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Gender Differences in Cannabis Use Disorder Symptoms: A Network Analysis

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Abstract

Importance. While cannabis use in women is increasing worldwide, research into gender differences in cannabis use disorder (CUD) symptomology is lacking. **Objective.** In response to limited effectiveness of addiction treatment, research focus has been shifting from clinical diagnoses towards interactions between symptoms, as patterns of symptoms and their interactions could be crucial in understanding etiological mechanisms in addiction. The aim of the current study was to evaluate the CUD symptom network and assess whether there are gender differences therein. **Design.** Cross-sectional. **Setting.** Online self-report study. **Participants.** A convenience sample of 1257 weekly cannabis users, including 745 men and 512 women. **Main outcome and measure.** Participants completed questionnaires assessing DSM-5 CUD symptoms and additional items on plans to quit or reduce use, cigarette use, and the presence of psychological diagnoses. Gender differences were assessed for all variables and an Ising model estimation method was used to estimate CUD symptom networks in men and women using network comparison tests to assess differences. **Results.** The estimated networks were dense with all symptoms except for *tolerance* and *risky use* being highly central to the network. There were gender differences in the prevalence of 6 of the 11 symptoms, but symptom networks did not differ between men and women. Cigarette use appeared to only be connected to the network through *withdrawal*, indicating a potential role of cigarette smoking in enhancing cannabis withdrawal symptoms. Furthermore, there were gender differences in the network associations of mood and anxiety disorders with CUD symptoms. **Conclusion and relevance.** While men and women differ in symptom prevalence, the pattern and weights of the associations between symptoms were found to be very similar. However, gender differences in the role of comorbidities in the network and the relation between smoking and withdrawal highlight the importance of gender differences in understanding CUD, which may have implications for treatment.

Introduction

Men compared to women use cannabis at almost double the rate.[1] However, cannabis use in women is increasing,[2] paralleling the increasing legalisation of cannabis use in multiple countries and US states.[1,3] Studies are suggestive of gender differences in acute cannabis effects,[4–6] withdrawal symptoms,[7,8] comorbidities,[9] and a faster transition from first use to cannabis use disorder (CUD) in women.[10] All of this could affect prevention and treatment efforts and highlights the importance of research into gender differences in cannabis use and CUD.

CUD is responsible for the most entries of treatment for Illicit Substance Use Disorders (SUDs) worldwide.[11] While CUD treatment efforts are unsuccessful for most, research into evidence-based CUD treatment is still limited.[12] In response to the limited effective treatment for mental health problems including CUD (24-35% abstinence after 6 months[13,14]), research interest has been shifting towards a symptom network approach; rather than focusing on a general clinical diagnosis, the network theory of mental disorders[15] proposes that individual symptoms and their interaction are crucial components in understanding the development and maintenance of mental disorders. Instead of viewing all symptoms as originating from a common cause, the mental disorder, symptoms should be estimated as entities that interact with each other in causal ways giving rise to mental health problems. These interactions between symptoms can be seen as a network in which the nodes represent the symptoms, and the edges represent the association between pairs of symptoms (accounting for the presence of all other symptoms). The structure of the network as well as the weight of the connections between symptoms could provide valuable insights into the development of mental disorders, how they can effectively be treated, and even how treatment could be tailored to an individual using idiographic network models.[e.g. 16]

This theoretical transition from diagnosis to symptoms is also reflected in the increasing number of studies using network models to assess mental disorders, such as depression,[17] psychosis,[18] and common comorbidities between psychopathologies.[19,20] However, while rapidly increasing, the number of studies assessing the symptom networks in SUDs is currently limited and

the evidence base too small to inform treatment. Rhemtulla et al. (2016) applied network models to substance abuse and dependence symptoms of a variety of substances, including cannabis, in a large sample of adult twins that used at least one illicit substance a minimum of six times in their life.[21] Across substances, *using more than planned* was the most central symptom, also showing a strong association with *tolerance*. However, there were substantial differences between substances in both edge weight between symptoms and centrality of specific symptoms in the network. Looking at cannabis, there was a strong association between *inappropriate timing of use*, *the time it takes to use and recover from it*, and *the interference of use with work and other obligations*. While this study showed the feasibility of using a network approach in assessing CUD symptoms, replication using the most recent DSM-5 CUD symptoms as well as the assessment of the potentially crucial role of gender is needed.

