Risk of Mental Disorders in Children of Parents with Alcohol or Heroin Dependence: A Controlled High-Risk Study

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Key Words

Psychopathology • High-risk offspring • Co-parent • Substance use disorders

Abstract

Aim: To assess the specific effect of alcohol dependence (AD) or heroin dependence (HD) in patients and their spouses on the risk of psychopathology in their 276 6.0- to 17.9-year-old children (mean 11.3 years). **Methods:** The sample included 101 offspring of patients with AD, 23 of patients with HD, and 152 of medical controls, as well as their 2 parents. Participants were assessed using semistructured diagnostic interviews and family history reports by psychologists blind to patient diagnoses. **Results:** Children of HD and AD patients had largely elevated rates of recurrent major depressive disorder. Children of HD patients were also at an increased risk for attention deficit hyperactivity disorder and substance use disorders (SUD). There were interactions between SUD in the 2 parents to increase the risk of SUD in offspring. **Conclusions:** These results emphasize the need for prompt identification and treatment of these children and highlight the need to pay clinical attention not only to the patient, but also to the co-parent in order to optimize prevention in offspring.

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Introduction

Excessive alcohol and illicit drug use are major public health issues. Indeed, they are associated with severe medical complications, disruption of life course, loss of productivity, and delinquency [1–8]. The familial aggregation of alcohol use disorders has been demonstrated by a large number of studies using alcoholic probands from both treatment and community settings [9–18]. Although there are fewer studies on the familiarity of drug use disorders, the existing family studies also support familial aggregation of these disorders [19–21]. Therefore, the children of alcohol- and drug-dependent parents represent a population at risk for mental health problems and social malfunctioning. The study of offspring of parents with psychoactive substance dependence ('high-risk design') is a potent strategy to assess the impact of these parental psychopathologies on early psychiatric manifestations of their children [22]. The better understanding of the problems these youth experience is essential in order to promote primary and secondary prevention.

During the last two decades, twelve controlled studies of the minor offspring (in the age range between 6 and 18 years) of parents with DSM-IV alcohol or illicit drug dependence have been conducted using standardized

methods including direct diagnostic interviews of parents and children and samples of at least 20 children in each group (table 1). The majority but not all of these studies found higher rates of various Axis-I disorders in high-risk offspring. Indeed, seven of the nine studies focusing on the offspring of alcoholic parents provided evidence of elevated rates of psychopathology in these children. The increased morbid risk involved substance use disorders (SUD) and disruptive behavioral disorders (DBD) in three studies as well as major depressive disorder (MDD), anxiety disorders and attention deficit hyperactivity disorder (ADHD) in two studies. Regarding the children of drug-dependent parents, three [23–25] out of five studies documented increased rates of Axis-I disorders in these children. In addition, one study on offspring of parents with either alcohol or drug use disorders documented high-risk offspring to exhibit increased rates of SUD and DBD compared to children of controls [21, 23–33].

However, the large majority of studies did not take into account other factors than parental SUD that could influence the risk of psychopathology in offspring, such as the very frequent comorbid disorders in parents. Moreover, only the studies of Wilens et al. [23] and Marmorstein et al. [33] separately recruited offspring of alcohol- and drug-dependent parents, which allowed them to determine the specific effects of the two types of parental addiction by comparing the two groups of children. In the study of Hill et al. [24], which included multiplex families with high risk for alcohol dependence (AD), the effects of parental AD and secondary drug disorders were assessed.

Given evidence of spouse similarity for SUD [25, 34], the inclusion of the effect of the co-parent's SUD in the analyses is of particular relevance. However, among these twelve high-risk studies, only a small number of studies on AD assessed the effects of alcohol from both parents. Among them, Reich et al. [27] reported an association between the number of alcoholic parents and the risk of several specific psychiatric disorders in offspring, whereas Hill and Hruska [26] could not find such an association with respect to internalizing or externalizing disorders in offspring. Moreover, Hill and Muka [28] found an additive effect rather than an interaction between AD in the 2 parents regarding the risk of overall psychopathology in offspring. Using a sample from the general population, Lieb et al. [31] documented higher levels of alcohol use in children with 2 alcoholic parents as compared to those with 1 alcoholic parent, whereas the risk of alcohol abuse or dependence in children did not differ by the number of affected parents. With respect to drug disorders, only the study of Hill et al. [24] tested the effects of

secondary drug disorders in both parents on child psychopathology.

Given the scarce data available on the effect of specific SUD in the 2 parents on offspring psychopathology, the goals of the present study, conducted in a European urban area, were (1) to investigate the associations between AD or heroin dependence (HD) in probands and Axis-I mental disorders in their offspring, adjusting for demographic variables in families and comorbid disorders in probands, and (2) to assess the effect of parental concordance for SUD on psychopathology in children.

