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Parental separation and early substance involvement: Results from children of alcoholic and cannabis dependent twins

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ABSTRACT

Background: Risks associated with parental separation have received limited attention in research on children of parents with substance use disorders. We examined early substance involvement as a function of parental separation during childhood and parental alcohol and cannabis dependence.
Method: Data were drawn from 1318 adolescent offspring of monozygotic (MZ) or dizygotic (DZ) Australian twin parents. Cox proportional hazards regression analyses were conducted predicting age at first use of alcohol, first alcohol intoxication, first use and first regular use of cigarettes, and first use of cannabis, from parental separation and both parent and cotwin substance dependence. Parent and cotwin alcohol and cannabis dependence were initially modeled separately, with post hoc tests for equality of effects.
Results: With few exceptions, risks associated with parental alcohol versus cannabis dependence could be equated, with results largely suggestive of genetic transmission of risk from parental substance (alcohol or cannabis) dependence broadly defined. Controlling for parental substance dependence, parental separation was a strong predictor for all substance use variables, especially through age 13.
Conclusion: Together, findings underscore the importance of parental separation as a risk-factor for early substance involvement over and above both genetic and environmental influences specific to parental alcohol and cannabis dependence.

1. Introduction

Compared with children of non-alcoholic parents, children of alcoholics (COAs) report earlier and more frequent use of alcohol as well as tobacco, cannabis, and other illicit drugs, and are at greater risk of alcohol problems during adolescence and adulthood (Lieb et al., 2002; Schuckit and Smith, 1996; Sher et al., 1991). By some reports, COAs are four to six times as likely to develop an alcohol use disorder at some point in their life (Chassin et al., 1991; Russell, 1990). Comparatively less is known about children whose parents abuse other drugs; however, paternal illicit drug use has been linked with earlier tobacco use, and problem use of alcohol, tobacco and illicit drugs (Clark et al., 1998, 1999).

While risks for early and problem substance use associated with parental alcoholism are widely documented, not all COAs initiate use at early ages, and for those offspring who show signs of problem use, many "mature out" during adulthood (Labouvie, 1996; Maisto et al., 2002). Furthermore, COAs experience a range of adversities that often follow from but are not exclusive to parental alcoholism, and many such "non-specific" risks have considerable consequences (Jacob and Johnson, 1997). Parental separation or divorce provides a strong example as alcoholic parents are at increased risk of marital dissolution (Waldron et al., 2013) and compared to children from intact married families, children of divorce also report earlier use of alcohol, tobacco, and cannabis (Hoffman and Su, 1998; Short, 1998), heavier use of these substances (Doherty

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Table 1
Risk group by hypothesized family environmental, genetic, and G × E risks.

Risk group	Risk to offspring due to:			
	Environment	Genes	G × E	
1.	Parent affected	High	High	High
2.	Parent UN, MZ cotwin affected	Low	High	Low
3.	Parent UN, DZ cotwin affected	Low	Intermediate	Low
4.	Parent and cotwin UN	Low	Low	Very low

Note: UN = unaffected (neither alcohol nor cannabis dependent); G × E = gene by environment interaction.

and Needle, 1991; Hoffmann, 1995; Needle et al., 1990), and higher rates of problem use (Fergusson et al., 1994; Hoffmann and Johnson, 1998).

Surprisingly, risks to offspring associated with parental separation have received limited attention in research on children of alcoholic or other drug addicted parents. Using a Children-of-Twins (COT) design (Gottesman and Bertelsen, 1989; Heath et al., 1985; Nance and Corey, 1976), we examine whether parental separation predicts early substance involvement over and above risks from parental alcohol or cannabis dependence, including genetic risks. Genetic variation has been reported for alcohol abuse and dependence (Heath et al., 1997; McGue, 1994) and a variety of drug use disorders, including cannabis abuse and dependence (Kendler and Prescott, 1998; Lynskey et al., 2002), with genetic variation also observed for initiation, regular use, and problem substance use during adolescence (Maes et al., 1999; McGue et al., 2000; Rhee et al., 2003). Heritable influences on marital status are reported as well, including genetic variation in likelihood of marriage (Trumbetta et al., 2007) and risk of divorce (McGue and Lykken, 1992), with at least one report of genetic covariation between alcohol dependence and both marital timing and survival (Waldron et al., 2011).

