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**Network dynamics of depressive symptoms in antidepressant medication treatment:
Secondary analysis of eight clinical trials**

Running title: Symptom networks during antidepressant trials

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Abstract

Depression can be viewed as a network of depressive symptoms that tend to reinforce each other via feedback loops. Specific symptoms of depression may be differently responsive to antidepressant treatment, and some symptoms may be more important than others in the overall improvement of depression associated with treatment. We pooled prospective data from eight industry-sponsored placebo-controlled trials for paroxetine, fluoxetine and imipramine (total n=3559) to examine whether improvements in specific depressive symptoms were more strongly related to improvements in other depressive symptoms among patients on active antidepressant treatment as compared to placebo. Depressive symptoms were assessed with the 17-item Hamilton Depression Rating Scale. Data on treatment was dichotomized into active treatment (receiving any antidepressant agent) vs placebo. Time-lagged longitudinal analyses suggested that improvement in three symptoms – depressed mood, insomnia, and suicidality – had a broader overall impact on subsequent improvement in other depressive symptoms in the antidepressant condition compared to placebo (i.e. greater out-strength). Moreover, improvements in depressed mood and insomnia were more likely to follow the improvements in other symptoms in the antidepressant condition compared to placebo (i.e. greater in-strength). These results from clinical trial data suggest that depressed mood, insomnia, and suicidality may be particularly important in accounting for the remission and recovery in response to antidepressant treatment.

Introduction

The network approach to mental disorders postulates that mental disorders arise from the interactive associations between distinct symptoms.^{1–3} Depression has been studied from a network perspective, mostly by examining cross-sectional networks of depressive symptoms^{4–7} but also by examining dynamic networks comprising symptom associations over time.^{3,8} Dynamic networks can be particularly useful for understanding how changes in specific symptoms are related to changes in other symptoms, and which symptoms are most central and have the broadest impact on other symptoms.

Understanding the temporal dynamics in the improvement of symptoms may be particularly relevant in the context of depression treatment, because different symptoms may be differently responsive to antidepressants.⁹ For instance, a multitrial study showed that depressed mood was associated with a greater antidepressant treatment response than the depression sum score or any other individual symptom.¹⁰ Another study found that depressed mood responded to antidepressant treatment more rapidly than the depression sum score, outperforming placebo already after one week of treatment.¹¹ Thus, the overall response to antidepressant treatment may depend on the symptom profile of the patient. However, there are no studies of antidepressant medication that have assessed whether there are differences in how changes in specific depressive symptoms predict the improvement of other symptoms during the course of clinical trials.

We used data from eight industry-sponsored placebo-controlled antidepressant trials to examine the dynamic associations between symptom improvements over time among patients on active antidepressant treatment vs placebo. We did not have specific hypotheses about the symptoms that would have the broadest influence on other symptoms. However, we hypothesized that the improvements in different symptoms would be more strongly related to improvements in other symptoms among patients on active antidepressant treatment as compared to placebo treatment.

Materials and methods

Sample

We used data from eight industry-sponsored, US Food and Drug Administration (FDA)-registered, placebo-controlled trials for paroxetine (GSK/003, GSK/009, GSK/115, GSK/448, GSK/449, GSK/487, GSK/810, GSK/874), fluoxetine (GSK/115) and imipramine (GSK/003) from GlaxoSmithKline (Brentford, UK). All trials were conducted between 1985 and 2010 among adults

with major depression and included symptom-level data on depressive symptoms measured with the 17-item Hamilton Depression Rating Scale (HDRS-17). Depressive symptoms were assessed at baseline and repeatedly after baseline; there were 5–8 post-baseline assessments depending on trial. Minimum trial length was 6 weeks and maximum 12 weeks.

We included all the randomized patients with baseline assessment and at least one post-baseline assessment of depressive symptoms. The full eligible population thus included 3559 patients. Of them, 129 were not included in the analysis on *longitudinal symptom improvements* (see Statistical analysis section for details) as they did not have the three repeated measurements on depressive symptoms required to examine longitudinal improvements (improvement between time t and time $t + 1$, predicting improvement between time $t + 1$ and $t + 2$). Thus, the analysis on longitudinal symptom improvements was conducted in a subsample of 3430 patients.

Measures

Depressive symptoms were recorded with the 17-item Hamilton Depression Rating Scale (HDRS-17). The 17 items assess depressed mood, feelings of guilt, suicidality, early-night insomnia, middle-night insomnia, insomnia during early morning hours, difficulties in work and activities, retardation, agitation, psychic anxiety, somatic anxiety, gastrointestinal (GI) problems, general somatic symptoms, genital symptoms, hypochondria, weight loss and lack of insight (i.e. acknowledgement of being ill). Responses to items were given on scales ranging either 0–4 or 0–2, where higher values indicate greater severity.

A change in each symptom over each two consecutive assessments was coded either as improvement (if symptom score decreased between time t and $t + 1$) or no improvement (if symptom score remained the same or increased between time t and $t + 1$) (1/0).

Data on treatment was dichotomized into active treatment (receiving antidepressant agent) vs placebo (1/0).

Statistical analysis

Network structures of improvements in depressive symptoms were assessed separately among patients receiving active treatment vs placebo. Network structures consist of nodes and edges. In our analysis, improvements in depressive symptoms represent the nodes, and the associations between symptom improvements represent the edges. In networks based on cross-sectional data, no

direction of association can be assumed between nodes. Thus, such networks are called undirected, whereas networks that contain directed (temporal) information from one node to another are called directed networks. Weighted networks include edge weights that specify the magnitude of associations between the nodes in a network.

The network associations between symptom improvements were assessed in two independent analyses. First, we estimated weighted, undirected networks depicting cross-sectional associations between improvements in all depressive symptoms (improvements from time t to time $t + 1$) to assess whether improvement in some symptoms is particularly likely to co-occur with improvement in other symptoms. We refer to this as the analysis on *cross-sectional improvements*. Second, as the primary interest, we estimated weighted, directed networks depicting time-lagged longitudinal associations from improvement in each symptom (from time t to time $t + 1$) to subsequent improvement in all other symptoms (from time $t + 1$ to time $t + 2$) to evaluate whether improvement in specific symptoms is particularly predictive of subsequent improvement in other symptoms. We refer to this as the analysis on *longitudinal improvements*.

The edge weights (i.e., magnitude of the network associations) were estimated with 2-step meta-analysis where we first conducted series of logistic regression analyses separately within each trial. To calculate edge weights of undirected networks assessing *cross-sectional improvements* in depressive symptoms, we conducted a series of logistic regression analyses where improvement in each symptom between time t and $t + 1$ was used to predict improvement in all other symptoms between time t and $t + 1$. Separate models were fitted for each exposure-outcome combination, adjusting for age, sex and cross-sectional improvement in all other symptoms except the exposure and outcome symptoms. To calculate edge weights of directed networks assessing *longitudinal improvements* in depressive symptoms, we used improvement in each symptom between time t and $t + 1$ to predict subsequent improvement in all symptoms between time $t + 1$ and $t + 2$ (including autoregressive associations, i.e. improvement in symptom i predicting subsequent improvement in the same symptom i). Again, separate models were fitted for each exposure-outcome combination, this time adjusting for age, sex, the time interval between study visits and the time-lagged improvement (from t to $t + 1$) in all symptoms except the exposure symptom. We used all available data from each patient so a patient could contribute up to eight person-observations in the analysis on cross-sectional improvements and seven person-observations in the analysis on longitudinal improvements. For example, in the analysis of longitudinal improvements, improvement between assessment times 1 and 2 would predict subsequent improvement between assessment times 2 and

3, improvement between assessment times 2 and 3 would predict subsequent improvement between assessment times 3 and 4, and so on throughout the follow-up period. Robust standard errors were used in all analyses to consider the repeated measurements within individuals.

We then pooled the edge weight estimates obtained from the eight trials in a meta-analysis and used the pooled weights to estimate the networks. Only statistically significant paths ($p < 0.05$ in a two-sided test) were included. Autoregressive paths (from improvement in symptom i between time t and $t + 1$ to improvement in the same symptom i between time $t + 1$ and $t + 2$) obtained from the meta-analysis were not included in the directed networks, as we were interested in assessing the relative importance of improvement in each symptom predicting improvement in other symptoms. As autoregressive paths were negative (improvement of a symptom between t and $t + 1$ decreased the likelihood of further improvement of the same symptom between $t + 1$ and $t + 2$), their inclusion would have interfered with the estimation of the centrality parameters of interest. We visualized the networks using the pooled estimates and calculated the centrality indices for those networks. These were done using the qgraph package in R. For the undirected cross-sectional networks, we assessed *strength* (i.e., sum of weights connected to each symptom) as the relevant centrality parameter, which indicated how connected improvement in each symptom is with cross-sectional improvement in other symptoms. For the directed longitudinal networks, we assessed *out-strength* (i.e., sum of weights from each symptom to others), indicating how connected improvement in each symptom is with subsequent improvement in other symptoms and *in-strength* (i.e., sum of weights to each symptom from others), indicating how likely improvement in each symptom follows after prior improvement in other symptoms. Confidence intervals for centrality indices were calculated by resampling values for the centrality indices 500 times from a distribution with the pooled estimates and standard errors obtained from the meta-analysis as the distribution mean and standard deviation.

In the primary analysis described above, the edges included in the networks were selected based on statistical significance, which may bias the selection of the edges. As a sensitivity analysis, we estimated the associations between symptom improvements using LASSO (least absolute shrinkage and selection operator) regression. We pooled all data and conducted adaptive LASSO logistic regression analyses to estimate the edge weights to be included in networks of cross-sectional symptom improvements (improvement in each symptom between time t and $t + 1$ predicting improvement in all other symptoms between time t and $t + 1$) and longitudinal symptom improvements (improvement in each symptom between time t and $t + 1$ predicting improvement in

all symptoms between time $t + 1$ and $t + 2$). Furthermore, following a reviewer's suggestion, we additionally conducted a network intervention analysis.¹² We pooled all data and estimated cross-sectional LASSO-regularized networks for each study visit to assess the sequential symptom-specific treatment effects. The cross-sectional networks included all depressive symptoms measured on the original HDRS-17 scales (ranging 0–2 or 0–4) and a dichotomous variable indicating the treatment condition.

Statistical analyses were conducted in Stata 16.0 (StataCorp, College Station, TX) and R (R Core Team, 2017). The code for the primary analysis is provided in **Supplementary Codes 1–2**.

Results

The 3559 eligible patients contributed a total of 22944 person-observations across the eight trials. A total of 2526 (71%) patients were on active treatment. There were 2066 (58%) women and the mean age was 47.0 (SD, 16.0). **Supplementary Figure 1** presents the mean scores of depressive symptoms across the follow-up.

The networks for cross-sectional and longitudinal improvements in depressive symptoms are shown in **Figures 1–2**. A total of 73 edges were included in the networks of cross-sectional improvements in the placebo condition and 93 in the active treatment condition. A total of 53 edges were included in the networks of longitudinal improvements both in the placebo and active treatment conditions. In both treatment conditions, improvement in each depressive symptom was associated with both cross-sectional and longitudinal improvement in at least one other symptom. The associations in all networks were largely positive, indicating that improvement in each symptom was mostly associated with cross-sectional or longitudinal improvement (instead of deterioration or no change) in other depressive symptoms. The magnitudes of all network associations are presented in **Supplementary Tables 1–2** (odds ratios for cross-sectional improvements ranged 0.74–3.22 in the active treatment condition and 0.66–3.07 in the placebo condition; odds ratios for longitudinal improvements ranged 0.70–1.66 in the active treatment condition and 0.75–1.95 in the placebo condition).

Figure 3 shows how improvement in each depressive symptom between time t and $t + 1$ was cross-sectionally related to improvements in other symptoms during the same time interval t and $t + 1$. The highest strength estimates were observed for depressed mood and difficulties in work and activities, indicating that improvement in these symptoms was most connected with cross-sectional

improvement in other depressive symptoms (**Figure 3, Figure 1**). We observed a higher strength estimate for suicidality among those on active treatment (e.g., point estimates non-overlapping with confidence intervals, **Supplementary Table 3, Figure 3, Figure 1**), as compared to those on placebo. Similarly, greater strength estimates in the active treatment condition were observed for agitation, general somatic symptoms and hypochondria (**Supplementary Table 3, Figure 3, Figure 1**).

Figure 4 shows the main results of interest, that is, how improvement in each symptom between time t and $t + 1$ was longitudinally related to improvements in other symptoms between time $t + 1$ and $t + 2$. The highest out-strength estimate was observed for suicidality, which indicated that improvement in suicidality had the highest overall impact on longitudinal improvement in other symptoms (**Figure 4, Figure 2**). Moreover, the out-strength estimate for suicidality was higher among those on active treatment compared to placebo (**Supplementary Table 4, Figure 4, Figure 2**). Greater out-strength estimates in the active treatment condition were also observed for depressed mood, insomnia (early in the night, in the middle of the night or during early morning hours) and difficulties in work and activities (**Supplementary Table 4, Figure 4, Figure 2**).

The highest in-strength estimate was observed for insight, both among those on active treatment and placebo, indicating that improvement in insight was particularly likely to occur after improvement in other symptoms. The placebo condition demonstrated a higher in-strength estimate for insight compared to the active treatment condition. By contrast, those on active treatment had higher in-strength estimates for depressed mood, insomnia (in the middle of the night or during early morning hours) and GI symptoms (**Supplementary Table 4, Figure 4, Figure 2**).

Supplementary Figures 2–5 present the networks and centrality estimates after adaptive LASSO selection. A total of 105 edges were included in the networks of cross-sectional improvements in the placebo condition and 111 in the active treatment condition. A total of 127 edges were included in the networks of longitudinal improvements in the placebo condition and 136 in the active treatment condition. As in the primary analysis on cross-sectional symptom improvements, the strength estimates for suicidality and general somatic symptoms were higher among those on active treatment as compared to placebo. In contrast, strength estimates for agitation and hypochondria did not differ between the treatment conditions (**Supplementary Figures 2–3**). As in the primary analysis on longitudinal symptom improvements, the out-strength estimates for suicidality, depressed mood, and insomnia (early in the night, in the middle of the night or during early

morning hours) were higher among those on active treatment. Likewise, those on active treatment had higher in-strength estimates for depressed mood, insomnia (during early morning hours) and GI symptoms. In contrast to the primary analysis on longitudinal symptom improvements, the out-strength estimate for difficulties with work and activities did not differ between the treatment conditions (**Supplementary Figures 4–5**). Results from the network intervention analysis indicated that active antidepressant treatment was first and most consistently associated with improvement in depressed mood, which was strongly associated with difficulties in work and activities, suicidality, guilt, retardation and psychic anxiety (**Supplementary Figure 6**).

Discussion

We pooled data from eight industry-sponsored placebo-controlled antidepressant trials to examine symptom-specific patterns in the improvement of depression among patients on active antidepressant treatment and placebo. In both treatment conditions, improvement in each depressive symptom was associated with both cross-sectional and longitudinal improvement in at least one other symptom. Improvement in one symptom was mostly associated with improvement—instead of deterioration or no change—in other symptoms. In both treatment conditions, improvements in depressed mood and difficulties in work and activities were most likely to co-occur with improvements in the other symptoms. In time-lagged longitudinal analysis, improvement in suicidality was most broadly connected with later improvements in other symptoms (i.e., high network out-strength). Improvements in other symptoms, in turn, were most likely to be observed as improvements in insight (i.e., high network in-strength).

