The symptom network structure of depressive symptoms in late-life: Results from a European population study

Running title: The network structure of depressive symptoms in late-life

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Abstract

The network theory conceptualizes mental disorders as complex networks of symptoms influencing each other by creating feedback loops leading to a self-sustained syndromic constellation. Symptoms central to the network have the greatest impact in sustaining the rest of symptoms. This analysis focused on the network structure of depressive symptoms in late-life because of their distinct etiologic factors, clinical presentation, and outcomes. We analyzed cross-sectional data from wave 2 of the 19 country Survey of Health, Ageing, and Retirement in Europe (SHARE) and included non-institutionalized adults aged 65 years or older (mean age 74 years, 59% females) endorsing at least one depressive symptom on the EURO-D scale for depression (N=8,557). We characterized the network structure of depressive symptoms in late-life and used indices of “strength”, “betweenness”, and “closeness” to identify symptoms central to the network. We used a case-dropping bootstrap procedure to assess network stability. Death wishes, depressed mood, loss of interest, and pessimism had the highest values of centrality. Insomnia, fatigue and appetite changes had lower centrality values. The identified network remained stable after dropping 74.5% of the sample. Sex or age did not significantly influence the network structure. In conclusion, death wishes, depressed mood, loss of interest, and pessimism constitute the “backbone” that sustains depressive symptoms in late-life. Symptoms central to the network of depressive symptoms may be used as targets for novel, focused interventions and in studies investigating neurobiological processes central to late-life depression.

1. Introduction

Late-life depression is heterogeneous in clinical presentation, biological contributors, and treatment response [1,2]. The network approach to psychopathology is a recent development that may provide unique information on the dynamic relationship among the symptoms of depression and identify symptom targets for novel treatments that may ultimately improve outcomes [3].

The theoretical premise of the network approach is that psychiatric symptoms may trigger and accentuate each other [3]. For instance, worries may lead an individual to develop insomnia, and insomnia in turn, may worsen this person's mood. Symptoms may also reinforce one another by creating a feedback loop, or lead to multiple reciprocal interactions, e.g. depressed mood could lead to low self-esteem, thus reinforcing excessive worries, and at the same time prompt feelings of guilt or death thoughts. These interactions may lead to the development of a self-sustained symptom constellation.

The network theory of psychopathology is a flexible and dynamic approach that accounts for the onset and maintenance of psychiatric symptoms. New advanced analytic tools made it possible to extract the structure of psychiatric symptoms from clinical data and visualize it as a network of symptoms[4–6]. In a network, each symptom is represented as a node that is connected to other symptoms through lines of varying thickness (edges). Each edge represents the strength of the statistical association detected between two symptoms, which reflects the probability that two symptoms activate each other through biological, psychological or other processes. Symptom networks are built to be *sparse* and display only the most meaningful associations between symptoms [7]. The position of nodes within the network is important, with the more interconnected symptoms more centrally placed. Conceptually, central symptoms are more likely to activate other symptoms and, thus, play a major role in causing the onset of a syndrome and/or maintaining it. In theory, targeting central symptoms with biological or psychosocial interventions, rather than peripheral symptoms can be highly effective [6]. In the network theory, symptoms can be activated by their neighbor symptoms, or by factors that are external to their network, i.e. "external field factors". These may include adverse life events, such as bereavement [8], symptoms of other mental disorders [9] or medical illnesses [10]. Network analysis allows to identify "bridge symptoms" that mediate the transition among different syndromes [9]. Finally, once a network has been activated and has become self-sustained, even removing the triggering external field factor (e.g. resolution of an economic problem) may be insufficient to deactivate the network and lead to clinical recovery. This phenomenon is termed "hysteresis" [4] and is consistent with clinical experience.

Studies of symptom networks have provided insight into the pathogenesis, symptom dynamics and outcome of depression in adults [4,11–13]. These findings, however, are not directly applicable to depressive symptoms in late-life, which are often accompanied by neurocognitive symptoms and may have different neurobiological contributors [14], including aging related brain network changes [15,16], microvascular disease [17,18], inflammation [19] and other medical comorbidities leading to specific symptom dynamics. In support of this view, are studies demonstrating an over-representation of somatic symptoms, agitation and pessimism in late-life depression [20,21]. Network structure analyses could provide information on the relationships among different symptoms and their relative importance in influencing their clinical presentation [22]. This analysis focuses on the network structure of depressive symptoms in late-life using a large, random sample of European and Israeli older adults with a wide range of depressive symptoms. Based on clinical literature [20,21], our hypothesis was that pessimism and somatic symptoms would have a central position within the network of depressive symptoms.

