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Antisocial Characteristics and Early Life Adversity Predict Substance Use Disorders in Young Adults: The Oklahoma Family Health Patterns Project

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Abstract

Objective: A family history (FH+) of alcoholism or other substance use disorders (SUD) is an SUD risk factor in the offspring, although not all FH+ develop an SUD. To explore SUD predictors, we examined the joint impact of antisocial characteristics and exposure to early life adversity (ELA) among physically healthy young adults.

Methods: We tested 727 persons, 18-30 years of age, diagnosed with (N = 220) and without (N = 507)an SUD to identify the strongest predictors, including: (a) a family history of SUD (FH+), (b) manifestation of antisocial tendencies using the Socialization scale of the California Personality Inventory (CPI-So), and (c) exposure to ELA,(d) along with symptoms of depression.

Results: Recursive partitioning for SUD showed that antisocial CPI-So scores were the best single predictor of SUD status, correctly classifying 68% of the sample. CPI-So scores were progressively more antisocial in persons who had an SUD, were FH+, and had greater ELA (all *ps* ≤ .0002). Principal components analysis found that CPI-So items comprising *Home Life and Family Relationships* along with *Impulsivity and Norm Violation* accounted for most of the variance in SUD status.

Conclusion: Antisocial characteristics predicted SUD status in adulthood. FH+ persons are prone to antisocial characteristics and they are frequently exposed to ELA, which in turn may foster manifestation of an externalizing phenotype. Future studies on FH+ interactions with ELA exposure are called for in studies of SUD, focusing on social connectedness and disinhibition as two risk-prone behavioral phenotypes.

ABBREVIATIONS

ANOVA: Analysis of Variance; BDI: Beck Depression Inventory; CDIS-IV: Computerized Diagnostic Interview Schedule for DSM-IV; CPI-So: California Personality Inventory Socialization Scale; DSM-IV: Diagnostic and Statistical Manual of The Mental Disorders, 4th Edition; ELA: Early Life Adversity; FH+: Having A Family History of Alcohol or Other Substance Use Disorder; FH-RDC: Family History Research Diagnostic Criteria; OFHP: Oklahoma Family Health Patterns Project; PCA: Principal Components Analysis; SUD: Alcohol or Other Substance Use Disorder

INTRODUCTION

The Oklahoma Family Health Patterns project (OFHP) is a study of risk factors for alcohol and other substance use disorders (SUD) in young adults with a parental history of SUD (FH+). Risk factors in FH+ represent an unknown combination of genetic and environmental influences. Genetic factors are estimated to account for about 40% of the lifetime prevalence of alcoholism [1-3], with a smaller impact of family environment [4]. However, many FH+ never develop an SUD, and although the determining factors are not fully understood [5], it appears that SUD outcomes depend on expression of a heritable, risk-prone, behavioral phenotype [6-8], that is vulnerable to childhood maltreatment [9], and that contributes further to risk for an SUD [10-14].

FH+ adolescents and young adults commonly display a pattern of disinhibitory behavior, variously termed "behavioral under control" [15,16] or "neurobehavioral disinhibition" [17,18] consistent with the frequent comorbidity of externalizing disorders and risk for SUD. In similar fashion, others have

emphasized both disinhibitory tendencies and low adherence to norms as predicting poor SUD outcomes under the term "social deviance proneness" [19]. In contrast persons who are high in "conscientiousness" have better health outcomes including fewer SUDs [6]. Examination of externalizing characteristics in FH+, regardless of SUD status, reveals subfactors including antisocial tendencies, impulsivity, and sensation seeking along with externalizing psychopathology [20,21] that contribute to risky drinking practices. Key questions surround the joint contributions of genetic factors and environment to manifestation of these risk-prone phenotypes. Twin and adoption studies show that SUD and the contributing characteristic of social deviance have a degree of coinheritance [4,8,22,23], and they appear to contribute additively to SUD risk [24]. However, twin studies strongly suggest a minimal environmental impact in persons with no genetic background and a larger impact in persons from SUD-positive families [4,9], indicative of a gene-by-environment interaction.

In prior work on the OFHP cohort, we have observed that nonabusing FH+ persons have much lower (i.e., antisocial) average scores on the California Personality Inventory Socialization scale (CPI-So) [25,26] than do FH–, and these scores are progressively lower in subjects with a greater number of alcoholic first degree relatives, suggesting a genetic diathesis but leaving unresolved the impact of family environment. In addition to presumed genetic contributors, childhood maltreatment is recognized as an environmental contributor to these same antisocial characteristics and risky behavioral tendencies [27-29], and our FH+ subjects report substantially elevated exposure to early life adversity (ELA) that in turn contributes to increased impulsivity and mood instability [30], and to initiation of drinking at an early age [26,30,31]. Consistent with these findings, mood instability has been associated with risk for substance abuse [15]. In studies of brain function, FH+ children show a clustering of temperamental, behavioral, and biochemical changes that suggest a possible alteration in the functioning of the brain's limbic system that may be seen in emotionally or motivationally relevant situations [1,17,32].

