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**Major depression and alcohol use disorder in adolescence: Does comorbidity lead to poorer
outcomes of depression?**

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Abstract

Background: Comorbid major depression (MD) and alcohol use disorder (AUD), particularly in adolescents, have been shown to be associated with poorer subsequent MD outcomes

Methods: Longitudinal data were used to model associations between a four-level classification of MD/AUD during the period 15-18 years (neither; MD-only; AUD-only; comorbid MD/AUD) and MD over the period 18-35 years. These associations were then adjusted for confounding by a series of factors measured in childhood.

Results: The three disorder groups had rates of adult MD during the period 18-35 years that were significantly ($p < .05$) higher than that of the group with no disorder. Furthermore, those in the comorbid MD/AUD group had significantly ($p < .05$) higher rates of adult MD than those in the AUD-only group, and marginally ($p < .10$) higher rates of adult MD than those in the MD-only group. After adjustment for confounding, the difference in rates of adult MD between the MD-only group and the MD/AUD group were no longer statistically significant. The factors that explained the associations were gender, childhood behavior problems, and exposure to physical and sexual abuse.

Limitations. The data were obtained by self-report, and may have been subject to biases.

Conclusions: The results of these analyses suggest that marginally higher rates of depression to age 35 amongst the comorbid MD/AUD group were explained by increased exposure to adverse childhood circumstances amongst members of the comorbid group. Adolescent MD/AUD comorbidity is likely to be a risk marker, rather than a causal factor in subsequent MD.

Keywords: alcohol use disorders; major depression; comorbidity; longitudinal study

1. Introduction

The association between alcohol use disorders (AUDs) and mental disorders is well-recognized and has been the subject of a large number of recent studies (Hasin and Delker, 2015). The comorbidity between AUDs and major depression (MD) has received considerable attention, with a number of studies finding that MD and AUD comorbidity is common (Grant and Harford, 1995; Grant et al., 1996; Teesson et al., 2009) and in particular comorbidity at earlier stages of development (Beesdo-Baum et al., 2015; Langenbach et al., 2010; Wittchen et al., 1996). A key question arising from this literature is the extent to which comorbidity early in the developmental sequence predicts worse outcomes than non-comorbid depression at early stages (Essau, 2011; Kaminer et al., 2007).

A number of studies have suggested that early MD/AUD comorbidity predicts poorer subsequent MD outcomes. Hasin and Grant (2002), using data from the US National Longitudinal Alcohol Epidemiologic Survey, found that prior AUD significantly increased the risk of subsequent MD, despite not consuming alcohol at the time of measurement. Fein (Fein, 2013) reported that individuals with both short- and long-term histories of alcoholism had greater risks of both lifetime and current MD, in a study using retrospective data. Similar findings were reported by DiSchlafani et al (Di Sclafani et al., 2007), in a group of long-term abstinent alcoholics.

On the other hand, some evidence suggests that comorbidity is not predictive of a higher risk of later depression. For example, in a large longitudinal study of comorbidity in adolescence and early adulthood, the difference in depressive symptom severity between those with high and low alcohol problems diminished over time, and was minimal by early adulthood (Marmorstein, 2009). Briere et al (Brière et al., 2014), using longitudinal data, also reported that comorbidity was not associated with increased risk of subsequent MD. Relatedly, there is evidence from clinical data in adults suggesting the presence of alcohol or substance use disorder comorbidity does not worsen the outcome of treatment for depression (Davis et al., 2010; Mulder et al., 2006).

There may, however, be several issues arising from the previous literature that lead to difficulties in interpretation of these discrepant findings. For example, many studies in this area have relied on clinical, small or selected samples (Davis et al., 2010; Di Sclafani et al., 2007; Fein, 2013; Mulder et al., 2006), or have employed a limited range of variables to test for potential confounding (e.g. (Brière et al., 2014; Grant et al., 1996; Marmorstein, 2009). One way to address these issues is to employ data from a longitudinal study employing a general population sample, with repeated measurements of MD over time, and with data pertaining to a wide variety of possible confounding factors.

In this study we used data from a longitudinal birth cohort study to investigate the effect of comorbidity between MD and AUD in adolescence on MD outcomes in adulthood, net of confounding factors. In particular, the study examined: a) whether individuals with comorbid MD/AUD in adolescence had higher rates of adult MD than individuals with either disorder, or no disorder; and b) the extent to which a series of individual and environmental factors could account for increased rates of MD in adulthood amongst individuals with comorbid MD/AUD in adolescence. This was achieved by comparing rates of MD during the follow-up period (18 to 35 years) between four groups: those with comorbid MD/AUD; those with MD or AUD alone; and those with neither condition; during the period 15 to 18 years.

