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Sadness and the continuum from well-being to depressive disorder: Findings from a representative US population sample

Running title: Sadness and the depressive continuum

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Contributors

Sarah Tebeka carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted.

Pierre A. Geoffroy, Yann Le Strat and Caroline Dubertret revised the manuscript, and approved the final manuscript as submitted.

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Conflicts of Interest

The authors have no conflicts of interest relevant to this article to disclose.

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Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ABSTRACT

Objective: Sadness is a common symptom in the general population. We tested the hypothesis that sadness is an intermediate state on a continuum from well-being to major depressive disorder (MDD).

Methods: Using data from The National Epidemiologic Study of Alcohol and Related Conditions III (NESARC-III), a large and representative US population sample, we assessed the prevalence of sadness, its sociodemographic and clinical correlates, using three non-overlapping groups: (i) non-depressed sad participants, (ii) non-sad non-depressed participants and (iii) depressed participants. We estimated sensitivity and specificity of sadness.

Results: Sadness was frequent in the general population 34.3%), and present in almost all participants with MDD (99.6%). Sad (N=4,593) and MDD participants (N=4,593) and 7,889 respectively) shared common sociodemographic characteristics. Compared to controls, sad and MDD participants presented more psychiatric disorders, including anxiety, substance use, psychotic, eating and personality disorders. Sadness was an intermediate state, sad individuals reporting more psychiatric disorders than controls, but less than participants with MDD. Sadness demonstrated a very high sensitivity (99.6 %), with a good specificity (83.8%) for MDD.

Limitations: The NESARC assessed sadness over lifetime, which may involve memorization bias.

Conclusion: Our study confirms the existence of a depressive continuum. Sadness is frequent in general population, and shares correlates with MDD. We have also shown a continuum where sadness is an intermediate state between well-being and psychiatric disorders. With high sensitivity and specificity, sadness appears as a clear MDD prodrome and at-risk state, and may be a symptom of a transdiagnostic distress process.

Key words

- Anxiety/Anxiety disorders
- Bipolar disorder
- Depression
- Eating disorders
- Epidemiology
- Substance Use Disorders

Abbreviations

- AOR: adjusted odd ratio
- AUD: alcohol use disorder
- BD: bipolar I disorder
- CI: confidence interval
- GAD: generalized anxiety disorder
- MDD: major depressive disorder
- OR: odds ratio
- PTSD: post-traumatic stress disorder

INTRODUCTION

The continuum from mental well-being to psychiatric disorders has been described for decades (Shevlin et al., 2016; van Os et al., 2009). A better understanding of this continuum is of major interest in order to better disentangle the physiopathology, and to identify at-risk states. Numerous studies have particularly studied the place of psychotic symptoms within a continuum (Ayuso-Mateos et al., 2010; Kingdon, 2009; Lewinsohn et al., 2000; Shevlin et al., 2016; van Os et al., 2009). Linscott and van Os have proposed two conditions to confirm the psychotic continuum hypothesis: first, psychotic symptoms must exist and be more frequent in non-clinical population than characterized psychotic disorder; symptoms and characterized disorders should share same correlates and risk factors (van Os et al., 2009).

Following this methodology, we recently tested the hypothesis that depressive symptoms also lies along a continuum (Tebeka et al., 2018). In a sample of 38,694 participants, we showed that depressive symptoms ranged from non-pathological sadness (reported by 29.8% of the sample), to major depressive disorder according to DSM-5 criteria (MDD, reported by 12.0% of the sample). In this previous work, sadness and MDD shared socio-demographic and clinical correlates. Moreover, sadness appeared to be an intermediate state between mental health and MDD. Participants with sadness and participants with MDD were more likely to report non-depressive psychiatric disorders than participants without sadness or MDD, participants with sadness constituting an intermediate group between MDD and controls. The results were consistent with a depressive continuum hypothesis. Finally, we also suggested that sadness could be used as a screener of "at risk" mental state, with a very high sensitivity for MDD (94.2%) and as expected, poor specificity (36.3%) (Tebeka et al., 2018).

