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The developmental origin of adolescent alcohol use: Findings from the Mater University Study of Pregnancy and its outcomes

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Abstract

Background: It is unclear whether fetal alcohol exposure contributes to alcohol use in adolescence. In this study, we examine the association between maternal alcohol use in pregnancy and adolescents' drinking patterns at age 14.
Methods: The association of maternal alcohol exposure with early drinking was examined in 4363 adolescents taking part to the Mater University Study of Pregnancy (MUSP) and its outcomes, a population based birth cohort study commenced in Brisbane (Australia) in 1981. Mothers and children were followed up at birth, 5 and 14 years after the initial interview. Maternal alcohol use was assessed before and during pregnancy and at the 5 years follow-up. Adolescents' alcohol use was assessed at child age 14.
Results: In multivariable analysis those born of mothers who consumed 3+ glasses during pregnancy were at increased risk to report drinking 3+ glasses compared with those whose mothers reported no drinking or drinking up to 2 glasses. Comparisons controlling for drinking before pregnancy and at age 5 found the averaged odds ratio of maternal drinking in pregnancy on risk of reporting alcohol consumption of 3 and more glasses at age 14 was 2.74 (CI 1.70, 4.22).
Conclusion: Our study suggests that they maybe a biological origin of early drinking. Further studies are needed to better disentangle the nature of the association and the role of other possible confounding factors.

Keywords: Perinatal addiction; Maternal alcohol use; Risk factors; Children of alcoholics; Adolescent drinking

1. Introduction

Age at onset of alcohol use is by far the strongest predictor of alcohol related disorders in youth and adulthood (Bonomo et al., 2004; Flory et al., 2004; Grant et al., 2001; Wells et al., 2004). Those who engage in even episodic heavy drinking at an early age are more likely to become excessive drinkers (Grant et al., 2001), dependent on alcohol (Bonomo et al., 2004), and to experience long-term, adverse health outcomes (Oesterle et al., 2004; Wells et al., 2004). As the social and personal costs of these outcomes are far-reaching, identifying the causes of early drinking is important for the development of effective public health interventions.

A range of proximal factors have been associated with early uptake of alcohol in adolescence. A permissive environment conducive to alcohol use, deviant behaviour and poor school performance, have all been found to predict drinking initiation in the teen years (Ellickson et al., 2003; Herrenkohl et al., 2001). Familial influences and particularly parental alcohol consumption during the developmental years are also related to an increased risk of early drinking (Merikangas et al., 1998b). More distal predictors of alcohol use in adolescence are, however, poorly understood. Emerging evidence points to a relationship between in utero exposure to alcohol and the development of subtle neurobehavioral difficulties, and there are a handful

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of studies which have found a relationship between prenatal alcohol exposure and later development of alcohol disorders (Alati et al., 2006; Baer et al., 1998, 2003). To date only one adequately controlled study has found a contribution of maternal drinking in mid-pregnancy to early uptake of alcohol at age 14 (Baer et al., 1998). The effect was independent of in utero exposure to smoking and other drugs, maternal drinking at other time periods and family alcohol problems. Baer's and colleagues' findings on prenatal alcohol exposure and adolescents' alcohol problems are yet to be replicated. This dearth of evidence is in contrast to a considerable body of work documenting the relationship between in utero alcohol exposure and the development of early uptake of alcohol consumption in adolescent animals (Nizhnikov et al., 2006; Spear and Molina, 2005). Recent experiments suggest more severe effects when alcohol is administered all at once rather than gradually, with the effect holding even for small quantities of injected ethanol (Arias and Chotro, 2005; Chotro and Arias, 2003). However, neuro-developmental outcomes resulting from animal studies are not easily generalisable to humans. Animals differ from humans in their level of susceptibility to substances and more importantly in the timing and stages of brain development during pregnancy and at the time of birth.

