In Utero Alcohol Exposure and Prediction of Alcohol Disorders in Early Adulthood

A Birth Cohort Study

Rosa Alati, PhD; Abdullah Al Mamun, PhD; Gail M. Williams, PhD; Michael O'Callaghan, MD; Jake Moses Najman, PhD; William Bor, MD

Context: Little is known about the contribution of fetal alcohol exposure to the development of alcohol disorders in early adulthood.

Objective: To examine the independent effect of maternal alcohol use during early vs late periods in pregnancy on the time of onset of alcohol disorders in offspring.

Design: Follow-up study of the Mater–University of Queensland Study of Pregnancy and Its Outcomes (MUSP), a population-based birth cohort study commenced in Brisbane, Australia, in 1981 and designed to examine the association of maternal alcohol exposure with the onset of alcohol disorders. Mothers and children were followed up at birth, 6 months, and 5, 14, and 21 years after the initial interview. Maternal alcohol use was assessed before pregnancy, in early and late pregnancy, and at the 5- and 14-year follow-up visits. Alcohol disorders in early adulthood were assessed at age 21 years using the lifetime version of the Composite International Diagnostic Interview–computerized version.

Setting: Population-based birth cohort study.

Participants: A subsample of 2138 participants for whom complete data were available at the 21-year follow-up.

Main Outcome Measure: Onset of alcohol disorder from adolescence to 21 years of age.

Results: In utero alcohol exposure of 3 or more glasses was associated with alcohol disorders. The fully adjusted odds ratios (95% confidence intervals) of developing early-onset alcohol disorders at age 21 years were 2.95 (1.62-5.36) for those exposed to maternal drinking in early pregnancy and 1.35 (0.69-2.63) for those exposed in late pregnancy. There was also a strong association between alcohol exposure in early pregnancy and late-onset alcohol disorders (odds ratio, 3.29 [95% confidence interval, 1.74-6.24]).

Conclusions: Our results provide support for a biological origin of adult alcohol disorders and suggest that the association is not explained solely by maternal drinking or smoking during childhood and adolescence or other intervening factors. Further research is needed to understand the mechanisms underlying the association.

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Author Affiliations: Schools of Population Health (Drs Alati, Al Mamun, Williams, and Najman), Medicine (Dr O'Callaghan), Social Science (Dr Najman), and Psychiatry (Dr Bor), The University of Queensland, Herston, Australia; and Mater Children's Hospital (Dr O'Callaghan) and South Brisbane Child & Youth Mental Health Services (Dr Bor), South Brisbane, Australia.

A CONSIDERABLE BODY OF EVIDENCE[1-5] suggests that exposure to maternal drinking in childhood is an independent predictor of a range of children's mental, cognitive, and behavioral difficulties, including delinquency and alcohol disorders. The contribution of fetal alcohol exposure to the development of alcohol disorders later in life is, on the contrary, relatively understudied. Two notable exceptions are Baer and colleagues' reports[6,7] on the Seattle Longitudinal Study of Alcohol and Pregnancy. In one report,[6] the authors found an independent contribution of maternal drinking in midpregnancy to the early uptake of alcohol at age 14 years. A second report[7] based on the same cohort reported significant positive associations between alcohol exposure in midpregnancy and alcohol problems at age 21 years. In both studies the authors were able to adjust for maternal demographic characteristics, maternal tobacco and drug use during pregnancy, and family and maternal alcohol problems after pregnancy.[6,7]

This dearth of evidence is surprising if one considers that in utero alcohol exposure can affect the structure and function of the fetus, interfere with the development of the central nervous system, and cause a range of disabilities[4] including deficits in social behavior later in adulthood.[1,8] As opposed to the lack of evidence in humans, there is extensive evidence of an association between in utero ethanol exposure and the development of early ethanol acceptance and ingestion in animals.[9] Recent experiments[10,11] have found that rats of dams injected with moderate doses of ethanol ingested a greater amount of ethanol in adolescence than those that were injected with water only, with the effects being more severe when ethanol was administered all at once rather than gradu-

ally. Similar results replicated in human studies would carry considerable implications for public health intervention. First, such studies would suggest that even small quantities of alcohol exposure, if consumed in a single session, may cause in utero neurodevelopmental changes that in turn lead to the early onset of alcohol disorders in youth. Second, they would provide support for the role of a biological origin of alcohol disorders.