There were some differences in the relative importance of depressive symptoms between people with and without active antidepressant treatment. First, improvement in depressed mood was more strongly connected with subsequent improvements in other symptoms among those on active treatment compared to placebo. Depressed mood is one of the two central symptoms for the diagnosis of major depressive disorder.^{13,14} Depressed mood has previously been associated with a greater, and more rapid, antidepressant treatment response than when treatment response was assessed with the full HDRS-17 sum score or any other individual HDRS-17 item.^{10,11} These findings have suggested that depressed mood may be particularly important in the effectiveness of antidepressant treatment. Our current finding adds evidence to this hypothesis by demonstrating that antidepressant treatment may amplify the cascading improvements in other symptoms that follow the improvements in depressed mood. This amplifying effect might be related to an increased neuroplasticity that has been suggested to account for effectiveness of antidepressants.¹⁵

Improvements in two indicators of insomnia (middle in the night and during early morning hours) were more connected with subsequent improvements in the rest of the symptoms among those on antidepressant treatment compared to those on placebo. Persistent insomnia has been associated with lower efficacy of depression treatment¹⁶ and worse prognosis of people in treatment for depression.¹⁷ Although antidepressant treatments have not demonstrated consistently beneficial effects on sleep,^{18,19} our results suggest improvement in insomnia may trigger improvement in other symptoms particularly among people on active antidepressant treatment.

Depressed mood and insomnia stood out from the other symptoms also in that improvements in the other symptoms were particularly likely to be observed as improvements in depressed mood and insomnia among those receiving antidepressant treatment, as compared to those on placebo. These findings suggest that depressed mood and insomnia may be particularly important to overall symptom improvement associated with antidepressant treatment. If improvements in depressed mood and insomnia trigger similar activation in other symptoms, which then leads to further improvement in depressed mood and insomnia, such feedback loops may be particularly relevant in driving remission and recovery. Whether such processes exist and appear more prominent among people on antidepressant treatment needs to be evaluated further.

Previous studies using network analysis³ and direction of dependence methods²⁰ have suggested that suicidality may be a particularly central symptom in reinforcing other depressive symptoms. We also found that improvement in suicidality was most strongly connected with subsequent improvement in other symptoms. This association was even greater among those receiving antidepressant treatment compared to placebo. Thus, suicidality may also be a central depression symptom in activating the improving symptom network in response to antidepressant treatment. Somewhat different symptoms appeared to trigger changes in suicidality in the antidepressant condition compared to placebo: functional improvement in work and activities was less likely to lead to subsequent improvement in suicidality only in the antidepressant condition. This would be in agreement with the suggestion that, in the absence of improvement in suicidal thoughts, functional improvement may heighten suicide risk among people with severe depression.²¹ However, this may not be related to antidepressant use as such; the evidence for a link between antidepressant use and increased suicidality in adults is weak,^{22–24} and after the LASSO selection, we observed the association of functional improvement with lack of improvement in suicidality also in the placebo group.

Our study has limitations. Although our data is from randomized trials, our analytic strategy does not allow causal conclusions because the trials did not manipulate specific symptoms. The causal dynamics underlying symptom improvement is not known, and apart from the potential risk of overadjustment,²⁵ we accounted for improvement in all other depressive symptoms and other relevant confounders in estimating the network edges. The application of strength centrality parameters is limited in symptom networks, as the parameters are calculated as the absolute sum of edge weights and thus do not account for the distinction between positive and negative associations between symptoms.²⁶ However, most network connections in our study were positive and we took this limitation into account in all our conclusions. We used dichotomous measures for symptom improvement, which inevitably results in loss of information about the magnitude of improvement, and does not address the distinction between deterioration and no change in detail. While dichotomous improvement scores are clinically relevant, measurement error may induce correlations between them that can affect the interpretation of our results. In order to determine temporal ordering, our time-lagged analysis examined how symptom change between assessment time t and $t + 1$ predicted symptom change between assessment time $t + 1$ and $t + 2$, with assessments mostly spaced by one or two weeks. It would be important to determine whether weekly or biweekly assessments provide the optimal time lag to identify symptom-specific dynamics or whether the network dynamics change at shorter or longer time intervals. Our analysis assessed the difference between those on active antidepressant treatment and placebo without distinguishing between paroxetine, fluoxetine and imipramine. However, it is possible that different antidepressants act differently on specific depressive symptoms.¹⁰ Finally, our study sample comprised adults meeting the standard eligibility criteria for antidepressant trials, which limits the generalizability of these results.

In conclusion, we observed that improvements in specific symptoms of depression were more strongly associated with improvements in other depressive symptoms. Depressed mood, insomnia, and suicidality appeared to be particularly important to the networks of symptom improvement in the antidepressant group as compared to the placebo group. While our analysis examined symptom improvement among all eligible patients throughout the trials, future studies could examine symptom-specific improvements by focusing only on particular groups of individuals who have specific symptom(s) at baseline in order to assess whether the treatment prognosis differs by baseline symptom profile. Studies are also needed to assess potential drug-specific effects, address symptom improvement in idiographic network models that take into account possible individual

differences,^{27–29} and further elucidate the sequential development and order of symptom improvement to understand the more detailed dynamics of symptom-specific treatment effects.

Supplementary information is available at *Molecular Psychiatry* website.

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Conflict of Interest. The authors declare no conflict of interest.

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Figure legends

Figure 1. Undirected networks for cross-sectional associations between improvements in depressive symptoms

Placebo

Active treatment

N=3559 (n=1033 (29%) placebo, n=2526 (71%) active treatment)

Abbreviations: depr, depressed mood; guilt, feelings of guilt; suic, suicidality; inse, insomnia (early); insm, insomnia (middle); insl, insomnia (late); work, difficulties in work and activities; reta, retardation; agit, agitation; apsy, anxiety (psychic); asom, anxiety (somatic); gast, gastrointestinal problems; soma, general somatic symptoms; geni, genital symptoms; hypc, hypochondria; wtls, weight loss, insg; lack of insight.

Blue connections represent positive associations, red connections represent negative associations. Thicker lines (edges) represent stronger associations (positive or negative).

Figure 2. Directed networks for time-lagged longitudinal associations between improvements in depressive symptoms

Placebo

Active treatment

N=3430 (n=1013 (30%) placebo, n=2417 (70%) active treatment)

Abbreviations: depr, depressed mood; guilt, feelings of guilt; suic, suicidality; inse, insomnia (early); insm, insomnia (middle); insl, insomnia (late); work, difficulties in work and activities; reta, retardation; agit, agitation; apsy, anxiety (psychic); asom, anxiety (somatic); gast, gastrointestinal problems; soma, general somatic symptoms; geni, genital symptoms; hypc, hypochondria; wtls, weight loss, insg; lack of insight.

Autoregressive paths were not included in networks. Blue connections represent positive associations, red connections represent negative associations. Thicker lines (edges) represent stronger associations (positive or negative).

Figure 3. Strength (centrality) estimates of networks comprising cross-sectional associations between symptom improvements

N=3559 (n=1033 (29%) placebo, n=2526 (71%) active treatment)

Open circles represent those receiving placebo, whereas filled circles represent those receiving active treatment. Strength estimates are standardized. Stars denote those strength estimates that differed between the treatment conditions based on resampling (e.g. mutually non-overlapping point estimates and confidence intervals between the placebo and active treatment conditions).

Figure 4. Out-strength and in-strength (centrality) estimates of networks comprising time-lagged longitudinal associations between symptom improvements

N=3430 (n=1013 (30%) placebo, n=2417 (70%) active treatment)

Open circles represent those receiving placebo, whereas filled circles represent those receiving active treatment. Out-strength and in-strength estimates are standardized. Stars denote those out-strength and in-strength estimates that differed between the treatment conditions based on resampling (e.g. mutually non-overlapping point estimates and confidence intervals between the placebo and active treatment conditions).

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Supplementary material

Supplementary Table 1. Adjusted log odds for undirected associations between cross-sectional symptom improvements

Supplementary Table 2. Adjusted log odds for directed associations between time-lagged longitudinal symptom improvements

Supplementary Table 3. Strength (centrality) estimates and confidence intervals of networks comprising cross-sectional associations between symptom improvements after resampling

Supplementary Table 4. Out-strength and in-strength (centrality) estimates and confidence intervals of networks comprising time-lagged longitudinal associations between symptom improvements after resampling

Supplementary Figure 1. Mean scores of depressive symptoms across the follow-up

Supplementary Figure 2. Undirected networks for cross-sectional associations between improvements in depressive symptoms after LASSO selection

Supplementary Figure 3. Strength (centrality) estimates of networks comprising cross-sectional associations between symptom improvements after LASSO selection

Supplementary Figure 4. Directed networks for time-lagged longitudinal associations between improvements in depressive symptoms after LASSO selection

Supplementary Figure 5. Out-strength and in-strength (centrality) estimates of networks comprising time-lagged longitudinal associations between symptom improvements after LASSO selection

Supplementary Figure 6. Network intervention analysis

Supplementary Code 1. Stata code for creating the edgelist (for directed networks) and weight matrices (for undirected networks)

Supplementary Code 2. R code for time-lagged longitudinal (directed) and cross-sectional (undirected) network analyses

Supplementary Table 1. Adjusted log odds for undirected associations between cross-sectional symptom improvements

		Placebo				Active treatment			
Between		Log odds	2.50 %	97.50 %	p-value	Log odds	2.50 %	97.50 %	p-value
guil	depr	0.73	0.57	0.89	0.000	0.67	0.57	0.77	0.000
suic	depr	0.57	0.39	0.75	0.000	0.71	0.61	0.82	0.000
suic	guil	0.43	0.25	0.60	0.000	0.64	0.53	0.75	0.000
inse	depr	0.30	0.13	0.47	0.001	0.28	0.18	0.38	0.000
inse	guil	0.18	0.00	0.35	0.051	0.16	0.06	0.27	0.002
inse	suic	0.19	0.00	0.38	0.046	0.36	0.24	0.48	0.000
insm	depr	0.33	0.17	0.50	0.000	0.20	0.10	0.30	0.000
insm	guil	0.14	-0.03	0.32	0.105	0.03	-0.07	0.14	0.521
insm	suic	0.11	-0.09	0.31	0.270	0.12	0.01	0.24	0.038
insm	inse	0.89	0.72	1.07	0.000	0.70	0.59	0.80	0.000
insl	depr	0.31	0.14	0.49	0.000	0.20	0.10	0.30	0.000
insl	guil	0.26	0.08	0.44	0.004	0.14	0.04	0.25	0.007
insl	suic	0.15	-0.05	0.35	0.148	0.07	-0.05	0.18	0.266
insl	inse	0.47	0.29	0.64	0.000	0.53	0.42	0.64	0.000
insl	insm	1.12	0.95	1.29	0.000	1.17	1.07	1.28	0.000
work	depr	1.03	0.87	1.19	0.000	0.94	0.85	1.03	0.000
work	guil	0.43	0.27	0.60	0.000	0.34	0.24	0.44	0.000
work	suic	0.26	0.08	0.44	0.006	0.28	0.18	0.39	0.000
work	inse	0.26	0.08	0.43	0.004	0.09	-0.02	0.19	0.095
work	insm	0.19	0.02	0.37	0.028	0.15	0.05	0.26	0.003
work	insl	0.00	-0.18	0.18	0.964	0.24	0.13	0.34	0.000
reta	depr	0.50	0.32	0.67	0.000	0.49	0.39	0.59	0.000
reta	guil	0.35	0.17	0.53	0.000	0.29	0.18	0.40	0.000
reta	suic	0.26	0.07	0.46	0.009	0.26	0.15	0.38	0.000
reta	inse	0.05	-0.14	0.24	0.615	-0.02	-0.13	0.09	0.745
reta	insm	0.29	0.10	0.48	0.003	0.01	-0.11	0.12	0.914
reta	insl	0.11	-0.08	0.30	0.252	0.18	0.07	0.30	0.002
reta	work	0.56	0.38	0.73	0.000	0.55	0.45	0.65	0.000
agit	depr	0.26	0.09	0.44	0.003	0.20	0.10	0.31	0.000
agit	guil	0.13	-0.06	0.31	0.175	0.18	0.08	0.29	0.000
agit	suic	0.11	-0.08	0.30	0.256	0.12	0.01	0.24	0.039
agit	inse	0.09	-0.08	0.27	0.302	0.19	0.08	0.29	0.001
agit	insm	0.16	-0.02	0.34	0.087	0.15	0.04	0.26	0.006
agit	insl	0.13	-0.06	0.31	0.192	0.08	-0.03	0.19	0.171
agit	work	0.16	-0.01	0.33	0.069	0.04	-0.07	0.14	0.499
agit	reta	0.13	-0.06	0.32	0.176	0.02	-0.09	0.13	0.753
apsy	depr	0.59	0.43	0.75	0.000	0.61	0.51	0.70	0.000
apsy	guil	0.49	0.33	0.65	0.000	0.49	0.40	0.59	0.000
apsy	suic	0.31	0.13	0.48	0.000	0.30	0.20	0.41	0.000
apsy	inse	0.09	-0.08	0.26	0.306	0.15	0.04	0.25	0.007
apsy	insm	0.18	0.01	0.35	0.039	0.17	0.07	0.28	0.001
apsy	insl	0.28	0.10	0.45	0.002	0.06	-0.05	0.16	0.285
apsy	work	0.52	0.36	0.69	0.000	0.39	0.29	0.48	0.000
apsy	reta	0.33	0.17	0.50	0.000	0.31	0.21	0.41	0.000
apsy	agit	0.54	0.37	0.71	0.000	0.54	0.45	0.64	0.000
asom	depr	0.21	0.04	0.37	0.014	0.21	0.11	0.31	0.000
asom	guil	0.04	-0.14	0.21	0.690	0.18	0.08	0.28	0.000
asom	suic	0.28	0.10	0.46	0.002	0.18	0.06	0.29	0.002
asom	inse	0.20	0.03	0.38	0.024	0.23	0.13	0.33	0.000
asom	insm	0.20	0.02	0.38	0.033	0.07	-0.04	0.18	0.194
asom	insl	0.11	-0.07	0.29	0.246	0.17	0.07	0.28	0.001
asom	work	0.34	0.17	0.51	0.000	0.17	0.07	0.27	0.001
asom	reta	0.15	-0.03	0.34	0.096	0.15	0.05	0.26	0.005
asom	agit	0.38	0.21	0.55	0.000	0.27	0.17	0.38	0.000
asom	apsy	0.49	0.32	0.65	0.000	0.42	0.32	0.51	0.000

