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Childhood sexual abuse and risks for licit and illicit drug-related outcomes: a twin study

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ABSTRACT

Background. This study examined the relationships between self-reported childhood sexual abuse (CSA) and drug-related outcomes in an Australian twin panel.

Method. A semi-structured psychiatric interview was conducted in 1996–2000 by telephone with young adult Australian twins (mean age 29·9 years). Data reported here are from 6050 twins who responded to both CSA and drug-related items.

Results. A history of CSA was associated with significant risk for subsequently occurring regular smoking and use of each illicit drug class. Further CSA-associated risk was found among regular users, for nicotine and alcohol dependence, and among illicit drug users, for abuse/dependence of most drug classes. In same-sex discordant pairs, significant risk for regular smoking and illicit drug use was found in twins with a history of CSA compared to their non-abused co-twins. Similar analyses for abuse/dependence found significant risk for opioids, any illicit drug, and any non-cannabis illicit drug. CSA was associated with significantly earlier drug use. Despite the association of CSA with risk for early-onset cannabis use and regular smoking, risks for illicit drug outcomes associated with CSA and with either form of early-onset use combine in near-additive fashion.

Conclusions. CSA is associated with risk for subsequently occurring regular smoking and illicit drug use and abuse/dependence. Risks for drug use are mildly attenuated with control for familial contributions; similar risks for abuse/dependence remain significant for opioids and for illicit drugs combined across classes. Although we found evidence of earlier onset drug use with CSA, risks associated with CSA and with early-onset use combine in a largely additive manner.

INTRODUCTION

A high prevalence of childhood abuse has been reported in samples of adolescents (Harrison *et al.* 1989; Clark *et al.* 1997) and adults (Bartholomew *et al.* 2002; Simpson & Miller, 2002) receiving substance use disorders (SUDs) treatment. Although maltreatment occurs in various forms, childhood sexual abuse (CSA) is the most studied (Simpson & Miller, 2002). In adolescents receiving SUDs treatment, a history of CSA was associated with earlier initiation of licit and illicit drug use (Harrison *et al.* 1989). Similarly, earlier injection drug use occurs in adult injection drug users with a history of CSA (Ompad *et al.* 2005).

Ethically and legally mandated reporting has caused investigators to reject prospective, naturalistic examinations for other research designs. Anonymous, questionnaire-based assessment of large, school-ascertained samples (Harrison *et al.* 1997; Bensley *et al.* 1999) have found CSA-associated risk for licit and illicit substance use including earlier initiation and greater

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frequency of use. Given that Lynskey *et al.* (2003) found early-onset cannabis use (i.e. prior to age 17) to be a significant risk factor for use and abuse/dependence of other illicit drugs in their sample, CSA-associated earlier onset substance use could also be a source of risk for these more distal outcomes.

Examinations in general population samples that have obtained CSA history by retrospective report from young adults have confirmed associations with substance dependence (Mullen *et al.* 1993; Fergusson *et al.* 1996*b*; Molnar *et al.* 2001). However, reports have also noted that parental SUDs are associated with significant risk for offspring CSA (Fergusson *et al.* 1996*b*; Fleming *et al.* 1997; Nelson *et al.* 2002; Walsh *et al.* 2003). As SUDs are known to be moderately heritable (Heath *et al.* 1997; Tsuang & Lyons, 1998; Kendler *et al.* 2003), it is possible that parental SUDs may be a source of risk in offspring for both CSA and drug-related outcomes. Unfortunately, investigations in general population samples have included limited assessment of, and control for, parental psychopathology.

Twin studies (Kendler *et al.* 2000; Nelson *et al.* 2002) enable additional methods of controlling for familial background while estimating adversity-associated risk. Because twins share family background risk factors, co-twin control comparisons made in CSA-discordant pairs provide a useful means of estimating CSA-associated risk. Optimally, comparisons limited to monozygotic (MZ) twins would enable complete control for genetic and family environmental risk factors. However, because only data from pairs discordant for both CSA and the examined outcome are informative for these analyses, sample size limitations generally necessitate including discordant dizygotic (DZ) pairs (Kendler *et al.* 2000; Nelson *et al.* 2002).

Kendler *et al.* (2000) assessed CSA history by a mailed questionnaire and substance dependence by an in-person interview in adult female twins. They found CSA-associated risks for alcohol and any illicit drug dependence that remained significant, with inclusion of family functioning measures as covariates. The risks were greatest when CSA involved intercourse. They examined risks in CSA-discordant pairs in analyses that incorporated varying degrees of CSA and discordance. All odd ratios were greater than unity for alcohol dependence (half reached significance). For drug dependence, most risks fell below significance, presumably limited by the small numbers (5–15) of doubly-discordant pairs.

