HHS Public Access

Author manuscript

*Alcohol Clin Exp Res*. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

*Alcohol Clin Exp Res*. 2015 July ; 39(7): 1166–1173. doi:10.1111/acer.12766.

# Parental separation and offspring alcohol involvement:Findings from offspring of alcoholic and drug dependent twin fathers

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## Abstract

**Background—**We examined associations between parental separation during childhood and offspring alcohol involvement, adjusting for genetic and environmental risks specific to parental alcohol and cannabis/other illicit drug dependence.

**Methods—**The sample consisted of 1828 offspring of male twins from the Vietnam-Era Twin Panel, who completed a telephone diagnostic interview. Cox proportional hazards regression analyses were conducted predicting onset of first use, transition from first use to first alcohol dependence (AD) symptom, and transition from first use to AD diagnosis from paternal and avuncular AD and drug dependence (DD) history, parental separation, and offspring and family background characteristics. Paternal/avuncular DD/AD was based on the DSM-III-R; offspring and maternal AD were based on DSM-IV criteria.

**Results—**Paternal DD/AD predicted increased offspring risk for all transitions, with genetic effects suggested on rate of transitioning to AD diagnosis. Parental separation was predictive of increased risk for early alcohol use, but a reduced rate of transition to both AD symptom onset and onset of AD. No interactions between separation and familial risk (indexed by paternal or avuncular DD/AD) were found.

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**Conclusion—**Findings highlight the contribution of both parental separation and paternal substance dependence in predicting timing of offspring alcohol initiation and problems across adolescence into early adulthood.

### Keywords

alcohol involvement; parental separation or divorce; parental alcohol dependence; parental drug dependence; offspring of twins

## Introduction

Compared to children raised in intact families, children whose parents separate or divorce report earlier use of alcohol (Donovan & Molina, 2011; Flewelling & Bauman, 1990; Short, 1998) and higher rates of problem drinking (Dube et al., 2002; Hoffmann & Johnson, 1998; Hope et al., 1998; Wolfinger, 1998). Likewise, children of alcoholics report earlier and more frequent alcohol use than children of nonalcoholic parents (Chassin et al., 1991; Wong et al., 2006), and are at especially high risk of problem drinking (Lieb et al., 2002; Russell, 1990; Schuckit & Smith, 1996). Elevated rates of early and problem drinking are also observed in children of other drug using and dependent parents (Clark et al., 1998, 1999).

Despite well-documented associations between marital instability and alcohol use disorder (Cranford, 2014; Kessler et al., 1998; Waldron et al., 2011), relatively few studies of parental separation and offspring substance involvement consider correlated risk from parental alcohol or other drug dependence. Parental separation during childhood may be uniquely predictive of early drinking by offspring, which in turn increases risk of dependent use (Grant & Dawson, 1997; Grant et al., 2001). It is also possible that the relationship between parental separation and offspring alcohol involvement can be accounted for by risk factors common to parental separation and substance dependence, including heritable risks (for a review, see Dick & Agrawal, 2008).

In research on children of alcoholics, there are a growing number of studies that model jointly risk from parental separation and parental alcoholism (e.g., Dube et al., 2002; Thompson et al., 2008, 2013; Waldron et al., 2014b). This includes a handful of genetically informative Offspring-of-Twins (OOT) analyses (Gottesman & Bertelsen, 1989; Heath et al., 1985; Nance & Corey, 1976), where genetic and environmental risks to offspring are inferred from twin-parent and co-twin histories of alcoholism. For example, following from earlier analyses of adolescent and young adult offspring of male twins (Jacob et al., 2003), Sartor and colleagues (2007) examined onset of alcohol use and time to alcohol dependence from first use using a survival-analytic framework. Parental divorce uniquely predicted earlier initiation of alcohol use, with no significant effect of parental separation on timing of transition from first use to alcohol dependence. However, neither study modeled parental divorce as time-varying, instead assuming parental separation to predate offspring alcohol involvement.

More recently, Waldron and colleagues (Waldron et al., 2014a) examined timing of alcohol use and first intoxication in a sample of adolescent offspring of male and female Australian twins. Here, a time-varying measure of parental separation or divorce was modeled. Results

indicated pronounced effects of parental separation on risk of alcohol initiation and intoxication during very early adolescence (before age 13) and moderate effects from middle adolescence onward, when controlling for genetic and environmental risks from parental alcohol and cannabis dependence as part of the OOT design. Unfortunately, risk of alcohol dependence was not examined as few offspring had aged through the period of highest risk for developing problem use.

