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Association between Gestational Age at Birth and Alcohol Use in the Avon Longitudinal Study of Parents and Children (ALSPAC)

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Abstract

Background—The relationship between gestational age at birth and alcohol use measures in early adulthood was examined in a large UK community-based birth cohort (ALSPAC).

Methods—A series of linear and logistic regression models were used to test for main effects of a continuous measure of gestational age at birth (GA) on a range of alcohol use measures, and moderation of these associations by sex. In addition, mediation analyses assessed the extent to which significant associations between GA and alcohol use operated indirectly, through influences of the parental environment and/or childhood measures of emotional and behavioral health.

Results—Earlier GA significantly predicted never drinking by age 18, but was not associated with other measures of alcohol use behavior among young adult drinkers (i.e. SRE, AUDIT, or DSM-IV-TR Criteria for Alcohol Dependence). The association between earlier GA and never drinking by age 18 was moderated by sex, such that females born early were less likely to have

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ever had a drink by age 18. In the full sample, childhood measures of emotional and behavioral health were found to mediate the association between earlier GA and never drinking by age 18. This association was not mediated by parenting factors.

Conclusions—Earlier GA is associated with never drinking alcohol in early adulthood, in females. Emotional and behavioral difficulties experienced in early childhood may mediate the relationship between earlier GA and never drinking by age 18.

Keywords

ALSPAC; gestational age at birth; alcohol dependence; parental environment; emotional and behavioral difficulties

Introduction

Although improvements in care for babies born preterm have reduced mortality rates, neonatal morbidity persists. Babies born preterm are at increased risk for neurodevelopmental impairment (Johnson, Marlow 2011, Moster, Terje & Markestad 2008, Marlow et al. 2005, Nosarti, Murray & Hack 2010, Wood et al. 2000). Although overall health effects tend to lessen over time (Johnson, Bowler & Yudkin 2003), there remains a residual morbidity that may compromise how these children function during adolescence and adulthood (Johnson, Bowler & Yudkin 2003, Saigal, Doyal 2008, Moster, Terje & Markestad 2008, Jarvis et al. 2003, Hack et al. 2005). The risk of psychiatric problems requiring hospitalization is increased in young adults who were born preterm, and may originate from obstetric and neonatal complications resulting in damage to the immature nervous system (Lindstrom, Lindblad & Hjern 2009). Yet, being born earlier is also associated with lower rates of criminality (D'Onofrio et al. 2013) and substance use, including alcohol use (Cooke 2004, Johnson, Bowler & Yudkin 2003). Explanations for what amounts to a protective effect of lower gestational age at birth (GA) for these traits remain unclear.

There is emerging evidence of a protective effect between earlier birth and alcohol use/abuse in young adults (Hack 2006, Cooke 2004, Johnson, Bowler & Yudkin 2003, Nosarti, Murray & Hack 2010, Lindstrom, Lindblad & Hjern 2009). For example, a cohort of US young adults born preterm report lower rates of alcohol use than those born full-term, among female participants only (Hack 2006). A similar sex-limited relationship between preterm birth (GA < 37 weeks) and alcohol use is reported for a UK sample of female young adults (Cooke 2004). Further support for this protective relationship is found in a sample of young adults from the UK, which does not formally test for moderation by sex (Johnson, Bowler & Yudkin 2003). Two studies of young adults utilizing health records from the Swedish National Board of Health and Welfare examine the relationship between preterm birth and alcohol abuse and dependence. The first study reports an association between moderate preterm birth (32-36 completed weeks of gestation) and increased risk for adult-onset psychiatric admissions for alcohol dependence (Nosarti, Murray & Hack 2010). In contrast, the second finds no association between preterm birth and addictive disorders, derived from ICD diagnosis codes (Lindstrom, Lindblad & Hjern 2009).

The question that remains is how can earlier birth be both protective against initial alcohol use, but a risk factor for abuse, dependence, or hospitalization among users. Different developmental patterns of alcohol use may provide an explanation. Relative to individuals born full-term, those born preterm are at an increased risk for emotional and behavioral difficulties – such as attention-deficit/hyperactivity, social, and emotional problems – which have been shown to influence alcohol use in later life (Bhutta et al. 2002, Johnson, Marlow 2011). However, a firm understanding of the direction of these associations remains unclear. While a couple of population-based studies find earlier GA to be associated with attention-deficient/hyperactivity (Delobel-Ayoub et al. 2006, Sucksdorff et al. 2015), conduct problems (Delobel-Ayoub et al. 2006), and peer problems (Delobel-Ayoub et al. 2006), an intervention study finds no association between GA and childhood behavior, after adjusting for potential confounding (Yang, Fombonne & Kramer 2011),

Studies investigating the association between emotional and behavioral difficulties and later alcohol use typically provide evidence for the associations between conduct problems or hyperactivity and later alcohol use. One longitudinal cohort study in New Zealand finds that children with high scores for conduct disorder at age 8 consume more alcohol and have higher rates of alcohol-related problems, relative to children with low conduct problem scores (Lynskey, Fergusson 1995). Another study using the same birth cohort reports associations between conduct problems in adolescence and later substance use, abuse, and dependence, after controlling for attention problems (Fergusson, Horwood & Ridder 2007). One study investigating risk factors for substance use within adolescents in the Northeastern US finds that ADHD in childhood is associated with increased risk for elevated use and abuse of alcohol, and that childhood ADHD symptoms (e.g. inattention) predicts later substance use. The development of conduct disorder among those with childhood ADHD is associated with the highest levels of substance use and associated problems (Molina, Pelham 2003). These findings suggest that the potential associations between earlier GA and alcohol use could be indirectly effected by the experience of emotional and behavioral difficulties in childhood.