The current report examines the relationship between CSA and licit and illicit drug outcomes in a large Australian young adult twin cohort. We extend findings from previous reports by: (1) providing separate estimates of risk for two classes of licit drugs and five classes of illicit drugs; (2) excluding individuals whose use of the specific drug being examined predated their first occurrence of CSA; (3) separately estimating CSA-associated risks for (*a*) drug use and (*b*) drug-related disorders among users; (4) using a large sample of CSA-discordant twins to estimate CSA-associated risks controlling for family background factors; and (5) estimating the risks associated with CSA only, early-onset substance use only, and both in combination, and examining whether a significant interaction is seen that would have important implications for prevention efforts.

METHOD

Sample

The young adult cohort of the Australian Twin Register is a volunteer panel composed of twins born 1964–1971 (Heath *et al.* 2001; Nelson *et al.* 2002; Lynskey *et al.* 2002, 2003; Knopik *et al.* 2004). Nearly all were registered by parents between 1980 and 1982 in response to approaches through school systems or mass media. Twins were recontacted and verbal consent obtained according to the protocol approved by the institutional review boards of Washington University School of Medicine and the Queensland Institute of Medical Research. Data reported here were collected between 1996 and 2000 by a comprehensive telephone assessment administered to all consenting cohort members by trained lay interviewers.

Of 4010 pairs that could be traced, interviews were completed with both members of 2765 pairs (69% pairwise response rate) and one member of 735 pairs (78% individual response rate). The current sample includes all 6050 individuals with data available for both CSA and drug use. The sample is 55·5% female;

mean age is 29·9 years (S.D. = 2·5). The educational background of the sample suggests no major social class bias: 45·6% did not graduate from high school, 20·3% had a high school diploma without post-secondary education, and 34·1% had some post-secondary education. The prevalence and characteristics of CSA in this cohort have been observed (Nelson *et al.* 2002) to resemble general population reports (Fergusson *et al.* 1996*b*; Fleming, 1997; Holmes & Slap, 1998). The rates of illicit drug use are similar to those reported in an Australian epidemiological study (Australian Institute of Health and Welfare, 1999).

Assessment of illicit drug-related outcome measures

A standardized psychiatric diagnostic assessment adapted from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz *et al.* 1994) was administered by telephone. The interview enabled lifetime DSM-IV (APA, 1994) diagnoses including nicotine (cigarettes only) dependence and alcohol dependence. Regular use of nicotine (at least weekly for 3 consecutive weeks) and alcohol (at least monthly for 6 consecutive months) was also queried.

The interview's illicit drug section assessed two of four abuse criteria and four of seven dependence criteria. Drug use disorders were operationalized according to Lynskey *et al.* (2002, 2003) (i.e. abuse as endorsement of either abuse criterion; probable dependence as endorsement of two or more dependence criteria). The abuse assessment, though diagnostic, would miss cases with maladaptive use limited to non-assessed categories. The non-diagnostic dependence assessment has excellent sensitivity and specificity for DSM-IV drug dependence (Lynskey *et al.* 2002, 2003). We combined abuse and dependence within each drug class as in Lynskey *et al.* (2003). We examined use (i.e. any whatsoever) and abuse/dependence of five classes of illicit drugs: (1) cannabis; (2) opiates; (3) sedatives (including benzodiazepines and barbiturates); (4) stimulants; and (5) cocaine. For the discordant pair analyses, two composite variables were coded to reflect the use of any, and any non-cannabis, illicit drug. Composite variables were similarly coded for any, and any non-cannabis, illicit drug abuse/dependence. Early-onset use was defined as occurring before age 17 years for cannabis (Lynskey *et al.* 2003) and before age 16 for regular smoking.

Assessment of CSA

A composite variable for CSA was derived from five component questions (Nelson *et al.* 2002): (1) Before age 18, were you ever forced into sexual intercourse or any other form of sexual activity? (2) Before you were 16 years old, were there any sexual contacts between you and anyone other than a family member who was 5 or more years older than you were? By sexual contact I mean their touching your sexual parts, you touching their sexual parts, or sexual intercourse (coded positively where subjects responded to a follow-up question that contact was 'ever forced'). (3) Before you were 16 years old, were there any sexual contacts between you and any family members, like a parent or step-parent, grandparent, uncle, aunt, brother or sister, or cousin? By sexual contact I mean their touching your sexual parts, you touching their sexual parts, or sexual intercourse (coded positively where subjects responded to further questions that contact involved either an adult or the use of force by a child). The final two questions contain descriptions in parentheses that were not read aloud to protect confidentiality (they appeared in a booklet mailed to respondents). This section was skipped if respondents misplaced their booklets. (4) How about event no. 5 [You were raped (someone had sexual intercourse with you when you did not want to, by threatening you or using some degree of force)]? (Included within CSA when first occurred before age 18.) (5) Apart from event no. 5 did event no. 6 [You were sexually molested (someone touched or felt your genitals when you did not want them to)] ever happen to you? A binary CSA variable was coded positive with endorsement of any of these items. Data were excluded from individuals who reported an onset $\geqslant$18 years for all endorsed CSA items or from those refused to respond to a CSA component question without endorsing another component item. Data from nine individuals missing CSA onset were excluded from analyses requiring onset information. Although age 17 is the highest upper limit commonly used for CSA onset, our sample's mean onset is similar to values observed in general population samples.