gast	depr	0.26	0.07	0.45	0.007	0.29	0.17	0.41	0.000
gast	guil	0.21	0.01	0.40	0.037	0.03	-0.10	0.15	0.675
gast	suic	0.27	0.06	0.49	0.013	0.13	0.00	0.25	0.056
gast	inse	0.30	0.10	0.51	0.004	0.24	0.12	0.36	0.000
gast	insm	0.06	-0.14	0.25	0.560	0.19	0.07	0.31	0.002
gast	insl	-0.03	-0.24	0.17	0.770	0.18	0.06	0.30	0.004
gast	work	0.23	0.02	0.43	0.029	0.21	0.09	0.32	0.000
gast	reta	0.33	0.12	0.54	0.002	0.18	0.06	0.30	0.003
gast	agit	0.06	-0.14	0.26	0.556	0.11	-0.01	0.23	0.073
gast	apsy	0.21	0.01	0.41	0.038	0.05	-0.06	0.17	0.342
gast	asom	0.29	0.10	0.48	0.002	0.28	0.17	0.40	0.000
soma	depr	0.55	0.38	0.72	0.000	0.44	0.34	0.54	0.000
soma	guil	0.22	0.05	0.40	0.013	0.31	0.20	0.41	0.000
soma	suic	0.07	-0.13	0.26	0.501	-0.17	-0.29	-0.05	0.004
soma	inse	0.03	-0.16	0.22	0.749	0.15	0.04	0.26	0.006
soma	insm	0.22	0.02	0.41	0.028	0.17	0.07	0.28	0.002
soma	insl	0.12	-0.07	0.31	0.202	0.10	-0.01	0.21	0.070
soma	work	0.71	0.54	0.89	0.000	0.78	0.68	0.88	0.000
soma	reta	0.28	0.09	0.47	0.004	0.31	0.21	0.42	0.000
soma	agit	0.05	-0.14	0.24	0.620	0.11	0.01	0.22	0.035
soma	apsy	0.25	0.07	0.43	0.007	0.22	0.12	0.32	0.000
soma	asom	0.39	0.21	0.56	0.000	0.31	0.21	0.41	0.000
soma	gast	0.15	-0.07	0.36	0.177	0.19	0.07	0.31	0.002
geni	depr	0.34	0.15	0.53	0.000	0.28	0.17	0.40	0.000
geni	guil	0.38	0.20	0.57	0.000	0.13	0.01	0.25	0.032
geni	suic	0.13	-0.09	0.35	0.236	0.02	-0.11	0.16	0.730
geni	inse	0.19	-0.02	0.40	0.078	0.01	-0.11	0.14	0.811
geni	insm	-0.02	-0.23	0.18	0.830	0.20	0.08	0.32	0.001
geni	insl	0.22	0.01	0.42	0.036	0.14	0.02	0.27	0.022
geni	work	0.46	0.27	0.65	0.000	0.35	0.24	0.47	0.000
geni	reta	0.07	-0.13	0.27	0.493	0.23	0.11	0.35	0.000
geni	agit	0.09	-0.12	0.30	0.386	0.06	-0.06	0.18	0.308
geni	apsy	0.33	0.14	0.53	0.001	0.09	-0.03	0.20	0.134
geni	asom	0.17	-0.03	0.36	0.091	0.28	0.17	0.39	0.000
geni	gast	-0.01	-0.26	0.23	0.911	0.13	-0.01	0.26	0.060
geni	soma	0.37	0.17	0.56	0.000	0.41	0.29	0.52	0.000
hycp	depr	0.13	-0.06	0.32	0.194	0.21	0.10	0.33	0.000
hycp	guil	0.39	0.20	0.58	0.000	0.23	0.12	0.34	0.000
hycp	suic	0.11	-0.10	0.32	0.290	0.28	0.16	0.41	0.000
hycp	inse	0.25	0.05	0.45	0.014	0.02	-0.09	0.14	0.706
hycp	insm	-0.12	-0.33	0.09	0.250	0.13	0.01	0.24	0.033
hycp	insl	0.20	0.00	0.40	0.047	0.07	-0.05	0.19	0.261
hycp	work	0.14	-0.05	0.34	0.152	0.17	0.05	0.29	0.005
hycp	reta	0.39	0.19	0.60	0.000	0.25	0.13	0.37	0.000
hycp	agit	0.16	-0.03	0.36	0.099	0.29	0.17	0.40	0.000
hycp	apsy	0.44	0.26	0.61	0.000	0.26	0.15	0.37	0.000
hycp	asom	0.52	0.32	0.71	0.000	0.54	0.43	0.66	0.000
hycp	gast	0.20	-0.02	0.41	0.077	0.27	0.14	0.39	0.000
hycp	soma	0.37	0.16	0.57	0.000	0.22	0.11	0.34	0.000
hycp	geni	0.28	0.05	0.51	0.015	0.30	0.17	0.42	0.000
wtls	depr	0.17	-0.03	0.37	0.093	0.06	-0.06	0.18	0.315
wtls	guil	0.13	-0.09	0.35	0.236	-0.02	-0.14	0.10	0.737
wtls	suic	0.37	0.14	0.61	0.002	0.19	0.06	0.32	0.005
wtls	inse	-0.11	-0.34	0.12	0.350	0.09	-0.04	0.22	0.162
wtls	insm	0.14	-0.07	0.36	0.192	-0.04	-0.16	0.09	0.585
wtls	insl	0.18	-0.04	0.39	0.104	0.08	-0.05	0.21	0.219
wtls	work	0.01	-0.21	0.23	0.942	0.03	-0.09	0.15	0.595
wtls	reta	-0.14	-0.38	0.10	0.244	0.05	-0.08	0.18	0.434
wtls	agit	-0.02	-0.24	0.19	0.827	0.03	-0.09	0.15	0.620
wtls	apsy	0.08	-0.12	0.28	0.418	-0.06	-0.17	0.06	0.335

wtls	asom	0.12	-0.09	0.33	0.263	0.07	-0.05	0.19	0.271
wtls	gast	1.05	0.84	1.27	0.000	0.86	0.74	0.99	0.000
wtls	soma	-0.05	-0.28	0.18	0.648	0.06	-0.06	0.18	0.347
wtls	geni	0.14	-0.11	0.38	0.284	0.14	0.01	0.27	0.039
wtls	hypc	0.18	-0.07	0.43	0.155	0.00	-0.14	0.13	0.969
insg	depr	0.51	0.19	0.83	0.002	0.20	0.01	0.39	0.044
insg	guil	0.32	0.00	0.65	0.052	0.33	0.13	0.52	0.001
insg	suic	0.32	-0.03	0.68	0.077	-0.01	-0.24	0.21	0.906
insg	inse	0.24	-0.10	0.58	0.170	0.07	-0.13	0.28	0.487
insg	insm	-0.41	-0.79	-0.04	0.032	0.08	-0.13	0.28	0.467
insg	insl	0.26	-0.07	0.59	0.125	0.09	-0.11	0.29	0.383
insg	work	0.02	-0.32	0.36	0.901	0.11	-0.09	0.30	0.292
insg	reta	0.18	-0.16	0.52	0.312	0.32	0.11	0.53	0.002
insg	agit	0.28	-0.05	0.60	0.100	0.21	0.00	0.41	0.046
insg	apsy	0.06	-0.24	0.37	0.678	0.08	-0.11	0.27	0.427
insg	asom	0.34	0.03	0.66	0.032	0.23	0.02	0.43	0.028
insg	gast	-0.06	-0.45	0.33	0.762	0.10	-0.13	0.33	0.412
insg	soma	0.08	-0.28	0.43	0.666	0.13	-0.08	0.33	0.219
insg	geni	0.46	0.09	0.84	0.016	0.14	-0.09	0.37	0.245
insg	hypc	0.36	0.00	0.72	0.049	0.68	0.47	0.89	0.000
insg	wtls	0.32	-0.04	0.68	0.082	-0.30	-0.56	-0.03	0.029

Abbreviations: depr, depressed mood; guil, feelings of guilt; suic, suicidality; inse, insomnia (early); insm, insomnia (middle); insl, insomnia (late); work, difficulties in work and activities; reta, retardation; agit, agitation; apsy, anxiety (psychic); asom, anxiety (somatic); gast, gastrointestinal problems; soma, general somatic symptoms; geni, genital symptoms; hypc, hypochondria; wtls, weight loss, insg; lack of insight

Adjusted for age, sex and cross-sectional improvement in all other symptoms except the exposure and outcome symptoms. All estimates are pooled across 8 trials.

Associations with $p > 0.05$ were not included in the network analysis.

Supplementary Table 2. Adjusted log odds for directed associations between time-lagged longitudinal symptom improvements

From ^a	To ^b	Placebo				Active treatment			
		Log odds	2.50 %	97.50 %	p-value	Log odds	2.50 %	97.50 %	p-value
depr	depr	-0.93	-1.10	-0.76	0.000	-0.97	-1.07	-0.88	0.000
depr	guil	0.08	-0.10	0.26	0.389	0.10	-0.01	0.20	0.081
depr	suic	-0.03	-0.26	0.20	0.778	-0.05	-0.18	0.08	0.467
depr	inse	-0.13	-0.32	0.06	0.174	0.02	-0.09	0.14	0.695
depr	insm	0.07	-0.12	0.26	0.468	-0.05	-0.16	0.06	0.331
depr	insl	0.06	-0.14	0.27	0.552	-0.01	-0.13	0.10	0.843
depr	work	0.10	-0.07	0.27	0.248	0.20	0.10	0.30	0.000
depr	reta	-0.10	-0.31	0.10	0.321	0.12	0.01	0.24	0.039
depr	agit	-0.13	-0.33	0.07	0.195	0.06	-0.06	0.17	0.332
depr	apsy	0.17	0.00	0.34	0.051	0.09	-0.01	0.19	0.083
depr	asom	0.10	-0.09	0.29	0.299	0.15	0.05	0.26	0.004
depr	gast	-0.01	-0.23	0.22	0.945	0.06	-0.07	0.19	0.357
depr	soma	0.09	-0.10	0.27	0.374	0.07	-0.04	0.18	0.226
depr	geni	-0.01	-0.22	0.21	0.948	-0.06	-0.18	0.07	0.379
depr	hypc	-0.12	-0.34	0.10	0.291	0.00	-0.12	0.13	0.988
depr	wtls	-0.10	-0.35	0.15	0.436	0.01	-0.12	0.13	0.918
depr	insg	-0.25	-0.68	0.18	0.255	-0.20	-0.43	0.03	0.085
guil	depr	0.15	-0.03	0.32	0.102	0.07	-0.03	0.17	0.158
guil	guil	-1.34	-1.56	-1.12	0.000	-1.28	-1.41	-1.16	0.000
guil	suic	-0.25	-0.49	-0.01	0.041	-0.14	-0.28	0.01	0.061
guil	inse	0.00	-0.19	0.20	0.988	-0.09	-0.21	0.03	0.156
guil	insm	0.15	-0.04	0.34	0.129	0.01	-0.10	0.13	0.837
guil	insl	-0.05	-0.26	0.16	0.633	-0.03	-0.14	0.09	0.677
guil	work	0.09	-0.08	0.27	0.299	0.06	-0.04	0.16	0.246
guil	reta	-0.01	-0.22	0.20	0.931	0.07	-0.05	0.19	0.247
guil	agit	0.02	-0.18	0.22	0.847	0.10	-0.02	0.22	0.097
guil	apsy	-0.08	-0.25	0.10	0.401	0.05	-0.05	0.16	0.317
guil	asom	0.13	-0.06	0.31	0.180	0.02	-0.09	0.13	0.769
guil	gast	0.00	-0.24	0.23	0.981	0.03	-0.10	0.16	0.676
guil	soma	0.22	0.03	0.41	0.024	0.12	0.01	0.23	0.039
guil	geni	0.01	-0.21	0.24	0.910	0.09	-0.04	0.21	0.166
guil	hypc	0.10	-0.12	0.32	0.395	0.16	0.03	0.29	0.017
guil	wtls	-0.05	-0.30	0.20	0.691	0.11	-0.02	0.24	0.088
guil	insg	0.11	-0.31	0.53	0.611	0.22	0.00	0.45	0.054
suic	depr	0.18	-0.02	0.37	0.071	0.15	0.03	0.26	0.011
suic	guil	0.27	0.06	0.47	0.010	0.27	0.14	0.39	0.000
suic	suic	-0.79	-1.08	-0.51	0.000	-0.64	-0.81	-0.47	0.000
suic	inse	0.25	0.04	0.46	0.020	0.19	0.06	0.33	0.004
suic	insm	0.04	-0.17	0.25	0.730	0.21	0.09	0.34	0.001
suic	insl	0.10	-0.12	0.31	0.372	0.15	0.02	0.27	0.025
suic	work	0.19	0.01	0.37	0.036	0.05	-0.07	0.16	0.415
suic	reta	0.27	0.05	0.50	0.016	0.11	-0.02	0.24	0.099
suic	agit	-0.05	-0.27	0.16	0.632	0.06	-0.07	0.19	0.355
suic	apsy	0.24	0.05	0.43	0.013	0.20	0.09	0.32	0.001
suic	asom	0.06	-0.14	0.27	0.557	0.12	0.00	0.24	0.049
suic	gast	0.21	-0.04	0.46	0.107	0.27	0.13	0.41	0.000
suic	soma	0.06	-0.15	0.27	0.579	0.02	-0.10	0.14	0.764
suic	geni	0.01	-0.23	0.25	0.952	0.01	-0.14	0.15	0.944
suic	hypc	0.30	0.08	0.53	0.009	0.08	-0.07	0.22	0.304
suic	wtls	0.29	0.02	0.56	0.035	0.08	-0.06	0.23	0.272
suic	insg	0.01	-0.45	0.48	0.952	0.40	0.15	0.65	0.002
inse	depr	0.07	-0.10	0.25	0.407	0.07	-0.03	0.18	0.160
inse	guil	0.07	-0.12	0.27	0.448	0.07	-0.05	0.19	0.260
inse	suic	0.05	-0.19	0.28	0.700	0.09	-0.05	0.24	0.200
inse	inse	-0.87	-1.10	-0.65	0.000	-1.01	-1.16	-0.86	0.000