Replications of these findings in human studies would provide support for a biological origin of some cases of early drinking through a 'programming' effect on the brain's natural reward circuitry and confirm emerging evidence pointing to in utero alcohol exposure in the development of addictions (Alati et al., 2006; Baer et al., 2003; Barr et al., 2006). On the other hand, the possibility remains that the effect found is not explained by intrauterine mechanisms, but maybe due to shared familial, environmental and modelling factors, which existing studies have not been able to appropriately taken into account.

In the present study we will examine the effect of exposure to moderate quantities of alcohol consumption before, during and after pregnancy on drinking patterns in adolescence, taking into account a range of potential confounding factors such as maternal characteristics, familial influences and environmental exposures.

2. Methods

2.1. Participants

We used data from the Mater University Study of Pregnancy and its outcomes, a birth cohort study of women and babies enrolled in the study at the Mater Misericordiae Hospital in Brisbane, Australia, between 1981 and 1984. This is a pre-birth prospective cohort study which examines the impact of social, psychological and obstetric factors on pregnancy outcomes. Further details on the study design, sampling, response rates and demographic characteristics of the overall sample are presented in greater detail elsewhere (Keeping et al., 1989; Najman et al., 2005). In brief, 7223 consecutive women were interviewed in hospital at their antenatal visit (about 18 weeks into gestation). The mothers were interviewed again (in hospital) at 3–5 days and at 6 months after the birth. Mothers and their children were followed up at 5 and 14 years after the birth of the child. At 14 years, children were administered their first questionnaire. Data analysed for this paper were taken from the antenatal visit, birth, 5- and 14-year follow-up data. Ethics committee approval was obtained from the University of Queensland and the Mater Misericordiae Hospital at each stage of the study.

2.2. Instruments

2.2.1. Outcome. Measures of quantity of alcohol consumption per drinking occasion (0, 1 or 2 glasses, 3 or 4 glasses, 5 or 6 glasses, 7 or more glasses) were obtained at child 14 year. Children were asked how often they drank alcohol and how much alcohol they drank at those times. The quantity item was categorised into 'Never used alcohol' '1 or 2 glasses' '3+ glasses'. In order to obtain a measure of quantity/frequency of consumption we used in sensitivity analysis a frequency measure ('how often do you drink alcohol?' 'Daily, a few times a week, a few times a month, a few times a year, rarely, never) to ascertain whether the adolescents had consumed 3+ glasses at least 'a few times a month'.

2.2.2. Main predictor. Quantities of alcohol consumed by mothers per drinking occasion were obtained at each phase of the study (0, 1 or 2 glasses, 3 or 4 glasses, 5 or 6 glasses, 7 or more glasses). At baseline, when women were on average at 18 weeks of gestation, two maternal reports were obtained. One was a recall of quantity of alcohol consumed before pregnancy (women were asked how much they usually drank "before" they became pregnant) and one was a current report of quantity of alcohol use (women were asked how much they had drunk alcohol "since becoming pregnant"). At 3–5 days after birth, mothers reported on the quantity of consumption in the last 3 months of pregnancy (women were asked how much they had usually drunk "in the last 3 months" of pregnancy). Participants were again asked how much they drank alcohol at the 5-year follow-up. Maternal quantity of alcohol use was initially defined as a three category variable (no alcohol/<1 glass, 1–2 glasses, 3+ glasses). After initial analysis showed that there was an association only between the amount of 3+ glasses and the outcome of interest, maternal drinking was categorised into 'no alcohol/up to 2 glasses' '3+ glasses'. In order to compare the effect of maternal alcohol use in pregnancy with the individual/environmental/modelling effect of maternal drinking before pregnancy and during child development, we combined maternal alcohol use at all phases according to whether the women had consumed 3+ glasses before, during and/or at 5 years using the maximum discrimination available. An eight category predictor variable was obtained, which aimed at differentiating the pregnancy exposures from the pre-pregnancy and the 5-year exposures. Finally we used the frequency measure 'How often do you drink alcohol?' to ascertain women's frequency of drinking "before" they became pregnant, "since becoming pregnant", "in the last 3 months of pregnancy" and at the 5 years follow-up. Prompts were 'Daily, a few times a week, a few times a month, rarely, never' for the pregnancy assessments. For the 5 years assessments prompts were 'Daily, a few times a week, a few times a month, a few times a year, rarely, never'. For both quantity and frequency measures timeframe was not specified at the 5-year follow-up. In multivariable analysis, we combined maternal alcohol use over the four phases according to whether the women had consumed 'Up to 3+ glasses, a few times a year' or '3+ glasses at least a few times a month'.

