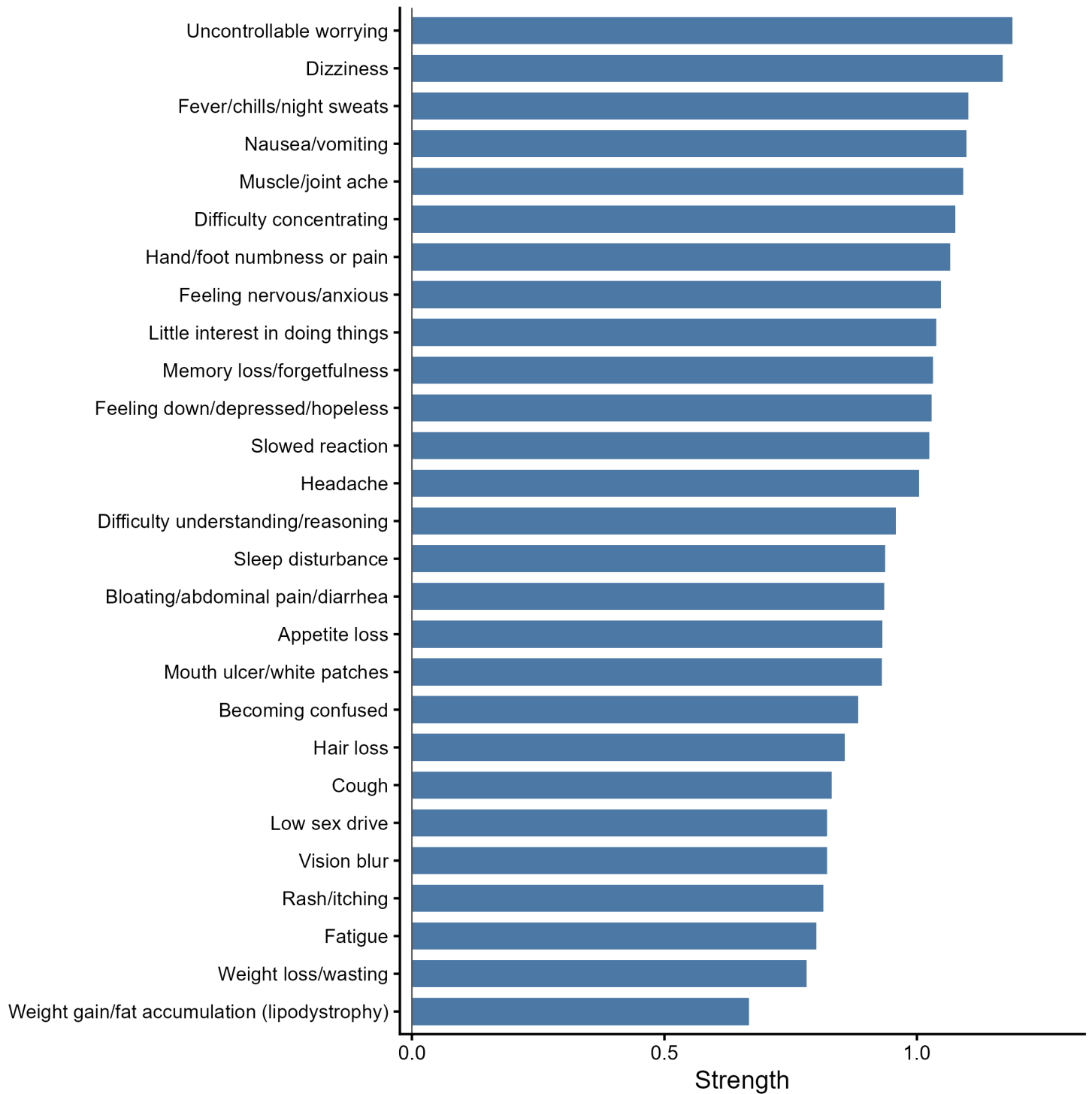


Figure 2

Node strength ranking in the composite symptom experience network among PLWH. Higher values denote greater overall connectivity with other symptoms in the network