2. Methods

2.1 Study design

This study analyzed data of the Survey of Health, Ageing and Retirement in Europe (SHARE), which collected information on health, well-being, economic circumstances and social networks of adults 50 years and older from 19 European countries and Israel [23]. This analysis used data from SHARE Wave 2, release 5 (DOI: 10.6103/SHARE.w2.500) [23–25].

We analyzed data of participants aged 65 years or older, who completed the depression scale EURO-D, and endorsed at least 1 EURO-D items. We examined the structure of depressive symptoms across the full spectrum of severity without imposing restrictions based on the number of symptoms or diagnostic caseness [26]. This decision was based on literature indicating that even mild depressive symptoms in late-life may increase suicidal ideation, disability, and healthcare utilization in older adults [27–32] and is consistent with the atheoretical, data-based network structure approach.

2.2 Assessment of depressive symptoms

The EURO-D [33,34] is a scale for depression developed to harmonize data from five other instruments, i.e. the Geriatric Mental State-AGECAT-package [35], the SHORT-CARE [36], the Comprehensive Psychopathological Rating scale [37], the Centre for Epidemiological Studies Depression scale [38], and the Zung Self-Rating Depression Scale [39]. Harmonization was based on expert opinion and probabilistic modelling of a large, random sample with a wide range of late-life depressive symptoms.

The final version of EURO-D comprises twelve dichotomous items (presence/absence) of symptoms of major depression, i.e. depressed mood, pessimism, death wishes, guilt, sleep

problems, loss of interest, irritability, loss of appetite, fatigue, concentration difficulties, lack of enjoyment, tearfulness. EURO-D encompasses all DSM-V symptoms but includes appetite loss instead of weight loss [40,41]. The total score ranges from 0 to 12. The EURO-D has acceptable reliability, internal consistency, validity, and external validity [34,42] even across non-European countries [43].

2.3 Network estimation

The network structure was estimated by analyzing EURO-D data using the Enhanced Least Absolute Shrinkage and Selection Operator (eLASSO) method [5]. eLASSO combines logistic regression analyses with an optimization procedure to identify the best set of connections for each symptom, while excluding spurious associations among them. Thus, it does not rely on assumptions that hampered earlier statistical methods, such as normality of data or aciclicity of associations, conditions unlikely to be met in psychiatric syndromes. In each iteration of eLASSO, each variable is regressed onto the others to estimate the strength of their associations, while controlling for all other associations. The algorithm takes into account a penalty parameter to obtain sparsity and uses the Extended Bayesian Information Criterion (EBIC), a Goodness-of-Fit measure to select the best set of neighbor variables for each *node* (symptom). The final network is automatically constructed and selected when each node (representing a symptom) is connected to a *definite* number of other nodes through *edges* of different weights, representing the strength of their direct association [5]. The network is visualized using the Fruchterman-Reingold algorithm [44]. In the network layout, the thickness of edges is used to indicate the strength of associations among nodes. The color of the edge indicates the direction of the association (green edges indicate positive associations, red edges indicate negative associations). Symptoms with stronger and more numerous associations are placed closer to each other and more centrally within the network. Furthermore, network analysis provides quantitative centrality indices for each node that depend on the unique configuration of the network.

In this paper, we report on the network centrality measures of *Strength*, *Betweenness* and *Closeness* among depressive symptoms. *Strength* is the sum of the weight of all direct connections between a specific symptom and the others. *Betweenness* indicates how often a symptom lies on the shortest indirect path between other nodes, facilitating their connections (proportion of pathways). *Closeness* indicates how strongly a node is indirectly connected to other nodes in the network (the inverse of the sum of the distances) [6]. Centrality measures are reported as standardized values (z-scores). Centrality of a symptom is not a measure of the symptom's prevalence. Instead, centrality refers to the role of a symptom within a network, i.e. central symptoms are those with stronger connections with other symptoms or mediating more often the connections among other symptoms.