Published research from the OFHP to date has been confined to those subjects that were free of an SUD history. The present study extends this work to a broader sample of persons who met diagnostic criteria for an SUD during screening. The goal of the current analysis was to evaluate a range of inherited and environmental predictors of SUD status,focusing on:(a) being FH+ for SUD, (b) manifesting antisocial tendencies, (c) level of ELA exposure, and(d) symptoms of depression as a manifestation of mood instability [33]. In doing so, we carried out two analyses. The first used a hypothesis-free, machine-learning search algorithm (Bootstrap Forest recursive partitioning)[34]to identify the single measure among these four that best predicted SUD status in our sample. The second analysis dissected the results of the first analysis to more fully understand the characteristics most predictive of SUD and to examine relationships among these SUD predictors.

MATERIALS AND METHODS

Participants

We tested data from 727 physically healthy young adults recruited from the local community who were18-30 years of age and completed screening for the OFHP (Table 1). All participants signed a consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center in Oklahoma City, OK and were paid for participating.

Screening, Inclusion and Exclusion criteria

Subjects were recruited using advertisements in local newspapers, flyers posted in locations frequented by persons of the desired age range including college campuses, direct contact via campus job fairs and student activities, and electronic media including Craig's List and campus list servers directed to students and staff. This multipronged approach to subject recruitment is preferable to a single source of volunteers, such as students or campus employees, and is superior to random telephone dialing in terms of attracting the needed numbers of volunteers [35]. Subjects were screened by telephone to ensure general conformity with entrance criteria followed by a laboratory visit for further evaluation. Physical health was assessed through a medical history checklist and self-report of current good health. Psychiatric history was assessed using the computerized version of the Diagnostic Interview Schedule updated for DSM-IV diagnoses (C-DIS-IV) [36], administered by a trained assistant under the supervision of a licensed clinical psychologist.

Inclusion criteria

Current good physical health and no use of CNS-acting medications, history of neurological impairment or diabetes mellitus. Normal intelligence based on Shipley Institute of Living verbal scale score ≥ 20 [37]. Having been raised by at least one biological parent and being in contact with them.

Exclusions

Suspected maternal alcoholism during subject's gestation; inability of subject or parent to provide credible report of family alcohol use patterns for two generations; history of Axis I disorder except past depression or abuse of alcohol or drugs (all absent> 60 days).

Procedures

We conducted an exploratory retrospective analysis of data from the OFHP data set. The first analysis consisted of a decision tree recursive partitioning of the data set with the goal of identifying the single variable that best discriminated SUD positive from SUD negative subgroups. We next conducted a principle components analysis to refine the results of the first analysis. All data collection procedures are described elsewhere [30,38,39].

Analytic variables

SUD status: A personal history of alcohol or any other substance use disorder was assessed using the C-DIS-IV diagnostic interview modules for alcohol and substance use disorders. Absence of SUD history was coded 0 and presence was coded 1.

Family history of alcoholism or substance use disorder: FH classification was established using Family History Research

Diagnostic Criteria (FH-RDC), which have a high degree of inter-rater reliability for reports of substance use disorders [40]. Inclusion criteria required that each prospective volunteer be raised by at least one biological parent, be in touch with that parent, and adoptees were excluded from consideration. Persons were considered FH+ if either biological parent met criteria for alcohol or other substance use disorder by subject report. FH– was those reporting an absence of SUD in their biological parents and grandparents. The reliability of subjects'FH-RDC reports was verified by parent interview in 52% of the cases participating in the full study protocol, and these yielded 90% agreement between the two sources. FH– were coded 0 and FH+ were coded 1.

Externalizing characteristics: We modeled externalizing characteristics using CPI-So scores, which incorporate poor childhood relationships,(non)conformity to social norms, disinhibited behaviors, and lack of empathy and remorse for transgressions [25]. The combination of behavioral restraint and norm adherence captured by the CPI-So scale suggests overlap with the concepts of externalizing, behavioral undercontrol, and neurobehavior disinhibition referred to above. Occupational groups that manifest greater-than-usual conformity to rules and regulations, such as nurses, engineers, and accountants, have average scores ≥ 30. Scores ≤ 29 are seen in groups with lower levels of social conformity, including shoplifters, alcoholics, drug abusers, and incarcerated persons [25]. CPI-So scores are predictive of SUD in young adults, and these scores agree with clinical measures of ASPD in alcoholic patients [41]. Accordingly, we coded persons with CPI-So scores ≤ 29 as 1 and those scoring ≥ 30 as 0 on externalizing.