In the present study, we employed an OOT design to examine associations between parental separation and offspring alcohol involvement, over and above genetic and environmental risks specific to parental alcohol, cannabis, and other illicit drug dependence. Following Sartor et al. (2007), we examined both onset of alcohol use and time to alcohol dependence from first use. We also examined time to first AD symptom from first use, which has yet to be examined. Additionally, a time-varying measure of parental separation was modeled to ensure onset of separation prior to alcohol involvement, consistent with Waldron et al. (2014a). Based on prior findings, we hypothesized that parental separation would remain a significant predictor of timing of alcohol use and timing of transition from use to first AD symptom and AD diagnosis.

## Materials and Methods

### Participants

Participants were biological (genetic) offspring of male twins from the Vietnam Era Twin Registry (VETR), a national registry of monozygotic and dizygotic twin pairs who served in the military during the Vietnam era (1965–1975). Construction of the registry and method of determining zygosity have been previously reported (Eisen et al., 1987; Eisen et al., 1989; Henderson et al., 1990). In the present study, we analyze data collected from twin-families participating in two complementary OOT projects initiated in 2001 and 2004, respectively: offspring of twin fathers concordant or discordant for alcohol dependence (AD; Project 1; for details see Jacob et al., 2003) and offspring of twin fathers concordant or discordant for illicit drug dependence (DD; Project 2; for details see Scherrer et al., 2008). Both studies included offspring of unaffected twin pairs (as controls) as well as the biological or custodial mothers of the offspring. Offspring were eligible to participate if the twin gave permission to contact them (Project 1, but not Project 2, also required permission from the mother before contacting offspring). Experienced staff from the Institute for Survey Research (ISR) at Temple University conducted all data collection. Participants gave verbal consent prior to being interviewed and parents provided written consent for their minor aged offspring to be interviewed. All study procedures were approved by the Institutional Review Board at the participating institutions.

Project data were merged by taking data from all offspring in Project 2 (the more recent data source) and adding non-overlapping individuals from Project 1 (249 offspring participated in both studies). The combined studies included 1919 offspring (1080 and 839 for Projects 1 and 2 respectively). The present analyses are limited to the 1828 offspring who had complete data for paternal/avuncular DD/AD history and had information on parental separation/divorce and its timing. These offspring were from 1063 families (476 with one offspring interviewed, 409 with two, and 178 with three).

## Measures

Individual measures for the twin fathers were drawn from the Diagnostic Interview Schedule (DIS-III-R; Robins et al., 1989), which was administered in 1992 (see Tsuang et al., 1996, 1998); DSM-III-R substance dependence diagnoses were created from the DIS. The offspring and spouses of the twins in both projects completed a telephone adaptation of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) in 2001–2004, from which a DSM-IV alcohol dependence diagnosis was created.

**Offspring alcohol involvement—**As part of the SSAGA, offspring reported lifetime alcohol use and problem drinking. Ages of onset were assessed for first full drink, first DSM-IV AD symptom (of drinkers), and third AD symptom (of those with DSM-IV AD).

**Parental substance dependence—**Based on the AD and DD statuses of the father and his co-twin, offspring were classified into one of seven groups representing different levels of genetic and environmental risk for the offspring. Paternal substance dependence was the most proximal indicator of risk, and thus took precedence over uncle status. DD was also presumed to represent greater risk than AD and thus was given precedence in group assignment. Offspring whose father had a history of DSM-III-R illicit drug dependence were assigned to risk group D1 (regardless of AD status); offspring whose father had no history of DD but had a history of DSM-III-R AD were assigned to risk group A1. Offspring in these groups are, on average, at high genetic and high environmental risk. Additional risk groups were based on the twin pair's zygosity and the uncle's DD/AD status when the father was not DD or AD. Offspring whose uncle was an MZ co-twin of their father were assigned to group D2 if the co-twin was DD, and to group A2 if the MZ uncle was AD (these offspring are at high genetic risk because their father is genetically identical to his co-twin, but reduced environmental risk since they were not raised by a substance dependent father). Offspring whose uncle was a DZ co-twin of their father were assigned to group D3 if the co-twin was DD, and to group A3 if the DZ uncle was AD (moderate genetic risk because their father shares approximately 50% of his segregating genes with his co-twin, but again reduced environmental risk). The comparison group for all analyses was offspring with no DD or AD diagnosis in either the father or the uncle (low genetic, low environmental risk). Because offspring genetic risk is inherited from both parents, maternal history of AD and heavy cannabis use (as an indicator of DD) were controlled for statistically, as described below.