2. Methods

2.1 Participants

The data were gathered from the Christchurch Health and Development Study (CHDS). In this study a birth cohort of 1265 children (635 males, 630 females) born in the Christchurch (New Zealand) urban region in mid-1977 has been studied at birth, 4 months, 1 year and annually to age 16 years, and again at 18, 21, 25, 30 and 35 years (Fergusson and Horwood, 2001; Fergusson et al., 1989). The original cohort was comprised of 97% of all individuals born in Christchurch during the study entry

period. All study information was collected on the basis of signed consent from study participants and is fully confidential. All aspects of the study have been approved by the Canterbury (NZ) Ethics Committee. Sample sizes ranged from 1025 (age 18) to 962 (age 35), representing 79% to 82% of the surviving sample at each observation. The primary driver of sample loss over the course of the study has been emigration from New Zealand, with loss of contact.

2.2. Late adolescent major depression/alcohol use disorder classification (ages 15-18)

At the assessments at ages 16 and 18 years, participants were interviewed using items from the Composite International Diagnostic Interview (CIDI)(World Health Organization, 1993), in order to assess DSM-III-R (age 16) (American Psychiatric Association, 1987) and DSM-IV (age 18) (American Psychiatric Association, 1994) criteria for major depression (MD) and alcohol abuse dependence (alcohol use disorder; AUD). This information was used to classify participants into four groups, based on their history of MD and AUD during the period 15-18 years. These groups were: Neither MD nor AUD (comparison group); AUD-only; MD-only; and MD/AUD. Sample sizes at these ages were n = 982 (age 16) and n = 1025 (age 18).

2.3 Outcome measure - Major depression in adulthood (ages 18-21; 21-25; 25-30; 30-35 years)

At the assessments from ages 21 to 35 years, cohort members were interviewed concerning symptoms of MD that had occurred since the previous assessment, again using items from the CIDI to assess DSM-IV criteria for major depression. On this basis, cohort members who met DSM-IV criteria for MD at any time during an assessment period (18-21 years; 21-25 years; 25-30 years; and 30-35 years) were classified as having MD during that period. Sample sizes at these assessments were: n = 1011 (age 21); n = 1003 (age 25); n = 987 (age 30); and n = 962 (age 35).

2.4 Covariate factors

A number of potential confounding factors were abstracted from the study database, on the basis that they have been shown to be related to both MD and AUD in adolescence and adulthood. These factors included:

2.4.1 Childhood socioeconomic and demographic factors

2.4.1.1 *Gender*. Measured at birth.

2.4.1.2 *Maternal age*. Measured at birth.

2.4.1.3 *Family living standards (ages 0-10)*. At each year a global assessment of the material living standards of the family was obtained via interviewer rating on a five point scale that ranged from 1 = "very good" to 5 = "very poor". These ratings were summed over the 10 year period to give a measure of family living standards during this period.

2.4.2 Childhood family dysfunction

2.4.2.1 *Parental maladaptive behaviour (alcohol problems/criminal offending)*. At age 15, the parents of cohort members were questioned concerning their history of alcoholism or alcohol problems and criminal offending. On this basis, 11.9% of the sample were classified as having a parental history of alcoholism/alcohol problems, and 12.4% of the sample as having a parental history of criminal offending.

2.4.2.2 *Exposure to family adversity (0-15 years)*. A measure of family adversity was calculated using a count of 38 different measures of family disadvantage during the period 0-15 years, including measures of disadvantaged parental background, poor pre-natal health practices and perinatal outcomes, and disadvantageous child-rearing practices (Fergusson et al., 1994).

2.4.3 Childhood behaviour problems (conduct, attention, anxious/withdrawn, ages 7-9). At ages 7-9 years, information on child behavior problems was obtained from parental and teacher report. Parental reports were obtained from an interview with the child's mother using a behavior questionnaire that combined items from the Rutter, Tizard, and Whitmore (1970) and Conners (1970) questionnaires. Also, the child's class teacher completed a combined version of the Rutter et al. (1970) and Conners (1969) teacher questionnaires. Factor analysis of the item-level report data showed that these reports that formed uni-dimensional scales reflecting the extent of parent-reported and teacher reported behavior problems in three domains (Fergusson and Horwood, 1993; Fergusson et al., 1991): a) conduct problems (aggressive, oppositional, and conduct disordered behaviour); b) attentional problems (restless, inattentive, or hyperactive behaviors); and c) anxious/withdrawn behaviors (shy, anxious or withdrawn behaviour). For the purposes of the present analysis, the parent and teacher reports were summed for each domain and the resulting scores averaged over the three year period to produce three scale score measures reflecting the extent of the child's tendencies to conduct problems, attentional problems, and anxious/withdrawn behavior problems at ages 7-9.

2.4.4 Childhood abuse exposure

2.4.4.1 Childhood exposure to sexual abuse (0-16 years). At ages 18 and 21 years sample members were questioned about their experience of sexual abuse during childhood (<16 years) (Fergusson et al., 1996). Questioning spanned an array of abusive experiences from episodes involving non-contact abuse (e.g. indecent exposure) to episodes involving attempted or completed intercourse. Sample members who reported an abusive episode were then questioned further about the nature and context of the abuse. Using this information a 4-level scale was devised reflecting the most extreme form of sexual abuse reported by the young person at either age. This classification was: no sexual abuse; non-contact abuse only; contact sexual abuse not involving attempted or completed intercourse; attempted/completed oral, anal, or vaginal intercourse.