Early life adversity: ELA and low SES are associated with a wide range of negative health outcomes [42] including SUD [43]. ELA scores were derived during the clinical interview from items on the posttraumatic stress disorders module on the C-DIS-IV, which has a high degree of test-retest and inter instrument reliability [44]. None of the subjects met full diagnostic criteria for PTSD. The items used for ELA assessment are closely similar to the life events assessed retrospectively in the studies by Caspi [10] as follows: *Physical or Sexual Adversity* (Have you ever been mugged or threatened with a weapon or ever experienced a break-in or robbery? Have you ever been raped or sexually assaulted by a relative? Have you ever been raped or sexually assaulted by someone not related to you?), and *Emotional Adversity* (Before you were 15, was there a time when you did not live with your biological mother for at least 6 months? Before you were 15, was there a time when you did not live with your biological father for at least 6 months?). ELA scores from the interview items ranged from 0 (no adverse events) to 5 events.

SES was calculated using Hollingshead and Redlich's system based on the highest occupational level attained by the primary breadwinner of the subject's childhood household [45].

Composite ELA scores ranging from 0 (no adverse events) to 5, plus the SES values falling into the upper (0), middle (1), and lower (2) third of the distribution for our subject population, yielded composite ELA scores ranging from 0 – 8. These composite scores were then recoded as 0, 1, and ≥ 2 for analysis.

Depressive symptoms: Internalizing disorders, and specifically depression, are highly comorbid with alcoholism[33,46] and are prevalent in FH+ young adults and their relatives [47]. Individual symptoms of depression and mood instability were assessed using scores on the Beck Depression Inventory (BDI) [33,48]. None of the subjects met full diagnostic criteria for current depression on the CDIS-IV. BDI scores ≤ 10 were coded 0 and scores ≥ 11 were coded 1.

RESULTS

Demographics

Table 1 shows demographic characteristics of the SUD+ and SUD– groups. The groups did not differ on Shipley mental age scores or racial composition. Compared to SUD–, SUD+ persons were older more likely to be male and less educated. SUD+ persons displayed a range of characteristics associated with risk for alcohol and drug abuse, including: higher BDI scores, lower CPI-So scores, FH+ status and higher family densities of alcoholism, risky drinking practices (higher AUDIT scores), an earlier age at first drink, experimentation with more drugs of abuse and were more likely to smoke tobacco.

Recursive partitioning analysis

We used decision tree recursive partitioning as a non-theory based empirical analysis to identify the best predictor of SUD status in the OFHP data set. Recursive partitioning is a data-mining tool that uses a partition strategy to progressively convert a heterogeneous starting population into a branching structure of progressively more homogeneous subpopulations. The sorting variable that maximally separates the remaining target population is identified at each recursive branch. Decision rules based on diminishing returns provide a stopping point and thus define the final model.

The analysis used the Bootstrap Forest algorithm (JMP 10 Pro) to fit a model predicting SUD status. The number of predictors was restricted to four for analytical efficiency and represented family and personal characteristics thought to be highly predictive of SUD risk: 1) being FH+ for alcoholism, 2) scoring in the antisocial range on the CPI-So, 3) symptoms of depression based on the Beck Depression Inventory (BDI) [49], and 4) degree of exposure to ELA. The statistician was blind to the nature of the predictor and outcome variables and the goals of the project.

The database was first randomly divided into two datasets for model training (70% of sample) and validation (30% of sample). The derived model used the four independent variables described to grow a forest of 100 randomly generated unique decision trees. The final estimate is the average of the predicted values from each tree. The bootstrap methodology used for model building, randomization of sorting variables and validation therefore created a final model that avoided the usual collinearity problem associated with single-model methodologies.

Goodness-of-fit was measured using the Receiver Operating Characteristic (ROC) curve [50]. Unlike R^2 metrics that range between 0 and 1, the area under ROC curve (AUC) ranges from 0.5 (assignments no better than chance) to 1.0 (perfect

Table 1: SUD group demographics, alcohol and drug use, and predictor variables.

	SUD–	SUD+	*t* or X^2	p-value
N	507	220	220	
Age	23.3 (0.14)	23.9 (0.22)	2.4	0.017
Sex % M (N M/F)	33 (169/338)	44 (97/123)	7.6	0.006
Race (N, %)			6.18	0.41
White	409 (69%)	186 (31%)		
Black	56(78%)	16(22%)		
American Indian	22(71%)	9 (29%)		
Other	20(69%)	9(31%)		
Education (yr)	15.1 (0.09)	14.8 (0.14)	2.16	0.032
Shipley Mental Age (yr)	17.4 (0.07)	17.2 (0.10)	1.55	0.122
Family History (N, % FH+)	246(49%)	155(70%)	29.8	0.0001
FH density (0-6)	0.86 (0.05)	1.45 (0.09)	5.98	0.0001
AUDIT	3.48 (0.13)	6.66 (0.33)	9.06	0.0001
Age of first drink	16.8 (0.2)	14.9 (0.2)	5.57	0.0001
Alcohol Abuse (N, %)	0	161 (73%)		
Alcohol Dependence (N, %)	0	103 (47%)		
Drug Abuse (N, %)	0	50 (23%)		
Drug Dependence (N, %)	0	36 (16%)		
Drugs ever tried (N)	1.30 (0.07)	3.01 (0.14)	11.02	0.0001
Smoking (N, %)	59 (12%)	69 (30%)	36.3	0.0001
CPI-So	31.1 (0.2)	26.6 (0.4)	11.2	0.00001
CPI-So (N, % ≥ 30)	333(66)	73(33)	0.0001	
Beck Depression Inventory score	5.8 (0.3)	8.4 (0.5)	4.85	0.0001
Depression (N, % BDI > 10)	91 (18)	73 (33)	19.3	0.0001
ELA (N, %)			17.95	0.0001
0	221(44%)	63 (29%)		
1	164(32%)	76(35%)		
2+	122 (24%)	81 (36%)		