**Parental separation—**Parent separation or divorce prior to offspring age 18 was coded based on parent reports of marital and cohabitation histories and offspring report of separation from a biological parent for reasons of parental relationship dissolution. In most cases, offspring age at parental separation was defined as the minimum age of separation reported by the biological mother or the offspring. In cases with reported parental separation but no age available from mother or offspring, offspring age at parental separation was coded from father's report of year of separation ($n$ = 22) or step/adoptive mother's report of year her husband separated ($n$ = 5).

**Covariates—**A number of demographic, familial and individual-level risk factors were modeled as covariates in adjusted models. In addition to offspring sex and age at interview (divided into four dummy-variables based on birth quintiles, with the youngest quintile used as the comparison group), we included dummy-variables for offspring self-reported history of 3+ conduct symptoms prior to age 18, 5+ depression symptoms with impairment, suicidality (ideation, plan, or attempt), social phobia (with avoidance or marked distress when not avoided), generalized anxiety symptoms (excessive anxiety/worry with interference in 1+ situation before age 18, or 3+ situations age 18 or older), 2+ sudden-onset panic attacks, any traumatic event(s) prior to age 18 (life-threatening accident, natural disaster witnessing serious injury/death, being physically assaulted, being threatened), childhood physical abuse/neglect, and rape or molestation before age 18. With the exceptions of physical abuse/neglect and suicidality, ages of onset were available for all of the above and they were included as time-varying covariates. Offspring DSM-IV inattention, hyperactivity and oppositional defiant disorder were queried in mother interviews, with two dummy-variables coded to distinguish affected offspring from those with missing parent-report data (18.6 – 21.6% each). Additional family characteristics included as covariates in each final model were maternal DSM-IV AD and history of heavy cannabis use (150+ times lifetime), with a dummy-variable included for cases where mother's substance history was missing (8.5% for AD, 8.7% for heavy cannabis use), and family income (a set of dummy-variables based on father's report, <$20,000, $20,000–$100,000, and >$100,000, with the middle income group used as the referent category).

## Analytic Strategy

Survival analyses were performed in STATA version 11.1 (StataCorp, 2009), with the Huber-White robust variance estimator used to compute standard errors and confidence intervals adjusted for non-independence of twin-family data. Cox proportional hazards (PH) regression was conducted to predict timing of alcohol involvement (separately for first alcohol use, first AD symptom, and AD diagnosis) from father and co-twin substance dependence and parental separation. We also conducted tests of interactions between parental separation and father substance dependence. Consistent with earlier work using an Australian sample (Waldron et al., 2014a), father and co-twin AD and DD risk groups were initially modeled separately, with post-hoc tests for equality. Parental separation was modeled as a time-varying covariate to ensure that only its occurrence prior to or during the same year as the transition of interest (initiation, first symptom, or AD diagnosis) was counted toward risk for transitioning. Offspring from intact families were right-censored on this variable at age at interview if younger than 18 years: these individuals were not assessed throughout childhood (defined as birth through age 18), and thus contribute to prediction through their age at interview only. In the case of maternal death ($n$=23), individuals from intact families were right-censored at offspring age when their mother died. Control variables with available ages of onset were also modeled as time-varying covariates. In models predicting timing of first AD symptom and timing of AD diagnosis, offspring entered the analysis (risk-set) at onset of alcohol use. To adjust for the temporal proximity from alcohol initiation to onset of any AD symptom and AD diagnosis, age at first use was included as an additional covariate in the fully adjusted models. In these analyses, age at initiation was modeled as a series of 7 dummy-variables with first standard drink occurring:

before age 13, at ages 13, 14, 15, 17, 18, and at age 19+, with the modal age of initiation (16 years) used as the referent group. For all survival analyses, the Efron approximation (Efron, 1977) was used for survival ties. The Grambsch and Therneau test of Schoenfeld residuals (Grambsch & Therneau 1994) was employed to examine potential violation of the proportional hazards assumption, with age-interactions modeled to correct observed violations (Cleves et al., 2004); tests equating hazard ratios across risk periods were conducted post-hoc using a p-value of 0.05 for statistical significance.