2.2.3. Potential confounders. Measures of maternal smoking were also obtained at each phase of data collection. Mothers reported how much they had smoked in the previous week and, at the baseline interview, they recalled their smoking habits before they became pregnant. At 3–5 days after delivery ('late pregnancy'), mothers reported their smoking habits in the previous 3 months. We created a variable comprising the following categories: never smoked, smoked during pregnancy (this group included those who responded 'yes' to smoking at the antenatal visit and/or in the third trimester, regardless of smoking at other periods), 'smoked at other times, but not during pregnancy' (women who reported being smokers at other times but not during the pregnancy period), 'smoking at all times' (women who consistently reported smoking at all phases).

Potential early life confounders included sex of the child, maternal age (13–19; 20–34 and 35 or more), education (did not complete secondary school, completed secondary school, completed further/higher education) and marital status (married, cohabiting and single) were measured at the baseline interview. Biological factors such as gestational age and birthweight were extracted from the obstetric records at birth.

Maternal mental health was measured at the 5-year follow-up using the Delusions-Symptoms-States Inventory (DSSI) (Bedford and Foulds, 1978). The DSSI contains two 7-item subscales measuring depression and anxiety, which have been found to correlate strongly with other scales of depression including

the Beck Depression Inventory (Najman et al., 2000). Child's behaviour problems were assessed at child age 5 using a summarised, dichotomised version of the internalising and externalising symptom subscales of the CBCL (Achenbach, 1991). The use of the CBCL in the MUSP study, as well as their validity and internal consistency has been described in previous papers (Alati et al., 2004). We also included a measure of child rearing practices. At the 5-year follow-up mothers were asked at what age they would allow their children to (1) go to the movies (2) go on holidays by themselves, (3) travel alone on a bus, (4) stay at home alone and (5) drink alcohol. The index exhibited acceptable internal consistency (Cronbach's alpha = .61) and scores were reclassified into: no control, some control, and strict control. Finally, at the 14-year follow-up, mothers were asked whether the biological father and/or any of the full brothers and sisters of the study child ever had alcohol problems (Prompts included: yes/no).

2.3. Analytical strategy

We first explored univariable associations between maternal drinking, potential confounders and adolescent drinking using chi square tests. Factors significant in this analysis were selected for the multivariable analysis. We fitted progressive multinomial logistic regression models with a 3-level categorical end point ("Never used alcohol, "1 or 2 glasses," and "3+ glasses") and maternal alcohol exposure over the life course. This analysis was restricted to the 4363 adolescents for whom complete data was available. This analysis was restricted to the 4363 adolescents for whom complete data were available. Firstly, odds ratios were calculated for each category with "Always ≤2 for drinking occasion" as the reference category. Model 1 was adjusted by child sex, model 2 was adjusted by maternal smoking over the child's life course, birth weight, gestational age, maternal education, age and marital status at baseline, model 3 also included maternal anxiety and depression and child behaviour at age 5. Secondly, we constructed comparisons of drinking in pregnancy, within strata defined by all combinations for the pre-pregnancy and 5 years time periods.