Methods

Subjects

The data from the present study stemmed from a controlled family study. Psychiatric probands were patients with AD or HD, consecutively recruited from the inpatient and outpatient facilities of the psychiatric departments of Lausanne and Geneva, Switzerland. Inclusion criteria for the psychiatric probands were: (1) lifetime DSM-IV AD or HD, and (2) permission to enroll at least 1 of their children in the age range of 6.0–17.9 years in the study. Comparison probands were recruited from orthopedic inpatient and outpatient facilities in the same medical centers. Inclusion criteria for the comparison probands were: (1) the absence of lifetime DSM-IV AD or HD, and (2) the same criterion for inclusion of offspring as that of the AD and HD cases.

A total of 50 alcohol (participation = 63.3%) and 15 heroin addicts (participation = 45.5%) as well as 81 orthopedic controls (participation = 71.0%) agreed to enroll at least 1 of their children in the required age range in the present study. Among the 15 heroin addicts, 6 also met DSM-IV lifetime dependence criteria for cocaine, 2 for hallucinogens, 4 for cannabis, and 7 for alcohol. Only 3 of them met criteria for HD alone. Probands who enrolled their children in the study did not differ from those who did not enroll their children in the study with respect to demographic variables or comorbid disorders except for ADHD. HD probands who enrolled their children in the study did not exhibit this comorbid disorder at all whereas a lifetime diagnosis of ADHD was reported by 15.2% of those HD probands who did not enroll their children in the study.

The offspring sample ($n = 276$) included all of the probands' children aged between 6.0 and 17.9 years (mean 11.3, SD 3.46, 48% girls). There were 101 offspring of probands with AD, 23 offspring of probands with HD, and 152 offspring of comparison probands. The majority of families included 1 ($n = 52$) or 2 ($n = 65$) children, whereas 29 families had 3 or more children. Diagnostic information was also collected on 144 (91%) of the 158 current or past partners of the probands, who were the biological co-parents of the children enrolled in the study.

Procedures

Participants were interviewed by masters-level psychologists or psychiatrists who completed intensive training over a 3-month period. Training included supervision of videotaped interviews by clinically experienced senior psychologists and each interview

was reviewed by a senior clinical psychologist. Each family member was interviewed by a different psychologist, and interviewers and reviewers were blind to the disease status of all other members in a given family.

Diagnostic information on probands and biological co-parents was obtained using the Diagnostic Interview for Genetic Studies (DIGS) [35]. The French translation of the DIGS revealed high κ coefficients for inter-rater reliability and slightly lower coefficients for test-retest reliability for major Axis-I diagnoses including mood [36] and SUD [37]. Offspring were directly interviewed with a French translation of the modified version of the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E) [38], which has been used in previous high-risk studies such as the Yale Family Study [21]. The K-SADS-E has been found to be a reliable and valid instrument for obtaining lifetime diagnoses in prepubertal children and adolescents [39, 40]. Inter-rater reliability analyses of videotaped interviews of children using our French translation of the K-SADS-E revealed high κ coefficients for major psychiatric diagnoses, ranging from 0.84 for depression and 0.86 for separation anxiety disorder to 1.0 for social phobia and psychosis. In addition to eliciting DSM-IV criteria for substance abuse and dependence, the K-SADS-E also elicits information on alcohol and drug consumption, defined as the consumption of alcohol or drugs at least once a week for a period of several months, without meeting criteria for abuse or dependence. Moreover, the K-SADS-E collects information on exposure to traumatic events including accidents, crimes, domestic violence and physical or sexual abuse.

Family history information was collected from all participating first-degree family members over the age of 15 years, using the Family History-Research Diagnostic Criteria (FH-RDC) [41]. The validity of the French version of the FH-RDC has previously been established by our group through the assessment of agreement between diagnoses relying on direct interviews and family history reports for a series of diagnoses in adults [42, 43] and children [44].

Diagnoses were assigned according to a best-estimate procedure [45], which relied on the combining of information from direct interviews, family history reports and medical records where available. Diagnoses on non-interviewed subjects were based on family history information alone. In addition to the diagnoses based on DSM-IV criteria, diagnoses of subthreshold mood syndromes in offspring were assigned using the algorithmically defined classification postulated by Angst et al. [46]. Accordingly, subthreshold depression was defined as either (recurrent) brief depression (≤ 5 DSM-IV depressive symptoms for 2–13 days) or minor depression (3–4 depressive symptoms for ≥ 2 weeks). Subthreshold bipolar disorder was defined as the occurrence of hypomanic episodes without major depressive episodes, brief mania (euphoria or irritability and at least 3 or 4 manic symptoms, respectively, for 2–3 days) or minor mania (euphoria or irritability and 1–2 or 2–3 manic symptoms, respectively, for ≥ 4 days).

Socioeconomic status was assessed using the Hollingshead scale [47], which allows for the establishment of the socioeconomic level of the family based on the professional level of each of the 2 parents.

This research project was approved by the local institutional review board. All participants gave written informed consent for their own participation prior to the assessments. In addition, parents gave written consent for the participation of their children.