The current study aimed to assess gender differences in CUD symptoms using a network approach in individuals that used cannabis at least once per week during the last year. First, we constructed a network including the 11 items of the Mini International Neuropsychiatric Interview (MINI) DSM-5 interview to assess the interaction between symptoms of CUD. Second, we assessed whether men and women differed in the prevalence of specific symptoms. Third, we assessed potential gender differences in the symptom networks as well as differences in pairwise symptom associations and measures of centrality. Fourth, exploratory analyses were run to assess the role of plans to quit or reduce cannabis use, daily cigarette smoking, and comorbid mental health problems in the CUD symptom networks in both men and women.

Methods

Sample

Data were collected online as part of the screening process for an MRI study on CUD. All procedures were approved by the ethics committee of the department of psychology of the University of Amsterdam (2018-DP-9616). Participants were aged between 18-30 and only included if they consented to the storage and use of the screening data, indicated using cannabis at least once a

week during the last year and identified as either man or women. A total of 1267 individuals (59.3% men) met these inclusion criteria.

Measures

Qualtrics online questionnaire software was used. Age and gender ('What is your gender?'; answers: man, woman, other) were assessed and a digitalized Dutch version of the DSM-5 CUD section of the MINI 7.0.2[22] was administered to assess 11 CUD symptoms (Table 1). Participants also reported the average number of days per week they used cannabis over the last year and whether they had plans to either quit or reduce cannabis use. To assess other substance use, participants reported daily cigarettes use (yes/no), completed the alcohol use disorder identification test (AUDIT)[23], and reported lifetime use of other substances (excluding alcohol, cigarettes and cannabis). To assess history of mental health problems, participants reported lifetime diagnoses of any psychological disorder. Disorders that fit within the categories of mood disorder (dysthymia, depression & bipolar disorder), anxiety disorder (social anxiety, generalized anxiety disorder, OCD & PTSD) or externalizing disorder (ODD, ADHD & ADD) were included in the analysis.

Data Analysis

Gender differences on all measures were assessed using Mann-Whitney U tests (violation of normality assumption) or chi-square tests (categorical variables) using JASP 0.14.1.0.[24] All other analyses were performed with R version 4.0.2.[25] Network analysis was performed for the full sample and separately for men and women with the eLasso method and the Ising model using the R package Bootnet[26] (default = "IsingFit"). Model selection was based on the Extended Bayesian Information Criterion (EBIC) with gamma = 0.25 and the AND-rule. Strength centrality was estimated with the R package qgraph.[27] Bootstrapped confidence intervals (1000 bootstraps) were used to investigate accuracy of edge-weights (eFigures 2-7), case-dropping bootstraps (1000 bootstraps) were used to investigate the stability of strength centrality (eFigures 8-10), and bootstrapped difference tests (1000 bootstraps) were used to test for significant differences between edges within the same network (eFigure 11).[26] To test for gender differences in the network structure, global strength,

strength of all nodes, and weight of all edges, we performed a network comparison test with the R package NetworkComparisonTest[28] (1000 iterations, gamma = 0.25, AND-rule).

Results

Sample characteristics

On average, participants used cannabis 5.3 days per week (*SD* = 1.9; Table 2). Their average CUD severity score was 5.0 (*SD* = 3.0), indicative of moderate CUD. Men scored higher on CUD severity, cannabis use days per week, and alcohol use and related problems (AUDIT). Women were more likely to have self-reported diagnoses of mood and anxiety disorders (Table 2).