There is evidence of the fetal environment modifying the development of the central nervous system and being influential in the etiology of chronic diseases[12,13] and common mental health disorders.[14,15] To our knowledge, no argument has been made for a fetal origin of alcohol disorders. However, gene-alcohol interactions may modify the expression of genes involved in the developing nervous system and predispose individuals to later alcohol disorders by acting on the mesolimbic dopamine system.[16] Modification of the mesolimbic system appears to be associated with the development of dependence in adult humans and other species.[16]

In a previous study[17] using data from a large Australian birth cohort study, our group explored factors associated with the development of alcohol problems at age 21 years and found that maternal alcohol consumption measured when the child was 14 years old was one of the most important predictors of alcohol abuse and disorders in early adulthood. In the present study, we examined the independent effect of maternal alcohol use at different developmental periods on alcohol disorders in offspring. Because animal studies show that in utero alcohol exposure leads to earlier as well as greater ingestion of alcohol,[9] we also explored the relationship between the level of exposure and early and late onset of the disorder.

METHODS

PARTICIPANTS

We used data from the Mater–University of Queensland Study of Pregnancy and Its Outcomes (MUSP), a prospective study of women and their babies who were initially interviewed at their first antenatal visit at the Mater Misericordiae Hospital in Brisbane, Australia, between 1981 and 1984. The original sample consisted of 7223 mothers and their babies who were followed up at birth (3-5 days after birth), and at 6 months and 5, 14, and 21 years after birth. Our cohort consisted of a selected subsample of 2555 youth whom we were able to locate at the 21-year follow-up phase of the study and who agreed to complete the lifetime version of the Composite International Diagnostic Interview–computerized version (CIDI-Auto).[18] This group represents 35.4% of the 7223 offspring in the original birth cohort. Written informed consent from the mother was obtained at all data collection phases. Written informed consent was also obtained from the offspring at the 21-year follow-up visit.

MEASURES

Outcome

At the 21-year phase, we used the CIDI-Auto[18] to assess the onset of alcohol abuse disorders from adolescence to age 21 years, according to *DSM-IV* diagnostic criteria.[19] Some 25% of the youth (n=640), met criteria for alcohol abuse disorders; 6.1% of these also met criteria for alcohol dependence. We used the age-at-first-onset variable of the CIDI-Auto to create a 3-category measure: a reference category for those who met no criteria for a disorder, a category of early onset (for those who met criteria for a disorder between 13 and 17 years of age), and a category of late onset (for those who met criteria for an alcohol disorder between 18 and 21 years of age).

Predictors

We measured the quantity of alcohol consumption at any drinking occasion (0, 1 or 2 glasses, 3 or 4 glasses, 5 or 6 glasses, and ≥7 glasses) at each phase of the data collection. No specific quantity of alcohol was mentioned in the questionnaire, but current guidelines estimate approximately 10 g per standard drink. At the antenatal visit, when women were on average at 18 weeks of gestation (early pregnancy), 2 maternal reports of alcohol consumption were obtained: a recall of the quantity of alcohol consumed before pregnancy and a current report of the quantity of alcohol use. At 3 to 5 days after delivery, mothers were asked to report on the quantity of the alcohol consumed in the last 3 months of pregnancy (late pregnancy). The same question was administered at the 5- and 14-year follow-up visits. We first recategorized each variable for each of the phases of follow-up into "no alcohol/up to 2 glasses" and "3 or more glasses." To compare the independent effect of maternal alcohol use in pregnancy with the environmental and modeling effect of maternal drinking during the other periods, we combined maternal alcohol use at the 5 phases according to whether the women had consumed 3 or more glasses throughout pregnancy (ie, they reported consuming ≥3 glasses at the antenatal visit and/or during the third trimester) or at other times. We found that 50.0% (n=1068) of those who had complete alcohol data at all phases (n=2138) had never exceeded alcohol use of 2 glasses at any given occasion, 41.0% (n=869) had consumed 3 or more glasses at some stage before and/or after pregnancy (but not during pregnancy), and 9.4% of the mothers (n=201) had consumed that quantity during pregnancy.

We further separated this latest category into those who reported having consumed 3 or more glasses only in early pregnancy (n=82 [3.8%]), those who reported having consumed that amount only in late pregnancy (n=83 [3.9%]), those who reported consuming that quantity during both pregnancy periods (n=36 [1.7%]), and those who had consumed 3 or more glasses at other time periods but not during pregnancy (n=869 [40.6%]). The categories are mutually exclusive.

