

Mental illness and cardiovascular disease: A longitudinal study

The influence of individual depression symptoms on cardiovascular diseases

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Abstract

This longitudinal study examines the influence of individual depression symptoms on cardiovascular disease indicators over time. Utilising data from the Cardiovascular Risk in Young Finns Study , the research applies a cross-lagged panel network analysis to explore temporal effects and symptom dynamics. The study considers the impact of various factors, including smoking habits, BMI, and demographics, on the relationship between depressive symptoms and CVD traits.

The analysis employs LASSO regression to construct network models, revealing that certain depressive symptoms significantly impact CVD indicators using the glmnet package. Notably, variables such as acetate and pessimism exhibit strong influence, while insulin levels, diastolic, and systolic blood pressures are notably affected by depressive symptoms. This study identifies suicidal thoughts or wishes as having the strongest predictive power in the networks.

Limitations include a small and ethnically homogeneous sample size, challenges in model validation, and the absence of expert validation. Despite these limitations, the study provides valuable insights into the complex interplay between mental health and cardiovascular health, highlighting the importance of considering individual depressive symptoms in the context of cardiovascular risk.

keywords: *cardiovascular, depression, cross lagged panel network, glmnet*

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Introduction

According to current research and the listing of the World Health Organisation (WHO), about three hundred million people suffered from a mental illness in 2019, with depressive disorder being the most prevalent among them (de Hert et al., 2018; Smith & De Torres, 2014; Stapelberg et al., 2012). A mental illness is hereby defined by a noticeable disruption in an individual's cognitive functions, emotional management, or behaviour (Manderscheid et al., 2010; Smith & De Torres, 2014; Spitzer & Endicott, 2018). Individuals with mental illness typically encounter difficulty or distress in functional domains, like walking, communication, and handling emotions. These individuals have, for example, difficulty with getting out of bed or finding motivations to do something, or other symptoms like difficulty sleeping and fatigue (Hare et al., 2013). Hereby the last two symptoms are commonly associated with depression as mentioned by Hare et al. (2013) Besides the limitations in functional behaviours, people suffering from mental illnesses exhibit higher rates of detrimental health behaviour, such as smoking and having a poor diet (Goodell et al., 2011; Walker et al., 2015).

The current expectation is that depression will be the leading cause of worldwide disability by 2030 (de Hert et al., 2018; Liu et al., 2020; Walker et al., 2015). Currently 14.3% of all the deaths each year around the globe can be contributed by mental disorders. However the relationship between mental disorders and mortality is difficult to identify. Possible explanation for this is that most individuals with mental disorders do not succumb from their condition directly, but often to cardiovascular disease (CVD), and other chronic illnesses like: infections, suicide, and various other causes (Goodell et al., 2011; Walker et al., 2015).

Individuals diagnosed with mental illness often face a notably shortened lifespan, primarily attributed to CVD. On average, the expected lifespan for individuals diagnosed with a mental illness is 10 to 20 years less than the general population (de Hert et al., 2018; Rossm et al., 2022). In the study by de Hert et al. (2018), more than 20% of the patients with CVD showed signs of depression, with 33% of the patients exhibiting depressive symptoms. Additionally a connection has also been found where individuals with severe depression exhibit a higher risk for CVD (Hare et al., 2013). It has been known for a long time that there is a relation between stress and CVD (Dhar & Barton, 2016; Musselman et al., 1998). Stressful occurrences, such as natural disasters, have been positively correlated with a rise in acute cardiovascular events. Hereby stress is also a possible cognitive symptom of mental illnesses (Dhar & Barton, 2016; Sabin & Sackeim, 1997).

In most parts of the developed world, CVD is the leading cause of death, based on data from the World Bank for these regions (Gaziano et al., 2006). (Gaziano et al., 2006) mentioned that because of this a lot of studies are focusing on curing and understanding CVD. This study will delve into the connections between several types of mental illnesses and various traits of CVD. The aim of this study is to understand to what extent these relationships are influenced by important depressive factors, such as having difficulty to relax or not feeling to wake up (de Beurs et al., 2001; Katainen et al., 1999).

For this study the premise that mental illness diagnoses correlates with poorer cardiovascular health will be adopted, based on the research of de Hert et al. (2018), Hare et al. (2013) and others. Besides that these correlations lessen after adjusting for psychotropic medication usage and additional factors (such as age, gender, education, employment, smoking history, body mass index (BMI), diabetes, and physical activity), as mentioned by Dhar and Barton (2016), Goodell et al. (2011), Sabin and Sackeim (1997), and Walker et al. (2015).

Drawing upon data from the Cardiovascular Risk in Young Finns Study (YFS), the aim is to interpret the extent to which these relationships are influenced by key factors (Aatola et al., 2014; Åkerblom et al., 1985). It was established in 1980 to gain insight about the effects of aging within the Finnish population and why some people develop CVD during their life. The research was carried out in medical schools around Finland (Turku, Helsinki, Kuopio, Tampere, and Oulu).

The focus of this study is to understand the temporal relationships between the individual depressive symptoms and indicators of CVD, considering a small number of influential factors (i.e., a person's age and sex). Based on literature, we hypothesised that certain individual depressive symptoms correlate with poorer cardiovascular health over time (Nielsen et al., 2021; Rossom et al., 2022; Whooley & Wong, 2013). Furthermore, psychotropic medications and other factors like age, gender, education level, employment status, smoking habits, BMI, diabetes status, and physical activity, will diminish these associations. For this study the covariance that will be focused on are age, BMI, sex and smoking habits. Within this research the following questions will be answered:

1. *Are there relationships between the individual depressive symptoms and the cardiovascular disease indicators overtime, based on a cross lagged panel network? Are there reciprocal relationships?*
2. *Which depressive symptom has the most impact on cardiovascular disease over time?*

To approximate the effect of individual depressive symptoms and CVD traits a cross lagged panel network (CLPN) will be estimated (Kenny, 1975; Wysocki et al., 2022). A CLPN (Cross-Lagged Panel Network) is a discrete time structural equation model that incorporates network analysis techniques to measure and analyse panel data with multiple variables over time (Kuiper & Ryan, 2018). For example, it can determine whether the value of variable X at an earlier time point (t) predicts the value of variable Y at a later time point ($t+1$), or vice versa, thereby revealing the directional influences between variables over time (Funkhouser et al., 2021; Wysocki et al., 2022). Hereby it is important to note that the selected variables for each time point are measured at the same time, and that the relationship stays constant over time.

Theoretical Framework

Research Related to Depression

Most studies related to depression, utilise summation scores to quantify its severity. This has the possibility that crucial symptom dynamics are overlooked, with the use of an evolving depressive symptom network (Fried et al., 2014; Fried & Nesse, 2015). Therefore, for this study, the assumption will be made that depression represents more than just the sum of its individual symptoms. When calculating a summation score the individual's depression symptoms are changed to a single value, the result of this is that it makes all the different values equal. This will result in the details being forgotten. It has been proposed that individual symptoms are distinct entities with independent causal significance based on the genetic information (Fried et al., 2014; Fried & Nesse, 2015). Within these kinds of studies the individuals are classified based on a threshold score of the symptoms. When a person reaches a certain threshold a diagnosis can be given. Hereby an individual must exhibit five or more symptoms as mentioned by the DSM-5, to qualify for a diagnosis (Fried & Nesse, 2015). Different persons can have different symptoms and sub-symptoms, which can lead to roughly 1000 unique combinations.

Research Related to Cardiovascular Disease

Because of the global health burden of CVD, a lot of studies focus on identifying risk factors, developing preventive measures, and creating effective treatment (Dhar & Barton, 2016; Gaziano et al., 2006). Given the complexity of CVD, it is crucial to use diverse approaches to comprehensively understand and address the workings resulting in CVD (Diez et al., 2010; Lusis & Weiss, 2010; MacLellan et al., 2012). As a result of the complexity, current studies are working on using a system-based approach. Where a network is created with the selected CVD variables (i.e., aneurysms) (Lusis & Weiss, 2010). This approach integrates multiple layers of biological data to understand the intricate network of interactions that contribute to CVD (Diez et al., 2010; Lusis & Weiss, 2010; MacLellan et al., 2012). Within this research the biological data will be based on a survey and experiments from the YFS (Åkerblom et al., 1985).

Network Perspective

Network models like CLPN, gives insight to show why symptoms cluster (Cramer et al., 2010; Fried & Nesse, 2015; Schmittmann et al., 2013). These network models attempt to capture these underlying processes by depicting direct relationships among lower-level variables (i.e., individual symptoms such as having difficulty with getting out of bed), rather than treating them as manifestations of a high-level variable. (Cramer et al., 2010; Fried & Nesse, 2015; Wysocki et al., 2022). This is based on the assumption that these low-level variables can have an impact on the high-level variables. A high-level variables refers hereby to the diagnosed illnesses such as depression.

When using a CLPN, it is assumed that the variables of X are independent of the variable y (Wysocki et al., 2022), and that as long as the group is homogeneous, the network may represent all the individuals within the model. A stronger connected network has stronger feedback among the individual symptoms and therefore might be associated with an increased vulnerability to depression (van Borkulo et al., 2015).

Knowledge Gap

CLPN has been used in previous studies, to investigate specific depression symptoms individually. These studies examined the causal relationship between these symptoms and a depression diagnose, without any relation with CVD (Hwang et al., 2021; Ren et al., 2023; Schlechter et al., 2023). Besides research on depression, CLPN has been used a lot within the field of psychology (Funkhouser et al., 2021; Schlechter et al., 2022; Wysocki et al., 2022). As discussed in the Introduction, extensive research has explored the link between CVD and depression (de Hert et al., 2018; Dhar & Barton, 2016; Rossom et al., 2022; Whooley & Wong, 2013). But these studies did not use a network approach to explore the relationships. Moreover, most of these studies use depression as the sum of its parts, instead of looking at each individual symptom. As mentioned before, a network approach has been used for depression and CVD research, for example with Stapelberg et al. (2011) and Valenza (2023). But they did not implement a CLPN to measure the temporal effects over time. A comparable analysis has previously been conducted using the YFS, but solely on cross-sectional data without delving into individual depressive symptoms (Raitakari et al., 2008). Hakulinen et al. (2016) looked at the YFS with a network approach, but instead focused on the social networks of the participants. Other research has been done with the YFS related to CVD and depression. However, these studies did not use a network approach (Elovainio et al., 2006, 2010, 2015). Nonetheless, these studies have demonstrated a wide association between genetic liability to mental illnesses, particularly depressive disorders with CVD, even after accounting for potential confounding factors (Veeneman et al., 2024).

Longitude Analysis

Besides a network approach to look at the causal relationships of the symptoms and depression, this study will also focus on the effects overtime. A longitudinal study is useful, because the relationship between risk factors and the emergence of illness can be analysed over different durations (Belle et al., 2004; Schaie, 2005). Furthermore, statistical testing can be used to examine changes over time for the entire group or specific individuals. This is because the data is collected over multiple individuals for a designated group. The advantages of longitudinal studies include the ability to analyse the individual time elements within the cohort, connect events to specific exposures, and follow possible changes over time (Farrington, 1991; Schaie, 2005).

Method

Study Population

As mentioned in the Introduction the YFS began in 1980 with selecting participants from the ages 3, 6, 9, 12, 15 and 18 years. These participants were randomly selected from different cities in Finland with medical schools and their rural communities, to get different socioeconomic backgrounds and varying CVD risks (Åkerblom et al., 1985; Juonala et al., 2013; Raitakari et al., 2008). In this way the final samples could better represent the Finnish children. This decision resulted in the population size being relatively small, with around 3595 participants. The participants were grouped based on gender and randomly ordered in the given cohort (Åkerblom et al., 1985; Juonala et al., 2013; Raitakari et al., 2008). All participants provided written informed consent, and the study received approval from local ethics committees (Juonala et al., 2013). Multiple cross-sectional studies have been conducted after 1980, with the studies being mostly three years apart.

The rural communities were selected based on the following criteria: (a) their industrial composition closely aligned with the average of other rural communities within the same province; (b) there were sufficient individuals in the age cohort, with a minimum of 25 boys and girls in the given rural community; (c) the distance travelled within the community was not extensive; and (d) there was an equal number of urban and rural participants within the sample of each area.

Data Selection

Within this study, certain CVD and other variables were selected from the YFS dataset seen in Table 3.1. For the depressive variables the revised Beck's Depression Inventory (BDI) was used (Aaron T. Beck & Ranieri, 1996; Katainen et al., 1999). To connect the datasets it was required that the data collected came from the same year and cohort. This resulted in the selected data being from 2007, 2011 and 2012 (Elovainio et al., 2015; Juonala et al., 2013).

Person Variables

As previously mentioned, in this study it is acknowledged that the relationship of depression and CVD might be influenced by additional variables, such as a person's age. Previous studies highlighted the potential impact of medication usage alongside other factors such as age, gender, education, employment status, smoking history, body mass index (BMI), presence of diabetes, and levels of physical activity (Dhar & Barton, 2016; Goodell et al., 2011; Sabin & Sackeim, 1997; Walker et al., 2015). Variables related to an individual's demographic characteristics, such as age, gender, BMI, and smoking status were selected as covariate to investigate their potential influence. To assess their relationships, an ordinary least squares (OLS) regression was applied to residualised these variables using the python statsmodel (Dismuke & Lindrooth, 2006; Seabold & Perktold, 2010).

Depressive Variables

The main variables of interest to measure mental health were the individual depressive symptoms, which enabled a deeper understanding of the specific symptoms related to cardiovascular health (Fried et al., 2014; Fried & Nesse, 2015). As mentioned before the BDI was used to assess the depressive symptoms (Hakulinen et al., 2016; Katainen et al., 1999; Palmer & Binks, 2008). In the beginning this study was done on a small randomly selected sample size, but extended when the YFS continued their study on the Finnish population (Katainen et al., 1999). The dataset consisted of 21 variables, where the intensity of depressive symptoms was measured using a four-point Likert scale, ranging from 0='not at all' to 3='very much' (Palmer & Binks, 2008). These symptoms included feelings of sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleep pattern, irritability, changes in appetite, difficulty concentrating, tiredness or fatigue, and loss of interest in sex. These symptoms were selected because of their relation with a range of somatic and cognitive experiences related to depression (Aaron T. Beck & Ranieri, 1996; Palmer & Binks, 2008).

Other depression scores (for example changes in sleeping patterns and changes in appetite) were calculated by summing item scores. This resulted in a total score with the range 0-63, where higher scores on the scale indicate a heightened degree of depressive symptoms (Aaron T. Beck & Ranieri, 1996; Palmer & Binks, 2008). These scores were interpreted in such a way that 0-13 indicated minimal depressive symptoms, 14–19 mild, 20–28 moderate, and 29–63 severe. These values were imputed to match the Likert scale based on the given interpretation (Aaron T. Beck & Ranieri, 1996; Palmer & Binks, 2008). This resulted in all the scores being between 0 and 3.

Table 3.1: CVD variables selected from the YFS (Åkerblom et al., 1985; Juonala et al., 2013).

Cardiovascular risk factors	Details
Anthropometry	Age Sex BMI kg/m ²
Smoking	Yes/No
Biochemistry	Diastolic blood pressure ¹ (mm Hg) Systolic blood pressure ² (mm Hg) Acetate ³ (mmol/L) Apolipoprotein ⁴ (mmol/L) Total cholesterol ⁵ (mmol/L) LDL cholesterol (mmol/L) HDL cholesterol (mmol/L) Triglycerides ⁸ (mmol/L) Glucose ⁷ (mmol/L) C-reactive Protein ⁸ (mg/L) Insulin ⁹ (mU/L)

Cardiovascular Variables

In some of the follow-up studies related to the YFS, the participants underwent physical examinations and had blood samples taken besides the normal questioner and tests (Juonala et al., 2013). Health factors including in these tests included: serum lipoproteins, insulin, obesity indices, blood pressure and other risk factors such as: C-reactive protein (CRP), homocysteine, asymmetric dimethylarginine (ADMA), adiponectin and leptin. Blood pressure for example is a central indicator for cardiovascular health (Schaare et al., 2023). Increased blood pressure stands as a significant contributor to CVD, frequently linked with stress and mental health disorders. Additionally, an extensive set of metabolic variables has been analysed in combination with heart rates (Åkerblom et al., 1985; Juonala et al., 2013; Raitakari et al., 2008).