Although sadness is a "gate symptom" for MDD diagnosis, being one of the two cardinal criteria with anhedonia, it is relevant to assess the clinical value of this frequent

symptom. The aims of the present study were threefold. First, we wanted to replicate and confirm the existence of a depressive continuum in a non-European sample. Second, we wanted to assess the strength of the associations between sadness and non-depressive psychiatric disorders. Thirdly, we wanted to test the sensitivity and specificity of sadness to screen Major Depressive Disorder (MDD).

METHODS

Sample

The National Epidemiologic Study of Alcohol and Related Conditions III (NESARC-III) is a nationally representative survey of U.S. civilian population. It included 36,309 participants, 18 years and older, in 2012-2013. Reponses rates was 60.1% in NESARC-III (Grant et al., 2014). Trained interviewers conducted face-to-face interviews. More information on NESARC-III sample are available.

The research protocol, including informed consent procedures, received ethical approval from the institutional review boards of Westat and the National Institutes of Health for NESARC-III.

Measures

Sociodemographic Measures

Age at interview was categorized into four age-bands (18-29 years, 30-44 years, 45-59 years, 60+ years). Educational level was classified into: (i) less than high school, (ii) high school graduate and (iii) some college or higher. Marital status was classified into (i) married, (ii) widowed/separated/divorced and (iii) never married. Personal income during a year was classified into: (i) \$0-19,999, (ii) \$20,000-34,999, (iii) \$35,000-69,999, and (iv) \$70,000 or

greater. Race/ethnicity was categorized into: (i) White, (ii) Black, (iii) American Indian/Alaska Native, (iv) Asian/Native Hawaiian/Pacific Islander and (v) Hispanic/Latino. Region of residence was classified into: (i) Northeast, (ii) Midwest, (iii) South, and (iv) West. Sex, urbanicity and US born was collected.

Sadness

Sadness was assessed lifetime by a single question: "In your entire life, have you ever had a time when you felt sad, blue, depressed, or down nearly every day for at least 2 weeks?".

Assessment of psychiatric disorders

The AUDADIS-IV was used to assess psychiatric diagnoses according to DSM-IV criteria (Chatterji et al., 1997). We reported lifetime prevalence for MDD (excluding bipolar disorder), bipolar disorder (BD), any anxiety disorders (including panic disorder, social phobia, and generalized anxiety disorder), Post-Traumatic Stress Disorder (PTSD), eating disorders (including anorexia nervosa, bulimia nervosa and binge eating disorder) and personality disorders (including schizotypal, borderline and antisocial personality disorders), substance use disorders (SUD, including tobacco, alcohol and cannabis), and psychotic disorder (Bourgin et al., 2019; Tebeka et al., 2016). The AUDADIS-IV used a single question to screen suicide attempts.

Statistical analyses

In order to make comparisons easier, we used the same statistics to our previous work (Tebeka et al., 2018).

We divided the sample into three independent groups as follows: 1) participants without neither sadness nor MDD (controls), 2) participants with sadness but without MDD and 3) participants with MDD, with or without sadness (MDD).

We compared the prevalence of sadness and the sociodemographic characteristics in the three groups, to valid the continuum criterion proposed by van Os and Linscott (Linscott and van Os, 2013). We also compared the prevalence of psychiatric disorders in the three groups.

Weighted estimates and standard errors (SEs) were computed using SUDAAN, version 11.01 (Research Triangle Park, NC). This software implements a Taylor linearization to adjust SEs of estimates for complex survey sampling design effects including clustering data.

Multivariate logistic regression models were estimated with simultaneous entry of socio-demographics covariates. Adjusted odds ratios (ORs), 95% confidence intervals (CIs) are presented to reflect association strength and significance.

Finally, the sensitivity and specificity of sadness for MDD risk were estimated. We also calculate the sensitivity and specificity for the other co-occurring psychiatric disorders: anxiety, substance use, personality, psychotic and eating disorders.

RESULTS

Prevalence rate of sadness (Table 1).

The prevalence of sadness was 34.29% in our sample (12,449 of 36,309 participants interviewed). Sadness without MDD concerned 12.65% of our sample.

The prevalence of MDD was 21.73%. In the MDD subgroup, almost all participants reported sadness (99.54%).

Sociodemographic characteristics (Table 1).

