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Longitudinal reciprocal associations between depression, anxiety, and substance use disorders over three decades of life

Introduction

Depressive (DD), anxiety (AD) and substance use disorders (SUD) (i.e., alcohol and drug use disorders) are among the leading causes of disability-adjusted life-years in the age group 25-49 years worldwide, especially in countries with higher socio-demographic index (Vos et al., 2020). Research evidence based on large epidemiological studies showed strong associations between DD, AD and SUD in terms of comorbidity (Lai et al., 2015; Virtanen et al., 2020) with clinical implications for treatment outcomes (Hobbs et al., 2012). Different disorders may co-occur by chance (i.e., without causal linkage) due to selection bias (e.g., higher prevalence of comorbidity in patients seeking care than in the general population) and due to causal associations (Mueser et al., 1998; Torrens et al., 2015).

However, in the scientific literature, there still exists a significant gap in understanding the longitudinal reciprocal associations between these disorders over long periods of time. Few longitudinal studies with at least 10-year follow up have been published. Their findings showed that adolescents with depression and anxiety symptoms are at increased risk for alcohol use disorders into young adulthood (10-year follow up) compared with young adults with low levels of adolescent depression and anxiety symptoms, after adjusting for potential confounding factors (McKenzie et al., 2011). Conversely, long-term concurrent users of cigarette, alcohol, and marijuana were more likely to show generalized AD and DD in adulthood compared with occasional users of alcohol (Brook et al., 2016). Another study (Degenhardt et al., 2013) reported that adolescent cannabis dependence was consistently associated with AD, but not DD, in late young adulthood (at 15-year follow up). Furthermore, in a recent study we showed that frequent cannabis use during adolescence predicted

the occurrence of DD in a 30-year prospective study into middle adulthood (Hengartner et al., 2020). However, none of these studies modelled auto-regressive and cross-lagged effects simultaneously.

The main objective of the present study was to test the longitudinal reciprocal associations between AD, DD and SUD using data from a prospective study of young adults followed up for 30 years. Two previous studies analysed the stability of AD and DD and their comorbidity over time (Merikangas et al., 2003) as well as different disorder trajectories (Paksarian et al., 2016) using data from the Zurich Cohort Study. Based on our previous research and in light of research findings presented above, we expected (1) to observe a certain degree of disorder stability over time (i.e., auto-regressive effects); (2) that DD and AD would predict SUD over time (cross-lagged effects); (3) that SUD would predict DD and AD (cross-lagged effects); and (4) that AD and DD would prospectively predict each other (cross-lagged effects).

Methods

Participants and sampling procedure

The Zurich Study started with a sample of 4547 subjects (m=2201; f=2346) representative of the canton of Zurich in Switzerland, who were screened in 1978 with the Symptom Checklist 90-Revised (SCL-90-R) (Derogatis, 1977) when males were 19 and females 20 years old. Male and female participants were sampled with different approaches. In Switzerland, every man of Swiss nationality must undertake a military screening test at the age of 19. With the consent of the military authorities, but independently of their screening procedure, we randomly screened 50% of all the male conscripts in this age group from the canton of Zurich. The refusal rate was <1%. Female participants were identified from the complete electoral register of the canton of Zurich (which includes only people of Swiss nationality, as immigrants have no voting rights). Again, 50% of the women were randomly selected and received questionnaires by mail; 75% responded.

To increase the probability of the development of psychiatric syndromes, a sub-sample of 591 subjects was selected for interview, with two-thirds consisting of high scorers (defined by the 85th percentile or higher of the global severity index [GSI] of the SCL-90) and a random sample of those with scores below the 85th percentile. Such a two-phase procedure, consisting of initial screening and subsequent interview with a stratified high-risk sub-sample, is a recommended approach in epidemiologic research (Burdett et al., 2016; Dunn et al., 1999). Altogether, seven interview waves were conducted: in 1979 (m=292; f=299), 1981 (m=220; f=236), 1986 (m=225; f=232), 1988 (m=200; f=224), 1993 (m=192; f=215), 1999 (m=162; f=205), and 2008 (m=144; f=191). The corresponding attrition rates were 0%, 22.8%, 22.7%, 28.3%, 31.1%, 37.9%, and 43.3%. In short, after 30 years, more than half of all interviewees continued to participate in the study.