Data Analysis

Between-group analyses of demographic and clinical characteristics were performed using ANOVA, χ^2 and Fisher's exact tests as appropriate. In order to assess the associations between the proband's dependence (independent variable) and the risk of psychopathology in children (dependent variable) with adjustment for demographics variables and comorbid disorders in probands, generalized linear models were applied [48]. These models account for the lack of independence of the observations by introducing a block-diagonal exchangeable correlation structure, where each block corresponds to a given family. All analyses were also adjusted for socioeconomic status, as this variable may be associated with the child's risk of SUD [49]. Analyses were run separately for each child diagnostic outcome, and could only be applied for disorders with a lifetime prevalence of at least 5% in offspring. In a second step, drug and alcohol disorder status (abuse and dependence) of the co-parent as well as their interaction terms with the respective variable in probands were entered into the models. This enabled us to test potential interactions between the proband's and co-parent's alcohol and drug disorders (also adjusting for the co-parent's mood and anxiety disorders) on the risk of psychopathology in offspring. Additional complementary models considered the familial situation (the child living with both biological parents versus not) and the child's exposure to traumatic events as assessed in the K-SADS-E.

Statistical analyses were performed using the GENMOD procedure of the Statistical Analysis System, version 9.2.

Results

Demographic Characteristics and Comorbid Disorders in Probands

The characteristics of probands are provided in table 2. The only significant difference for demographic characteristics across proband groups was the lower proportion of married subjects among HD probands compared to the two other groups.

Regarding comorbid disorders, probands differed in the proportion of mood, anxiety, DBD and antisocial personality disorder (ASPD). Indeed, both HD and AD probands had increased rates of bipolar disorders (BPD), whereas only AD probands revealed significantly increased rates of MDD. Alcoholic probands also exhibited anxiety disorders more frequently than both heroin addicts and comparison probands, whereas DBD and ASPD were only found to be more frequent among heroin addicts compared to controls.

Demographic Characteristics and Psychopathology in Co-Parents

Diagnostic information could be collected on 86% of the biological co-parents of alcoholic probands, 81.3% of those of heroin addicts, and 96.5% of those of controls.

Table 1. Controlled high-risk studies (>20 subjects per group) of HD and AD probands with direct diagnostic interviews of offspring younger than 18 years since 1990

Study	Parents					Offspring			
	parents with substances disorders			comparison parents		high-risk		low-risk	
	n	diagnosis (diagnostic system)	source	n	source	n	mean age range	n	mean age range
Hill and Hruska (1992) [26]	38	AD (DSM-III)	Members of multiplex families with high risk for AD (2 brothers with AD of whom one was treated)	27	Advertisement. 2 brothers with absence of psychopathology.	53	8–18	42	8–18
Reich et al. (1993) [27]		AD (DSM-III-R)	Hospitalized alcoholics, convicted felons, hospitalized medical controls and their siblings		Siblings of hospitalized alcoholics and convicted felons, hospitalized medical controls and their siblings not alcoholics	1 alcoholic parent: 82 2 alcoholic parents: 22	11.5 6–18 14.5 6–18	51	11.7 6–18
Hill and Muka (1996) [28]	24	AD (DSM-III)	Members of multiplex families with high risk for AD (2 sisters with AD of whom 1 was treated)	28	2 sister volunteers from census. No AD, drug dependence, recurrent depression or schizophrenia.	38	11.3 8–18	38	11.3 8–18
Merikangas et al. (1998) [21]	52	Any alcohol or drug (anxiolytics, sedatives, benzodiazepines or marijuana) disorders (DSM-III-R)	Treated subjects	35	Random-digit dialing procedure. No psychiatric disorders.	77	12.5 7–18	57	12 7–18
Nunes et al. (1998) [29]	30 39	Opiate with MDD (DSM-III-R) Opiate without MDD	Treated subjects	28 22	MDD, no drug (DSM-III-R) No MDD, no drug (DSM-III-R)	29 B 19 G 33 B 33 G	11.4 6–17 10.5 6–17	26 B 24 G 18 B 27 G	12.7 6–17 13.5 6–17
Kuperman et al. (1999) [30]	165	AD (DSM-III), without antisocial personality disorder	Treated subjects	67	Community. No AD, antisocial personality disorder.	266	7–17	118	7–17
Lieb et al. (2002) [31]		Alcohol dependence or abuse (DSM-IV)	Community sample		Community sample without alcohol use disorders	1 AD parent: 14–24 469 both AD parents: 74	14–24	1,866	14–24
Wilens et al. (2002) [23]	16 14	Opioid dependence (DSM-III-R) AD (DSM-III-R)	Outpatients	66	Employees of a hospital without drug or alcohol use disorders	22 22	11.4 6–18 11.4 6–18	139	11.6 6–18
Clark et al. (2004) [25]	294	Drug dependence or abuse (DSM-III-R)	Treated subjects, advertisement	319	Advertisement. No adult Axis-I disorder.	553	10.7 6–14	614	10.9 6–14
Hill et al. (2008) [24]		AD (DSM-III) Secondary drug dependence in either parent (DSM-III)	Members of multiplex families with high risk for AD (2 same-sex siblings with AD of whom 1 was treated)		Volunteers consisting of same-sex sibling pairs without substance dependence	124 182 50 70	8–11 12–18 8–11 12–18	93 156 75 129	8–11 12–18 8–11 12–18
Diaz et al. (2008) [32]		AD (DSM-IV)	Treated subjects		Parents of control children recruited in schools, no alcohol	371	12.5 6–17	147	12.2 6–17
Marmorstein et al. (2009) [33]	270 50	AD (DSM-III-R) Drug dependence	Community sample	280	Community sample without substance dependence	540 100	17.5	560	17.5

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. B = Boys; G = girls. ¹ Conduct disorder. ² Alcohol abuse. ³ Oppositional defiant disorder. ⁴ Separation anxiety disorder. ⁵ GAD/overanxious disorder. ⁶ Drug abuse. ⁷ AD. ⁸ Substance dependence.