inse	inse	0.20	0.00	0.40	0.054	0.22	0.10	0.34	0.000
inse	inse	0.21	0.01	0.41	0.040	0.30	0.18	0.41	0.000
inse	work	-0.05	-0.23	0.14	0.620	0.04	-0.07	0.14	0.525
inse	reta	0.19	-0.02	0.39	0.073	0.04	-0.08	0.16	0.517
inse	agit	0.15	-0.04	0.35	0.125	0.00	-0.13	0.12	0.989
inse	apsy	0.00	-0.18	0.18	0.986	-0.02	-0.13	0.09	0.709
inse	asom	0.08	-0.12	0.28	0.409	-0.03	-0.14	0.09	0.653
inse	gast	0.15	-0.07	0.37	0.190	0.07	-0.06	0.21	0.289
inse	soma	0.17	-0.03	0.38	0.103	0.07	-0.05	0.18	0.249
inse	geni	0.16	-0.06	0.38	0.165	0.04	-0.09	0.17	0.541
inse	hypc	0.05	-0.17	0.28	0.634	-0.04	-0.18	0.10	0.547
inse	wtls	0.16	-0.09	0.42	0.207	0.02	-0.11	0.16	0.729
inse	insg	0.18	-0.18	0.55	0.322	0.18	-0.06	0.43	0.136
inse	depr	0.23	0.06	0.41	0.008	0.14	0.03	0.24	0.010
inse	guil	0.15	-0.04	0.34	0.120	0.10	-0.02	0.21	0.108
inse	suic	0.15	-0.08	0.39	0.190	0.02	-0.13	0.16	0.804
inse	inse	-0.01	-0.21	0.20	0.939	0.11	-0.02	0.24	0.085
inse	inse	-1.44	-1.69	-1.19	0.000	-1.36	-1.50	-1.21	0.000
inse	inse	0.14	-0.06	0.34	0.181	0.15	0.03	0.28	0.014
inse	work	0.18	0.00	0.37	0.056	0.14	0.04	0.25	0.008
inse	reta	0.15	-0.05	0.36	0.145	0.12	-0.01	0.24	0.066
inse	agit	0.12	-0.07	0.32	0.213	0.22	0.10	0.34	0.000
inse	apsy	0.16	-0.02	0.34	0.083	0.11	0.00	0.22	0.044
inse	asom	-0.01	-0.20	0.19	0.955	0.12	0.01	0.23	0.040
inse	gast	-0.10	-0.34	0.14	0.398	0.12	-0.01	0.26	0.073
inse	soma	0.12	-0.07	0.31	0.225	0.06	-0.05	0.17	0.305
inse	geni	0.16	-0.05	0.37	0.139	0.12	-0.01	0.25	0.063
inse	hypc	0.25	0.03	0.47	0.023	0.10	-0.03	0.24	0.123
inse	wtls	0.10	-0.14	0.34	0.413	0.07	-0.07	0.21	0.345
inse	insg	0.08	-0.33	0.48	0.714	0.14	-0.10	0.39	0.257
inse	depr	-0.03	-0.21	0.15	0.749	0.15	0.04	0.25	0.005
inse	guil	0.07	-0.12	0.26	0.451	0.00	-0.12	0.11	0.953
inse	suic	0.05	-0.19	0.30	0.683	0.04	-0.10	0.18	0.597
inse	inse	-0.06	-0.27	0.16	0.605	0.25	0.12	0.37	0.000
inse	inse	-0.07	-0.28	0.14	0.526	0.18	0.06	0.30	0.003
inse	inse	-1.26	-1.50	-1.01	0.000	-1.23	-1.38	-1.08	0.000
inse	work	0.09	-0.10	0.27	0.349	0.01	-0.09	0.12	0.821
inse	reta	-0.04	-0.25	0.17	0.706	0.08	-0.04	0.21	0.196
inse	agit	0.21	0.01	0.40	0.036	0.11	-0.02	0.23	0.090
inse	apsy	0.05	-0.13	0.22	0.603	0.10	0.00	0.21	0.060
inse	asom	0.10	-0.09	0.28	0.290	0.11	-0.01	0.22	0.062
inse	gast	0.16	-0.07	0.40	0.176	0.05	-0.08	0.19	0.442
inse	soma	0.12	-0.09	0.33	0.257	0.05	-0.07	0.16	0.429
inse	geni	0.11	-0.12	0.34	0.343	0.13	0.00	0.27	0.050
inse	hypc	0.21	-0.02	0.43	0.068	0.04	-0.09	0.18	0.512
inse	wtls	0.03	-0.21	0.28	0.787	0.00	-0.14	0.13	0.956
inse	insg	0.10	-0.30	0.50	0.630	-0.20	-0.45	0.05	0.124
work	depr	0.03	-0.13	0.20	0.690	0.00	-0.10	0.10	0.996
work	guil	0.02	-0.17	0.20	0.867	-0.02	-0.13	0.10	0.787
work	suic	-0.29	-0.52	-0.05	0.017	-0.35	-0.49	-0.21	0.000
work	inse	0.33	0.14	0.52	0.001	0.01	-0.11	0.13	0.863
work	inse	0.12	-0.06	0.31	0.197	0.16	0.05	0.27	0.004
work	inse	-0.01	-0.21	0.18	0.884	0.04	-0.07	0.16	0.448
work	work	-1.01	-1.19	-0.83	0.000	-0.88	-0.98	-0.78	0.000
work	reta	-0.20	-0.40	0.01	0.068	-0.11	-0.23	0.01	0.067
work	agit	0.10	-0.09	0.29	0.288	0.07	-0.05	0.19	0.239
work	apsy	0.00	-0.18	0.17	0.970	0.02	-0.08	0.12	0.726
work	asom	0.10	-0.08	0.29	0.284	0.03	-0.08	0.14	0.607
work	gast	0.14	-0.09	0.37	0.225	0.04	-0.09	0.17	0.541
work	soma	0.12	-0.07	0.32	0.213	0.13	0.02	0.24	0.020

work	geni	-0.02	-0.24	0.19	0.833	0.17	0.04	0.29	0.008
work	hypc	-0.14	-0.37	0.08	0.210	-0.01	-0.13	0.12	0.924
work	wtls	-0.18	-0.44	0.07	0.153	-0.10	-0.22	0.03	0.130
work	insg	0.15	-0.21	0.52	0.414	0.27	0.03	0.50	0.025
reta	depr	0.06	-0.11	0.23	0.496	0.07	-0.03	0.18	0.177
reta	guil	0.22	0.03	0.41	0.026	0.05	-0.08	0.17	0.463
reta	suic	0.12	-0.12	0.36	0.323	-0.10	-0.25	0.05	0.183
reta	inse	0.08	-0.13	0.28	0.470	0.06	-0.07	0.19	0.374
reta	insm	0.03	-0.17	0.23	0.764	0.10	-0.02	0.22	0.103
reta	insl	0.16	-0.04	0.37	0.121	0.09	-0.04	0.22	0.162
reta	work	0.27	0.10	0.45	0.002	0.16	0.05	0.27	0.003
reta	reta	-1.20	-1.48	-0.92	0.000	-1.37	-1.53	-1.20	0.000
reta	agit	0.14	-0.06	0.34	0.163	0.03	-0.09	0.16	0.603
reta	apsy	0.11	-0.07	0.29	0.239	0.09	-0.02	0.20	0.112
reta	asom	0.07	-0.14	0.27	0.527	0.05	-0.07	0.17	0.448
reta	gast	-0.04	-0.28	0.21	0.770	0.03	-0.11	0.16	0.685
reta	soma	-0.06	-0.26	0.15	0.585	0.04	-0.08	0.16	0.522
reta	geni	0.38	0.15	0.61	0.001	0.04	-0.10	0.17	0.596
reta	hypc	0.04	-0.21	0.29	0.757	0.07	-0.06	0.21	0.294
reta	wtls	0.28	0.03	0.53	0.027	0.08	-0.05	0.21	0.239
reta	insg	0.53	0.14	0.93	0.008	0.09	-0.17	0.35	0.507
agit	depr	0.15	-0.02	0.33	0.086	0.04	-0.06	0.15	0.417
agit	guil	0.16	-0.03	0.34	0.099	-0.03	-0.15	0.08	0.567
agit	suic	0.00	-0.23	0.23	0.998	-0.12	-0.27	0.03	0.114
agit	inse	0.10	-0.11	0.30	0.343	-0.09	-0.22	0.03	0.140
agit	insm	0.08	-0.12	0.27	0.456	0.04	-0.08	0.16	0.502
agit	insl	0.05	-0.15	0.25	0.595	-0.02	-0.14	0.10	0.738
agit	work	0.22	0.05	0.39	0.011	0.01	-0.09	0.12	0.811
agit	reta	0.28	0.08	0.48	0.007	0.04	-0.09	0.16	0.580
agit	agit	-1.26	-1.51	-1.01	0.000	-1.20	-1.36	-1.05	0.000
agit	apsy	0.18	0.00	0.36	0.047	0.02	-0.09	0.13	0.682
agit	asom	0.25	0.06	0.44	0.011	0.08	-0.03	0.19	0.162
agit	gast	-0.01	-0.25	0.23	0.914	0.11	-0.03	0.24	0.125
agit	soma	0.20	0.01	0.39	0.036	-0.01	-0.13	0.11	0.866
agit	geni	0.20	-0.02	0.43	0.081	-0.05	-0.18	0.09	0.502
agit	hypc	0.10	-0.12	0.33	0.375	0.19	0.06	0.32	0.005
agit	wtls	0.05	-0.20	0.31	0.680	0.00	-0.14	0.14	1.000
agit	insg	0.37	-0.03	0.77	0.073	0.03	-0.22	0.27	0.839
apsy	depr	0.16	-0.01	0.32	0.062	0.06	-0.04	0.16	0.230
apsy	guil	0.25	0.07	0.43	0.006	0.10	0.00	0.21	0.061
apsy	suic	0.18	-0.05	0.40	0.119	-0.05	-0.18	0.09	0.490
apsy	inse	0.08	-0.10	0.26	0.383	-0.01	-0.13	0.10	0.802
apsy	insm	0.21	0.02	0.40	0.028	0.03	-0.08	0.14	0.575
apsy	insl	0.05	-0.15	0.24	0.643	0.20	0.08	0.31	0.001
apsy	work	0.12	-0.05	0.30	0.154	0.14	0.05	0.24	0.003
apsy	reta	0.18	-0.02	0.38	0.077	0.03	-0.09	0.14	0.663
apsy	agit	-0.10	-0.31	0.10	0.307	-0.11	-0.23	0.00	0.056
apsy	apsy	-1.09	-1.27	-0.90	0.000	-1.11	-1.21	-1.00	0.000
apsy	asom	0.10	-0.09	0.28	0.313	0.09	-0.01	0.20	0.083
apsy	gast	-0.06	-0.28	0.17	0.613	-0.02	-0.15	0.11	0.753
apsy	soma	0.04	-0.15	0.23	0.655	0.17	0.06	0.27	0.002
apsy	geni	0.24	0.03	0.46	0.028	0.12	0.00	0.24	0.054
apsy	hypc	0.08	-0.14	0.31	0.467	-0.04	-0.17	0.08	0.484
apsy	wtls	-0.09	-0.32	0.14	0.448	-0.01	-0.13	0.11	0.891
apsy	insg	-0.37	-0.77	0.04	0.078	0.00	-0.23	0.22	0.983
asom	depr	0.13	-0.03	0.30	0.113	0.09	0.00	0.19	0.061
asom	guil	0.08	-0.10	0.26	0.357	0.02	-0.09	0.13	0.688
asom	suic	0.01	-0.22	0.25	0.915	-0.03	-0.17	0.10	0.638
asom	inse	0.13	-0.06	0.32	0.192	0.07	-0.05	0.19	0.233
asom	insm	0.02	-0.17	0.21	0.866	-0.01	-0.12	0.10	0.872

asom	insl	-0.05	-0.25	0.14	0.590	-0.06	-0.18	0.05	0.283
asom	work	0.13	-0.04	0.30	0.145	0.02	-0.08	0.12	0.647
asom	reta	0.39	0.20	0.58	0.000	0.09	-0.03	0.20	0.128
asom	agit	-0.06	-0.25	0.14	0.588	0.00	-0.12	0.12	0.950
asom	apsy	0.17	0.00	0.35	0.055	0.07	-0.03	0.17	0.161
asom	asom	-1.43	-1.67	-1.19	0.000	-1.33	-1.46	-1.21	0.000
asom	gast	0.10	-0.12	0.33	0.371	0.05	-0.08	0.18	0.468
asom	soma	0.38	0.20	0.57	0.000	0.10	-0.01	0.21	0.074
asom	geni	0.13	-0.08	0.34	0.234	0.03	-0.09	0.16	0.600
asom	hypc	0.19	-0.04	0.41	0.103	-0.01	-0.13	0.12	0.923
asom	wtls	0.05	-0.19	0.29	0.674	0.05	-0.08	0.18	0.443
asom	insg	-0.05	-0.46	0.37	0.824	-0.13	-0.37	0.11	0.286
gast	depr	0.11	-0.08	0.30	0.263	0.05	-0.07	0.16	0.402
gast	guil	0.14	-0.08	0.35	0.209	0.06	-0.07	0.19	0.405
gast	suic	0.35	0.10	0.61	0.007	0.05	-0.12	0.21	0.590
gast	inse	0.26	0.05	0.48	0.016	0.12	-0.02	0.26	0.083
gast	insm	0.15	-0.07	0.37	0.170	0.11	-0.03	0.24	0.116
gast	insl	0.09	-0.14	0.32	0.439	0.03	-0.10	0.17	0.648
gast	work	0.26	0.06	0.45	0.010	0.06	-0.06	0.18	0.294
gast	reta	0.09	-0.14	0.32	0.435	0.03	-0.12	0.17	0.721
gast	agit	0.19	-0.04	0.41	0.104	0.06	-0.08	0.20	0.376
gast	apsy	0.18	-0.03	0.38	0.091	0.10	-0.02	0.22	0.091
gast	asom	-0.03	-0.25	0.19	0.805	0.07	-0.06	0.20	0.307
gast	gast	-1.55	-1.94	-1.15	0.000	-1.81	-2.06	-1.55	0.000
gast	soma	0.28	0.06	0.50	0.013	0.15	0.02	0.27	0.027
gast	geni	0.45	0.21	0.69	0.000	0.15	0.01	0.30	0.041
gast	hypc	0.12	-0.14	0.37	0.376	0.12	-0.02	0.27	0.102
gast	wtls	-0.31	-0.63	0.01	0.061	-0.14	-0.30	0.02	0.088
gast	insg	0.09	-0.40	0.57	0.723	0.21	-0.05	0.46	0.116
soma	depr	0.03	-0.16	0.22	0.777	0.07	-0.04	0.18	0.192
soma	guil	0.15	-0.05	0.36	0.149	0.06	-0.06	0.18	0.319
soma	suic	-0.16	-0.41	0.09	0.215	-0.17	-0.31	-0.02	0.028
soma	inse	-0.07	-0.28	0.15	0.545	-0.05	-0.18	0.07	0.409
soma	insm	0.13	-0.08	0.34	0.211	-0.03	-0.15	0.08	0.559
soma	insl	0.09	-0.12	0.30	0.414	0.08	-0.04	0.20	0.182
soma	work	0.21	0.02	0.40	0.029	0.09	-0.02	0.19	0.106
soma	reta	-0.05	-0.28	0.17	0.648	-0.03	-0.16	0.09	0.607
soma	agit	0.08	-0.12	0.29	0.425	-0.12	-0.25	0.01	0.070
soma	apsy	0.17	-0.02	0.36	0.081	0.09	-0.01	0.20	0.085
soma	asom	0.18	-0.02	0.38	0.075	0.00	-0.12	0.12	0.998
soma	gast	-0.05	-0.29	0.20	0.713	-0.03	-0.17	0.10	0.621
soma	soma	-1.50	-1.79	-1.22	0.000	-1.26	-1.39	-1.13	0.000
soma	geni	0.30	0.08	0.53	0.009	0.16	0.03	0.29	0.019
soma	hypc	-0.08	-0.34	0.18	0.540	-0.11	-0.25	0.03	0.112
soma	wtls	0.15	-0.10	0.41	0.232	-0.07	-0.20	0.07	0.343
soma	insg	0.62	0.25	0.99	0.001	-0.07	-0.32	0.18	0.590
geni	depr	0.06	-0.14	0.25	0.580	0.06	-0.06	0.18	0.325
geni	guil	-0.10	-0.33	0.13	0.407	0.14	0.01	0.26	0.036
geni	suic	0.01	-0.27	0.28	0.970	0.02	-0.15	0.18	0.837
geni	inse	0.13	-0.12	0.38	0.296	0.08	-0.06	0.22	0.261
geni	insm	0.00	-0.24	0.24	0.990	-0.01	-0.14	0.13	0.921
geni	insl	0.24	0.00	0.47	0.049	0.03	-0.11	0.17	0.671
geni	work	0.01	-0.19	0.22	0.897	0.13	0.01	0.25	0.031
geni	reta	0.01	-0.24	0.26	0.943	0.00	-0.15	0.14	0.974
geni	agit	0.25	0.02	0.48	0.037	-0.08	-0.23	0.07	0.289
geni	apsy	0.16	-0.05	0.37	0.137	-0.02	-0.14	0.11	0.765
geni	asom	0.05	-0.18	0.27	0.681	0.03	-0.11	0.16	0.678
geni	gast	-0.13	-0.42	0.16	0.386	0.09	-0.07	0.24	0.261
geni	soma	0.11	-0.13	0.34	0.377	0.18	0.05	0.31	0.006
geni	geni	-1.30	-1.68	-0.92	0.000	-0.98	-1.16	-0.79	0.000