Participants with sadness and those with MDD were more likely than controls to be women (46.44% of women in controls, 57.46% in sad people, in 65.12% in MDD), non-married (60.27% of women in controls, 54.36% in sad people, in 52.47% in MDD) and divorced (11.54% of women in controls, 17.33% in sad people, in 18.85% in MDD). Participants with sadness and those with MDD were also more likely than controls to have lower personal incomes (13.70% of high household incomes in controls, 10.91% in sad people, in 9.98% in MDD) and to be born in U.S. (81.56% of women in controls, 86.29% in sad people, in 90.25% in MDD sample). They were no difference on urbanicity and region of residence between the three groups.

- Table 1 about here -

Clinical characteristics of the sample.

The prevalence of suicide attempt was 1.34% in controls, 9.11% in sad people and 14.32% in MDD. Participants with sadness and those with MDD presented respectively 28.08% and 43.37% anxiety disorders, 49.50% and 57.90% SUD and 4.17% and 3.75% psychotic disorder. Participants with sadness and those with MDD presented respectively 2.67% and 4.32% eating disorders, and 20.68% and 27.44% personality disorders (**Table 2**).

All psychiatric disorders (previous suicide attempts, anxiety disorders, SUD, psychotic disorder, eating disorders and personality disorders) were significantly associated with both sadness and MDD status, in comparison to controls (**Table 2**).

Compared with participants with MDD, those with sadness were significantly less likely to be diagnosed with various psychiatric disorder, including previous suicide attempts (OR=1.55; 95% IC [1.31-1.83]), anxiety disorders (OR=1.84; 95% IC [1.69-2.01]), SUD

(OR=1.33; 95% IC [1.22-1.46]), eating disorders (OR=1.42; 95% IC [1.11-1.81]) and personality disorders (OR=1.43; 95% IC [1.29-1.59]) (**Table 2**).

Validity of sadness as a marker of depression

Sadness demonstrated a very high sensitivity (SE = 99.6%), with a good specificity (SP = 83.8%) for MDD.

Sadness had a lower sensitivity for other disorders (35.1% for anxiety disorders, 20.7% for substance use disorders, 42.0% for personality disorders, 37.1% for psychotic disorders and 42.6% for eating disorders). The specificity of sadness was also high for all psychiatric disorders assessed: 86.6% for anxiety disorders, 86.7% for substance use disorders, 86.1% for personality disorders, 84.2% for psychotic disorders and 84.1% for eating disorders (Table S1).

DISCUSSION

In an independent sample representative of the general US population, we replicated our previous findings on the continuous nature of sadness. Sadness was frequent both in the general population and in participants with MDD. Its prevalence was 34.3% in the whole sample, ranging from a low 12.6% of non-MDD participants to a high 99% in participants with MDD. We also confirmed that participants with sadness without MDD and those with MDD shared the same sociodemographic correlates: woman gender, never-married and separated marital status, low- and medium-income level, and being US born.

In the same way, as in our previous study in French population sample, we confirmed a positive association between sadness and various psychiatric disorders. In this study, we had a broader assessment of psychiatric disorders, as cannabis use disorder, eating disorders and personality disorders. They were all associated with sadness. Of note, these associations

remained significant after adjustments for sociodemographic variables. The rates of psychiatric disorders in participants with sadness without MDD were higher than controls, but lower than that observed in participants with MDD. Thus, sadness appears as an intermediate state between mental well-being and MDD, validating the symptom severity continuum hypothesis (Ayuso-Mateos et al., 2010).

The prevalence of sadness was comparable in this US sample to the prevalence found in our previous European study (Tebeka et al., 2018). Moreover, the sociodemographic correlates of sadness found in this study, in particular women gender, education level, marital status and incomes, were similar to those found in previous studies concerning depressive symptoms (Moreno-Küstner et al., 2016; Schomerus et al., 2013).

At first glance, migration status exhibit discrepant results between US and French sample. Being born in the U.S was associated with sadness in the sample, while an inverse association between migratory status (first, second and third generations separated or pooled) and sadness was found in the French sample. Immigration in Europe is usually associated with poorer health conditions, specially psychiatric disorders (Bourque et al., 2011; Mindlis and Boffetta, 2017; Rolland et al., 2017). However, U.S studies describe an "immigrant paradox'": immigrants have better health outcomes than non-migrants. This has been particularly described for many psychiatric disorder, specially mood, anxiety and psychotic disorders (Oh et al., 2015; Salas-Wright et al., 2018, 2014).