Note: SUD = Personal history of any substance use disorder. Shipley Mental Age = estimated mental age from the Shipley Institute of Living scale. AUDIT = Alcohol Use Disorders Identification Test. FH density = Number of alcoholic relatives among parents and grandparents. CPI-So = Socialization scale from the California Personality Inventory. ELA = early life adversity.
Entries show M ± SEM unless specified otherwise. Comparisons are Student's *t* test or X^2.

assignment). The AUC of the final model applied to the validation data provides insight on the sorting efficiency possible when the same model is applied to other datasets. The sensitivity (to identify true positives) and specificity (to identify true negatives) of the derived model was also examined.

Sorting efficiency: The final bootstrap forest model, based on the average of 100 trees, revealed two sorting variables (CPI-So score and FH status) provided approximately 85% of the sorting efficiency, as shown in (Figure 1). The ROC curve analysis indicated good sorting efficiency of the model in both the training (AUC = 0.70) and the validation samples (AUC = 0.73) as shown in (Figure 2). This suggests this bootstrap forest model may also apply to other SUD datasets.

Goodness of fit: We next tested the adequacy of the bootstrap forest model to correctly assign individuals to their respective SUD groups. Goodness of fit to the validation data was tested using confusion matrices based on 0.30 vs. 0.40 assignment thresholds (Table 2). Assignment thresholds are the operator's choice of a statistical probability required for that a given individual to be assigned to the SUD+ or – group as a result of the decision tree. A threshold of 0.5 would be equal to chance. In this case, the statistician was told that the "target group," in this case the SUD+, constituted approximately 1/3 of the data set. Accordingly, as shown in Table (2A), use of a 0.30 threshold resulted in a sensitivity of 0.80, indicating 80% correct identification of SUD+ persons. However, this high sensitivity came at the cost of lower specificity, seen in a 60% correct identification of SUD– persons. The overall model accuracy was (89 + 56) / 218 = 67%. By comparison, Table (2B) shows the results using a 0.4 threshold. In this case, sensitivity (correct SUD+ assignment) dropped to 59%, while specificity rose to 73%, compared with the corresponding cell entries in Table (1A). However, the overall accuracy of this model remained the same, (108 + 41) / 218 = 68%, while the SUD+/– assignment percentages were more stable across the training and validation data sets. Accordingly, the results show that both models had an assignment accuracy approaching 70%, suggesting that changing the assignment threshold may tune the model to have better detection of either SUD+ (80%, as in 2A) or SUD– (73%, as in 2B) status depending on the goal of a given analysis.

CPI-So scores for FH and ELA groups: Based on the initial result showing the discriminative value of the CPI-So scores, we illustrated in Figure 3 full-scale CPI-So scores for SUD+ and SUD– groups in relation to FH-status and ELA exposure. The bars show an orderly relationship in which CPI-So scores are progressively lower for groups that are SUD+, FH+, and have had ELA exposure.

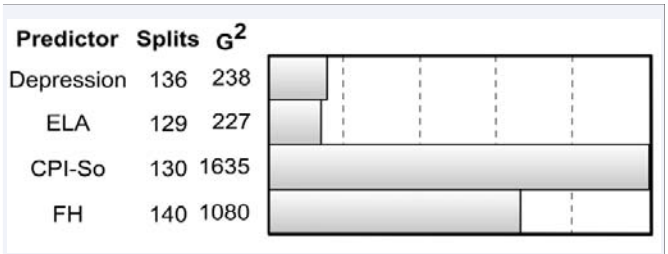

Figure 1 Comparison of four predictors of SUD status. The G2value is similar to a χ2, and higher values indicate greater departure from chance in the predictive value of the given variable. Classifications were dichotomized as follows: BDI depression score ≥ 10, As a predictor of SUD status, CPI-So scores are better than FH of alcoholism, early life adverse experience, or symptoms of depression. The splits column represents the number of decision branches each variable appeared in in the final model.