geni	hycp	0.04	-0.23	0.31	0.798	0.09	-0.07	0.24	0.270
geni	wtls	0.45	0.16	0.73	0.002	0.05	-0.11	0.21	0.556
geni	insg	0.51	0.10	0.92	0.014	0.10	-0.17	0.37	0.464
hycp	depr	0.07	-0.12	0.26	0.446	0.08	-0.03	0.20	0.159
hycp	guil	0.32	0.10	0.54	0.004	0.07	-0.06	0.20	0.296
hycp	suic	0.15	-0.12	0.41	0.275	-0.19	-0.35	-0.02	0.026
hycp	inse	-0.08	-0.31	0.16	0.533	0.03	-0.11	0.17	0.685
hycp	insm	0.02	-0.20	0.23	0.884	0.00	-0.14	0.13	0.955
hycp	insl	-0.03	-0.26	0.20	0.812	0.08	-0.05	0.22	0.240
hycp	work	-0.01	-0.21	0.18	0.905	0.04	-0.08	0.15	0.509
hycp	reta	0.15	-0.09	0.39	0.232	0.11	-0.03	0.24	0.122
hycp	agit	0.30	0.08	0.52	0.007	0.09	-0.05	0.22	0.219
hycp	apsy	0.10	-0.11	0.31	0.340	0.07	-0.05	0.19	0.269
hycp	asom	0.14	-0.08	0.36	0.223	0.10	-0.02	0.23	0.113
hycp	gast	0.17	-0.09	0.42	0.200	-0.01	-0.16	0.14	0.909
hycp	soma	0.07	-0.16	0.30	0.541	0.01	-0.12	0.13	0.915
hycp	geni	-0.04	-0.31	0.24	0.785	-0.02	-0.16	0.13	0.830
hycp	hycp	-1.28	-1.63	-0.92	0.000	-0.94	-1.12	-0.76	0.000
hycp	wtls	0.00	-0.29	0.28	0.995	0.11	-0.04	0.27	0.139
hycp	insg	0.67	0.25	1.09	0.002	0.41	0.16	0.65	0.001
wtls	depr	0.11	-0.10	0.32	0.292	0.17	0.06	0.28	0.003
wtls	guil	-0.19	-0.45	0.06	0.129	0.14	0.01	0.27	0.038
wtls	suic	0.27	0.00	0.54	0.047	0.05	-0.11	0.21	0.557
wtls	inse	-0.12	-0.36	0.13	0.348	0.04	-0.10	0.19	0.570
wtls	insm	0.25	0.02	0.49	0.034	-0.02	-0.15	0.12	0.795
wtls	insl	0.06	-0.19	0.31	0.637	0.05	-0.08	0.19	0.459
wtls	work	0.08	-0.13	0.29	0.466	0.15	0.04	0.27	0.010
wtls	reta	0.06	-0.20	0.32	0.663	0.05	-0.09	0.20	0.462
wtls	agit	0.09	-0.15	0.33	0.464	0.02	-0.12	0.16	0.748
wtls	apsy	0.15	-0.06	0.37	0.158	0.02	-0.10	0.15	0.717
wtls	asom	0.15	-0.09	0.38	0.213	0.19	0.07	0.32	0.003
wtls	gast	0.42	0.14	0.70	0.003	0.51	0.36	0.66	0.000
wtls	soma	0.07	-0.17	0.31	0.586	0.09	-0.04	0.22	0.160
wtls	geni	-0.20	-0.49	0.09	0.182	0.15	0.00	0.30	0.053
wtls	hycp	0.29	0.02	0.56	0.036	0.15	-0.01	0.30	0.059
wtls	wtls	-1.31	-1.82	-0.81	0.000	-1.15	-1.36	-0.93	0.000
wtls	insg	-0.01	-0.52	0.50	0.973	0.21	-0.09	0.50	0.165
insg	depr	0.23	-0.10	0.57	0.175	0.07	-0.13	0.27	0.490
insg	guil	0.03	-0.33	0.38	0.887	-0.05	-0.29	0.18	0.657
insg	suic	0.25	-0.21	0.71	0.281	0.29	0.02	0.56	0.033
insg	inse	0.04	-0.34	0.41	0.841	-0.06	-0.32	0.19	0.616
insg	insm	0.32	-0.07	0.71	0.106	0.00	-0.22	0.22	0.973
insg	insl	0.10	-0.31	0.50	0.640	0.05	-0.18	0.29	0.660
insg	work	0.27	-0.06	0.59	0.109	-0.05	-0.26	0.16	0.645
insg	reta	0.48	0.13	0.84	0.008	-0.15	-0.40	0.11	0.267
insg	agit	0.10	-0.31	0.50	0.645	0.41	0.19	0.63	0.000
insg	apsy	0.37	0.04	0.69	0.027	-0.01	-0.22	0.20	0.915
insg	asom	0.46	0.11	0.82	0.011	0.15	-0.06	0.36	0.171
insg	gast	0.01	-0.41	0.44	0.947	0.14	-0.10	0.38	0.263
insg	soma	0.19	-0.20	0.58	0.339	0.13	-0.10	0.35	0.280
insg	geni	0.38	-0.07	0.83	0.099	0.24	-0.01	0.50	0.058
insg	hycp	0.53	0.13	0.93	0.009	0.36	0.12	0.60	0.004
insg	wtls	0.18	-0.34	0.70	0.495	0.17	-0.08	0.42	0.175
insg	insg	0.44	-0.51	1.39	0.366	-1.34	-2.77	0.10	0.068

^a Improvement between t and $t + 1$

^b Improvment between $t + 1$ and $t + 2$

Abbreviations: depr, depressed mood; guil, feelings of guilt; suic, suicidality; inse, insomnia (early); insm, insomnia (middle); insl, insomnia (late); work, difficulties in work and activities; reta, retardation; agit,

agitation; apsy, anxiety (psychic); asom, anxiety (somatic); gast, gastrointestinal problems; soma, general somatic symptoms; geni, genital symptoms; hypc, hypochondria; wtls, weight loss, insg, lack of insight

Adjusted for age, sex, the time interval between study visits and the time-lagged improvement (from t to $t+1$) in all symptoms except the exposure symptom. All estimates are pooled across 8 trials.

Associations with $p > 0.05$ and autoregressive associations were not included in the network analysis.

Supplementary Table 3. Strength (centrality) estimates and confidence intervals of networks comprising cross-sectional associations between symptom improvements after resampling

Strength	Placebo			Treated		
	Mean	2.50 %	97.50 %	Mean	2.50 %	97.50 %
Depressed mood	2.36	1.99	2.71	2.45	2.14	2.75
Guilt	0.42	0.03	0.81	0.71	0.34	1.07
Suicidality	-0.31	-0.75	0.12	0.23	-0.12	0.59
Insight	-0.94	-1.45	-0.43	-1.08	-1.49	-0.67
Insomnia (early)	-0.37	-0.72	0.04	-0.39	-0.69	-0.11
Insomnia (middle)	0.37	-0.10	0.79	-0.02	-0.35	0.29
Insomnia (late)	-0.39	-0.71	-0.06	-0.41	-0.73	-0.10
Work and activities	1.25	0.84	1.65	1.15	0.83	1.44
Retardation	-0.05	-0.45	0.32	0.14	-0.23	0.50
Agitation	-1.65	-1.94	-1.37	-1.07	-1.37	-0.79
Psychic anxiety	1.21	0.82	1.60	0.44	0.12	0.76
Somatic anxiety	0.20	-0.26	0.68	0.23	-0.15	0.64
Gastrointestinal problems	-0.36	-0.79	0.11	-0.88	-1.22	-0.54
General somatic symptoms	-0.01	-0.39	0.38	0.39	0.04	0.71
Genital symptoms	-0.14	-0.59	0.32	-0.47	-0.84	-0.15
Hypochondria	-0.14	-0.63	0.33	0.43	0.06	0.83
Weight loss	-1.46	-1.70	-1.21	-1.83	-2.09	-1.57

Boldface denotes those strength estimates that differed between the treatment conditions based on resampling (e.g. mutually non-overlapping point estimates and confidence intervals between the placebo and active treatment conditions).

Supplementary Table 4. Out-strength and in-strength (centrality) estimates and confidence intervals of networks comprising time-lagged longitudinal associations between symptom improvements after resampling

Out-strength

	Placebo			Treated		
	Mean	2.50 %	97.50 %	Mean	2.50 %	97.50 %
Depressed mood	-1.56	-1.79	-1.36	-0.30	-0.66	0.08
Guilt	-0.81	-1.24	-0.26	-0.71	-1.01	-0.39
Suicidality	1.31	0.49	2.08	2.66	2.02	3.14
Insight	1.34	0.31	2.20	0.87	0.02	1.73
Insomnia (early)	-1.22	-1.52	-0.94	-0.23	-0.54	0.10
Insomnia (middle)	-0.77	-1.21	-0.32	0.52	0.06	1.07
Insomnia (late)	-1.23	-1.52	-0.93	0.17	-0.26	0.67
Work and activities	-0.59	-1.05	-0.12	0.91	0.31	1.58
Retardation	1.11	0.26	1.93	-0.94	-1.19	-0.70
Agitation	0.28	-0.34	0.93	-0.89	-1.17	-0.61
Psychic anxiety	-0.43	-0.93	0.09	-0.23	-0.60	0.18
Somatic anxiety	-0.33	-0.75	0.14	-1.26	-1.47	-1.10
Gastrointestinal symptoms	1.01	0.35	1.71	-0.65	-1.01	-0.27
General somatic symptoms	0.25	-0.53	1.02	-0.61	-0.95	-0.25
Genital symptoms	0.75	-0.14	1.66	-0.34	-0.73	0.06
Hypochondria	0.49	-0.31	1.28	-0.07	-0.60	0.45
Weight loss	0.39	-0.35	1.14	1.11	0.54	1.69

In-strength

	Placebo			Treated		
	Mean	2.50 %	97.50 %	Mean	2.50 %	97.50 %
Depressed mood	-1.38	-1.78	-1.00	-0.08	-0.73	0.63
Guilt	0.14	-0.57	0.86	-0.23	-0.96	0.47
Suicidality	0.31	-0.57	1.21	1.20	0.19	2.21
Insight	2.46	1.31	3.16	1.40	0.30	2.40
Insomnia (early)	-0.23	-0.89	0.47	-0.60	-1.15	0.00
Insomnia (middle)	-0.97	-1.51	-0.43	0.45	-0.20	1.21
Insomnia (late)	-0.98	-1.47	-0.42	0.55	-0.12	1.31
Work and activities	0.34	-0.39	1.13	0.97	0.19	1.72
Retardation	0.81	-0.09	1.65	-1.61	-1.99	-1.29
Agitation	-0.41	-0.97	0.22	0.02	-0.77	0.85
Psychic anxiety	-0.34	-1.07	0.40	-1.01	-1.44	-0.57
Somatic anxiety	-0.50	-1.17	0.23	-0.11	-0.86	0.65
Gastrointestinal problems	-1.02	-1.52	-0.54	0.49	-0.16	1.19
General somatic symptoms	0.22	-0.53	0.94	0.41	-0.36	1.24
Genital symptoms	0.76	-0.08	1.63	-0.06	-0.80	0.75
Hypochondria	0.75	-0.26	1.77	0.23	-0.70	1.16
Weight loss	0.05	-0.74	0.94	-2.02	-2.33	-1.73

Boldface denotes those out-strength and in-strength estimates that differed between the treatment conditions based on resampling (e.g. mutually non-overlapping point estimates and confidence intervals between the placebo and active treatment conditions).

Supplementary Figure 1. Mean scores of depressive symptoms across the follow-up

Estimates are marginal linear predictions from linear multilevel regression with random intercepts.

Supplementary Figure 2. Undirected networks for cross-sectional associations between improvements in depressive symptoms after LASSO selection

Placebo

Active treatment

N=3559 (n=1033 (29%) placebo, n=2526 (71%) active treatment)

Abbreviations: depr, depressed mood; guil, feelings of guilt; suic, suicidality; inse, insomnia (early); insm, insomnia (middle); insl, insomnia (late); work, difficulties in work and activities; reta, retardation; agit, agitation; apsy, anxiety (psychic); asom, anxiety (somatic); gast, gastrointestinal problems; soma, general somatic symptoms; geni, genital symptoms; hypc, hypochondria; wtls, weight loss, insg, lack of insight.

Blue connections represent positive associations, red connections represent negative associations. Thicker lines (edges) represent stronger associations (positive or negative).

Supplementary Figure 3. Strength (centrality) estimates of networks comprising cross-sectional associations between symptom improvements after LASSO selection

N=3559 (n=1033 (29%) placebo, n=2526 (71%) active treatment)

Open circles represent those receiving placebo, whereas filled circles represent those receiving active treatment. Strength estimates are standardized.

Supplementary Figure 4. Directed networks for time-lagged longitudinal associations between improvements in depressive symptoms after LASSO selection

Placebo

Active treatment

N=3430 (n=1013 (30%) placebo, n=2417 (70%) active treatment)

Abbreviations: depr, depressed mood; guilt, feelings of guilt; suic, suicidality; inse, insomnia (early); insm, insomnia (middle); insl, insomnia (late); work, difficulties in work and activities; reta, retardation; agit, agitation; apsy, anxiety (psychic); asom, anxiety (somatic); gast, gastrointestinal problems; soma, general somatic symptoms; geni, genital symptoms; hypc, hypochondria; wtls, weight loss, insg; lack of insight.

Autoregressive paths were not included in networks. Blue connections represent positive associations, red connections represent negative associations. Thicker lines (edges) represent stronger associations (positive or negative).

Supplementary Figure 5. Out-strength and in-strength (centrality) estimates of networks comprising time-lagged longitudinal associations between symptom improvements after LASSO selection

N=3430 (n=1013 (30%) placebo, n=2417 (70%) active treatment)

Open circles represent those receiving placebo, whereas filled circles represent those receiving active treatment. Out-strength and in-strength estimates are standardized.

Supplementary Figure 6. Network intervention analysis

Abbreviations: trt, treatment; depr, depressed mood; guilt, feelings of guilt; suic, suicidality; inse, insomnia (early); insm, insomnia (middle); insl, insomnia (late); work, difficulties in work and activities; reta, retardation; agit, agitation; apsy, anxiety (psychic); asom, anxiety (somatic); gast, gastrointestinal problems; soma, general somatic symptoms; geni, genital symptoms; hypc, hypochondria; wtls, weight loss, insg; lack of insight.