Data analysis

We used SAS (SAS Institute, 2000) and the Stata Statistics and Data Analysis Package version 6.0 (Stata Corporation, 1999) for analyses. An α-level of 0·05 was required for significance. The robust variance estimator option in STATA adjusted all 95% confidence intervals (CIs) for the statistical non-independence of observations from twin pairs.

We calculated the prevalence of drug use, by CSA history, in women and men. We calculated the prevalence, by CSA history, of licit drug dependence in regular users, and illicit drug abuse/dependence in (ever) users.

We performed survival analysis using Cox proportional hazard regression models to estimate the CSA-associated risk, controlling for gender, for regular licit drug use and use of each illicit drug class. These analyses treated CSA as a time-dependent covariate to calculate hazard ratios, estimating outcome risks associated with the prior experience of CSA. We similarly examined the risk with the prior experience of CSA, controlling for gender, for: (1) licit drug dependence, limited to regular users; and (2) illicit drug abuse/dependence, limited to users of that drug class, using the age at first use for each drug as a conservative estimate for abuse/dependence onset (not obtained).

We performed discordant pair analyses using conditional logistic regression to estimate the risk in CSA-positive *versus* CSA-negative pair members to examine CSA-associated risks controlling for the contribution of familial factors. Data from DZ opposite-sex pairs were excluded to eliminate bias due to gender differences in substance use and CSA prevalence. The remaining same-sex CSA-discordant pairs ($n=$ 280) included 96 MZ female, 111 DZ female, 31 MZ male and 42 DZ male pairs. Only data from doubly-discordant pairs (i.e. discordant for both CSA and the outcome being examined) are informative for these analyses. Odds ratios (ORs) are easily calculated as the ratios of the number of pairs in which the twin with a history of CSA is also outcome-positive (n_{21}) to pairs in which the twin reporting CSA is outcome-negative (n_{12}). The outcomes examined included the regular use of licit drugs and the use and abuse/dependence of illicit drugs of the various classes, any illicit drug, and any non-cannabis illicit drug. We excluded pairs in which the CSA-positive twin reported first use of the illicit drug being examined predated CSA onset. We report n_{21} and n_{12} separately by zygosity with ORs and 95% CIs only for the combined group. We used an option in STATA to test whether the risk estimates differed by zygosity or gender and reported values separately when we found significant interactions.

To test for the contribution of CSA to the age at onset of drug use, we fit a series of linear regression models that controlled for gender for which all values are in units of age (years). The intercept is the mean onset for CSA-negative women, and regression coefficients represent the incremental changes associated with CSA and male gender. We excluded individuals whose first use of the examined drug predated CSA onset. We used logistic regression to examine the CSA-associated risk, controlling for gender, for early-onset cannabis use. We coded dummy variables to represent a history of both CSA and early-onset cannabis use, CSA without early-onset cannabis use, or early-onset cannabis use without CSA for use in logistic regression analyses examining the risk for use and abuse/dependence of the illicit drug classes, controlling for gender. Additional logistic regression analyses that included main effects for gender, CSA, and early-onset cannabis use and an interaction term (CSA $\times$ early-onset cannabis use) evaluated whether significant interactions were found. We repeated these analyses substituting early-onset regular smoking for early-onset cannabis use and including cannabis outcomes as dependent variables.

RESULTS

A history of CSA was reported by 17·4% of women and 6·0% of men (OR 3·31, 95% CI 2·73–4·00). CSA began early [mean age 10·7 years (S.D. $=4·09$)] and was preceded uncommonly by regular licit drug use and rarely by illicit drug use (regular smoking preceded CSA in 69 of 477 individuals reporting both; the similar ratios for other substances are: regular alcohol use 30/643; cannabis use 24/542; opioid use 0/101; sedative use 5/145; stimulant use 3/245; and cocaine use 0/92).