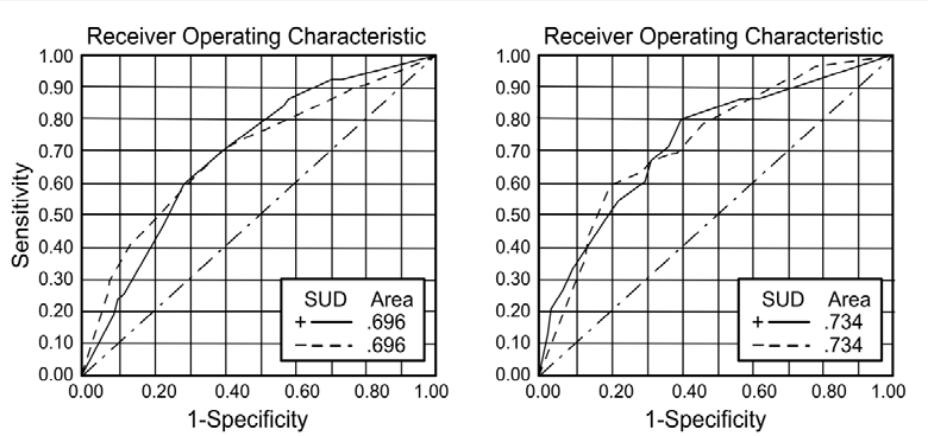

Figure 2 Receiver operating characteristic (ROC) curves representing correct identification of SUD +/– persons using cutoff criteria of .3 (left) and .4 (right). A completely blind model would assign this criterion a value of .5, indicating category assignment with an unbiased probability. Instead, the values .3 and .4 were chosen because they more closely mirror the proportion of SUD+ persons in the sample being analyzed in this data set.

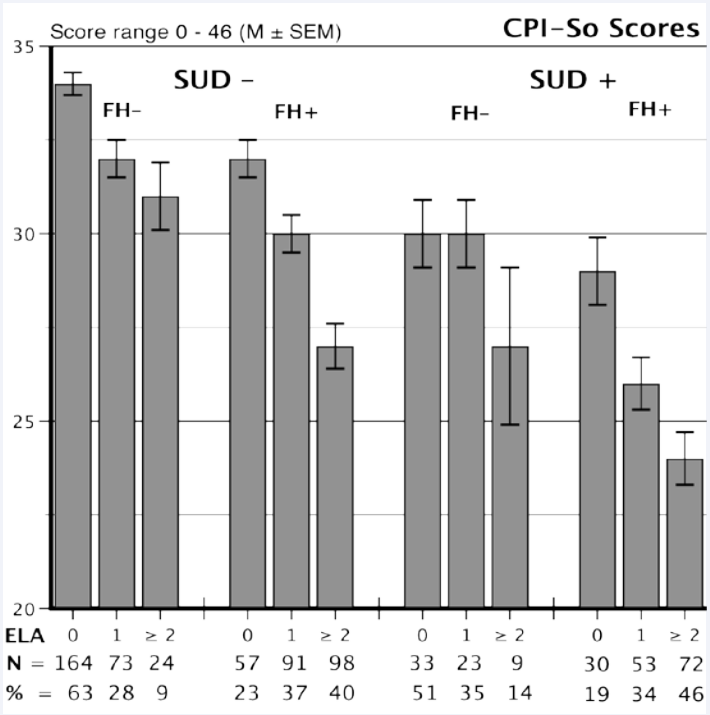

Figure 3 Scores on the California Personality Inventory Socialization scale (CPI-So) in relation to a family history of alcoholism (FH+) and experience of early life adversity (ELA) for persons with and without alcohol and other substance use disorders (SUD+/–). N = number of persons in each subgroup. % = percentages of persons with 0, 1, and ≥ 2 ELA within each SUD x FH subgroup.

An analysis of variance of CPI-So scores for the SUD +/–, FH +/–, and ELA 0, 1, ≥ 2 groups is shown in Table (3), left column. FH, ELA, and SUD status all had significant additive (main effect) relationships to CPI-So scores (*ps* ≤ .04) with no 2-way or 3-way interactions.

CPI-So item endorsement

The CPI-So was designed to capture common language concepts of social adjustment, and its items cover multiple domains of norm adherence, interpersonal connectedness, empathy, behavioral regulation, and risk-taking [25].To reduce this complexity, we compared SUD+/– rates of endorsement on each CPI-So item using independent samples *t*-tests for proportions. The Satterth waite approximation was used in cases of unequal variance. Effect sizes were then calculated using Cohen's *d*. As shown in Supplemental Table (1), SUD+/– groups differed at $p \leq .05$ in rates of endorsement on 32 of the 46 CPI-So items. Effect sizes were generally in the small-to-medium range. However, two items had large (>.8) effect sizes ("I have never done any heavy drinking" and "I have used alcohol excessively")

and were eliminated in the next stages of analysis since they presented a possible confound with independent prediction of SUD status.

CPI-So principal components analysis

Since CPI-So item responses are binary, we first computed the tetrachoric correlation for each pair of items, and items were coded consistent with *positive* socialization. The correlation matrix was then subjected to an exploratory PCA using a varimax rotation procedure. To interpret the factors, we focused on items with factor loadings 0.40 or greater [51]. Simple component (or factor) scores from this principal-components solution were created using a unit-weighting procedure that summed the items with loadings ≥ 0.40. Items with cross-loadings were excluded from the component scores.