2.4.4.2 Parental use of physical punishment (childhood physical abuse). At ages 18 and 21 sample members were asked to describe the extent to which their parents used physical punishment during childhood (Fergusson and Lynskey, 1997). Separate questioning was conducted for mothers and fathers. This information was used to create a 4-level scale reflecting the most severe form of physical punishment reported for either parent: parents never used physical punishment; parents rarely used physical punishment; at least one parent used physical punishment on a regular basis; at least one parent used physical punishment too often or too severely, or treated the respondent in a harsh or abusive manner.

2.4.4.3 Parental intimate partner violence (IPV). At the age of 18, sample members were questioned concerning their experience of interparental violence during their childhood (prior to age 16 years). The questioning was based on a series of eight items derived from the Conflict Tactics Scale (CTS; Straus, 1979). The items were chosen on the basis that the behaviors could have been readily observed and reported on by the participant, and also to span the potential range of violent behavior from verbal abuse to physical assault. The eight items used included: a) threaten to hit or throw something at the other parent; b) push, grab, or shove other parent; c) slap, hit, or punch other parent; d) throw, hit, kick, or smash something (in the other parent's presence); e) kick other parent; f) choke or strangle other parent; g) threaten other parent with a knife, gun, or other weapon; h) call other parent names or criticize other parent (put other parent down). Participants were asked to rate the frequency with which they observed each behavior on a 3-point scale (never, occasionally, frequently). Separate questioning was conducted for violence initiated by the father against the mother and for violence initiated by the mother against the father, and combined into a single scale score representing overall exposure across both parents.

2.5 Statistical analyses

The data analyses took place over three steps. In the first step, the bivariate associations between the classification of adolescent MD/AUD and the repeated measures of MD in adulthood were obtained by fitting a logistic Generalized Estimating Equation (GEE) model to the data. These models were of the form:

$$\text{Logit}(Y_{it}) = B_0 + B_1X_i + u_i \quad (\text{EQ1})$$

where $\text{Logit}(Y_{it})$ represented the log odds of MD at time t for individual i , X_i was the classification of MD/AUD during the period 15-18 years, and u_i the individual specific error term. The measure of MD/AUD was represented by three dummy variables, which allowed Wald chi squared tests of differences between groups. Estimates of the odds ratio (OR) and 95% confidence interval (CI) were obtained by exponentiating the fitted model parameters (e^B). The fitted models also included age terms (not shown) to allow for across time changes in the rate or mean of each outcome, as well as age x MD/AUD classification interaction terms. This and adjusted models below were fitted using Stata 12.

In the second step, the bivariate associations between the MD/AUD classification in adolescence and the potential confounding factors noted above were obtained via one-way ANOVA with Duncan's test applied to examine differences between classification groups. These models were fitted using SAS 9.4.

In the final step, the model shown in EQ1 (above) was extended to include the potential confounding factors noted above, over a series of four steps. At each step, statistically significant ($p < .05$) confounding factors were retained for the next step, while those factors that were not statistically significantly associated with MD in adulthood were dropped from further analyses. All covariate factors were entered into the models in their original metrics. In the first step, the associations between MD/AUD classification in adolescence and MD in adulthood were adjusted for childhood socio-economic and demographic factors. In the second step, the associations were adjusted for the significant confounding factors from the first step, and for measures of childhood

family dysfunction. In the third step, the associations were adjusted for the significant confounding factors from the first two steps, and for measures of childhood behaviour problems. In the final step, the associations were adjusted for all prior significant confounding factors, and for exposure to abuse in childhood.

2.6 Examining bias due to sample attrition

To examine the effects of sample losses on the representativeness of the sample, the obtained samples with complete data at each age, were compared with the remaining sample members on a series of socio-demographic measures collected at birth. This analysis suggested that there were statistically significant ($p < .01$) tendencies for the obtained samples to under-represent individuals from socially disadvantaged backgrounds characterized by low parental education, low socio-economic status and single parenthood. To address this issue, the data weighting methods described by Carlin et al. (1999) were used to examine the possible implications of selection effects arising from the pattern of missing data. These analyses produced essentially the same pattern of results to those reported here, suggesting that the conclusions of this study were unlikely to have been influenced by selection bias.