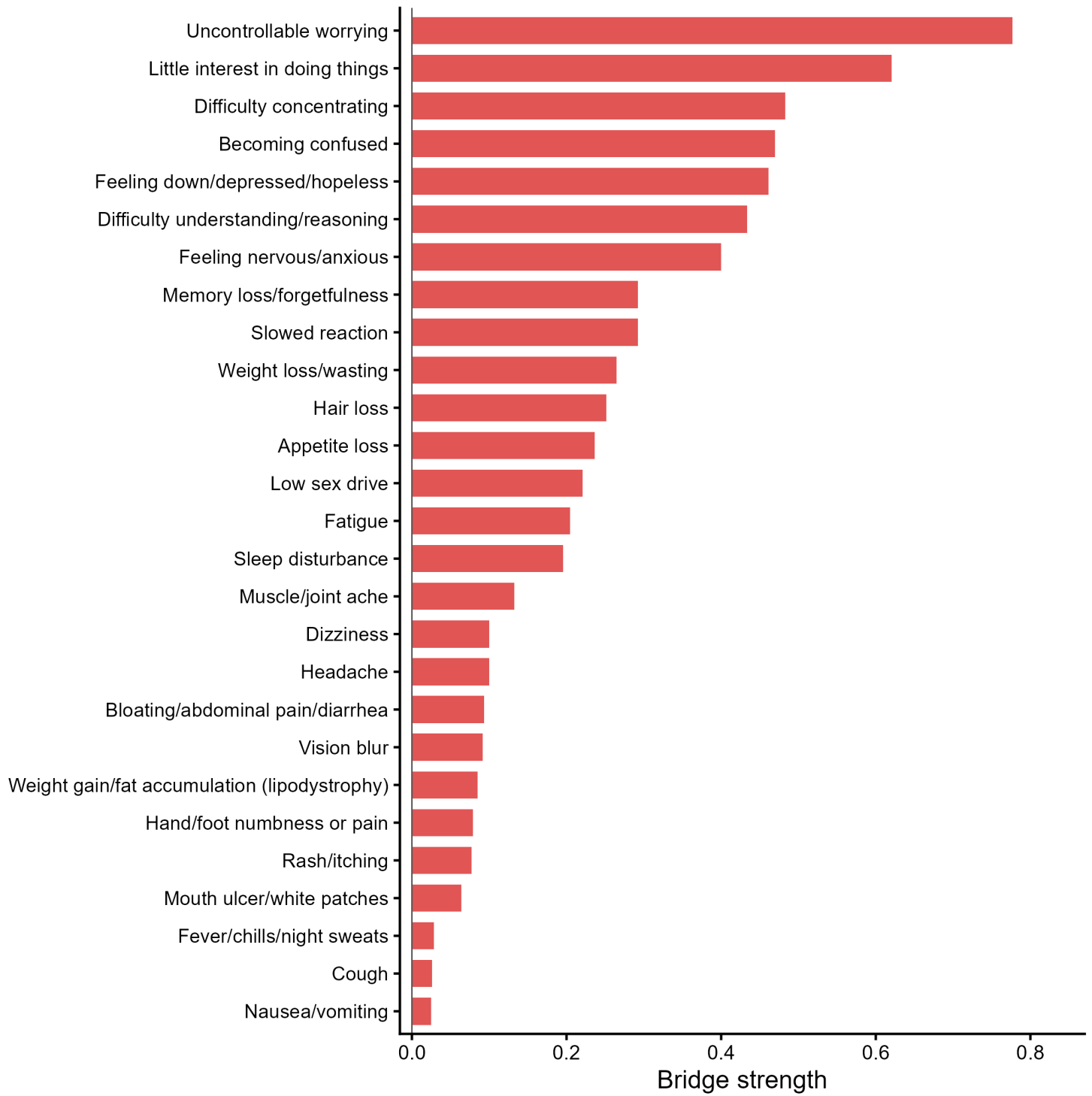


Figure 3

Bridge strength ranking in the composite symptom experience network among PLWH. Higher values denote greater connectivity across physical, cognitive, and psychological symptom domains.