We also asked the women, "How often do you drink alcohol?" at each of the 5 phases to obtain a combined measure of quantity/frequency of consumption. Possible answers were daily, a few times a week, a few times a month, a few times a year, rarely, and never. We combined maternal alcohol use over the 5 phases according to whether the women had consumed up to 2 glasses, a few times a year or 3 or more glasses at least a few times a month during pregnancy (during early or late pregnancy or both) or at other times (not during pregnancy). Because fewer women drank alcohol this frequently during pregnancy, it was not possible to determine which of the 2 periods was more critical.

Potential Confounders

Measures of maternal smoking were obtained at each phase of data collection. Mothers were asked to report whether and how much they had smoked in the previous week. In addition, at the antenatal visit women were asked to recall their smoking habits before they became pregnant. At 3 to 5 days after delivery, mothers reported their smoking habits of the previous 3 months. We defined smoking status as: never smoked, smoked

during pregnancy (women who responded yes to smoking at the antenatal visit and/or in the third trimester), and smoked at other times but not during pregnancy (women who did not report smoking during pregnancy but reported being smokers before pregnancy and/or at any of the other follow-up phases). These categories are mutually exclusive.

Confounders measured at the first antenatal visit included the child's sex and the mother's sociodemographic position, determined from her age (13-19, 20-34, or ≥35 years), education (did not complete high school, completed high school, or completed education beyond high school), and marital status (married, cohabiting, or single). Biological factors such as the child's gestational age and birth weight were extracted from the obstetric records at birth.

Confounders measured at the 5- and 14-year follow-up visits included maternal mental health status and the child's behavioral problems. Maternal depression and anxiety were assessed at all phases using the Delusions-Symptoms-States Inventory.[20] The Delusions-Symptoms-States Inventory contains two 7-item subscales measuring depression and anxiety that have been found to correlate strongly with other scales of depression, including the Beck Depression Inventory.[21] The child's behavioral problems were assessed at age 14 years using the internalizing and externalizing symptom subscales of the Youth Self-report version of the Child Behavior Checklist.[22] The use of the Youth Self-report in the MUSP study, as well as its validity and internal consistency, has been described in previous reports.[23] Scale scores were dichotomized into 2 categories, with a 10% cut-off for cases.

At the 14-year follow-up visit, supplementary information was available on 2 items. Mothers were asked whether the biological father of their child ever had an alcohol problem and whether any of the full brothers and sisters of the study child ever had alcohol problems (yes/no).

ANALYTICAL PROCEDURE

Univariable associations between our main predictor (maternal alcohol consumption), potential confounders, and alcohol disorder onset were explored using χ^2 tests and unadjusted multinomial logistic regressions, with the outcome variable including categories of no disorders (reference category), early onset, and late onset. Factors that were significant in this analysis were selected as potential confounders (or effect modifiers) in the multivariable analysis. Multivariable associations were assessed by progressive multinomial logistic regression models. This analysis was conducted on 2138 participants for whom complete data were available at all phases. Model 1 was adjusted by child sex; model 2 was further adjusted by maternal smoking over the child's life course, birth weight, gestational age, maternal education, and age and marital status at baseline; and model 3 also included maternal anxiety and depression and the child's behavior at age 14 years. Because preliminary analyses showed that maternal anxiety at the 5-year follow-up and maternal depression at the 14-year follow-up were associated with the child's alcohol disorders in youth, we used these measures at the 2 periods to adjust for maternal mental health problems. 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 conducted 2 sensitivity analyses. We repeated our final analysis on the quantity/frequency combined measure categorized as 3 or more glasses at least a few times a month, either during pregnancy or at other times but not during pregnancy. To ensure that the results were not driven by the choice of the cut-off for defining the quantity and frequency of maternal alcohol consumption, we also conducted sensitivity analyses in which all analyses were repeated with alcohol use set at 5 or more glasses a few times a month (outside the pregnancy period) to assess whether this would increase the risk during other periods. Finally, we replicated our analysis on a restricted sample (n=1922), excluding from the 2138 cohort 216 cases for whom there was a maternal report of paternal (n=196) or sibling (n=20) alcohol problems at age 14 years.

