Is adolescent alcohol use associated with self-reported hypomanic symptoms in adulthood? - Findings from a prospective birth cohort.

Melissa Fasteau[a], Daniel Mackay[b], Daniel J. Smith[b], Thomas D. Meyer[a*]

[a]McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA

[b]University of Glasgow, UK

[*]Correspondence to: Thomas D. Meyer, PhD., McGovern Medical School, Department of Psychiatry and Behavioral Sciences, University of Texas HSC, 1951 East Rd (BBSB 3118), Houston, TX, 77054, USA

Abstract

High rates of alcohol use disorder (AUD) are reported in people with major depression (MD) and bipolar disorder (BD). Substance abuse problems in adolescence may also indicate risk for future onset of mood disorders, especially BD. Data collected from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large UK birth cohort, allowed information to be collected over several different time points and to test whether problematic alcohol use at age 16 was predictive of vulnerability to hypomanic symptoms at age 23.

Controlling for a participant's gender, SES, marital status of the mother, a likely history of maternal depression, and adolescents' level of depressive symptoms at age 16, a hierarchical linear regression revealed that self-reported alcohol use in adolescence predicted the future onset of hypomanic/manic symptoms. Limitations include attrition and relying solely on self-ratings. Despite these limitations, the results suggest problematic alcohol use in adolescence predicts a vulnerability to hypomanic or manic symptoms.

1 Introduction

High rates of alcohol use disorders (AUD) have been reported in people with major depression (MD) and bipolar disorder (BD) (e.g. Goodwin and Jamison, 2007). The presence of either mood disorder or AUD increases the risk of the other disorder (Boden and Fergusson, 2011). In adolescence, AUD is typically found at a low prevalence rate, but increases during adulthood (Briere et al., 2014). Furthermore, AUD during adolescence is predictive for MD in early adulthood (Briere et al., 2014).

Several hypotheses might explain the comorbidity between mood disorders and AUD. For example, based on their longitudinal data of a birth cohort, Fergusson et al (2009) suggested that AUD may lead to increased risk of major depression, via physiological changes within the brain. Duffy's (2015) staging model also suggests based on prospective data that substance related problems in adolescence at familial risk for BD might be indexing early-stage mood

disorders, especially BD. Another hypothesis is that there are shared genetic or other vulnerability factors such as a sensitive behavioral activation system, specifically increased impulsivity and fun-seeking (Alloy et al., 2009; Duffy et al., 2010). In clinical settings, people with mood spectrum disorders may consume alcohol as a method to self-medicate and deal with mood swings which may or may have not reached yet the level of clinical relevance (Khantizan, 1985; McDonald and Meyer, 2011), and Singh et al. (2015) raised the possibility that underlying temperaments and their associated behaviors might increase the risk for misuse.

Of interest from the perspective of BD, Angst et al. (2006) and Merikangas et al. (2008) provided some evidence that most of the comorbidity between AUD and mood disorders is due to the presence of 'bipolarity'. This means that alcohol related problems are more closely related to BD and might indicate a possibility of unrecognized BD in depressed patients or subsyndromal manic symptoms. Therefore increased alcohol use or fluctuations in alcohol use could be indicating that individuals use it to try to alleviate prodromal symptoms such as mood swings or indicate vulnerability to bipolar disorders (Alloy et al., 2009; Krumm-Merabet and Meyer, 2005; McDonald and Meyer; 2011, Meyer and Wolkenstein, 2010). Therefore, based on the literature problematic adolescent alcohol use may predict the future onset of hypomanic symptoms in young adulthood. While ideally this should be studied in a longitudinal study following a sufficiently large cohort over time, there is the issue of feasibility and power. For example, the internationally well-known Dunedin Multidisciplinary Health and Development Study only identified 29 cases of mania in a birth cohort by age 26 (Kim-Cohen et al., 2003) which limits power to finding associations.

We used data from a longitudinal study, the Avon Longitudinal Study of Parents and Children (ALSPAC), a study of a large birth cohort in the UK, studied from birth (in 1991 to

1992) (e.g. Boyd et al., 2013; Fraser et al., 2013; Geulayov et al., 2016). At age 23 the Hypomania Checklist-32 (HCL-32, Angst et al., 2005) was included for the very first time to assess a history of hypomanic symptoms. In a prior report with regards to this vulnerability to BD, we found that higher general intelligence at age 15 was predictive of vulnerability for BD in form of higher HCL-32 scores (Smith et al., 2015). Using this data set enabled us to look this time at whether there is a link between AUDs in adolescence (age 16) and possible history of (hypo)manic symptoms assessed at age 23. We predicted that AUD-related problems in adolescence are predictive of future hypomanic/manic symptoms in young adulthood after controlling for other factors such as depressive symptoms during adolescence or maternal depression.

2 Method

2.1. Description of ALSPAC cohort and study sample:

The Avon Longitudinal Study of Parents and Children (ALSPAC, www.bristol.ac.uk/alspac) is a United Kingdom birth cohort, from the geographical area of Avon in Southwest, England. ALSPAC recruited 14,541 pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992. 14,541 is the *initial* number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99. Of these *initial* pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven

onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above.[1]

The number of new pregnancies not in the initial sample (known as Phase I enrollment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrollment are described in more detail in the cohort profile paper which should be used for referencing purposes: <http://ije.oxfordjournals.org/content/early/2012/04/14/ije.dys064.full.pdf+html>.