3. Results

3.1 Associations between adolescent MD/AUD classification (ages 15-18) and rates of adult MD (ages 18-21, 21-25, 25-30, and 35-30)

Table 1 shows the cohort classified into four groups based on their history of alcohol use disorder (AUD) and major depression (MD) during the period 15 to 18 years (see Methods). For each group, the Table shows the proportion of individuals meeting DSM-IV criteria for MD during each

subsequent assessment period (ages 18-21; 21-25; 25-30; and 30-35 years). The Table also reports on the population-averaged rate of major depression for each group over the four assessment periods, and estimates of the odds ratio (OR) and 95% confidence interval (CI) for each group, derived from logistic GEE models (see Methods). Finally the Table also shows the results of planned comparisons (Wald X^2) between each of the groups. The Table shows:

1. Rates of MD were significantly ($p < .05$) higher in each of the three disorder groups (AUD-only; MD-only; MD/AUD) than in the comparison group. Odds of MD during the period 18 to 35 years amongst the three disorder groups ranged from 1.62 to 4.07 times higher than in the comparison group.
2. Rates of MD were also significantly ($p < .05$) higher in the MD-only and MD/AUD group than in the AUD-only group. The population-averaged rates show that 21.2% of the AUD-only group met criteria for MD on at least one occasion during the period 18-35 years, as compared with 33.9% of the MD-only group, and 40.7% of the MD/AUD group.
3. Rates of MD during the period 18 to 35 years were marginally ($p < .10$) higher in the MD/AUD group than in the MD-only group.

INSERT TABLE 1 HERE

3.2 Associations between MD/AUD classification (ages 15-18) and potential confounding factors

One explanation for the differences in rates of adult MD amongst the adolescent MD/AUD classification groups, as shown in Table 1, was that members of each group may have been exposed to varying levels of adverse family, individual and related circumstances in childhood that influenced both: a) the extent to which the individual would meet criteria for either MD or AUD during the period 18-35 years; and b) the extent to which the individual would be at risk for MD during

adulthood (ages 18-35 years). In order to address this issue, a series of potentially confounding factors related to family adversity and dysfunction, childhood behavioral problems, and exposure to childhood abuse were obtained from the study database, and compared across the MD/AUD classification groups using one way ANOVA (see Methods). While a range of factors was examined, only those factors which were found to be significantly ($p < .05$) associated with MD/AUD classification are displayed in Table 2, which shows mean scores (for continuous measures) or percentages (for dichotomous measures) for each MD/AUD classification group, as well as pairwise tests of significance (Duncan's test). The Table shows that, in general, the MD/AUD group had the highest rates of exposure to adverse childhood circumstances, as compared with the MD-only group, the AUD-only group, and the no disorder comparison group. For example, the rate of exposure to the most severe form of childhood sexual abuse (attempted/completed sexual penetration) was 21.0% for the MD/AUD group, as compared with 10.9% for the MD-only group, 1.6% for the AUD only group, and 3.2% for the comparison group. These data suggest that the MD/AUD group was exposed to particularly high levels of adverse childhood and family circumstances, as compared with the MD-only, AUD-only, and comparison groups.

INSERT TABLE 2 HERE

3.3 Associations between MD/AUD classification (ages 15-18) and rates of MD (ages 18-21, 21-25, 25-30, and 35-30), after adjustment for confounding factors

In order to examine the extent to which exposure to adverse childhood and adolescent circumstances may have contributed to the associations between MD/AUD classification (ages 15-18) and subsequent rates of MD during adulthood, the GEE model shown in Table 1 was extended to include terms representing the confounding factors shown in Table 2, over a series of steps. In the

first step, childhood socioeconomic and demographic factors were entered; in the second step, measures of family adversity and dysfunction during childhood and adolescence were added to the model; in the third step, measures pertaining to childhood behavioral problems were entered into the model; and in the final step, three measures of exposure to abuse in childhood were entered. At each step, those factors that were not statistically significantly ($p < .05$) associated with the outcome measure (major depression in adulthood) were eliminated from further analyses. For these analyses, all measures were entered in their original metrics (see Methods). The results of these analyses are displayed in Table 3, which show estimates of the OR and 95% CI for each depression classification group, at each step of adjustment. The Table shows:

1. Adjustment for confounding reduced the magnitude of the association between each of the MD/AUD classification groups and risk of adult depression, but the extent of this reduction differed by group. Control for confounding had relatively little effect on the AUD-only group, whereas for the MD-only group the OR was reduced from 3.15 (unadjusted) to 2.56 (Model 4). The reduction was even greater for the MD/AUD group, where the OR was reduced from a strong OR of 4.20 (unadjusted) to a moderate OR of 2.93 (Model 4).
2. The effects of specific sets of confounding factors also had differential effects on the association between each of the MD/AUD classification groups and risk of adult depression. For example, for the MD/AUD group, the association was most strongly affected by controlling for exposure to abuse in childhood, where the OR was reduced from 3.55 (Model 3) to 2.93 (Model 4).
3. Between groups comparisons showed that, after adjustment for all confounding factors (Model 4), the difference between the MD-only and MD/AUD groups was no longer marginally significant ($X^2 (1) = 0.65, p > .40$). However, the MD-only group ($X^2 (1) = 6.02, p < .05$) and MD/AUD ($X^2 (1) = 8.11, p < .01$) groups had significantly higher rates of MD during the period 18 to 35 years than those in the AUD-only group, after adjustment for confounding.