In order to explore whether familial alcohol problems affected the observed associations, we also excluded from our fully adjusted model 510 subjects for whom there were maternal reports of either paternal ($n = 449$) or sibling ($n = 61$) alcohol problems at the 14-year follow-up. This was done to assess whether familial problems accounted for what otherwise appeared to be the effect of maternal alcohol consumption. A likelihood ratio test, which was computed to test statistical evidence for a difference between males and females, found no sex interaction in the reported effects. We also conducted sensitivity analyses in order to ensure that the results were not driven by the choice of cut-off for defining the quantity/frequency of maternal alcohol consumption. We used a quantity/frequency outcome measure categorised as 'never >2 glasses' and "3+ 'a few times a month"' to assess whether the overall results were consistent with those obtained in the main analysis. Similarly, we used a quantity/frequency exposure measure of maternal drinking categorised as 'never >2 glasses' '3+ glasses at least a few times a month'. Finally we included in the fully adjusted model a measure of child rearing to explore whether maternal monitoring style confounded the above associations. Analyses were conducted using STATA 10 and SAS 9.1.

2.3.1. Loss to follow-up. As there were only 4363 complete cases (out of the 7223 birth cohort sample), in the fully adjusted model, we used inverse probability weighting with robust estimates for standard errors to account for those lost to follow-up from the 7223 original cohort members. We used an exploratory logistic regression model to identify predictors of attrition. Those lost to follow-up were more likely to be born of mothers who were less educated ($p < 0.001$), more likely to be single ($p < 0.001$), to smoke ($p < 0.01$) and to be anxious ($p < 0.001$). There were no differences between those lost to follow-up and those still in the study according to maternal alcohol consumption in pregnancy. We fitted these measures in a logistic regression model (response vs. non-response as outcome) to determine weights for each individual using the inverse-probability of response and repeated all multivariate analyses including the weighting adjustments (Hogan et al., 2004).

3. Results

Table 1 presents univariable associations expressed in percentages between maternal alcohol consumption at the different time periods and adolescents' drinking patterns at age 14. At all

Table 1
Univariable associations between maternal alcohol use at different time periods and child's drinking patterns at age 14

	N	Child's alcohol use at child age 14		
		Never used alcohol	1–2 glasses	3+ glasses
Maternal alcohol use before pregnancy	$n = 5121$	$n = 4295$	$n = 462$	$n = 364$
Never < 1 glass	1238	88.8	5.8	5.4
1 or 2 glasses	2334	84.4	9.7	5.9
3+ glasses	1549	79.1	10.5	10.3
p-Value	x^2: 43.87, $p = 0.001$			
Maternal alcohol use in early pregnancy	$n = 5115$	$n = 4289$	$n = 462$	$n = 364$
Never < 1 glass	3211	85.8	8	6.2
1 or 2 glasses	1599	81.4	10.7	7.9
3+ glasses	305	76.4	11.1	12.5
p-Value	x^2: 16.77, $p = 0.001$			
Maternal alcohol use in late pregnancy	$n = 5137$	$n = 4311$	$n = 462$	$n = 364$
Never < 1 glass	3611	85.4	8.3	6.3
1 or 2 glasses	1242	81.2	10.6	8.2
3+ glasses	284	77.1	10.6	12.3
p-Value	x^2: 14.13, $p = 0.001$			
Maternal alcohol use at child age 5	$n = 4547$	$n = 3836$	$n = 398$	$n = 313$
Never < 1 glass	1329	89.6	6.1	4.3
1 or 2 glasses	1978	85.6	8.6	5.8
3+ glasses	1240	76.8	11.8	11.5
p-Value	x^2: 81.10, $p = 0.001$			

Table 2
Univariable associations between maternal alcohol use at different time periods and child's drinking patterns at age 14