In COT studies, genetic and environmental risks are inferred from parent and cotwin history of substance dependence, with outcomes of offspring from a minimum of four groups compared, each with varying degrees of genetic risk and environmental exposure. In the present analysis, these groups include: offspring whose parent is substance dependent (Group 1); offspring of an unaffected parent whose monozygotic (MZ) cotwin is substance dependent (Group 2); offspring of an unaffected parent whose dizygotic (DZ) cotwin is substance dependent (Group 3); and offspring from control families, where neither parent nor cotwin, regardless of zygosity, is substance dependent (Group 4). Hypothesized risks to offspring are summarized in Table 1.

Following from quantitative genetic theory, if the association between parental substance dependence and offspring substance involvement results from rearing environment, offspring of affected parents should demonstrate greater risk, compared with unaffected parents (Group 1 > Groups 2–4). If the association results from genes shared between parents and their children, i.e., genetic transmission, offspring at high genetic risk should exhibit earlier involvement than offspring at intermediate genetic risk regardless of environmental risk (Groups 1 and 2 > Group 3). A pattern consistent with gene–environment interaction (G × E) is evident if offspring reared by an alcoholic or drug dependent parent exhibit greater risk, compared to offspring of unaffected parents, with offspring of an unaffected parent whose cotwin is also unaffected at lowest risk (Group 1 > Groups 2–3 > Group 4).

To date, a handful of COT studies of alcoholic families have been conducted. For early and problem use of alcohol, evidence of environmental transmission from parental alcoholism has been documented in some but not all reports (Duncan et al., 2006; Jacob et al., 2003; Sartor et al., 2007; Slutske et al., 2008). COT studies based on twin and cotwin history of divorce have been conducted as well, with evidence broadly suggestive of environmental transmission across a range of substance use outcomes (D'Onofrio et al., 2005, 2007). The present study is distinct from earlier work in that we examine *timing* of alcohol, cigarette and cannabis involvement as a function of parental separation or divorce, employing a COT design to control for genetic and environmental risks from parental substance dependence, including risks from parental cannabis dependence.

2. Methods

2.1. Participants

Participants were drawn from two studies of Australian children of twins selected from a young adult twin panel born between 1964 and 1971 (Heath et al., 2001; Knopik et al., 2006). Following initial contact by mailed questionnaire in 1989 (thus, the "1989" cohort), twins completed diagnostic telephone interviews during 1997–2002. Pairs where at least one twin had biological children ages 7–24 and one twin met DSM-IV criteria for alcohol use disorder (AUD; operationalized as alcohol dependence (AD) in male twins and either AD or alcohol abuse (AB) in female twins) were subsequently recruited for participation in one of two coordinated follow-up studies: Mothers and Their Children (MATCH) and Parental Alcoholism and Child Environmental Risk (PACER). A random sample of control pairs, where at least one twin had biological children ages 7–24, but neither twin met criteria for AUD, was also recruited. MATCH twins were selected from female same-sex pairs from both the 1989 cohort and an older "1981" cohort described elsewhere (see Heath et al., 1997; Waldron et al., 2009). PACER twins were selected from male same- and opposite-sex pairs from the 1989 cohort only. Assessment of twin parents by telephone interview began in 2000 and 2005 for MATCH and PACER studies, respectively. During the same period, offspring ages 11–24 were invited to complete an interview, also by telephone. From the 1989 cohort, 1341 offspring completed MATCH or PACER interviews, of whom 23 (<2%) were excluded from analyses because of missing data on twin substance dependence, parental separation, and/or offspring substance involvement, resulting in a final sample of 1318 offspring. Samples sizes by risk group(s) are shown in Table 2, with sample characteristics provided in Table 3.

2.2. Measures

Twins completed telephone adaptations of the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999). Much of the SSAGA was retained at reinterview, with additional items from the Family History Assessment Module (FHAM; Rice et al., 1995) included to assess biological coparent psychopathology. To assess offspring psychopathology, parent-report items from the Diagnostic Interview for Children and Adolescents (DICA; Herjanic and Reich, 1982) and the Child SSAGA (C-SSAGA-P; Kuperman et al., 2001) were also incorporated. Offspring completed either the child (ages 11–14) or adolescent (ages 15+) version of the SSAGA, also adapted for telephone administration.

2.2.1. Offspring substance involvement. Lifetime use and age at first use of alcohol, cigarettes, and cannabis were assessed in the offspring interview. History of alcohol intoxication and regular smoking were also assessed. Onset of regular smoking was coded from age at first regular use of cigarettes, the latter defined as (a) having smoked 100 or more cigarettes, or (b) smoking between 20 and 99 cigarettes and having smoked at least once per week for a period of two months or more.