The initial allocation to the two groups, above and below the 85th percentile of the GSI, remained stable throughout the study; the dropouts were more frequent among the extremely high and extremely low GSI scorers (Eich et al., 2003). We repeated the attrition analyses after the most recent interview. There we found, in addition, no significant difference between those who had left the study and those who remained with regard to socio-economic status and education level as measured at the study outset, or in their initial psychopathological impairment according to the nine SCL-90-R subscales. However, there was a moderate gender bias, with more dropouts among men (OR=1.82; 95% CI=1.31-2.53; p<0.001).

Instruments and measures

Interviews were conducted using the "Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology" (SPIKE) (Angst et al., 1984). This semi-structured interview, developed for epidemiological surveys in psychiatric research, collects data on socio-demography, psychopathology, substance use, medication, health services use, impairment, and social activity. Its reliability and validity are good and have been reported elsewhere

(Angst et al., 2005). Unlike other diagnostic interviews (e.g. CIDI, SCID), which focus on DSM diagnoses using a top-down approach with multiple cut-offs, the SPIKE interview uses a bottom-up approach that assesses the past-year presence of about 14 somatic and 15 psychiatric syndromes and checks symptoms, duration, frequency and recency of episodes, distress, impairment and treatment. All diagnoses assessed the recent 12-month prevalence and were repeatedly assessed at each measurement occasion, i.e. in 1979, 1981, 1986, 1988, 1993, 1999 and finally in 2008. For further information, see Angst et al. (2016).

DD was diagnosed according to DSM-III-R criteria for a major depressive episode; AD diagnosis followed DSM-III criteria for generalized AD and panic disorder and the DSM-III-R criteria for phobias (agoraphobia, social phobia, and specific phobia) and for obsessive-compulsive disorder. Finally, SUD comprised alcohol abuse and dependence as well as drug abuse and dependence, diagnosed according to DSM-IV criteria at each assessment wave.

A number of covariates assessed by the SPIKE were considered, including gender, cold family climate, a low level of social support, a low education level, and low parental income. The participants rated the family climate at age 20/21 according to four proposed descriptors: warm (and cordial), neutral, tense, and broken. Because the last category was very rarely endorsed, "tense" and "broken" were combined into a new category labelled cold. Social support at age 20/21 was operationalized based on self-reported instrumental and socio-affective help received from family members, friends, and partners. Parental income at age 20/21 was rated as low if it was under 3000 Swiss Francs per household. Education level at age 20/21 was rated as low if the highest level of attainment was primary school or lower.

Ethics

The Zurich Cohort Study was approved by the ethics committee of the canton of Zurich (KEK) as fulfilling all the relevant ethical, legal and data privacy protection requirements and is in accordance with the declaration of Helsinki of the World Medical Association. All participants gave

their written informed consent. The strict data protection requirements under Swiss legislation effective at the time of the inception of the study prevent us from making the data freely available. However, full analysis scripts and original data outputs for the purpose of validating and reproducing the results can be obtained from the first author upon request.

Statistical Analysis

Descriptive statistics and gender differences in the variables of interest were tested using Chi-squared tests using SPSS 25.0 statistical software package for Windows. The Chi-squared test is a significance test ordinarily used to explore the association between nominal variables. For the Chi-squared test, the Cramer's *V* is the most used test of effect size and it is interpreted in the same way as the correlation coefficient (McHugh, 2013). A series of Bayesian Structural Equation Models (BSEM) were fitted to explore issues of causal direction between AD, DD and SUD. For it we conducted an autoregressive cross-lagged path analysis. Specifically, baseline correlations and reciprocal longitudinal predictions between the variable of interest were tested in Model 1, and gender was added as covariate in Model 2 (Figure 1a and 1b). All BSEM were conducted with SPSS Amos Version 23 using default priors for all parameters (Arbuckle, 2014; IBM, 2020).