	Child's drinking patterns at age 14		
	Never used alcohol	1 or 2 glasses	3+ glasses
Maternal drinking patterns over the child's life course	$n=3791$	$n=394$	$n=309$
YES before/NO during/NO after pregnancy	82.31	9.42	8.27
YES before/YES during/NO after pregnancy	83.84	6.06	10.10
YES before/NO during/YES after pregnancy	78.38	10.19	11.43
YES before/YES during/YES after pregnancy	74.19	12.90	12.90
Always ≤2 glasses for drinking occasion	88.23	7.40	4.38
NO before/YES during/NO after pregnancy	89.55	5.97	4.48
NO before/NO during/YES after pregnancy	77.76	12.83	9.42
NO before/YES during/YES after pregnancy	55.17	10.34	34.48
x^2: 127.089, $p=0.0001$			
Maternal tobacco use over the child life course	$n=3777$	$n=393$	$n=310$
No smoker	87.0	8.0	4.9
Smoker in pregnancy	82.9	8.1	8.9
Smoker before and after (not in pregnancy)	83.3	7.5	9.2
Smoker at all times	79.9	11.0	9.1
x^2: 42.37, $p=0.001$			
Gender	$n=4324$	$n=464$	$n=366$
Male	84.0	8.9	7.1
Female	83.8	9.1	7.1
x^2: 0.05, $p=0.9$			
Birthweight	$n=4323$	$n=464$	$n=366$
>3.50	84.3	9.0	6.7
3.01–3.50	82.7	9.1	8.3
2.51–3.00	85.0	9.2	5.8
∼<2.50	87.1	8.1	4.8
x^2: 8.83, $p=0.2$			
Maternal age at the antenatal visit	$n=4324$	$n=464$	$n=366$
35 years plus	83.3	10.3	6.4
20–34 years	84.5	8.8	6.8
13–19 years	80.8	9.9	9.3
x^2: 8.24, $p=0.08$			
Maternal marital status at the antenatal visit	$n=4290$	$n=462$	$n=363$
Married	85.0	8.8	6.2
Cohabiting	76.8	12.0	11.2
Single	83.9	9.0	7.1
x^2: 32.42, $p=0.001$			
Family income at the antenatal visit	$n=4078$	$n=446$	$n=351$
10,400 or more	83.8	9.3	6.9
10,399 or less	83.31	8.79	7.9
x^2: 1.77, $p=0.4$			
Maternal depression at child age 5	$n=3834$	$n=401$	$n=314$
Non-depressed	84.3	9.0	6.7
Depressed	84.2	5.9	9.9
x^2: 6.66, $p=0.04$			
Maternal anxiety at child age 5	$n=3834$	$n=401$	$n=314$
Non-anxious	84.4	9.1	6.6
Anxious	83.8	7.5	8.7

Table 2 (*Continued*)

	Child's drinking patterns at age 14		
	Never used alcohol	1 or 2 glasses	3+ glasses
x^2: 5.38, $p = 0.07$			
Child aggressive symptoms at age 5	$n = 3844$	$n = 404$	$n = 317$
Normal	84.3	8.9	6.8
Case	83.5	8.7	7.8
x^2: 0.67, $p = 0.7$			
Child internalising symptoms at age 5	$n = 3842$	$n = 403$	$n = 317$
Normal	84.0	9.2	6.8
Case	85.9	5.8	8.3
x^2: 7.91, $p = 0.02$			

time periods, adolescents born of mothers who reported drinking 3+ glasses per occasion at any of the four follow-up phases were more likely to report drinking at age 14 with the association being stronger amongst those reporting higher consumption.

Table 2 shows univariable associations between maternal alcohol and tobacco use over the life course, a range of possible confounding factors and drinking patterns at child age 14. There were significant associations between maternal alcohol and tobacco consumption and child's drinking patterns in adolescents. Maternal marital status at the antenatal visit as well as maternal depression and child's internalising symptoms measured at the 5-year follow-up were also significantly associated with adolescents consuming greater quantities of alcohol at age 14.

Table 3 presents multivariable associations between maternal alcohol consumption and child's drinking patterns. There was an increased risk of consuming 1 or 2 glasses amongst adolescents whose mothers reported drinking 3+ glasses per occasion during, before and after pregnancy, however adjustment for maternal smoking during the life course attenuated the strength of the association.