## Results

### Preliminary analyses

Descriptive statistics by risk group are summarized in Table 1. For survival models where no differences were observed between AD and DD risk groups (A1 versus D1, A2 versus D2, A3 versus D3), a combined phenotype was examined: *either* DD or AD. Results of Cox regression models predicting onset of alcohol use, transition from use to first AD symptom, and transition from use to AD diagnosis are shown in Tables 2–4, respectively. For each outcome, three models are presented. In Model I, risk group only was modeled. In Model II, parental separation was included; and in Model III, control variables including maternal substance history, socio-demographic characteristics, and comorbid psychopathology and childhood trauma were added. Effects specific to risk group and parental separation are shown in Tables 2–4; effects of all predictors, including all control variables, are presented in Supplementary Tables 1–3.

### Cox analyses of alcohol initiation

In Model I, offspring of substance dependent fathers (Group 1) were at a 28% increased hazard of alcohol use onset, compared to controls (Group 4), see Table 2. Risk to offspring of unaffected fathers with a DD/AD MZ or DZ co-twin (Groups 2 and 3, respectively) was slight and non-significant. In post-hoc tests, risk to Group 1 was greater than Group 2, with non-significant differences between the other groups. In Model II, risk to Group 1 offspring was again increased, relative to Group 4 (*HR* = 1.24), although differences among Groups 1–3 were non-significant in post-hoc tests. A violation of the proportional hazards assumption was observed for parental separation, necessitating modeling of an age interaction. Parental separation was associated with a 3.71 times higher hazard of alcohol initiation through age 12, and with approximately a 62% increased hazard over ages 13–15, with no differences from age 16 onwards. In Model III, controlling for family background and offspring characteristics, Group 1 offspring were at a 29% increased hazard of alcohol use, with differences among Groups 1–3 non-significant. In addition, parental separation was associated with a 3.24 times higher hazard of alcohol use through age 12, with a 20% higher hazard from age 13 onwards. Interactions between father DD/AD and parental separation were tested by adding an interaction term to Models II and III; no interaction terms were significant ($p > 0.05$).

### Cox analyses of first alcohol dependence symptom

In Model I, Group 1 and Group 2 offspring were at 20% and 30% increased hazards of transitioning from alcohol use to an AD problem respectively, compared to Group 4 (see

Table 3). Risk to offspring whose DZ uncle was AD (Group 3b) was significantly increased compared to Group 4 as well (HR=1.36). In post-hoc tests, Group 2 (MZ uncle DD/AD) and Group 3b (DZ uncle AD) also had an increased hazard for alcohol initiation compared to Group 3a (dad unaffected, MZ uncle DD). The effects of risk group in Models II and III were nearly identical to those in Model I in both magnitude and significance, except that Groups 3a and 3b were not significantly different from each other and could be combined into a single "DZ uncle DD/AD" group. Whereas in Model II the effect of parental separation on timing of first AD symptom was non-significant, in Model III a protective effect was observed, with parental separation predicting a 19% decreased hazard of transitioning to any AD symptom. Interactions between father DD/AD and parental separation were tested by adding an interaction term to Models II and III; no interaction terms were significant ($p > 0.05$).

### Cox analyses of alcohol dependence

In Model I, Group 1 offspring were at a 58% increased hazard of transitioning from alcohol use to AD, compared to Group 4 (see Table 4). Risk to offspring in Groups 2 and 3 was non-significant. Group 1 risk was greater than that for Group 3, but other group differences non-significant. A similar pattern was observed when parental separation was included in Model II, where the effect of parental separation on timing of AD was non-significant. In Model III, offspring in Groups 1 and 2 were at 59% and 79% increased hazards of transitioning from use to AD, respectively. Risk to Group 3 offspring was non-significant, as were differences among Groups 1–3. Parental separation predicted a 35% decreased hazard of transitioning to AD. Interactions between father DD/AD and parental separation were tested by adding an interaction term to Models II and III; no interaction terms were significant ($p > 0.05$).