BSEM analyses were conducted on both the total (n= 591) and completer subsample (n= 252). Estimation was based on independent Markov Chain Monte Carlo (MCMC) algorithm with 50,000 iterations (of which the first 500 were discarded as the burn-in phase). MCMC algorithm is most effective when the acceptance rate is between .2 and .5 (IBM, 2018). Model convergence was monitored by potential scale reduction with values <1.10 and <1.002 suggesting convergence and conservative convergence, respectively (Gelman et al., 2004). Model fit was evaluated using posterior predictive *p*-value (PPp). If the model fit is good, the replicated data generated under the model looks like the observed data or, put differently, the observed data looks plausible under the posterior predictive distribution (Gelman et al., 2013). The fit of a model to data is checked drawing simulated

values from the joint posterior predictive distribution of replicated data and comparing these samples to the observed data with discrepancies between the simulations and the data indicating potential failing of the model (Gelman et al., 2013). The PPp is the probability that the replicated data could be more extreme than the observed data (Gelman et al., 2013). PPp values around 0.5 indicate an excellent-fitting model while an extreme value (i.e., PPp < 0.05) indicates misspecification and poor fit (Cain and Zhang, 2019; Muthén and Asparouhov, 2012). The Bayesian credible interval is the most used measures of uncertainty in Bayesian inference to summarize the posterior distribution (Hespanhol et al., 2019). It shows a range within which most of the distribution lies (Box and Tiao, 1973). This type of interval has two properties: the density for every point inside the interval is greater than that for every point outside; for a given probability content the interval should be as short as possible (Box and Tiao, 1973). Consequently, it is also called *highest posterior density interval*. For more details see Box and Tiao (1973) and Gelman et al. (2013).As part of a sensitivity analysis, we repeated BSEM analyses using MPLUS version 7 (Muthén and Muthén, 2015). In MPLUS, a 95% confidence interval is produced for the difference in fit statistic for the real and replicated data. PPp value around 0.5 and zero falling close to the middle of the confidence interval indicate an excellent-fitting model (Muthén and Asparouhov, 2012). Finally, the Bayesian estimation approach in both Amos and MPLUS is similar to Full-Information Maximum Likelihood (FIML) in dealing with missing data. In Amos, Bayesian estimation uses maximum likelihood-based parameter estimates of observed data assuming that parameter values are estimated, not known (Arbuckle, 2014). With Bayesian analysis in MPLUS, modelling with missing data gives asymptotically the same results as maximum-likelihood estimation under missing at random assumption (Muthén and Muthén, 2015).

[insert Figure 1a, 1b about here]

Results

Missing value analysis

Chi-squared test were used to test significant differences between the subsamples of participants with and without missing data on each occasion, that is, differences between participants excluded and included from the completer subsample. Differences were tested for gender (male vs. female), cold family climate (yes vs. no), low level of social support (yes vs. no), low education level (yes vs. no), and low parental income (yes vs. no) as well as for AD, DD and SUD as assessed in 1979. Findings showed that participation on each occasion was associated with gender ($\chi2$= 14.02, df= 1, p< .001, Cramer's V= 0.154) and SUD ($\chi2$= 10.09, df= 1, p< .01, Cramer's V= 0.131). Male gender (65.1%, standardized residual= 1.7) compared to female (49.8%, standardized residual= -1.7) predicted missing data at least on one occasion. Moreover, diagnosis of SUD (8%, Stand. Residual= 2.0) compared to no SUD (2%, Stand. Residual= - 2.3) in 1979 predicted missing data at least on one evaluation. The other factors were not related to missingness. These results suggest that BSEM analyses could benefit from multiple imputation. Restricting the analysis to the completer subsample could produce biased results since there are systematic differences between participants with missing data and those with complete data (Madley-Dowd et al., 2019; Nguyen et al., 2017). Therefore, the inclusion of those variables in the imputation model should improve the reliability of findings obtained. Despite that, for the sake of completeness we also report findings of BSEM for the completer subsample.

Descriptive statistics

The 12-month prevalence of every disorder for each time point in the total and completer subsample is presented in Table 1.

[insert Table 1 about here]

Chi-squared tests showed gender differences in the total sample on each occasion. Table 2 displays the significantly higher prevalence of AD in females compared to males. By contrast, males showed higher prevalence of SUD than females on each occasion. DD were more prevalent among females than in males mainly in young adulthood (i.e., the first three measurement occasions).