Results													
lifetime Axis-I disorders in high-risk (H) and low-risk (L) offspring, %													
any		BPD		MDD		anxiety		DBD		ADHD		substance use	
H	L	H	L	H	L	H	L	H	L	H	L	H	L
37.8	33.3			11.3	9.5	22.6	21.4	5.7 ¹	2.4 ¹	3.8	2.4	3.8 ²	0 ²
61	49.5			22	15.7	30.5 ⁶	7.8 ⁶	14.6 ¹	9.8 ¹	19.5	15.7	7.3 ²	5.9 ²
90.9	49.5**			40.9	15.7	40.9 ^{6, **}	7.8 ⁶	17.1 ³	9.8 ³	40.9*	15.7	27.3 ^{2, *}	5.9 ²
								40.9 ^{1, ***}	9.8 ¹				
								50 ^{3, **}	9.8 ³				
60.5**	28.9					39.5	18.4	13.2	2.6	13.2	2.6		
41.6	28.1			11.7	3.5	10.4	10.5	15.6 ^{1, **}	0 ¹	13	15.8	20.5***	0
								11.7 ³	3.5 ³				
				6.9	23.0	20.7	30.8	27.5 ¹	15.4 ¹	20.6	15.4	8.3	7.7
				15.8	25.0	21.1	41.7	10.5 ¹	8.3 ¹	0	4.2	0	2.2
				3.0	5.6	15.2	16.7	3 ¹	5.6 ¹	15.2	5.6		
				12.1	11.1	24.3	25.9	0 ¹	7.4 ¹	9.1	3.7		
						13.9 ^{4, *}	5.9 ⁴	14.3 ¹	8.5 ¹	13.2	5.9	5.6 ²	7.6 ²
						9.8 ^{5, *}	2.5 ⁵	6.4 ³	5.9 ³			1.9 ⁶	5.1 ⁶
												22 ²	19 ²
												13 ^{7, ***}	7 ⁷
												24 ²	19 ²
												16 ^{7, **}	7 ⁷
59**	28	5	0	27*	9	45**	15	23 ^{1, **}	1 ¹	23*	4	5	1
41		0		23*		32		9 ^{1, *}		14		18*	
				2.4*	0.9	8.1*	6.2	2.3 ^{1, **}	0.3 ¹	7.4**	4.2		
34.7	22.6	0	0	3.2	0	6.5 ⁴	6.5 ⁴	4.0 ¹	0 ¹	16.9**	7.5	0	0
		0.5	0	14.8**	3.8	0.5 ⁴	1.9 ⁴	12.1 ^{3, ***}	2.2 ³			14.3**	3.8
								21.2 ^{1, ***}	3.8 ¹	13.2**	5.1	14.8 ^{8, *}	6.4 ⁸
								27.5 ^{3, ***}	7.1 ³				
32.0	24.0												
62.9***	32.6												
37.7***	12.6			3.3	0	4.2 ⁴	1.5 ⁴	3.6 ³	0.7 ³	11.1	4.4		
						4.8 ⁵	0 ⁵						
								24.8 ¹	4.8 ¹	5.7	0.6	15.4 ⁷	1.1 ⁷
								10.5 ³	3.3 ³				
								33 ¹	4.8 ¹	14	0.6	23 ⁷	1.1 ⁷
								34 ³	3.3 ³				

Table 2. Sample characteristics of probands and offspring

	HD probands (n = 15)	AD probands (n = 50)	Control probands (n = 81)	Statistic	p value	Pairwise comparison
Demographic						
Female, %	40.0	44.0	43.2	$\chi^2 = 0.08$	n.s.	
Age, mean (SD)	38.8 (4.7)	41.6 (6.4)	41.1 (7.0)	$F_2 = 1.03$	n.s.	
Married, %	33.3	66.0	80.3	$\chi^2 = 14.16$	<0.001	AC
Number of offspring included, mean (SD)	1.53 (0.74)	2.02 (0.96)	1.88 (0.75)	$F_2 = 2.03$	n.s.	
Lifetime Axis-I psychiatric disorders, %						
Bipolar disorders	20.0	26.0	2.5	$\chi^2 = 16.75$	<0.001	AB
Major depressive disorders	40.0	44.0	17.3	$\chi^2 = 11.80$	0.002	B
Any anxiety disorders	6.7	44.0	9.9	$\chi^2 = 22.10$	<0.0001	BC
Antisocial personality	20.0	8.0	1.2	FET	<0.01	A
Childhood disruptive behavioral disorders	26.7	14.3	4.9	$\chi^2 = 7.68$	<0.05	A
ADHD	0.0	8.0	2.5	FET	n.s.	
	Offspring of HD probands (n = 23)	Offspring of AD probands (n = 101)	Offspring of controls (n = 152)	Statistic	p value	Pairwise comparison
Demographic						
Girls, %	47.8	47.5	46.7	$\chi^2 = 0.02$	n.s.	
Age, mean (SD)	11.3 (3.46)	11.8 (3.37)	11.3 (3.33)	$F_2 = 0.61$	n.s.	
Socioeconomic status in the family	3.3 (0.7)	3.0 (1.0)	3.5 (1.1)	$F_2 = 7.91$	<0.001	B
Living with both biological parents, %	43.5	48.5	77.0	$\chi^2 = 25.74$	<0.0001	AB
Exposure to traumatic events, %	31.8	23.0	12.4	$\chi^2 = 7.46$	0.02	AB
Directly interviewed, %	95.7	86.1	95.4	$\chi^2 = 7.54$	<0.05	B