The parental environment experienced by children born preterm could also influence a relationship between earlier GA and alcohol use. Since individuals born preterm are at risk for many health outcomes (Jarvis et al. 2003, Saigal, Doyal 2008, Baraldi, Filippone 2007, Johnson, Marlow 2011, Marlow et al. 2005, Wood et al. 2000), parents may seek to provide a more protective environment by monitoring peer relationships and the activities that their child participates in, which could result in reducing the child's likelihood of alcohol use. For example, children born preterm may be less likely to initiate substance use because of delayed establishment of peer relationships that encourage drinking (Behrman, Butler 2007). How parents provide this protective environment for their children may also influence this relationship, such that the more control and discipline parents have over the activities that their child participates in, the less likely it might be that the child begins drinking by age 18. Meanwhile, if the parent is cold to the child, it is possible that the child will seek more support from peers, who might encourage drinking behavior, putting the child at potentially greater risk for drinking.

The aim of this study was to further understand the relationship between GA and alcohol-related measures utilizing data from a large UK community-based birth cohort. The present study was designed to answer the following questions: (1) Is GA associated with alcohol use in young adulthood? (2) Do results corroborate the protective effect of earlier GA on alcohol use seen in other studies? (3) Does the relationship between GA and alcohol use differ by sex? (4) Does variation in measures of early emotional and behavioral difficulties and/or parental environment serve a mechanistic function with respect to associations between GA and alcohol use?

In accordance with previous literature findings, the association between earlier GA and never drinking by age 18 was expected to be moderated by sex, such that females would be more likely to endorse never drinking by age 18. Furthermore, the association between GA and alcohol use measures was hypothesized to be mediated by measures of the parental environment, as well as emotional and behavioral health in early childhood (Figure 1). A hypothesis regarding the direction(s) of indirect effects was not proposed since the literature does not provide strong guidance in this area. Thus, how specific measures of childhood emotional and behavioral health and parental environment were expected to mediate the association between GA and alcohol use was not proposed and our approach treated these as a broader concept, with only predefined sub-dimensions to be tested.

Materials and Methods

Sample

Analyses were conducted on data obtained from the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC is an ongoing population-based study investigating a wide range of environmental and other influences on the health and development of children (<http://www.alspac.bris.ac.uk>; Boyd et al., 2012). 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 were a total of 14,676 fetuses, 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 that 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.

The number of new pregnancies not in the initial sample (“Phase I”) 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 enrolment are described in more detail in the cohort profile paper, available at: <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 fetuses. Of this total sample of 15,458 fetuses, 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 (1,432 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.

ALSPAC parents and children have been followed-up regularly since recruitment, with data obtained through questionnaires completed by mothers, children and teachers, and through clinical assessments. The study website contains details of all the data that is available through a fully searchable data dictionary, available at: <http://bris.ac.uk/alspac/researchers/data-access/data-dictionary/>. Ethical approval for the study was obtained from ALSPAC Ethics and Law Committee, and the Local Research Ethics Committee.

The analytic sample in this study included individuals who provided data on GA and measures of alcohol use including: self-reports of never drinking by age 18, Self-Rating of the Effects of Alcohol (SRE), the Alcohol Use Disorders Identification Test (AUDIT), and DSM-IV-TR criteria for alcohol dependence. A total of 4,202 individuals meeting these criteria were retained for this study.

Measures

Gestational Age—Gestational age at birth (GA) was treated as a continuous variable in analyses examining the association between duration of pregnancy and alcohol use measures.

Alcohol Use—Alcohol use measures were collected in clinics at age 17, during which they were asked whether they had ever had a whole drink; age at first whole drink and the number of whole drinks; their current frequency of alcohol use; the maximum number of drinks they have consumed in a 24 hour period; their sensitivity to alcohol when they first started drinking and currently; the number of drinks they have consumed in the past 6 months and past 30 days; how many drinks they have in a typical drinking day; frequency of binge drinking; and a report of how frequently they have experienced a number of alcohol use problems that correspond relatively well to the Diagnostic and Statistical Manual of Mental Disorders IV-TR Criteria for Alcohol Dependence. These items were extracted from the Semi-Structured Assessment of the Genetics of Alcoholism interview, developed by the Collaborative Study on the Genetics of Alcoholism. These measures are explained in greater detail in the paragraphs below.

Never Drinking by Age 18: The self-reported measure of never drinking by age 18 was measured by: “Have you ever had a whole drink? (A “whole drink” is a small bottle or ½ pint of beer, a small glass of wine or a “shot” of whisky, gin, or vodka.)” Never drinking by age 18 was treated as a binary variable [i.e., yes (or “nondrinker”) = 1; no (or “drinker”) =

0]. Only individuals indicating that they had drank alcohol by age 18 years were asked to respond to Self-Rating of the Effects of Alcohol (SRE), Alcohol Disorders Identification Test (AUDIT), and Diagnostic Statistical Manual IV-TR (DSM-IV-TR) criteria measures.

Self-Rating of the Effects of Alcohol (SRE): The SRE is a valid and reliable retrospective measure of low level of response to alcohol, treated as a continuous variable in analyses. Respondents were asked to report the number of standard drinks (10-12 grams of ethanol) required to experience certain behavioral effects of intoxication during the first five times of drinking (i.e. 'first 5 SRE') and within the last three months of drinking (i.e. 'last 3 SRE'), which were treated as separate outcomes in analyses. For each of these measures, higher scores indicated lower levels of response, which in turn predicts elevated risk for future alcohol problems (Ray, Hart & Chin 2011, Schuckit, Smith & Tipp 1997).