2.2.2. Parental substance dependence. DSM-IV AD was directly assessed in the 1997–2002 interview, with new onsets coded from parent interviews. An abbreviated assessment of cannabis dependence was included in the 1997–2002 interview only. Based on published sensitivity analyses (Lynskey et al., 2002), cannabis dependence was defined as 2 or more of 4 symptoms assessed (use of larger amount/over longer period than intended; tolerance; continued use despite problems; persistent desire to cut down) within a 12-month period. We computed separately for alcohol and cannabis dependence, three dummy variables corresponding to hypothesized genetic and environmental risks, i.e., Groups 1–3, with control families (Group 4) comprising the reference group.

Biological coparent history of substance use or disorder was also coded as offspring phenotypes depend on behavior of both parents even when mating is random (Eaves et al., 2005). Consistent with research documenting strong within-family agreement (Waldron et al., 2012), coparent alcoholism was coded positive by twin, coparent or offspring report. In MATCH, AD symptoms experienced by biological coparents were assessed without regard to temporal clustering; thus, a probable dependence diagnosis was coded. In PACER, twins were asked only whether "drinking ever caused the biological (mother/father) of (child1/2/3) to have problems with health, family, job or police, or other problems," an item that originated in the Family History Research Diagnostic Criteria assessment (FHRDC; Andreasen et al., 1977), and whether they ever felt that the coparent was an "excessive drinker." In both MATCH and PACER, offspring ages 15 and older were asked similar questions, that is, whether "drinking ever caused your biological (mother/father) to have

Table 2
Sample sizes by risk group: combined MATCH and PACER samples.

Risk group	AD[a]		CannD[b]		AD or CannD	
	n_{twins}	$n_{offspring}$	n_{twins}	$n_{offspring}$	n_{twins}	$n_{offspring}$
Parent affected	189	312	79	129	222	362
Parent UN, MZ cotwin affected	37	62	33	53	50	83
Parent UN, DZ cotwin affected	74	122	47	79	76	131
Parent and cotwin UN	484	822	610	1031	436	742

Note: AD = alcohol dependence; CannD = cannabis dependence; UN = unaffected (neither alcohol nor cannabis dependent).
[a] Coded without regard to cannabis dependence.
[b] Coded without regard to alcohol dependence.

problems. . .," and whether they were an "excessive drinker." Endorsement of both problem and excessive drinking was required to code a coparent positive by twin report (in PACER) or offspring report. Neither MATCH nor PACER interviews included assessment of cannabis dependence symptoms experienced by biological coparents; instead, coparent *recurrent* use was coded from twin or coparent report, defined as lifetime use of cannabis on 11 or more occasions. Parental cannabis use was not assessed by offspring report. Given 15% missingness, two dummy variables were coded to distinguish coparent recurrent use from missing coparent cannabis data, with coparents having never used or used on less than 11 occasions comprising the reference group.

2.2.3. Parental separation. History of biological parent separation or divorce prior to offspring age 18 was coded from parent and offspring interviews. Separations for non-relationship reasons (for example, one parent working overseas or incarcerated) were not coded, nor were subsequent separations between a biological parent and stepparent, where assessment was limited. Offspring age at parental separation was computed from parent report of year marriage or marriage-like relationship or, if missing, age offspring last lived with both biological parents assessed of both parents and offspring.

2.2.4. Control variables. To ensure specificity of effects, a number of demographic, familial and individual-level risks were included as control variables. In addition to offspring sex and age at interview, twin sex, and twin age and education as of the 1997–2002 interview were included among demographic control variables. Dummy variables for having not finished high school and completion of any tertiary education were computed, with high school only comprising the reference group. Control variables for parent comorbid psychopathology include twin and biological coparent history of DSM-IV major depressive disorder (MDD) and a non-diagnostic measure of antisocial personality disorder (ASP). MDD and ASP were assessed of twins in the 1997–2002 interview and both twins and coparents in parent interview. For coparent MDD and ASP, two dummy variables were coded to distinguish affected coparents from those with missing data (11% each for MDD and ASP). Twin history of regular smoking was also assessed in the 1997–2002 interview, with coparent regular smoking queried in parent and offspring interviews. Control variables for offspring comorbid psychopathology include DSM-IV conduct disorder, MDD, social phobia, generalized anxiety disorder, and suicidality (ideation, plan, or attempt), assessed in the offspring interview. Offspring DSM-IV inattention, hyperactivity and oppositional defiant disorder were queried in parent interviews, with two dummy variables coded to distinguish affected offspring from those with missing parent-report data (8% each).