[insert Table 2 about here]

Longitudinal autoregressive cross-lagged path analysis

Next, we conducted BSEM with MCMC to compare two models exploring the longitudinal relationships between AD, SUD, and DD from 1979 to 2008. Model fit indices of the two models for the total sample and the completer subsample using SPSS Amos are shown in Table 3. The results indicate that model 2 had the best fit to our data for both the total and the completer subsample (see also Table 1S, Supplementary material, for a summary of model fit indices using MPLUS).

[insert Table 3 about here]

Table 4 and Figure 2 present the results of the BSEM model 2 in the total sample and the subsample with complete data at each measurement occasion (see also Table 2S, Supplementary material). AD (except during young adulthood) and SUD strongly predicted themselves over the entire time period (autoregressive paths). DD recurrently predicted itself despite not consistently over time (i.e., at two-, seven-, and nine-year follow ups).

Both DD and AD predicted SUD during young adulthood (cross-lagged paths). In particular, AD negatively predicted SUD at two years follow up, while DD positively predicted it. DD predicted subsequent AD in adulthood, whereas AD did not predict subsequent DD. Finally, DD in 1986 predicted substance use disorder in 1988 which in turn predicted DD in 1993.

Female gender was consistently associated with DD and AD over time. By contrast, male gender was associated with SUD only in young adulthood.

The results of the BSEM models performed in MPLUS yielded comparable results (Table 3S and Figure 1S in supplementary material).

[insert Figure 2a, 2b about here]

[insert Table 4 about here]

Discussion

The aim of this study was to examine the longitudinal associations (i.e. temporal dynamics) between DD, AD and SUD in a cohort of adults followed over 30 years. Based on longitudinal autoregressive cross-lagged path analyses we found that SUD strongly predict itself over subsequent measurement occasions from young adulthood (age 20/21) through middle adulthood (age 49/50). AD predicted the subsequent occurrence of AD starting at age 27/28 while DD predicted itself at 2- (from age 20/21 to 22/23), 7- (from 27/28 to 34/35) and 9-year (from 40/41 to 49/50) follow ups. That is, DD showed more stability as age increased. These findings were in line with those of previous studies (Essau et al., 2018; McCabe et al., 2018; Merikangas et al., 2003; Seeley et al., 2019; Steinert et al., 2014; Wells et al., 2006) and supported the first study hypothesis of disorders stability and/or recurrence over time possibly due to socio-economic risk factors (Harvey et al., 2018; Lorant et al., 2007; Lund et al., 2018).

In addition to the auto-regressive paths, we detected also several cross-lagged associations. To our knowledge this study was the first to show longitudinal reciprocal associations between DD and SUD in young and middle adulthood over a period of 30 years. DD at age 20/21, 27/28 and 29/30 predicted SUD at age 22/23, 29/30 and 34/35, respectively. Conversely, SUD at age 20/21 and 29/30 predicted DD at age 22/23 and 34/35, respectively. These results expand knowledge from previous studies with

short- (Haynes et al., 2005; Li et al., 2020; Wolitzky-Taylor et al., 2012; Worley et al., 2012) and long-term (Brook et al., 2016; McKenzie et al., 2011) follow-up. Therefore, the results support our second and third hypotheses (except for the relationship between AD and SUD).

AD negatively predicted SUD in young adulthood while SUD did not predict subsequent AD. Previous studies (Brook et al., 2016; Degenhardt et al., 2013; Dyer et al., 2019; Haynes et al., 2005; Kushner, 1999; McKenzie et al., 2011; Schleider et al., 2019; Wolitzky-Taylor et al., 2012) that mainly focused on the relationships between AD and alcohol use disorder reported mixed findings. Accordingly, we found no evidence of a clear and consistent pattern of association between AD and SUD over a long time period using both AMOS and MPLUS. In consequence, it seems that the associations between AD and SUD in young adulthood were perhaps spurious chance findings or methodological artefacts. Furthermore, controlling for the effect of DD may have disentangled the previously reported associations between AD and SUD suggesting that those associations are largely non-casual (Goodwin et al., 2004). However, our study did not distinguish among the various AD and SUD diagnoses, instead it focused on the analysis of general disorder categories. This could have masked specific associations (e.g., positive associations between generalised anxiety disorder and alcohol use disorders). Further research is needed to clarify this aspect.