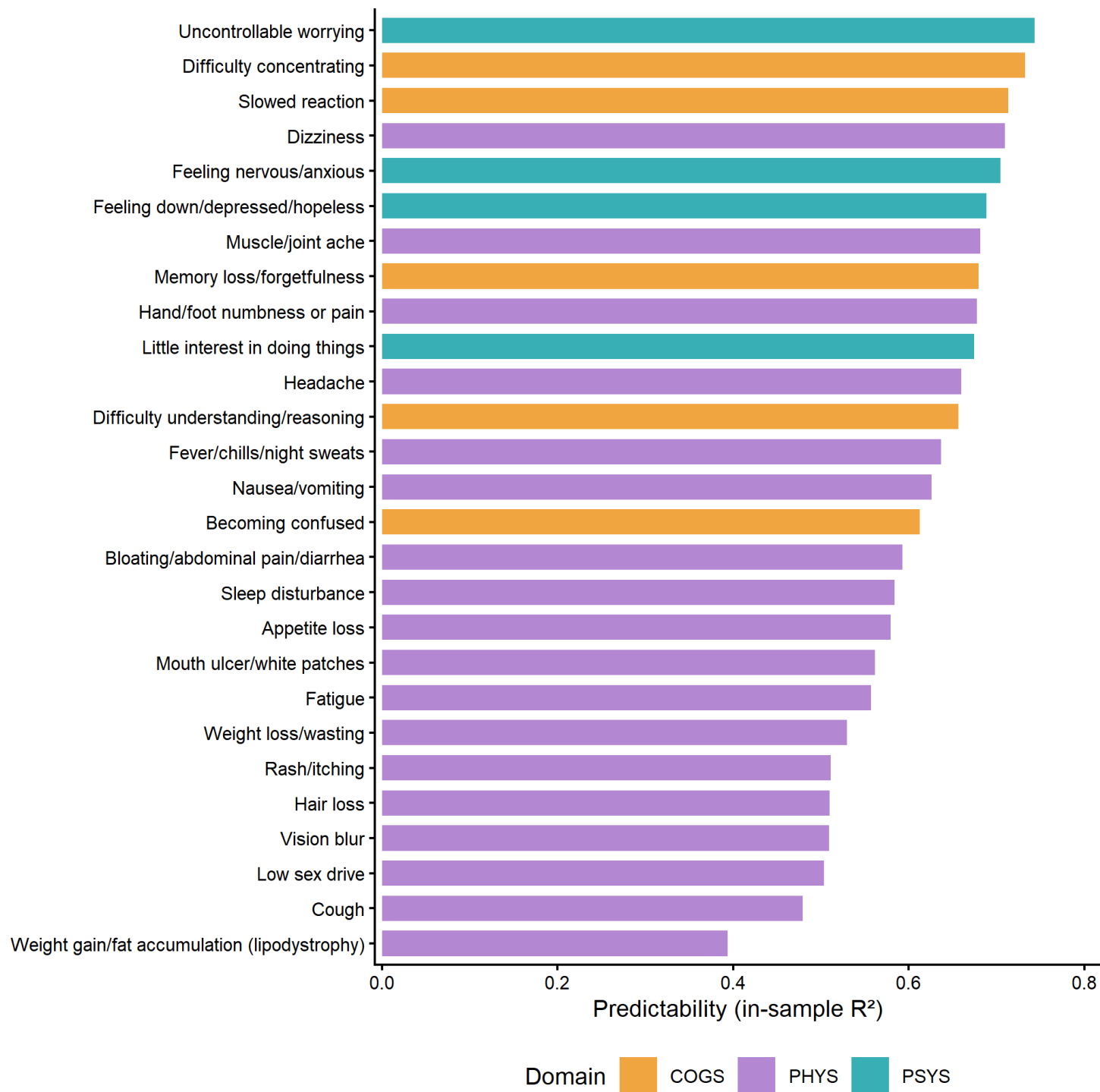


Figure 4

Node predictability in the composite symptom experience network among PLWH. In-sample R^2 was derived from the primary EBICglasso precision matrix and denotes the proportion of observed variance in each symptom reproduced by the remaining network nodes.