The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 foetuses. Of this total sample of 15,458 foetuses, 14,775 were live births and 14,701 were alive at 1 year of age. A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon (see also for example Boyd et al., 2013; Fraser et al., 20103). The final sample of this prospective cohort study was 15445 participants (see also Figure 1: Flowchart).

At baseline, parents provided extensive information at baseline on their own health, demographics and lifestyle. They have completed regular postal questionnaires about their child's health and development from birth. The children attended a number of assessment clinics starting at age 7. Please note that the study website contains details of all the data that is

[1] Some of the information in the following paragraphs might not be directly relevant for the current analyses but to fully comply with ALSPAC rules we added the descriptions of the original recruitment waves.

available through a fully searchable data dictionary" and reference the following webpage: <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>

Participants from the original ALSPAC cohort for who the ALSPAC group still had valid contact information were invited to complete a questionnaire called "Your Life now (21+)", which included the HCL-32 questions (see Smith et al., 2015). 3343 provided sufficient data to calculate HCL-32 scores (Figure 1). While the respondents in that year had a greater proportion of females, higher maternal social class, and lower rates of maternal depression, these seem to reflect selective attrition effects often observed in many, especially longitudinal studies (Smith et al., 2015). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees in the UK (see also Smith et al., 2015).

With regards to the present report, our sample (n = 1910) also included more females (n = 1270, 66.5%). The ethnic distribution of the sample included 97.7% Caucasian (n = 1867), and 2.3% non-Caucasian (including Black Caribean, Black African, Other Black, Indian, and Chinese). The average age of participants was 21.9 years (263.17 months, n = 1895; SD = 6.04, range: 249-278).

The Registrar-General's Social Classes was used to describe the mother's social class as follows: professional occupations (n=164, 8.6%), managerial and technical occupations (n=662, 34.7%), skilled non-manual occupations (n= 700, 36.6%), skilled manual occupations (n=86, 4.5%), partly skilled occupations (n=111, 5.8%), and unskilled occupations (13, 0.7%) (citation: http://www.celsius.lshtm.ac.uk/). In the final study sample of 1910, the parents of 1670 participants (87.3%) mortgaged homes and 46 (2.4%) participants owned homes, 89 (4.7%) participants lived in rented accommodations, 64 (3.5%) lived in council houses, and 41 (2.1%) reported having other living situations without specifying them.

2.2. Measures

2.2.1. Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001)

The AUDIT is a self-rating questionnaire that assesses alcohol use and identifies problematic and dangerous use. It includes 10 items assessing hazardous alcohol use, dependence symptoms, and harmful alcohol use, each item rated along 0 to 4 points, based on frequency, amount, and effects of use (Team, 2009). This instrument has been used extensively and is validated among a variety of clinical settings and in large scale studies. It was completed the first time in the cohort at age 16, and the total sum score was used.

2.2.2. Hypomania Checklist-32 (HCL-32) (Angst et al., 2005)

The HCL-32 is a self-rated questionnaire assessing lifetime history of hypomanic symptoms with 32 yes or no questions resulting in a composite score. The HCL-32 has been used extensively and is validated in large scale studies and a variety of clinical settings, in which is used as a clinically useful screening tool for BD (for review: Meyer et al., 2014). While over the last decades several valid and reliable measures have been developed to assess vulnerability for BD (e.g. GBI, Depue et al., 1989; HPS, Eckblad and Chapman, 1986), we decided to use the HCL-32 because the other measures tap more into a temperament while the HCL-32 screens for BD using assessing a history of hypomanic symptoms (Waugh et al., 2013).

2.2.3. Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987)

A likely history of maternal depression was identified through a ten question self-report measured at three time points over the course of pregnancy and shortly after giving birth. We include this since several studies have shown family aggregation of mood disorders (e.g. Duffy et al., 2010). The response format assesses symptoms of depression in the past 7 days, and each

item is answered on a 4 point scale with some items being reverse coded. Based on the published cut-off scores it was determined if at any time depressive symptoms were sufficiently severe to suspect depression. If the mother expressed sufficiently intense depressed symptoms at least once, it was coded as a likely history of depression.

2.2.4. Mood and Feelings Questionnaire (MFQ, Angold et al., 1995)

Likely adolescent depression was assessed using the widely used MFQ (Davis et al., 2006; Kent et al., 1997) at age 16. This response format for each item is 0 to 3 (0 = not true, 1 = sometimes, and 2 = true), assessing symptoms of depression in the past two weeks. The total score can range from 0 to 26.

2.3.Statistical Methods

The HCL-32 data of 3343 participants could be used, and 1910 participants provided sufficient information on all relevant variables to be included in the analysis. Missing items were replaced if they did not exceed more than 10% of the scale items. For example, for the HCL-32 up to three items were allowed to be missing and be replaced by the sample item mean for that individual.