CUD symptom network

Figure 1A represents the full sample symptom network in which the nodes represent all MINI CUD symptoms and edges represent partial associations (controlled for all other associations) between those symptoms. The network was dense (mean weight = .365), with 43 non-zero edges over 55 possible edges. As can be seen from the weight of the edges, *craving* was strongly associated with several other symptoms including *failed quit attempts*, *withdrawal*, and *tolerance*, but also *time spent on use* and *social effects*. Furthermore, there was a strong association between *using more than planned* and having experienced *failed quit attempts*. While most symptoms were strongly interconnected and similarly central based on strength, *tolerance* and *risky use* were less interconnected. *Risky use* was connected to the rest of the network solely through *social effects* and *health effects*, while *tolerance* had the strongest direct relationship with *craving*. This was also reflected in the low strength of *tolerance* and *risky use* (eFigure 1A).

CUD symptoms in men and women

Men and women were equally likely to report *using more than planned* (1), *reducing or giving up activities* (9), and *experiencing craving* (4), *health problems* (8), or *withdrawal symptoms* (11; Table 3). However, men more often reported *failed attempts to reduce or quit use* (2), a *substantial time investment* (3), *less time spend on responsibilities* (5), *social effects* (6), *risky use* (7), and *tolerance* (10).

Gender differences in CUD symptom networks

Estimated CUD symptom networks of men (Figure 1D) and women (Figure 1C) were similar; they did not differ in structure (M = .597, p = .936), global strength (S = .108, p = .973) or centrality (strength: lowest p-value = .191; eFigure 1B-1C). Like the network including the full sample, the networks were dense (men: mean weight = .342, 38 non-zero edges over 55 possible edges; women: mean weight = .344, 37 non-zero edges over 55 possible edges). Most associations appeared similar between genders, except for t*olerance*; for men *tolerance* was connected through *craving, time investment and responsibilities*, while in women *tolerance* was connected through u*sing more than expected, less activities* and *responsibilities*. When comparing specific edges between genders, there only appeared to be one significant difference in the association between *time investment* and *tolerance* (p = .023); while there was a direct association between *tolerance* and *time investment* in men, even after controlling for the presence of all other associations, this association was not observed in women.

Exploratory analyses & gender differences

Exploratory analyses showed that *cigarette use* was only associated with the CUD symptom network through *withdrawal* and *time investment,* a potential effect of the co-occurrence of nicotine dependence in these individuals (Figure 2A). *Plans to quit* and *plans to reduce* were strongly related to each other but differentially connected to symptoms. *Plans to reduce* were primarily related to previous *failed attempts to reduce or quit*, while *plans to quit* were also associated with real-life outcomes of heavy use, such as *health problems*, *less activities*, *social effects*, and effects on *responsibilities*. The presence of *externalizing disorders* was not connected to the network. However, the presence of *mood disorders* was connected through *withdrawal* and was highly connected to the presence of *anxiety disorders*, which in turn was only connected to the network through *mood disorders*.

Comparing these networks across genders (Figure 2B-2C), while *daily smoking* was only connected to the network in men, this did not constitute a significant difference between networks

(p = .770). The connection of *anxiety* and *mood disorders* with the network did differ between men and women. In men, *anxiety* was connected to *failed reduce or quit attempts* while this was not the case in women (significant difference, p = .004). Also, in men, *mood disorders* were only connected through a strong association with *anxiety* while the reverse is true for women, in which *anxiety* was only related to the network through a strong association with *mood disorders*. However, *mood disorders* in women connected to the rest of the network differently than anxiety did in men. The primary associations were with *craving* (significant difference, p = .033) and *withdrawal* (no significant difference, p = .299). In these explorative models, the difference in the association between *time investment* and *tolerance* was still significant (p = .006). Additional differences were observed in the associations between *responsibilities* and *risky use* (p = .037) and between *less activities* and *tolerance* (p = .031), which were only present in women, and in the association between *craving* and *social effects* (p = .039), which was only present in men. When correcting results for multiple comparisons with the Holm–Bonferroni method, the gender difference in the relationship between *anxiety* and *failed reduce or quit attempts* remained significant.