2.4 Estimation of network accuracy and stability

The accuracy and stability of the symptom network were examined using three, recently described procedures [44]. The stability of node properties was estimated using a *case dropping bootstrap procedure*. In this analysis, a growing proportion of cases is subtracted from the dataset in multiple waves, while re-estimating the network structure and node centrality indices. A network is considered stable if a large part of the sample can be excluded from the dataset without observing significant changes in the indices of nodes' centrality. Stability was depicted graphically and quantified by calculating the Correlation Stability Coefficient (CS-C). The CS-C is the maximum proportion of cases that can be dropped from the sample without significantly affecting centrality indices. A network is considered stable if node centrality indices from the subsamples are correlated with the indices calculated from the total sample at a value of r = 0.7 or higher. Generally, the CS-C is required to be above 0.5, indicating that 50% of the sample can be dropped while maintaining similar centrality indices [44].

The accuracy of edge weights was estimated by calculating their Confidence Intervals (CIs) with a *non-parametric bootstrap procedure*. To this end, observations are randomly re-sampled to create multiple new datasets from which 95% CIs are calculated. In this analysis, we performed 2,500 permutations and used *bootstrapped difference tests* to evaluate differences in the network's properties. This test relies on 95% CIs, to determine if two edge-weights or two node centrality indices differ significantly from one-another.

2.5 Comparison of network characteristics by gender and age

We conducted exploratory analyses to examine whether network characteristics differ by gender and age. We used the Network Comparison Test (NCT), a permutation test that assesses the difference between two networks (e.g. network of females vs. network of males) based on several measures [11]. We applied the NCT on subsamples defined by gender and age (the latter by splitting the sample at the median age of 74) using 2,500 permutations. This procedure assesses the global strength of the networks by comparing the overall level of network connectivity across groups divided by the weighted sum of the absolute connections. Next, we compared the *distributions of edge weights* in each network in order to characterize the structure of the network. Finally, we compared the differences in strength for each edge between the two networks, controlling for multiple tests (Holm-Bonferroni correction of p values). Code relative to all analyses is available upon request.

3. Results

3.1 Sample

A total of 8,557 individuals endorsed 1 or more EURO-D depression scale item and comprised the study sample. Their female to male ratio was 1.22/1, their mean EURO-D score was

3.07 (SD=2.17) and the most frequently endorsed symptoms were depressed mood, sleep problems and fatigue, all with a prevalence above 40% (Table 1).

3.2 Network structure and centrality measures analysis

The network of EURO-D symptoms was organized around the complex of death wishes, loss of interest, depressed mood, and pessimism all displaying high values of strength and betweenness (Figure 1). Closeness for these symptoms was slightly higher than that of other symptoms (Table 2 and Figure 2). Death wishes showed the strongest, most direct connections with depressed mood, pessimism and guilt. Pessimism and loss of interest were strongly interconnected and were placed within a cluster that comprised also lack of enjoyment and concentration difficulties. Loss of interest was also connected with loss of appetite and fatigue. Sleep problems were situated at the periphery of the network. Sleep problems were mainly connected with depressed mood, loss of appetite and death wishes; loss of appetite and fatigue were highly interconnected and mainly influenced by loss of interest. Depressed mood was connected to fatigue and loss of sleep with a moderate strength.

Another distinct cluster of symptoms was organized around depressed mood and composed of guilt, tearfulness and irritability. All connections had positive associations, except for two weak negative pathways between pessimism and irritability, and between pessimism and tearfulness.

A weighted adjacency matrix describes the numerical interactions between symptoms (Supplementary Table 1).

3.3 Network accuracy and stability

The case-dropping subset bootstrap procedure showed that the values of betweenness, closeness and strength remained stable even after dropping large proportions of the sample (Figure 3). The CS-C for betweenness was 74.5% indicating that 74.5% of the sample could be dropped while still maintaining a high correlation (R= 0.71) with the values from the whole sample. Similarly, 78.1% and 85.4% of the sample could be dropped without significantly affecting the values of closeness and strength, respectively.

Bootstrapped 95% CIs for the estimated edge-weights were narrow, suggesting that the estimates were reliable (Supplementary Figure 1). Also, edge weights were highly variable; the bootstrapped difference tests revealed consistently that a large proportion of the comparisons among edge weights were statistically significant (Supplementary Figure 2). Also, the strength of most nodes were statistically different from one another in individual comparisons (Supplementary Figure 3).