Using PCA, we examined 3- and 4-component solutions for the CPI-So item scores. The 4–component solution explained 43% of the total variance. The fourth component was comprised of a single item and was dropped from further analysis. The remaining 3 factors explained a modestly lower 39% of the total variance in full-scale CPI-So scores, with the component structure shown in Supplemental Table (2). The eigen value (λ) of the first principal component (λ_1 = 11.3) was over 3 times greater than the next largest component (λ_2 = 3.47). The first rotated component accounted for 25.7% of the total variance, the second component 7.9%, and the third component 5.1%. Based on item content, we named these components: *Home Life and Family Relationships*, *Impulsivity and Norm Violation*, and *Positive Social Outlook and Connectedness*. These labels correspond well with the SUD predictors identified in an independent unpublished analysis [25] and in the Minnesota Twin Study [52].

Sixteen items were excluded from further analysis; 10 items did not load on any component (loadings< 0.40) and 6 had cross-loadings of approximately equivalent magnitude.

Logistic Regression of CPI-So components in predicting SUD

We next carried out logistic regression to predict the likelihood of a person having an SUD from scores on each of the 3 CPI-So components listed above using the Logistic procedure from SAS® version 9.2 (SAS Institute Inc., 1999).

The overall likelihood ratio was significant, $\chi^2(4)=80.47$, $p<.0001$, $R^2=10.5\%$, Nagelkerke's R^2 = 14.7%, AUC = 0.698. The score on *Positive Social Outlook and Connectedness* did not reach significance, but the log odds of an SUD diagnosis was predicted by lower scores on components, *Home Life and Family Relationships* and *Impulsivity and Norm Violation* (Supplemental Table 3; *p*'s <.0001). For each point increase in the CPI-So component scores (i.e., in the more prosocial direction), the odds of being SUD+ decreased by13% (from1.0 to 0.87)for *Home Life and Family Relationships* and by 25% (from 1.0 to 0.75) for *Impulsivity and Norm Violation*.

Multivariable prediction of SUD status

We next addressed whether adding FH status and ELA exposure to the CPI-So full-scale or component scores led to increased prediction of individual SUD status. A four-predictor logistic regression analysis was fitted to the data based on FH, ELA, and the 2 CPI-So components, *Home Life and Family Relationships* and *Impulsivity and Norm Violation*. The addition of FH and ELA to the CPI-So component scores significantly increased the likelihood ratio of predicting SUD status from $\chi^2(5)$ = 80.47, as shown above, to $\chi^2(5)=90.7$, $p<.0001$, $R^2=11.7\%$, Nagelkerke's R^2 = 16.5, AUC = 0.711. As expected, the log odds of an individual being classified SUD+ was related to more antisocial CPI-So component scores (Supplemental Table 4; $p<.001$). Additionally, the odds of being classified SUD+ were increased from 1.0 to 1.83 in those with an FH+ status. In the presence of the other two predictors, ELA alone was not a significant predictor of SUD classification ($p> .05$, Supplemental Table 4).

Receiver operator characteristic model comparisons

ROC analysis was used to calculate area under the curve (AUC) for each of the models described above as well as alternative models with FH and ELA as predictors. The model including the component scores on *Home Life and Family Relationships* and on *Impulsivity and Norm Violation* showed significant improvement in prediction of SUD status relative to chance and FH status alone (Table 4). The AUC for the CPI-So 2-component model was nominally lower than that for the full-scale CPI-So total score. FH alone had the lowest AUC value. And adding ELA did not improve the predictive ability of the original model, with all these AUC values clustering around .70 (Table 4). These model comparisons are consistent with an interpretation in which SUD outcome reflects FH status as a background variable, ELA as an intermediate reflection of life experience, and antisocial tendencies, represented by CPI-So scores, as a phenotypic manifestation or direct behavioral contributor to alcohol and drug use [53].

Analysis of variance on CPI-So component scores: For further illustration, we conducted a second ANOVA using the summed score from the two components, *Home Life and Family Relationships* and *Impulsivity and Norm Violation*, as the dependent variable and SUD +/–, FH +/–, and ELA 0, 1, ≥ 2 groups as the independent variables with the results shown in the right columns of Table (3). The results were similar to the analysis on full scale CPI-So scores, suggesting that the majority of variance in SUD status is captured by antisocial characteristics reflected in these two component scores. This finding also points to the role of ELA in predicting SUD+ status due to the greater ELA exposure among FH+ (Table 1). A behaviorally disinhibited phenotype captured in low CPI-So scores may represent a final common pathway to SUD risk with apparently additive contributions from FH status and ELA exposure.

DISCUSSION

We examined predictors of SUD status in the OFHP cohort, comparing variables identified in prior studies and our own research, including: FH of alcoholism, exposure to ELA, antisocial and disinhibitory tendencies from the CPI-So scale, and symptoms of depression scored from the BDI. The CPI-So total score, indexing antisocial and disinhibitory characteristics, was the best single predictor of SUD status, assigning nearly 70% of the subjects to the correct SUD group, and performing

Table 2: Confusion matrices and sensitivity and specificity of SUD group classification resulting from Bootstrap Forest analysis of training (A) and validation (B) data sets.