Women and men with a history CSA more commonly reported regular smoking and use of

Table 1. *Comparison of the prevalence (%) of licit and illicit substance outcomes by gender and childhood sexual abuse (CSA) status*

	Women ($n=3357$)		Men ($n=2693$)		Women		Men	
	CSA +	CSA −	CSA +	CSA −	CSA +	CSA −	CSA +	CSA −
Licit	Regular use				Dependence (among regular users)			
Nicotine	63·8	47·8	68·9	52·5	66·1	53·3	77·5	59·2
Alcohol	85·9	86·3	92·6	93·0	32·7	14·9	45·0	32·1
Illicit	Any use				Abuse/dependence (among users)			
Cannabis	71·7	49·0	82·0	67·8	34·9	19·4	50·0	34·8
Opioids	11·5	4·2	23·0	6·8	37·3	16·2	29·7	10·5
Sedatives	18·0	6·9	27·3	7·7	14·3	6·3	27·3	7·7
Stimulants	29·2	13·8	49·1	24·0	24·1	16·9	32·9	20·4
Cocaine	9·1	3·9	25·5	7·2	11·3	7·3	12·2	10·4

Table 2. *Hazard ratios (and 95% confidence intervals, in parentheses) reflecting the risk for licit and illicit substance outcomes associated with the prior experience of childhood sexual abuse (CSA), controlling for male gender ($n=6050$)*

	CSA	Male	CSA	Male
Licit	Regular use		Dependence (among regular users)	
Nicotine	**1·49 (1·32–1·67)**	**1·13 (1·05–1·23)**	**1·49 (1·31–1·69)**	**1·22 (1·11–1·34)**
Alcohol	1·06 (0·97–1·15)	**1·38 (1·31–1·45)**	**1·99 (1·71–2·33)**	**2·19 (1·95–2·46)**
Illicit	Any use		Abuse/dependence (among users)	
Cannabis	**1·73 (1·57–1·92)**	**1·62 (1·51–1·74)**	**1·73 (1·46–2·05)**	**1·84 (1·61–2·10)**
Opioids	**3·09 (2·43–3·95)**	**1·70 (1·37–2·11)**	**2·60 (1·60–4·22)**	0·65 (0·40–1·06)
Sedatives	**3·00 (2·44–3·69)**	**1·21 (1·00–1·46)**	**2·61 (1·43–4·78)**	1·46 (0·80–2·64)
Stimulants	**2·28 (1·96–2·66)**	**1·82 (1·61–2·06)**	**1·54 (1·13–2·11)**	1·27 (0·98–1·65)
Cocaine	**2·89 (2·25–3·71)**	**2·08 (1·66–2·60)**	1·22 (0·58–2·53)	1·27 (0·66–2·44)

Values are in bold face where hazard ratio is significant ($p<0·05$).

each class of illicit drug examined, but not regular alcohol use (Table 1). Survival analysis revealed that, controlling for gender, a history of CSA is associated with significant risk for subsequently occurring regular smoking and use of all examined classes of illicit drugs (Table 2). The strongest effects were observed for opioids, sedatives and cocaine, the least prevalent drug classes. CSA is thus associated with significant risk for regular smoking and cannabis use, two fairly normative behaviours in our sample, but not with the almost ubiquitous regular alcohol use. Greater risk is observed for use of the less-prevalent illicit drugs.

Among regular users, a history of CSA was found by survival analysis to be associated with risk for nicotine and alcohol dependence. Similarly, among those reporting illicit drug use, a history of CSA was associated with significant risk for subsequently occurring abuse/dependence of each examined class of drugs other than cocaine; the strongest effects were observed for opioids and sedatives. Among those who have initiated substance use, CSA-associated risk for substance use disorders is observed.

In CSA-discordant same-sex pairs, significant risk for regular smoking and use of cannabis, opioids, sedatives and cocaine was seen in twins reporting a history of CSA compared to their non-sexually abused co-twins; the risk for stimulant use fell just below significance (Table 3). Analyses that combined drug categories found significant risk in the twins with a history of CSA compared to their non-abused co-twins for any illicit drug use and any non-cannabis illicit drug use. In similar examinations of drug abuse/dependence, risk estimates exceeded unity for all drug classes, but reached significance only for opioids (OR 6·50). Significant abuse/dependence risk was found for any illicit drug (OR 1·78) and any non-cannabis

Table 3. *Comparison of drug use and abuse/dependence in CSA+ versus CSA− members of same-sex discordant pairs (n = 280 pairs)*