3.4 Gender and age effects

Comparing networks between females (n= 4,721) and males (n= 3,836) did not yield significant differences in network global strength (females: 19.598 vs. males: 19.539; S=0.06, p=0.96), distribution of edge weights (M=0.36, p=0.76) or individual edge weights (all p values >0.05 after Holm-Bonferroni correction). Plots appear in Supplementary Figures 4, 5 and 6.

Subdividing the sample at the median age (74 years), did not yield significant differences between younger (n=4,241) and older (n=4,316) individuals (difference in global strength: younger: 19.22762; older: 19.84491; S: 0.6713, p=0.60; distribution of edge weights: M= 0.30, p=0.94; all p >0.05). Plots are reported in Supplementary Figures 7, 8 and 9.

4. Discussion

The principal finding of this study is that death wishes, loss of interest, depressed mood, and pessimism are the central hub in the depressive symptom network structure that may trigger or sustain the rest of depressive symptoms in late-life. Contrary to our hypothesis somatic symptoms such as fatigue, sleep problems and appetite changes were identified as peripheral symptoms. The depressive symptom network structure was estimated from a large population representative of community dwelling older adults who filled a self-rated depression scale. Rigorous statistical testing demonstrated a high degree of network stability.

To our knowledge, this study is the first to characterize the network structure of depressive symptoms in late-life. Death wishes were the most central symptom in the network of late-life depressive symptoms. They are common in both major and minor late-life depression and are associated with increased mortality [45]. Death wishes were mainly connected to depressed mood, pessimism and guilt, all of which found to be risk factors of suicide in psychiatric samples [46,47]. Death wishes are part of a continuum extending from active suicidal intent, to plans, and ultimately to suicidal behavior [48]. Adverse life events and medical and psychiatric comorbidity may trigger the progression of death wishes to suicidal ideation and suicidal behavior [49]. Suicidal ideation is under-reported by older adults [21,46,50], in part because of stigmatizing beliefs [51]. However, it is common in older adults with functional impairment [52], acute physical illnesses [53,54], and subthreshold depression [55]. Thus, death wishes may be a proxy for suicidal ideation and an important treatment target.

Pessimism was identified as one of the central depressive symptoms in the network of old adults but not in the network of younger adults [4,11,56]. In late-life, pessimism may result from stressors [57], including bereavement [8,58], economic and social problems [59,60] and physical illnesses [61,62]. Contrary to our expectation, somatic symptoms had low centrality in the network of depressive symptoms in late-life even though their prevalence is high [20,21]. A potential explanation is that somatic symptoms are prevalent in late-life regardless whether they are caused by depression, medical illnesses, or an interaction of depression with medical illnesses [63]. Another possibility is

that symptoms of medical illnesses serve as “bridge symptoms” that trigger the onset of depressive symptoms [9,10,64] rather than being central in the depressive symptom network.

Our analysis documents both similarities and differences in the depressive symptom structure of older and younger adults. Loss of interest and depressed mood were central in the depressive symptom network structure of both old and younger adults [4,11,56]. Death wishes and pessimism were central depressive symptoms in the network of older adults but they were peripheral symptoms in younger adults [4,56]. Fatigue and appetite changes were consistently found among the most central depressive symptoms in young adults [11,56] but were not central symptoms in our older participants. Other factors that may account for differences in the network structure of depressive symptoms in late- and early-life include a higher prevalence of cognitive dysfunction, endocrine and immune systems’ changes in older individuals [17,65,19,66–69]. Nonetheless, differences in depressive symptom network structure between older and younger adults need to be confirmed by direct comparison studies.

Identification of distinct neurobiological targets suitable for treatment development is a concern central to the NIMH research agenda for depression [70]. “Syndrome reduction” has been used to shorten the distance from complex clinical syndromes to circuit dysfunction, e.g. instead of searching for circuit dysfunction in the entire depressive syndrome, a considerable body of work has focused on anhedonia [71]. The study of symptom network structure provides a data-based syndrome reduction and offers a focus for neurobiological studies by identifying depressive symptoms of high centrality. Identifying the centrality of death wishes, depressed mood, loss of interest, and pessimism in the depressive symptom network structure in late-life may be followed by focused studies using cognitive neuroscience, neuroimaging and other biomarkers[72] to interrogate their underlying neurobiological dysfunction, e.g. dysfunction of the cognitive control, reward, and salience networks and their interaction.