### Subsidiary analyses

Given the observed delay in transition from alcohol initiation to onset of AD symptoms and AD diagnosis associated with parental separation in the fully adjusted models, we conducted a series of subsidiary analyses. Simple logistic regression analyses predicting the development of AD symptoms and AD diagnosis from parental separation without any other predictors indicated that parental separation was associated with significantly increased lifetime risk of having at least one DSM-IV AD symptom (OR=1.34 [95% CI: 1.05–1.70] and a somewhat increased lifetime risk of DSM-IV AD (OR=1.17 [0.85–1.63]).

## Discussion

A growing number of studies have documented unique risk from parental separation for early and problem drinking, controlling for parental history of alcoholism. The present study extends previous genetically informative research in this area by modeling genetic and environmental risk from parental alcohol and drug dependence history, with a time-varying measure of parental separation. Our focus on timing of alcohol transitions, including onset of first use, first alcohol dependence symptom, and alcohol dependence diagnosis, further extends previous studies by capturing the dynamic nature of drinking behavior, including

possible shifts in the relative contribution of these risk factors across adolescence into young adulthood.

In all models, paternal history of DD/AD was predictive of increased risk for all alcohol outcomes. Risk associated with paternal DD/AD was modest for age at first use and transition from first use to AD symptom (a 19–29% increased hazard). A much stronger effect of paternal history was observed for the transition from first use to AD diagnosis (a 58–62% increased hazard), consistent with findings by Jacob et al. (2003) and Sartor et al. (2007). Additionally, there was some evidence of genetic influence on the transition to AD diagnosis: risk among offspring with an affected MZ uncle was increased, with effect sizes (HR range: 1.54–1.79) comparable to those observed for offspring of affected fathers. In contrast, offspring with an affected DZ uncle were comparable to control offspring in their risk of developing AD (HR range: 0.92 – 1.04), with one exception (for age at first use, the offspring with an AD DZ uncle had a 36% increased hazard, which was greater than those with a DD DZ uncle and the control offspring). There was little evidence that mother's AD or heavy cannabis use provided additional predictive utility above and beyond father's DD/AD history. (see Supplemental Tables 1–3)

In the fully adjusted model, parental separation predicted earlier offspring alcohol initiation relative to offspring from intact families, with hazard of use increased more than threefold before age 13 and 20% from age 13 onwards. However, the effect of parental separation was reversed for both AD symptom onset and onset of AD. In final models adjusting for all covariates, parental separation was associated with a 19% and 35% *reduced* rate of transitioning. Simple regression analyses to clarify this finding confirmed that parental separation was associated with significantly increased lifetime risk of having at least one DSM-IV AD symptom. Given that individuals whose parents separated were much more likely to have a full drink of alcohol before age 13, this delay in transition associated with parental separation may simply reflect differences in the ease of access to alcohol and density of alcohol-using peers in early adolescence. As a consequence of limited access and opportunity to use alcohol, early drinkers may exhibit slower transitions to alcohol problems but accumulate more years at risk, yielding a higher cumulative risk of dependence. While somewhat unexpected for divorce, this pattern is consistent with a growing literature linking early initiation to delayed transitions to dependence (e.g., Jackson, 2010; Sartor et al., 2007; Sartor et al., 2008), and also was observed in the present sample. As shown in Supplementary Tables 2 and 3, individuals who began drinking earlier (i.e., before age 16) progressed more slowly to first dependence symptom and dependence diagnosis initially, but were at increased risk of developing AD symptoms six or more years after initiation.

The present findings highlight the contributions of both paternal substance dependence and parental separation to offspring alcohol involvement examined across adolescence and early adulthood. Among the many strengths of our study is a sample that is substantially larger with offspring several years older than in previous reports (e.g., Jacob et al., 2003; Sartor et al., 2007; Waldron et al., 2014a); consequently, we have increased statistical power to detect risk of alcohol problems and disorder relative to earlier work. The selection for DD as well as AD in the twin fathers also generalizes findings from studies focusing only on paternal AD, showing roughly equivalent prediction for paternal DD. Furthermore, fathers' AD/DD

histories were derived from their own reports, unlike other studies that have relied on family history. Finally, and importantly, we used time-varying covariates to ensure the temporal primacy of parental separation relative to alcohol transitions. As noted, the effect of parental separation on alcohol involvement varied considerably by age or “risk period”, underscoring the importance of modeling time-varying risk where age of onset data are available.