FET = Fisher's exact test; A = HD probands vs. controls; B = AD probands vs. controls; C = HD probands vs. AD probands; ADHD = attention deficit hyperactivity disorder.

Table 3. Sample characteristics of co-parents

Characteristic	Spouse of			Statistic	p value	Pairwise comparison
	HD proband (n = 16)	AD proband (n = 57)	controls (n = 85)			
Demographic						
Female, %	56.3	54.4	57.7	$\chi^2 = 0.14$	n.s.	
Age, mean (SD)	41.3 (4.8)	41.3 (5.6)	41.7 (7.3)	$F_2 = 0.07$	n.s.	
Interviewed, %	31.3	49.1	67.1	$\chi^2 = 9.28$	0.01	AB
Lifetime Axis-I psychiatric disorders, %						
Any disorder	46.2	46.9	46.3	$\chi^2 = 0.00$	n.s.	
Bipolar disorders	7.7	10.2	6.1	FET	n.s.	
Major depressive disorders	7.7	31.6	30.5	$\chi^2 = 3.03$	n.s.	
Schizoaffective disorder unipolar	0.0	2.0	2.4	FET	n.s.	
Any anxiety disorders	15.4	16.3	19.5	$\chi^2 = 0.27$	n.s.	
AD	23.1	10.2	1.2	FET	0.003	AB
Alcohol abuse	0.0	6.1	7.3	FET	n.s.	
Drug abuse or dependence	30.8	2.0	3.7	FET	0.003	AC
Disruptive behavioral disorders	12.5	5.9	1.5	FET	n.s.	
ADHD, %	0.0	2.9	3.1	FET	n.s.	

FET = Fisher's exact test; A = HD vs. controls; B = AD vs. controls; C = HD vs. AD; ADHD = attention deficit hyperactivity disorder.

Table 4. Lifetime prevalence of psychiatric disorders in all offspring

Offspring disorders	All offspring (n = 276)			χ^2	p	pairwise comparisons
	HD proband (n = 23)	AD proband (n = 101)	controls (n = 152)			
Any disorder	60.9	63.4	42.1	11.9	0.003	B
Any mood disorder	21.7	29.7	17.1	7.9	n.s.	
Any depression	17.4	25.7	17.1	2.9	n.s.	
Any MDD	13.0	15.8	11.18	1.2	n.s.	
MDD recurrent	8.7	5.0	0.7	FET	0.01	AB
MDD single	4.4	9.9	8.5	FET	n.s.	
SAD	0.0	3.0	0.7	FET	n.s.	
Dysthymia	0.0	1.0	2.6	FET	n.s.	
Subthreshold depression	4.4	6.9	5.9	0.2	n.s.	
Any BPD	4.4	4.0	0.0	FET	0.02	B
BPD I or II, SAM	4.4	3.0	0.0	FET	0.03	
Subthreshold BPD	0.0	1.0	0.0	FET	n.s.	
Any anxiety disorder	34.8	43.6	25.7	8.8	0.01	B
Separation anxiety	26.1	32.7	18.4	6.7	0.03	B
GAD	0.0	3.0	0.0	FET	n.s.	
Panic disorder	4.4	1.0	2.0	FET	n.s.	
Agoraphobia	0.0	4.0	3.3	FET	n.s.	
Social phobia	13.0	15.8	9.9	2.0	n.s.	
PTSD	0.0	2.0	0.7	FET	n.s.	
Disruptive disorders	13.0	13.8	7.9	2.5	n.s.	
ADHD	21.7	8.9	5.9	6.6	0.03	A
Alcohol or cannabis ab/dep	17.4	5.0	2.0	FET	0.01	A
Alcohol ab/dep	8.7	4.0	2.0	FET	n.s.	
Cannabis ab/dep	17.4	3.0	1.3	FET	0.002	AC
Alcohol consumption	50.0	42.5	34.7	2.7	n.s.	
Cannabis consumption	13.6	9.2	2.1	FET	0.01	AB

FET = Fisher's exact tests; A = HD vs. controls; B = AD vs. controls; C = HD vs. AD; MDD = major depressive disorder; SAD = unipolar schizoaffective disorder; BPD = bipolar disorder; GAD = generalized anxiety disorder; PTSD = post-traumatic stress disorder; ADHD = attention deficit hyperactivity disorder; ab/dep = abuse or dependence.