Symptom nodes derived from network structure analysis may serve as a vehicle for novel streamlined psychosocial treatments targeting symptoms central to the network and sustaining the rest of depressive symptoms. Knowledge that death wishes depressed mood, loss of interest, and pessimism drive the rest of depressive symptoms may lead to development of streamlined behavioral interventions targeting the most prominent symptoms among them in the individual patient [16]. Such parsimonious interventions may be suitable for the treatment for depression or for prevention of depression in at risk populations. Efficacious psychosocial interventions for late life depression exist [73] but they are rarely used correctly in the community because of their complexity. Identifying distinct, clinically meaningful targets that can be addressed by a finite number of psychotherapy techniques, matching the skill set of community clinicians may streamline psychotherapy for late-life depression and increase its public health impact [16].

This study should be viewed in the context of its limitations. The EURO-D scale, although it covers the most important symptoms of depression [34], it may not adequately rate symptom severity

[56]. Future studies may examine whether the depressive symptom network structure varies across different levels of depression severity and among patients meeting criteria for depressive syndromes. While consistent with the atheoretical, data-based approach of network analysis, inclusion of individuals with few depressive symptoms or not restricting inclusion to subjects with depressed mood or lack of pleasure may be limitations of this study. However, selecting participants with one of the principal symptoms of depression (depressed mood and lack of pleasure) did not alter the structure of the network significantly. Neurocognitive symptoms are common in late-life depression and may reflect network abnormalities related to its pathophysiology but they were inadequately characterized in our sample. Focused studies using detailed assessment may identify neurocognitive abnormalities associated with depressive symptoms central to the network structure. The effect of age of depression onset, bereavement, and medical burden on the depressive symptom network may be another focus for future studies. Lastly, the cross-sectional design of this study does not allow conclusions on the temporal dynamic relationships or directionality of the interactions among symptoms.

In conclusion, network analysis of depressive symptoms in a community population revealed that death wishes, depressed mood, diminished interest, and pessimism constitute the "backbone" that sustains the depressive symptom structure in late life. Symptoms central to the depressive symptom network in late-life may be used as targets for novel, streamlined interventions and provide a data-based focus for studies investigating neurobiological processes of late-life depression.

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Conflict of Interest

Dr. Alexopoulos has been on the speakers' bureaus of Lundbeck, Otsuka, and Allergan. No other authors report conflicts of interest.

Supplementary information is available at MP's website

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Table 1. Sample characteristics (n=8557)

Age, mean (SD), y	74.0 (10.4)
Gender, %, F	59.4
Marital status, %, married	69.9
Years of education, mean (SD)	10.4 (4.3)
Current smoker, %	21.9
BMI, mean (SD)	26.2 (6.1)
N. of chronic diseases, mean (SD)	1.80 (1.58)
Physical inactivity, %	13.0
EURO-D score, mean (SD)	3.07 (2.17)
EURO-D caseness (score ≥4), %	33.1
Depression lifetime, %	21.9
Drugs for anxiety or depression, %	7.5
Prevalence of symptoms, %	
Depressed mood	48.3
Pessimism	19.7
Death wishes	8.9
Guilt	10.0
Sleep problems	42.5
Loss of interest	12.9
Irritability	33.8
Loss of appetite	11.6
Fatigue	44.1
Concentration difficulties	24.9
Lack of enjoyment	17.0
Tearfulness	33.2

Table 2. Standardized centrality measures of nodes in the network (z-scores)

	Strength	Betweenness	Closeness
Death wishes	2.03	2.90	2.09
Loss of interest	1.30	0.46	0.53
Depressed mood	1.03	0.29	1.25
Pessimism	0.11	0.29	0.81
Fatigue	-0.02	-0.06	0.21
Loss of appetite	0.26	-0.41	-0.29
Lack of Concentration	-0.51	-0.58	-0.57
Lack of Enjoyment	-0.53	-0.58	-0.80
Tearfulness	-0.69	-0.58	-0.41
Irritability	-0.81	-0.58	-1.04
Sleep problems	-1.08	-0.58	-1.19
Guilt	-1.09	-0.58	-0.58