Results from the current analyses must be considered in light of several limitations, however. Our reliance on lifetime history of parental substance dependence may underestimate the impact of chronic substance dependence. For example, some parents may have remitted prior to starting a family, or had delayed DD/AD onset that post-dated childrearing. We also cannot know from these data why parents separated, or for how long relationship problems existed prior to separation. Although tests of interactions between paternal substance dependence and parental separation were not significant, if substance dependence was a primary reason for separation, it is possible that the departure of a substance dependent parent from the home might reduce risk to offspring. In addition, we did not examine genetic and environmental sources of risk from parental separation. In the handful of studies to do so, findings are generally suggestive of environmental transmission from parental separation to alcohol problems (D’Onofrio et al., 2005, 2007), but equivocal regarding timing on alcohol use (D’ Onofrio et al., 2006). Analyses that model genetic and environmental risks from both parental substance dependence and parental separation would advance this line of inquiry (for a review, see McAdams et al., 2014). There are also limits to generalizability of the present findings. Our sample is predominantly Caucasian, and extension to other racial/ethnic groups is critical. Lastly, not all offspring had passed through the peak period of risk for the onset of alcohol problems, although this limitation may be overcome with additional data collection as the sample ages.

In conclusion, the present study provides an important extension to previous research exploring the unique contribution of parental separation in the development of early and problem drinking by modeling genetic and environmental risk from parental alcohol and drug dependence history with a time-varying measure of parental separation. Our findings highlight the contribution of both parental separation and paternal substance dependence in predicting timing of offspring alcohol involvement across adolescence and early adulthood.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

The United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. Numerous organizations have provided invaluable assistance in conducting this study, including: Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible.

This study was supported by the Department of Veterans Affairs Health Services Research and Development Service and the Cooperative Studies Program (Study 992), NIH grants AA012640, AA011667, AA07728,

AA011998, AA017688, AA017921, DA014363, and DA023696, and a grant from the Robert E. Leet and Clara Guthrie Patterson Trust.

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**Table 1**

Offspring, parent and family characteristics: Sample sizes (%) and Means (SD)

| | Total Sample (n=1828) | Father DD/AD (n=951) | MZ uncle DD/AD (n=236) | DZ uncle DD/AD (n=218) | Neither DD/AD (n=423) |
|---|---|---|---|---|---|
| *Offspring substance involvement* | | | | | |
| Alcohol initiation, *n (%)* | 1531 (83.9) | 814 (85.9) | 200 (84.8) | 178 (82.0) | 339 (80.1) |
| Age of initiation, *M (SD)* | 15.9 (2.7) | 15.6 (2.7) | 16.2 (2.5) | 15.8 (2.9) | 16.2 (2.6) |
| Any DSM-IV AD symptom | 1015 (55.5) | 561 (59.0) | 135 (57.2) | 113 (51.8) | 206 (48.7) |
| Age at 1st symptom, *M (SD)*, of those with 1+ symptom | 18.9 (2.9) | 18.7 (2.9) | 19.0 (2.9) | 18.7 (2.8) | 19.2 (2.9) |
| DSM-IV AD | 259 (14.2) | 163 (17.2) | 35 (14.8) | 19 (8.7) | 42 (10.0) |
| Age at 3rd symptom, *M (SD)*, of those with AD | 20.0 (3.0) | 20.0 (3.0) | 19.8 (2.6) | 20.8 (3.8) | 20.1 (2.7) |
| *Parental Separation* | | | | | |
| Parental separation | 381 (20.8) | 254 (26.7) | 32 (13.6) | 39 (17.9) | 56 (13.2) |
| Offspring age at parental separation | 7.3 (4.8) | 7.3 (4.9) | 5.7 (4.2) | 8.2 (4.0) | 7.6 (4.9) |
| *Offspring characteristics* | | | | | |
| Offspring age, *M (SD)* | 21.4 (4.3) | 21.5 (4.3) | 21.4 (4.3) | 20.7 (4.1) | 21.4 (4.4) |
| Offspring sex, *n (%)* male | 911 (49.9) | 483 (50.8) | 116 (49.2) | 109 (50.5) | 203 (48.1) |
| 3+ conduct disorder symptoms | 117 (6.5) | 79 (8.4) | 9 (3.8) | 6 (2.8) | 23 (5.5) |
| 5+ depression symptoms | 271 (14.8) | 162 (17.0) | 29 (12.3) | 22 (10.1) | 58 (13.7) |
| Suicidality | 438 (24.2) | 236 (25.1) | 59 (25.1) | 44 (20.4) | 99 (23.7) |
| Social Phobia | 214 (11.7) | 118 (12.2) | 32 (13.6) | 20 (9.2) | 44 (10.4) |
| Generalized Anxiety Disorder | 153 (8.4) | 86 (9.1) | 20 (8.5) | 17 (7.9) | 30 (7.2) |
| 2+ panic attacks | 172 (9.5) | 97 (10.3) | 26 (11.1) | 16 (7.4) | 33 (7.9) |
| Childhood trauma | 530 (29.3) | 297 (31.5) | 60 (25.5) | 61 (28.2) | 112 (26.9) |
| Childhood rape/molestation | 141 (7.8) | 78 (8.3) | 18 (7.7) | 15 (7.0) | 30 (7.2) |
| Childhood physical abuse/neglect | 102 (5.6) | 76 (8.0) | 6 (2.6) | 5 (2.3) | 15 (3.6) |
| Inattention (mother report, of 1488 offspring with mother inattention report) | 117 (7.9) | 67 (8.7) | 22 (11.5) | 6 (3.4) | 22 (6.3) |
| Hyperactivity (mother report, of 1485 offspring with mother hyperactivity report) | 53 (3.6) | 33 (4.3) | 6 (3.2) | 6 (3.4) | 8 (2.3) |
| Oppositional-Defiant (mother Report, of 1433 offspring with mother ODD report) | 204 (14.2) | 123 (16.7) | 30 (16.3) | 17 (10.0) | 34 (9.9) |