Based on the knowledge of social and demographic influences associated with substance abuse and BD (e.g. Eid et al., 2014; Harrell et al., 2013L Ranning et al., 2016), several factors were identified which needed to be controlled for when looking at the association between alcohol use and vulnerability to BD. These factors included gender (male/female), marital status of the mother, maternal social class (own/rent home), likelihood of adolescent depression, and likelihood of maternal history of depression (assessed at 18 weeks gestation, 8 weeks after birth, and 8 months after birth). We assessed stability of marital status. Marital status was assessed at eight weeks gestation and the child's sixth birthday, and we used this information to determine

whether or not the mother's marital status changed over time. Homeownership was used as a proxy variable for socioeconomic status of the mother and created as a dichotomous variable for the analysis. The category "Yes" includes people who owned or mortgaged homes. The variable "No" combines people who rented, had council housing and all other living situations.

Variables were coded as follows. Marital status (stable single, stably married, and all else/other) was dummy coded and "other/all else" as the reference category. Homeownership was defined as $0 = $ No, $1 = $ Yes, and sex was coded as $1 = $ Male, $2 = $ Female. Likely maternal depression as assessed by the EPDS is coded as $0 = $ No depression across three time points and $1 = $ likely history of depression.

All transformations and analyses were conducted with SPSS. To account for skew and kurtosis, variables were transformed to create normality if needed and appropriate. Only for the AUDIT a transformation was deemed appropriate, and the square root transformation was used.

The main analysis, a hierarchical regression was conducted in SPSS with the HCL-32 total score used as the dependent variable. 1910 participants were included. In the first block, gender, socioeconomic status, and marital status were entered to control for potential confounds. The second block included the mother's likely history of depression (measured at different time points by EPDS) and participant's self-reported level of depression at age 16 (measured by the MFQ). The third block included the participant's AUDIT score at age 16. All results were calculated using IBM SPSS V21.

3 Results

3.1. The final sample

To evaluate the equivalence of the final sample (n = 1910) of which we had complete data, we tested for potential differences compared to the sample who responded to the assessment at age 22/23 (Table 1). Using the available data, participants in the final sample did not significantly differ in their HCL-32 scores, $t_{(3341)} = 1.66$, $p = 0.10$. Furthermore, although there was a significant group difference with respect to age, this corresponded to a negligible effect size, $t_{(3294)} = -1.95$, $p = 0.05$, Cohen's d $= 0.07$ (0.001-0.139). Additionally the included and excluded participants samples did not differ in how they felt on the day they completed the questionnaires assessed by an HCL-32 item on a scale from 1 to 7 (M = 4.25, SD = 1.08 vs. M = 4.27, SD = 1.12 respectively). Importantly for our analyses, participants in the final sample did not differ from the remaining sample in the likelihood that the mothers might have suffered from depression, $\chi^2_{(1)} = 1.58$, $p = 0.21$. The likelihood that the participant experienced depressive symptoms the week prior to the assessment at age 16, as measured by MFQ did also not significantly differ, $t_{(2698)} = 1.19$, $p = 0.24$. Participants also did not differ in their reported alcohol use, as measured by the AUDIT, $t_{(2343)} = 0.87$, $p = 0.39$. However, the final sample differed from the remaining one with regard to a higher percentage of females (66.5% vs. 61.7%) in the included sample, $\chi^2_{(1)} = 8.24$, $p = 0.004$. The rates of families owning versus renting homes differed in that more families rented homes in the excluded sample (18.1% vs. 10.2%), $\chi^2_{(1)} = 40.77$, $p = <0.001$. Additionally the stability of maternal marital status differed in that more mothers in the included sample remained married, $\chi^2_{(2)} = 127.35$, $p <0 .001$.

3.2. Main analysis

The hierarchical linear regression led to the following results [2]: Model 1, including sex, homeownership, and marital status as predictors of a vulnerability to hypomanic symptoms was significant therefore explaining significant variance in self-reported vulnerability to BD (Model 1: $F_{(4, 1905)} = 5.369$, $R = 0.106$, $p < 0.001$). When we added a likely history of maternal depression and participants' self-rated depressive symptoms at age of 16 as predictors for hypomanic symptoms in Model 2, the model remained significant (Model 2: $F_{(6, 1903)} = 10.109$, $p < 0.001$, $R = 1.76$, and $\Delta R^2 = 0.03$ was significant as well. When the AUDIT scores were included in the final block, the overall model remained significant (Model 3: $F_{(7, 1902)} = 13.51$, $p < 0.001$, $R = 0.218$, $R^2 = 0.047$). The change in R^2 was also significant, showing that the AUDIT improved prediction by $\Delta R^2 = 0.016$.

In this final model only gender, participant depression, and AUDIT scores emerged as significant predictors. The results revealed that males overall had higher HCL-32 scores, and that self-reported depressive symptoms at age 16 predicted higher HCL-32 scores at age 23. However, most importantly, after controlling for all those variables, self-reported higher levels of alcohol abuse symptoms predicted increased vulnerability to hypomanic symptoms at age 23 as hypothesized.

4   Discussion

Using a longitudinal data set we explored whether self-reported alcohol use measured by AUDIT scores will predict increased vulnerability for BD after controlling for several other variables. In line with our hypothesis the results revealed that alcohol related problems indeed

---

[2] We re-ran the analyses eliminating the alcohol and drug-related items from the HCL-32 which did not change the results (available on request). We therefore present the results for the full HCL-32 composite score for comparison with other studies.

predicted higher HCL-32 scores, but levels of depressive symptoms at age 16, and gender did so as well.