2.3. Analytic strategy

Analyses were performed in STATA version 12 (StataCorp, 2011), with the Huber–White robust variance estimator used to compute standard errors and confidence intervals adjusted for non-independence of twin-family data. Time-to-event data were analyzed using survival analysis to assess likelihood as well as timing of onset. Cox proportional hazards (PH) regression was conducted predicting onset of substance involvement from parental separation and parent and cotwin substance dependence. Parent and cotwin alcohol and cannabis dependence were initially modeled separately, with post hoc tests for equality. Where no significant differences were observed, twin alcohol and cannabis dependence were examined as a combined phenotype, that is, *either* alcohol or cannabis dependence. Parental separation was modeled as a time-varying covariate to ensure onset prior to or during the same year as initiation. Offspring from intact families were right-censored at age at last interview if younger than 18 years. In the case of parental death, intact families were right-censored at offspring age when their parent(s) died. Post hoc tests of interactions between parental separation and parental substance dependence were also conducted. The Efron approximation (Efron, 1977) was used for survival ties. To examine potential violation of the PH assumption, the Grambsch and Therneau test of Schoenfeld residuals (Grambsch and Therneau, 1994) was employed, with age-interactions modeled to correct observed violations (Cleves et al., 2004).

3. Results

There were no differences in offspring age or sex by parental AD or cannabis dependence. Offspring of separated parents were slightly older ($r = 0.19$, $p < 0.0001$), with no differences in offspring

Table 3
Sample characteristics, by twin/parent history of alcohol and cannabis dependence.

	AD+/CannD+ $n_{offspring} = 79$	AD+/CannD− $n_{offspring} = 233$	AD−/CannD+ $n_{offspring} = 50$	AD−/CannD− $n_{offspring} = 956$
Offspring age, *M* (SD)	14.48 (3.02)	14.26 (2.94)	15.36 (2.94)	14.23 (2.83)
Offspring sex, *n* (%) female	43 (54)	112 (48)	22 (44)	480 (50)
Twin age[a], *M* (SD)	30.05 (2.02)	30.78 (2.24)	30.92 (2.51)	30.89 (2.04)
Twin sex, *n* (%) female	36 (36)	117 (50)	25 (50)	620 (65)
Twin education[a]				
<12 years, *n* (%)	14 (18)	42 (18)	13 (26)	128 (13)
13+ years, *n* (%)	21 (27)	38 (17)	8 (16)	255 (27)
Offspring substance use				
Alcohol, *n* (%)	37 (47)	93 (40)	34 (68)	344 (36)
Age of onset, *M* (SD)	13.59 (2.19)	14.17 (2.03)	14.06 (2.42)	14.23 (1.85)
Alcohol intoxication, *n* (%)	29 (37)	66 (29)	25 (50)	206 (22)
Age of onset, *M* (SD)	14.93 (1.49)	15.47 (1.55)	15.04 (1.86)	15.49 (1.73)
Cigarettes, *n* (%)	29 (37)	70 (30)	25 (50)	200 (21)
Age of onset, *M* (SD)	13.62 (2.54)	13.48 (2.17)	11.88 (3.60)	13.59 (2.69)
Regular smoking, *n* (%)	13 (16)	24 (10)	6 (12)	67 (7)
Age of onset, *M* (SD)	14.54 (2.11)	15.33 (1.74)	14.67 (1.37)	15.13 (1.89)
Cannabis, *n* (%)	25 (32)	32 (14)	11 (22)	86 (9)
Age at first use, *M* (SD)	14.72 (2.13)	15.75 (1.59)	15.18 (3.16)	15.58 (1.75)
Parental separation, *n* (%)	46 (58)	80 (34)	26 (52)	223 (23)
Age of onset, *M* (SD)	5.83 (4.62)	6.16 (4.49)	5.85 (4.17)	6.77 (4.86)

Note: AD = alcohol dependence; CannD = cannabis dependence.
[a] As of the 1997–2002 diagnostic interview.

Table 4
Hazard ratios and (95% confidence intervals) from Cox proportional hazards regression models of first alcohol use.

Predictor (risk period)	Model I[a]	Model II[b]	Model III[c]
Risk group			
1. Parent AD+ or CannD+	1.43 (1.18–1.74)	1.29 (1.03–1.60)	1.14 (0.88–1.47)
2a. Parent AD−, MZ cotwin AD+ (<14)	2.82 (1.69–4.72)	2.68 (1.60–4.50)	⊤
2b. Parent CannD−, MZ cotwin CannD+ (<14)	1.11 (0.62–2.01)	0.93 (0.47–1.82)	1.76 (1.08–2.85)
2c. Parent UN, MZ cotwin AD+ or CannD+ (≥14)	1.05 (0.54–2.01)	0.93 (0.40–2.16)	⊥
3. Parent UN, DZ cotwin AD+ or CannD+	1.18 (0.88–1.58)	1.22 (0.89–1.67)	1.04 (0.72–1.50)
Parental separation (<11)	–	14.86 (3.94–56.04)	13.04 (2.84–59.95)
Parental separation (11–13)	–	2.76 (1.99–3.82)	2.22 (1.58–3.14)
Parental separation (≥14)	–	1.49 (1.16–1.90)	1.41 (1.06–1.88)