Figure Legends

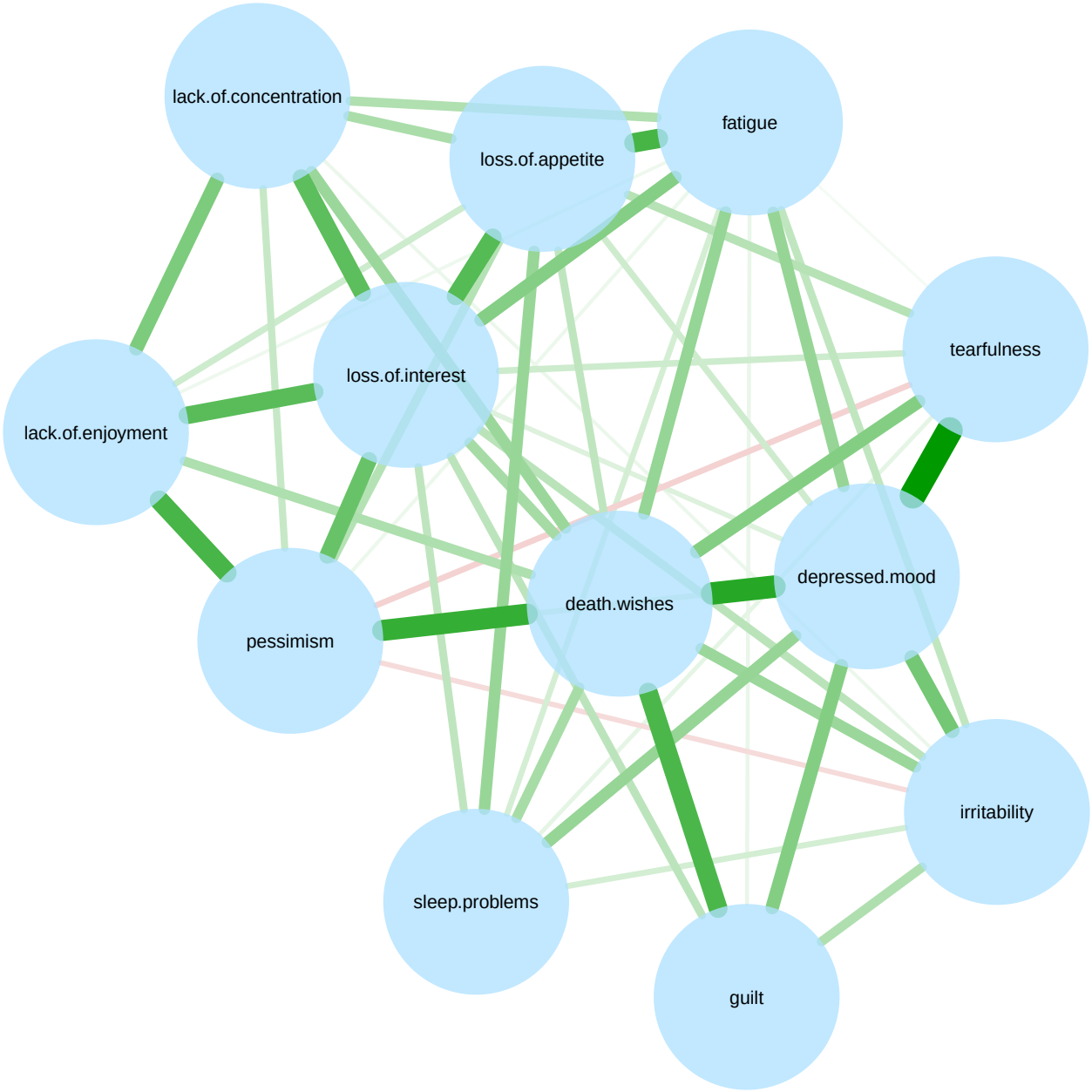
Figure 1. Symptom network of depressive symptoms in late-life

The network represents the relationships between 12 depressive symptoms of the EURO-D rating scale. In the diagram represents, symptom nodes with stronger connections are closer to each other. Lines between nodes (edges) are colored in green when they represent positive correlations and in red when they represent negative correlations. The edge thickness is proportional to the strength of the association between symptom nodes.