After controlling for depression and sociodemographic information, the AUDIT scores in adolescence appear to predict HCL-32 scores in early adulthood. This fits to other research suggesting that alcohol use could be a vulnerability factor for the onset of BD (Simhandl et al., 2016; Winokur, 1999). There are several ways in which alcohol use and BD could be linked to each other. One way is that BD or a vulnerability to BD increases the likelihood of consuming more alcohol because of trying to cope with mood lability and/or symptoms; another mechanism could be that potentially shared underlying risk factors such as impulsivity or a dysregulation of the behavioral activation system increase the likelihood to develop both conditions, or the use of alcohol alters the sensitivity of the brain to develop BD (e.g. Boden and Ferguson, 2011; Meyer et al., 2012, Ng et al., 2016). While we had no specific hypothesis for the relationship between sociodemographic factors and vulnerability for BD, gender emerged as a predictor with males presenting with higher HCL-32 scores. This also fits to past research, which shows that males tend to have higher HCL-32 scores than females, especially in clinical samples (Baur et al., 2016, Waugh et al., 2014). In this study, we also controlled for socioeconomic status and marital stability. Although one could speculate that higher SES and a more unstable home environment in form of divorce and remarriage might increase vulnerability for BD, in our study those variables did not significantly contribute to the prediction of self-rated vulnerability to hypomanic symptoms decades later.

Our data supports the past literature's description of male gender being associated with manic symptoms. Hendrick et al. (2000) and Roy-Byrne et al., (1985) suggest males with a history of depression are at a greater risk of developing manic symptoms. Furthermore, the high

comorbidity of manic symptoms and alcohol and drug use in males may lead to more psychiatric problems. Hendrick et al. (2000) found that men were twice as likely as women to have a comorbid alcohol or other substance abuse diagnosis. It is important to note that even with this difference, females are also at risk for comorbid bipolar disorder and substance abuse. Overall, our results fit with recent epidemiological work suggesting a specific link between alcohol use problems and bipolar disorder (Angst et al., 2006; Merikangas et al., 2008).

The analysis did not reveal an association between a likely history of maternal depression and future vulnerability to BD in the offspring. However, the presence of a likely history of maternal depression was based on repeated self-assessments of depressive symptoms during and after pregnancy. Within the data collected, the mothers were given the EPDS (Cox et al., 1996), which is not equivalent to a structured interview or a clinical diagnosis of a mood disorder in mothers. As this scale measures recent symptoms of depression, this measure does not account for possible depressive episodes prior to pregnancy and after the first year of the child's life. It is possible the mothers experienced depression at times when it was not measured.

Contrary to maternal depression, participant adolescent depressive symptoms at age 16 predicted future risk for hypomanic symptoms. In BD, manic symptoms frequently begin in the mid-20s and depressive symptoms typically first occur during puberty (e.g., Judd et al., 2002, APA, 2013), and an earlier onset of mood symptoms is related an increased risk of BD (Perlis et al., 2004). Therefore, this finding concurs with past literature suggesting adolescent depressive symptoms suggest a vulnerability of future hypomanic symptoms. We found evidence that adolescent depression might be indicative of future hypomanic symptoms which is consistent with prior research.

Most importantly, as predicted adolescent alcohol use was linked to self-reported vulnerability for hypomanic symptoms in early adulthood. This is in line with the staging model, suggesting substance related problems in adolescence, especially when there is a familial risk for BD, may indicate an early stage of developing mood disorders (e.g. Duffy, 2015). Alcohol use could also be a way to express impulsivity and fun-seeking behaviors, often occurring in the context of BD (Alloy et al., 2009, Duffy et al., 2010). Another explanation of adolescent alcohol use could include the attempt to self-medicate and cope with mood swings, which may or may not have reached the stage of clinical relevance (Khantizan, 1985; McDonald and Meyer, 2011).

Limitations

One major limitation is attrition, which has been found with respect to the overall response rate in the ALSPAC study (Smith et al., 2015). Attrition from the total cohort could affect the final results of this study as women and better educated individuals were more likely to remain in the study (refer to limitations in Smith et al., 2015). Generalizations to broader samples should be made with caution. Another limitation is the reliance on self-ratings for all variables of interest. As reviewed previously, these self-reports may be subject to reporting biases, such as young adults may be more likely or reluctant to endorse sexual activity and alcohol use (Smith et al., 2015). Therefore, we do not know whether the self-rated depression in adolescents and mothers reflect clinically relevant mood disorders or not. Similarly, while the AUDIT is used as a screening tool for alcohol use disorders (e.g. Hays et al., 1995; Rubinsky et al., 2013), we do not know the sensitivity and specificity in this particular sample. Furthermore, the HCL-32 was developed as a screening tool for a lifetime history of (hypo)manic symptoms, and while it has been proven to be sufficiently valid for that purpose (see Meyer et al., 2014), it is only a proxy variable for vulnerability; Other measures such as the GBI (Depue et al., 1981) or the

Hypomanic Personality Scale (Eckblad and Chapman, 1986) might have been more appropriate to assess trait-like vulnerability and cyclothymic temperament, but they were considered to be too long to be used in this sample. Despite the 6-7 year gap in the assessments. it would have been difficult to claim for any of these trait-like measures, even more so than for the HCL-32, that we can be sure that the onset of alcohol use preceded the onset of hypomanic symptom and that alcohol use was not already reflecting an onset of hypomania symptoms. Last but not least other risk factors for BD were not considered such as family history of BD, impulsivity, or self-reported mood swings during adolescence (e.g. Angst et al., 2003; Goodwin and Jamison, 2007; Ng et al., 2016). Furthermore, reporting hypomanic symptoms in the general population is not necessarily indicating vulnerability to BD as some studies have shown Despite these limitations, we found some evidence that adolescent alcohol use might be either indicating or predicting vulnerability for BD in early adulthood.