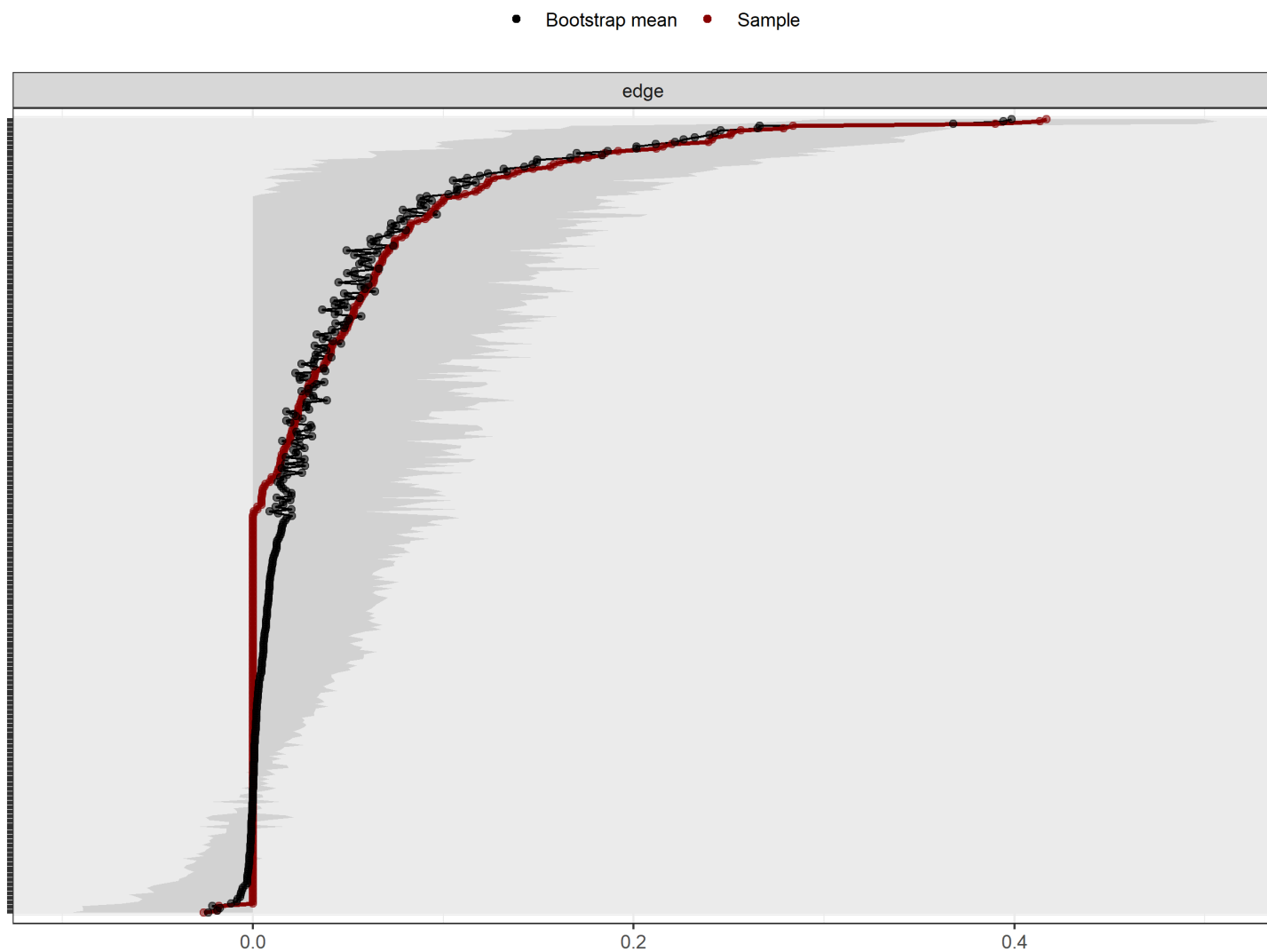


Figure 5

Nonparametric bootstrap results for edge-weight accuracy. Horizontal lines represent 95% confidence intervals; narrower intervals indicate more precise edge-weight estimates.