Alcohol Disorders Identification Test (AUDIT): The AUDIT is a 10-item measure developed by the World Health Organization used to screen for and quantify hazardous drinking. Individual items were scored from 0 to 4 where five choices are given, and 0, 2, or 4 where three choices were given (Appendix). Item responses were summed across the ten indicators to create a composite score, which ranged from 0 to 40 (Barbor et al. 1989). This composite score was treated as an ordinal variable where scores of 0-7 indicated low level of alcohol problems ("Low Level of Alcohol Problems", coded as 0), scores of 8-15 indicated a medium level of alcohol problems ("Hazardous Drinking"; coded as 1) that suggests the need for simple advice focused on reduction of hazardous drinking, and scores of 16 to 19 represented a high level of alcohol problems ("Harmful Drinking"; coded as 2) requiring brief counseling and continued monitoring of drinking behavior, and 20 and above warrant further diagnostic evaluation for alcohol dependence ("Potential Alcohol Dependence"; coded as 3) (Allen et al. 1997, Barbor et al. 1989, Pal, Jena & Yadav 2004).

Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM-IV-TR) Criteria for Alcohol Dependence: To meet criteria for alcohol dependence using DSM-IV-TR criteria, individuals had to have displayed a "maladaptive pattern of drinking, leading to clinically significant impairment or distress" and endorsed 3 symptoms to meet criteria for "alcohol dependence" in the past 12-month period (American Psychiatric Association 2000). A binary variable indicative of meeting DSM-IV-TR criteria for alcohol dependence (AD) was derived from symptom counts (AD = 1; not = 0).

Emotional and Behavioral Health

Emotional and behavioral health was assessed via maternal-report using the Rutter Parent Scale for Preschool Children at age 3.5 years (Elander, Rutter 1996) and teacher-report using the Strengths and Difficulties Questionnaire (SDQ) at ages 8 and 11 years (Goodman et al. 2000). The timing of these measures were chosen because children born before 37 weeks have been found to exhibit higher rates of emotional and behavioral difficulties early in development (Spittle et al. 2009) and it has been found that assessment in later childhood may identify more subtle problems than those identifiable by two years of age (Salt, Redshaw 2006). Looking at a range of ages between early and later childhood allows for the determination of whether the magnitude and specificity of indirect associations changes over

time. The Rutter Parent Scale for Preschool Children included subscales on behavioral problems, prosociality (e.g. consideration of other people's feelings), hyperactivity (e.g. has poor concentration or short attention span), emotional difficulties (i.e. appears miserable, unhappy, tearful, or distressed), and conduct problems (i.e. fights with other children). The Strengths and Difficulties Questionnaire included subscales on prosociality (e.g. considerate of other people's feelings), hyperactivity (i.e. easily distracted, concentration wanders), emotional difficulties (e.g. often unhappy, downhearted), conduct problems (i.e. often has temper tantrums or hot tempers), and peer problems (e.g. rather solitary, tends to play alone). For the Rutter Parent Scale for Preschool Children and the Strengths and Difficulties Questionnaire, raters (e.g. mothers and teachers) are given a description of behaviors and asked to rate the extent to which each statement describes the child on a scale with the following options: certainly true, sometimes true, and not true. For each of the subscales, sum scores were created, where higher scores for each of these subscales were indicative higher levels of the construct it was measuring. In general, high scores on emotional difficulties, conduct difficulties and hyperactivity and low scores on prosociality indicate high levels of psychological problems.

Parental Environment

Maternal reports provided three measures of the parental environment at age 6.4 years: six items measuring maternal control, six items measuring maternal coldness, and seven items measuring maternal discipline. For these measures, factor scores were computed and each of these three measures was treated as a continuous variable (Appendix).

Statistical Analysis

Statistical software and procedures—Association analyses were conducted using statistical procedures - Proc Freq, Proc Means, and Proc Logistic - in SAS (version 9.3, SAS Institute Inc., Cary, NC). Mplus, Version 6.12 (Muthen and Muthen 1998-2011) was used to calculate indirect effects in mediation models via a product of coefficients strategy (MacKinnon et al. 2002; Preacher & Hayes, 2004), where the ratio of the product of discrete path coefficients (e.g., predictor to mediator, and mediator to outcome) over the normal-theory SE for that product is evaluated with respect to a z-distribution.

Differences in birth, mother, and father characteristics across drinkers and non-drinkers by age 18—Chi-square tests and t-tests were conducted to determine whether there were differences between drinkers and non-drinkers in terms of birth characteristics (i.e. sex, length, head circumference, and birth weight), mother characteristics (i.e. age at delivery, occupational class, and educational status), and father characteristics (i.e. occupational class and educational status).

Associations between GA and never drinking at age 18—Logistic regression was used to test for a main effect of GA on never drinking by age 18. We then tested whether sex moderated the effect of GA on never drinking by simultaneously regressing the outcome (i.e. never drinking) on the predictor (i.e. GA), moderator (i.e. sex), and an interaction term (i.e. GA $\times$ sex). When the interaction term significantly adds to the prediction of never drinking by age 18 (i.e. GA $\times$ sex is statistically significant, even after accounting for the main effects

of GA and sex on never drinking at age 18 separately), the initial regression was reanalyzed, separately by sex, and stratified results were reported (Barron & Kenny, 1986; Holmbeck 1997; Aiken & West, 1991). For each between or within group main effect, a series of multiple mediation analyses were conducted to determine the extent to which GA influences never drinking by age 18 directly and/or indirectly, through emotional and behavior difficulties at 3.5 years, 8 years, and 11 years, and parental environments at 6.4 years. Within models, mediation was assessed at the level of the general construct (i.e., the total indirect effect through childhood measures of *emotional and behavior health* or *parental environment*) as well as the individual sub-dimensions of the construct (e.g., specific indirect effects through *prosociality* or *maternal control*).