Despite limitations, these results suggest that adolescent alcohol use might be indicating an increased risk for future onset of hypomanic or even manic symptoms. However, future research needs to include validated and reliable clinical assessments in addition to self-reports to evaluate the link between clinically relevant symptoms over time. In addition to diagnostic measures it would also be essential to test theoretically derived hypotheses about how stress and life events might trigger or maintain problematic alcohol use in adolescence and interact with a vulnerability to develop mood disorders. Further research could also explore the role of other substances, such as marijuana, as a possible predictor for future hypomanic symptoms.

References

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders (5th ed.): Washington, D.C.

Babor, T.F., Higgins-Biddle, J.C., Saunders, J. B., Monteiro, M.G., World Health Organization, 2001. AUDIT - The Alcohol Use Disorders Identification Test: Guidelines for use in Primary Care. Geneva: World Health Organization.

Alloy, L. B., Bender, R. E., Wagner, C. A., Whitehouse, W. G., Abramson, L. Y., Hogan, M. E., et al., 2009. Bipolar spectrum–substance use co-occurrence: Behavioral approach system (BAS) sensitivity and impulsiveness as shared personality vulnerabilities. J. Pers. Soc. Psychol. 97(3), 549.

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C. H., Perry, B. D., et al., 2006. The enduring effects of abuse and related adverse experiences in childhood. Eur. Arch. Psychiatry Clin. Neurosci. 256(3), 174-186.

Avon Longitudinal Study of Parents and Children (ALSPAC) (2014). Data Dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Accessed 1 September 2015.

Angold, A., Costello, E. J., Messer, S. C., Pickles, A., Winder, F., Silver, D., 1995 The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. Int. J. Methods Psychiatr. Res. 5, 237 - 249.

Angst, J., Gamma, A., Endrass, J., Rössler, W., Ajdacic-Gross, V., Eich, D., et al., 2006. Is the association of alcohol use disorders with major depressive disorder a consequence of undiagnosed bipolar-II disorder? Eur. Arch. Psychiatry Clin. Neurosci. 256(7), 452-457.

Angst, J., Gamma, A., & Endrass, J. (2003). Risk factors for the bipolar and depression spectra. Acta Psychiat. Scand. 108, 15-19.

Angst, J., Adolfsson, R., Benazzi, F., Gamma, A., Hantouche, E., Meyer, T. D., et al.2005. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. J. Affect. Disord. 88(2), 217-233.

Bauer, I. E., Gálvez, J. F., Hamilton, J. E., Balanzá-Martínez, V., Zunta-Soares, G. B., Soares, J. C., et al., 2016. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. J. Psychiatr. Res. 74, 1-7.

Boden, J. M., Fergusson, D. M. (2011). Alcohol and depression. Addiction, 106(5), 906-914.

Boyd A., Golding J., Macleod J., Lawlor D.A., Fraser A., Henderson J., et al., 2013. Cohort profile: the 'Children of the 90s' – the index offspring of the Avon Longitudinal Study of Parents and Children. Int. J. Epidemiol. 42, 111–127.

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(3), 526-533.

Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. Br. J. Psychiatry 150:782-786.

Cox, J. L., Chapman, G., Murray, D., Jones, P., 1996. Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J. Affect. Disord. 39(3), 185-189.

Depue, R. A., Slater, J. F., Wolfstetter-Kausch, H., Klein, D., Goplerud, E., Farr, D., 1981. A behavioral paradigm for identifying persons at risk for bipolar depressive disorder: A conceptual framework and five validation studies. J. Abnorm. Psychol. 90, 381-437.

Duffy, A., 2015. Early identification of recurrent mood disorders in youth: the importance of a developmental approach. Evid. Based Ment. Health, 18(1), 7-9.

Duffy, A., Alda, M., Hajek, T., Sherry, S. B., Grof, P., 2010. Early stages in the development of bipolar disorder. J. Affect. Disord. 121(1), 127-135.

Eckblad, M., Chapman, L.J., 1986. Development and validation of a scale for hypomanic personality. J. Abnorm. Psychol. 95, 214-222.

Eid, L., Heim, K., Doucette, S., McCloskey, S., Duffy, A., Grof, P., 2013. Bipolar disorder and socioeconomic status: what is the nature of this relationship? Int. J.Bipolar Disord. 1:9, doi:10.1186/2194-7511-1-9.

Fergusson, D. M., Boden, J. M., Horwood, L. J., 2009. Tests of causal links between alcohol abuse or dependence and major depression. Arch. Gen. Psychiatry 66(3), 260-266.

First, M. B., Spitzer, R. L., Gibbon, M., Wiliams, J. B., 1995. Structured clinical interview for the DSM-IV axis I disorders. New York: New York State Psychiatric Institute.

Fraser A., Macdonald-Wallis C., Tilling K., Boyd A., Golding J., Davey Smith G., et al. 2013. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int. J. Epidemiol. 42, 97–110.