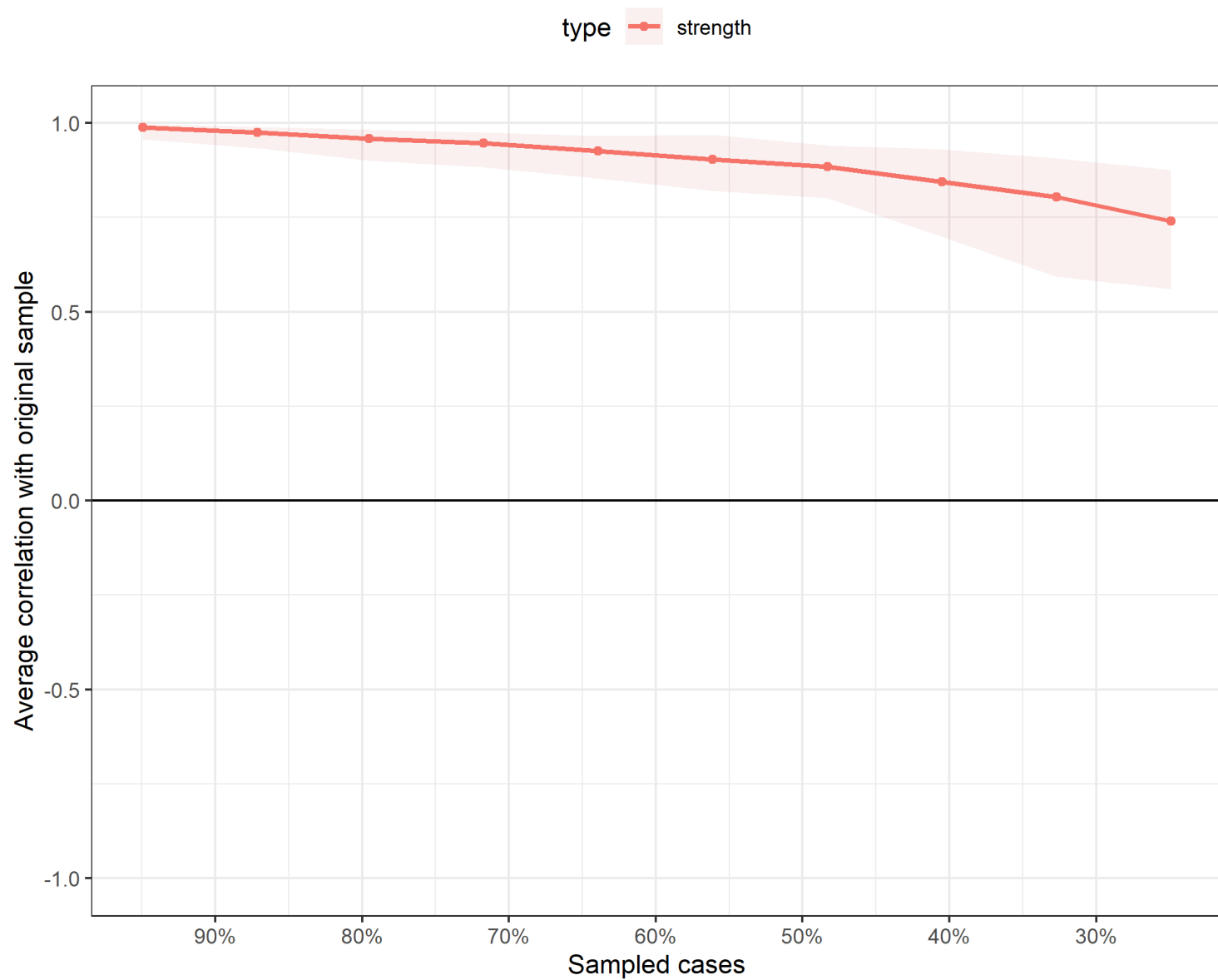


Figure 6

Case-dropping bootstrap analysis of node strength. The plot shows correlations between node strength estimates in subsamples and those in the original sample across retained sample proportions.