DD predicted the subsequent occurrence of AD at two occasions in adulthood, but AD did not predict the subsequent occurrence of DD. These findings partially confirmed our fourth hypothesis. A recent meta-analytic study (Jacobson and Newman, 2017) showed that DD predicted AD over time and vice versa. However, only half of the included studies controlled for baseline depression or anxiety. Moreover, only one study examined bidirectional longitudinal relationships between the disorders (Merikangas et al., 2003). Thus, those findings on bidirectional associations should be interpreted considering these limitations. Our results indicate that DD often precede AD, but AD could also be a secondary manifestation of DD. Jacobson and Newman (2017) discussed different mechanisms by which DD may predict AD, such as, increasing fear and avoidance, social rejection, and feelings of worthlessness. Future longitudinal studies should explore mediators and moderators

of this relationship. Finally, in line with previous studies (Asher and Aderka, 2018; Brand et al., 2019; Erol and Karpyak, 2015; Salk et al., 2017; White, 2020), female gender was associated with DD and AD while male gender was associated with SUD (although only in young adulthood). The increased risk of DD and AD in women is multifactorial and could be due to psychobiological factors (e.g., female sex hormones, stress susceptibility) or increased exposure to socio-environmental adversity (e.g., lower economic position, more victimization) (Kuehner, 2017).

The findings of this study have important implications for research and practice. Regarding research, we suggest that future studies should aim at carving the factors that may predispose some individuals to recurrent episodes and longitudinal comorbidity. For instance, it has been shown that about half of all people with depression have one single episode and fully recover thereafter; others, however, have recurrent episodes and a small minority (about 10-15%) even has a chronic course (Steinert et al., 2014; ten Have et al., 2018). The most important research question therefore is why some people fully recover, even flourish after going through emotional disturbances (Rottenberg et al., 2018), while others do not. Our results also have clinical and public health implications highlighting the need for early identification and treatment of DD, AD and SUD. Unfortunately, treatment outcomes are often disappointing (Leichsenring et al., 2019) and increased treatment rates do not seem to reduce the prevalence and burden of common mental disorders on a population level (Jorm et al., 2017; Ormel et al., 2019). A reformation of mental health services, which mostly focus on issuing psychiatric diagnoses and prescribing psychopharmacological drugs while largely neglecting social, economic, and cultural determinants, and a comprehensive socio-environmental approach to prevention and mental health promotion, including affordable housing, safe income, social equality, interpersonal connectedness, and security, therefore appears necessary (Gardner and Kleinman, 2019; Lund et al., 2018; Ormel and VonKorff, 2021; Priebe et al., 2013; van Os et al., 2019; VanderWeele, 2017).

Some limitations should be considered in interpreting our findings. A specific birth cohort participated in the study, possibly limiting generalizability of the findings to other populations (e.g.,

different geographic areas, clinical populations). The 30-year attrition rate was 43% despite such a rate may be expected over long-term follow-up studies. The interview waves for assessment of mental disorders did not occur at regular intervals. Further, the variable time between follow-ups may have missed disorder episodes that started and ended between study waves, which may have influenced the analytic estimates of associations. Despite these limitations, the Zurich Cohort Study is the longest prospective study of a community sample of adults providing valuable knowledge of the longitudinal relationships between DD, AD and SUD.

Conclusions

Longitudinal research on reciprocal associations between DD, AD and SUD has mainly been limited by the short period of time under investigation and the use of self-report measures evaluating symptoms. The present study analysed the course of DD, AD and SUD from young adulthood (age 20/21) through middle adulthood (age 49/50) using repeated assessments with a comprehensive semi-structured psychopathological interview. Findings indicated disorders stability over time as well as bidirectional associations between DD and SUD emphasizing the importance of a comprehensive mental health approach to prevention and treatment of mental disorders. Future studies should take into account the biopsychosocial factors underlying the persistence and remission of mental disorders.