The results of these analyses suggest that higher rates of depression to age 35 amongst the comorbid MD/AUD group, as compared to the MD-only group, could be explained by increased exposure to adverse childhood circumstances amongst members of the comorbid group, rather than the comorbidity itself. Furthermore, the key confounding factors that explained this association were gender (OR = 1.59; 95%CI: 1.29-1.95), childhood behavior problems (conduct problems OR = 1.02, 95% CI: 1.01-1.03; anxious/withdrawn behavior OR = 1.03, 95%CI: 1.00-1.06), and exposure to physical abuse (OR = 1.36, 95%CI: 1.16-1.59) and sexual abuse (OR = 1.23, 95%CI: 1.10-1.37), all of which increased both the risk of adolescent comorbidity, and adult major depression.

INSERT TABLE 3 HERE

4. Discussion

The present study used data from a 35-year longitudinal study to examine the extent to which the associations between measures of MD and AUD in late adolescence were predictive of MD in adulthood (ages 18 to 35 years), comparing those meeting criteria for either MD or AUD (during the period 15-18 years) with individuals who met criteria for both MD and AUD during that period. The results of these analyses indicated the following general conclusions.

First, those with either disorder, or with comorbid MD and AUD, had higher rates of MD in adulthood than those who had neither disorder during the period 15-18 years. However, it was also the case that those who met criteria for MD in late adolescence had higher rates of MD in adulthood than those with neither disorder, or with AUD only. This finding is in agreement with a range of studies suggesting that, for many individuals, MD is a life-course persistent disorder, and that early MD is a strong predictor of recurrent MD later in life (Bohman et al., 2010; Brugha et al., 1997; Fergusson et al., 2007; Solomon et al., 1997).

Further, a key finding was that those with comorbid MD/AUD in late adolescence had marginally higher rates of MD in adulthood, as compared with those meeting criteria for MD only. This pattern of results is congruent with findings of poorer MD outcomes amongst those with comorbid AUD, as opposed to those with MD alone (Di Sclafani et al., 2007; Fein, 2013; Hasin and Grant, 2002). The results contrast, however, with a number of studies failing to find differences in MD outcomes between comorbid AUD and sole MD groups (Brière et al., 2014; Davis et al., 2010; Marmorstein, 2009; Mulder et al., 2006). One of the primary reasons for this difference may be that the longitudinal nature of the study, examining MD to age 35, provides a much broader time frame in which individuals may experience recurrent MD.

A critical strength of the present analyses was that, using the extensive CHDS database to control for potential confounding factors, it proved possible to examine the extent to which the pattern of disorder in late adolescence played a causal role in the incidence of adult MD. Analyses showed that those in the MD/AUD group in late adolescence had been exposed to relatively higher levels of adverse family circumstances, had higher rates of childhood behavior problems, and were more likely to have been exposed to a range of abuse in childhood. Furthermore, those in the MD/AUD group were more likely to be females, with previous research showing a clear pattern of increased levels of internalizing disorder amongst females as compared with males (Grigoriadis and Robinson, 2007; Kramer et al., 2008). It could be argued that higher rates of MD in adulthood was due to increased exposure to adversity in childhood, and a particular pattern of individual characteristics and childhood behavior, rather than the comorbidity itself. The results indicated that, after controlling for potential confounding factors, there was no longer a marginally significant difference between the MD/AUD group and the MD-only group. These findings suggested that the observed difference in rates of adult MD in these groups could be attributed to higher levels of exposure to adverse childhood circumstances and personal characteristics that put the individual at higher risk of both MD and AUD in adolescence, rather than to the comorbidity between disorders, *per se*. An implication of these findings is that, while early comorbidity may be a stronger risk

indicator for adult psychopathology than the diagnosis of MD itself, it is unlikely to be the case that comorbid alcohol misuse and MD in adolescence plays a causal role in poorer MD outcomes in adulthood.

The present findings, indicating a lack of a causal role of early comorbidity in predicting later depression outcomes, suggests that programs and interventions aimed specifically at treating adolescents with comorbidity are not likely to be more effective than programs dealing with depression generally. Indeed, the present results suggests that the main causal drivers of later depression are likely to be adverse childhood circumstances, childhood behavior problems, and abuse exposure, and that reduction of the incidence of depression in adulthood may be more fruitfully achieved via screening processes and treatment aimed at these issues.

One interesting finding to emerge from the control for confounding was the strong effect of abuse exposure in explaining the associations between MD/AUD in adolescence and adult MD. It has become increasingly clear in recent years that exposure to abuse in childhood, and in particular exposure to sexual abuse, is one of the strongest predictors of adult psychopathology (Cutajar et al., 2010; Fergusson et al., 2008; Fergusson et al., 2013; Keyes et al., 2012). The present findings serve to further elucidate this linkage across the lifespan to age 35, and suggest that interventions and treatments designed for victims of abuse pay particular attention to the possibility of increased risk of comorbid depression and alcohol use disorder. In addition, the pattern of findings also indicates the lasting role of childhood behavior problems in adult psychopathology (Fergusson et al., 2010; Zahn-Waxler et al., 2008).