Explanation Cardiovascular Variables

To understand the data mentioned in Table 3.1, an analysis will be given about each variable and its relation to CVD:

¹ The diastolic blood pressure level, which measures minimal blood pressure between heartbeats, is linked to hypertension and thus CVD (Beevers et al., 2001; Celler et al., 2021). ² Systolic blood pressure, measured during a heartbeat, can lead to hypertension, paralleling the effects of high diastolic pressure (Bundy et al., 2017). ³ The average acetate level, a common short-chain fatty acid in plasma, can directly and indirectly lower heart rate and arterial pressure (Poll et al., 2021). ⁴ Apolipoproteins, essential for maintaining lipid balance and involved in cholesterol transport and clearance, have varying impacts; for instance, higher levels of Apolipoprotein-III can elevate triglycerides, increasing the risk for CVD (Eichner et al., 2002). ⁵ Elevated total levels of low-density lipoprotein (LDL) and high-density lipoprotein cholesterol (HDL) correlate with a higher risk of CVD, as does an elevated LDL level alone. Similarly, increased HDL levels are significant markers (J. Koskinen et al., 2009; J. S. Koskinen et al., 2023; Mattiuzzi et al., 2020). ⁶ Average triglyceride levels in the blood, particularly higher non-fasting triglyceride levels, are associated with an increased risk of cardiovascular disease (Nordestgaard & Varbo, 2014). ⁷ glucose levels are crucial as they are closely linked to type 2 diabetes, a condition characterised by the body's inability to regulate blood sugar, leading to persistent high levels, significantly raising the risk of CVD (Kelly et al., 2009). ⁸ C-reactive Protein (CRP), an acute-phase protein found in plasma, is higher in CVD patients and may correlate with CVD in older populations (Tracy et al., 1997). ⁹ Lastly, the average insulin level of a given patient, when higher, the assumption is made that it indicates increasing insulin resistance, which is a potential risk factor for cardiovascular disease (Adeva-Andany et al., 2019; J. Koskinen et al., 2009).

Missing Data

The missing data was identified to understand the missing patterns by reviewing attrition rates across waves. Based on the assumption that the data is missing at random (MAR) or missing completely at random (MCAR) multiple imputation by chained equations was done using an interpolation function.

Analysis

To better understand the low-level relations based on high-level variables, the low-level variables were represented as nodes within a network, with the connections between them represented as edges. The weight of the edges indicated the strength of each connection, where a negative weight signified a negative relationship.

Within this research, the models were computed for three consecutive time points, as mentioned earlier based on the available cohorts, which yielded two distinct network models (i.e., T1 → T2, T2 → T3) to assess symptom prediction over time. The data was transformed using linear regressions employing the LASSO regularisation technique. LASSO regression is used to determine the variables and their respective regression coefficients that result in a model where the prediction errors are minimised (Ranstam & Cook, 2018). A constraint was added to the model parameters that made the regression coefficients go towards zero.

To do this the `glmnet` package was used, using a gaussian distribution for the mean squared error criterion on categorical data (Schlechter et al., 2023; Tay et al., 2023). The parameters for the gaussian distribution were based on a 20-fold cross-validation (Tay et al., 2023). This also means that the CLPN has a higher chance to contain edges that are part of the true population network, but has the downside that some false positive edges arise because of the overestimated network (Funkhouser et al., 2021).

The output was transformed into coefficients that allowed edge weights greater than 1 to indicate a positive relationship, while edge weights below 1 suggested a negative relationship. Edge weights of exactly 1 indicated no relationship. These values were placed in a matrix where the x-axis were the next timestep and the y-axis the previous timestep. For each network a separate reduced network was constructed. For this network the edges between the same category (i.e., depression → depression or CVD → CVD) were removed, but the self edges were kept. This way different insights can be gained on the effects of depression on CVD.

To delve deeper into the examination the matrix was transformed into a network object using `bootnet` (Epskamp et al., 2018). To make this work an empty network was constructed and the given graph was overwritten by the weighted matrix. Edges that were below a given threshold ($threshold = 0.3$) were removed from the graph. The threshold was arbitrarily chosen based on the network, so that variables with little to no impact did not change the clearance of the final results. This included the self edges where the coefficient was below the threshold.

Centrality & Sensitivity

Additionally, to explore temporal effects, various centrality metrics were calculated to gain insight into the importance of specific symptoms within the network structure, and to identify which edges and nodes significantly differ from one another (Odenthal et al., 2023).

Two centrality metrics that were used on selected nodes, were the cross-lagged in-expected-influence and the out-expected-influence (Chavez-Baldini et al., 2022; Schlechter et al., 2023). Cross-lagged out-expected-influence (CLOEI) calculated the expected influence of a node at time t on its adjacent nodes at the next timestep (i.e., to what extent this symptom influences other symptoms). Where cross-lagged in-expected-influence (CLIEI) calculated how a node's neighbourhood at timestep t has influences on the node itself in the next timestep. In other words it shows to what extend a node is predicted by its neighbours (Schlechter et al., 2023; Zainal & Newman, 2023).

Both CLIEI and CLOEI were determined by summing the total directed edge weights starting from a selected node and its neighbourhood, to help quantify the importance of some symptoms over the other (Oenthal et al., 2023; Zainal & Newman, 2023). Besides the CLIEI and the CLOEI, the other centrality metrics used were betweenness and closeness in combination with the in and out-strength of each node. (Albert & Barabási, 2002; Rodrigues, 2019). Betweenness centrality measures how often a node acts as a bridge along the shortest paths between pairs of nodes in a network, while closeness centrality measures how quickly a node can reach all other nodes in the network.

Additionally, the edge weight accuracy was estimated using bootstrapping with replacement and computed 95% confidence intervals (CI) for stability assessment using the bootnet library (Epskamp et al., 2018). The edge weight accuracy was used to see which symptom connections are more important than other connections (Li. et al., 2024; Schlechter et al., 2023). Following each resampling, the cross-lagged panel analysis rerun the dynamics of relationships among variables across time. The results were aggregated across multiple iterations. To assess the stability of central driver nodes within the network despite sample reduction, the bootstrapping technique was used to generate subsets that drop a percentage of samples from the analysis (Schlechter et al., 2023).

Validation

To validate the model, experts were asked to study the networks, with the goal of looking at the differences between the time points. Their examination was assisted by a detailed list identifying robust connections within the networks, pinpointing key driver nodes that exert significant influence, and assessing the accuracy of edge weights using bootstrapping between nodes. The goal of this method was to comprehensively assess the evolution of network dynamics over time, revealing important shifts and confirming the model's ability to predict connections between given depression and CVD symptoms.

Result

Descriptives

Descriptive statistics of the population within the dataset are shown in Table 4.1. Table 4.2 displays corresponding statistics for CVD variables. Table 4.3 presents the descriptive statistics for depressive symptoms. As shown in Table 4.1, the vast majority of participants do not smoke. Moreover, a slightly higher percentage of men smoke compared to women, with a difference of 6.80% in 2007. The average BMI within the YFS population is below the obesity diagnose level ($BMI \geq 30\text{kg}/\text{m}^2$), where a healthy BMI sits between a score of 18.50 and 25 (Blüher, 2020; Gallagher et al., 2000).

An analysis of the Table 4.2 reveals various developments. The acetate level of the participants showed minor variations, maintaining a consistent average round 0.05. Where the maximum acetate level decreases with 0.43 points and increases again with around the same amount. The insulin levels fluctuate significantly over different time points. The average insulin level was 9.39 in 2007 and increased to 17.72 in 2011, because of the maximum level being 7117.42 mU/L, an increase of 6463.12 mU/L. Insulin levels as a whole have a large variation within the samples as depicted by the standard deviation being 14.54 and 17.72 in 2007 and 2011 respectfully. In 2012 the standard deviation decreased significantly with 191.66 points, because the maximum value decreased from 7117.42 mU/L to 89.00 mU/L.

Another variable with a high variation is the diastolic blood pressure, with a standard deviation being around 10 in all the years. In 2007, the average C-reactive Protein (CRP) level was 1.81 mg/L, with a maximum value of 98.34 mU/L. The maximum CRP values remained consistently higher than the average across all years, but not as much as the previously mentioned variables.

As shown in Table 4.3, many participants reported low levels of depressive symptoms across all time points. The low level of depressive symptoms were especially visible in 2011, where a significant majority, 94.94%, reported no suicidal thoughts or wishes. The highest percentage of participants reporting "very much" was 2.67%, which was related to changes in sleep patterns in both 2007 and 2011. In 2011 all the participants noted a change in appetite and sleep pattern, indicated by the 0% of people reporting "not at all". A decrease of 68.08% and 51.39% from 2007 to 2011. Most participants reported experiencing moderate changes related to these symptoms, with 99.56% and 98.14% falling into the "other" category. In 2007, about half of the participants noted having moderate changes in their sleeping pattern.

Table 4.1: Characteristics of the participants within the YFS, measured at the given time points

	Women (<i>N</i> =1832) Mean (or %) SD	Men (<i>N</i> =1764) Mean (or %) SD
Age in 2007	37.53 4.99	37.35 4.99
Measures from 2007		
Smoking (No)	85.15%	78.35%
BMI	25.44 4.57	26.55 3.83
Measures from 2011		
Smoking (No)	86.50%	81.99%
BMI	26.15 4.92	26.89 3.97
Measures from 2012		
Smoking (No)	79.05%	70.26%
BMI	24.58 4.24	25.62 3.71

Table 4.2: Levels of the CVD biochemical variables, measured at three different time points (*N* = 3596).

		2007				2011				2012			
		Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD
Diastolic blood pressure	(mm Hg)	42.00	124.67	75.95	10.38	42.00	114.00	74.99	9.52	40.00	118.00	70.87	9.96
Systolic blood pressure	(mm Hg)	77.33	199.33	120.82	13.10	83.33	178.67	118.99	12.69	80.67	180.00	116.83	12.06
Acetate	(mmol/L)	0.03	0.74	0.05	0.02	0.03	0.31	0.05	0.01	0.02	0.91	0.04	0.03
Apolipoprotein	(mmol/L)	0.75	3.64	1.59	0.24	0.92	2.64	1.58	0.22	0.57	2.68	1.49	0.24
Total cholesterol	(mmol/L)	2.00	8.70	5.04	0.83	2.40	11.20	5.17	0.85	2.50	11.10	5.16	0.89
LDL cholesterol	(mmol/L)	0.48	6.56	3.09	0.72	0.75	7.05	3.27	0.74	0.80	7.90	3.27	0.76
HDL cholesterol	(mmol/L)	0.52	2.98	1.32	0.33	0.48	3.50	1.33	0.31	0.31	2.82	1.29	0.29
Triglycerides	(mmol/L)	0.34	14.10	1.39	0.82	0.34	33.97	1.34	1.04	0.30	12.90	1.35	0.77
Glucose	(mmol/L)	3.14	23.20	5.34	0.85	3.14	22.15	5.36	0.78	3.50	20.30	5.06	0.77
C-reactive protein	(mg/L)	0.07	98.34	1.81	3.43	0.05	83.91	1.71	2.84	0.03	64.90	1.91	3.59
Insulin	(mU/L)	0.00	654.30	9.39	14.54	0.06	7117.42	17.72	197.09	1.00	89.00	7.82	5.43

Table 4.3: Prevalence of symptoms of depression over three time points ($N = 3596$)

	2007			2011			2012		
	Percentage 'not at all'	Percentage 'very much'	Other	Percentage 'not at all'	Percentage 'very much'	Other	Percentage 'not at all'	Percentage 'very much'	Other
Agitation	78.36%	0.03%	21.61%	78.78%	0.06%	21.16%	78.36%	0.06%	21.58%
Changes in appetite	68.08%	0.83%	31.09%	0.00%	0.44%	99.56%	70.33%	0.67%	29.00%
Changes in sleep pattern	51.39%	2.67%	45.94%	0.00%	1.86%	98.14%	53.17%	2.67%	44.16%
Concentration difficulty	81.84%	0.08%	18.08%	79.23%	0.22%	20.55%	83.26%	0.06%	16.69%
Crying	89.24%	0.95%	9.82%	90.24%	0.64%	9.12%	89.91%	1.08%	9.01%
Guilty feelings	67.44%	0.44%	32.12%	72.58%	0.22%	27.20%	72.94%	0.22%	26.84%
Indecisiveness	88.38%	0.03%	11.60%	89.68%	0.03%	10.29%	90.10%	0.03%	9.87%
Irritability	76.72%	0.22%	23.05%	74.08%	0.25%	25.67%	77.09%	0.14%	22.78%
Loss of energy	68.27%	0.11%	31.62%	60.82%	0.14%	39.04%	68.72%	0.17%	31.12%
Loss of interest	83.87%	0.17%	15.96%	80.98%	0.06%	18.97%	82.31%	0.06%	17.63%
Loss of interest in sex	74.58%	1.20%	24.22%	68.66%	1.06%	30.28%	72.58%	1.36%	26.06%
Loss of pleasure	78.34%	0.42%	21.25%	77.03%	0.19%	22.78%	77.98%	0.50%	21.52%
Past failure	86.21%	0.31%	13.49%	87.85%	0.14%	12.01%	87.90%	0.25%	11.85%
Pessimism	79.70%	0.44%	19.86%	82.70%	0.19%	17.10%	82.04%	0.53%	17.44%
Punishment feelings	88.88%	0.33%	10.79%	91.55%	0.11%	8.34%	89.93%	0.31%	9.76%
Sadness	84.18%	0.08%	15.74%	86.12%	0.08%	13.79%	86.68%	0.17%	12.15%
Self-criticalness	80.03%	0.22%	19.74%	84.18%	0.14%	15.68%	83.90%	0.17%	15.93%
Self-dislike	85.37%	0.14%	14.49%	85.60%	0.03%	14.38%	85.40%	0.06%	14.54%
Suicidal thought or wishes	93.19%	0.03%	6.79%	94.94%	0.08%	4.98%	94.30%	0.06%	5.65%
Tiredness or fatigue	76.86%	0.25%	22.89%	72.64%	0.11%	27.25%	77.00%	0.08%	22.91%
Worthlessness	86.60%	0.39%	13.01%	89.52%	0.25%	10.23%	88.01%	0.28%	11.71%

Note. Percentages represent the proportion of participants reporting different levels of each symptom, ranging from 0='not at all' to 3='very much'. Values 1 and 2 are grouped together in the 'other' column, indicating moderate to significant levels. (Palmer & Binks, 2008).

Cross-lagged Edges

Figure 4.1 shows the four CLPN models across selected cohorts, two of which are reduced networks. These models visualise cross-symptom coefficients through edges; no edges are visible when correlations are zero. The models reveal consistent and varying patterns of cross-lagged effects among symptoms. For example, the edge from pessimism to insulin shows a significantly positive coefficient in the 2007 to 2011 period, suggesting that insulin levels increase when participants report higher levels of pessimism about themselves. This edge completely disappears when entering the next timestep 2011 → 2012. Similarly, when the network is reduced, a strong connection observed in 2007 → 2011 disappears in the subsequent period from 2011 to 2012 as seen in Figure 4.1.

Another notable connection in the initial timestep was the edge from acetate to insulin. This edge showed a negative connection, indicating that higher acetate levels corresponded to lower insulin levels. Similar to the previous edge, this connection ceased to exist in the following timestep and was replaced with a strong positive connection between acetate → glucose. Acetate also has a strong edge with diastolic blood pressure in the same timestep. Almost no edges were found between both of the cholesterol metrics and the total amount of cholesterol, except in timestep 2007 → 2011 having only a small connection. In both timesteps, many edges were directed towards the systolic blood pressure and insulin nodes, suggesting that several other nodes influence these variables to some extent. While these individual edges may not be strong, their sheer number indicates significant influence from multiple factors. The same applies to the diastolic blood pressure, although it loses many connections when the network is reduced.