Green connections represent positive associations, red connections represent negative associations. Thicker lines (edges) represent stronger associations (positive or negative). For each symptom, the proportion of variance explained by other symptoms is visualized by a ring around each node (completely filled and empty rings indicate 100% and 0% variance explained, respectively).

Data from Weeks 9 and 10 were combined into Week 10 for the analysis.

Supplementary Code 1. Stata code for creating the edgelists (for directed networks) and weight matrices (for undirected networks)

```
// TIME-LAGGED LONGITUDINAL IMPROVEMENT
// LOGISTIC REGRESSION WITH ROBUST SEs

// active treatment
clear
set matsize 2500
matrix sub=J(2312,7,.)
local nrow 0
foreach data in 003 009 115 448 449 487 810 874 {
    clear
    use gsk`data'_h17
    di `data'

    // gen fwd_outcome
    foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        bysort pid: gen fwd_`outcome'=`outcome'[_n+1]
    }
    // gen fwd_outcome2
    foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        bysort pid: gen fwd2_`outcome'=`outcome'[_n+2]
    }
    //change scores, concurrent
    foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        bysort pid: gen diff`outcome'=fwd_`outcome'-`outcome'
    }
    //change scores, lagged
    foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        bysort pid: gen diff2`outcome'=fwd2_`outcome'-fwd_`outcome'
    }
    // concurrent improvement
    foreach v in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        recode diff`v' (min/-1=1) (0/max=0), gen(d`v')
    }
    // lagged improvement
    foreach v in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        recode diff2`v' (min/-1=1) (0/max=0), gen(d2`v')
    }
    // follow-up time
    bysort pid: gen futime=visit[_n+1]-visit

local kk 0
forvalues s=1/17 {
    local ++kk
    logit d2h`s' age sex futime dh* if arm==1, robust cluster(pid)

forvalues b=1/17 {

local ++nrow
lincom dh`b'

matrix sub[_nrow',1]=`data'
matrix sub[_nrow',2]=`b'
matrix sub[_nrow',3]=`s'
matrix sub[_nrow',4]=r(estimate)
matrix sub[_nrow',5]=r(estimate)-1.96*r(se)
matrix sub[_nrow',6]=r(estimate)+1.96*r(se)
```



```

matrix sub[`,nrow',7]=r(estimate)/r(se)
    }
}

matrix list sub

matrix colnames sub = study from to weight lci uci zscore
clear
svmat sub, names(col)
label define sympl 1 depr 2 Guil 3 suic 4 inse 5 insm 6 insl 7 work 8 reta 9 agit 10 apsy 11 asom 12 gast 13
soma 14 geni 15 hypc 16 wtls 17 insg
label values from to sympl

//      meta-analysis
*
forvalues q=1/17 {
    forvalues d=1/17 {
        tab weight if from==`q' & to==`d'
    }
}

foreach o in weight lci uci zscore {
    gen t`o'=.
}

forvalues q=1/17 {
    forvalues d=1/17 {
        metan weight lci uci if from==`q' & to==`d', nograph fixedi
        replace tweight=r(ES) if tweight==. & from==`q' & to==`d'
        replace tlci=r(ci_low) if tlci==. & from==`q' & to==`d'
        replace tuci=r(ci_upper) if tuci==. & from==`q' & to==`d'
        replace tzscore=r(p_z) if tzscore==. & from==`q' & to==`d'
    }
}

egen tag_from_to=tag(from to)
keep if tag_from_to

replace tweight=0 if abs(tzscore)>=0.05
replace tuci=0 if abs(tzscore)>=0.05
replace tlci=0 if abs(tzscore)>=0.05

keep from to tweight tlci tuci
drop if from==to
*save gsk_lagrev_treat_r_dist , replace

keep from to tweight

*save gsk_lagrev_treat_fig , replace

// placebo
clear
set matsize 2500
matrix sub=J(2312,7,.)
local nrow 0
foreach data in 003 009 115 448 449 487 810 874 {
    clear
    use gsk`data'_h17

```

```

di `data'

// gen fwd_outcome
foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  bysort pid: gen fwd_`outcome'=`outcome'[_n+1]
}
// gen fwd_outcome2
foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  bysort pid: gen fwd2_`outcome'=`outcome'[_n+2]
}
//change scores, concurrent
foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  bysort pid: gen diff`outcome'=fwd_`outcome'-`outcome'
}
//change scores, lagged
foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  bysort pid: gen diff2`outcome'=fwd2_`outcome'-fwd_`outcome'
}
// concurrent improvement
foreach v in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  recode diff`v'(min/-1=1) (0/max=0), gen(d`v')
}
// lagged improvement
foreach v in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  recode diff2`v'(min/-1=1) (0/max=0), gen(d2`v')
}
// follow-up time
bysort pid: gen futime=visit[_n+1]-visit

local kk 0
forvalues s=1/17 {
  local ++kk
  logit d2h`s' age sex futime dh* if arm==0, robust cluster(pid)

  forvalues b=1/17 {

    local ++nrow

    lincom dh`b'

        matrix sub[_nrow',1]=`data'
        matrix sub[_nrow',2]=`b'
        matrix sub[_nrow',3]=`s'
        matrix sub[_nrow',4]=r(estimate)
        matrix sub[_nrow',5]=r(estimate)-1.96*r(se)
        matrix sub[_nrow',6]=r(estimate)+1.96*r(se)
        matrix sub[_nrow',7]=r(estimate)/r(se)
        }
    }

  matrix list sub

  matrix colnames sub = study from to weight lci uci zscore
  clear
  svmat sub, names(col)
  label define sympl 1 depr 2 guil 3 suic 4 inse 5 insm 6 insl 7 work 8 reta 9 agit 10 apsy 11 asom 12 gast 13
  soma 14 geni 15 hypc 16 wtls 17 insg
  label values from to sympl

```

```

//      meta-analysis
*
forvalues q=1/17 {
    forvalues d=1/17 {
        tab weight if from==`q' & to==`d'
    }
}

foreach o in weight lci uci zscore {
    gen t`o'=.
}

forvalues q=1/17 {
    forvalues d=1/17 {
        metan weight lci uci if from==`q' & to==`d', nograph fixedi
            replace tweight=r(ES) if tweight==. & from==`q' & to==`d'
        replace tlci=r(ci_low) if tlci==. & from==`q' & to==`d'
        replace tuci=r(ci_upp) if tuci==. & from==`q' & to==`d'
        replace tzscore=r(p_z) if tzscore==. & from==`q' & to==`d'
    }
}

egen tag_from_to=tag(from to)
keep if tag_from_to

replace tweight=0 if abs(tzscore)>=0.05
replace tuci=0 if abs(tzscore)>=0.05
replace tlci=0 if abs(tzscore)>=0.05

keep from to tweight tlci tuci
drop if from==to

*save gsk_lagrev_untreat_r_dist , replace

keep from to tweight

*save gsk_lagrev_untreat_fig , replace

// CROSS-SECTIONAL IMPROVEMENT
// LOGISTIC REGRESSION WITH ROBUST SEs

// active treatment
clear
set matsize 2500
matrix sub=J(2312,7,.)
local nrow 0
foreach data in 003 009 115 448 449 487 810 874 {
    clear
    use gsk`data'_h17
    di `data'

    // gen fwd_outcome
    foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        bysort pid: gen fwd_`outcome'=`outcome'[_n+1]
    }
    // gen fwd_outcome2
    foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {

```

```

bysort pid: gen fwd2_`outcome'=`outcome'[_n+2]
}
//change scores, concurrent
foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
bysort pid: gen diff`outcome'=fwd_`outcome'-`outcome'
}
//change scores, lagged
foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
bysort pid: gen diff2`outcome'=fwd2_`outcome'-fwd_`outcome'
}
// concurrent improvement
foreach v in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
recode diff`v'(min/-1=1) (0/max=0), gen(d`v')
}
// lagged improvement
foreach v in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
recode diff2`v'(min/-1=1) (0/max=0), gen(d2`v')
}

```

```

local kk 0
forvalues s=1/17 {
local ++kk
rename dh`s' oc`s'
logit oc`s' age sex dh* if arm==1, robust cluster(pid)
rename oc`s' dh`s'

```

```

forvalues b=1/17 {
local ++nrow
if `s'==`b' {
continue
}
lincom dh`b'

```

```

matrix sub[`nrow',1]=`data'
matrix sub[`nrow',2]=`b'
matrix sub[`nrow',3]=`s'
matrix sub[`nrow',4]=r(estimate)
matrix sub[`nrow',5]=r(estimate)-1.96*r(se)
matrix sub[`nrow',6]=r(estimate)+1.96*r(se)
matrix sub[`nrow',7]=r(estimate)/r(se)
}

```

```

matrix list sub

```

```

matrix colnames sub = study from to weight lci uci zscore

```

```

clear

```

```

svmat sub, names(col)

```

```

label define sympl 1 depr 2 guil 3 suic 4 inse 5 insm 6 insl 7 work 8 reta 9 agit 10 apsy 11 asom 12 gast 13

```

```

soma 14 geni 15 hypc 16 wtls 17 insg

```

```

label values from to sympl

```

```

// meta-analysis

```

```

*

```

```

forvalues q=1/17 {
forvalues d=1/17 {
tab weight if from==`q' & to==`d'
}
}
}

```

```

foreach o in weight lci uci zscore {
    gen t`o`=
}

forvalues q=1/17 {
    forvalues d=1/17 {
        if `q'!=`d' {
            di `q'
            di `d'
            metan weight lci uci if from==`q' & to==`d', nograph fixedi
            replace tweight=r(ES) if tweight==. & from==`q' & to==`d'
            replace tlci=r(ci_low) if tlci==. & from==`q' & to==`d'
            replace tuci=r(ci_upp) if tuci==. & from==`q' & to==`d'
            replace tzscore=r(p_z) if tzscore==. & from==`q' & to==`d'
        }
    }
}

egen tag_from_to=tag(from to)
keep if tag_from_to

keep from to tweight tlci tuci tzscore

replace tweight=0 if abs(tzscore)>=0.05
replace tuci=0 if abs(tzscore)>=0.05
replace tlci=0 if abs(tzscore)>=0.05

keep from to tweight tlci tuci

keep if from>to

*save gsk_treated_conc_r_dist, replace

keep from to tweight
reshape wide tweight, i(from) j(to)

*save gsk_treated_conc_r, replace

// placebo
clear

set matsize 2500
matrix sub=J(2312,7,.)
local nrow 0
foreach data in 003 009 115 448 449 487 810 874 {
    clear
    use gsk`data'_h17
    di `data'

    // gen fwd_outcome
    foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        bysort pid: gen fwd_`outcome'=`outcome'[_n+1]
    }
    // gen fwd_outcome2
    foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
        bysort pid: gen fwd2_`outcome'=`outcome'[_n+2]
    }
    //change scores, concurrent

```

```

foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  bysort pid: gen diff`outcome'=fwd_`outcome'-`outcome'
}
//change scores, lagged
foreach outcome in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  bysort pid: gen diff2`outcome'=fwd2_`outcome'-fwd_`outcome'
}
// concurrent improvement
foreach v in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  recode diff`v'(min/-1=1) (0/max=0), gen(d`v')
}
// lagged improvement
foreach v in h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 h11 h12 h13 h14 h15 h16 h17 {
  recode diff2`v'(min/-1=1) (0/max=0), gen(d2`v')
}

```

```

      local kk 0
forvalues s=1/17 {
  local ++kk
  rename dh`s' oc`s'
  logit oc`s' age sex dh* if arm==0, robust cluster(pid)
  rename oc`s' dh`s'
}

```

```

forvalues b=1/17 {

```

```

  local ++nrow
  if `s'==`b' {
    continue
  }

```

```

  lincom dh`b'

```

```

      matrix sub[`nrow',1]=`data'
      matrix sub[`nrow',2]=`b'
      matrix sub[`nrow',3]=`s'
      matrix sub[`nrow',4]=r(estimate)
      matrix sub[`nrow',5]=r(estimate)-1.96*r(se)
      matrix sub[`nrow',6]=r(estimate)+1.96*r(se)
      matrix sub[`nrow',7]=r(estimate)/r(se)
    }
  }

```

```

matrix list sub

```

```

matrix colnames sub = study from to weight lci uci zscore

```

```

clear

```

```

svmat sub, names(col)

```

```

label define sympl 1 depr 2 guil 3 suic 4 inse 5 insm 6 insl 7 work 8 reta 9 agit 10 apsy 11 asom 12 gast 13

```

```

soma 14 geni 15 hypc 16 wtls 17 insg

```

```

label values from to sympl

```

```

//      meta-analysis

```

```

*

```

```

forvalues q=1/17 {
  forvalues d=1/17 {
    tab weight if from==`q' & to==`d'
  }
}

```

```

    }

foreach o in weight lci uci zscore {
    gen t`o'=.
}

forvalues q=1/17 {
    forvalues d=1/17 {
        if `q'!=`d' {
            metan weight lci uci if from==`q' & to==`d', nograph fixedi
            replace tweight=r(ES) if tweight==. & from==`q' & to==`d'
            replace tlci=r(ci_low) if tlci==. & from==`q' & to==`d'
            replace tuci=r(ci_upp) if tuci==. & from==`q' & to==`d'
            replace tzscore=r(p_z) if tzscore==. & from==`q' & to==`d'
        }
    }
}

egen tag_from_to=tag(from to)
keep if tag_from_to

keep from to tweight tlci tuci tzscore

replace tweight=0 if abs(tzscore)>=0.05
replace tuci=0 if abs(tzscore)>=0.05
replace tlci=0 if abs(tzscore)>=0.05

keep from to tweight tlci tuci

keep if from>to

*save gsk_untreated_conc_r_dist, replace

keep from to tweight
reshape wide tweight, i(from) j(to)

*save gsk_untreated_conc_r, replace

```

Supplementary Code 2. R code for time-lagged longitudinal (directed) and cross-sectional (undirected) network analyses

```

library(bootnet)
library(qgraph)
library(plyr)
library(dplyr)
library(openxlsx)
library(cowplot)
library(foreign)
library(readstata13)
library(ggpubr)

## TIME-LAGGED LONGITUDINAL ANALYSIS (directed networks)

# Edgelists for directed graphs from stata
treat.lag.fig<-read.dta13("gsk_lagrev_treat_fig.dta", nonint.factors = TRUE)
placebo.lag.fig<-read.dta13("gsk_lagrev_untreat_fig.dta", nonint.factors = TRUE)

# Edgelists for resampling (including confidence intervals) from stata
tld<-read.dta13("gsk_lagrev_treat_r_dist.dta", nonint.factors = TRUE)
pld<-read.dta13("gsk_lagrev_untreat_r_dist.dta", nonint.factors = TRUE)

# Networks for time-lagged longitudinal networks
pdf("qgraphs_lagged_clean.pdf", width = 8, height = 4)
layout(t(1:2))
q.placebo.lag<-qgraph(placebo.lag.fig, title="Placebo", posCol="blue", negCol="red", layout="circle",
maximum=0.67)
q.treat.lag<-qgraph(treat.lag.fig, title="Active treatment", posCol="blue", negCol="red", layout="circle",
maximum=0.67)
dev.off()

# Centrality estimates for time-lagged longitudinal networks
centrality(q.treat.lag)
c.treat.lag<-centralityPlot(q.treat.lag, include=c("Degree","Strength","OutDegree","InDegree","OutStrength",
"InStrength"))

centrality(q.placebo.lag)
c.placebo.lag<-centralityPlot(q.placebo.lag,
include=c("Degree","Strength","OutDegree","InDegree","OutStrength", "InStrength"))

# Centrality plots
plag<-c.placebo.lag$data
plag$arm=c("Placebo")
tlag<-c.treat.lag$data
tlag$arm=c("Treatment")
lagc<-cbind(plag,tlag)
lagcos <-lagc[ which(lagc$measure=="OutStrength"),]
lagcis <-lagc[ which(lagc$measure=="InStrength"),]

colnames(lagcos) <-
c("graphp","typep","nodep","measurep","valuep","armp","graphpt","typet","nodet","measuret","valuet","armt")
colnames(lagcis) <-
c("graphp","typep","nodep","measurep","valuep","armp","graphpt","typet","nodet","measuret","valuet","armt")