Substance-related outcome	n_{21}/n_{12} MZ	DZ	Combined	Within-pair risk OR (95% CI)
Licit – regular use				
Nicotine	17/7	28/19	45/26	**1·73 (1·07–2·81)**
Alcohol	7/8	12/7	19/15	1·27 (0·64–2·49)
Illicit – any use				
Cannabis	19/17	29/12	48/29	**1·66 (1·04–2·62)**
Opioids	6/8	21/5	27/13	**2·08 (1·07–4·03)**
Sedatives	15/9	23/11	38/20	**1·90 (1·11–3·27)**
Stimulants	18/9	24/17	42/26	1·62 (0·99–2·63)
Cocaine	9/4	14/5	23/9	**2·56 (1·18–5·52)**
Any illicit drug	22/13	29/14	51/27	**1·89 (1·19–3·01)**
Non-cannabis illicit drug	23/11	36/22	59/33	**1·79 (1·17–2·74)**
Illicit – abuse/dependence				
Cannabis	11/11	21/14	32/25	1·28 (0·76–2·16)
Opioids	5/1	8/1	13/2	**6·50 (1·47–28·80)**
Sedatives	3/0	6/2	9/2	4·50 (0·97–20·83)
Stimulants	7/3	12/8	19/11	1·73 (0·82–3·63)
Cocaine	2/1	4/2	6/3	2·00 (0·50–8·00)
Any illicit drug	14/8	27/15	41/23	**1·78 (1·07–2·97)**
Non-cannabis illicit drug	8/3	16/8	24/11	**2·18 (1·07–4·45)**

CSA, Childhood sexual abuse; MZ, monozygotic; DZ, dizygotic; OR, odds ratio; CI, confidence interval. n_{21}, the number of doubly-discordant pairs in which the twin reporting CSA is also outcome-positive; n_{12}, the number of doubly-discordant pairs in which the twin reporting CSA is outcome-negative.

OR and 95% CI are for combined MZ and DZ same-sex pairs.

Values are in bold face where OR is significant ($p < 0{\cdot}05$).

illicit drug (OR 2·18). Using data from discordant same-sex pairs to control for familial contributions to risk, persistent CSA-associated risk is seen for regular smoking, use of most classes of illicit drugs, and abuse/dependence of opioids, any illicit drug, and any non-cannabis illicit drug.

Separate discordant pair analyses (results not shown) performed to determine whether risk estimates differed by zygosity found significantly greater risk in DZ (OR 4·20, 95% CI 1·58–11·14) than in MZ pairs (OR 0·75, 95% CI 0·26–2·16) only for opioid use. Similar analyses found significant gender differences only for cocaine use, with greater risk in male (OR 13·00, 95% CI 1·70–99·36) than in female (OR 1·25, 95% CI 0·49–3·17) pairs.

Regression analyses found a significant contribution for a history of CSA, controlling for gender, to age at onset of regular nicotine and alcohol use (Table 4). Similar effects on the age at first use of illicit drugs were seen for all drug classes, but fell below significance for sedatives and cocaine; the largest effects were observed for cannabis and opioids. We examined whether a history of CSA was also associated with risk for early-onset cannabis use (Lynskey *et al.* 2003) and found significant risk (OR 2·93, 95% CI 2·41–3·58), controlling for male gender (OR 2·03, 95% CI 1·72–2·40). These data confirm that CSA is associated with risk for earlier substance use onset.

An examination of the risks for the use of the other drug classes associated with both CSA and early-onset cannabis use, CSA alone, early-onset cannabis use alone, and male gender found significantly greater risk for the use of all examined classes of illicit drugs associated with a history of both CSA and early-onset cannabis use than with either risk factor alone (Table 5). A similar examination of the risks for abuse/dependence of the other illicit drugs classes observed greater risk associated with the presence of both CSA and early-onset cannabis use. Additional examinations revealed no significant interaction (CSA × early-onset cannabis use) in any model (all p values $> 0{\cdot}10$). Thus, in those reporting both CSA and early-onset cannabis use, the risks associated with either factor alone combine in a near-additive fashion (i.e. the

Table 4. *Results of multivariate regression analyses examining the contribution of childhood sexual abuse (CSA) status and gender to the onset of substance use*

		Regression coefficients (95% CI)	
	Intercept (95% CI)	CSA status	Male
Licit – regular use			
Nicotine ($n=3063$)	16·77 (16·60–16·93)	**−0·47 (−0·79 to −0·14)**	**−0·28 (−0·51 to −0·05)**
Alcohol ($n=5363$)	18·62 (18·51–18·73)	**−0·27 (−0·52 to −0·02)**	**−0·78 (−0·93 to −0·63)**
Illicit – use			
Cannabis ($n=3588$)	19·43 (19·24–19·62)	**−0·86 (−1·19 to −0·52)**	**−0·78 (−1·02 to −0·54)**
Opioids ($n=386$)	22·33 (21·60–23·06)	**−1·12 (−2·16 to −0·09)**	0·09 (−0·80 to 0·97)
Sedatives ($n=523$)	21·88 (21·27–22·50)	−0·42 (–1·36 to 0·51)	**−0·86 (−1·69 to −0·03)**
Stimulants ($n=1231$)	21·37 (21·02–21·73)	**−0·69 (−1·25 to −0·13)**	−0·02 (−0·45 to 0·41)
Cocaine ($n=381$)	23·01 (22·35–23·67)	−0·47 (–1·41 to 0·47)	0·64 (−0·15 to 1·43)