Some nodes within the networks were singletons, meaning their degree was zero (Albert & Barabási, 2002). Examples of these nodes include concentration difficulty and tiredness or fatigue in the 2007 to 2011 period, and irritability in the subsequent timestep. In the reduced networks, the same named nodes also were singletons. Additionally to an increase in the number of singletons due to the removal of edges that originally connected them to other nodes within the same group. There are also several self-edges observed, such as glucose, triglycerides, and systolic blood pressure in 2007 → 2011. Additionally, in the subsequent timestep, self-edges were observed for punishment feelings, diastolic blood pressure and cholesterol HDL. When examining the network, no cycles (i.e., paths that start and end at the same node) were detected.

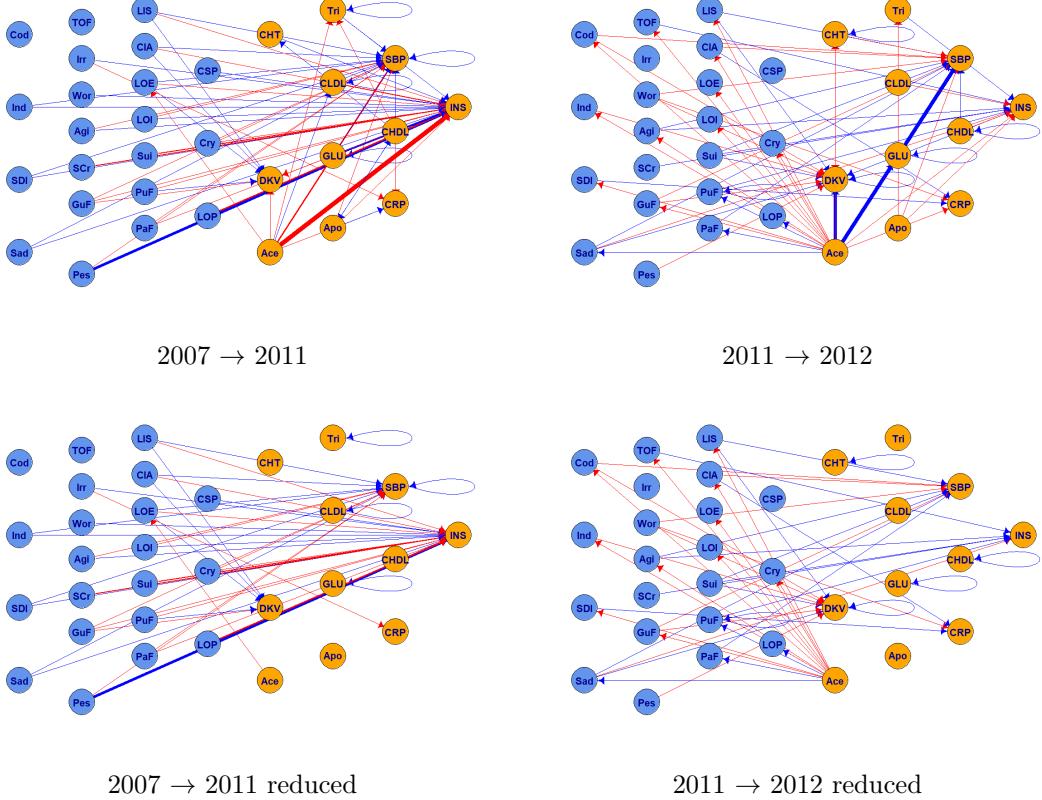


Figure 4.1: CLPN for all the timepoints.

Note. Full image can be found in Appendix III. Agi = agitation, CIA = changes in appetite, Cod = concentration difficulty, Cry = crying, GuF = guilty feelings, Irr = irritability, Ind = indecisiveness, LOE = loss of energy, LOI = loss of interest, LOP = loss of pleasure, LIS = loss of interest in sex, PaF = past failure, Pes = pessimism, PuF = punishment feelings, Sad = sadness, SCr = self criticalness, SDI = self dislike, Sui = suicidal thought or wishes, TOF = tiredness or fatigue, DKV = diastolic blood pressure, SBP = systolic blood pressure, Ace = acetate, Apo = apoprotein, CHT = cholesterol total, CLDL = cholesterol LDL, CHDL = cholesterol HDL, Tri = triglycerides, GLU = glucose, CRP = c-reactive protein, INS = insulide. The blue nodes represent the selected depression symptoms, and the orange nodes represent the cardiovascular symptoms. A red arrow indicates a negative relationship in the next time step, while a blue arrow indicates a positive one. All the edges were scaled by the highest weight within the entire network and multiplied by a factor of 0.2 to better visualise the stronger edges.

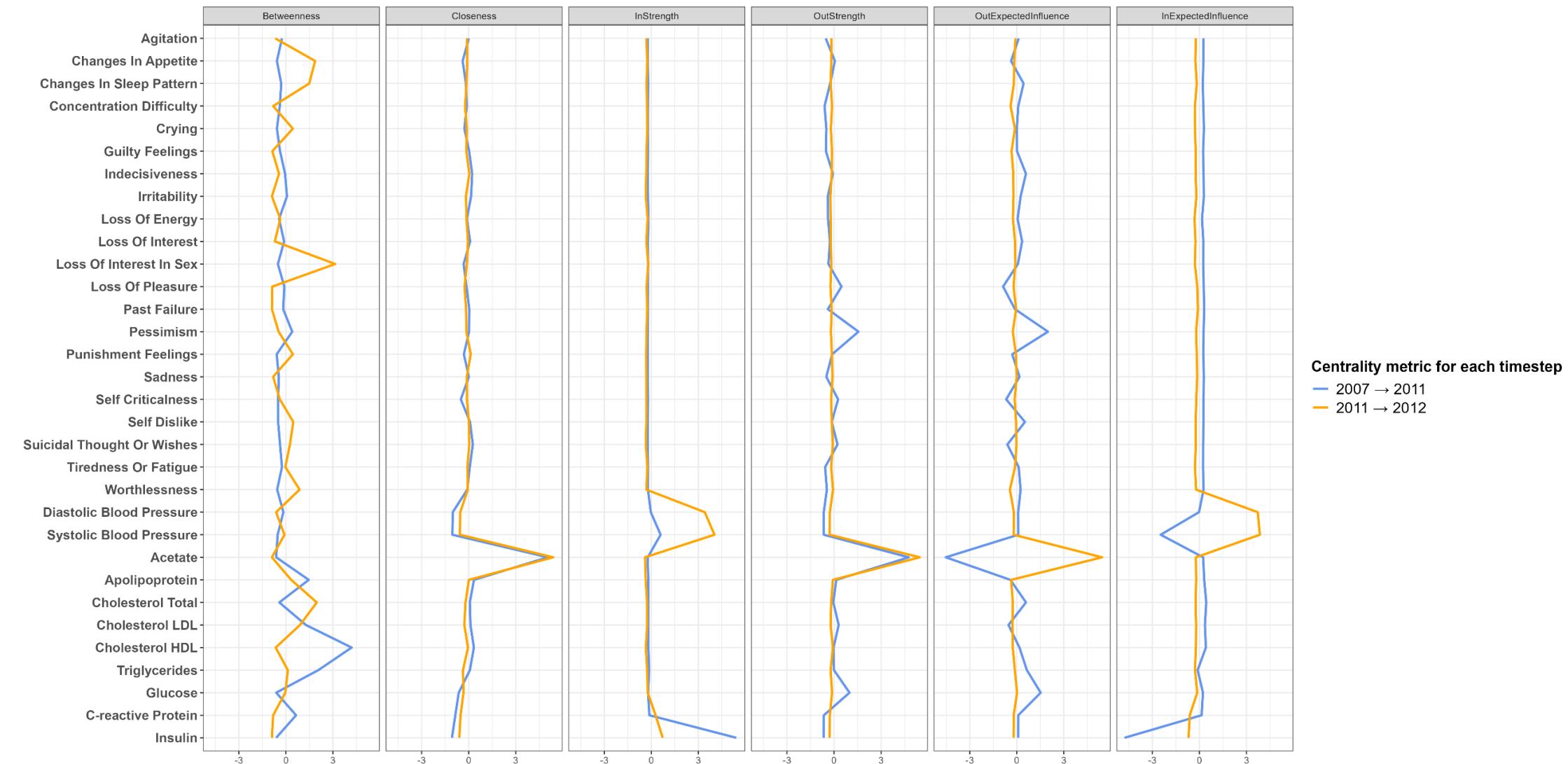


Figure 4.2: Different centrality metrics calculated for all the nodes for each timestep, using bootnet (Epskamp et al., 2018). Explanation of all the metrics are mentioned in the Method.

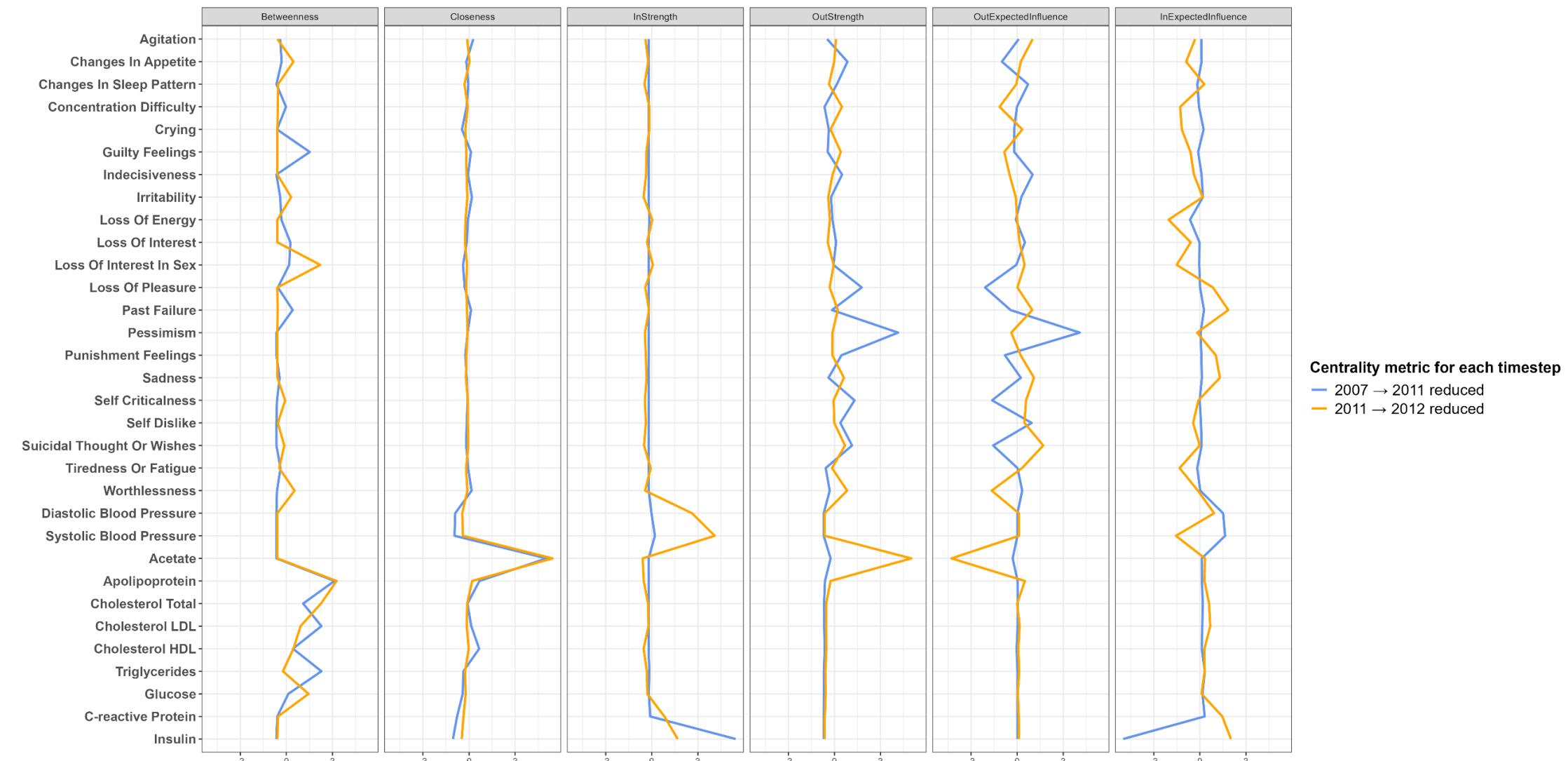


Figure 4.3: Different centrality metrics calculated for all the nodes for each timestep, using bootnet (Epskamp et al., 2018). Explanation of all the metrics are mentioned in the Method.

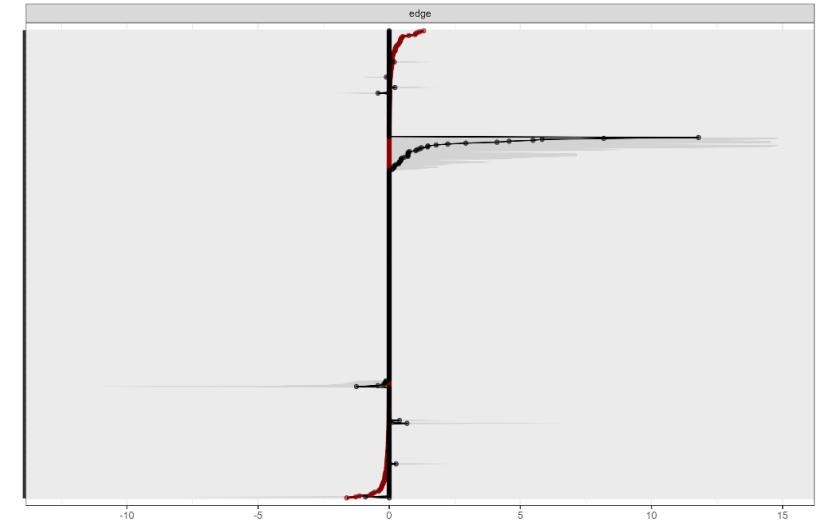
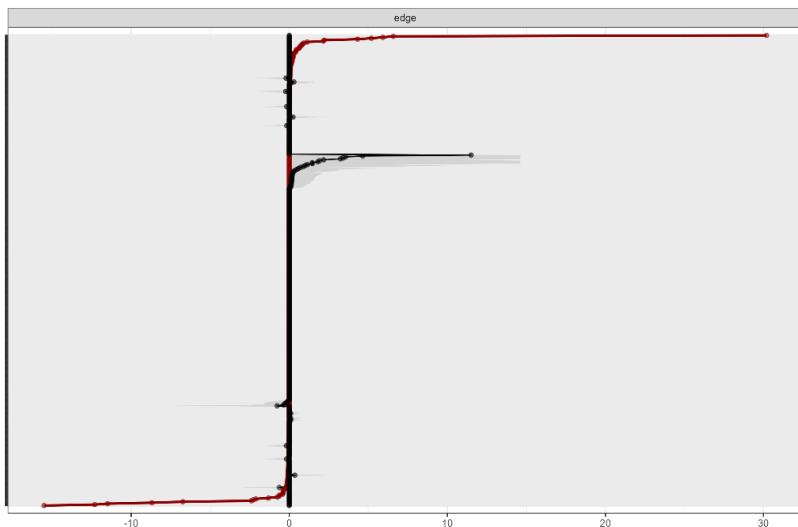
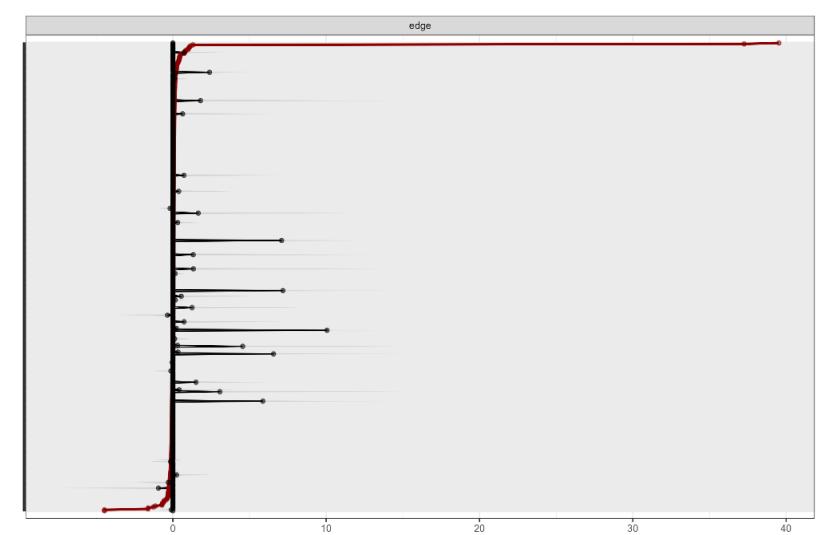
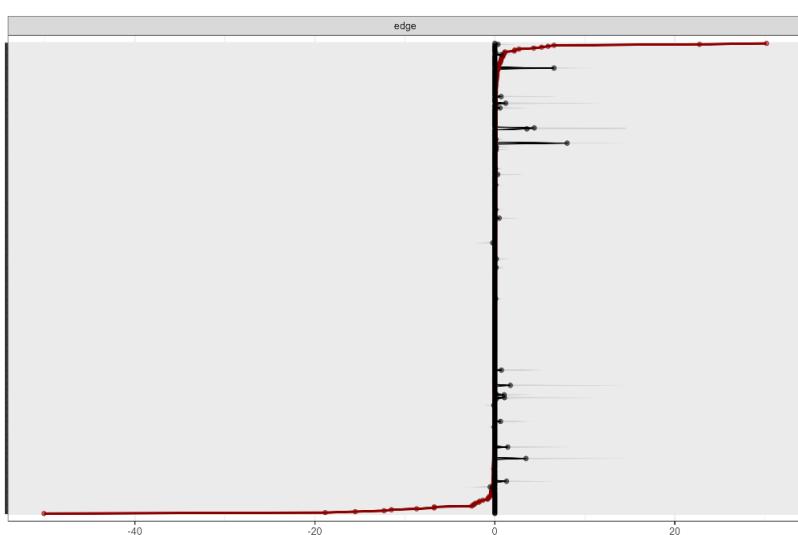