(A) Assignment threshold = 0.30					
Training Set (N = 509)			**Validation Set (N = 218)**		
	Predicted		**Predicted**		
Observed	**SUD–**	**SUD+**	**SUD–**	**SUD+**	**Accuracy**
SUD–	228 (64%)	131 (36%)	89 (60%)	59 (40%)	(89 + 56) / 218
SUD+	49 (33%)	101 (67%)	14 (20%)	56 (80%)	= 67%
Total	277	232	103	115	
(B) Assignment threshold = 0.40					
Observed	**SUD–**	**SUD+**	**SUD–**	**SUD+**	**Accuracy**
SUD–	265 (74%)	94 (26%)	108 (73%)	40 (27%)	(108 + 41) / 218
SUD+	67 (45%)	83 (55%)	29 (41%)	41 (59%)	= 68%
Total	332	177	137	81	

Note. Entries show N (%).

Table 3: Analysis of variance on CPI-So full-scale values and total of two component scores in relation to SUD status based on FH and ELA exposure.

Full CPI-So scale	**CPI-So component scores**			
	F value	***p*value**	***F* value**	***p*value**
SUD	14.63	0.0001	3.69	0.0002
FH	4.21	0.0404	3.81	0.0001
ELA	10.03	0.0016	4.38	0.0001
SUD*FH	< 1	0.97	< 1	0.58
SUD*ELA	< 1	0.76	< 1	0.59
FH*ELA	1.76	0.08	< 1	0.79
SUD*FH*ELA	< 1	0.72	< 1	0.43

Note: CPI-So component scores represent total score from items in components *Home Life and Family Relationships* and *Impulsivity and Norm Violation* listed in Supplemental Table 4. *F* and *p* values are based on Type III sums of squares.

better than having an FH+ history, being exposed to ELA, or reporting symptoms of depression. In the OFHP cohort, antisocial characteristics represented by lower CPI-So scores nonetheless appear to accumulate in relation to both genetic (FH+) and environmental characteristics represented by ELA exposure. (Figure 3) shows that CPI-So scores were progressively lower in FH+ persons and in those with a greater history of ELA exposure both of which contribute to SUD risk, with lowest scores seen in the SUD+, FH+, ELA ≥ 2 subjects. By way of interpretation, the CPI-So score for the highest SUD risk group (SUD+, FH+, ELA ≥ 2) had a mean of 24, which corresponds closely with a published mean of 23.9 among inpatients in treatment for alcoholism [41]. Persons with scores ≤ 24 are rated by peers as "undependable," "careless," and "reckless" [25]. In contrast, persons with scores ≥ 34, corresponding to our lowest risk group, are described by peers as "conservative," "reliable," and "organized." These divergent descriptors suggest that low full-scale CPI-So scores capture a broad range of behaviors that are consistent with such formulations as behavioral undercontrol, neurobehavior disinhibition, and low conscientiousness.

In multivariate prediction, CPI-So scores and FH background were similarly good univariate predictors of SUD status, although the two together did not improve on the predictive power of the CPI-So score alone, suggesting a shared source of variance, consistent with a model in which FH+ tend to inherit a disinhibitory temperament [54]. Depressive symptoms, despite their frequent comorbidity with SUD, did not contribute to prediction of SUD status in this sample. These findings may contribute to our understanding of how individual risk factors for SUD relate to one another, and they suggest directions for future research.

Prosocial vs. antisocial tendencies may be manifested early in development and be persistent predictors of future alcohol and drug experimentation. A prospective study of childhood and adolescent development in relation to alcohol and drug use seen during the last year of high school, found that 17-18 year old "frequent" users of alcohol and drugs were characterized in clinical interviews at ages 5-7 years as: undependable, inflexible with others, inconsiderate, transferring blame, less warm and likable, and ethically inconsistent, suggestive of a "lifelong social maladjustment" [55]. These clinician-rated characteristics in children are consistent with a complex antisocial and disinhibitory behavioral phenotype present in FH+ adolescents, variously described as "behavioral undercontrol" [15,56], "neurobehavior disinhibition" [17,18], "low conscientiousness" [6], or "social deviance proneness" [19], and captured in our low CPI-So scores. In the present sample, the data in Figure (3) suggest a continuum of SUD risk represented in systematically lower CPI-So scores

Table 4: Area under the curve for several models predicting SUD group membership.	
	0.62
CPI tot	0.72
CPI 1,2	0.7
CPI 1,2,3	0.7
FH & CPI 1,2	0.71
FH, CPI 1,2, ELA	.71
FH = family history of alcoholism. CPI-So = California Personality Inventory Socialization scale factors 1, 2, and 3. ELA = early life adversity.	

with each increase in SUD risk. Poor behavioral regulation in FH+ adolescents may increase risky drinking practices resulting in more severe consequences of their consumption [57], suggesting a behavioralvulnerability leading to alcohol experimentation leading to abuse or dependence[5].The present analysis indicates factors that may contribute to an SUD diagnosis in FH+.