Figure 2. Standardized centrality indices of symptoms (z-scores)

Figure 3. Stability of centrality indices by case dropping subset bootstrap

The case-drop bootstrap procedure evaluates if centrality of indices remains the same after re-estimating the network with fewer cases. The x axis reports the percentage of cases of the original sample used at each step (at 30%, N=2,568; at 20%, N=1,711). The y axis reports the average of correlations between (a) the centrality indices from the original network and (b) the centrality indices from networks that were re-estimated after dropping increasing percentages of cases. Each line indicates the correlations of betweenness, closeness and strength, while areas indicate 95% CI. The decrease in correlation was minimal when dropping up to 70% of the sample (not shown).


lack.of.concentration
loss.of.appetite
fatigue
tearfulness
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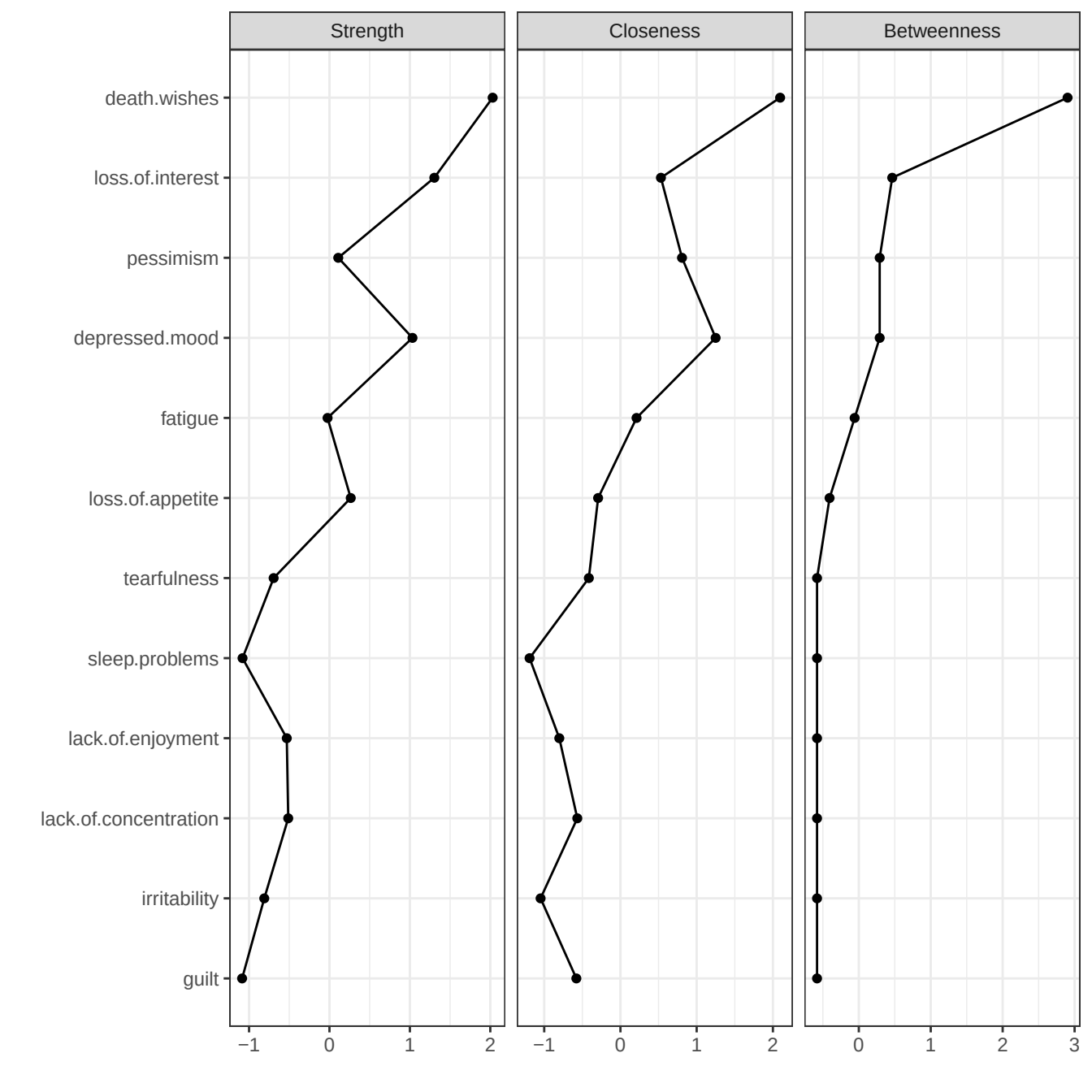
lack.of.enjoyment
depressed.mood
death.wishes
pessimism
irritability
sleep.problems
guilt