Figure 4.4: Stability of edge weight using a 95% CI (Epskamp et al., 2018). The solid red line indicates the edge weights in the given graph, with the CI in grey around the edges. The mean calculated by the bootstrapping is depicted in black.

Centrality

The plots in Figures 4.2 & 4.3 visualises all the different centrality measures for each node across the different timesteps and networks. What stands out is the high closeness centrality (i.e., how close a node is to other nodes) of acetate, which is around 4.50. Compared to the other values that lay between -0.50 and 0.50. This central position of acetate is also evident from its out-strength, which is also around 4.50 for all the different networks. Other variables with notable out-strength included pessimism in both the $2007 \rightarrow 2011$ networks and loss of pleasure in the full network. The betweenness of the nodes fluctuated significantly between networks. For example, cholesterol HDL had betweenness values around 4.70, 0.50, -1, and 0.50 across different networks or time points. Other nodes, such as loss of interest in sex and apoprotein, show similar fluctuations in their betweenness values across different networks or time points.

The out-expected influence of acetate varied across the networks. In the $2007 \rightarrow 2011$ and $2011 \rightarrow 2012$ reduced networks, the out-expected influence was negative for the node. However, in the $2011 \rightarrow 2012$ timestep, it changed to a large positive value. In the $2007 \rightarrow 2011$ reduced network, it remained around 0. This change is possibly related to the out-strength of the node. Similar to acetate, pessimism also exhibits a strong out-expected influence corresponding to its out-strength, but only in the first timestep. Suggesting that both these variables predict other variables in the given networks. Diastolic blood pressure is one of the variables that is predicted by other variables, as indicated by its high in-expected influence, especially in $2011 \rightarrow 2012$. Another variable exhibiting this behaviour is systolic blood pressure, which shows more fluctuating values, like the betweenness of cholesterol HDL. In the networks for both $2007 \rightarrow 2011$ and $2011 \rightarrow 2012$ reduced, systolic blood pressure had a negative in-expected influence. Whereby in the other two networks the influence was positive.

Stability of Edge Weights

For each network, the 95% CI for all the edge weights are shown in Figure 4.4. Most of the edge weights remain around the same level, with a few outliers related to the bootstrap mean scattered throughout the figure. The edge weight of the sampled population for $2007 \rightarrow 2011$ shows a large negative tail at the beginning of the figure, which is not seen in the other plots. This tail starts around an edge weight of -50. The other graph with such a tail is the reduced variant of $2007 \rightarrow 2011$, but there it starts at around -20. Due to the lack of a CI in the plot, most edge weights will be similar to those in the original sample. However, the values within the CI of the networks that were reduced, show a large spike in the top part of the figure, as seen in Figure 4.4.

Discussion

Within the networks, most of the selected depression parameters influenced the CVD parameters, consistent with findings from previous studies (de Hert et al., 2018; Hare et al., 2013; Rossom et al., 2022). Only a couple of depressive symptoms did not influence the CVD parameters. These symptoms were tiredness or fatigue and concentration difficulty, but only in 2007 → 2011. One would expect that feeling tired would have an effect on cardiovascular symptoms, as sleep abnormalities and fatigue are related to CVD and other possible diseases (Malhotra & Loscalzo, 2009; Wolk et al., 2005). Within the second timestep, the connection from fatigue is present but relatively weak.

As seen in Figure 4.1, acetate is an important node within all the normal networks. In the 2007 → 2011, acetate has a strong negative connection with the insulin levels of the participants, while in the 2011 → 2012, it has a strong positive connection with glucose levels. Based on this it is suggested that acetate is a strong indicator for other cardiovascular symptoms. Based on the 2011 → 2012, a higher level of acetate appears to lower depression symptoms, as suggested by the multiple outgoing negative edges. This connection was not initially expected to appear in the network, but it has been confirmed by previous studies (Poll et al., 2021; Skonieczna-Żydecka et al., 2018). Within the mentioned papers it was found that participants were depression was diagnosed, had a overall lower level of acetate within their body.

One would expect to see a larger edge between total cholesterol and the other types of cholesterol. Because total cholesterol is the sum of the other types, so increasing any one of them would increase the total cholesterol level. In the first timestep, total cholesterol is influenced by HDL cholesterol. The lack of connections is especially notable in the 2011 → 2012, where the only connection with total cholesterol is with acetate. In the same timestep, total cholesterol has an edge with itself, which is logical because if you increase the total cholesterol, the cholesterol will naturally increase. A possibility is that the edge weights were too low for the threshold to detect them and therefore are not visualised. In the model, a threshold was selected to enhance the visualisation of the networks. This threshold was made arbitrarily to increase visual clarity, resulting in the removal of edges with lower weights and consequently some information.

The insulin level, diastolic, and systolic blood pressure are mostly correlated to be impacted by depressive symptoms, as best seen in the reduced networks and Figures 4.2 & 4.3. Research by Nahshoni et al. (2004) and Taylor (2010) suggests that individuals with depression often experience alterations in heart rates. Where heart rates can have different impacts on CVD Beevers et al., 2001; Bundy et al., 2017. Several depressive symptoms influencing blood pressures include, but are not limited to, suicidal thoughts, loss of pleasure, sexual dysfunction, fatigue, and self-criticalness, indicating possible correlations with having a negative self image and cardiovascular symptoms later. The in-expected influences on these cardiovascular symptoms are also high, suggesting that they are influenced by a wide range of other variables as seen in Figures 4.2 & 4.3.

Overall, the output of the networks aligns with previous research findings. It also shows how assuming that depression consists of the sum of its parts can visualise crucial symptom dynamics. It is important to emphasise the effect of depressive symptoms on the heart rate of the patient as well as their insulin level, suggesting a strong correlation. This can be used to highlight the importance of mental health within a population, to counteract the rise of CVD cases. The importance of acetate on other cardiovascular symptoms and depressive variables needs to be mentioned, as the strong edge weight suggests possible consequences if left out of control. One would expect to have a larger confidence interval area when plotting the stability of edge weight in Figure 4.4. This is because as rows within the dataset will be dropped the mean edge weights will change over time. An explanation for this can be because of how the network is constructed as mentioned in the Limitations section later. Currently it suggests that the given edge weight is overall accurate. Another notable thing about the plots is that most of the edges lay close to zero suggesting a low significance of the edge weights.

Limitations

The current model is built on three years of data, enough for the current research, but makes it limited in scope. More cohorts within the dataset could better showcase the relational patterns overtime. Besides the years the data is sampled on a limited number of people ($N = 3596$), where a majority reported to not have any depressive complaints as seen in Table 4.3. The sampled participants are also collected from a majority ethnically white Finnish population, that makes that the result can be limited generalised for a broader population (Åkerblom et al., 1985; Peltola & Kivijärvi, 2023). Additionally, a couple of challenges were present when using a longitudinal study. Some individuals did not complete the follow-up questions, resulting in fewer participants over time (Schaie, 2005). To address this issue, imputation techniques were applied to handle the missing data.

When developing the model, a few limitations arose. To start with, little documentation was available about using the `glmnet` package in combination with creating a CLPN. The research this study is based on outlined the necessary steps, but considerable interpretation was needed to fully flesh out the details (Schlechter et al., 2023). This resulted in more difficulty with creating the network initially, consuming most of the research time. The validation steps of the network, based on the stability of the edge weights, were also challenging. One would have expected a larger CI to be visible in Figure 4.4. A plot related to the stability of centrality measures was also removed because it showed zero correlation with the main dataset, which is unexpected after dropping only 5% of the samples.

Another issue was the combination of the bootnet and glmnet packages. Since the bootnet function calculates a network differently, the output graph had to be overwritten with the glmnet output. Within this step possible problems could arrive, like the network not using the right graph. A way to circumvent this issue is to use a hybrid approach. This not only increases the validity of the study by allowing the comparison of multiple models, but it also benefits from more extensive documentation based on the research of Wysocki et al. (2022). Within their research they mostly use the lavaan package (Rosseel, 2012).

Due to time constraints related to the dataset, no validation step with experts was conducted. As a result, the robustness and accuracy of the data interpretation and findings may be impacted. Future iterations of this study should prioritise incorporating expert validation to ensure the validity of the conclusions drawn from the data.

Strength

Due to the lack of available documentation on the use of the glmnet package in a CLPN setting, one strength of this study was providing such documentation for creating new networks across the different timesteps. The code for this can be found in Appendix II. Another strength of this study was using a CLPN to estimate the temporal dynamics and interplay between depressive symptoms and CVD indicators. Hereby the network perspective helps to understand the clustering process of symptoms, as discussed by Cramer et al. (2010), Fried and Nesse (2015), and Schmittmann et al. (2013).

Future work

Future work can improve on this research by taking the points mentioned within the limitations such as using a hybrid approach to construct the model to better validate the data, as well as the possibility to include more years to further analyse the patterns. For future work the suggestion will be to include five years of possible times steps, giving the possibility to construct four networks. One can also use another network model Based on this study it is not clear how and why independent depressive and cardiovascular symptoms impacted one another. Studies based on this research can focus on this how and why, as well as finding more relations with possible other symptoms. The same study can also be conducted on different populations, as mentioned in Appendix I.

Summary

This study focused on examining the longitudinal relationship between individual depression symptoms and CVD indicators. Data from the YFS were utilised to investigate how specific depressive symptoms influenced CVD risk over time, taking into account factors such as smoking habits, BMI, and demographics.

To begin, the significant global burden of mental illness, particularly depression, and its association with CVD and reduced lifespan were highlighted. The goal was to explore the extent of relationships between variables and the impact of individual depressive symptoms (i.e., having difficulty with waking up or suicidal thought) on cardiovascular health (i.e., blood pressure, cholesterol and insulin levels) using a network perspective. Assumption that depression symptoms were a sum of their individual parts as mentioned by Fried et al. (2014) and Fried and Nesse (2015). To study this relationship a CLPN, to assess the connections between symptoms over time and to capture the underlying processes that contribute to depression and CVD.

For the study populations 3596 Finnish participants in combination with their demographics, biochemical, and depressive variables. The analysis utilised LASSO regression to create network models, assessing the influence of depressive symptoms on CVD indicators over time using the glmnet package. Centrality metrics were applied to evaluate the importance of specific symptoms within the network, and bootstrapping was used to validate the stability of edge weights. The results revealed varying patterns of cross-lagged effects among symptoms, with some connections changing or disappearing over time as seen in Figure 4.1. Certain nodes, such as acetate and pessimism, showed significant influence on the network. Shown in Figure 4.4 the stability of edge weights was generally consistent, although there were some exceptions. The levels of insulin, diastolic and systolic blood pressures were the CVD symptoms to receive the most influence from the depressive symptoms. Suggesting that people with mental illnesses experience different heart rates than people without.

While this study confirms findings of previous studies, it also reveals that the individual parts of depression can be used for crucial symptom dynamics. Several limitations arose during the study, including a small and ethnically homogeneous sample size, challenges in model validation, and the absence of expert validation due to time constraints. Despite these limitations, this study provides valuable documentation for creating CLPNs and demonstrates the utility of a network perspective in understanding symptom clustering. Future work is encouraged to expand the scope of the study by including more years of data and a broader population. As well as looking into why the depressive symptoms have an effect on the cardiovascular variables.

Conclusion

Based on the results, one can conclude that there is indeed a relationship between individual depressive symptoms and CVD indicators over time. To answer the question "*are there relationships between the individual depressive symptoms and the cardiovascular disease indicators overtime, based on a cross lagged panel network? Are there reciprocal relationships?*". This is mostly depended on the selected variable itself.

Where most of the variables showed a stable connection within all the timesteps, a couple of them stand out. This includes acetate, which has a strong impact on the other CVD symptoms as well as an effect on the depressive variables. Another group that stands out are the insulin level and the diastolic and systolic blood pressure. These cardiovascular symptoms are the most affected by the mental well being of a person. To answer the second research question "*which depressive symptom has the most impact on cardiovascular disease over time?*", suicidal thought or wishes has the strongest out-strength and out-expected influenced in most of the networks. These results underline the importance of mental well-being for the general population, as for a large amount of people depression can lead to cardiovascular disease later in life.