While this paper has a number of strengths relating to the longitudinal design and breadth of the data collection, it also has some limitations that should be borne in mind. First, the findings are based on a specific birth cohort assessed over a particular historical period. The extent to which the study findings generalise to other cohorts and settings remains to be established. Second, all measures were obtained via self-report, which may be subject to biases related to socially-desirable

responding. Third, although the study examined a wide range of factors that may have confounded the associations between comorbid disorders in adolescence and adult MD, it could be argued that any residual associations may be due to unmeasured sources of confounding. Finally, the present research focussed on the development of depression in adulthood; it would be useful for future research to examine the extent to which comorbidity in adolescence may be related to later persistence of MD in adulthood.

Notwithstanding these limitations, the results of present study indicate that that marginally higher rates of depression to age 35 amongst those with comorbid MD/AUD in adolescence, as compared to those with MD-only in adolescence, were largely explained by increased exposure to adverse childhood circumstances amongst those with comorbid MD/AUD. These findings suggest that comorbidity in adolescence is more likely to be a risk marker, rather than a cause, of poorer MD outcomes in adulthood.

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Conflict of Interest No conflict declared

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References

- American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders (3rd ed. - rev). American Psychiatric Association, Washington, DC.
- American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders (4th ed.). American Psychiatric Association, Washington DC.
- Beesdo-Baum, K., Knappe, S., Asselmann, E., Zimmermann, P., Brückl, T., Höfler, M., Behrendt, S., Lieb, R., Wittchen, H.U., 2015. The 'Early Developmental Stages of Psychopathology (EDSP) study': a 20-year review of methods and findings. *Soc. Psychiatry Psychiatr. Epidemiol.* 50, 851-866.
- Bohman, H., Jonsson, U., Paaren, A., Von Knorring, A.L., Olsson, G., Von Knorring, L., 2010. Long-term follow-up of adolescent depression. A population-based study. *Ups. J. Med. Sci.* 115, 21-29.
- Brière, F.N., Rohde, P., Seeley, J.R., Klein, D., Lewinsohn, P.M., 2014. Comorbidity Between Major Depression and Alcohol Use Disorder From Adolescence to Adulthood. *Compr. Psychiatry* 55, 526-533.
- Brugha, T.S., Bebbington, P.E., Stretch, D.D., MacCarthy, B., Wykes, T., 1997. Predicting the short-term outcome of first episodes and recurrences of clinical depression: a prospective study of life events, difficulties, and social support networks. *J. Clin. Psychiatry* 58, 298-306.
- Carlin, J.B., Wolfe, R., Coffey, C., Patton, G.C., 1999. Tutorial in biostatistics. Analysis of binary outcomes in longitudinal studies using weighted estimating equations and discrete-time survival methods: Prevalence and incidence of smoking in an adolescent cohort. *Stat. Med.* 18, 2655-2679.
- Conners, C.K., 1969. A teacher rating scale for use in drug studies with children. *Am. J. Psychiatry* 126, 884-888.
- Conners, C.K., 1970. Symptom patterns in hyperkinetic, neurotic and normal children. *Child Dev.* 41, 667-682.
- Cutajar, M.C., Mullen, P.E., Ogloff, J.R.P., Thomas, S.D., Wells, D.L., Spataro, J., 2010. Psychopathology in a large cohort of sexually abused children followed up to 43 years. *Child Abuse Negl.* 34, 813-822.

- Davis, L.L., Wisniewski, S.R., Howland, R.H., Trivedi, M.H., Husain, M.M., Fava, M., McGrath, P.J., Balasubramani, G.K., Warden, D., Rush, A.J., 2010. Does comorbid substance use disorder impair recovery from major depression with SSRI treatment? An analysis of the STAR*D level one treatment outcomes. *Drug and Alcohol Dependence* 107, 161-170.
- Di Sclafani, V., Finn, P., Fein, G., 2007. Psychiatric Comorbidity in Long-Term Abstinent Alcoholics. *Alcohol. Clin. Exp. Res.* 31, 795-803.
- Essau, C.A., 2011. Comorbidity of substance use disorders among community-based and high-risk adolescents. *Psychiatry Res.* 185, 176-184.
- Fein, G., 2013. Lifetime and Current Mood and Anxiety Disorders in Short-Term and Long-Term Abstinent Alcoholics. *Alcohol. Clin. Exp. Res.* 37, 10.1111/acer.12170.
- Fergusson, D.M., Boden, J.M., Horwood, L.J., 2007. Recurrence of major depression in adolescence and young adulthood and later mental health, education, and economic outcomes. *Br. J. Psychiatry* 191, 335-342.
- Fergusson, D.M., Boden, J.M., Horwood, L.J., 2008. Exposure to childhood sexual and physical abuse and adjustment in early adulthood. *Child Abuse Negl.* 32, 607-619.
- Fergusson, D.M., Boden, J.M., Horwood, L.J., 2010. Classification of behavior disorders in adolescence: Scaling methods, predictive validity and gender differences. *J. Abnorm. Psychol.* 119, 699-712.
- Fergusson, D.M., Horwood, L.J., 1993. The structure, stability and correlations of the trait components of conduct disorder, attention deficit and anxiety/withdrawal reports. *Journal of Child Psychology and Psychiatry* 34, 749-766.
- Fergusson, D.M., Horwood, L.J., Lloyd, M., 1991. A latent class model of child offending. *Criminal Behaviour and Mental Health* 1, 90-106.
- Fergusson, D.M., Horwood, L.J., Lynskey, M.T., 1994. The childhoods of multiple problem adolescents: A 15-year longitudinal study. *Journal of Child Psychology and Psychiatry* 35, 1123-1140.