With sensitivity about 99%, sadness is a relevant symptom to screen MDD. Sadness is the most common symptom for any given depressive episode. Over a life course in which a patient may have multiple episodes of depression, the probability of sadness during at least one episode is very high. Whereas we found a good specificity for sadness in MDD (83.8%), sadness is also a symptom significantly associated with other psychiatric disorders (anxiety, post-traumatic stress, eating, and personality disorders). **Thus, the specificity of sadness was**

also high for other psychiatric disorders (anxiety, substance use, personality, psychotic and eating disorders). These results suggest that sadness is not only a prodrome and atrisk state of MDD but may be a symptom of a transdiagnostic distress process. This hypothesis needs to be confirmed in prospective studies and might be the marker of a broader process of psychological distress, as well as a good screening marker of at-risk state and mental suffering

Some limits of this work should be kept in mind. On the one hand, a memory bias can affect the retrospective assessment of sadness over the entire life. Moreover, we did not compare bipolar disorders in our MDD groups because of the definition of this group, which exclude BD. In addition, the design of a cross-sectional study narrows the scope of our conclusions.

This replication study based on a representative of the U.S. population makes our first results more robust. It confirms the importance of considering the sadness symptom as an atrisk state. This simple assessment could be considered for early intervention to identify at-risk state, with a good specificity for MDD. These results consolidate the idea of a depressive continuum ranging from normal sadness to severe MDD. Further studies should assess if other symptoms, including anhedonia, also fit into a depressive continuum.

DECLARATION OF INTEREST

Authors have no conflicts of interest related to this work

DATA AVAILABILITY

This manuscript was prepared using a limited access data setobtained from the NIAAA and does not reflect the opinions or viewsof the NIAAA or the U.S. Government. Research data are not shared.

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TABLE 1. Sociodemographic characteristics in individuals with sadness without major depressive disorder (MDD), individuals with MDD and control subjects (no sadness, no MDD) – odd ratio (OR) adjusted for all other sociodemographic characteristics

	Control subjects (no sadness, no MDD)	Participants with sadness without MDD	Participants with MDD	sadness v	ipants with vithout MDD vs ontrols	Participants with sadness without MDD vs Participants with MDD		Participants with MDD vs controls	
	N= 23,827	N= 4,593	N= 7,889				0 = 1/ 0/=		
	% (SE)	% (SE)	% (SE)	OR	95% CI	OR	95% CI	OR	95% CI
Age									
18-29y	22.47 (0.45)	18.49 (0.68)	21.10 (0.59)	Ref		Ref		Ref	
30-44y	25.51 (0.35)	24.33 (0.85)	27.21 (0.64)	1.33	1.17-1.50	0.99	0.86-1.13	1.32	1.19-1.46
45-64y	32.84 (0.37)	39.05 (0.87)	39.30 (0.64)	1.59	1.40-1.80	0.84	0.73-0.97	1.37	1.25-1.50
65y+	19.18 (0.48)	18.13 (0.69)	12.39 (0.47)	1.11	0.96 -1.30	0.54	0.46-0.65	0.61	0.53-0.70
Sex									
Men	53.56 (0.37)	42.54 (0.83)	34.83 (0.67)	Ref		Ref			
Women	46.44 (0.37)	57.46 (0.83)	65.17 (0.67)	1.42	1.32-1.54	1.41	1.28-1.55	2.03	1.89-2.17
Education level									
Less than high	13.54 (0.46)	12.76 (0.73)	11.56 (0.53)	Ref		Ref		Ref	
school		, ,	, ,						
High school	26.10 (0.56)	26.63 (0.83)	24.32 (0.78)	1.07	0.93-1.23	0.91	0.78-1.07	0.96	0.85-1.08
Some college or	60.36 (0.78)	60.61 (1.07)	64.12 (0.97)	1.13	1.00-1.29	0.99	0.85-1.16	1.10	0.99-1.21
higher	(((((((((((((((((((((1111)						
Marital status									
Married/ Common-	60.27 (0.57)	54.36 (1.01)	52.47 (0.75)	Ref		Ref		Ref	
law									
Single / never	22.71 (0.49)	21.22 (0.83)	5.99 (0.33)	1.34	1.14-1.57	1.09	0.91-1.30	1.46	1.25-1.71
married									
Separated /	11.54 (0.25)	17.33 (0.62)	18.85 (0.45)	1.53	1.38-1.68	1.16	1.04-1.30	1.75	1.63-1.88
Divorced									
Widower	5.49 (0.19)	7.08 (0.41)	22.69 (0.64)	1.13	1.01-1.26	1.08	0.94-1.24	1.21	1.10-1.33
Personal incomes									
0 – 19,999 \$	41.98 (0.59)	48.32 (1.07)	49.13 (0.80)	Ref		Ref		Ref	
20,000 – 34,999\$	21.07 (0.35)	21.18 (0.77)	19.01 (0.52)	0.85	0.77-0.94	0.90	0.80-1.02	0.77	0.70-0.84