The group lost to follow-up in our study comprised mostly those who were unable to be located. We used 2 methods to assess whether loss to follow-up introduced bias in our findings. First, because there were only 2138 cases with complete data (of the 2555 who completed the CIDI-Auto) in the fully-adjusted model, we conducted multiple imputation of the data set to estimate imputed values for the missing items. Starting from a missing-at-random assumption,[24] we applied the stochastic switching regression method of van Buuren et al[25] to restore the representation of those lost to follow-up (using a procedure fully described elsewhere[26]) and repeated the analyses on the imputed data (data not shown). Next, 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 male ($P<.001$) and to be born of mothers who were less educated ($P=.08$) and who were more likely to smoke ($P<.002$), to be depressed ($P=.008$), to be anxious ($P=.03$), and to have 2 or more children at the time they presented at their first antenatal visit ($P=.03$). 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 (with response vs nonresponse as the outcome) to determine weights for each individual using the inverse probability of response and repeated all of the multivariable analyses, including the weighting adjustments.[24]

RESULTS

Of the 2555 offspring who completed the CIDI-Auto at age 21 years, 640 (25.0%) met the criteria for a lifetime diagnosis of alcohol disorders. Of these, 333 (13.0%) reported a disorder before 18 years of age (early onset) and 307 (12.0%), between 18 and 21 years of age (late onset).

Table 1 shows the univariable associations between maternal alcohol and tobacco consumption at the 5 phases of the study and early and late onset of alcohol disorders at age 21 years, comparing the early-onset and late-onset groups with the no alcohol disorders group. Women who had consumed 3 or more glasses per given occasion in early pregnancy were 2.47 to 2.04 times, respectively, more likely to have offspring with early and late onset of alcohol disorders, with the effect being stronger for early onset. Maternal drinking of 3 or more glasses during other periods (including late pregnancy) was also significantly associated with offspring's alcohol disorders.

Table 2 shows the associations between a range of potential confounders and early and late onset of alcohol disorders. Offspring meeting criteria for both early and late onset of alcohol disorders at age 21 years were more likely to have mothers with lower levels of education and greater symptoms of depression, to be male, and to report a higher prevalence of externalizing symptoms compared with those who did not meet *DSM-IV* criteria for alcohol disorders. For maternal education, marital status, and depression and the child's externalizing behavior, the data appear to suggest that the effect was stronger for early onset.

Table 1. Univariable Associations Between Maternal Alcohol Use and Onset of Alcohol Disorders at Age 21 Years*

Maternal Alcohol Use Over Time†	No.	Early Onset, %	Late Onset, %	No Disorder, %‡	Unadjusted OR (95% CI)	
					Early Onset	Late Onset
Before pregnancy	2540					
No alcohol/≤2 glasses	1763	12.5	10.6	76.9	1.00	1.00
≥3 Glasses	777	14.4	14.9	70.7	1.26 (0.98-1.61)	1.53 (1.19-1.97)
P value§		.002				
Early pregnancy	2536					
No alcohol/≤2 glasses	2387	12.4	11.6	76.0	1.00	1.00
≥3 Glasses	149	23.5	18.1	58.4	2.47 (1.64-3.72)	2.04 (1.30-3.20)
P value§		<.001				
Late pregnancy	2551					
No alcohol/≤2 glasses	2407	12.7	11.8	75.5	1.00	1.00
≥3 Glasses	144	18.8	16.7	64.6	1.72 (1.11-2.69)	1.66 (1.04-2.64)
P value§		.01				
At 5-y follow-up	2288					
No alcohol/≤2 glasses	1638	11.7	11.2	77.1	1.00	1.00
≥3 Glasses	650	14.5	14.8	70.8	1.35 (1.03-1.77)	1.43 (1.09-1.87)
P value§		.006				
At 14-y follow-up	2433					
No alcohol/≤2 glasses	1741	12.1	11.1	76.7	1.00	1.00
≥3 Glasses	692	14.2	14.5	71.4	1.26 (0.97-1.63)	1.39 (1.07-1.81)
P value§		.02				

Abbreviations: CI, confidence interval; OR, odds ratio.

*Of the 2555 offspring who completed the Composite International Diagnostic Interview–computerized version at age 21 years, 333 (13.0%) met *DSM-IV* criteria for early onset of an alcohol disorder (onset between ages 13 and 17 years) and 307 (12.0%) for late onset (onset between ages 18 and 21 years), and 1915 (75.0%) met no criteria for a disorder. Because of rounding, percentages may not total 100.