Associations between GA and alcohol-related outcomes among drinkers—We also examined the associations between GA and first 5 SRE, last 3 SRE, AUDIT, and DSM-IV Alcohol Dependence among drinkers in the sample. Linear regressions were used for continuous outcomes and logistic regressions were used for categorical and binary outcomes. Where main associations between GA and alcohol-related outcomes among drinkers were found to be significant, we tested whether these associations were moderated by sex and mediated by measures of childhood emotional and behavioral health or parental environment.

Results

Descriptive Characteristics of Nondrinkers and Drinkers

No significant differences in birth, mother, or father characteristics across non-drinkers and drinkers were observed (Table 1). In both groups, females made up the majority of the sample (57.5% of non-drinkers and 56.0% of drinkers). The average mother's age at birth was 29.2 (SE = 4.4) and 29.3 (SE = 4.6) years for non-drinkers and drinkers, respectively. More than three-quarters of mothers obtained the General Certificate of Education (GCE) Ordinary Level (O level) or higher, a subject-based academic qualification which is equivalent to receiving a high school diploma in the United States (81.6% and 81.5%, among non-drinkers and drinkers). Meanwhile, less than two-thirds of fathers obtained O levels or higher (65.1% and 65.2%, among non-drinkers and drinkers).

Emotional and Behavioral Health and Parental Environment Differences

Drinkers and non-drinkers significantly differed on emotional difficulties, behavioral difficulties, and prosociality at age 3.5 years (Table 2). On average, drinkers had lower scores on the emotional and behavioral difficulties subscales and higher scores on the prosocial subscale, relative to nondrinkers. This suggests that drinkers experience fewer emotional and behavioral difficulties in childhood and exhibit more prosocial characteristics relative to nondrinkers. Additionally, compared to nondrinkers, drinkers scored higher on the hyperactivity subscale at age 8, and lower on emotional symptoms at age 8 and peer problem subscales at age 8 and age 11. As for differences in parental environment, nondrinkers had higher maternal discipline factor scores than drinkers.

Association between GA and never drinking at age 18

GA and never drinking by age 18—A statistically significant association was found between earlier GA and self-report of never drinking by 18 years of age ($\beta = -0.084$, $SE = 0.035$, $p\text{-value} = 0.016$), such that earlier GA is associated with increased likelihood of never drinking by age 18 years (Table 3). Results revealed a significant interaction effect between GA and sex ($\beta = -0.07$, $SE = 0.04$, $p\text{-value} = 0.04$). Stratified analyses by sex indicated that the association between earlier GA and was only significant among females ($\beta = -0.15$, $SE = 0.05$, $p\text{-value} = 0.01$).

Mediation of the effect of GA on never drinking by age 18—The values of the individual path coefficients for the mediation models are list in Table 4. Later GA was associated with lower levels of hyperactivity at age 3.5 years, 8 years, and 11 years ($\beta = -.034$, $-.049$, $-.054$ respectively). Later GA was also associated with lower levels of emotional difficulties and peer problems at age 8 years ($\beta = -.049$ and $\beta = -.034$, respectively). No associations were found between GA and measures of the parental environment.

Associations between childhood measures of emotional and behavioral health and never drinking by age 18 showed that higher levels of emotional difficulties at each age were associated with never drinking at age 18 ($\beta = .056$, $.055$, $.045$). The same was true for peer problems at age 8 years and 11 years ($\beta = .086$, $.096$). A lower level of hyperactivity was associated with never drinking by age 18 ($\beta = -.053$). No association was found between measures of the parental environment and never drinking by age 18.

Multiple mediation analyses on the full sample (Table 5) demonstrate significant mediation by measures of emotional and behavioral health at age 3.5 years (total indirect effect: $\beta = -0.004$, $SE = 0.002$, ratio = -2.213), accounting for 10.2% of the total effect (indirect and direct). The indirect effect largely operated through *prosociality* (specific indirect effect: $\beta = -0.002$, $SE = 0.001$, ratio = -2.618). In addition, even though the total indirect effects of emotional and behavioral difficulties at 8 and 11 years of age were non-significant, there were some significant specific indirect effects. More specifically, at 8 years of age there were specific indirect effects through both *emotional difficulties* ($\beta = -0.003$, $SE = 0.001$, ratio = -2.043) and *peer problems* ($\beta = -0.003$, $SE = 0.001$, ratio = -2.651) that were offset by non-significant specific indirect effects through *hyperactivity* ($\beta = 0.003$, $SE = 0.001$, ratio = 1.850) and *conduct problems* ($\beta = 0.001$, $SE = 0.001$, ratio = $.673$) in the opposite direction. In contrast, neither measures of *emotional and behavioral health* at 11 years of age nor the *parental environment* at 6.4 years were shown to mediate the association between GA and never drinking at age 18. Parallel multiple mediation analyses were conducted with the female subsample, since a significant direct effect was found to be sex-limited (Table 3). Although there were no significant mediation effects seen in this sample results indicated the largest indirect effects (PA at 3.5 years, ED at 8 years, PP at 8 years) were consistent with the significant mediating effects in the full sample.

Associations between GA and alcohol-related outcomes among drinkers

No statistically significant associations were found between GA and the alcohol-related outcomes among drinkers (i.e. first 5 drinks SRE, last 3 months SRE, AUDIT, or DSM-IV

Alcohol Dependence; Table 6) and none of these associations were moderated by sex. Subsequent analyses of mediation pathways were unnecessary in the absence of significant direct associations.