35,000 – 69,999\$	23.25 (0.38)	19.59 (0.80)	21.88 (0.59)	0.68	0.60-0.77	1.11	0.97-1.28	0.75	0.68-0.82
> 70,000\$	13.70 (0.43)	10.91 (0.64)	9.98 (0.59)	0.66	0.57-0.76	0.94	0.79-1.12	0.60	0.52-0.69
Race/ethnicity									
White	63.42 (0.82)	67.08 (1.15)	74.00 (0.78)	Ref		Ref		Ref	
Black	12.68 (0.71)	12.25 (0.83)	8.84 (0.53)	0.84	0.76-0.93	0.60	0.54-0.68	0.50	0.46-0.55
Native American	1.26 (0.12)	2.15 (0.29)	2.13 (0.22)	1.44	1.06-1.95	0.82	0.60-1.11	1.19	0.94-1.51
Asian	6.67 (0.56)	4.55 (0.46)	3.57 (0.39)	0.77	0.62-0.97	0.78	0.63-0.95	0.62	0.52-0.74
Hispanic	15.97 (0.74)	13.97 (0.87)	11.47 (0.63)	0.92	0.81-1.04	0.76	0.67-0.86	0.69	0.62-0.77
Region of residence									
Northwest	17.84 (0.62)	18.70 (1.15)	19.19 (0.74)	Ref		Ref		Ref	
Midwest	21.27 (0.49)	22.21 (0.76)	21.67 (0.98)	0.95	0.79-1.15	0.90	0.75-1.07	0.86	0.73-1.01
South	37.58 (0.93)	35.93 (1.18)	36.12 (1.31)	0.89	0.73-1.07	1.00	0.85-1.17	0.88	0.77-1.01
West	23.31 (0.85)	23.16 (1.13)	23.01 (1.33)	0.97	0.80-1.17	0.98	0.83-1.16	0.96	0.83-1.10
Urbanicity									
Urban	78.94 (1.52)	78.63 (1.64)	78.23 (1.91)	Ref		Ref		Ref	
Rural	21.06 (1.52)	21.37 (1.64)	21.77 (1.91)	0.93	0.84-1.04	0.96	0.81-1.12	0.90	0.79-1.03
Nativity	_								
U.S. born	81.56 (0.58)	86.29 (0.77)	90.25 (0.51)	Ref		Ref		Ref	
Foreign born	18.44 (0.58)	13.71 (0.77)	9.75 (0.51)	0.74	0.64-0.87	0.74	0.63-0.89	0.55	0.49-0.62

Abbreviations: SE; Standard Error; OR, odds ratio; CI, confidence interval; MDD, Major Depressive Disorder

TABLE 2. Prevalence and odds ratio (OR) of psychiatric disorders comparing individuals with sadness without depressive disorders (MDD) to those with MDD, and control subjects adjusted for sociodemographic characteristics