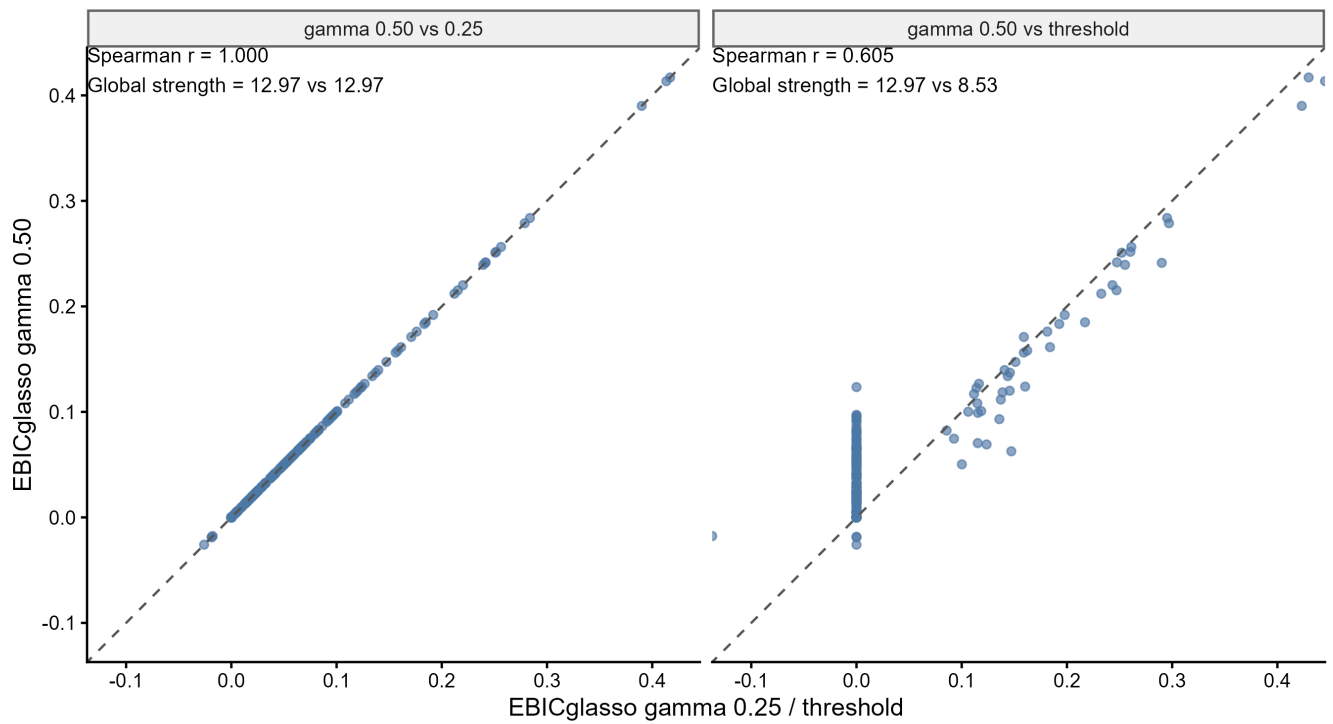


Figure 7

Robustness analysis of network estimation. Edge weights and global strength were compared across EBIC $\gamma=0.50$, $\gamma=0.25$, and threshold=TRUE specifications.