Bibliography

- Aaron T. Beck, R. B., Robert A. Steer, & Ranieri, W. F. (1996). Comparison of beck depression inventories-ia and-ii in psychiatric outpatients [PMID: 8991972]. *Journal of Personality Assessment*, 67(3), 588–597. https://doi.org/10.1207/s15327752jpa6703_13
- Aatola, H., Hutri-Kähönen, N., Juonala, M., Laitinen, T. T., Pahkala, K., Mikkilä, V., Telama, R., Koivisto, T., Lehtimäki, T., Viikari, J. S. A., Raitakari, O. T., & Kähönen, M. (2014). Prospective relationship of change in ideal cardiovascular health status and arterial stiffness: The cardiovascular risk in young finns study. *Journal of the American Heart Association*, 3(2), e000532. <https://doi.org/10.1161/JAHA.113.000532>
- Adeva-Andany, M. M., Martínez-Rodríguez, J., González-Lucán, M., Fernández-Fernández, C., & Castro-Quintela, E. (2019). Insulin resistance is a cardiovascular risk factor in humans. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 13(2), 1449–1455. <https://doi.org/https://doi.org/10.1016/j.dsx.2019.02.023>
- Åkerblom, H. K., Viikari, J., Uhari, M., Räsänen, L., Byckling, T., Louhivuori, K., Pesonen, E., Suoninen, P., Pietikäinen, M., Lähde, P.-L., Dahl, M., Aromaa, A., Sarna, S., & Pyörälä, K. (1985). Atherosclerosis precursors in finnish children and adolescents. i. general description of the cross-sectional study of 1980, and an account of the children's and families' state of health. *Acta Paediatrica*, 74(s318), 49–63. <https://doi.org/https://doi.org/10.1111/j.1651-2227.1985.tb10082.x>
- Albert, R., & Barabási, A.-L. (2002). Statistical mechanics of complex networks. *Rev. Mod. Phys.*, 74, 47–97. <https://doi.org/10.1103/RevModPhys.74.47>
- Beevers, G., Lip, G. Y. H., & O'Brien, E. (2001). Blood pressure measurement. *BMJ*, 322(7292), 981–985. <https://doi.org/10.1136/bmj.322.7292.981>
- Belle, G. V., Fisher, L. D., Heagerty, P. J., & Lumley, T. (2004). *Biostatistics: A methodology for the health sciences. longitudinal data analysis*. New York, NY: John Wiley; Sons. <https://doi.org/10.1198/000313005X55710>
- Blüher, M. (2020). Metabolically Healthy Obesity. *Endocrine Reviews*, 41(3), bnaa004. <https://doi.org/10.1210/endrev/bnaa004>
- Bundy, J. D., Li, C., Stuchlik, P., Bu, X., Kelly, T. N., Mills, K. T., He, H., Chen, J., Whelton, P. K., & He, J. (2017). Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. *JAMA Cardiology*, 2(7), 775–781. <https://doi.org/10.1001/jamacardio.2017.1421>
- Celler, B. G., Butlin, M., Argha, A., Tan, I., Yong, A., & Avolio, A. (2021). Are korotkoff sounds reliable markers for accurate estimation of systolic and diastolic pressure using brachial cuff sphygmomanometry? *IEEE Transactions on Biomedical Engineering*, 68(12), 3593–3601. <https://doi.org/10.1109/TBME.2021.3079578>
- Chavez-Baldini, U., Verweij, K., de Beurs, D., Bockting, C., Lok, A., Sutterland, A. L., van Rooijen, G., van Wingen, G., Denys, D., Vulink, N., & et al. (2022). The interplay between psychopathological symptoms: Transdiagnostic cross-lagged panel network model. *BJPsych Open*, 8(4), e116. <https://doi.org/10.1192/bjo.2022.516>

- Cramer, A. O. J., Waldorp, L. J., van der Maas, H. L. J., & Borsboom, D. (2010). Comorbidity: A network perspective. *Behavioral and Brain Sciences*, 33(2–3), 137–150. <https://doi.org/10.1017/S0140525X09991567>
- de Beurs, E., Van Dyck, R., Marquenie, L. A., Lange, A., Blonk, R. W., et al. (2001). De dass: Een vragenlijst voor het meten van depressie, angst en stress. *Gedragstherapie*, 34(1), 35–54.
- de Hert, M., Detraux, J., & Vancampfort, D. (2018). The intriguing relationship between coronary heart disease and mental disorders [PMID: 29946209]. *Dialogues in Clinical Neuroscience*, 20(1), 31–40. <https://doi.org/10.31887/DCNS.2018.20.1/mdehert>
- Dhar, A. K., & Barton, D. A. (2016). Depression and the link with cardiovascular disease. *Frontiers in Psychiatry*, 7. <https://doi.org/10.3389/fpsyg.2016.00033>
- Diez, D., Wheelock, Å. M., Goto, S., Haeggström, J. Z., Paulsson-Berne, G., Hansson, G. K., Hedin, U., Gabrielsen, A., & Wheelock, C. E. (2010). The use of network analyses for elucidating mechanisms in cardiovascular disease. *Molecular BioSystems*, 6(2), 289–304.
- Dismuke, C., & Lindrooth, R. (2006). *Ordinary least squares* (Vol. 93). American Society of Health-System Pharmacists Bethesda, MD, USA.
- Eichner, J. E., Dunn, S. T., Perveen, G., Thompson, D. M., Stewart, K. E., & Stroehla, B. C. (2002). Apolipoprotein E Polymorphism and Cardiovascular Disease: A HuGE Review. *American Journal of Epidemiology*, 155(6), 487–495. <https://doi.org/10.1093/aje/155.6.487>
- Elovainio, M., Keltikangas-Järvinen, L., Pulkki-Råback, L., Kivimäki, M., Puttonen, S., Viikari, L., Räsänen, L., Mansikkaniemi, K., Viikari, J., & Raitakari, O. T. (2006). Depressive symptoms and c-reactive protein: The cardiovascular risk in young finns study. *Psychological Medicine*, 36(6), 797–805. <https://doi.org/10.1017/S0033291706007574>
- Elovainio, M., Pulkki-Råback, L., Hakulinen, C., Ferrie, J. E., Jokela, M., Hintsanen, M., Raitakari, O. T., & Keltikangas-Järvinen, L. (2015). Childhood and adolescence risk factors and development of depressive symptoms: The 32-year prospective young finns follow-up study. *Journal of Epidemiology & Community Health*, 69(11), 1109–1117. <https://doi.org/10.1136/jech-2014-205352>
- Elovainio, M., Pulkki-Råback, L., Kivimäki, M., Jokela, M., Viikari, J., Raitakari, O. T., Telama, R., & Keltikangas-Järvinen, L. (2010). Lipid trajectories as predictors of depressive symptoms: The young finns study. *Health Psychology*, 29(3), 237. <https://doi.org/10.1037/a0018875>
- Epskamp, S., Borsboom, D., & Fried, E. I. (2018). Estimating psychological networks and their accuracy: A tutorial paper. *Behavior Research Methods*, 50, 195–212.
- Farrington, D. P. (1991). Longitudinal research strategies: Advantages, problems, and prospects. *Journal of the American Academy of Child Adolescent Psychiatry*, 30(3), 369–374. <https://doi.org/10.1097/00004583-199105000-00003>

- Fried, E. I., Nesse, R. M., Zivin, K., Guille, C., & Sen, S. (2014). Depression is more than the sum score of its parts: individual DSM symptoms have different risk factors. *Psychological Medicine*, 44(10), 2067–2076. <https://doi.org/10.1017/S0033291713002900>
- Fried, E. I., & Nesse, R. M. (2015). Depression sum-scores don't add up: Why analyzing specific depression symptoms is essential. *BMC medicine*, 13, 1–11.
- Funkhouser, C. J., Chacko, A. A., Correa, K. A., Kaiser, A. J. E., & Shankman, S. A. (2021). Unique longitudinal relationships between symptoms of psychopathology in youth: A cross-lagged panel network analysis in the abcd study. *Journal of Child Psychology and Psychiatry*, 62(2), 184–194. <https://doi.org/https://doi.org/10.1111/jcpp.13256>
- Gallagher, D., Heymsfield, S. B., Heo, M., Jebb, S. A., Murgatroyd, P. R., & Sakamoto, Y. (2000). Healthy percentage body fat ranges: An approach for developing guidelines based on body mass index123. *The American Journal of Clinical Nutrition*, 72(3), 694–701. <https://doi.org/https://doi.org/10.1093/ajcn/72.3.694>
- Gaziano, T., Reddy, K. S., Paccaud, F., Horton, S., & Chaturvedi, V. (2006). Cardiovascular disease. *Disease Control Priorities in Developing Countries*. 2nd edition.
- Goodell, S., Druss, B. G., Walker, E. R., & Mat, M. (2011). Mental disorders and medical comorbidity. *Robert Wood Johnson Foundation*, 2.
- Hakulinen, C., Elovainio, M., Pulkki-Råback, L., Böckerman, P., Viinikainen, J., Pehkonen, J., Raitakari, O. T., Keltikangas-Järvinen, L., & Hintsanen, M. (2016). Depressive symptoms and long-term income: The young finns study. *Journal of Affective Disorders*, 204, 120–123. <https://doi.org/https://doi.org/10.1016/j.jad.2016.06.028>
- Hare, D. L., Toukhsati, S. R., Johansson, P., & Jaarsma, T. (2013). Depression and cardiovascular disease: a clinical review. *European Heart Journal*, 35(21), 1365–1372. <https://doi.org/10.1093/eurheartj/eht462>
- Hwang, J., Toma, C. L., Chen, J., Shah, D. V., Gustafson, D., & Mares, M.-L. (2021). Effects of web-based social connectedness on older adults' depressive symptoms: A two-wave cross-lagged panel study. *J Med Internet Res*, 23(1), e21275. <https://doi.org/10.2196/21275>
- Juonala, M., Viikari, J. S., & Raitakari, O. T. (2013). Main findings from the prospective cardiovascular risk in young finns study. *Current opinion in lipidology*, 24(1), 57–64. <https://doi.org/10.1097/MOL.0b013e32835a7ed4>
- Katainen, S., Räikkönen, K., & Keltikangas-Järvinen, L. (1999). Adolescent temperament, perceived social support, and depressive tendencies as predictors of depressive tendencies in young adulthood. *European Journal of Personality*, 13(3), 183–207. [https://doi.org/https://doi.org/10.1002/\(SICI\)1099-0984\(199905/06\)13:3<183::AID-PER327>3.0.CO;2-Z](https://doi.org/https://doi.org/10.1002/(SICI)1099-0984(199905/06)13:3<183::AID-PER327>3.0.CO;2-Z)
- Kelly, T. N., Bazzano, L. A., Fonseca, V. A., Thethi, T. K., Reynolds, K., & He, J. (2009). Systematic review: Glucose control and cardiovascular disease in

- type 2 diabetes [PMID: 19620144]. *Annals of Internal Medicine*, 151(6), 394–403. <https://doi.org/10.7326/0003-4819-151-6-200909150-00137>
- Kenny, D. (1975). Cross-lagged panel correlation: A test for spuriousness. *Psychological Bulletin*, 82, 887–903. <https://doi.org/10.1037/0033-2909.82.6.887>
- Koskinen, J., Kähönen, M., Viikari, J. S., Taittonen, L., Laitinen, T., Rönnemaa, T., Lehtimäki, T., Hutri-Kähönen, N., Pietikäinen, M., Jokinen, E., Helenius, H., Mattsson, N., Raitakari, O. T., & Juonala, M. (2009). Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults. *Circulation*, 120(3), 229–236. <https://doi.org/10.1161/CIRCULATIONAHA.108.845065>
- Koskinen, J. S., Kytö, V., Juonala, M., Viikari, J. S. A., Nevalainen, J., Kähönen, M., Lehtimäki, T., Hutri-Kähönen, N., Laitinen, T. P., Tossavainen, P., Jokinen, E., Magnussen, C. G., & Raitakari, O. T. (2023). Childhood dyslipidemia and carotid atherosclerotic plaque in adulthood: The cardiovascular risk in young finns study. *Journal of the American Heart Association*, 12(7), e027586. <https://doi.org/10.1161/JAHA.122.027586>
- Kuiper, R. M., & Ryan, O. (2018). Drawing conclusions from cross-lagged relationships: Re-considering the role of the time-interval. *Structural Equation Modeling: A Multidisciplinary Journal*, 25(5), 809–823. <https://doi.org/10.1080/10705511.2018.1431046>
- Li., K., Ren., X., Ren., L., Tan., X., Zhao., M., Liu., C., Luo., X., Feng., Z., & Dai, Q. (2024). The ripple effect: Unveiling the bidirectional relationship between negative life events and depressive symptoms in medical cadets [PMID: 37664139]. *Psychology Research and Behavior Management*, 16, 3399–3412. <https://doi.org/10.2147/PRBM.S419991>
- Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., & Lyu, J. (2020). Changes in the global burden of depression from 1990 to 2017: Findings from the global burden of disease study. *Journal of Psychiatric Research*, 126, 134–140. <https://doi.org/https://doi.org/10.1016/j.jpsychires.2019.08.002>
- Lusis, A. J., & Weiss, J. N. (2010). Cardiovascular networks. *Circulation*, 121(1), 157–170. <https://doi.org/10.1161/CIRCULATIONAHA.108.847699>
- MacLellan, W. R., Wang, Y., & Lusis, A. J. (2012). Systems-based approaches to cardiovascular disease. *Nature Reviews Cardiology*, 9(3), 172–184.
- Malhotra, A., & Loscalzo, J. (2009). Sleep and cardiovascular disease: An overview. *Progress in cardiovascular diseases*, 51(4), 279. <https://doi.org/10.1016/j.pcad.2008.10.004>
- Manderscheid, R. W., Ryff, C. D., Freeman, E. J., McKnight-Eily, L. R., Dhingra, S., & Strine, T. W. (2010). Evolving definitions of mental illness and wellness. *Preventing chronic disease*, 7(1).
- Mattiuzzi, C., Sanchis-Gomar, F., & Lippi, G. (2020). Worldwide burden of ldl cholesterol: Implications in cardiovascular disease. *Nutrition, Metabolism and Cardiovascular Diseases*, 30(2), 241–244. <https://doi.org/https://doi.org/10.1016/j.numecd.2019.09.008>

- Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The Relationship of Depression to Cardiovascular Disease: Epidemiology, Biology, and Treatment. *Archives of General Psychiatry*, 55(7), 580–592. <https://doi.org/10.1001/archpsyc.55.7.580>
- Nahshoni, E., Aravot, D., Aizenberg, D., Sigler, M., Zalsman, G., Strasberg, B., Imbar, S., Adler, E., & Weizman, A. (2004). Heart rate variability in patients with major depression. *Psychosomatics*, 45(2), 129–134. <https://doi.org/https://doi.org/10.1176/appi.psy.45.2.129>
- Nielsen, R. E., Banner, J., & Jensen, S. E. (2021). Cardiovascular disease in patients with severe mental illness. *Nature Reviews Cardiology*, 18(2), 136–145. <https://doi.org/10.1038/s41569-020-00463-7>
- Nordestgaard, B. G., & Varbo, A. (2014). Triglycerides and cardiovascular disease. *The Lancet*, 384(9943), 626–635. [https://doi.org/10.1016/S0140-6736\(14\)61177-6](https://doi.org/10.1016/S0140-6736(14)61177-6)
- Odenthal, M., Schlechter, P., Benke, C., & Pané-Farré, C. A. (2023). Temporal dynamics in mental health symptoms and loneliness during the covid-19 pandemic in a longitudinal probability sample: A network analysis. *Translational Psychiatry*, 13(1), 162. <https://doi.org/10.1038/s41398-023-02444-z>
- Palmer, E. J., & Binks, C. (2008). Psychometric properties of the beck depression inventory-ii with incarcerated male offenders aged 18–21 years. *Criminal Behaviour and Mental Health*, 18(4), 232–242. <https://doi.org/10.1002/cbm.701>
- Peltola, M., & Kivijärvi, A. (2023). Ethnicity and race in youth (finland). In *Bloomsbury education and childhood studies*. <https://doi.org/10.5040/9781350934412.021>
- Poll, B. G., Xu, J., Jun, S., Sanchez, J., Zaidman, N. A., He, X., Lester, L., Berkowitz, D. E., Paolocci, N., Gao, W. D., & Pluznick, J. L. (2021). Acetate, a short-chain fatty acid, acutely lowers heart rate and cardiac contractility along with blood pressure. *Journal of Pharmacology and Experimental Therapeutics*, 377(1), 39–50. <https://doi.org/10.1124/jpet.120.000187>
- Raitakari, O. T., Juonala, M., Rönnemaa, T., Keltikangas-Järvinen, L., Räsänen, L., Pietikäinen, M., Hutri-Kähönen, N., Taittonen, L., Jokinen, E., Marniemi, J., Jula, A., Telama, R., Kähönen, M., Lehtimäki, T., Åkerblom, H. K., & Viikari, J. S. (2008). Cohort Profile: The Cardiovascular Risk in Young Finns Study. *International Journal of Epidemiology*, 37(6), 1220–1226. <https://doi.org/10.1093/ije/dym225>
- Ranstam, J., & Cook, J. A. (2018). LASSO regression. *British Journal of Surgery*, 105(10), 1348–1348. <https://doi.org/10.1002/bjs.10895>
- Ren, P., Liu, B., Xiong, X., Chen, J., & Luo, F. (2023). The longitudinal relationship between bullying victimization and depressive symptoms for middle school students: A cross-lagged panel network analysis. *Journal of Affective Disorders*, 341, 42–51. <https://doi.org/https://doi.org/10.1016/j.jad.2023.08.048>