Geulayov, G., Metcalfe, C., Gunnell, D., 2016. Parental suicide attempt and offspring educational attainment during adolescence in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Psychol. Med. 46(10), 2097-2107.

Goodwin, F. K., Jamison, K. R., 2007. Manic-depressive illness. Bipolar disorders and recurrent depression. (2nd ed.). New York: Oxford University Press.

Harrell, Z. A.., Huang, J. L., Kepler, D. M., 2013. Affluence and college alcohol problems: the relevance of parent- and child-reported indicators of socioeconomic status. J. Adolesc. 36(5), 893-897

Hays, R. D., Merz, J. F., Nicholas, R., 1995. Response burden, reliability, and validity of the CAGE, Short MAST, and AUDIT alcohol screening measures. Behav. Res. Methods Instrum. Comput. 27(2), 277-280

Hendrick, V., Altshuler, L. L., Gitlin, M. J., Hammen, C., 2000. Gender and bipolar illness. J. Clin. Psychiatry 61(5), 393-396.

Hooley, J. M., Parker, H. A., 2006. Measuring expressed emotion: an evaluation of the shortcuts. J. Family Psychol. 20(3), 386.

Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Maser, J., Solomon, D. A., et al., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch. Gen. Psychiatry 59(6), 530-537.

Kent, L., Vostanis, P., Feehan, C., 1997. Detection of major and minor depression in children and adolescents: evaluation of the Mood and Feelings Questionnaire. J. Child Psychol. Psychiatry 38(5), 565-573.

Kim-Cohen, J., Caspi, A., Moffitt, T. E., Harrington, H., Milne, B. J., & Poulton, R., 2003. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch. Gen. Psychiatry 60(7), 709-717.

Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders. Am. J. Psychiatry 142, 1259–1264.

McDonald, J.L., Meyer, T.D. 2011. Self-report reasons for alcohol use in bipolar disorders: Why drink despite the potential risks? Clin. Psychol. Psychother. Special Issue 18, 418–425.

Merikangas, K. R., Herrell, R., Swendsen, J., Rössler, W., Ajdacic-Gross, V., Angst, J., 2008. Specificity of bipolar spectrum conditions in the comorbidity of mood and substance use disorders: results from the Zurich cohort study. Arch. Gen. Psychiatry 65(1), 47-52.

Meyer, T.D., McDonald, J., Douglas, J., Scott, J., 2012. Motives for alcohol use across different mood states of bipolar disorders. J. Affect. Disord. 136, 926-932.

Miklowitz, D. J., Goldstein, M. J., Nuechterlein, K. H., Snyder, K. S., Mintz, J., 1988. Family factors and the course of bipolar affective disorder. Arch. Gen. Psychiatry 45(3), 225-231.

Miklowitz, D. J., Johnson, B. S. L., 2009. Social and familial factors in the course of bipolar disorder: basic processes and relevant interventions. Clin.Psychol.: Science and Practice, 16(2), 281-296.

Ng, T. H., Stange J. P., Black, C. L., Tirone, M. K., Weiss, R. B., Abramson, L. Y., et al., 2016. Impulsivity predicts the onset of DSM-IV-TR or RDC hypomanic and manic episodes in adolescents and young adults with high or moderate reward sensitivity. J.Affect. Disord. 198, 88–95.

Perlis, R. H., Miyahara, S., Marangell, L. B., Wisniewski, S. R., Ostacher, M., DelBello, M. P., et al. 2004. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol. Psychiatry 55(9), 875-881.

Ranning, A., Munk Laursen, T., Thorup, A., Hjorthoj, C., Nordentoft, M., 2016. Children of parents with serious mental illness: With whom do they grow up? A prospective, population-based study. J. Am. Acad. Child Adolesc. Psychiatry 55(11), 953-961.

Roy-Byrne P., Post R. M., Uhde T. W., Porcu, T., Davis, D., 1985. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. Acta Psychiat. Scand. 71(s317), 1-33.

Rubinsky, A. D., Dawson, D. A., Williams, E. C., Kivlahan, D. R., Bradley, K. A., 2013. AUDIT-C Scores as a Scaled Marker of Mean Daily Drinking, Alcohol Use Disorder Severity, and Probability of Alcohol Dependence in a US General Population Sample of Drinkers. Alcohol Clin. Exp. Res. 37(8), 1380-1390.

Shankman, S.A., Lewinsohn, P.M., Klein, D.N., Small, J.W., Seeley, J.R., Altman, S.E., 2009. Subthreshold conditions as precursors for full sydrome disorders: a 15-year longitudinal study of multiple diagnostic classes. J. Child Psychol. Psychiatry 50 (12), 1485–1494.

Simhandl, C., Radua, J., König, B., Amann, B. L., 2016. Prevalence and impact of comorbid alcohol use disorder in bipolar disorder: A prospective follow-up study. Aust. N. Z. J. Psychiatry, 50(4), 345-351.

Singh, S., Forty, L., Di Florio, A., Gordon-Smith, K., Jones, I., Craddock, N., et al., 2015. Affective temperaments and concomitant alcohol use disorders in bipolar disorder. J. Affect. Disord. 186, 226-231.