Note: AD = alcohol dependence; CannD = cannabis dependence; UN = unaffected (neither alcohol nor cannabis dependent). Where brackets are shown, reported risks (HRs) are equivalent across risk periods. Post-hoc tests of interactions between parental separation and parental substance dependence were nonsignificant with one exception – through age 10, risks were further increased for offspring of separated alcoholic or cannabis dependent parents [$HR_{\text{Model II}} = 5.32$ (95% CI: 1.11–25.48); $HR_{\text{Model III}} = 8.35$ (95% CI: 1.22–57.19)].

[a,b] Risk groups 2a > 1, 2b, 2c and 3, $p < 0.05$.

[c] Controlling for demographic characteristics, coparent substance use/dependence, and psychiatric comorbidities of parents and offspring, Risk groups 1 = 2 = 3, $p > 0.10$.

sex by parental separation. Twin parents with a history of AD or cannabis dependence were slightly younger at the 1997–2002 assessment ($r = -0.06$ and -0.07, $p < 0.05$, respectively), with fewer female twins than male meeting criteria for either disorder [$OR = 0.54$ (95% CI: 0.42–0.70) and $OR = 0.55$ (95% CI: 0.38–0.80), respectively]. Differences by parental separation in twin age or sex were nonsignificant. Compared to unaffected twins, rates of parental separation were higher for twins with a history of AD [$OR = 2.06$ (95% CI: 1.58–2.69)] or cannabis dependence [$OR = 3.69$ (95% CI: 2.55–3.85)]. Twin AD and cannabis dependence were moderately correlated (polychoric $r = 0.55$, $p < 0.0001$).

3.1. Survival analyses

Results from three survival models for each substance use variable are presented in Tables 4–8, all of which include risk group based on parent and cotwin substance dependence (AD, cannabis dependence or a combined phenotype). In Model I, risk group only is modeled. In Model II, parental separation is included as an additional predictor, with control variables including coparent substance use/disorder added in Model III. Below we provide detailed summary for alcohol use, with results of Model III only summarized for alcohol intoxication, smoking, regular smoking, and cannabis use.

3.1.1. Alcohol use. Results for first alcohol use are shown in Table 4. For all models, parent and cotwin alcohol and cannabis dependence could be equated in Groups 1 and 3, and Group 2 from age 14 onwards. In Model I, offspring of alcoholic or cannabis dependent parents (Group 1) were at 1.43 times higher risk of early drinking, compared to controls (Group 4). Through age 13, offspring of unaffected parents with an alcoholic identical cotwin (Group 2a) were at nearly three times greater risk of early drinking ($HR = 2.82$), with little to no risk observed of offspring of unaffected parents with a cannabis dependent identical cotwin (Group 2b), nor offspring of unaffected parents with an identical cotwin who is either alcohol or cannabis dependent (Group 2c), the latter from age 14 onwards. Risk to Group 3 was also small and nonsignificant. In post hoc tests, risk to Group 2a was greater than Groups 1, 2b, 2c, and 3, with nonsignificant differences among Groups 1, 2b, 2c and 3.

A similar pattern was observed when parental separation was included in Model II, with risks associated with parent or cotwin substance dependence reducing slightly. As with Model I, risk was higher for Group 2a than Groups 1, 2b, 2c and 3, with nonsignificant differences among Groups 1, 2b, 2c and 3. Through age 10, parental separation was associated with 14.86 times higher likelihood of early drinking. From ages 11 to 13, risks from parental separation predicted 2.76 times greater risk, and from age 14 onwards, approximately 50% greater risk.

In Model III, controlling for demographic characteristics, coparent substance use/dependence, and psychiatric comorbidities of both parents and offspring, risk to Groups 2a, 2b and 2c could be equated. While offspring of unaffected parents with an alcoholic or cannabis dependent identical cotwin were at 1.76 times higher risk of early drinking, and without age interaction, risk to Groups 1, 2 and 3 did not significantly differ in post hoc tests. Parental separation remained a strong predictor of early drinking in Model III, associated with 13.04 times higher likelihood of drinking through age 10, and 2.22 times higher likelihood from ages 11 to 13; from age 14 onwards, parental separation was associated with 41% higher likelihood of drinking.