CI, Confidence interval.
Values are in bold face where regression coefficient differs significantly from zero ($p<0·05$).

Table 5. *The contributions*[a] *to the risk for use and abuse/dependence of illicit drugs from childhood sexual abuse (CSA), early-onset substance use, and both ($n=6050$): (a) cannabis and (b) regular smoking*

Substance-related outcome	Both CSA and early-onset cannabis use ($n=185$)	CSA only ($n=559$)	Early-onset cannabis use only ($n=649$)	Male ($n=2693$)
Any use				
Opioids	**7·93 (5·46–11·51)**	**3·02 (2·19–4·16)**	**3·36 (2·56–4·40)**	**1·57 (1·25–1·97)**
Sedatives	**9·19 (6·53–12·92)**	**3·13 (2·36–4·14)**	**4·26 (3·35–5·42)**	1·06 (0·86–1·30)
Stimulants	**9·93 (7·27–13·56)**	**2·23 (1·79–2·79)**	**4·65 (3·88–5·57)**	**1·79 (1·55–2·08)**
Cocaine	**11·62 (7·99–16·89)**	**2·52 (1·73–3·66)**	**5·38 (4·15–6·97)**	**1·82 (1·42–2·34)**
Abuse/dependence				
Opioids	**22·93 (11·91–44·16)**	**7·11 (3·68–13·76)**	**4·93 (2·57–9·47)**	1·06 (0·63–1·77)
Sedatives	**32·20 (14·15–73·26)**	**9·80 (4·30–22·34)**	**7·21 (3·18–16·34)**	1·66 (0·85–3·21)
Stimulants	**11·11 (7·15–17·26)**	**2·83 (1·85–4·34)**	**4·80 (3·50–6·60)**	**1·89 (1·43–2·51)**
Cocaine	**27·15 (10·69–68·97)**	2·03 (0·43–9·63)	**11·11 (5·02–24·58)**	2·01 (0·98–4·12)

Substance-related outcome	Both CSA and early regular nicotine ($n=230$)	CSA only ($n=508$)	Early regular nicotine use only ($n=911$)	Male ($n=2692$)
Any use				
Cannabis	**7·97 (5·26–12·08)**	**2·21 (1·80–2·72)**	**3·28 (2·73–3·93)**	**2·11 (1·97–2·38)**
Opioids	**6·71 (4·66–9·65)**	**3·00 (2·15–4·19)**	**2·43 (1·87–3·17)**	**1·69 (1·35–2·12)**
Sedatives	**7·82 (5·71–10·70)**	**3·04 (2·27–4·06)**	**2·84 (2·26–3·56)**	1·15 (0·94–1·40)
Stimulants	**5·67 (4·24–7·58)**	**2·51 (2·01–3·15)**	**2·69 (2·28–3·17)**	**1·93 (1·67–2·23)**
Cocaine	**6·06 (4·12–8·92)**	**2·87 (2·03–4·06)**	**2·35 (1·80–3·07)**	**2·07 (1·63–2·63)**
Abuse/dependence				
Cannabis	**7·80 (5·81–10·48)**	**2·52 (1·97–3·21)**	**3·40 (2·85–4·05)**	**2·69 (2·30–3·15)**
Opioids	**18·90 (9·31–38·37)**	**9·26 (4·73–18·12)**	**4·56 (2·41–8·63)**	1·16 (0·70–1·93)
Sedatives	**25·17 (11·24–56·38)**	**10·49 (4·76–23·11)**	**4·98 (2·20–11·23)**	1·86 (0·98–3·54)
Stimulants	**9·75 (6·41–14·84)**	**2·57 (1·68–4·20)**	**3·36 (2·47–4·58)**	**2·09 (1·58–2·76)**
Cocaine	**11·27 (4·40–28·91)**	2·97 (0·93–9·48)	**3·31 (1·53–7·15)**	**2·46 (1·23–4·94)**

[a] Analyses control for gender; odds ratios and 95% confidence intervals are reported.
Values are in bold face where the odds ratio is significant ($p<0·05$).

absence of any interaction reaching significance indicates that the risks associated with CSA and with early cannabis use combine in a manner that does not significantly differ from additive).