Smith, D. J., Anderson, J., Zammit, S., Meyer, T. D., Pell, J. P., Mackay, D., 2015. Childhood IQ and risk of bipolar disorder in adulthood: prospective birth cohort study. Brit. J. Psychiatry 1(1), 74-80.

Tijssen, M.J., Van Os, J., Wittchen, H.U., Lieb, R., Beesdo, K., Mengelers, R., 2010. Evidence that bipolar disorder is the poor outcome fraction of a common developmental phenotype: an 8-year cohort study in young people. Psychol. Med. 40(02), 289-299.

Waugh, M. J., Meyer, T. D., Youngstrom, E. A., Scott, J., 2014. A review of self-rating instruments to identify young people at risk of bipolar spectrum disorders. J. Affect. Disord.160, 113-121.

Winokur, G., 1999. Alcoholism in bipolar disorder. In Goldberg, J.F., Harrow, M. (Eds). Bipolar disorders: clinical course and outcome, Washington DC: American Psychiatric Press, 185-197.

Fig 1: Flow chart with respect to ALSPAC sample

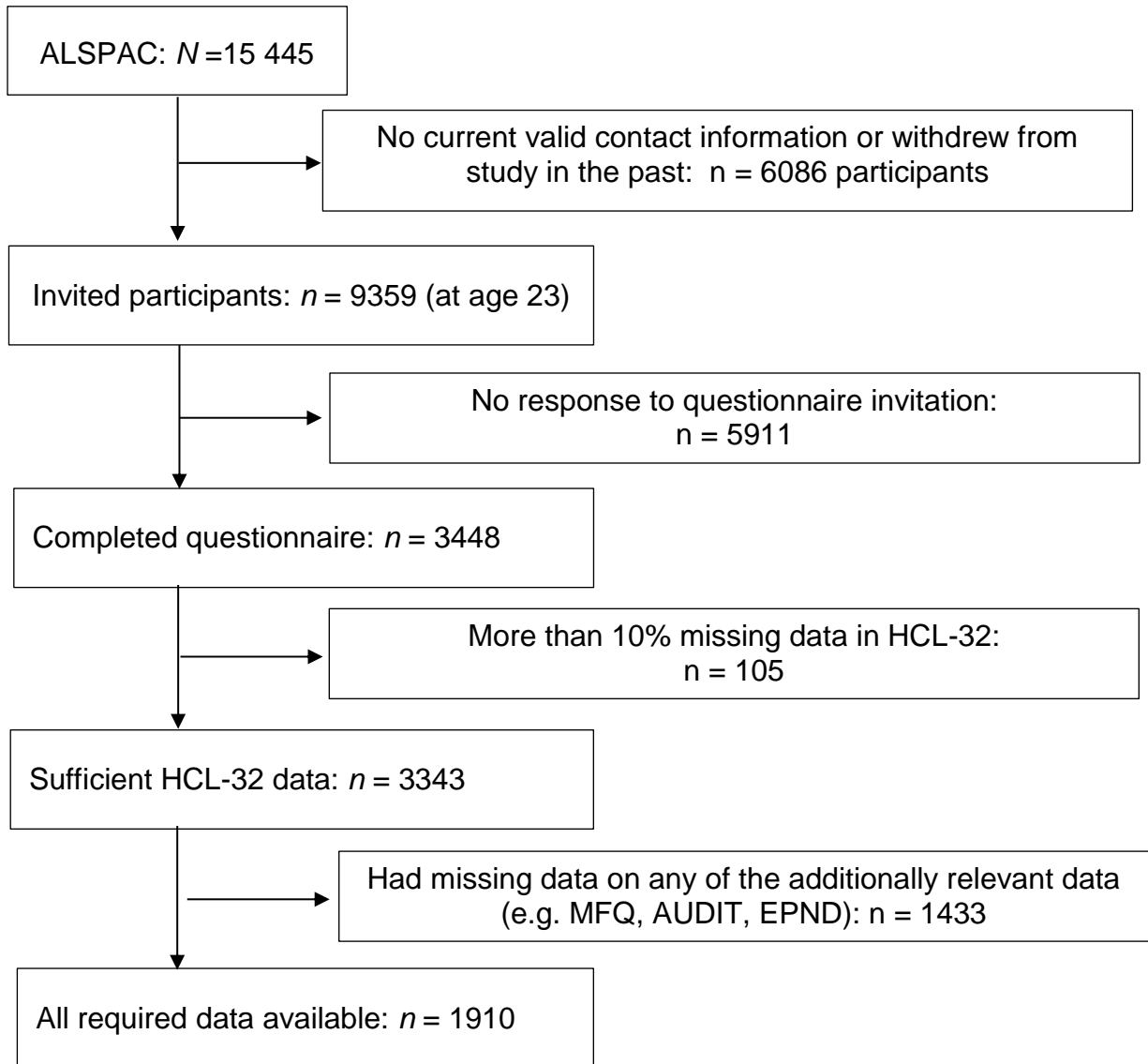```
┌─────────────────────────────┐
│ ALSPAC: N =15 445   │
└─────────────────────────────┘
         │   ┌──┐
         ├────────▶│ No current valid contact information or withdrew from │
         │   │ study in the past: n = 6086 participants   │
         ▼   └──┘
┌─────────────────────────────────────┐
│ Invited participants: n = 9359 (at age 23) │
└─────────────────────────────────────┘
         │   ┌──┐
         ├────────▶│ No response to questionnaire invitation: │
         │   │ n = 5911   │
         ▼   └──┘
┌─────────────────────────────────────┐
│ Completed questionnaire: n = 3448   │
└─────────────────────────────────────┘
         │   ┌──┐
         ├────────▶│ More than 10% missing data in HCL-32:   │
         │   │ n = 105   │
         ▼   └──┘
┌─────────────────────────────────────┐
│ Sufficient HCL-32 data: n = 3343   │
└─────────────────────────────────────┘
         │   ┌──┐
         ├────────▶│ Had missing data on any of the additionally relevant data │
         │   │ (e.g. MFQ, AUDIT, EPND): n = 1433   │
         ▼   └──┘
┌─────────────────────────────────────┐
│ All required data available: n = 1910 │
└─────────────────────────────────────┘
```

Table 1: Demographic Characteristics of Completed HCL-32 Compared to Final Study Sample

| Characteristic | Excluded Sample (N = 1433) | Final Study Sample (N =1910) | P |
|---|---|---|---|
| Gender -  Females n (%) | 884 (61.7) | 1270 (66.5) | 0.004 |

| | | | |
|---|---|---|---|
| Age (in months) (SD) | 263.61 (6.61) | 263.17 (6.04) | 0.05 |
| Homeownership *n* (%)   Own | 985 (81.9) | 1716 (89.8) | <0.001 |
| Likely history of maternal depression (EPDS) *n* (%) | 144 (18.0) | 307 (16.1) | 0.21 |
| MFQ *(at age 16) (SD)* | 5.83 (5.6) | 6.11 (5.6) | 0.24 |