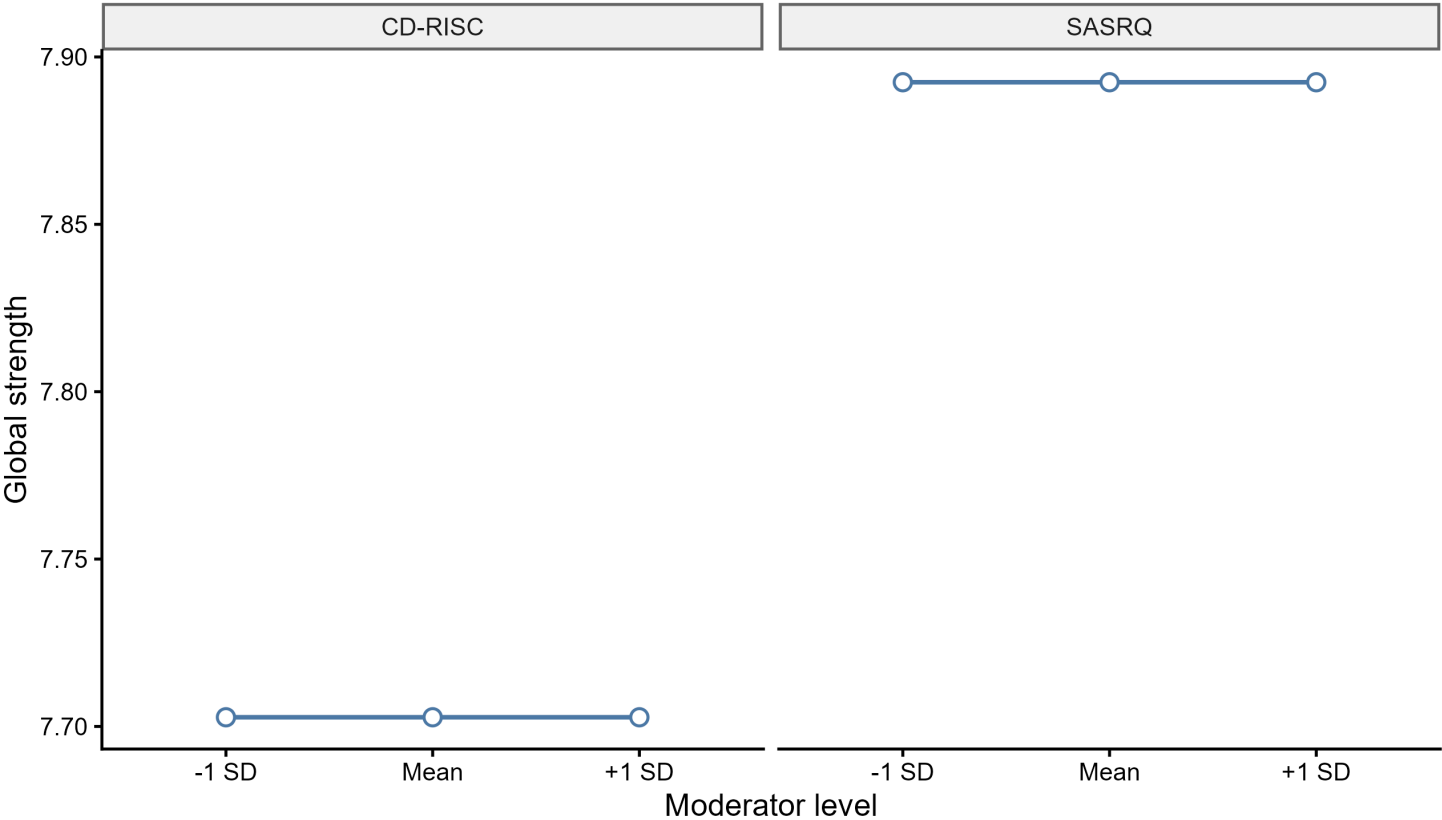


Figure 8

Conditional networks with SASRQ and CD-RISC as continuous moderators. Networks were estimated at low (−1 SD), mean, and high (+1 SD) moderator levels and compared by global strength, number of non-zero edges, and edge-weight pattern.