Discussion

We evaluated the associations between DSM-5 CUD symptoms in weekly cannabis users using a network approach, with a specific focus on gender differences. While several symptoms were more commonly reported by men than women, the pattern and strength of the associations between symptoms appeared similar between genders. However, exploratory analyses assessing the association of comorbid mental health problems with CUD symptoms did reveal gender differences; while the presence of *anxiety* and *mood disorders* were highly associated with each other in both men and women, the way they connected to the CUD symptom network was different.

The estimated CUD symptom network was dense, in line with a previous study assessing the DSM-4 CUD symptom network[21], and consistent between men and women. This density might theoretically affect the developmental trajectory of CUD; in denser networks, when one symptom occurs (e.g., *craving*) the pathology can more easily spread (i.e., other symptoms develop) through

the network because the initial symptom is connected to many other symptoms.[29] Strength and centrality were similar for most symptoms, except *risky use* and *tolerance*. *Tolerance* was primarily associated with other symptoms through *craving*, which could indicate that while there are reciprocal connections between *craving* and *tolerance*, *tolerance* only affects other symptoms through *craving*. *Risky use*, a former DSM-IV criteria of abuse rather than dependence, was only connected to the rest of the network through *responsibility, social effects*, and *health effects*. Consequently, risky cannabis users could represent a clinically relevant sub-group. Of note, only 16.7% reported *risky use* (Table 3). Dutch young adults (mean age = 21.7) may encounter limited situations in which risky use would occur (e.g., due to lack of car ownership), warranting future studies in diverse samples.

Men over-reported six out of eleven MINI CUD symptoms compared to women, while total CUD scores differed less than one point on average (Table 2). Interestingly, while symptom prevalence differed, symptom networks did not; when present, the symptoms interacted in the same way in men and women. So, while this could indicate that the CUD symptom network is activated through different symptoms, and that different symptoms might pose early warning signs for CUD in men and women, symptoms appear to interact in similar ways. As the network is dense and interconnected in both men and women, targeting treatment to those symptoms that are central and pose the biggest daily life problem for a specific individual will likely also help diminish other symptoms.[e.g. 29]

Plans to reduce or *quit*, which might trigger seeking treatment, closely related to each other. Having *plans to reduce*, was associated to the network through *failed attempts to quit* – potentially indicative of a lack of self-efficacy in quitting, but a persistent willingness to reduce use. However, *plans to quit* were associated with the network through several symptoms that are indicative of daily life negative effects (i.e., *social effects*, *health effects*, *less activities*, and affected *responsibilities*) – potentially initiating the desire to quit.[e.g. 30,31]

Given the high co-occurrence in cannabis users,[32] we assessed how daily cigarette smoking and the presence of mood disorders, anxiety disorders, and externalizing disorders were associated with CUD symptoms. Cigarette use was primarily related to the network through withdrawal, an association that might arise from associated nicotine withdrawal. While further investigation into different types of withdrawal symptoms and how they associate with CUD symptoms in cigarette users and non-users is crucial, our results highlight the importance of considering cigarette smoking in treatment for CUD to potentially prevent withdrawal-related relapse (i.e., further research is needed to assess whether simultaneous cessation negatively affects relapse rates[e.g. 33] or not[e.g. 34]). Notably, when looking at both men and women separately, daily smoking was connected to withdrawal only in men, but gender differences were not significant.

Looking at comorbidities, externalizing disorders were very prevalent (20.2%) but did not relate to the CUD symptom network. This indicates that weekly cannabis users with an externalizing disorder are not more or less likely to report one or more CUD symptoms compared to other weekly cannabis users. While having an externalizing disorder might be a risk factor for heavy cannabis use and CUD,[e.g. 35] within a group of weekly cannabis users, externalizing disorder presence may not influence CUD symptoms.