Those born of mothers who consumed 3+ glasses during pregnancy were at increased risk to report drinking 3+ glasses compared with those whose mothers reported no drinking or drinking up to 2 glasses. The association remained robust after adjusting for a variety of biological, environmental and familial factors. Drinking 3+ glasses before pregnancy, and before and after pregnancy was also associated with an increased risk of higher alcohol consumption at child age 14. Comparisons controlling for drinking before pregnancy and at age 5 found the averaged odds ratio of maternal drinking in pregnancy on risk of reporting alcohol consumption of 3 and more glasses at age 14 was 2.74 (CI 1.70, 4.22). After controlling for maternal drinking at the other time periods, children of those who drank $\leq$2 glasses before pregnancy, but reported increased drinking in pregnancy, had an averaged increased risk of alcohol use at age 14 [1.67 (CI 1.09, 2.58)] compared with children of mothers reporting no increase in alcohol use during pregnancy.

Exclusion of children for whom there were maternal reports of familial alcohol problems at child age 14 did not substantively alter the associations reported here. We repeated our analyses using an outcome measures more sensitive to the level of child alcohol consumption of 3+ glasses (at least a few times a month), and found no variation in the effect. Finally, we explored associations of maternal drinking of 3+ glasses (at least a few times a month) with drinking patterns of adolescents at age 14. Though some of the categories were dropped in the analyses due to fewer cases in some of the cells, results did not change substantially from those presented in this paper (data not shown).

Finally, a sensitivity analysis including the weighting adjustments and using the inverse-probability of response showed no substantive differences between the weighted and the non-weighted analysis (data not shown).

4. Discussion

In this study, we have explored whether maternal alcohol consumption at different stages of the child's early life course contributes to higher levels of drinking at child age 14. We found a weak but significant association of maternal drinking before pregnancy, which may reflect residual confounding from other maternal or parental factors which we were not able to measure in this study (Merikangas et al., 1998b). We also found associations of maternal drinking before and after pregnancy with child's greater consumption of alcohol in adolescence, a marker of environmental and/or modelling influences during child development, which are known to contribute to later alcohol problems (Lieb et al., 2002; Merikangas et al., 1998a). Our main objective was to assess a potential association between maternal drinking in pregnancy and adolescent patterns of alcohol use. We found an increased risk of early drinking amongst adolescence who had been exposed to maternal alcohol use in pregnancy, with a stronger effect in those who reported drinking higher quantity of alcohol (3+ glasses). Analysis comparing those exposed to higher quantity of alcohol consumption in pregnancy showed that the risk was increased amongst women who reported drinking 3+ glasses for drinking occasion during pregnancy compared with those exposed to $\leq$2 glasses per drinking occasion. These results held after controlling for alcohol consumption at the other two time periods. The evidence regarding a relationship between in utero alcohol exposure and early alcohol

Table 3
Multivariable associations between maternal alcohol consumption at different time periods and child's drinking patterns at age 14 expressed in OR (95% CI) (complete case analysis $n = 4363$)