Fergusson, D.M., Lynskey, M.T., 1997. Physical punishment/maltreatment during childhood and adjustment in young adulthood. *Child Abuse Negl.* 21, 617-630.

Fergusson, D.M., Lynskey, M.T., Horwood, L.J., 1996. Childhood sexual abuse and psychiatric disorder in young adulthood: I. Prevalence of sexual abuse and factors associated with sexual abuse. *J. Am. Acad. Child Adolesc. Psychiatry* 35, 1355-1364.

Fergusson, D.M., McLeod, G.F.H., Horwood, L.J., 2013. Childhood sexual abuse and adult developmental outcomes: Findings from a 30-year longitudinal study in New Zealand. *Child Abuse Negl.* 37, 664-674.

Grant, B.F., Harford, T.C., 1995. Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. *Drug Alcohol Depend.* 39, 197-206.

Grant, B.F., Hasin, D.S., Dawson, D.A., 1996. The relationship between DSM-IV alcohol use disorders and DSM-IV major depression: examination of the primary-secondary distinction in a general population sample. *J. Affect. Disord.* 38, 113-128.

Grigoriadis, S., Robinson, G.E., 2007. Gender issues in depression. *Ann. Clin. Psychiatry* 19, 247-255.

Hasin, D., Delker, E., 2015. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)—a huge resource for data and research findings. *Addiction* 110, 378-380.

Hasin, D.S., Grant, B.F., 2002. Major depression in 6050 former drinkers: Association with past alcohol dependence. *Arch. Gen. Psychiatry* 59, 794-800.

Kaminer, Y., Connor, D.F., Curry, J.F., 2007. Comorbid Adolescent Substance Use and Major Depressive Disorders: A Review. *Psychiatry (Edgmont)* 4, 32-43.

Keyes, K.M., Eaton, N.R., Krueger, R.F., McLaughlin, K.A., Wall, M.M., Grant, B.F., Hasin, D.S., 2012. Childhood maltreatment and the structure of common psychiatric disorders. *The British Journal of Psychiatry* 200, 107-115.

Kramer, M.D., Krueger, R.F., Hicks, B.M., 2008. The role of internalizing and externalizing liability factors in accounting for gender differences in the prevalence of common psychopathological syndromes. *Psychol. Med.* 38, 51-61.

- Langenbach, T., Spönlein, A., Overfeld, E., Wiltfang, G., Quecke, N., Scherbaum, N., Melchers, P., Hebebrand, J., 2010. Axis I comorbidity in adolescent inpatients referred for treatment of substance use disorders. *Child Adolesc. Psychiatry Ment. Health* 4.
- Marmorstein, N.R., 2009. Longitudinal associations between alcohol problems and depressive symptoms: early adolescence through early adulthood. *Alcoholism: Clinical and Experimental Research* 33, 49-59.
- Mulder, R.T., Joyce, P.R., Frampton, C.M., Luty, S.E., Sullivan, P.F., 2006. Six months of treatment for depression: outcome and predictors of the course of illness. *American Journal of Psychiatry* 163, 95-100.
- Rutter, M., Tizard, J., Whitmore, K., 1970. *Education, Health and Behaviour*. Longmans, London.
- Solomon, D.A., Keller, M.B., Leon, A.C., Mueller, T.I., Shea, M.T., Warshaw, M., Maser, J.D., Coryell, W., Endicott, J., 1997. Recovery from major depression. A 10-year prospective follow-up across multiple episodes. *Arch. Gen. Psychiatry* 54, 1001-1006.
- Straus, M., 1979. Measuring intrafamily conflict and violence: The conflict tactics (CT) scale. *Journal of Marriage & the Family* 41, 75-88.
- Teesson, M., Slade, T., Mills, K., 2009. Comorbidity in Australia: Findings of the 2007 National Survey of Mental Health and Wellbeing. *Aust. N. Z. J. Psychiatry* 43, 606-614.
- Wittchen, H.U., Perkonig, A., Reed, V., 1996. Comorbidity of Mental Disorders and Substance Use Disorders. *Eur. Addict. Res.* 2, 36-47.
- World Health Organization, 1993. *Composite International Diagnostic Interview (CIDI): core version 1.1*. World Health Organization, Geneva, Switzerland.
- Zahn-Waxler, C., Shirtcliff, E.A., Marceau, K., 2008. Disorders of childhood and adolescence: gender and psychopathology. *Annual Review of Clinical Psychology* 4, 275-303.