The prevalence of both mood (women: 27.9%; men: 12.9%) and anxiety disorders (women: 19.9%; men: 4.0%) was higher in women than men. Depression and anxiety were closely related to each other in both genders, but the way they were associated with the CUD symptoms differed. In men, anxiety disorders were related to CUD symptoms through failed attempts to reduce or quit, which could increase anxiety but also be increased by anxiety (i.e., possible feedback loop). Mood disorders were only related to CUD symptoms through anxiety disorders in men. In contrast, in women, depression was associated with CUD symptoms through craving and withdrawal, while anxiety only related to the rest of the network through mood disorders. This could indicate potential gender-specific self-medication mechanisms.[e.g. 36] Since using to reduce anxiety or depressive feelings is part of the withdrawal spectrum, these associations could be indicative of a self-

medication feedback loop between depression and using to feel better, which in turn also affects craving and additional CUD symptoms. Nevertheless, research into specific withdrawal symptoms is crucial to unravel these mechanisms.

Some limitations should be noted. First, the MINI DSM-5 CUD semi-structured interview[20] is not validated for use as an online self-report. While this warrants clinical validation, assessment of the DSM-5 CUD symptoms through online self-report can be highly informative as large-scale data collection is not feasible in in-person interview settings. Second, the current sample is a convenience sample and large samples based on set criteria that ensure matching on most variables are needed to confirm our results. Third, splitting the data by gender did affect our sample size, which resulted in two smaller groups of unequal size. However, sample size differences were not large enough to justify concerns with regards to the network comparison test results. Furthermore, we identified stable edges in women that were not present in men (eFigures 2-7), making it unlikely that sample size affected our outcomes. Fourth, individual time series data is needed to further assess and confirm the proposed development of symptomology based on current results.

Our study shows that CUD symptoms are highly interconnected and that while there are gender differences in prevalence of symptoms, the symptoms interact with each other in similar ways in men and women. However, gender differences in how comorbidities are associated with CUD symptoms as well as the association between cigarette use and withdrawal symptoms highlight the importance of further research into complex associations between these factors to inform clinical practice.

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Table 1. DSM-5 MINI cannabis use disorder (CUD) symptoms		
Label	Description	Item
1	Use more	During times when you use the drug, did you end up using more cannabis than you planned when you started?
2	Reduce or quit attempt	Did you repeatedly want to reduce or control your cannabis use? OR* Did you try to cut down or control your cannabis use but failed?
3	Time investment	On the days that you used cannabis, did you spend substantial time obtaining cannabis, using it, or recovering from its effects?
4	Craving	Did you crave or have a strong desired or urge to use cannabis?
5	Responsibilities	Did you spend less time meeting your responsibilities at work, at school or at home, because of your repeated cannabis use?
6	Social effects	If your cannabis use caused problems with your family or other people, did you still keep on using it?
7	Risky use	Did you use cannabis more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?
8	Health effects	Did you continue to use cannabis, even though it was clear that the cannabis has caused or worsened psychological or physical problems?
9	Less activities	Did you reduce or give up important work, social or recreational activities because of your cannabis use?
10	Tolerance	Did you need to use cannabis a lot more in order to get the same effect that you got when you first started using it or did you get much less effect with continues use of the same amount?
11	Withdrawal	When you cut down on heavy or prolonged use of the drug, did you have any of the following withdrawal symptoms?
* Both questions were asked as separate items and later score according to the scoring guidelines.		