- Rodrigues, F. A. (2019). Network centrality: An introduction. In E. E. N. Macau (Ed.), *A mathematical modeling approach from nonlinear dynamics to complex systems* (pp. 177–196). Springer International Publishing. https://doi.org/10.1007/978-3-319-78512-7_10
- Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software*, 48(2), 1–36. <https://doi.org/10.18637/jss.v048.i02>
- Rossom, R. C., Hooker, S. A., O'Connor, P. J., Crain, A. L., & Sperl-Hillen, J. M. (2022). Cardiovascular risk for patients with and without schizophrenia, schizoaffective disorder, or bipolar disorder. *Journal of the American Heart Association*, 11(6), e021444. <https://doi.org/10.1161/JAHA.121.021444>
- Schaare, H. L., Blöchl, M., Kumral, D., Uhlig, M., Lemcke, L., Valk, S. L., & Villringer, A. (2023). Associations between mental health, blood pressure and the development of hypertension. *Nature communications*, 14(1), 1953.
- Schaie, W., K. (2005). What can we learn from longitudinal studies of adult development?. *research in human development*. (2(3)), 133–158. https://doi.org/10.1207/s15427617rhd0203_4
- Schlechter, P., Ford, T., & Neufeld, S. (2023). The development of depressive symptoms in older adults from a network perspective in the English Longitudinal Study of Ageing. *Translational psychiatry*, 13(1). <https://doi.org/10.1038/s41398-023-02659-0>
- Schlechter, P., Hellmann, J. H., McNally, R. J., & Morina, N. (2022). The longitudinal course of posttraumatic stress disorder symptoms in war survivors: Insights from cross-lagged panel network analyses. *Journal of Traumatic Stress*, 35(3), 879–890. <https://doi.org/https://doi.org/10.1002/jts.22795>
- Schmittmann, V. D., Cramer, A. O., Waldorp, L. J., Epskamp, S., Kievit, R. A., & Borsboom, D. (2013). Deconstructing the construct: A network perspective on psychological phenomena [On defining and interpreting constructs: Ontological and epistemological constraints]. *New Ideas in Psychology*, 31(1), 43–53. <https://doi.org/https://doi.org/10.1016/j.newideapsych.2011.02.007>
- Scholtens, S., Smidt, N., Swertz, M. A., Bakker, S. J., Dotinga, A., Vonk, J. M., van Dijk, F., van Zon, S. K., Wijmenga, C., Wolffenbuttel, B. H., & Stolk, R. P. (2014). Cohort Profile: LifeLines, a three-generation cohort study and biobank. *International Journal of Epidemiology*, 44(4), 1172–1180. <https://doi.org/10.1093/ije/dyu229>
- Seabold, S., & Perktold, J. (2010). Statsmodels: Econometric and statistical modeling with python. *9th Python in Science Conference*.
- Sijtsma, A., Rienks, J., van der Harst, P., Navis, G., Rosmalen, J. G. M., & Dotinga, A. (2021). Cohort Profile Update: Lifelines, a three-generation cohort study and biobank. *International Journal of Epidemiology*, 51(5), e295–e302. <https://doi.org/10.1093/ije/dyab257>
- Skonieczna-Żydecka, K., Grochans, E., Maciejewska, D., Szkup, M., Schneider-Matyka, D., Jurczak, A., Łoniewski, I., Kaczmarczyk, M., Marlicz, W., Czerwińska-Rogowska, M., Pełka-Wysiecka, J., Dec, K., & Stachowska, E.

- (2018). Faecal short chain fatty acids profile is changed in polish depressive women. *Nutrients*, 10(12). <https://doi.org/10.3390/nu10121939>
- Smith, K., & De Torres, I. (2014). Mental Health: A world of depression. *Nature*, 515(181), 10–1038.
- Sobin, C., & Sackeim, H. A. (1997). Psychomotor symptoms of depression. *American Journal of Psychiatry*, 154(1), 4–17.
- Spitzer, R. L., & Endicott, J. (2018). Medical and mental disorder: Proposed definition and criteria. *Annales Médico-psychologiques, revue psychiatrique*, 176(7), 656–665. <https://doi.org/https://doi.org/10.1016/j.amp.2018.07.004>
- Stapelberg, N. J. C., Hamilton-Craig, I., Neumann, D. L., Shum, D. H., & McConnell, H. (2012). Mind and heart: Heart rate variability in major depressive disorder and coronary heart disease - a review and recommendations [PMID: 22528974]. *Australian & New Zealand Journal of Psychiatry*, 46(10), 946–957. <https://doi.org/10.1177/0004867412444624>
- Stapelberg, N. J. C., Neumann, D. L., Shum, D. H. K., McConnell, H., & Hamilton-Craig, I. (2011). A topographical map of the causal network of mechanisms underlying the relationship between major depressive disorder and coronary heart disease [PMID: 21500954]. *Australian & New Zealand Journal of Psychiatry*, 45(5), 351–369. <https://doi.org/10.3109/00048674.2011.570427>
- Tay, J. K., Narasimhan, B., & Hastie, T. (2023). Elastic net regularization paths for all generalized linear models. *Journal of Statistical Software*, 106(1), 1–31. <https://doi.org/10.18637/jss.v106.i01>
- Taylor, C. B. (2010). Depression, heart rate related variables and cardiovascular disease [Psychophysiology of Psychological Disorders]. *International Journal of Psychophysiology*, 78(1), 80–88. <https://doi.org/https://doi.org/10.1016/j.ijpsycho.2010.04.006>
- Tracy, R. P., Lemaitre, R. N., Psaty, B. M., Ives, D. G., Evans, R. W., Cushman, M., Meilahn, E. N., & Kuller, L. H. (1997). Relationship of c-reactive protein to risk of cardiovascular disease in the elderly. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 17(6), 1121–1127. <https://doi.org/10.1161/01.ATV.17.6.1121>
- Valenza, G. (2023). Depression as a cardiovascular disorder: Central-autonomic network, brain-heart axis, and vagal perspectives of low mood. *Frontiers in Network Physiology*, 3. <https://doi.org/10.3389/fnetp.2023.1125495>
- van Borkulo, C., Boschloo, L., Borsboom, D., Penninx, B. W. J. H., Waldorp, L. J., & Schoevers, R. A. (2015). Association of Symptom Network Structure With the Course of Depression. *JAMA Psychiatry*, 72(12), 1219–1226. <https://doi.org/10.1001/jamapsychiatry.2015.2079>
- Veeneman, R. R., Vermeulen, J. M., Bialas, M., Bhamidipati, A. K., Abdellaoui, A., Munafò, M. R., Denys, D., Bezzina, C. R., Verweij, K. J. H., Tadros, R., & et al. (2024). Mental illness and cardiovascular health: Observational and polygenic score analyses in a population-based cohort study. *Psychological Medicine*, 54(5), 931–939. <https://doi.org/10.1017/S0033291723002635>

- Walker, E. R., McGee, R. E., & Druss, B. G. (2015). Mortality in Mental Disorders and Global Disease Burden Implications: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, 72(4), 334–341. <https://doi.org/10.1001/jamapsychiatry.2014.2502>
- Whooley, M. A., & Wong, J. M. (2013). Depression and cardiovascular disorders. *Annual Review of Clinical Psychology*, 9(Volume 9, 2013), 327–354. <https://doi.org/https://doi.org/10.1146/annurev-clinpsy-050212-185526>
- Wolk, R., Gami, A. S., Garcia-Touchard, A., & Somers, V. K. (2005). Sleep and cardiovascular disease. *Current Problems in Cardiology*, 30(12), 625–662. <https://doi.org/https://doi.org/10.1016/j.cpcardiol.2005.07.002>
- Wysocki, A., Rhemtulla, M., van Bork, R., & Cramer, A. (2022). Cross-lagged network models. <https://doi.org/10.31234/osf.io/vjr8z>
- Zainal, N. H., & Newman, M. G. (2023). Elevated anxious and depressed mood relates to future executive dysfunction in older adults: A longitudinal network analysis of psychopathology and cognitive functioning. *Clinical Psychological Science*, 11(2), 218–238. <https://doi.org/10.1177/21677026221114076>

Appendices

Appendix I

This study was initially planned using the Lifelines biobank dataset (Scholtens et al., 2014; Sijtsma et al., 2021). However, due to delays related to obtaining access to the dataset, it was ultimately not used. The steps outlined in this research can still be applied to the Lifelines dataset. It is important to note that the preprocessing step may need to be adapted based on the available data from Lifelines dataset.

Appendix II

 <https://github.com/kingilsildor/Cross-Lagged-Model>

Appendix III

See next page.

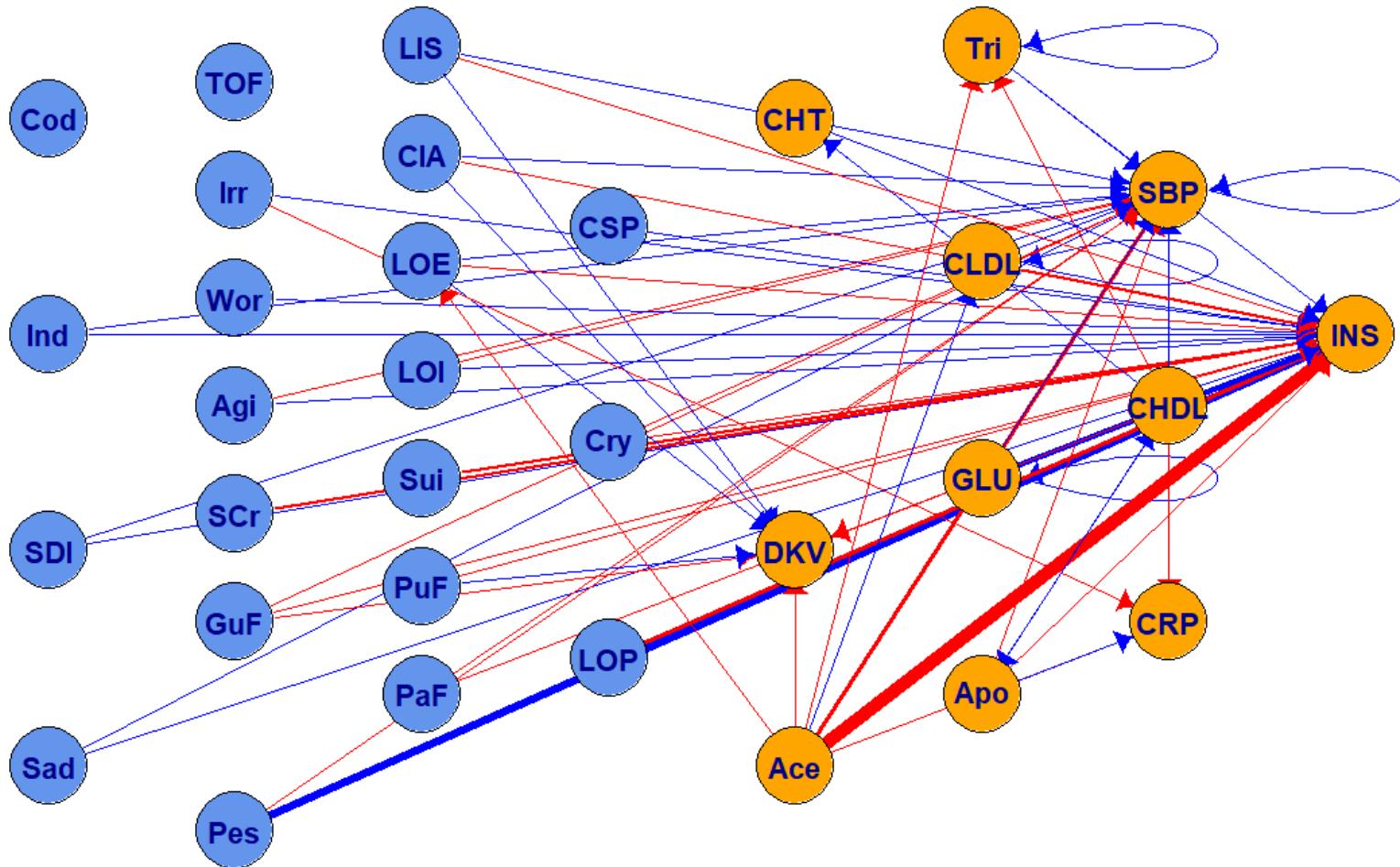


Figure 6.1: Full size image of the 2007 → 2011 network.

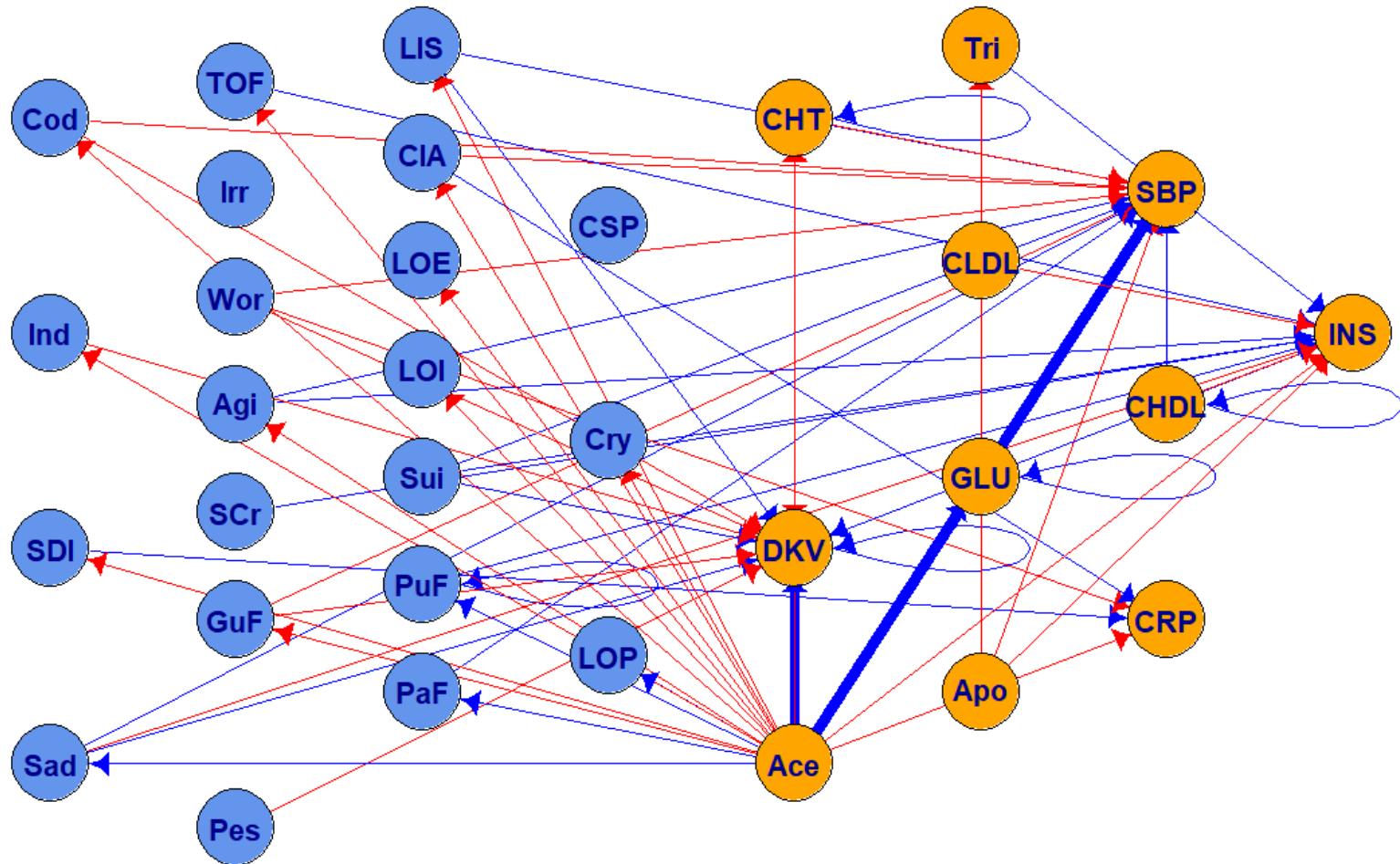


Figure 6.2: Full size image of the 2011 → 2012 network.