Table 5
Hazard ratios and (95% confidence intervals) from Cox proportional hazards regression models of first alcohol intoxication.

Predictor (risk period)	Model I[a]	Model II[b]	Model III[c]
Risk group			
1. Parent AD+ or CannD+	1.76 (1.39–2.24)	1.52 (1.20–1.93)	1.32 (0.95–1.83)
2a. Parent UN, MZ cotwin AD+ or CannD+ (<14)	7.62 (3.51–16.56)	6.27 (3.08–12.79)	7.39 (3.19–17.14)
2b. Parent UN, MZ cotwin AD+ or CannD+ (≥14)	1.45 (0.80–2.62)	1.37 (0.73–2.55)	1.70 (0.96–2.99)
3. Parent UN, DZ cotwin AD+ or CannD+	1.23 (0.80–1.90)	1.23 (0.81–1.86)	1.04 (0.60–1.80)
Parental separation (<14)	–	4.59 (2.37–8.90)	3.58 (1.72–7.45)
Parental separation (≥14)	–	1.51 (1.21–1.89)	1.56 (1.14–2.13)

Note: AD = alcohol dependence; CannD = cannabis dependence; UN = unaffected (neither alcohol nor cannabis dependent). Post hoc tests of interactions between parental separation and parental substance dependence were nonsignificant.

[a] Risk groups 2a > 1, 2b and 3, $p < 0.05$, Risk groups 1 > 2b and 3, $p < 0.10$.

[b] Risk groups 2a > 1, 2b and 3, $p < 0.05$.

[c] controlling for demographic characteristics, coparent substance use/dependence, and psychiatric comorbidities of parents and offspring, Risk groups 2a > 1, 2b and 3, $p < 0.05$.

Table 6
Hazard ratios and (95% confidence intervals) from Cox proportional hazards regression models of first cigarette use.

Predictor (risk period)	Model I[a]	Model II[b]	Model III[c]
Risk group			
1a. Parent AD+ (<9)	0.09 (0.01–0.89)	0.82 (0.01–0.80)	0.26 (0.09–0.82)
1b. Parent CannD+ (<9)	9.64 (3.24–28.66)	7.55 (2.53–22.50)	7.30 (2.78–19.16)
1c. Parent AD+ or CannD+ (≥9)	1.83 (1.39–2.42)	1.53 (1.13–2.07)	1.26 (0.85–1.86)
2. Parent UN, MZ cotwin AD+ or CannD+	2.14 (1.37–3.35)	1.95 (1.27–2.99)	2.22 (1.35–3.67)
3. Parent UN, DZ cotwin AD+ or CannD+	1.00 (0.61–1.62)	1.00 (0.62–1.61)	1.10 (0.67–1.81)
Parental separation (<14)	–	3.13 (2.21–4.43)	⊤ 1.77 (1.29–2.43) ⊥
Parental separation (≥14)	–	1.66 (1.13–2.41)	

Note: AD = alcohol dependence; CannD = cannabis dependence; UN = unaffected (neither alcohol nor cannabis dependent). Where brackets are shown, reported risks (HRs) are equivalent across risk periods. Post-hoc tests of interactions between parental separation and parental substance dependence were nonsignificant.
[a,b] Risk groups 1b > 1a, 1c, 2 and 3, $p < 0.05$, and Risk groups 1c, 2 > 3, $p < 0.05$.
[c] Controlling for demographic characteristics, coparent substance use/dependence, and psychiatric comorbidities of parents and offspring, Risk groups 1b > 1a, 1c, 2 and 3, $p < 0.05$.

Table 7
Hazard ratios and (95% confidence intervals) from Cox proportional hazards regression models of first regular smoking.

Predictor (risk period)	Model I[a]	Model II[b]	Model III[c]
Risk group			
1. Parent AD+ or CannD+	1.88 (1.22–2.90)	1.56 (1.00–2.45)	1.16 (0.68–1.99)
2. Parent UN, MZ cotwin AD+ or CannD+	3.03 (1.66–5.54)	2.57 (1.48–4.47)	2.72 (1.30–5.68)
3. Parent UN, DZ cotwin AD+ or CannD+	1.29 (0.54–3.08)	1.31 (0.56–3.06)	1.15 (0.45–2.93)
Parental separation (<14)	–	6.49 (2.30–18.38)	3.37 (1.11–10.25)
Parental separation (≥14)	–	1.47 (0.93–2.33)	0.98 (0.51–1.86)

Note: AD = alcohol dependence; CannD = cannabis dependence; UN = unaffected (neither alcohol nor cannabis dependent). Post hoc tests of interactions between parental separation and parental substance dependence were nonsignificant.
[a,b] Risk groups 1 = 2 = 3, $p > 0.10$.
[c] Controlling for demographic characteristics, coparent substance use/dependence, and psychiatric comorbidities of parents and offspring, Risk groups 2 > 1, $p < 0.05$.