We conducted a similar set of analyses for early-onset regular smoking (before age 16), finding significant CSA-associated risk (OR 2·38, 95% CI 1·99–2·85), controlling for male

gender (OR 1·39, 95% CI 1·20–1·61). We found a similar pattern of risks associated with either CSA or early-onset regular smoking alone or both in combination for outcomes that additionally included cannabis use and abuse/dependence (Table 5). Further analyses again confirmed the absence of significant interactions. The risks associated with a history of CSA, and with early-onset substance use, for the use and abuse/dependence of illicit drugs appear to be largely additive.

DISCUSSION

Our analyses strongly support the association of CSA with risk for licit and illicit drug-related outcomes. We found that CSA is associated with risk for subsequently occurring drug use and, among users, for drug-related disorders. In analyses limited to CSA-discordant same-sex pairs in which the non-abused co-twin served as a control for the contribution of familial factors, we found similar CSA-associated risks for substance use. Similar examinations revealed significant risk only for opioid, any illicit drug, and any non-cannabis illicit drug abuse/dependence. Although we found CSA to be a risk factor for earlier initiation of substance use, we observed that risks for illicit drug use and abuse/dependence associated with CSA combine in a largely additive manner with those from either early-onset cannabis use or early-onset regular smoking (i.e. no significant interaction).

Our findings are very consistent with prior studies that have examined the association of CSA with licit and illicit drug outcomes. Large, anonymous, school-based assessments of adolescents found CSA-associated risk for licit and illicit drug use, including the use of multiple classes of drugs (Harrison *et al.* 1997; Bensley *et al.* 1999). High CSA prevalence has been consistently reported in substance abuse treatment samples (Simpson & Miller, 2002). Significant associations with alcohol and drug abuse and dependence have been observed in community samples of young adults (Mullen *et al.* 1993; Fergusson *et al.* 1996*a*) and in the National Comorbidity Survey sample (Molnar *et al.* 2001). Our results describe CSA-associated risks more comprehensively: (1) for the subsequent occurrence of both drug use and, among users, of drug-related disorders, (2) extending to both licit and illicit drug-related outcomes, and (3) of greatest magnitude for outcomes involving opioids and sedatives.

Our report is the first to examine drug use in CSA-discordant male and female same-sex twin pairs. Reporting on the largest CSA-discordant pair sample to date, we found that regular smoking and use of each class of drugs (the result for stimulants fell just below significance) are reported more frequently by twins with a history of CSA than their non-abused co-twins. Given the consistency of our discordant pair and survival analysis results, we conclude that CSA-associated risks for regular smoking and illicit drug use are only mildly attenuated with co-twin control for the contributions of familial risk factors.

We previously reported significant CSA-associated risks for nicotine dependence and alcohol dependence in discordant pair analyses of this sample's data (Nelson *et al.* 2002). In similar analyses, Kendler *et al.* (2000) observed some significant risk for (any illicit) drug dependence and more consistent risk for alcohol dependence. As noted, their analyses had limited power. For most classes of illicit drugs, we probably faced similar limitations as best exemplified by the non-statistically significant OR of 4·5 for sedative abuse/dependence. The significant risks that we found for abuse/dependence combined across all drug classes, and for non-cannabis illicit drugs, suggest limited power for individual drug classes and are inconsistent with findings due to differing drug preferences between pair members.

Our finding of earlier drug use associated with CSA is consistent with prior reports. Earlier initiation of licit and illicit drug use has been reported for adolescents with a history of CSA assessed in either school (Harrison *et al.* 1997; Bensley *et al.* 1999) or treatment (Harrison *et al.* 1989) settings. Earlier injection drug use by those with a history of CSA has been reported in human immunodeficiency virus (HIV)-seropositive men (Holmes, 1997) and male and female injection drug users (Ompad *et al.* 2005). Our results examining the combined effects of CSA and early-onset regular smoking or cannabis use suggest that individuals with a history of CSA who develop early-onset substance use are at very high risk for

progression to other illicit drug use and abuse/dependence.

Additional study is needed to determine whether this progression can be prevented by identifying these individuals and intervening. Given that CSA-associated risks are likely to arise from a variety of sources, determining the best routes for intervention could prove challenging. Education could increase risk awareness, facilitating delayed substance use and progression. Community efforts could provide safe, supportive and substance-free alternatives to the dangerous, harsh or substance-laden home and extra-familial environments in which victimization often occurs. Treatment aimed at limiting psychiatric sequelae and attempted self-medication could diminish risk associated with emergent affective and anxiety disorders. Psychotherapy, in conjunction with the above, could aid formation of healthy relationships with contemporary peers, thereby slowing transitions to adult roles.