Maternal alcohol use over the child's life course	Child's drinking patterns at age 14						
		1 or 2			3 or more		
	%	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
YES before/NO during/NO after pregnancy	11.67	1.34 (0.96, 1.87)	1.31 (0.93, 1.84)	1.28 (0.90,1.80)	1.97 (1.36, 2.86)	1.79 (1.22, 2.61)	1.74 (1.18, 2.55)
YES before/YES during/NO after pregnancy	2.22	0.87 (0.38, 2.02)	0.8 (0.34, 1.87)	0.83 (0.35,1.94)	2.28 (1.11, 4.68)	1.97 (0.96, 4.05)	1.95 (0.94, 4.03)
YES before/NO during/YES after pregnancy	10.77	1.51 (1.08, 2.12)	1.44 (1.01, 2.05)	1.45 (1.02,2.06)	2.8 (1.97, 3.96)	2.46 (1.71, 3.54)	2.37 (1.64, 3.42)
YES before/YES during/YES after pregnancy	4.74	2.07 (1.34, 3.20)	1.85 (1.18, 2.91)	1.91 (1.21,3.02)	3.56 (2.26, 5.61)	3.03 (1.89, 4.85)	2.97 (1.84, 4.77)
Always ≤2 glasses for drinking occasion	57.55	1	1	1	1	1	1
NO before/YES during/NO after pregnancy	1.49	0.79 (0.29, 2.21)	0.8 (0.29, 2.24)	0.87 (0.31,2.43)	0.98 (0.30, 3.20)	1.03 (0.32, 3.35)	1.09 (0.33, 3.55)
NO before/NO during/YES after pregnancy	10.89	1.93 (1.41, 2.63)	1.89 (1.38, 2.59)	1.94 (1.41,2.67)	2.45 (1.70, 3.52)	2.30 (1.60, 3.33)	2.28 (1.57, 3.31)
NO before/YES during/YES after pregnancy	0.66	2.17 (0.63, 7.53)	2.18 (0.63, 7.55)	2.17 (0.62,7.54)	12.20 (5.36, 27.76)	12.27 (5.42, 27.78)	11.87 (5.22, 26.98)

Model 1: age adjusted; model 2: adjusted by variables in model 1 + smoking overtime; model 3: adjusted by variables in model 2+, birth weight, gestational age, family income, maternal age and marital status at the antenatal visit and maternal anxiety, depression, and child's behaviour at age 5.

uptake in offspring is limited. Of the studies published to date, three have found an effect in early adulthood (Alati et al., 2006; Baer et al., 2003; Barr et al., 2006). In this sample, the effect of in utero exposure to alcohol was not confined to the antenatal period, but appears to persist in childhood. In this respect, our study confirms existing knowledge that a range of environmental factors, including familial modelling influences also contribute to the association.

Our study provides some support for the hypothesis that mechanisms of neuro-plasticity suggested for the etiology of drug dependence may also contribute to the developmental pathways for adolescent drinking problems (Wise, 2002; Wolf et al., 2004). In order to support a cause-effect association between in utero exposure to alcohol and subsequent child alcohol problems, that is, that a foetal programming mechanism is potentially operating, the association would need to be specific to the antenatal period and not related to post-natal alcohol consumption. In this study there was an increased risk of early alcohol initiation amongst those exposed to greater alcohol use in pregnancy compared with those who were not, after controlling for maternal drinking patterns at other time periods. These groups were represented by small numbers of women (as one would expect). That women increase their alcohol consumption during pregnancy is arguably unlikely, therefore we cannot exclude that ours is a chance finding, maybe due to measurement error. On the other hand, it seems unlikely that women would report higher quantity of alcohol use in pregnancy if this was not the case. It is indeed possible that some women may have consumed slightly greater quantities of alcohol while pregnant. Normal patterns of alcohol consumption vary over time. For some respondents in the sample an increase in consumption may reflect this pattern of variability for example attendance of special events occurring in the same timeframe as pregnancy. So these results point to a possible foetal programming effect though the possibility of a chance finding remains and replications are needed to confirm the robustness of our findings and further explore the mechanisms behind these associations. Future, large birth cohort studies with repeated and more refined alcohol measures are needed to further demonstrate an independent contribution of in utero alcohol exposure to drinking patterns in adolescence.