Nearly 60% of these 86% of co-parents were directly interviewed, with a higher proportion among those of controls as compared to those of AD or HD probands (table 3). Co-parents did not differ by age or sex.

Regarding psychopathology, spouses of both HD and AD probands had higher rates of AD than those of controls. Moreover, spouses of heroin addicts exhibited drug abuse or dependence more frequently than the other co-parents.

Sociodemographic Characteristics and Psychopathology in Children

Ninety-one percent of offspring accepted the direct diagnostic interview, with a lower proportion in children of AD probands as compared to those of controls (table 2). Offspring did not differ in age or sex by parental diagnosis

status. However, offspring of psychiatric probands were less likely to be living with both parents but more likely to report exposure to traumatic events than those of controls. In addition, the socioeconomic status of the family was lower for children of AD probands than for children of controls.

Table 4 presents the lifetime prevalence rates of psychiatric disorders across the three groups of offspring. The offspring of both HD and AD probands revealed increased rates of recurrent MDD, whereas only the children of AD probands exhibited any Axis-I psychiatric disorder and any BPD more frequently than those of comparison probands. The offspring of AD probands were also found to be at an increased risk of any anxiety disorder and separation anxiety disorder compared to children of controls.

Table 5. Adjusted OR (95% CI) for psychiatric disorders in offspring of parents with SUD¹

	HD in proband	AD in proband
Any disorder	1.6 (0.7; 3.8)	1.1 (0.6; 2.2)
Any mood disorder	1.1 (0.4; 3.1)	1.0 (0.5; 2.2)
Any depression	0.9 (0.3; 2.8)	1.0 (0.4; 2.3)
Any MDD	1.3 (0.3; 5.3)	1.4 (0.4; 4.5)
MDD recurrent	8.1 (1.2; 55.3)*	7.9 (1.2; 49.4)*
MDD single	0.5 (0.1; 4.6)	0.8 (0.2; 2.8)
Any anxiety disorder	1.1 (0.4; 2.9)	1.0 (0.5; 2.1)
Separation anxiety	0.9 (0.3; 2.9)	0.7 (0.3; 1.5)
Social phobia	1.2 (0.3; 5.3)	1.3 (0.5; 3.8)
Disruptive disorders	1.2 (0.4; 4.1)	1.3 (0.6; 2.9)
ADHD	4.2 (1.2; 14.2)*	0.5 (0.1; 2.0)
Alcohol or cannabis ab/dep	16.1 (1.6; 166.6)*, ²	0.6 (0.0; 6.5) ²
Alcohol consumption	3.1 (1.4; 6.9)*, ²	0.8 (0.4; 1.6) ²
Drug consumption	5.3 (0.3; 103.5) ²	2.2 (0.2; 25.4) ²

MDD = Major depressive disorder; ADHD = attention deficit hyperactivity disorder; ab/dep = abuse or dependence. * $p < 0.05$.

¹ Adjusting for offspring age and sex, family socioeconomic status and proband comorbidity (MDD, bipolar disorders, anxiety disorders, disruptive disorders, and ADHD).

² Not adjusted for proband's ADHD.

Table 6. Psychopathology in offspring by SUD diagnoses of the 2 parents

Disorder in offspring	Disorder in co-parent	HD proband		AD proband		Control proband	
SUD	Drug ab/dep	50%	(3/6)	0%	(0/2)	0%	(0/4)
	Alcohol ab/dep	–	(0/0)	13.3%	(2/15)	0%	(0/14)
	No SUD	7.7%	(1/13)	4.2%	(3/72)	2.3%	(3/127)
Alcohol consumption	Drug ab/dep	66.7%	(4/6)	0%	(0/2)	75.0%	(3/4)
	Alcohol ab/dep	–	(0/0)	27.3%	(3/11)	38.5%	(5/13)
	No SUD	33.3%	(4/12)	45.5%	(30/66)	33.3%	(41/123)
ADHD	Drug ab/dep	16.7%	(1/6)	50%	(1/2)	0%	(0/4)
	Alcohol ab/dep	–	(0/0)	13.3%	(2/15)	0%	(0/14)
	No SUD	23.1%	(3/13)	5.6%	(4/72)	6.2%	(8/130)

SUD = Substance use disorders; ab/dep = abuse or dependence; ADHD = attention deficit hyperactivity disorder.

Moreover, children of HD probands had significantly increased rates of ADHD and alcohol or cannabis abuse/dependence than children of controls. These children also exhibited higher rates of cannabis abuse/dependence than children of alcoholic probands, whereas the offspring of probands with either type of substance dependence reported cannabis consumption more frequently than the offspring of controls.