Discussion

The current study examined the association between GA and measures of never drinking by age 18, first 5 SRE, last 3 SRE, AUDIT and DSM-IV Alcohol Dependence. Similar to two other studies (Cooke, 2004; Hack, 2006), this study showed an association between GA and never drinking by age 18, but only in females. Specifically, the current study demonstrated that, among females, being born earlier was protective against ever drinking. Sex did not, however, moderate the effect of GA on other alcohol-related measures, which did not have statistically significant main effects. Given that 18 years of age is below the typical onset for alcohol use disorders, particularly for females with lower overall rates than males, it is possible that the risk profile predicted by GA could differ for later assessments of alcohol use disorders (in adulthood).

Two alternative constructs were tested to account for the mediation between GA and alcohol use measures, emotional/behavioral health and the parental environment. The association between GA and never drinking by 18 was not mediated by childhood emotional and behavioral health or by the parental environment within females only. However, significant mediation of the association between GA and never drinking by 18 by measures of emotional and behavioral health, but not the parental environment, were observed in the full sample. The mediation of GA and never drinking by 18 was driven largely by *prosociality* at 3.5 years. Emotional and behavioral health measures at 8 years did not have a significant total indirect mediation effect on GA and never drinking by 18, even though both *emotional difficulties* and *peer problems* were found to have a significant specific indirect mediation effect. It is likely that the positive non-significant indirect effect of *hyperactivity* cancelled out the significant combined negative effects of *emotional difficulties* and *peer problems*. A conservative approach was adopted to avoid data dredging, by fitting mediation models for each variable simultaneously within each age. Thus, the results in Table 4 reflect the significant effect of the mediating residuals. The downside of this approach is that mediation effects in opposite directions could potentially suppresses one another and result in a non-significant total mediation effect (a composite of all the individual mediation effects). Since the goal for this part of the study was to explore only potential mechanisms of the main finding (the direct association) strong hypotheses regarding the direction of mediating effects was not made in advance.

Emotional and behavioral health measures at 11 years did not have a significant total indirect mediation effects on GA and never drinking by 18, though the specific indirect mediation effects of *emotional difficulties* and *peer problems* were the largest effects observed similar to the significant specific indirect effects observed at age 8. It should be noted that although no significant indirect effects were observed in the female only sample for any age (Appendix: Table 1) these results that parallel findings in the full sample provide encouraging evidence of the mediation of emotional/behavioral health measures that can be the focus of future research in females.

These findings suggest that emotional and behavioral difficulties prior to young adulthood (specifically *emotional difficulties* at 8 years, and *peer problems* at 8 years) have an indirect effect on the association between GA and never drinking by age 18 and can be influenced by other behavioral traits such as *hyperactivity*. It is possible that emotional and behavioral difficulties in early life reflect delayed or deficient development of behavioral and emotional regulation systems influencing stimuli response and attention. Poor function of these regulation systems may lead individuals towards risky behaviors, including substance use. Since these traits have been found to be relatively stable over the course of childhood/adolescence, individuals with the most persistent emotional and behavioral difficulties might be expected to develop more chronic and severe forms of SUDs in later adult life (Zucker et al. 2008).

Previous studies have demonstrated that emotional and behavioral health prior to adolescence predicts the initiation of alcohol use in early adolescence, as well as future heavy use and alcohol use disorders in later life (Mayzer, Puttler & Wong 2002). An ALSPAC study conducted by Dick et al. (2013) finds that emotional and conducts difficulties and sociability in early childhood (i.e. before age 5) is significantly associated with both alcohol consumption and problems in boys and girls at age 15.5 years. The negative association between increased conduct and emotional difficulties and alcohol consumption suggest the possibility that children with conduct and emotional difficulties have less opportunity to engage in normative adolescent experimentation and consumption of alcohol (Dick et al. 2013). It might also highlight a potential limitation of using self-reported drinking outcomes of troubled adolescent youth.

Another point to consider in future research related to the association between emotional and behavioral health and later alcohol problems is whether mothers drank during pregnancy. A study conducted by Murray et al. (2014) demonstrates that moderate drinking in pregnancy increases the risk for early onset and persistent conduct problems from 4 to 13 years, but not childhood limited or adolescent onset conduct problems (Murray et al. 2014). Since both preterm birth and heavy alcohol use during pregnancy contribute to a range of developmental problems for children, including growth restriction, neurocognitive deficits, and behavioral problems, we would expect that individuals at highest risk of alcohol problems are those who: had mothers who drank heavily during pregnancy, were born preterm, are males, experienced emotional and behavioral difficulties in early childhood, and initiated drinking by adolescence. Further study is needed to parse out the contributions of these effects, as our current study did not consider maternal drinking behavior during pregnancy or a measure of family history of alcohol use.

Unlike a study conducted by Manzardo, Madarasz, & Gabrielli (2011) demonstrating a significantly greater degree of prematurity among subjects who would later develop alcoholism, this study found no significant association between GA and alcohol dependence. That sample included 8,109 eligible subjects born at the Copenhagen University Hospital between 1959 and 1961, 448 (5.5%) of which received a formal diagnosis of alcohol at some point in their lifetime (Manzardo, Madarasz & Gabrielli 2011). One potential explanation for this could be that the Manzardo et al. (2011) study considered the development of alcoholism by age 45-47 years (in 2007), while ours was restricted to age 18 years. Overall,

less than 1% of our entire sample of UK 18-year olds met DSM-IV-TR criteria for alcohol dependence. As the study continues, we would expect to see a higher prevalence of alcohol dependence, as about 4% of adults in the UK were classified as alcohol dependent in 2011 (National Collaborating Centre for Mental Health 2011).