It is becoming increasingly clear that attempts at parsing risk to genetic and environmental components underestimate the complex biological underpinnings. Persistent alterations in stress responsivity have been observed in women with a history of CSA (Heim *et al*. 2000, 2001) and in adult rats repetitively separated as pups from their dams (Caldji *et al*. 1998, 2000). The latter also display long-lasting changes in morphine sensitization, tolerance and withdrawal (Kalinichev *et al*. 2001, 2002) and have reduced levels of both gamma-aminobutyric acid type A ($GABA_A$) and central benzodiazepine receptors in regions implicated in hypothalamic–pituitary–adrenal (HPA) axis regulation (Caldji *et al*. 1998, 2000). Thus, exposure to severe early trauma may lead to persistent alterations in gene expression. Furthermore, reports (Caspi *et al*. 2002, 2003) of significant $G \times E$ interactions involving childhood abuse and functional genetic polymorphisms for related outcomes (i.e. depression and antisocial behaviour) have had replications published (Eley *et al*. 2004; Foley *et al*. 2004; Kaufman *et al*. 2004; Kendler *et al*. 2005). Therefore, risk associated with a severe stressor is likely to alter gene expression, which, in genetically predisposed individuals, may be associated with risk for more distal sequelae. Similar investigations targeting risk for SUDs are clearly warranted and should incorporate recently reported additional layers of complexity (i.e. mitigation of risk with social support and gene–gene interaction) (e.g. Kaufman *et al*. 2006).

A variety of limitations must be considered when interpreting our results. As the twins were initially recruited as children, their parents may have been less likely to volunteer twins with a history of CSA. However, because more severe CSA is associated with greater risk for substance use and dependence (Mullen *et al*. 1993; Fergusson *et al*. 1996*a*; Kendler *et al*. 2000), any effect would probably have reduced associations. The similarity of our prevalence rates to those obtained in community samples (Fergusson *et al*. 1996*b*; Fleming, 1997; Holmes & Slap, 1998) suggests that our sample is reasonably representative. CSA is a complex construct; our use of a single binary variable is an oversimplification that may have led to underestimated CSA-associated risks. We chose to do so both to simplify interpretation of the discordant pair comparisons and because of limitations in our CSA assessment. Physical abuse (PA) is often present with CSA in families (Fleming *et al*. 1997; Dong *et al*. 2003; Walsh *et al*. 2003) and has also been associated with risk for drug-related outcomes (Simpson & Miller, 2002). We narrowed our focus to CSA largely because our PA assessment was much more limited. Additional analyses that incorporated PA with CSA into a more general construct, childhood abuse, yielded very similar results throughout (available on request), suggesting that the risks we observed probably extend beyond CSA to include PA. Our use of retrospective self-report data, while another potentially important source of bias, is largely unavoidable. One examination (Fergusson *et al*. 2000) of the stability of CSA reports found no relationship between variations in reports and psychiatric status before, during or after the reported abuse.

Despite the considerable size of our sample, power limitations impacted the significance of our discordant pair findings. We opted to combine data from pairs of different zygosity and sex to avoid further reductions in power. This makes interpretation of our findings less straightforward than analyses limited to MZ pairs (which completely control for genetic and

family environmental risk factors). However, it is important to recognize that even analyses limited to discordant MZ pairs cannot exclude the possibility of findings arising from a proximal latent factor (e.g. a difference in foetal environment) associated with risk for both variables in the model. Conversely, because the significant interactions involving covariates arose from analyses that further subdivided relatively small numbers of doubly-discordant pairs, we believe that they require replication. However, the significant interaction involving gender could reflect differential use patterns because, among the illicit drugs, the greatest risk in males was seen for cocaine. Similarly, an interaction involving zygosity could occur if a heritable trait (e.g. conduct disorder) is associated with increased risk for CSA and for opioid use. Our use of age 17 as the cut-off for CSA may have led to a more heterogeneous construct that included both early childhood molestation and adolescent victimization (e.g. date rape), to which heritable risks could be contributing. As participants remain at risk for drug-related outcomes, risks due to an earlier onset in CSA-positive twins may decrease over time.

In summary, our results strongly support the association between CSA and subsequently occurring licit and illicit drug outcomes. Our results confirm an earlier onset of regular licit and illicit drug use with CSA while finding no significant interaction between risks associated with CSA and with early-onset substance use. Further studies are needed to explore potential biological underpinnings (e.g. G × E interactions) and to determine whether risks for drug-related outcomes can be mitigated by identifying 'at-risk' individuals early and intervening.

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DECLARATION OF INTEREST

None.

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