3.1.2. Alcohol intoxication. Results for first alcohol intoxication are shown in Table 5. For all models, and across risk group, parent and cotwin alcohol and cannabis dependence could be equated. In the fully adjusted Model III, risk to Group 2 was significant through age 13, with offspring of unaffected parents with a substance dependent identical cotwin (Group 2a) at 7.39 times greater risk of early intoxication, compared to controls (Group 4). From age 14 onwards, risk to Group 2 was elevated, but nonsignificant. Through age 13, parental separation was uniquely associated with 3.58 times higher likelihood of early intoxication, and from age 14 onwards, 1.56 times higher likelihood.

3.1.3. Cigarette use. Results for first cigarette use are shown in Table 6. For all models, parent and cotwin alcohol and cannabis dependence could be equated in Groups 2 and 3, and in Group 1 from age 9 onwards. In the fully adjusted Model III, through age 8, offspring of cannabis dependent parents (Group 1b) were at 7.30 times increased risk of early smoking, compared to controls (Group 4). However, offspring of alcoholic parents (Group 1a), were at 74% *reduced* risk of early smoking, also through age 8. From age 9 onwards, risk to offspring of alcoholic or cannabis dependent parents (Group 1c) was nonsignificant. Offspring of unaffected parents with a substance dependent identical cotwin (Group 2) were at 2.22 times greater risk of early smoking, with offspring of unaffected parents with a fraternal cotwin who is substance dependent (Group 3) at little to no risk relative to controls. Parental separation uniquely predicted 77% higher likelihood of early smoking without significant age interaction.

3.1.4. Regular smoking. Results for onset of regular smoking are shown in Table 7. For all models, and across risk group, parent and cotwin alcohol and cannabis dependence could be equated. In Model III, Group 2 offspring of unaffected parents with a substance dependent identical cotwin were at 2.72 times higher risk of regular smoking, compared to controls (Group 4). Parental separation was uniquely associated with 3.37 times higher likelihood of regular smoking through age 13 only.

Table 8
Hazard ratios and (95% confidence intervals) from Cox proportional hazards regression models of first cannabis use.

Predictor (risk period)	Model I[a]	Model II[b]	Model III[c]
Risk group			
1. Parent AD+ or CannD+	2.33 (1.63–3.33)	1.97 (1.38–2.83)	1.45 (0.92–2.29)
2. Parent UN, MZ cotwin AD+ or CannD+	3.04 (1.68–5.52)	2.64 (1.52–4.59)	3.03 (1.64–1.61)
3. Parent UN, DZ cotwin AD+ or CannD+	1.01 (0.50–2.01)	1.01 (0.52–1.98)	0.64 (0.29–1.44)
Parental separation (<14)	–	5.09 (2.18–11.87)	3.25 (1.36–7.73)
Parental separation (14–17)	–	1.67 (1.15–2.44)	⊤ 1.35 (0.88–2.08) ⊥
Parental separation (≥18)	–	0.80 (0.31–2.10)	

Note: AD = alcohol dependence; CannD = cannabis dependence; UN = unaffected (neither alcohol nor cannabis dependent). Where brackets are shown, reported risks (HRs) are equivalent across risk periods. Post-hoc tests of interactions between parental separation and parental substance dependence were nonsignificant with one exception – through age 13, risks were further increased for offspring of separated alcoholic or cannabis dependent parents [$HR_{\text{Model III}} = 5.53$ (95% CI: 1.89–16.12)].
[a,b] Risk groups 1, 2 > 3, $p < 0.05$.
[c] Controlling for demographic, coparent substance use/dependence, and psychiatric comorbidities of parents and offspring, Risk groups 2 > 1 > 3, $p < 0.05$.

3.1.5. Cannabis use. Results for first cannabis use are shown in Table 8. For all models, and across risk group, parent and cotwin alcohol and cannabis dependence could be equated. In the fully adjusted Model III, risk to Group 2 only was significant, with offspring of unaffected parents with a substance dependent identical cotwin at 3.03 times higher risk of early cannabis use, compared to controls (Group 4). Parental separation was uniquely associated with over three times higher likelihood of early cannabis use through age 13 (*HR* = 3.25).