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Table 1 Observed frequency of anxiety, substance use, and depressive disorders on each occasion in the total sample and in the subsample (n= 252) with no missing data

Year	Diagnosis	Total sample	Subsample
		n (%)	n (%)
1979	AD	65 (11)	28 (11.1)

	SUD	32 (5.4)	5 (2)
	DD	44 (7.4)	17 (6.7)
1981	AD	37 (8.1)	22 (8.7)
	SUD	30 (6.6)	12 (4.8)
	DD	44 (9.6)	23 (9.1)
1986	AD	76 (16.6)	43 (17.1)
	SUD	84 (18.4)	40 (15.9)
	DD	47 (10.3)	30 (11.9)
1988	AD	103 (24.3)	58 (23)
	SUD	59 (13.9)	25 (9.9)
	DD	48 (11.3)	25 (9.9)
1993	AD	106 (26)	58 (23)
	SUD	57 (14)	29 (11.5)
	DD	55 (13.5)	27 (10.7)
1999	AD	86 (23.4)	52 (20.6)
	SUD	61 (16.6)	42 (16.7)
	DD	50 (13.6)	38 (15.1)
2008	AD	66 (19.7)	50 (19.8)
	SUD	69 (20.6)	45 (17.9)
	DD	41 (12.2)	34 (13.5)

AD: Anxiety Disorder, *SUD*: Substance Use Disorder, *DD*: Depressive Disorder.
The percentage in the column of total sample refers to the total number of participants for whom data was available on each occasion as reported in the text.

Table 2 Gender differences in the prevalence of disorders on each occasion in the total sample

Diagnosis	Year	Male n (%)	Female n (%)	Chi square tests of independence $\chi 2(1)$	Cramer's *V*
Anxiety disorder					
	1979	20 (6.8)	45 (15.1)	10.15**	0.131
	1981	10 (4.5)	27 (11.4)	7.26**	0.126
	1986	23 (10.2)	53 (22.8)	13.13***	0.169
	1988	36 (18)	67 (29.9)	8.15**	0.139
	1993	43 (22.4)	63 (29.3)	2.51	0.079
	1999	27 (16.7)	59 (28.8)	7.40**	0.142
	2008	22 (15.3)	44 (23)	3.12	0.097
Substance use disorder					
	1979	28 (9.6)	4 (1.3)	19.64***	0.182
	1981	22 (10)	8 (3.4)	8.10**	0.133
	1986	59 (26.2)	25 (10.8)	18.17***	0.199
	1988	46 (23)	13 (5.8)	26.08***	0.248
	1993	39 (20.3)	18 (8.4)	12.01**	0.172
	1999	40 (24.7)	21 (10.2)	13.63***	0.193
	2008	37 (25.7)	32 (16.8)	4.01*	0.109
Depressive disorder					
	1979	12 (4.1)	32 (10.7)	9.32**	0.126
	1981	11 (5)	33 (14)	10.54**	0.152
	1986	12 (5.3)	35 (15.1)	11.78**	0.161
	1988	23 (11.5)	25 (11.2)	0.01	0.005
	1993	20 (10.4)	35 (16.3)	2.98	0.086
	1999	18 (11.1)	32 (15.6)	1.56	0.065
	2008	11 (7.6)	30 (15.7)	4.98*	0.122

* $p < .05$; ** $p < .01$; *** $p < .001$.

Differences in prevalence of diagnosis were calculated according to the total number of participants for whom data was available on each occasion as reported in the text.

Table 3 Summary of model fit indices for the longitudinal causal associations between anxiety, substance use, and depressive disorders for the total sample and completer subsample

Model	Convergence statistic	Acceptance rate	PPp
Model 1, reciprocal longitudinal effects			
Total sample	1.0165	0.41	.40
Subsample	1.0206	0.35	.39
Model 2, reciprocal longitudinal effects, gender as covariate			
Total sample	1.0220	0.34	.43
Subsample	1.0250	0.19	.45

PPp: posterior predictive *p*-value.

Table 4 Results of Bayesian structural equation modelling (model 2) for the total sample (N= 591) and the subsample (n= 252)