| AUDIT *(at age 16) (SD)* | 6.49 (4.48) | 6.72 (5.00) | 0.39 |
| HCL-32 M (SD) | 14.88 (6.22) | 15.23 (6.19) | 0.10 |

Note: EPDS, Edinburgh Postnatal Depression Scale; MFQ, Mood and Feelings Questionnaire; AUDIT, Alcohol Use Disorders Identification Test; and HCL-32, Hypomanic Checklist-32. All samples completed the HCL-32, however, the cases excluded were missing items more than 10% of the items. The untransformed and raw means and standard deviations are displayed for the AUDIT and HCL-32.

Table 2: Results of the hierarchical regression predicting HCL-32 at age 22/23

| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Est (B) | 95% CI | T | p | Est (B) | 95% CI | t | P | Est (B) | 95% CI | t | p |
| Sex (male = 1, female = 2) | -1.26 | 1.84 , -0.68 | -4.23 | <0.001 | -1.64 | 2.23 , -1.05 | -5.46 | <0.001 | -1.59 | 2.17 , -1.00 | -5.31 | <0.001 |

| | B | 95% CI | OR | p | B | 95% CI | OR | p | B | 95% CI | OR | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Marital Status: Married vs. all else | -0.09 | -0.86, 0.68 | -0.22 | 0.83 | 0.05 | -0.72, 0.81 | 0.12 | 0.91 | 0.02 | -0.74, .078 | 0.05 | 0.96 |
| Marital Status: Stable Single vs. all else | 0.43 | -0.70; 1.56 | 0.75 | 0.45 | 0.46 | -0.66, 1.57 | 0.80 | 0.42 | 0.21 | -.90, 1.32 | .38 | 0.71 |
| Homeownership [a] | 0.82 | -0.12, 1.76 | 1.70 | 0.09 | 0.77 | -.017, 1.70 | 1.61 | 0.11 | 0.73 | -0.20, 1.65 | 1.54 | 0.13 |
| EPDS | | | | | 0.46 | -0.29, 1.21 | 1.21 | 0.23 | 0.46 | -0.28, 1.20 | 1.21 | 0.23 |
| MFQ | | | | | 0.15 | 0.10, 0.20 | 5.97 | <0.001 | 0.13 | 0.08, 0.18 | 5.00 | <0.001 |
| AUDIT | | | | | | | | | 0.94 | 0.62, 1.25 | 5.73 | <0.001 |
| $R^2$ | <0.01* | | | | 0.03* | | | | <0.05* | | | |
| Adjusted $R^2$ | <0.01* | | | | 0.03* | | | | 0.04* | | | |

Note: *$p$ <0.05, **$p$ <0.001. EPDS, Edinburgh Postnatal Depression Scale; MFQ, Mood and Feelings Questionnaire; AUDIT, Alcohol Use Disorders Identification Test; HCL-32, Hypomanic Checklist-32.
[a] If one uses maternal SES with its 6 categories (n = 1762) instead of 'Home ownership', the first block remains significant in explaining a small proportion of the variance, R = 0.112, $R^2$ = 0.01, p < 0.01. Compared to the SES class III (non-manual) as the most frequent one, the highest SES level I predicted

higher HCL scores at a trend level (Est (B) = 0.87, p = 0.093). The same was true for the SES class II with Est (B) = 0.61 (p = 0.058).

## Highlights

- Prospective study of the link between alcohol use and vulnerability to (hypo)mania

- Adolescent alcohol use predicted vulnerability to hypo(mania) at age 23

- AUDIT scores, adolescent depression and gender emerged as predictors.

- Future studies should examine whether alcohol use is an early manifestation of BD.