```



```
lagcos<-lagcos %>%
  select(nodep,valuep,valuert)
lagcis<-lagcis %>%
  select(nodep,valuep,valuert)
```

```
colnames(lagcos)<-c("symptom","osp","ost")
colnames(lagcis)<-c("symptom","isp","ist")
```

```
lagcos$symptomnum <- rep(NA,nrow(lagcos))
lagcos$symptomnum[lagcos$symptom=="depr"] <- 1
lagcos$symptomnum[lagcos$symptom=="guil"] <- 2
lagcos$symptomnum[lagcos$symptom=="suic"] <- 3
lagcos$symptomnum[lagcos$symptom=="insg"] <- 4
lagcos$symptomnum[lagcos$symptom=="inse"] <- 5
lagcos$symptomnum[lagcos$symptom=="insm"] <- 6
lagcos$symptomnum[lagcos$symptom=="insl"] <- 7
lagcos$symptomnum[lagcos$symptom=="work"] <- 8
lagcos$symptomnum[lagcos$symptom=="reta"] <- 9
lagcos$symptomnum[lagcos$symptom=="agit"] <- 10
lagcos$symptomnum[lagcos$symptom=="apsy"] <- 11
lagcos$symptomnum[lagcos$symptom=="asom"] <- 12
lagcos$symptomnum[lagcos$symptom=="gast"] <- 13
lagcos$symptomnum[lagcos$symptom=="soma"] <- 14
lagcos$symptomnum[lagcos$symptom=="geni"] <- 15
lagcos$symptomnum[lagcos$symptom=="hycp"] <- 16
lagcos$symptomnum[lagcos$symptom=="wtls"] <- 17
```

```
lagcos$symptom <- factor(lagcos$symptom, levels = lagcos$symptom[order(-lagcos$symptomnum)])
labels(lagcos$symptom)
levels(lagcos$symptom)
```

```
lagcos$symptom<-revalue(lagcos$symptom, c("depr"="Depressed mood*", "guil"="Guilt",
"suic"="Suicidality*", "insg"="Insight", "inse"="Insomnia (early)*", "insm"="Insomnia (middle)*", "insl"="Insomnia
(late)*", "work"="Work and activities*", "reta"="Retardation*", "agit"="Agitation*", "apsy"="Anxiety
(psychic)", "asom"="Anxiety (somatic)*", "gast"="GI symptoms*", "soma"="General somatic
symptoms*", "geni"="Genital symptoms*", "hycp"="Hypochondria", "wtls"="Weight loss"))
```

```
lagcis$symptomnum <- rep(NA,nrow(lagcis))
lagcis$symptomnum[lagcis$symptom=="depr"] <- 1
lagcis$symptomnum[lagcis$symptom=="guil"] <- 2
lagcis$symptomnum[lagcis$symptom=="suic"] <- 3
lagcis$symptomnum[lagcis$symptom=="insg"] <- 4
lagcis$symptomnum[lagcis$symptom=="inse"] <- 5
lagcis$symptomnum[lagcis$symptom=="insm"] <- 6
lagcis$symptomnum[lagcis$symptom=="insl"] <- 7
lagcis$symptomnum[lagcis$symptom=="work"] <- 8
lagcis$symptomnum[lagcis$symptom=="reta"] <- 9
lagcis$symptomnum[lagcis$symptom=="agit"] <- 10
lagcis$symptomnum[lagcis$symptom=="apsy"] <- 11
lagcis$symptomnum[lagcis$symptom=="asom"] <- 12
lagcis$symptomnum[lagcis$symptom=="gast"] <- 13
lagcis$symptomnum[lagcis$symptom=="soma"] <- 14
lagcis$symptomnum[lagcis$symptom=="geni"] <- 15
lagcis$symptomnum[lagcis$symptom=="hycp"] <- 16
lagcis$symptomnum[lagcis$symptom=="wtls"] <- 17
```

```
lagcis$symptom <- factor(lagcis$symptom, levels = lagcis$symptom[order(-lagcis$symptomnum)])
labels(lagcis$symptom)
```

```
levels(lagcis$symptom)
```

```
lagcis$symptom<-revalue(lagcis$symptom, c("depr"="Depressed mood*", "guil"="Guilt", "suic"="Suicidality",
"insg"="Insight", "inse"="Insomnia (early)", "insm"="Insomnia (middle)*", "insi"="Insomnia (late)*", "work"="Work
and activities", "reta"="Retardation*", "agit"="Agitation", "apsy"="Anxiety (psychic)", "asom"="Anxiety
(somatic)", "gast"="GI symptoms*", "soma"="General somatic symptoms", "geni"="Genital
symptoms", "hycp"="Hypochondria", "wtls"="Weight loss*"))
```

```
#
plot.lagcos<- ggplot(lagcos, aes(y=symptom)) +
  geom_point(aes(x=ost), size=2.6, shape=16, fill="black", color="black") +
  geom_point(aes(x=osp), size=2.6, shape=1, fill="white", color="black") +theme_bw()+
  theme(
    panel.grid.major.x = element_blank() , panel.grid.minor.x=element_blank(),
    panel.grid.major.y = element_line( size=.05, color="black" )
  ) +
  theme(text = element_text(size=16))+labs(y= " ", x = "Out-strength")+theme(axis.title.x = element_text(size
= 14, angle = 00)) + geom_vline(xintercept = 0, linetype="longdash", size=0.15)
```

```
plot.lagcis<- ggplot(lagcis, aes(y=symptom)) +
  geom_point(aes(x=ist), size=2.6, shape=16, fill="black", color="black") +
  geom_point(aes(x=isp), size=2.6, shape=1, fill="white", color="black") +theme_bw()+
  theme(
    panel.grid.major.x = element_blank() , panel.grid.minor.x=element_blank(),

    panel.grid.major.y = element_line( size=.05, color="black" )
  ) +
  theme(text = element_text(size=16))+labs(y= " ", x = "In-strength")+theme(axis.title.x = element_text(size =
14, angle = 00))+ geom_vline(xintercept = 0, linetype="longdash", size=0.15)
```

```
cplot_lagged<-plot_grid(plot.lagcos,
  plot.lagcis,
  ncol = 2)
```

```
aspect_ratio <- 1.37
```

```
height <- 7
```

```
ggexport(cplot_lagged, height = 7 , width = 7 * aspect_ratio, filename="cplots_lagged_clean.pdf")
```

```
# Resampling
```

```
head(tld,10)
```

```
# Standard errors and variances (calculated based on confidence intervals)
```

```
tld$sse=(tld$tuci-tld$tweight)/1.96
```

```
tld$var=((tld$tuci-tld$tweight)/1.96)^2
```

```
q.tld<-qgraph((tld[,c(1,2,3)]), posCol="blue", negCol="red", layout="circle")
```

```
c.tld<-centralityPlot(q.tld, include=c("Degree","Strength","OutDegree","InDegree","OutStrength",
"InStrength"))
```

```
c.tld.values<-c.tld$data
```

```
tld.pc.all <- c.tld.values[,c(3,4)] # empty template for values
```

```
set.seed(874971)
```

```
for (n in 1:500) {
```

```
  for (i in 1:272) {
```

```
    tld$rweight[i]=rnorm(1,mean=tld$tweight[i],sd=tld$sse[i])
```

```
  }
```

```

tld.analysis <- tld[, c(1,2,8)]
q.tld.analysis<-qgraph(tld.analysis, posCol="blue", negCol="red", layout="circle")
c.tld.analysis<-centralityPlot(q.tld.analysis,
include=c("Degree","Strength","OutDegree","InDegree","OutStrength", "InStrength"))
tld.pc.resamp<-c.tld.analysis$data

tld.pc.all <- cbind(tld.pc.all, tld.pc.resamp[,5])
}

tld.pc.df <- as.data.frame(tld.pc.all)
names(tld.pc.df)

tld.pc.df$mean<-apply(tld.pc.df[3:502],1,mean)
tld.pc.df$cil<-apply(tld.pc.df[3:502],1,quantile,0.025)
tld.pc.df$ciu<-apply(tld.pc.df[3:502],1,quantile,0.975)

tld.cis<-(tld.pc.df[,c("mean","cil","ciu")])
names<-tld.pc.all[,c(1,2)]
tld.cis<-cbind(names,tld.cis)
tld.cis.out <-tld.cis[ which(tld.cis$measure=="OutStrength"),]
tld.cis.in <-tld.cis[ which(tld.cis$measure=="InStrength"),]

head(pld,10)

# Standard errors and variances
pld$sse=(pld$tuci-pld$tweight)/1.96
pld$var=((pld$tuci-pld$tweight)/1.96)^2

q.pld<-qgraph((pld[,c(1,2,3)]), posCol="blue", negCol="red", layout="circle")
c.pld<-centralityPlot(q.pld, include=c("Degree","Strength","OutDegree","InDegree","OutStrength",
"InStrength"))
c.pld.values<-c.pld$data
pld.pc.all <- c.pld.values[,c(3,4)]
set.seed(874971)
for (n in 1:500) {
  for (i in 1:272) {
    pld$tweight[i]=rnorm(1,mean=pld$tweight[i],sd=pld$sse[i])
  }
  pld.analysis <- pld[, c(1,2,8)]
  q.pld.analysis<-qgraph(pld.analysis, posCol="blue", negCol="red", layout="circle")
  c.pld.analysis<-centralityPlot(q.pld.analysis,
include=c("Degree","Strength","OutDegree","InDegree","OutStrength", "InStrength"))
  pld.pc.resamp<-c.pld.analysis$data

  pld.pc.all <- cbind(pld.pc.all, pld.pc.resamp[,5])
}

pld.pc.df <- as.data.frame(pld.pc.all)
names(pld.pc.df)

pld.pc.df$mean<-apply(pld.pc.df[3:502],1,mean)
pld.pc.df$cil<-apply(pld.pc.df[3:502],1,quantile,0.025)
pld.pc.df$ciu<-apply(pld.pc.df[3:502],1,quantile,0.975)

pld.cis<-(pld.pc.df[,c("mean","cil","ciu")])

names<-pld.pc.all[,c(1,2)]
pld.cis<-cbind(names,pld.cis)
pld.cis.out <-pld.cis[ which(pld.cis$measure=="OutStrength"),]

```

```
pld.cis.in <- pld.cis[ which(pld.cis$measure=="InStrength"),]
```

```
lag.cis.out <- cbind(pld.cis.out,tld.cis.out)
lag.cis.in <- cbind(pld.cis.in,tld.cis.in)
```

```
names(lag.cis.out)[1] <- "nodep"
names(lag.cis.out)[2] <- "measurep"
names(lag.cis.out)[3] <- "meanp"
names(lag.cis.out)[4] <- "cilp"
names(lag.cis.out)[5] <- "ciup"
names(lag.cis.out)[6] <- "nodet"
names(lag.cis.out)[7] <- "measuret"
names(lag.cis.out)[8] <- "meant"
names(lag.cis.out)[9] <- "cilt"
names(lag.cis.out)[10] <- "ciut"
lag.cis.out
```

```
lag.cis.out$nodenum <- rep(NA,nrow(lag.cis.out))
lag.cis.out$nodenum[lag.cis.out$nodep=="depr"] <- 1
lag.cis.out$nodenum[lag.cis.out$nodep=="guil"] <- 2
lag.cis.out$nodenum[lag.cis.out$nodep=="suic"] <- 3
lag.cis.out$nodenum[lag.cis.out$nodep=="insg"] <- 4
lag.cis.out$nodenum[lag.cis.out$nodep=="inse"] <- 5
lag.cis.out$nodenum[lag.cis.out$nodep=="insm"] <- 6
lag.cis.out$nodenum[lag.cis.out$nodep=="insl"] <- 7
lag.cis.out$nodenum[lag.cis.out$nodep=="work"] <- 8
lag.cis.out$nodenum[lag.cis.out$nodep=="reta"] <- 9
lag.cis.out$nodenum[lag.cis.out$nodep=="agit"] <- 10
lag.cis.out$nodenum[lag.cis.out$nodep=="apsy"] <- 11
lag.cis.out$nodenum[lag.cis.out$nodep=="asom"] <- 12
lag.cis.out$nodenum[lag.cis.out$nodep=="gast"] <- 13
lag.cis.out$nodenum[lag.cis.out$nodep=="soma"] <- 14
lag.cis.out$nodenum[lag.cis.out$nodep=="geni"] <- 15
lag.cis.out$nodenum[lag.cis.out$nodep=="hypc"] <- 16
lag.cis.out$nodenum[lag.cis.out$nodep=="wtls"] <- 17
lag.cis.out
```

```
lag.cis.out <- lag.cis.out %>% arrange(nodenum)
write.xlsx(lag.cis.out, file = "lag.cis.out.clean.xlsx", colNames = TRUE, rowNames=TRUE, overwrite=TRUE)
```

```
names(lag.cis.in)[1] <- "nodep"
names(lag.cis.in)[2] <- "measurep"
names(lag.cis.in)[3] <- "meanp"
names(lag.cis.in)[4] <- "cilp"
names(lag.cis.in)[5] <- "ciup"
names(lag.cis.in)[6] <- "nodet"
names(lag.cis.in)[7] <- "measuret"
names(lag.cis.in)[8] <- "meant"
names(lag.cis.in)[9] <- "cilt"
names(lag.cis.in)[10] <- "ciut"
```

```
lag.cis.in$nodenum <- rep(NA,nrow(lag.cis.in))
lag.cis.in$nodenum[lag.cis.in$nodep=="depr"] <- 1
lag.cis.in$nodenum[lag.cis.in$nodep=="guil"] <- 2
lag.cis.in$nodenum[lag.cis.in$nodep=="suic"] <- 3
lag.cis.in$nodenum[lag.cis.in$nodep=="insg"] <- 4
lag.cis.in$nodenum[lag.cis.in$nodep=="inse"] <- 5
lag.cis.in$nodenum[lag.cis.in$nodep=="insm"] <- 6
lag.cis.in$nodenum[lag.cis.in$nodep=="insl"] <- 7
```

```

lag.cis.in$nodenum[lag.cis.in$nodep=="work"] <- 8
lag.cis.in$nodenum[lag.cis.in$nodep=="reta"] <- 9
lag.cis.in$nodenum[lag.cis.in$nodep=="agit"] <- 10
lag.cis.in$nodenum[lag.cis.in$nodep=="apsy"] <- 11
lag.cis.in$nodenum[lag.cis.in$nodep=="asom"] <- 12
lag.cis.in$nodenum[lag.cis.in$nodep=="gast"] <- 13
lag.cis.in$nodenum[lag.cis.in$nodep=="soma"] <- 14
lag.cis.in$nodenum[lag.cis.in$nodep=="geni"] <- 15
lag.cis.in$nodenum[lag.cis.in$nodep=="hycp"] <- 16
lag.cis.in$nodenum[lag.cis.in$nodep=="wtls"] <- 17
lag.cis.in