Strength
Closeness
Betweenness
death.wishes
loss.of.interest
pessimism
depressed.mood
fatigue
loss.of.appetite
tearfulness
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lack.of.enjoyment
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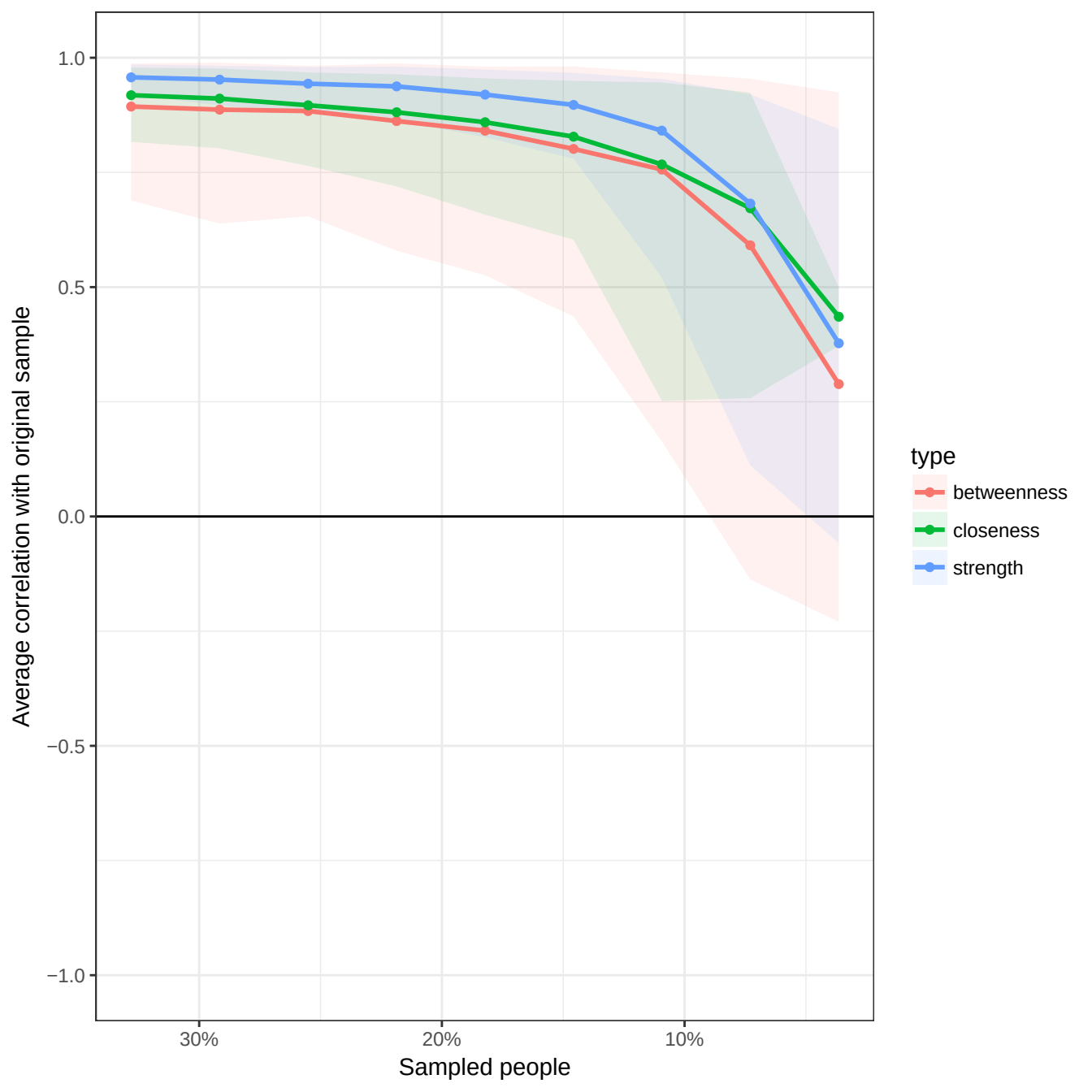
3


1.0
0.5
0.0
−0.5
−1.0
Average correlation with original sample
30%
20%
10%
Sampled people
type
betweenness
closeness
strength