Table 5 provides the adjusted odds ratios (OR) derived from the generalized multilevel mixed models assessing the risk of psychopathology in children. These models,

which adjusted for demographic characteristics in the families and comorbid disorders in probands, confirmed strong associations between AD and HD in probands and recurrent MDD in children. Moreover, HD in probands was associated with ADHD and SUD in offspring. Due to the rareness of alcohol and cannabis abuse/dependence in children, it was not possible to apply separate models for these specific substance disorders. However, alcohol consumption was significantly associated with HD in probands.

Effect of Co-Parental Disorders

Table 6 provides the rates of disorders in children by substance disorder status of the 2 parents. In co-parents, drug disorders (heroin, cocaine, marijuana abuse and dependence) were combined. The table was restricted to disorders significantly associated with the proband's SUD according to the generalized multilevel mixed models presented in table 5. As no child of a co-parent with drug or alcohol disorders exhibited recurrent MDD, this diagnosis could not be included in the table. Although the absolute numbers of affected children were small, it is remarkable that 3 out of 6 children with both parents affected by drug disorders met criteria for SUD. Moreover, 2 out of the 3 children who did not develop SUD in these families were less than 10 years old. Four (2 of them developed SUD) out of the 6 children with 2 parents with drug use disorders were no longer living with the 2 parents, whereas this was true for only one third of the offspring of families of HD probands and a co-parent without SUD.

With respect to alcohol consumption or ADHD in offspring, the rates of these disorders were not particularly high in children of parents who were concordantly affected by SUD.

Generalized multilevel mixed models revealed significant interactions between HD in probands and drug disorders in co-parents as well as between AD in probands and alcohol disorders in co-parents to affect the risk of SUD in children (with adjustment for comorbid mood and anxiety disorders in the two parents as well as ADHD and DBD in probands):

$$\begin{aligned} \text{Odds of SUD}_{\text{children}} = & -0.269 + (\text{effects of covariates}) \\ & + 0.080 \times \text{HD}_{\text{prob}} - 0.003 \times \text{AD}_{\text{prob}} - 0.007 \times \text{HD}_{\text{co-par}} \\ & - 0.009 \times \text{AD}_{\text{co-par}} + 0.333 \times \text{HD}_{\text{prob}} \times \text{HD}_{\text{co-par}} \\ & + 0.151 \times \text{AD}_{\text{prob}} \times \text{AD}_{\text{co-par}} \end{aligned}$$

The drug-drug and alcohol-alcohol interactions were significant at $p = 0.0066$ and $p = 0.0335$, respectively. This means that the combined effect of 2 affected parents on the risk for a child was higher than what would be expected for the product of the effect of each affected parent. These interactions remained statistically significant after adjustment for the family factor 'living with both parents' ($p = 0.0067$ and $p = 0.0338$, respectively) as well as after adjustment for exposure to traumatic events ($p = 0.0015$ and $p = 0.0006$, respectively).

With respect to alcohol consumption and ADHD in children, the models did not reveal significant interactions between parental substance use diagnoses. Moreover, after introducing the main effects of co-parental

disorders into the models, the association between HD in probands and alcohol consumption ($\text{OR} = 2.2$, 95% CI 0.7–6.7) or ADHD ($\text{OR} = 3.4$, 95% CI 0.6–18.8) in children no longer reached statistical significance.

Regarding the risk of recurrent MDD in offspring, which was not associated with drug or alcohol disorders in co-parents, we could establish that the elevated rates of this disorder in offspring of HD and AD probands was not due to mood disorders in co-parents or the family factor 'living with both parents' given that the model adjusting for these two factors still revealed significant associations between the proband's HD or AD and the offspring's recurrent MDD ($\text{OR} = 9.8$, 95% CI 1.5–63.3 and $\text{OR} = 10.7$, 95% CI 1.1–106.5, respectively). The models including the child's exposure to traumatic events still provided similar results for the association between HD or AD in probands and the offspring's recurrent MDD ($\text{OR} = 5.9$, 95% CI 0.7–51.0 and $\text{OR} = 16.4$, 95% CI 2.0–136.0, respectively), although the association between the proband's HD and the child's recurrent MDD failed to reach statistical significance.

Discussion

The most salient findings of the present study are: (1) children of parents with both HD or AD have approximately 8 times elevated rates of recurrent MDD; (2) children of parents with HD but not with AD are at a more than 3 times increased risk of ADHD and approximately 16 times increased risk of SUD than children of controls after adjustment for demographic characteristics and the proband's comorbid disorders, and (3) parental concordance for drug and alcohol disorders is likely to be associated with a particularly high risk of early SUD in offspring.

Although we did not observe a significantly elevated overall risk of Axis-I mental disorders in our young sample after adjustment for demographic variables in children and comorbid disorders in probands, our findings of an elevated risk of specific mental disorders in these offspring at high risk support and extend those of the majority of previous research in this field [21, 23–25, 27, 28, 30–32]. Indeed, several but not all studies have documented increased rates of mood disorders or internalizing disorders in the offspring of heroin addicts [23–25] as well as in offspring of probands with AD [23, 24]. However, the largely increased rate of the recurrent depression subtype regardless of the type of proband's SUD has not been demonstrated before. Interestingly and in contrast

to our expectations, we did not find higher rates of psychopathology in the offspring of HD probands as compared to that of alcoholic probands with the exception of ADHD and SUD. The significantly elevated rate of ADHD in the offspring of HD but not AD probands corroborates a similar finding in the study of Wilens et al. [23].