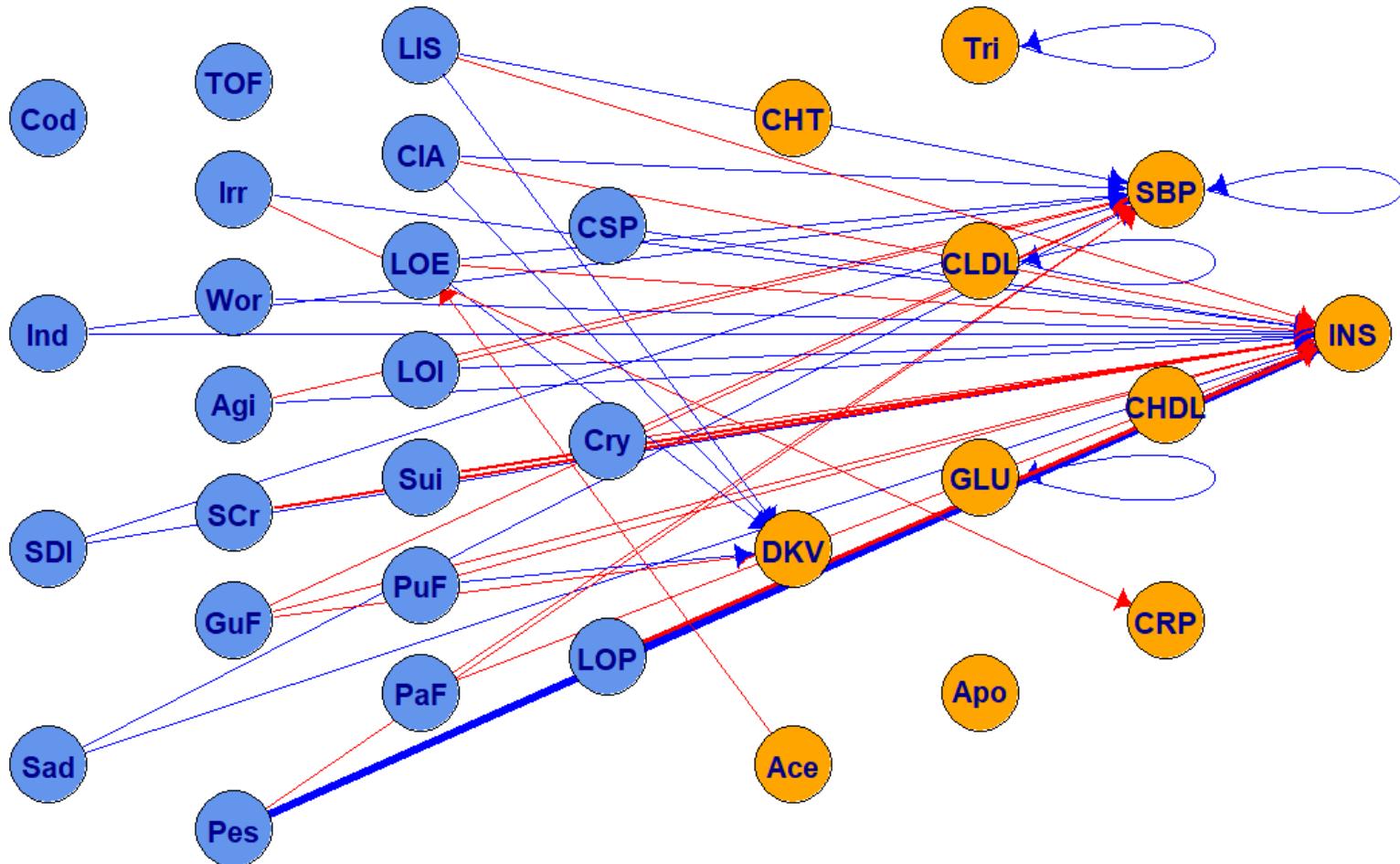


Figure 6.3: Full size image of the 2007 → 2011 reduced network.

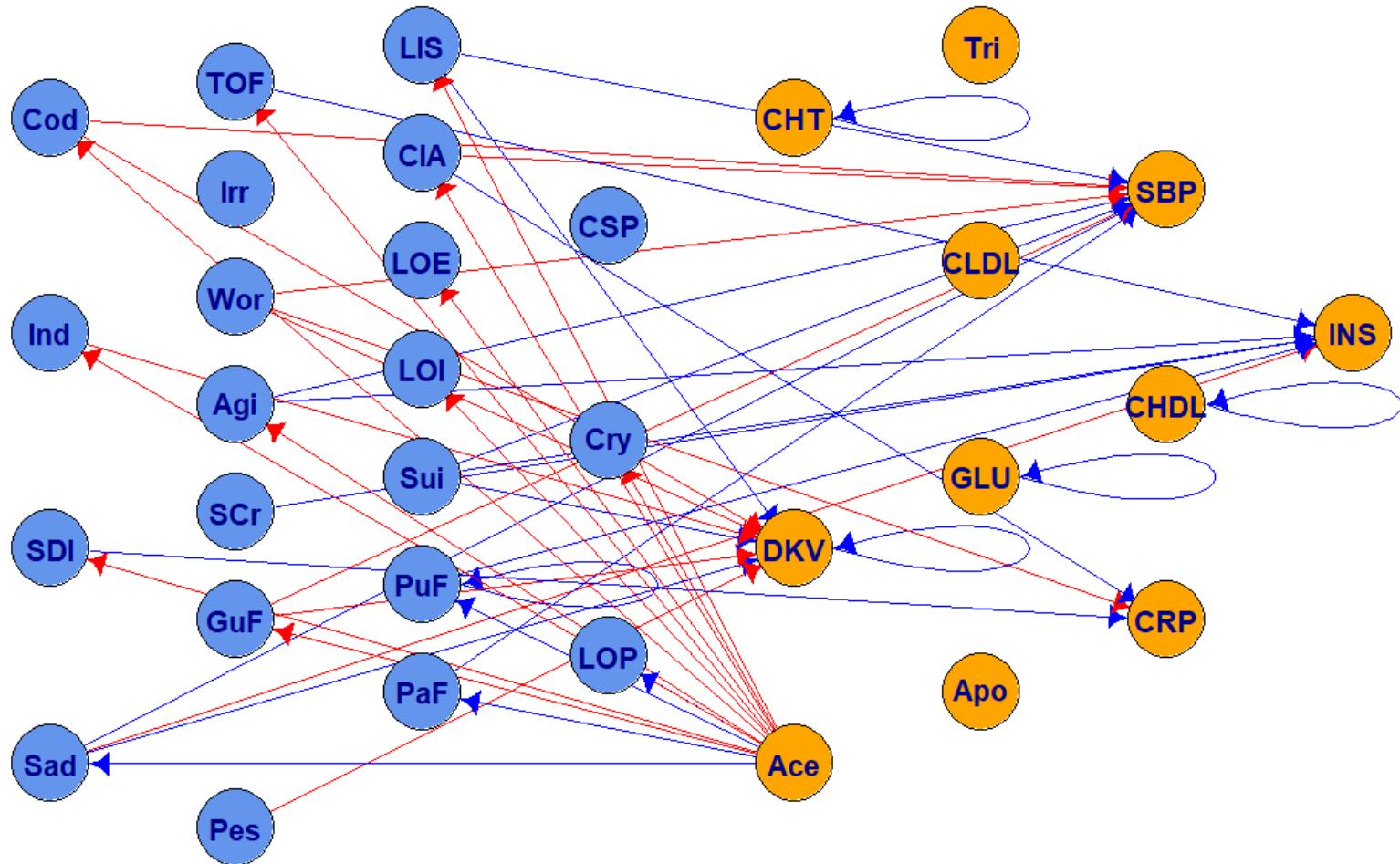


Figure 6.4: Full size image of the 2011 → 2012 network.

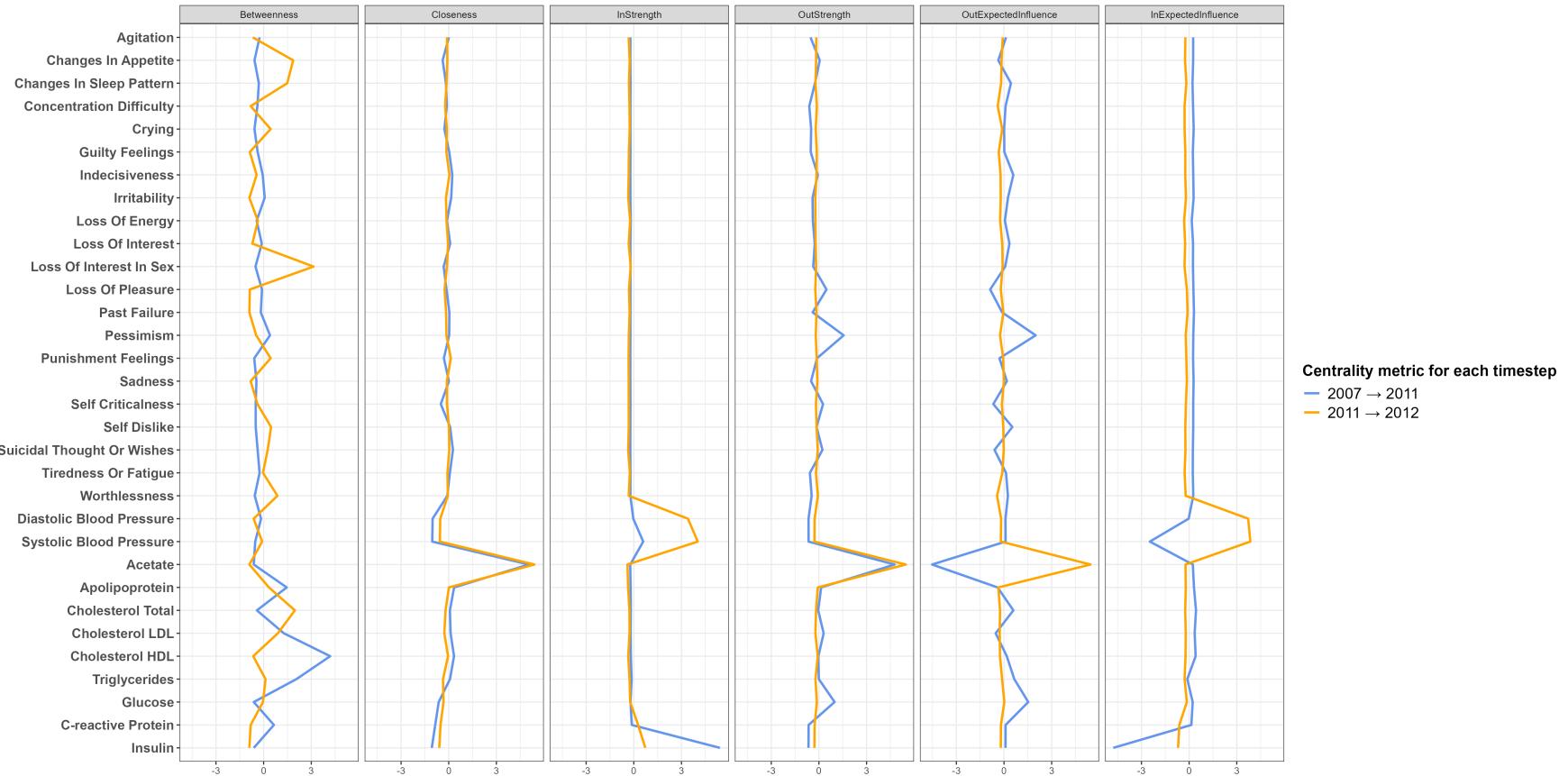


Figure 6.5: Full size image of the centrality metrics for the networks.

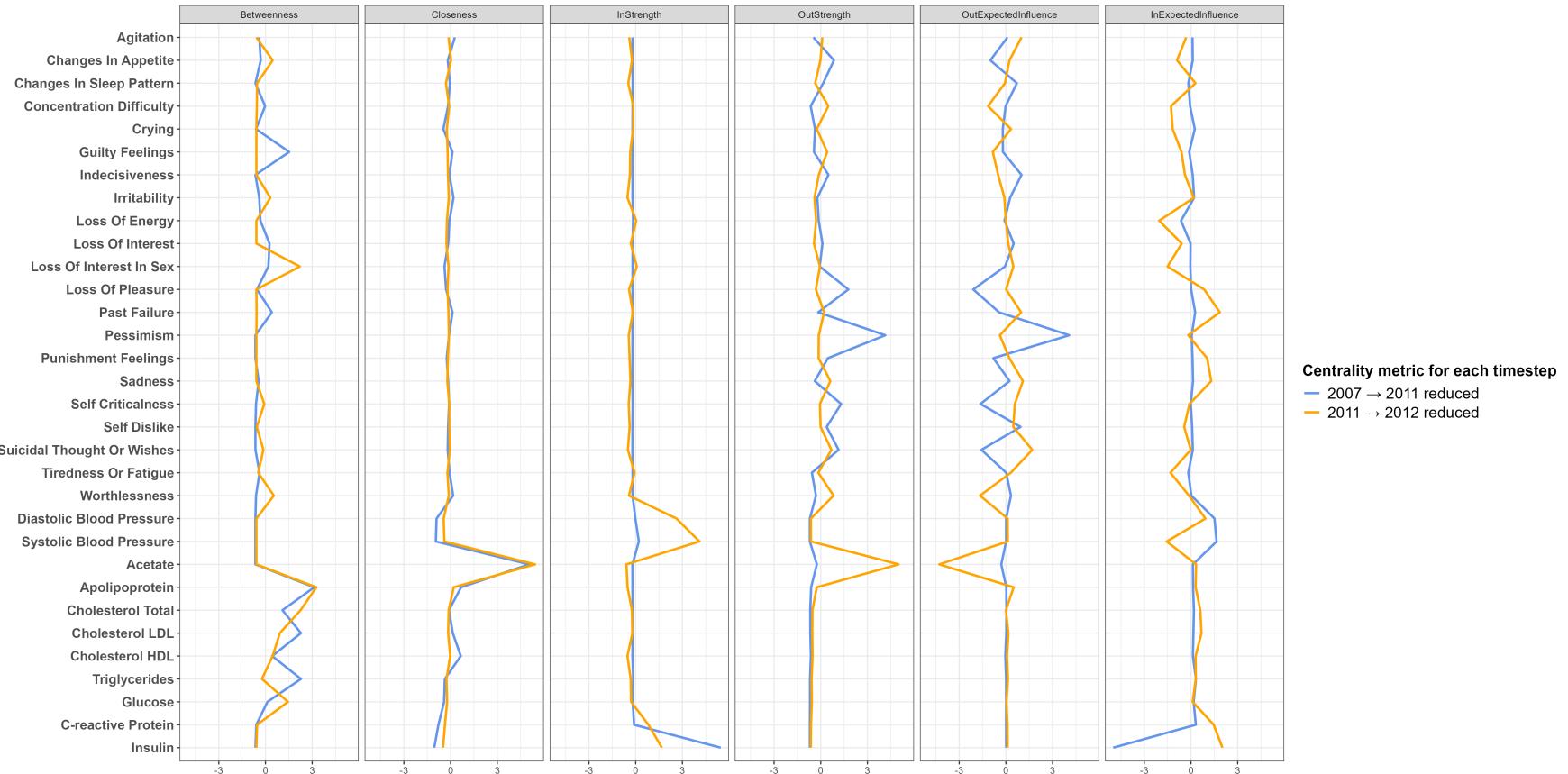


Figure 6.6: Full size image of the centrality metrics for the reduced networks.