Table 1. Associations between depression classification (ages 15-18) and rates of major depression, ages 18-21, 21-25, 25-30, and 30-35 years.

% reporting MD	Depression Classification			
	Neither MD nor AUD (n = 634)	AUD-only (n = 130)	MD-only (n = 192)	MD/AUD (n = 100)
Ages 18-21	14.7	19.0	41.7	48.5
Ages 21-25	14.6	22.3	34.8	42.3
Ages 25-30	13.4	27.1	34.1	35.1
Ages 30-35	14.0	15.8	24.6	36.6
Population averaged % (ages 18-35)	14.2 ^a	21.1 ^b	33.9 ^{c†}	40.7 ^{c†}
OR (95% CI)	1	1.62	3.15	4.20
	--	(1.19 – 2.20)	(2.48 – 4.00)	(3.14 – 5.62)

Note: differing superscripts (a, b, c) indicate statistically significant ($p < .05$) differences

[†] The difference between the MD-only and MD/AUD group was marginally significant ($p < .10$)

Table 2. Associations between depression classification (ages 15-18) and potential confounding factors.

Measure	Depression Classification			
	Neither MD nor AUD	AUD-only	MD-only	MD/AUD
% male gender	34.4 ^a	66.9 ^a	30.7 ^c	35.0 ^c
Mean (SD) maternal age	26.08 ^a (4.74)	25.46 ^{a,b} (5.00)	25.79 ^{a,b} (5.11)	24.90 ^b (4.35)
Mean (SD) living standards (ages 0-10)	28.31 ^a (4.41)	28.30 ^a (4.60)	28.90 ^{a,b} (4.94)	29.38 ^b (4.40)
Mean (SD) conduct problems (ages 7-9)	49.16 ^a (7.28)	50.74 ^a (7.60)	49.95 ^a (7.85)	52.63 ^b (8.87)
Mean (SD) attention problems (ages 7-9)	19.73 ^a (4.65)	20.89 ^b (4.83)	19.50 ^a (5.32)	21.38 ^b (5.69)
Mean (SD) anxious/withdrawn behaviour (ages 7-9)	25.79 ^{a,b} (3.52)	25.37 ^b (3.62)	26.55 ^{a,c} (3.63)	26.73 ^c (3.25)
% parental history of alcohol problems	8.0 ^a	12.2 ^a	16.3 ^a	24.0 ^b
% parental history of criminal offending	9.7 ^a	15.4 ^{a,b}	17.6 ^{b,c}	25.0 ^c
Mean (SD) family adversity score	6.61 ^a (4.89)	7.60 ^{a,b} (5.49)	8.32 ^{b,c} (6.19)	8.98 ^c (5.28)
% exposed to most severe level of childhood sexual abuse	3.2 ^a	1.6 ^a	10.9 ^b	21.0 ^c
% exposed to most severe level of childhood physical abuse	3.7 ^a	6.2 ^{a,b}	10.4 ^{b,c}	13.0 ^c
Mean (SD) parental IPV score	8.81 ^a (1.54)	9.35 ^b (2.26)	9.78 ^b (3.02)	10.73 ^c (3.78)

Note: differing superscripts (a, b, c) indicate statistically significant ($p < .05$) differences

Table 3. Associations between depression classification (ages 15-18) and rates of major depression, ages 18-35, after adjustment for confounding factors.

	Model 1 Adjusted for childhood socio-demographic factors	Model 2 Model 1 + adjustment for childhood family dysfunction	Model 3 Model 1+2, + adjustment for childhood behaviour problems	Model 4 Model 1-3, + adjustment for exposure to abuse in childhood
Depression classification (ages 15-18)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Neither MD nor AUD (comparison group)	1 (--)	1 (--)	1 (--)	1 (--)
AUD-only	1.70 (1.25 – 2.52)	1.66 (1.21 – 2.28)	1.70 (1.24 – 2.34)	1.65 (1.20 – 3.29)
MD-only	2.84 (2.23 – 3.61)	2.79 (2.18 – 3.58)	2.76 (2.16 – 3.58)	2.56 (1.99 – 3.29)
MD/AUD	3.80 (2.83 – 5.09)	3.69 (2.74 – 4.96)	3.55 (2.63 – 4.80)	2.93 (2.14 – 4.03)
Statistically significant (p<0.05) confounding factors	1,2	1,6	1,7,9	1,4,6,10,11

Confounding factors: 1 = gender; 2 = maternal age; 3 = childhood family living standards; 4 = parental history of alcohol problems; 5 = parental history of criminal offending; 6 = family adversity score; 7 = conduct problems (ages 7-9); 8 = attention problems (ages 7-9); 9 = anxious/withdrawn behaviour; 10 = childhood sexual abuse exposure; 11 = childhood physical abuse exposure; 12 = parental IPV.