Paths	*Model 2* – Total sample		*Model 2* – Subsample	
	Mean (SD)	**95% Credible Intervals**	**Mean (SD)**	**95% Credible Intervals**
AD79 → AD81	.373 (.188)	-.003, .741	2.621 (.980)*	1.097, 4.814
AD79 → SUD81	-.951 (.542)*	-2.232, -.137	-.817 (1.218)	-3.034, 1.815
AD79 → DD81	-.103 (.224)	-.580, .284	4.968 (2.273)*	.798, 8.762
SUD79 → SUD81	1.978 (.692)*	.940, 3.430	1.923 (.970)*	.394, 4.237
SUD79 → AD81	.216 (.292)	-.319, .850	1.842 (.851)*	.581, 3.594
SUD79 → DD81	.588 (.370)*	.016, 1.626	5.196 (2.230)*	1.015, 9.694
DD79 → DD81	.444 (.243)*	.025, .917	.087 (.920)	-1.767, 1.764
DD79 → SUD81	.876 (.513)*	.196, 2.048	.995 (.861)	-.174, 2.897
DD79 → AD81	.144 (.185)	-.223, .516	.629 (.714)	-.788, 1.949
AD81 → AD86	.164 (.143)	-.128, .432	.303 (.221)	-.090, .730
AD81 → SUD86	.322 (.241)	-.091, .921	.675 (.468)*	.112, 1.742
AD81 → DD86	.144 (.158)	-.171, .447	.283 (.215)	-.143, .739
SUD81 → SUD86	.494 (.159)*	.225, .830	.551 (.528)*	.095, 1.929
SUD81 → AD86	.132 (.106)	-.063, .353	-.029 (.134)	-.256, .291
SUD81 → DD86	.141 (.107)	-.051, .368	.088 (.172)	-.184, .531
DD81 → DD86	.156 (.177)	-.199, .520	-.125 (.153)	-.471, .167
DD81 → SUD86	.015 (.218)	-.391, .472	-.075 (.170)	-.470, .217
DD81 → AD86	-.123 (.172)	-.502, .188	-.206 (.211)	-.713, .110
AD86 → AD88	.368 (.115)*	.150, .599	.308 (.144)*	.033, .604
AD86 → SUD88	.038 (.188)	-.323, .430	-.058 (.300)	-.695, .483
AD86 → DD88	.208 (.121)	-.033, .450	.241 (.155)	-.044, .557
SUD86 → SUD88	.978 (.183)*	.622, 1.355	1.531 (.644)*	.635, 2.903
SUD86 → AD88	.079 (.087)	-.084, .267	.172 (.117)	-.005, .441
SUD86 → DD88	.054 (.092)	-.130, .238	.148 (.116)	-.056, .398
DD86 → DD88	.256 (.132)*	.015, .531	.129 (.196)	-.276, .527
DD86 → SUD88	.445 (.205)*	.057, .893	.779 (.446)*	.095, 1.710
DD86 → AD88	.170 (.123)	-.060, .420	.231 (.171)	-.112, .562
AD88 → AD93	.224 (.116)*	.005, .457	.061 (.146)	-.213, .362
AD88 → SUD93	-.029 (.161)	-.362, .289	-.097 (.230)	-.676, .305
AD88 → DD93	-.068 (.142)	-.364, .198	-.576 (.365)	-1.465, .017
SUD88 → SUD93	.704 (.161)*	.425, 1.050	.422 (.145)*	.211, .839
SUD88 → AD93	.066 (.064)	-.058, .196	.009 (.062)	-.119, .138
SUD88 → DD93	.228 (.093)*	.071, .446	.260 (.168)*	.049, .722
DD88 → DD93	.261 (.134)*	.006, .519	.310 (.266)	-.144, .919
DD88 → SUD93	.354 (.194)*	.008, .780	.189 (.198)	-.168, .601
DD88 → AD93	.388 (.128)*	.148, .643	.484 (.167)*	.169, .814
AD93 → AD99	.370 (.111)*	.162, .597	.354 (.167)*	.039, .696