The CPI-So scale is psychometrically complex [25], and a deconstruction of the scale identified item sets that we labeled *Home Life and Family Relationships* and *Impulsivity and Norm Violation*, which together captured most of the SUD predictive variance found in using the full scale (Supplemental Table 4). Items in *Home Life and Family Relationships* point to a disrupted family environment in FH+ households, reflectingthe greater prevalence of ELA exposure among our FH+ subjects (Table 1). In turn the items labeled *Impulsivity and Norm Violation* are consistent with a disinhibitory tendency toward risky drinking patterns[58], that may contribute to an SUD. The low CPI-So scores in FH+ are consistent with the view that antisocial tendencies form a temperament characteristic that isinherited and manifested at a very early age [16,52]such that a disruptive family environment and poor parenting practices may act on this vulnerable phenotype[59]. Prior analyses in the OFHP study observed that exposure to ELA predicts: 1)poorer cognitive functioning, 2) impulsive tendencies, seen in faster discounting of delayed rewards, and 3) ahigher body mass index, indicating poorer weight regulation [30]. ELA also predicts blunted endocrine and autonomic responses to psychological stress, similar to the stress blunting seen in alcoholic patients [60-62]. In turn blunted stress reactivity isincreasingly recognized as a risk-associated phenotype encompassing reduced aversion to environmental threats and less suppression of risky behaviors [63-65].These effects were not explained by age, sex, race, education, or symptoms of depression.

A positive family history is a well-established risk factor for alcoholism [1,66] that appears to share an inheritance with antisocial tendencies [8]. FH+ manifest a disinhibitory phenotype to a greater degree than FH– persons, resulting in risk-taking and proneness to an SUD. ELA exposure appears to contribute to development of this phenotype in a dose-response fashion. The present results are consistent with a model of SUD risk in which a behaviorally disinhibited and antisocial phenotype is a proximal contributor to misuse of alcohol and recreational drugs and that this phenotype is progressively more pronounced in FH+ persons and those with ELA exposure. In this view, antisocial and disinhibitory characteristics are part of a final common pathway to SUD, with FH and ELA being additive contributors to these antisocial traits. A significant question is whether FH+ persons are differentially vulnerable to ELA exposure. The present analysis, pointed primarily toward an additive effect of ELA and family history on CPI-So scores, although the analysis of full-scale scores suggested a modestly greater response to ELA in FH+ persons than in FH– (F = 1.76, p = .08, Table 3, Figure 3) suggesting a lack of statistical power to identify potential gene-by-environment effects in the present data. In a large twin study, Hicks and colleagues reported a differential expression of externalizing behaviors in persons with a genetic vulnerability when exposed to stressful life events [9].

Although the present data are behavioral in nature, the analysis comports with current perspectives on brain function in relation to disinhibition and SUD risk [63]: 1) Alcoholic patients show reduced prefrontal cortex volume [67] along with cognitive and inhibitory deficits and poor regulation of affect [68-70], undoubtedly reflecting damage due to heavy consumption. 2) Neuroimaging studies in FH+ persons show altered structure and functional response in the region of the amygdala and the striatum [71-75]. 3) FH+ subjects from the OFHP cohort and an independent sample of 11-14 year olds, show reduced white matter integrity in frontocortical and frontostriatal fiber tracts including the *anterior corona radiata,* consistent with reduced myelination, and suggesting impaired prefrontal-limbic communication [76].White matter impairment was correlated in both samples with the number of SUD+ relatives [76], and in the older sample, white matter impairment predicted an earlier age at first drink. Accordingly, the current results may be seen as consistent with modified activity in the prefrontal cortex and limbic system activity, or defective prefrontal communication.

LIMITATIONS

This is not a random population sample. The OFHP was designed to examine characteristics of FH+ young adults. As a result, 31% of persons who volunteered for screening (222 of 707) qualified for some level of SUD diagnosis by C-DIS-IV criteria. This number is substantially higher than the 12-month prevalence of SUD diagnosis of 4% in the US population and higher than the lifetime prevalence of 20% [77]. Similarly, the number of FH+ persons without an SUD may be higher than expected since we actively selected a sample of FH+ lacking substance use disorders. A second limitation is that the present analysis was designed around variables known or strongly suspected of an association with risk for an SUD. It would be useful to explore other sets of variables as potential risk factors to uncover less well-understood relationships.

CONCLUSION

Antisocial characteristics and behavioral disinhibition may represent a risk-associated phenotype that is prevalent in FH+ persons and that is increased in persons exposed to stress during childhood and adolescence. The present results are consistent with a model in which families with a high prevalence of SUD create a disrupted home environment that further contributes to a risky behavioral phenotype in vulnerable offspring [78].These findings together argue for intensive gene-by-environment

studies that will contribute to an understanding of how some FH+ avoid developing an SUD, despite an unfavorable family environment, and on the other hand why some FH–also go on to develop an SUD.

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