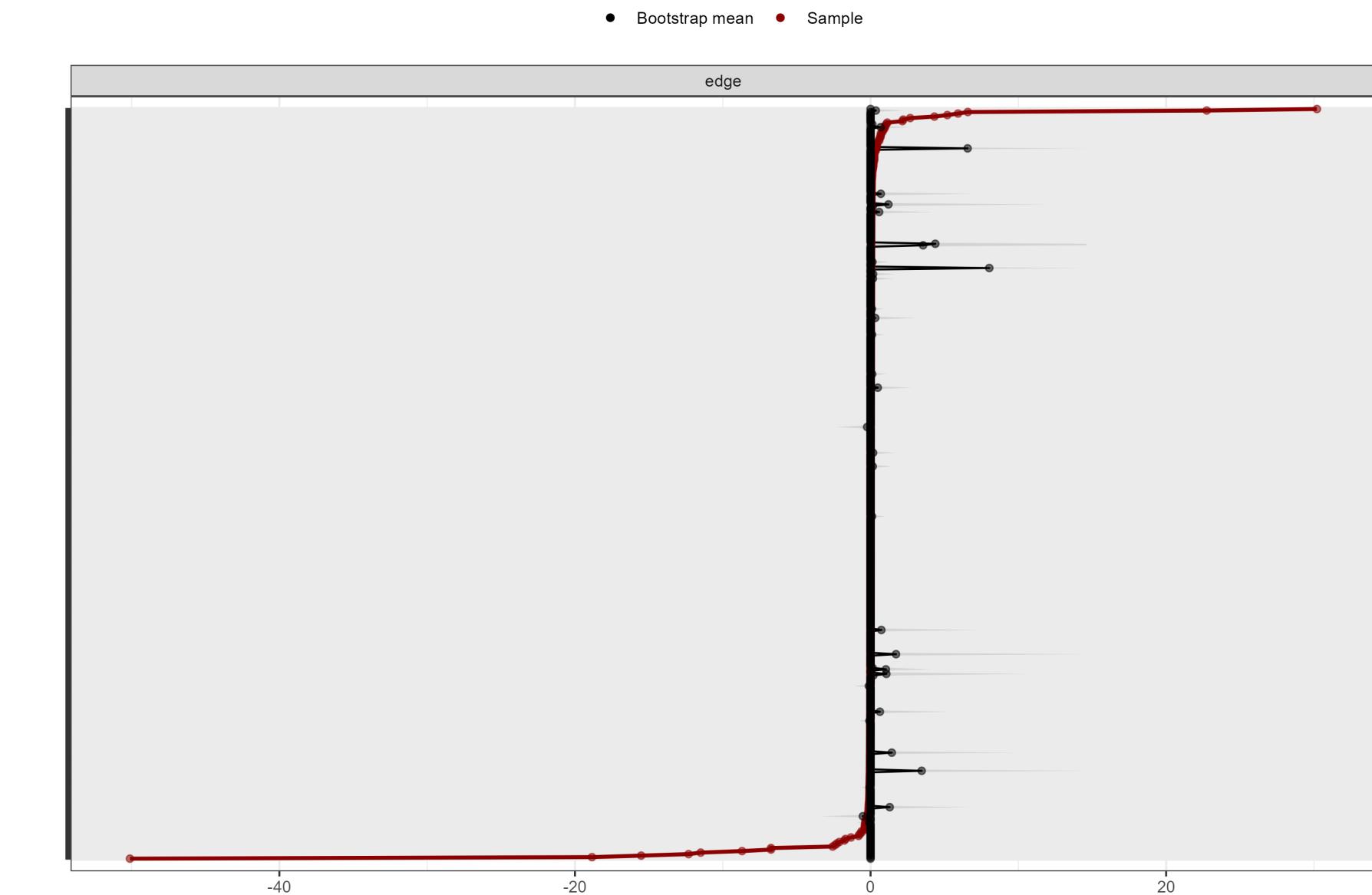


Figure 6.7: Full size image of the $2007 \rightarrow 2011$ stability of edges.

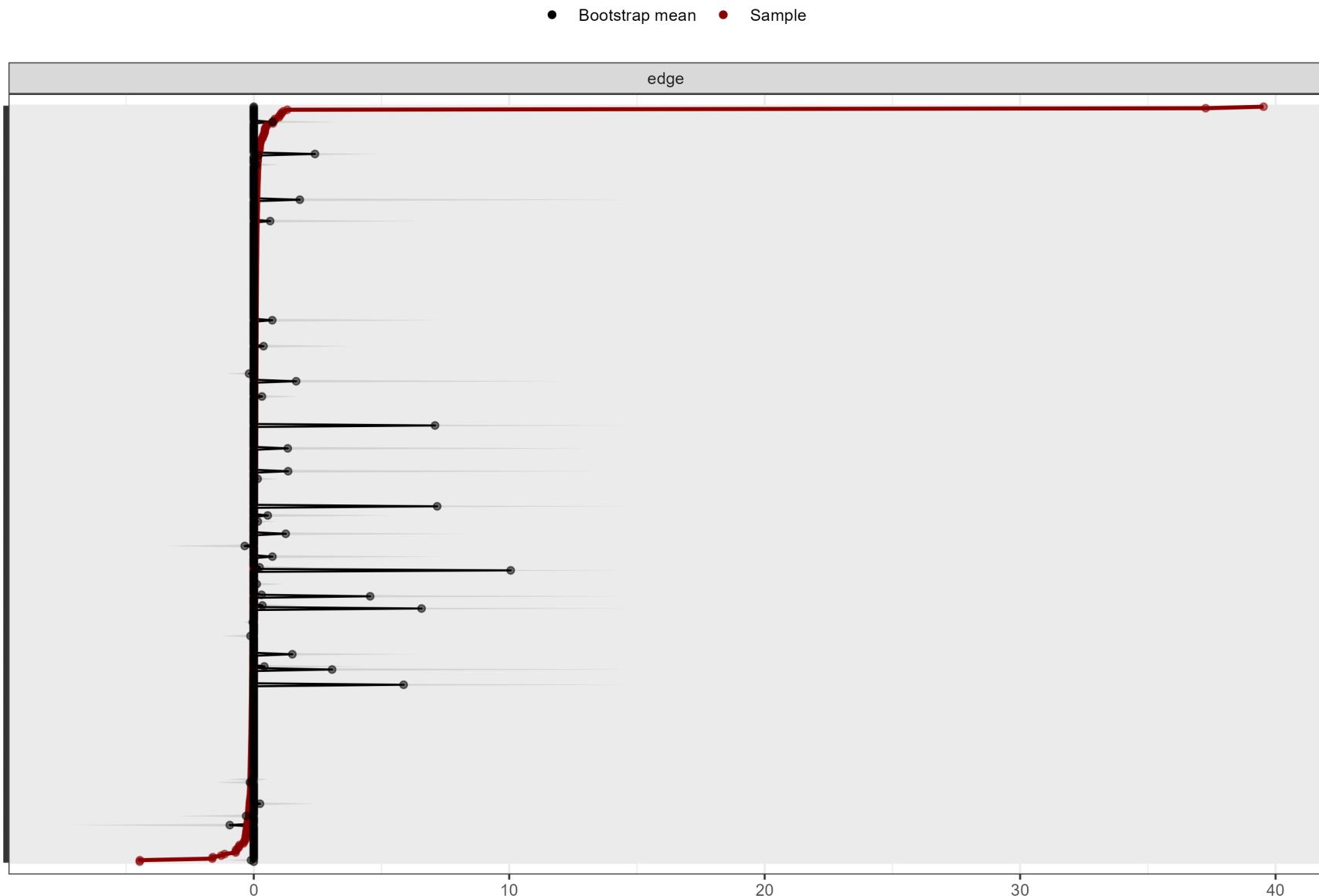


Figure 6.8: Full size image of the $2011 \rightarrow 2012$ stability of edges.

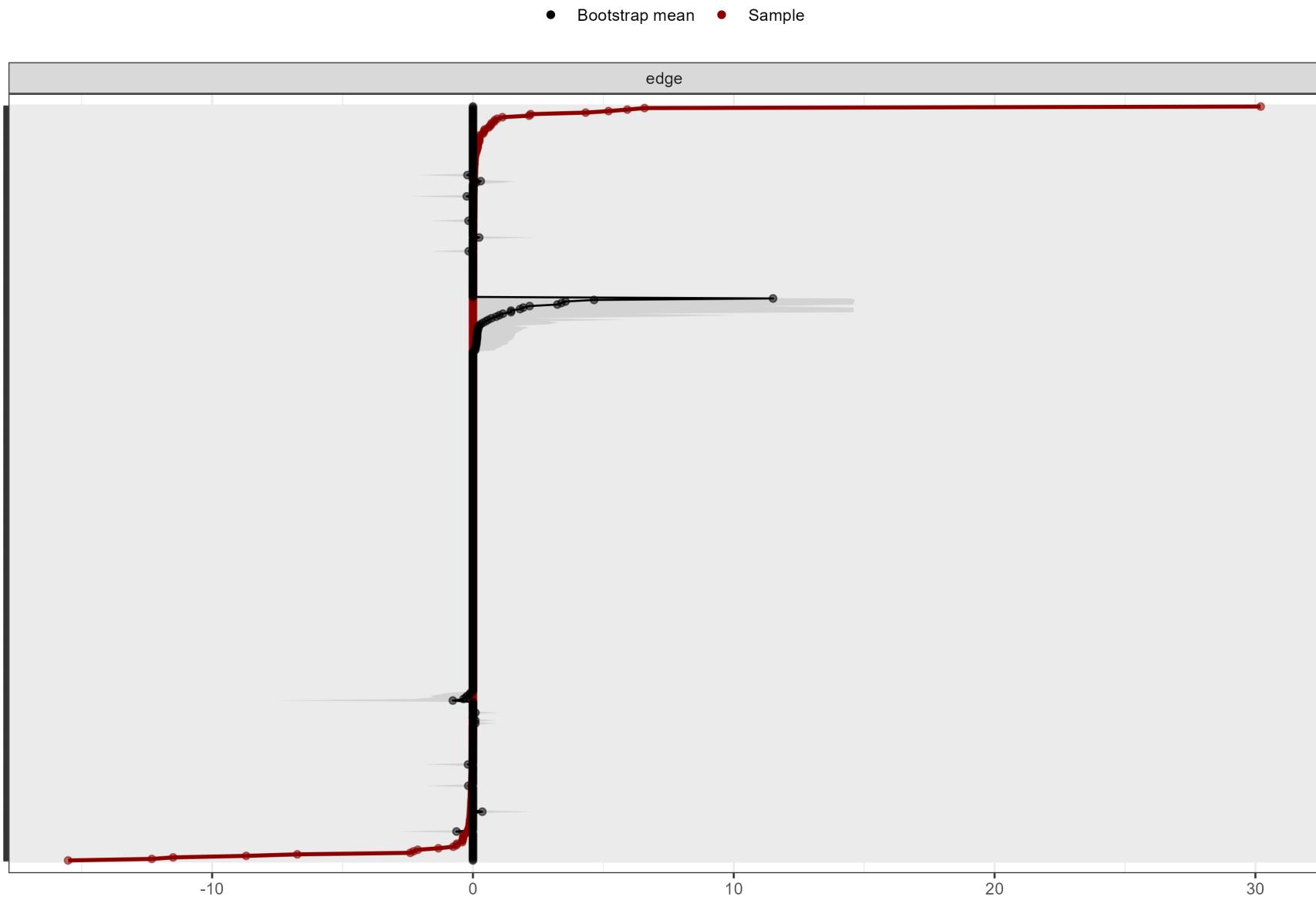


Figure 6.9: Full size image of the $2007 \rightarrow 2011$ reduced stability of edges.

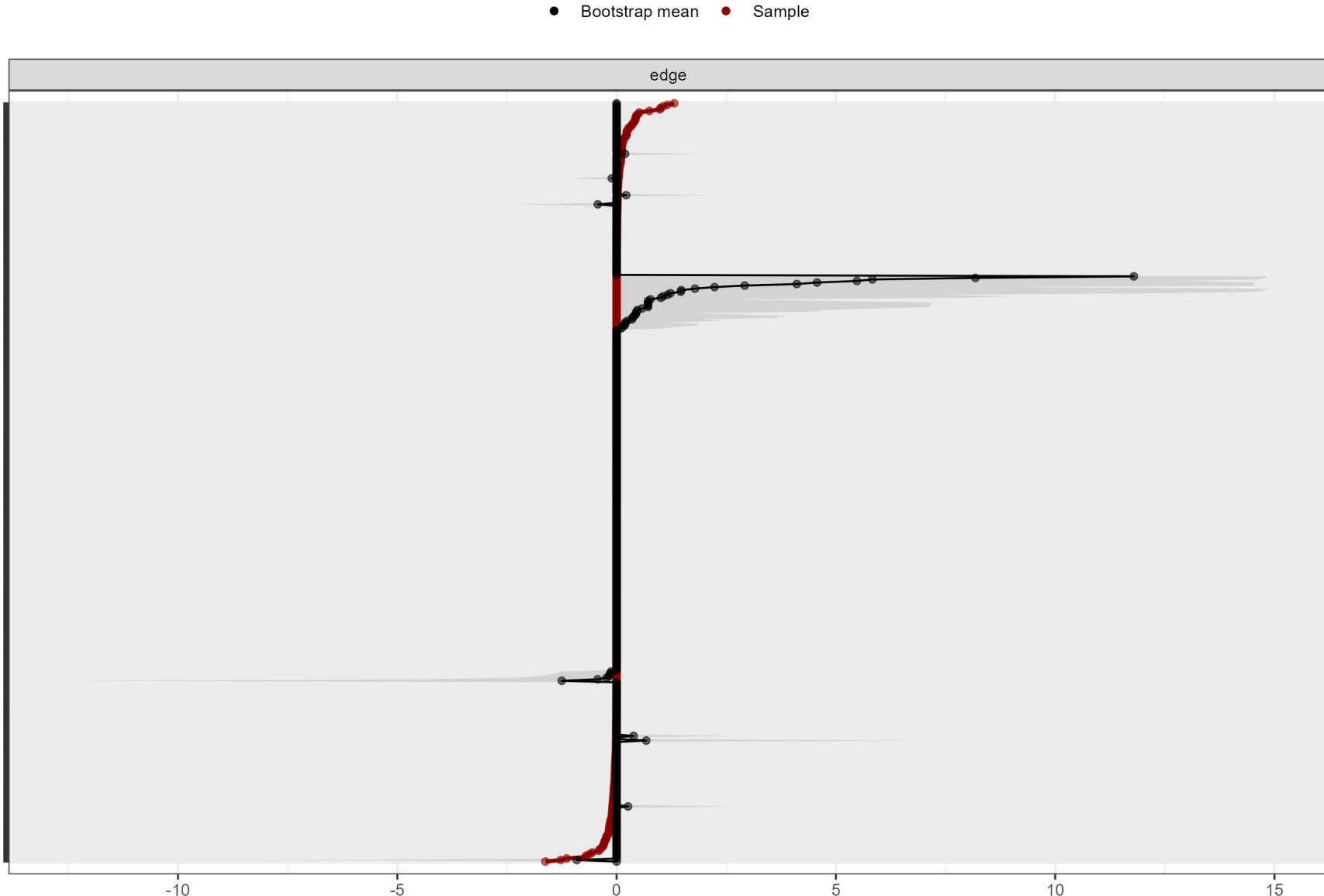


Figure 6.10: Full size image of the $2011 \rightarrow 2012$ reduced stability of edges.