Similar to all longitudinal studies, the ALSPAC sample may suffer from problems related to attrition and initial cohort selection. Given these samples were not obtained from a hospital-based cohort, disability and socioeconomic status may have contributed to the failure to follow-up some participants. Failure to follow-up should not have affected estimates of the association between GA and never drinking by age 18, as long as attrition was not dependent upon either baseline or alcohol use variables. In other words, the association would have been underestimated in the case that attrition was higher among drinkers or in the case that attrition was higher among those born at earlier gestational ages and overestimated in the case that attrition was higher among nondrinkers or in the case that attrition was higher among those born at later gestational ages. Additionally, since sibling pairs were not included in the analyses we were unable to determine whether familial confounding affected results of this study. Familial confounding occurs when observed associations are confounded by unmeasured familial factors, such as common genes and shared environment. For example, familial confounding would be suggested in the case that the association between GA and alcohol use measures is found between unrelated individuals, but not within full sibling pairs (Lundberg et al. 2010).

Despite these potential limitations, this study contributes to an emerging set of literature showing that being born earlier is protective against alcohol use in females. This finding is consistent with studies showing that, relative to individuals born full term, individuals born preterm are less likely to be diagnosed with alcohol and substance use disorders (Hack 2006, Nosarti, Murray & Hack 2010, Lindstrom, Lindblad & Hjern 2009, Johnson, Bowler & Yudkin 2003).

Conclusion

This study replicated previous findings demonstrating that being born earlier is protective against ever drinking alcohol by young adulthood. More specifically, it was shown that earlier GA was associated with never drinking in young adulthood, using a population-based sample (ALSPAC), and that this association was sex-limited, in that the association was limited to females. Additionally, measures of emotional and behavioral health in childhood, such as *prosociality* at 3.5 years, *emotional difficulties* at 8 years, and *peer problems* at 8 years, mediated the effect of GA on never drinking by age 18.

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Appendix

Measures of Alcohol-Related Outcomes

Self-Rating of the Effects of Alcohol (SRE)

Respondents were asked to report the number of standard drinks (10-12 grams of ethanol) required to experience the given behavioral effects of intoxication in the first in the first 5 times he/she ever drank (SLE_first5), in the 3 months that he/she started drinking at least once a month (SLE_last3), and in the period of heaviest drinking (separately) (Ray, Hart & Chin 2011, Schuckit, Smith & Tipp 1997)

- How many full drinks did it take for you to feel tipsy/have a buzz?
- How many full drinks did it take for you to feel a bit dizzy, or to begin to slur your speech?
- How many full drinks did it take you to begin stumbling, or walking in an uncoordinated manner?
- How many drinks did it take you to pass out, or fall asleep when you did not want to?

Alcohol Disorders Identification Test (AUDIT)

Each item has three or five responses to choose from and there are four distinct response patterns. These responses are scored from 0 to 4 where five choices are given and 0, 2, or 4 where three choices are given for each individual item.

Response pattern 1 (i.e. “never”, “monthly or less”, “2-4 times a month”, “2-3 times a week”, or “4 or more times a week”) corresponds with the item asking: “How often do you have a drink containing alcohol?”

Response pattern 2 (i.e. “never”, “less than monthly”, “monthly”, “weekly”, and “daily or almost daily”) corresponds with the following items: “How often do you have six or more drinks on one occasion?”, “How often during the last year have you found that you were not able to stop drinking once you had started?”, “How often during the last year have you failed to do what was normally expected of you because of drinking?”, “How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?”, “How often during the last year have you had a feeling of guilt or remorse after drinking?”, and “How often during the last year have you been unable to remember what happened the night before because of your drinking?”

Response pattern 3 (i.e. “1 or 2”, “3 or 4”, “5 or 6”, “7 to 9”, and “10 or more”) corresponds to the item: “How many drinks containing alcohol do you have on a typical day when you are drinking?”

Response pattern 4 (i.e. “no”, “yes, but not in the last year”, and “yes, during the last year”) corresponds to the following two items: “Have you or someone else been injured because of your drinking?” and “Has a relative, friend, or doctor, or other health care worker been concerned about your drinking or suggested you cut down?”

Measures of Parental Environment (provided by mother)

Maternal Control (6 items)

- “Mother insists that child goes to bed at bedtime”,
- “Mother insists child eats food provided”,
- “Mother insists that child is polite to adults”,
- “Mother insists that child is considerate of others”,
- “Mother insists child keeps self clean”
- “Mother insists child keeps belongings tidy”.

Maternal Coldness (6 items)

- “Mother threatens child over tantrum”,
- “Mother says hurtful things she regrets when child has tantrum”,
- “Mother leaves child's tantrum for someone else to cope with”,
- “Mother shouts at child when child has tantrums”,
- “Mother does other about child's tantrums”,
- “Mother starts by being firm with child but gives way.”

Maternal Discipline (7 items)

- “Mother ignores child's tantrum”,
- “Mother sends child for time out for tantrum”,
- “Mother cuddles child when child has tantrum” (reverse coded),
- “Mother tries to reason with child over tantrum”,
- “Mother slaps child when child has tantrum”
- “Mother tries to distract child when has tantrum”
- “Mother thinks child likes being with mother.”