	Control subjects (no sadness, no MDD)	Participants with sadness without MDD	Participants with MDD	Participants with sadness without MDD vs controls		Participants with sadness without MDD vs Participants with MDD		Participants with MDD vs controls	
	N= 23,827	N= 4,593	N= 7,889						
	% (SE)	% (SE)	% (SE)	OR	95% CI	OR	95% CI	OR	95% CI
Suicide attempt	1.34 (0.09)	9.11 (0.58)	14.32 (0.54)	6.45	5.38-7.73	1.55	1.31-1.83	10.26	8.73-12.04
Any Substance Use disorder	37.02 (0.58)	49.50 (0.96)	57.90 (0.75)	1.75	1.61-1.90	1.33	1.22-1.46	2.36	2.20-2.53
Alcohol use disorder	24.38 (0.51)	32.76 (0.86)	41.15 (0.85)	1.63	1.49-1.80	1.37	1.23-1.53	2.27	2.10-2.45
Tobacco use disorder	23.00 (0.50)	34.07 (0.87)	38.93 (0.82)	1.71	1.57-1.85	1.18	1.07-1.29	2.05	1.90-2.21
Cannabis use disorder	4.35 (0.21)	7.88 (0.47)	11.11 (0.55)	1.96	1.69-2.27	1.43	1.21-1.68	2.83	2.46-3.25
Bipolar disorder	1.25 (0.10)	16.16 (0.62)	0 (0)	15.88	13.32-18.93	-		-	
Any anxiety disorder	10.11 (0.29)	28.08 (0.67)	43.37 (0.77)	3.14	2.87-3.45	1.84	1.69-2.01	5.81	5.31-6.36
Panic disorder	1.98 (0.13)	8.74 (0.45)	12.97 (0.54)	4.06	3.36-4.90	1.39	1.20-1.62	5.69	4.82-6.71
Social anxiety disorder	1.61 (0.12)	5.69 (0.36)	8.79 (0.42)	3.37	2.80-4.06	1.51	1.29-1.76	5.05	4.31-5.91
Generalized anxiety disorder	2.66 (0.13)	11.92 (0.53)	20.38 (0.57)	4.45	3.85-5.15	1.82	1.61-2.06	8.14	7.06-9.40
Post-traumatic stress disorder	2.03 (0.12)	11.22 (0.55)	15.52 (0.62)	5.40	4.64-6.29	1.33	1.16-1.53	7.50	6.54-8.61
Any eating disorder	0.69 (0.06)	2.67 (0.29)	4.32 (0.24)	3.44	2.68-4.41	1.42	1.11-1.81	4.84	3.96-5.93
Anorexia nervosa	0.37 (0.05)	1.27 (0.24)	1.86 (0.18)	2.93	1.87-4.58	1.18	0.78-1.77	3.36	2.60-4.35
Bulimia nervosa	0.07 (0.02)	0.31 (0.09)	0.71 (0.14)	4.08	1.71-9.76	1.90	0.92-3.93	6.21	3.20-12.06
Binge eating disorder	0.26 (0.04)	1.32 (0.18)	1.95 (0.17)	4.55	3.18-6.52	1.37	0.96-1.96	6.65	4.78-9.24
Any personality disorder	5.55 (0.22)	20.68 (0.79)	27.44 (0.72)	4.55	4.03-5.14	1.43	1.29-1.59	6.67	6.00-7.42
Antisocial	1.41 (0.09)	4.61 (0.36)	4.88 (0.33)	3.53	2.90-4.30	1.07	0.87-1.32	4.00	3.34-4.78
Borderline	3.93 (0.17)	17.87 (0.74)	24.21 (0.65)	5.29	4.67-5.98	1.43	1.28-1.60	7.74	6.95-8.63
Schizotypal	1.61 (0.11)	9.00 (0.49)	10.05 (0.49)	5.82	4.91-6.89	1.11	0.94-1.31	6.87	5.75-8.20
Psychotic disorder	1.28 (0.15)	4.17 (0.42)	3.75 (0.31)	3.08	2.29-4.13	0.89	0.69-1.15	2.84	2.27-3.55

Abbreviations: SE; Standard Error; OR, odds ratio; CI, confidence interval; PTSD, post-traumatic stress disorder; MDD, Major Depressive Disorder

TABLE S1. Sensitivity and specificity of sadness for psychiatric disorders.

	Sensitivity	Specificity
Major depressive disorder	0.996	0.84
Any anxiety disorder	0.35	0.866
Any substance use disorder	0.21	0.87
Any eating disorder	0.42	0.24
Psychotic disorder	0.37	0.84
Any personality disorder	0.42	0.86