Table 2. Sample characteristics								
Measure		**Women (N = 512)**		**Men (N = 745)**		**Total (N = 1257)**		
		M (SD)	**Mdn**	**M (SD)**	**Mdn**	**M (SD)**	**Mdn**	**Comparison test**
General	Age	21.8 (3.2)	21	21.6 (3.1)	21	21.7 (3.1)	21	U = 184529.50, p = .324
Cannabis use	CUD severity score	4.7 (2.9)	4	5.2 (3.0)	5	5.0 (3.0)	5	U = 209065.50, p = .004
	Last year days per week	5.1 (2.1)	6	5.5 (1.8)	6	5.3 (1.9)	6	U = 210461.50, p < .001
	Plans to reduce	N = 270 (52.7%)		N = 409 (54.9%)		N = 679 (54.0%)		X^2(1, N = 1255) = .653, p = .419
	Plans to quit	N = 59 (11.5%)		N = 114 (15.3%)		N = 173 (13.8%)		X^2(1, N = 1255) = 3.721. p = .054
Other substance use	Daily cigarette use	N = 317 (61.9%)		N = 472 (63.4%)		N = 789 (62.8%)		X^2(1, N = 1257) = .270, p = .603
	AUDIT score	7.2 (4.9)	6	8.4 (5.7)	7	7.9 (5.4)	7	U = 211899.50, p < .001
	Other substance use	76.3 (204.1)	20	112.9 (573.8)	22	98.0 (460.8)	21	U = 201795.00, p = .080
Mental Health	Mood disorder	N = 143 (27.9%)		N = 96 (12.9%)		N = 239 (19.0%)		X^2(1, N = 1257) = 44.599, p <.001
	Anxiety disorder	N = 97 (19.9%)		N = 30 (4.0%)		N = 127 (10.1%)		X^2(1, N = 1257) = 74.358, p < .001
	Externalizing disorder	N = 95 (18.6%)		N = 159 (21.3%)		N = 254 (20.2%)		X^2(1, N = 1257) = 1.462, p = .227
Note: AUDIT = alcohol use disorder identification test; CUD = cannabis use disorder; M = mean; Mdn = median; SD = standard deviation								

Table 3. Gender differences in reported cannabis use disorder symptoms						
Symptom		**Women (N = 512)**	**Men (N = 745)**	**Comparison test**	**Result**	**Total (N = 1257)**
		N (%)	**N (%)**			**N (%)**
1	Use more	273 (53.3%)	385 (52.2%)	χ^2 = (1, N = 1257) = .149, p = .743	M = W	662 (52.7%)
2	Reduce or quit	270 (52.7%)	437 (58.6%)	χ^2 = (1, N = 1257) = 4.326, p = .038	M > W	707 (56.2%)
3	Time investment	194 (37.9%)	333 (44.7%)	χ^2 = (1, N = 1257) = 5.775, p = .016	M > W	527 (41.9%)
4	Craving	340 (66.4%)	512 (68.7%)	χ^2 = (1, N = 1257) = .747, p = .387	M = W	852 (67.8%)
5	Responsibilities	201 (39.3%)	369 (49.5%)	χ^2 = (1, N = 1257) = 12.920, p <.001	M > W	570 (45.3%)
6	Social effects	126 (24.6%)	244 (32.8%)	χ^2 = (1, N = 1257) = 9.686, p = .002	M > W	370 (29.4%)
7	Risky use	56 (10.9%)	154 (20.7%)	χ^2 = (1, N = 1257) = 20.661, p < .001	M > W	210 (16.7%)
8	Health effects	230 (44.9%)	320 (43.0%)	χ^2 = (1, N = 1257) = .478, p = .489	M = W	550 (43.8%)
9	Less activities	114 (22.3%)	174 (23.4%)	χ^2 = (1, N = 1257) = .204, p = .651	M = W	288 (22.9%)
10	Tolerance	331 (64.6%)	559 (75.0%)	χ^2 = (1, N = 1257) = 15.832, p < .001	M > W	890 (70.8%)
11	Withdrawal	263 (51.4%)	367 (49.3%)	χ^2 = (1, N = 1257) = .538, p = .463	M = W	630 (50.1%)
Note: N and percentages reflect the number and the percentage of individuals that reported experiencing the presented symptom.						