†No specific quantity of alcohol was mentioned in the questionnaire, but current guidelines estimate approximately 10 g per standard drink.

‡Reference category for the multinomial logistic regression.

§Calculated using the χ^2 test for statistical significance.

Table 3 shows the percentages of those in each of the mutually exclusive exposure groups as a function of a range of potential confounders. There were no significant differences between the mother's alcohol consumption during the different periods and the child's sex, birth weight, and internalizing symptoms at age 14 years. There were also no significant associations with maternal education, anxiety, and depression. Mothers who drank 3 or more glasses of alcohol in pregnancy were also more likely to be smokers, to be cohabiting or single, and to have children with greater numbers of externalizing symptoms at age 14 years.

Table 4 shows the multivariable associations between maternal alcohol consumption and youth alcohol disorders at age 21 years adjusted for a range of potential confounders. Sex-adjusted analyses showed that offspring of mothers who had consumed 3 or more glasses of alcohol during early pregnancy had almost 4 times the odds of developing early onset of alcohol disorders at age 21 years compared with those whose mothers drank no more than 2 glasses at any time. The association remained robust after adjusting for a variety of biological and environmental factors. However, the introduction of maternal smoking over the child's life course (model 2) attenuated the strength of the association between maternal alcohol use in pregnancy and alcohol disorders at age 21 years, as did the inclusion of maternal depression and the child's externalizing behavior at age 14 years (model 3). A weaker association between maternal drinking in late pregnancy and later alcohol problems in youth were mostly confounded by maternal characteristics and the child's externalizing behavior at age 14 years. Offspring of mothers who consumed 3 or more glasses of alcohol during early pregnancy had 3 times the odds of reporting late onset of alcohol disorders compared with those whose mothers drank no more than 2 glasses at any time. This maternal drinking pattern during other periods was also associated with the child's meeting criteria for late-onset alcohol disorders.

We conducted further analysis using the quantity/frequency measure of maternal alcohol consumption described in the "Methods" section. In the fully adjusted model, the odds ratios (ORs) (95% confidence intervals [CIs]) of developing early-onset alcohol disorders were 2.06 (1.27-3.35) in those exposed to maternal drinking of 3 or more glasses a few times a month during pregnancy and 1.15 (0.84-1.58) in those exposed at other times but not during pregnancy, compared with those exposed to 3 or more glasses a few times a year. Those whose mothers consumed 3 or more glasses a few times a month during pregnancy were also more likely to meet the criteria of late-onset alcohol disorders (OR, 2.12 [1.27-3.54]) compared with those exposed to the same quantity but less frequently. There was also a risk of meeting criteria for late-onset alcohol disorders among those exposed to the highest quantity/frequency pattern during other periods (OR, 1.61 [95% CI, 1.18-2.19]) compared with those exposed to less frequent use (data not presented). When we conducted sensitivity analyses in which all analyses were repeated with alcohol use set to 5 or more glasses a few times a month outside the pregnancy period, the results were no different from those presented herein.

Additional sensitivity analyses yielded results consistent with those reported in Table 4. To account for a genetic contribution of other family members to alcohol dis-

Table 2. Univariable Associations Between Other Potential Confounders and Onset of Alcohol Disorders at Age 21 Years*