In contrast to most previous research, we could control for the effects of comorbid disorders in probands and co-parents, given the systematic collection of diagnostic information on the 2 parents. This allowed us to show that the elevated risk of recurrent MDD in the high-risk children was not due to the direct parent-offspring transmission of these disorders. This increased risk could be attributable either to particular environmental circumstances in the families of dependent probands or genetic factors shared by SUD and MDD. However, although the factors 'living with both biological parents' and the child's exposure to traumatic events, which can be considered as indicators of the child's exposure to stress, were found to be associated with the proband's SUD, the adjustment for these factors in our models only slightly affected the results. In addition, it has been recently shown that the occurrence of early childhood disorders, such as MDD, is likely to increase the risk of the subsequent development of SUD [50].

Regarding the risk of ADHD, the strong association between this disorder in offspring and HD in probands was no longer significant after adjusting for co-parental variables. However, the OR >3 together with the large CI is an indicator of insufficient statistical power to accurately establish this association.

As to SUD, the effect of parental concordance on the risk of psychopathology in children is difficult to establish given that offspring of 2 parents with these disorders are rare. In our study, after the inclusion of co-parental variables, our results were compatible with an interaction between SUD in the 2 parents in relation to the risk of these disorders in children. The finding of a particularly high risk for SUD in children of parents concordant for these disorders is in line with previous studies that documented an association between the number of affected parents and psychopathology [27, 28] or alcohol consumption [31] in children. Our observation according to which children of concordantly affected parents were more likely to live with only 1 biological parent could indicate that they were exposed to a less stable familial environment. Moreover, having at least 1 non-affected biological parent is likely to have a protective effect on the child. However, the interactions between SUD in the 2

parents remained significant after the adjustment for the factors 'living with both biological parents' and the child's exposure to traumatic events. Alternatively, the high risk of SUD in children of concordantly affected biological parents could be attributable to genetic interaction.

Strengths and Limitations

In contrast to previous high-risk research on SUD, which rarely included probands with both AD and HD, the design of the present study allowed us to simultaneously compare the risk of specific DSM-IV disorders in the offspring of probands with both major subtypes of dependences to that of children of a medical comparison group. Moreover, the collection of diagnostic information on the biological co-parent enabled us to examine the association between the SUD of the 2 parents and the risk of mental disorders in offspring. In addition, unlike most previous studies which lumped several drug disorders together, our results are based on a homogeneous proband group of heroin addicts and we were able to adjust for the effects of co-morbid disorders in probands, which are very common in patients with drug or AD.

The results of the present study should be considered in the context of several limitations. First, our offspring sample and in particular that of probands with HD was small and the latter proband group also revealed selection bias with respect to comorbid lifetime ADHD (absence of this disorder in HD probands). Accordingly, conclusions regarding the children of heroin addicts need to be taken with caution. Moreover, the size of the samples in our study was too small to accurately estimate the prevalence of relatively rare disorders in childhood and adolescence such as BPD. Similarly, our small sample size did not allow us to adjust for the effect of rare co-morbid disorders in the co-parents. Second, although probands who agreed to enroll at least 1 of their children in the study and those who did not were found to differ only with respect to the rates of comorbid ADHD among heroin addicts, we have no information on children of the latter probands. It is possible that highly disrupted families, which were most severely affected by the proband's disorder, were less likely to participate. As the offspring in such families are likely to be at a higher risk of psychopathology and malfunctioning, the present study may provide a too optimistic picture of the children of SUD parents. Third, diagnoses of approximately 5% of the offspring of HD and control probands as well as approximately 14% of the offspring of AD probands were based on family history reports rather than direct inter-

views. Given the significantly lower proportion of interviewed offspring of probands with AD, the rates of psychopathology in these children could have been underestimated. Fourth, although a lifetime history of mental disorders was collected for 91% of biological co-parents, we had no direct diagnostic interview and had to rely on family history reports for 43% of them.

Implications

The findings of the present study have several potential clinical implications. First, the higher risk of early recurrent depression, SUD and ADHD in the offspring of these families emphasizes the need to pay particular attention to these children. The prompt identification and treatment of early psychopathology in these children may be critical for the prevention of the development of more severe SUD and other mental disorders. Second, the find-

ing of an interaction between SUD in the 2 parents to affect the risk of SUD in their children supports the involvement of co-parental disorders in the development of psychopathology in children of AD and HD patients and highlights the need to pay clinical attention not only to the affected proband but also to his/her partner in order to optimize prevention in offspring.

Longitudinal studies that follow high-risk youth through adolescence and early adulthood are necessary to determine to which extent early recurrent depression and SUD are only a temporary phenomenon or a predictor of subsequent severe SUD. Similarly, prospective research would also allow the study of the links between ADHD and early manifestations of mood disorders and the later development of SUD and other adult mental disorders.

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