```

```

# Save resampled point estimates and confidence intervals for in-strength estimates
lag.cis.in <- lag.cis.in %>% arrange(nodenum)
write.xlsx(lag.cis.in, file = "lag.cis.in.clean.xlsx", colNames = TRUE, rowNames=TRUE, overwrite=TRUE)

```

CROSS-SECTIONAL ANALYSIS (undirected networks)

```

# Weights matrixes for undirected graphs from stata
untreat.conc1 <- read.dta13("gsk_untreated_conc_r.dta", nonint.factors = TRUE) #####

untreat.conc <- untreat.conc1[,-1]
rownames(untreat.conc) <- untreat.conc1[,1]
untreat.conc <- rbind(c(rep(NA,17)),untreat.conc)
untreat.conc <- cbind(untreat.conc,c(rep(NA,17)))

rownames(untreat.conc) <-
c("depr","guil","suic","inse","insm","insl","work","reta","agit","apsy","asom","gast","soma","geni","hycp","wtls","i
nsg")

colnames(untreat.conc) <-
c("depr","guil","suic","inse","insm","insl","work","reta","agit","apsy","asom","gast","soma","geni","hycp","wtls","i
nsg")

untreat.conc<-as.matrix(untreat.conc)
m.untreat.conc <- untreat.conc

makeSymm <- function(m.untreat.conc) {
  m.untreat.conc[upper.tri(m.untreat.conc)] <- t(m.untreat.conc)[upper.tri(m.untreat.conc)]
  return(m.untreat.conc)
}
m.untreat.conc<-makeSymm(m.untreat.conc)

diag(m.untreat.conc) <- 0

treat.conc1 <- read.dta13("gsk_treated_conc_r.dta", nonint.factors = TRUE)

treat.conc <- treat.conc1[,-1]
rownames(treat.conc) <- treat.conc1[,1]
treat.conc <- rbind(c(rep(NA,17)),treat.conc)
treat.conc <- cbind(treat.conc,c(rep(NA,17)))

rownames(treat.conc) <-
c("depr","guil","suic","inse","insm","insl","work","reta","agit","apsy","asom","gast","soma","geni","hycp","wtls","i
nsg")

```

```

colnames(treat.conc) <-
c("depr","guil","suic","inse","insm","insl","work","reta","agit","apsy","asom","gast","soma","geni","hypc","wtls","i
nsg")

treat.conc<-as.matrix(treat.conc)
m.treat.conc <- treat.conc

makeSymm <- function(m.treat.conc) {
  m.treat.conc[upper.tri(m.treat.conc)] <- t(m.treat.conc)[upper.tri(m.treat.conc)]
  return(m.treat.conc)
}
m.treat.conc<-makeSymm(m.treat.conc)

diag(m.treat.conc) <- 0

# Networks for cross-sectional networks
pdf("qgraphs_cross_clean.pdf", width = 8, height = 4)
layout(t(1:2))
q.placebo.conc<-qgraph(m.untreat.conc, title="Placebo", posCol = "blue", negCol = "red", layout="circle",
maximum=1.171, labels=colnames(m.untreat.conc))
q.treat.conc<-qgraph(m.treat.conc, title="Active treatment", posCol = "blue", negCol = "red", layout="circle",
maximum=1.171, labels=colnames(m.treat.conc))
dev.off()

# Centrality estimates for cross-sectional networks
c.placebo.conc<-centralityPlot(q.placebo.conc)
c.treat.conc<-centralityPlot(q.treat.conc)

pconc<-c.placebo.conc$data
pconc$arm<-c("Placebo")
tconc<-c.treat.conc$data
tconc$arm<-c("Treatment")
concc<-cbind(pconc,tconc)

colnames(concc) <-
c("graphp","typep","nodep","measurep","valuep","armp","graphpt","typet","nodet","measuret","valuet","armt")

concs<-concc %>%
  select(nodep,valuep,valuet)

colnames(concs)<-c("symptom","strp","strt")

concs$symptomnum <- rep(NA,nrow(concs))
concs$symptomnum[concs$symptom=="depr"] <- 1
concs$symptomnum[concs$symptom=="guil"] <- 2
concs$symptomnum[concs$symptom=="suic"] <- 3
concs$symptomnum[concs$symptom=="inse"] <- 4
concs$symptomnum[concs$symptom=="insg"] <- 5
concs$symptomnum[concs$symptom=="inse"] <- 5
concs$symptomnum[concs$symptom=="insm"] <- 6
concs$symptomnum[concs$symptom=="insl"] <- 7
concs$symptomnum[concs$symptom=="work"] <- 8
concs$symptomnum[concs$symptom=="reta"] <- 9
concs$symptomnum[concs$symptom=="agit"] <- 10
concs$symptomnum[concs$symptom=="apsy"] <- 11
concs$symptomnum[concs$symptom=="asom"] <- 12
concs$symptomnum[concs$symptom=="gast"] <- 13
concs$symptomnum[concs$symptom=="soma"] <- 14
concs$symptomnum[concs$symptom=="geni"] <- 15
concs$symptomnum[concs$symptom=="hypc"] <- 16

```

```

concs$symptomnum[concs$symptom=="wtls"] <- 17

concs$symptom <- factor(concs$symptom, levels = concs$symptom[order(-concs$symptomnum)])
labels(concs$symptom)
levels(concs$symptom)

concs$symptom<-revalue(concs$symptom, c("depr"="Depressed mood", "guil"="Guilt", "suic"="Suicidality*",
"insg"="Insight", "inse"="Insomnia (early)", "insm"="Insomnia (middle)", "insl"="Insomnia (late)", "work"="Work
and activities", "reta"="Retardation", "agit"="Agitation*", "apsy"="Anxiety (psychic)*", "asom"="Anxiety
(somatic)", "gast"="GI symptoms*", "soma"="General somatic symptoms*", "geni"="Genital
symptoms", "hycp"="Hypochondria*", "wtls"="Weight loss*"))

plot.concs<- ggplot(concs, aes(y=symptom)) +
  geom_point(aes(x=strt), size=3, shape=16, fill="black", color="black") +
  geom_point(aes(x=strp), size=3, shape=1, fill="white", color="black") +theme_bw()+
  theme(
    panel.grid.major.x = element_blank() , panel.grid.minor.x=element_blank(),

    panel.grid.major.y = element_line( size=.1, color="black" )
  ) +
  theme(text = element_text(size=17))+labs(y= " ", x = "Strength")+theme(axis.title.x = element_text(size =
15, angle = 00))+ geom_vline(xintercept = 0, linetype="longdash", size=0.15)

plot.concs

aspect_ratio <- .735
height <- 7
ggsave(plot.concs, height = 7 , width = 7 * aspect_ratio, filename="cplots_cross_clean.pdf")

# Resampling

# Weights matrixes for resampling (with confidence intervals) from stata
cpd <- read.dta13("gsk_untreated_conc_r_dist.dta", nonint.factors = TRUE)
ctd <- read.dta13("gsk_treated_conc_r_dist.dta", nonint.factors = TRUE) #####

head(cpd)

cpd$se=(cpd$tuci-cpd$tweight)/1.96
cpd$var=((cpd$tuci-cpd$tweight)/1.96)^2

#empty dataframe
node <-
c('agit','apsy','asom','depr','gast','geni','guil','hycp','inse','insg','insl','insm','reta','soma','suic','work','wtls')
cpd.pc.all <- data.frame(node)

#come up with rweight
set.seed(874971)
for (n in 1:500) {
  for (i in 1:136) {
    cpd$rweight[i]=rnorm(1,mean=cpd$tweight[i],sd=cpd$se[i])
  }
  cpd.long<-cpd[,c(1,2,8)]

  cpd.wide<-reshape(cpd.long, idvar = "from", timevar = "to", direction = "wide")

  cpd.new <- cpd.wide[,-1]

```

```

rownames(cpd.new) <- cpd.wide[, 1]
cpd.new <- rbind(c(rep(NA, 17)), cpd.new)
cpd.new <- cbind(cpd.new, c(rep(NA, 17)))
rownames(cpd.new) <-
c("dep", "guil", "suic", "inse", "insm", "insl", "work", "reta", "agit", "apsy", "asom", "gast", "soma", "geni", "hycp", "wtls", "i
nsg")
colnames(cpd.new) <-
c("dep", "guil", "suic", "inse", "insm", "insl", "work", "reta", "agit", "apsy", "asom", "gast", "soma", "geni", "hycp", "wtls", "i
nsg")
cpd.new <- as.matrix(cpd.new)
m.cpd.new <- cpd.new
makeSymm <- function(m.cpd.new) {
  m.cpd.new[upper.tri(m.cpd.new)] <- t(m.cpd.new)[upper.tri(m.cpd.new)]
  return(m.cpd.new)
}
m.cpd.new <- makeSymm(m.cpd.new)
diag(m.cpd.new) <- 0
q.cpd.analysis <- qgraph(m.cpd.new, posCol="blue", negCol="red", layout="circle")
c.cpd.analysis <- centralityPlot(q.cpd.analysis)
cpd.pc.resamp <- c.cpd.analysis$data
cpd.pc.all <- cbind(cpd.pc.all, cpd.pc.resamp[, 5])

}

cpd.pc.df <- as.data.frame(cpd.pc.all)
nrow(cpd.pc.all)

colnames(cpd.pc.all)

cpd.pc.all$ka <- rowMeans(cpd.pc.all[2:501])

cpd.pc.df$mean <- apply(cpd.pc.df[2:501], 1, mean)
cpd.pc.df$ciL <- apply(cpd.pc.df[2:501], 1, quantile, 0.025)
cpd.pc.df$ciU <- apply(cpd.pc.df[2:501], 1, quantile, 0.975)
cpd.pc.df$median <- apply(cpd.pc.df[2:501], 1, quantile, 0.5)

cpd.cis <- (cpd.pc.df[, c("mean", "ciL", "ciU")])

cpd.cis <- cbind(node, cpd.cis)

head(ctd)

ctd$se = (ctd$tuci - ctd$tweight) / 1.96
ctd$var = ((ctd$tuci - ctd$tweight) / 1.96)^2

node <-
c('agit', 'apsy', 'asom', 'depr', 'gast', 'geni', 'guil', 'hycp', 'inse', 'insg', 'insl', 'insm', 'reta', 'soma', 'suic', 'work', 'wtls')
ctd.pc.all <- data.frame(node)
ctd.pc.all

set.seed(874971)
for (n in 1:500) {
  for (i in 1:136) {
    ctd$tweight[i] = rnorm(1, mean = ctd$tweight[i], sd = ctd$se[i])
  }
  ctd.long <- ctd[, c(1, 2, 8)]
}

```



```

ctd.wide<-reshape(ctd.long, idvar = "from", timevar = "to", direction = "wide")

ctd.new <- ctd.wide[,-1]
rownames(ctd.new) <- ctd.wide[,1]
ctd.new <- rbind(c(rep(NA,17)),ctd.new)
ctd.new <- cbind(ctd.new,c(rep(NA,17)))
rownames(ctd.new) <-
c("dep","guil","suic","inse","insm","insl","work","reta","agit","apsy","asom","gast","soma","geni","hypc","wtls","i
nsg")
colnames(ctd.new) <-
c("dep","guil","suic","inse","insm","insl","work","reta","agit","apsy","asom","gast","soma","geni","hypc","wtls","i
nsg")
ctd.new<-as.matrix(ctd.new)
m.ctd.new<-ctd.new
makeSymm <- function(m.ctd.new) {
  m.ctd.new[upper.tri(m.ctd.new)] <- t(m.ctd.new)[upper.tri(m.ctd.new)]
  return(m.ctd.new)
}
m.ctd.new<-makeSymm(m.ctd.new)
diag(m.ctd.new) <- 0
q.ctd.analysis<-qgraph(m.ctd.new, posCol="blue", negCol="red", layout="circle")
c.ctd.analysis<-centralityPlot(q.ctd.analysis)
ctd.pc.resamp<-c.ctd.analysis$data
ctd.pc.all <- cbind(ctd.pc.all, ctd.pc.resamp[,5])

}

ctd.pc.df<-as.data.frame(ctd.pc.all)

colnames(ctd.pc.df)

ctd.pc.df$mean<-apply(ctd.pc.df[2:501],1,mean)
ctd.pc.df$cil<-apply(ctd.pc.df[2:501],1,quantile,0.025)
ctd.pc.df$ciu<-apply(ctd.pc.df[2:501],1,quantile,0.975)

ctd.cis<-(ctd.pc.df[,c("mean","cil","ciu")])
ctd.cis<-cbind(node,ctd.cis)

conc.cis<-cbind(cpd.cis, ctd.cis)

names(conc.cis)[1] <- "nodep"
names(conc.cis)[2] <- "meanp"
names(conc.cis)[3] <- "cilp"
names(conc.cis)[4] <- "ciup"
names(conc.cis)[5] <- "nodet"
names(conc.cis)[6] <- "meant"
names(conc.cis)[7] <- "cilt"
names(conc.cis)[8] <- "ciut"
conc.cis

conc.cis$nodenum <- rep(NA,nrow(conc.cis))
conc.cis$nodenum[conc.cis$nodep=="depr"] <- 1
conc.cis$nodenum[conc.cis$nodep=="guil"] <- 2
conc.cis$nodenum[conc.cis$nodep=="suic"] <- 3
conc.cis$nodenum[conc.cis$nodep=="insg"] <- 4
conc.cis$nodenum[conc.cis$nodep=="inse"] <- 5
conc.cis$nodenum[conc.cis$nodep=="insm"] <- 6
conc.cis$nodenum[conc.cis$nodep=="insl"] <- 7
conc.cis$nodenum[conc.cis$nodep=="work"] <- 8

```

```
conc.cis$nodenum[conc.cis$nodep=="reta"] <- 9
conc.cis$nodenum[conc.cis$nodep=="agit"] <- 10
conc.cis$nodenum[conc.cis$nodep=="apsy"] <- 11
conc.cis$nodenum[conc.cis$nodep=="asom"] <- 12
conc.cis$nodenum[conc.cis$nodep=="gast"] <- 13
conc.cis$nodenum[conc.cis$nodep=="soma"] <- 14
conc.cis$nodenum[conc.cis$nodep=="geni"] <- 15
conc.cis$nodenum[conc.cis$nodep=="hypc"] <- 16
conc.cis$nodenum[conc.cis$nodep=="wtls"] <- 17
```

```
conc.cis
```

```
conc.cis<-conc.cis %>% arrange(nodenum)
```

```
conc.cis
```

```
write.xlsx(conc.cis, file = "cross.cis.clean.xlsx", colNames = TRUE, rowNames=TRUE, overwrite=TRUE)
```