This study has some limitations. Firstly, it lacks the level of sophistication applied to measuring alcohol consumption today. Our measures of maternal alcohol consumption are not totally consistent with current screening measures, which assess quantity, frequency and variability over a specific time period (National Health and Medical Research Council, 2001). In this study, the timeframe for alcohol use was not specified at the 5-year follow-up. This may have introduced error in the results, though given the time length between the two assessments (pregnancy and 5 year) drinking patterns reported at the 5-year assessment are likely to reflect current use at the time of the follow-up. We could assess quantity and to some extent frequency of alcohol consumption. Sensitivity analyses using a measure of 3+ glasses consumed at a frequency of 'a few times a month' yielded results consistent with those presented in this paper. In addition, existing evidence suggests that validity and reliability of self-reported drinking measures like those used in

this study are generally reasonable (Del Boca and Darkes, 2003; Gruenewald and Johnson, 2006). Nevertheless, future studies with greater capacity to assess patterns of alcohol consumption during pregnancy should assess the risk associated with more frequent exposure to alcohol consumption.

Also, the measures used to assess pre-pregnancy alcohol use data referred to 'before becoming pregnant', rather than 'prior to pregnancy awareness'. Ideally the study should have specifically elicited quantity and frequency of alcohol use before knowledge of pregnancy. Although it is possible that some of the patterns of pre-pregnancy drinking may involve drinking in very early pregnancy, such measurement error would be likely to produce an underestimate of the pregnancy effect, rather than affecting our results in the opposite direction (that is: towards the null). Further, women reported on the number of 'glasses' they drank (rather than 'standard drinks') and written or visual guidance on the size of the glasses was not provided. This terminology was consistent throughout the phases of the study, thus measurement error, had it occurred, is likely to be non-differential or again, may underestimate the size of the effect presented here. Nevertheless, future studies with more sophisticated repeated measures of alcohol use from pre-pregnancy through to offspring's adolescence are needed to test the robustness of our findings.

Notwithstanding these limitations, it is worth noting that the measures used in this study are comparable to routinely collected measures of alcohol consumption used at the time the study was designed and they compare well with similar items used in other internationally established and large-scale birth cohort studies. Given the very limited research undertaken on this subject the present study makes a rare contribution to the corpus of knowledge in this area.

We could not measure genetic contributions, which is difficult in studies where genetic data is not available. More broadly we had little capacity to assess the extent of paternal contribution to adolescent alcohol consumption. Patterns of paternal alcohol use can reflect both genetic and environmental influences, therefore we cannot exclude the possibility that drinking by fathers, other family members and/or peer influences for which we did not have information, may have modified our findings. We used limited information collected at age 14 on paternal and siblings' alcohol problems and found that familial alcohol problems did not attenuate the relationship between pregnancy exposure and later drinking patterns in adolescence (Lieb et al., 2002). Future studies with better capacity to separate maternal in utero effects from environmental exposure during childhood and adolescence, including paternal drinking over time, drinking from other family members and the substance use patterns of peers are needed to confirm the robustness of our findings.

Finally the loss to follow-up is of concern. The multivariable analysis was conducted on 60.4% of the original sample and it is possible that loss to follow-up may have introduced bias in our results. Our results might underestimate the association between maternal and offspring's alcohol use, if loss to follow-up was more common in mothers who consumed greater quantities of alcohol in pregnancy. However, it is worth noting that there were no differences amongst those who remained or were lost to follow-up according to maternal alcohol consumption measured at baseline. Finally, attaching inverse probability weighting to subjects included in the analyses to restore the representation of those lost to follow-up, did not produce any differences between the weighted and non-weighted results, further suggesting that attrition is unlikely to have biased our results.

In conclusion, our results suggest an association between maternal drinking of 3 and more glasses during pregnancy and in childhood and early uptake and greater consumption of alcohol in adolescence. Other large-scale longitudinal studies with better capacity to assess the contribution of maternal drinking at different time periods to child's drinking in adolescence are needed to better disentangle the nature of the association.

Conflicts of interest

None.

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Contributors: RA and AC developed the study aim and design. AAM and GMW advised on statistical methods and analysis. The main analysis was undertaken by RA who also wrote the first draft of the paper. MO and WB contributed to the first draft and to the interpretation of the data. JMN, GMW, MO and WB set up, and are responsible for the conceptual development and continued management of the Mater University Study of Pregnancy and its outcomes. All authors contributed to the final version of the paper.

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