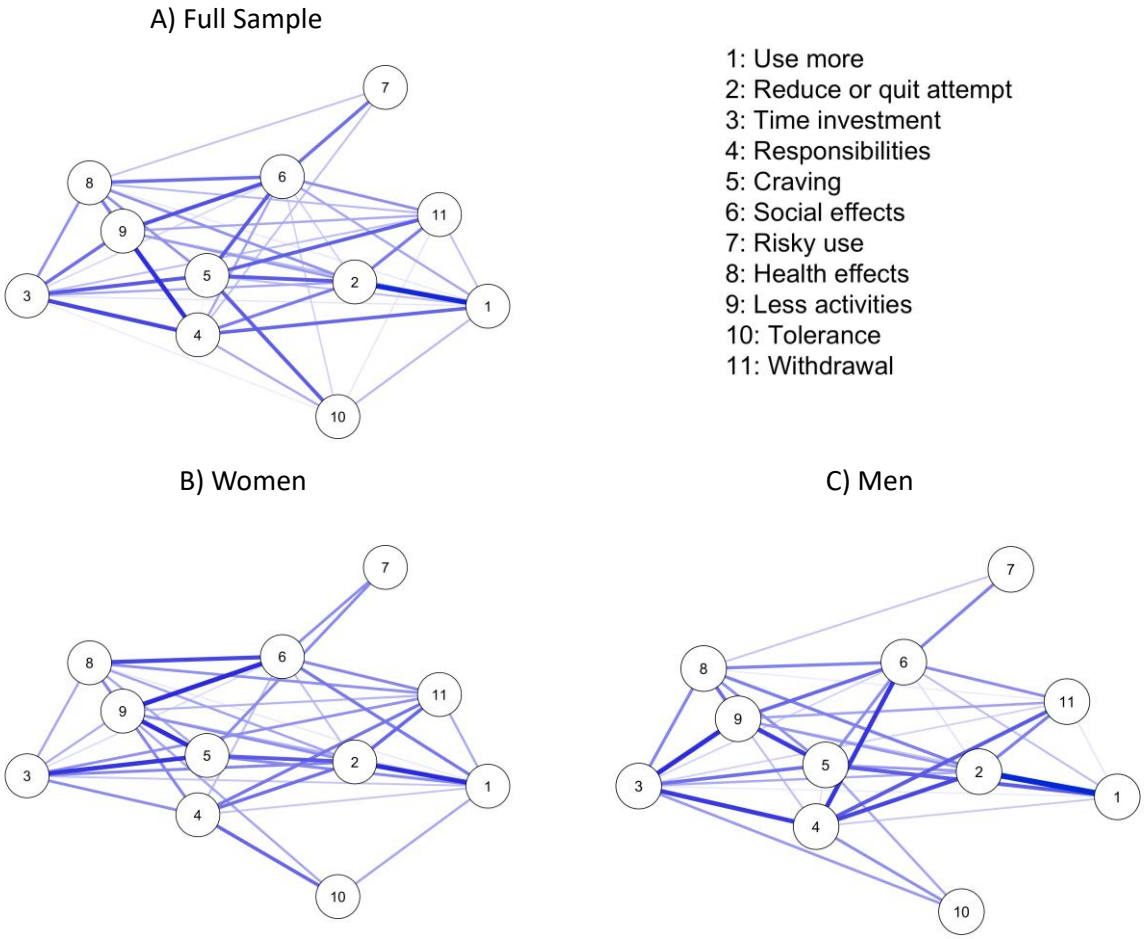

Figure 1. cannabis use disorder (CUD) symptom networks. Nodes represent the eleven MINI CUD symptoms. The edges represent their positive associations, controlled for all other associations. Larger edge width reflects larger edge weight. To improve comparability edge widths were scaled to the largest edge weight across the three networks (edge weight = 1.141). To ensure network clarity and comparability, the average of the Spring layout of the full sample network and women network was used to plot all networks.