AD93 → SUD99	.038 (.138)	-.241, .298	.300 (.228)	-.085, .814
AD93 → DD99	.128 (.115)	-.093, .368	.171 (.142)	-.114, .443
SUD93 → SUD99	.630 (.154)*	.378, 1.003	1.105 (.264)*	.635, 1.636
SUD93 → AD99	.088 (.096)	-.089, .296	.457 (.219)*	.123, .944
SUD93 → DD99	.113 (.092)	-.068, .291	.152 (.100)	-.032, .377
DD93 → DD99	.216 (.145)	-.067, .505	.040 (.177)	-.239, .499
DD93 → SUD99	.253 (.173)	-.090, .606	-.183 (.335)	-.906, .491
DD93 → AD99	.018 (.159)	-.313, .312	-.277 (.204)	-.662, .140
AD99 → AD08	.485 (.146)*	.225, .790	.300 (.180)	-.013, .698
AD99 → SUD08	.114 (.148)	-.158, .418	.141 (.199)	-.235, .579
AD99 → DD08	-.160 (.151)	-.471, .122	-.187 (.204)	-.651, .168
SUD99 → SUD08	.683 (.176)*	.392, 1.058	.562 (.158)*	.304, .942
SUD99 → AD08	-.016 (.094)	-.207, .175	.027 (.102)	-.171, .239
SUD99 → DD08	.103 (.104)	-.080, .331	.065 (.134)	-.161, .404
DD99 → DD08	.566 (.173)*	.248, .922	.474 (.236)*	.117, 1.065
DD99 → SUD08	-.271 (.183)	-.664, .045	-.362 (.215)	-.787, .053
DD99 → AD08	.354 (.143)*	.085, .663	.336 (.154)*	.039, .641
Gender → AD81	.297 (.244)	-.142, .807	-.713 (.426)	-1.555, .137
Gender → SUD81	.080 (.353)	-.524, .863	.385 (.751)	-.878, 2.241
Gender → DD81	.649 (.348)*	.150, 1.655	-.363 (1.107)	-3.284, 1.445
Gender → AD86	.557 (.241)*	.164, 1.143	.842 (.369)*	.302, 1.677
Gender → SUD86	-.267 (.231)	-.731, .214	-.572 (.339)	-1.323, .103
Gender → DD86	.463 (.225)*	.049, .976	.528 (.313)*	.039, 1.212
Gender → AD88	.107 (.148)	-.181, .398	.282 (.183)	-.076, .642
Gender → SUD88	-.800 (.262)*	-1.370, -.337	-.670 (.369)*	-1.440, -.025
Gender → DD88	-.202 (.166)	-.558, .101	.032 (.215)	-.392, .479
Gender → AD93	.229 (.143)	-.042, .514	.176 (.202)	-.203, .595
Gender → SUD93	.035 (.229)	-.442, .507	-.004 (.264)	-.498, .581
Gender → DD93	.535 (.213)*	.163, .982	1.024 (.610)*	.247, 2.766
Gender → AD99	.303 (.164)*	.003, .662	.892 (.369)*	.346, 1.963
Gender → SUD99	-.230 (.195)	-.602, .178	.011 (.403)	-.627, 1.128
Gender → DD99	.215 (.166)	-.102, .563	.250 (.195)	-.080, .702
Gender → AD08	.033 (.172)	-.313, .368	.159 (.213)	-.249, .589
Gender → SUD08	.103 (.211)	-.268, .556	.158 (.261)	-.327, .710
Gender → DD08	.410 (.216)*	.040, .930	.534 (.289)*	.048, 1.297
Covariances				
AD79 ↔ DD79	.448 (.088)*	.267, .610	.122 (.168)	-.211, .420
AD79 ↔ SUD79	.097 (.121)	-.131, .345	-.666 (.161)*	-.865, -.260
DD79 ↔ SUD79	.045 (.126)	-.198, .293	-.175 (.209)	-.564, .244
Gender ↔ AD79	.327 (.077)*	.171, .476	.433 (.110)*	.197, .633
Gender ↔ DD79	.290 (.088)*	.108, .453	.182 (.146)	-.118, .447
Gender ↔ SUD79	-.509 (.090)*	-.664, -.318	-.112 (.162)	-.387, .222

Mean: estimate posterior mean (averaging across the MCMC samples)*, SD*: standard deviation (likely distance between the posterior mean and the unknown true parameter).

AD: Anxiety Disorder, *DD*: Depressive Disorder, *SUD*: Substance Use Disorder, *Gender*: male= "0", female= "1".

* 95% credible interval does not include zero.

Figures legends

Figure 1 Causal paths tested using Bayesian Structural Equation Models for **(a)** model 1, with no covariate and **(b)** model 2, with gender as a covariate

Figure 2 Longitudinal autoregressive and cross-lagged paths between anxiety, substance use, and depressive disorders tested with Bayesian structural equation model using SPSS Amos **(a)** for the total sample (n=591) and **(b)** for the completer subsample (n=252)