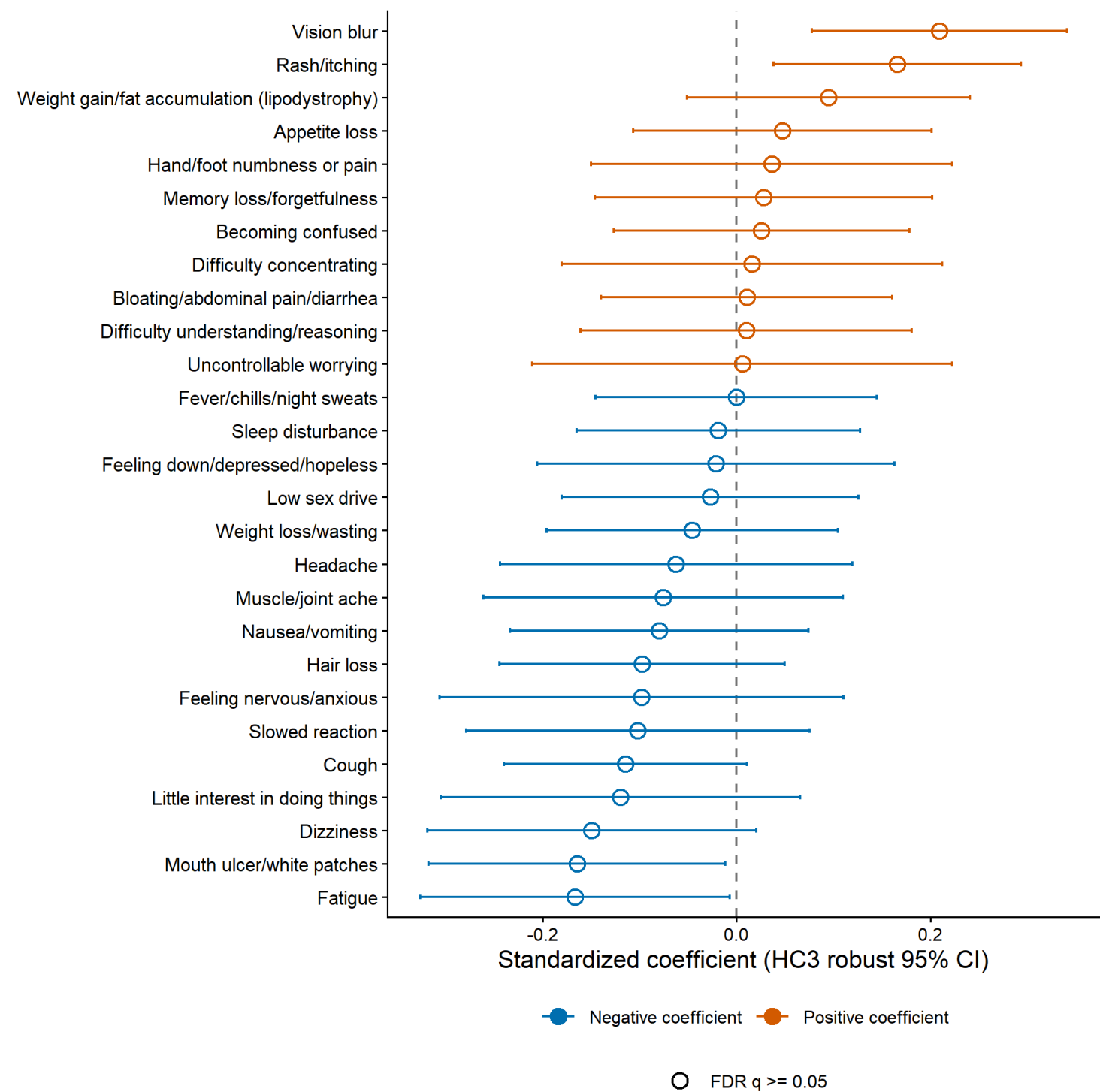


Figure 9

Symptom associations with the overall MOS-HIV domain mean score. The forest plot presents coefficients and HC3-robust 95% confidence intervals for all 27 z-standardized composite symptom experience scores. The full

multivariable model was adjusted for sex, age, educational level, annual income, marital status, and number of comorbid chronic diseases. No symptom remained significant after FDR correction.

Supplementary Files

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