*Alcohol Clin Exp Res*. Author manuscript; available in PMC 2016 July 01.

| | Total Sample (n=1828) | Father DD/AD (n=951) | MZ uncle DD/AD (n=236) | DZ uncle DD/AD (n=218) | Neither DD/AD (n=423) |
|---|---|---|---|---|---|
| *Family Background* | | | | | |
| Mother AD (of 1703 mothers with AD self-report) | 171 (10.0) | 120 (13.6) | 14 (6.5) | 17 (8.4) | 20 (5.0) |
| Mother heavy cannabis use (of 1646 mothers with cannabis self-report) | 67 (4.1) | 49 (5.8) | 3 (1.4) | 8 (4.1) | 7 (1.8) |
| Family income | | | | | |
| Less than $20,000 | 49 (2.7) | 39 (4.2) | 3 (1.3) | 3 (1.4) | 4 (1.0) |
| $20,000–$100,000 | 1432 (79.8) | 767 (81.7) | 189 (82.5) | 166 (78.7) | 310 (74.7) |
| Greater than $100,000 | 313 (17.5) | 133 (14.2) | 37 (16.2) | 42 (19.9) | 101 (24.3) |

*Note*. DD = drug dependent; AD = alcohol dependent.

## Table 2

Hazard Ratios and (95% Confidence Intervals) from Cox Proportional Hazards Regression Models of Age at First Standard Drink of Alcohol

| Predictor (risk period) | Model I | Model II | Model III[b] |
|---|---|---|---|
| *Risk Group* | | | |
| 1. Father DD or AD | 1.28 (1.11 – 1.47) | 1.24 (1.07 – 1.43) | 1.29 (1.10 – 1.50) |
| 2. Father unaffected, MZ uncle DD or AD | 1.09 (0.91 – 1.30) | 1.08 (0.90 – 1.29) | 1.17 (0.97 – 1.42) |
| 3. Father unaffected, DZ uncle DD or AD | 1.10 (0.89 – 1.36) | 1.09 (0.88 – 1.34) | 1.10 (0.88 – 1.38) |
| 4. Father and uncle unaffected (referent group) | 1.00 | 1.00 | 1.00 |
| Parental separation (< 13)[a] | -- | 3.71 (2.07 – 6.65) | 3.24 (1.77 – 5.91) |
| Parental separation (13 – 15)[a] | -- | 1.62 (1.27 – 2.05) | ⊤ 1.20 (1.03 – 1.40) ⊥ |
| Parental separation (≥ 16)[a] | -- | 1.08 (0.91 – 1.28) | |

*Note*. DD = drug dependent; AD = alcohol dependent. Where brackets are shown, reported risks (HRs) are equivalent across risk periods. Differences between Risk Groups 1–3 non-significant except Model I, Risk Group 1>2, $p < 0.05$.