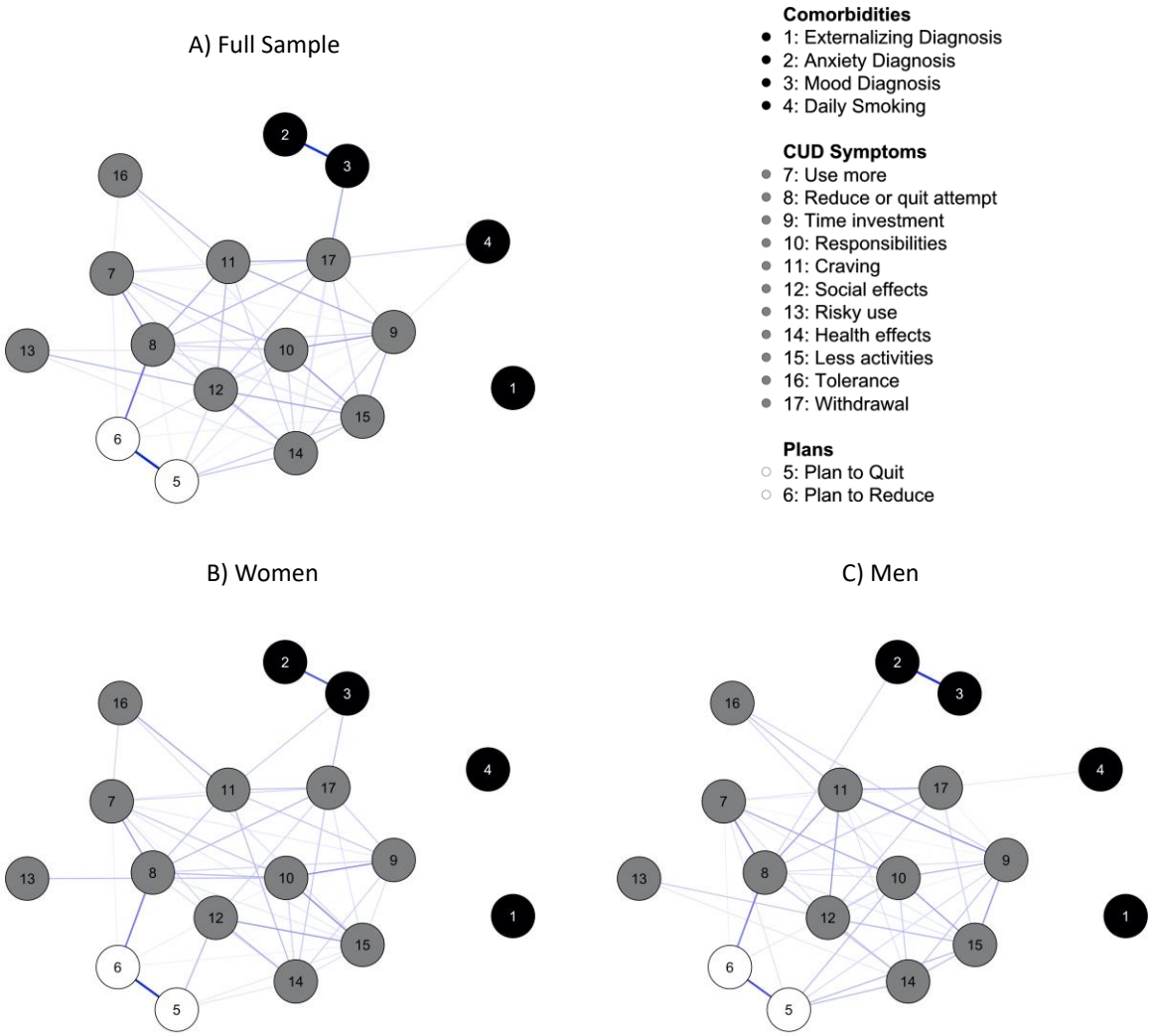

Figure 2. Cannabis use disorder (CUD) symptom networks including exploratory variables. Nodes represent the eleven MINI CUD symptoms and additional exploratory variables. The edges represent their positive associations, controlled for all other associations. Larger edge width reflects larger edge weight. To improve comparability edge widths were scaled to the largest edge weight across the three networks (edge weight = 2.039). To ensure network clarity and comparability, the Spring layout of the full sample network was used to plot all networks.