Table 1
Effect Coefficients and Test-Statistics for Mediation of
the Association between GA and Drinking Status by
Age 18 by Emotional and Behavioral Difficulties in
Childhood and Parental Environment in Females Only

Mediation Models	R ²	Indirect Effects				Direct Effect			Total Effect (indirect + direct)			Mediated Proportion
		Effect(s)	β	SE	Ratio	β	SE	Ratio	β	SE	Ratio	
EBH at 3.5 years	.035	Total	-.002	.002	-1.230	-.066	.021	-3.164	-.068	.021	-3.279	.029
		BP	.000	.001	-.697							
		PS	-.002	.001	-1.693							
		HA	.000	.001	-.085							
		ED	.000	.000	.102							
		CD	.000	.000	.567							
EBH at 8 years	.055	Total	-.004	.003	-1.187	-.064	.021	-3.060	-.068	.021	-3.281	.059
		PS	.000	.001	.128							
		HA	.000	.001	.216							
		ED	-.002	.001	-1.353							
		CD	.000	.000	.119							
		PP	-.002	.001	-1.670							
EBH at 11 years	.034	Total	-.002	.004	-.513	-.066	.021	-3.125	-.068	.021	-3.281	.029
		PS	.000	.000	-.030							
		HA	.000	.001	.122							
		ED	-.001	.001	-.645							
		CD	.000	.003	.077							
		PP	-.002	.002	-1.282							
PE at 6.4 years	.062	Total	-.007	.015	-.502	-.061	.025	-1.722	-.068	.021	-3.282	.179
		CT	-.002	.008	-.232							
		MC	-.004	.010	-.388							
		MD	-.002	.009	-.202							

Notes: EBH = Emotional and Behavioral Health; PE = Parental Environment; BP = Behavioral Problems; PS = Prosociality; HA = Hyperactivity; ED = Emotional Difficulties; CD = Conduct Problems/Disorder; PP = Peer Problems; CT = Maternal Control; MC = Maternal Coldness; MD = Maternal Discipline. Critical ratios (i.e. Z-scores) correspond to the following *p*-values: 1.96 (*p* .05); 2.58 (*p* .01); 3.29 (*p* .001). Boldface type denotes significant effects.

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Figure 1. Mediation Model

Table 1
Sample characteristics by never drinking by age 18 years old in ALSPAC

	Non-drinker (N = 216)	Drinker (N = 3986)	Chi-Square/T-test (X ² or t, df, p-value)
Birth Characteristic			
Sex			.016, 1, .898
Male (N, %)	94 (43.5)	1751 (44.0)	
Female (N, %)	122 (56.5)	2232 (56.0)	
Length (mean, SD)	50.3 (2.8)	50.7 (2.5)	1.880, 3134, .061
Head circumference (mean, SD)	34.7 (2.2)	34.8 (1.5)	.810, 183, .418
Birth weight (mean, SD)	3363.7 (605.3)	3425.9 (534.1)	1.420, 216, .156
Mother Characteristic			
Age at delivery (mean, SD)	29.2 (4.4)	29.3 (4.6)	.360, 3951, .722
Occupational Class			.578, 3, .902
Unskilled, semi-skilled manual (N, %)	21 (12.8)	444 (14.0)	
Skilled manual or non-manual (N, %)	70 (42.7)	1260 (39.8)	
Managerial and clerical (N, %)	59 (36.0)	1181 (37.3)	
Professional (N, %)	14 (8.5)	279 (8.9)	
Educational Status			.928, 3, .819
Less than O level (N, %)	37 (18.4)	702 (18.5)	
O level (N, %)	76 (37.8)	1524 (40.1)	
A level (N, %)	39 (19.4)	752 (19.8)	
University Degree (N, %)	49 (24.4)	822 (21.6)	
Father Characteristic			
Occupational Class			.813, 3, .846
Unskilled, semi-skilled manual (N, %)	57 (32.4)	1119 (33.9)	
Skilled manual or non-manual (N, %)	23 (13.1)	405 (12.3)	
Managerial and clerical (N, %)	65 (36.9)	1268 (38.4)	
Professional (N, %)	31 (17.6)	509 (15.4)	
Educational Status			4.347, 3, .226
Less than O level (N, %)	70 (34.8)	1321 (34.8)	
O level (N, %)	41 (20.4)	1001 (26.3)	
A level (N, %)	31 (15.4)	490 (12.9)	
University Degree (N, %)	59 (29.3)	988 (26.0)	

Table 2
Differences in mediator/moderator measures by never drinking by age 18

	Non-drinker Mean (SD)	Drinker Mean (SD)	t, df, p-value
<i>Emotional and behavioral health</i>			
<i>Rutter Parent Scale for Preschool Children (3.5 years)</i>			
Emotional difficulties score	2.9 (1.8)	2.5 (1.6)	-2.73, 194, .007
Conduct difficulties score	3.5 (2.4)	3.5 (2.3)	.13, 3581, .895
Hyperactivity score	2.7 (1.8)	2.7 (1.8)	-.85, 3581, .397
Prosocial score	14.6 (3.9)	15.6 (3.5)	3.08, 194, .002
Behavior difficulties score	13.2 (6.0)	12.1 (5.4)	-2.52, 3581, .012
<i>Strength and Difficulties Questionnaire</i>			
Prosocial score			
8 years	8.0 (2.4)	8.2 (2.1)	1.57, 2382, .117
11 years	8.1 (2.3)	8.1 (2.2)	-0.09, 1958, .931
Hyperactivity score			
8 years	1.2 (1.6)	1.6 (2.2)	3.21, 145, .002
11 years	2.1 (2.7)	2.0 (2.3)	-.58, 122, .562
Emotional symptoms score			
8 years	1.5 (1.8)	1.1 (1.7)	-2.19, 2387, .028
11 years	1.6 (2.1)	1.2 (1.8)	-1.97, 120, .051
Conduct problems score			
8 years	.4 (.9)	.5 (1.2)	1.25, 144, .215
11 years	.5 (1.0)	.5 (1.1)	-.05, 1969, .959
Peer problems score			
8 years	1.8 (2.2)	1.1 (1.7)	-3.62, 128, <.001
11 years	1.8 (2.2)	1.0 (1.7)	-3.88, 120, <.001
<i>Parental Environment at 6.4 years</i>			
Maternal Control Factor Score	-.5 (.6)	.1 (1.1)	.72, 154, .472
Maternal Coldness Factor Score	.5 (1.2)	.4 (1.1)	-.16, 154, .874
Maternal Discipline Factor Score	1.6 (.2)	.1 (1.0)	-2.06, 154, .041