[a] Age interaction modeled due to proportional hazard violation. Levels indicate risk of initiating alcohol use before age 13, across ages 13–15, and at age 16 or later among those who experienced parental separation.

[b] Controlling for maternal AD and history of cannabis use, offspring sex and birth cohort, family income, mother report of offspring inattention, hyperactivity and oppositional defiant disorder, and offspring self-report of conduct disorder, depression, suicidality, social phobia, generalized anxiety disorder, panic attacks, childhood trauma, childhood physical abuse/neglect and childhood rape/molestation. See Supplementary Table 1 for individual hazards.

## Table 3

Hazard Ratios and (95% Confidence Intervals) from Cox Proportional Hazards Regression Models of First DSM-IV Alcohol Dependence Symptom from First Standard Drink of Alcohol

| Predictor (risk period) | Model I | Model II | Model III[a] |
|---|---|---|---|
| *Risk Group* | | | |
| 1. Father DD or AD | 1.20 (1.02 – 1.41) | 1.22 (1.03 – 1.43) | 1.19 (1.01 – 1.41) |
| 2. Father unaffected, MZ uncle DD or AD | 1.30 (1.04 – 1.64) | 1.31 (1.04 – 1.65) | 1.36 (1.09 – 1.71) |
| 3a. Father unaffected, DZ uncle DD | 0.95 (0.72 – 1.26) | ⊤ 1.19 (0.95 – 1.48) ⊥ | ⊤ 1.18 (0.94 – 1.48) ⊥ |
| 3b. Father unaffected, DZ uncle AD | 1.36 (1.03 – 1.78) | | |
| 4. Father and uncle unaffected (referent group) | 1.00 | 1.00 | 1.00 |
| Parental separation | -- | 0.89 (0.77 – 1.03) | 0.81 (0.68 – 0.95) |

*Note*. DD= drug dependent; AD = alcohol dependent. Differences between Risk Groups 1–3 non-significant except Model I, Risk Group 2>3a and 3b>3a, $p < 0.05$.

[a]Controlling for maternal AD and history of cannabis use, offspring sex and birth cohort, family income, mother report of offspring inattention, hyperactivity and oppositional defiant disorder, and offspring self-report of conduct disorder, depression, suicidality, social phobia, generalized anxiety disorder, panic attacks, childhood trauma, childhood physical abuse/neglect and childhood rape/molestation, and age at first standard drink of alcohol. See Supplementary Table 2 for individual hazards.

## Table 4

Hazard Ratios and (95% Confidence Intervals) from Cox Proportional Hazards Regression Models of DSM-IV Alcohol Dependence Diagnosis from First Standard Drink of Alcohol

| Predictor (risk period) | Model I | Model II | Model III[a] |
|---|---|---|---|
| *Risk Group* | | | |
| 1. Father DD or AD | 1.58 (1.11 – 2.24) | 1.62 (1.14 – 2.30) | 1.59 (1.09 – 2.32) |
| 2. Father unaffected, MZ uncle DD or AD | 1.54 (0.96 – 2.46) | 1.55 (0.97 – 2.47) | 1.79 (1.07 – 2.98) |
| 3. Father unaffected, DZ uncle DD or AD | 0.92 (0.55 – 1.54) | 0.94 (0.56 – 1.57) | 1.04 (0.60 – 1.81) |
| 4. Father and uncle unaffected, | 1.00 | 1.00 | 1.00 |
| Parental separation | -- | 0.82 (0.61 – 1.11) | 0.65 (0.46 – 0.92) |

*Note*. DD= drug dependent; AD = alcohol dependent. Differences between Risk Groups 1–3 non-significant except Models I and II, Risk Group 1 > 3, $p < 0.05$.

[a]Controlling for maternal AD and history of cannabis use, offspring sex and birth cohort, family income, mother report of offspring inattention, hyperactivity and oppositional defiant disorder, and offspring self-report of conduct disorder, depression, suicidality, social phobia, generalized anxiety disorder, panic attacks, childhood trauma, childhood physical abuse/neglect and childhood rape/molestation, and age at first standard drink of alcohol. See Supplementary Table 3 for individual hazards.