4. Discussion

Despite well-documented associations between problem substance use and relationship instability, risks to COAs associated with parental separation or divorce have received limited empirical attention, and this is especially true of children of parents with other drug dependence. In the present study, we examined initiation of substance involvement as a function of parental separation using a Children-of-Twins (COT) design to control for both genetic and environmental risks associated with parental substance dependence. Although parental alcohol and cannabis dependence were initially modeled separately, with few exceptions, effects could be equated. Thus, for most models we subsequently examined risks from parental substance dependence broadly defined, i.e., parental history of alcohol *or* cannabis dependence.

Having a substance dependent parent was generally predictive of earlier onset alcohol use, drinking to intoxication, smoking, regular smoking, and cannabis use. However, across most substance use variables, offspring of unaffected parents with a substance dependent identical cotwin exhibited greater risk of early involvement than offspring of substance dependent parents. Risk to offspring of unaffected parents with a substance dependent fraternal cotwin was on average small and nonsignificant. While suggestive of genetic versus environmental transmission from parental substance dependence, a somewhat different pattern was observed for cigarette use. Risk to offspring of unaffected parents with a substance dependent identical (but not fraternal) cotwin was elevated in models of early smoking; however, risk was much greater for offspring of cannabis dependent parents, especially through age 8, than for offspring of alcoholic parents or unaffected parents. Thus, for very early use of cigarettes, results suggest an environmental mode of transmission from parental cannabis versus alcohol dependence, perhaps involving modeling of smoking behavior. Relatively permissive attitudes regarding underage substance use, particularly smoking, might also play a role.

Controlling for both genetic and environmental risks from parental substance dependence, parental separation was associated with early initiation across substance classes, with effects of separation most pronounced through ages 10 or 13. Controlling for parental separation only, a slight reduction in risks from parental substance dependence was observed, suggesting partial mediation at best. A greater reduction was observed with additional adjustment for demographic characteristics, coparent substance use/dependence, and psychiatric comorbidities of both parents and offspring. In most models, having a substance dependent parent was no longer predictive, except for onset of smoking as a function of parental cannabis dependence, described above. In contrast, effects of parental separation remained strong, suggesting parental separation confers unique risks beyond demographic, familial and individual-level influences highly correlated with parental substance dependence.

There are a number of limitations to our study suggesting cautious interpretation of findings, including incomplete assessment of major domains of risk. For example, we do not know *why* parents separated, and reason for relationship dissolution may have important implications. While post hoc tests of interactions were largely nonsignificant, if substance dependence was the primary cause of separation and removal from the home of the alcoholic or other drug-addicted parent worked to reduce offspring risk, our understanding of parental separation as a risk-factor would need reconsidering. Data on prior separations is also limited, leaving open the possibility that some parents may have separated before final dissolution, and that parents in families coded as intact previously separated and since reconciled.

Regarding parental substance use or disorder, we assessed lifetime history of alcohol and cannabis dependence approximately ten years prior to offspring assessment. Because some parents may no longer meet criteria during childrearing years, our results likely underestimate risks from ongoing, chronic alcohol or cannabis use by twin parents. Additionally, we examined recurrent use of cannabis by coparents, defined as having used cannabis on 11 or more occasions lifetime, which may or may not reflect problem use, and may or may not be ongoing. Given that onset or remission data are not available for all twins, nor any coparents, measures of parenting behavior will be especially informative. Unfortunately, a direct measure of environmental exposure, or parenting "under the influence," was not administered.

There are also a range of risks, both genetic and environmental, correlated with parental separation that remain unmeasured. It will be important for future research to examine more proximal risks from both parental substance dependence and separation in samples of sufficient size to parse potentially mediated or moderated effects. In the present study, statistical power was limited, including power to examine separately maternal versus paternal substance dependence and, in some cases, alcohol versus cannabis dependence. Lastly, participants are almost exclusively European ancestry, reflecting the predominantly Caucasian population from which twin parents were ascertained. Replication in a more diverse sample is critical, as is cross-national replication.

Despite these limitations, our findings underscore the importance of parental separation as a risk-factor for substance involvement independent of parental alcohol or cannabis dependence while highlighting very early adolescence as a particularly vulnerable period for children whose parents are separated, and, thus, a potential focus of targeted substance abuse prevention beyond family history.

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Contributors

Heath, Bucholz and Martin designed the study and Heath, Bucholz, Glowinski and Waldron wrote the protocol. Waldron managed the literature searches and summaries of previous related work. Waldron undertook the statistical analysis, and author Waldron wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict declared.

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