Table 3
Association between gestational Age at birth and not drinking by age 18

	Coefficient (S.E.)	p-value
Full Sample	-.084 (.035)	.016*
Male	-.006 (.057)	.924
Female	-.150 (.046)	.001*

Table 4

Path Coefficients for Multiple Mediation Models

Gestational Age at Birth to Potential Mediator					Potential Mediator to Never Drinking by Age 18					Gestational Age at Birth to Never Drinking by Age 18				
Rutter Parent Scale for Preschool Children (3.5 years)														
ED	CD	HA	PS	BP	ED	CD	HA	PS	BP					
-.007	-.015	-.034	.070	-.077	.056	-.002	.017	-.032	.015					-.034
Strength and Difficulties Questionnaire (8 years)														
ED	CD	HA	PS	PP	ED	CD	HA	PS	PP					
-.049	-.016	-.049	.009	-.034	.055	-.032	-.053	-.034	.086					-.036
Strength and Difficulties Questionnaire (11 years)														
ED	CD	HA	PS	PP	ED	CD	HA	PS	PP					
-.016	-.014	-.053	.008	-.015	.045	-.011	.005	.006	.096					-.037
Parental Environment (6.4 years)														
CT	MC	MD			CT	MC	MD							
.028	.004	.004			-.247	.107	-.048							-.032

Notes: EBH = Emotional and Behavioral Health; PE = Parental Environment; BP = Behavioral Problems; PS = Prosociality; HA = Hyperactivity; ED = Emotional Difficulties; CD = Conduct Problems/Disorder; PP = Peer Problems; CT = Maternal Control; MC = Maternal Coldness; MD = Maternal Discipline. **Boldface** indicates that *p*-value < .05

Table 5
Effect Coefficients and Test-Statistics for Mediation of the Association between GA and Never Drinking by Age 18 by Emotional and Behavioral Difficulties in Childhood and Parental Environment in Full Sample

Mediation Models	R ²	Effect(s)	Indirect Effects			Direct Effect			Total Effect (indirect + direct)			Mediated Proportion
			β	SE	Ratio	β	SE	Ratio	β	SE	Ratio	
EBH at 3.5 years	.037	Total	-.004	.002	-2.213	-.034	.016	-2.125	-.039	.016	-2.404	.102
		BP	-.001	.001	-1.821							
		PS	-.002	.001	-2.618							
		HA	-.001	.001	-0.828							
		ED	.000	.001	-0.750							
		CD	.000	.000	0.125							
EBH at 8 years	.071	Total	-.003	.003	-.937	-.036	.016	-2.204	-.039	.016	-2.404	.077
		PS	.000	.001	-.578							
		HA	.003	.001	1.850							
		ED	-.003	.001	-2.043							
		CD	.001	.001	.673							
		PP	-.003	.001	-2.651							
EBH at 11 years	.042	Total	-.002	.002	-1.014	-.037	.016	-2.260	-.039	.016	-2.404	.051
		PS	.000	.000	.288							
		HA	.000	.001	-.293							
		ED	-.001	.001	-1.051							
		CD	.000	.001	.264							
		PP	-.001	.001	-1.237							
PE at 6.4 years	.091	Total	-.007	.010	-.666	-.032	.019	-1.722	-.039	.016	-2.413	.179
		CT	-.007	.010	-.702							
		MC	.000	.003	.174							
		MD	.000	.002	-.117							

Notes: EBH = Emotional and Behavioral Health; PE = Parental Environment; BP = Behavioral Problems; PS = Prosociality; HA = Hyperactivity; ED = Emotional Difficulties; CD = Conduct Problems/ Disorder; PP = Peer Problems; CT = Maternal Control; MC = Maternal Coldness; MD = Maternal Discipline. Critical ratios (i.e. Z-scores) correspond to the following p-values: 1.96 (p .05); 2.58 (p .01); 3.29 (p .001). Boldface type denotes significant effects.

Table 6
Gestational Age and Alcohol Use Outcomes by 18 years in ALSPAC

Alcohol Use Variable	Coefficient (S.E.)	p-value
Self Ratings of the Effect of Alcohol (SRE)		
SRE First 5 Times of Drinking	-.063 (.042)	.132
SRE Last 3 Months of Drinking	-.100 (.055)	.069
Alcohol Use Disorders Identification Test (AUDIT)	-.030 (.043)	.457
AUDIT, as a categorical outcome		
Low Level of Alcohol Problems (AUDIT score: 0 - 7)	Reference	Reference
Hazardous Drinking (AUDIT score: 8 - 15)	-.011 (.019)	.543
Harmful Drinking (AUDIT score: 16 - 19)	-.006 (.045)	.896
Potential Alcohol Dependence (AUDIT score: > 19)	.006 (.063)	.923
DSM-IV-TR: Alcohol Dependence	.029 (.051)	.573