Confounder	No.	Early Onset, %	Late Onset, %	No Disorder, %†	Unadjusted OR (95% CI)	
					Early Onset	Late Onset
Sex	2555					
Male	1251	19.0	16.6	64.4	1.00	1.00
Female	1304	7.3	7.6	85.1	0.29 (0.22-0.37)	0.35 (0.27-0.45)
P value‡		<.001				
Maternal smoking over time	2181					
No smoker	1148	9.3	11.6	79.1	1.00	1.00
Smoker in pregnancy	808	16.1	13.4	70.5	1.94 (1.47-2.55)	1.29 (0.98-1.70)
Smoker before and after (not in pregnancy)	225	13.8	10.7	75.6	1.55 (1.00-2.38)	0.96 (0.61-1.53)
P value‡		<.001				
Birth weight, kg	2554					
>3.50	1043	13.2	12.5	74.3	1.00	1.00
3.01-3.50	990	13.1	12.4	74.4	0.99 (0.76-1.28)	0.99 (0.76-1.30)
≤3.00	521	12.5	10.4	77.2	0.91 (0.66-1.25)	0.80 (0.57-1.12)
P value‡		.72				
Gestational age, quartiles	2555					
1	565	13.1	12.0	74.9	1.00	1.00
2	818	14.3	9.8	75.9	1.08 (0.78-1.48)	0.80 (0.57-1.13)
3	585	12.8	13.2	74.0	0.99 (0.70-1.40)	1.11 (0.78-1.57)
4	587	11.4	14.0	74.6	0.87 (0.61-1.25)	1.16 (0.82-1.65)
P value‡		.21				
Maternal education	2537					
Beyond high school	503	8.0	9.7	82.3	1.00	1.00
Completed high school	1626	13.5	12.2	74.3	1.88 (1.32-2.68)	1.39 (1.00-1.94)
Did not complete high school	408	17.7	13.0	69.4	2.63 (1.74-3.99)	1.58 (1.04-2.40)
P value‡		<.001				
Maternal marital status	2538					
Married	2068	11.9	11.9	76.2	1.00	1.00
Cohabiting	222	18.5	11.7	69.8	1.70 (1.18-2.46)	1.07 (0.69-1.66)
Single	248	18.6	12.1	69.4	1.72 (1.21-2.45)	1.11 (0.74-1.68)
P value‡		.004				
Maternal anxiety at 5-y follow-up	2286					
Not anxious	1952	11.8	11.9	76.2	1.00	1.00
Anxious	334	16.5	13.8	69.8	1.52 (1.10-2.10)	1.26 (0.89-1.78)
P value‡		.03				
Maternal depression at 14-y follow-up	2435					
Not depressed	2275	12.0	11.8	76.1	1.00	1.00
Depressed	160	21.3	15.6	63.1	2.13 (1.41-3.20)	1.59 (1.01-2.52)
P value‡		<.001				
Internalizing symptoms (at 14-y follow-up)	2437					
Normal	2191	12.9	12.0	75.2	1.00	1.00
Case	246	11.8	12.2	76.0	0.91 (0.60-1.37)	1.01 (0.67-1.51)
P value‡		.88				
Externalizing symptoms (at 14-y follow-up)	2437					
Normal	2215	11.4	11.7	76.9	1.00	1.00
Case	222	26.1	15.3	58.6	3.00 (2.15-4.21)	1.73 (1.16-2.58)
P value‡		<.001				

*Of the 2555 offspring who completed the Composite International Diagnostic Interview–computerized version at age 21 years, 333 (13.0%) met *DSM-IV* criteria for early onset of an alcohol disorder (onset between ages 13 and 17 years) and 307 (12.0%) for late onset (onset between ages 18 and 21 years); 1915 (75.0%) met no criteria for a disorder. Because of rounding, percentages may not total 100.

†Reference category for the multinomial logistic regression.

‡Calculated using the χ^2 test for statistical significance.

orders in youth, we repeated all analyses in a restricted sample of offspring from which we excluded those whose fathers and/or siblings had an alcohol disorder at the 14-year follow-up. In the fully adjusted model, the ORs (95% CIs) for the associations between exposure to maternal alcohol consumption of 3 or more glasses and early-onset disorders were 2.78 (1.53-5.04) for early pregnancy, 1.21 (0.61-2.40) for late pregnancy, and 1.94 (0.77-4.90) for both periods. Similar point estimates were found for the association of maternal alcohol consumption and late-onset alcohol disorders (ORs [95% CIs]: 2.78 [1.42-5.38], 1.51 [0.75-3.05], and 2.52 [0.94-6.72] for exposure to ≥3 glasses in early pregnancy, late pregnancy, and during both periods, respectively).

In a sensitivity analysis using the imputed data set, we found point estimates that were consistent with those reported herein (data not presented). Finally, when we included weighting adjustment for factors that predicted nonresponse between the 2555 offspring and the original 7223 birth-cohort participants and repeated the analy-

Table 3. Associations Between Potential Confounders and Maternal Use Over Time*

Confounder	No.	≤2 Glasses, %	≥3 Glasses, %			
			In Early Pregnancy	In Late Pregnancy	During Both Pregnancy Periods	Not During Pregnancy†
Sex	2363					
Male	1312	55.9	55.4	53.8	71.79	54.55
Female	1051	44.1	44.6	46.2	28.21	45.45
			$\chi^2 = 4.728$; $P = .31$			
Maternal smoking over time	2332					
Nonsmoker	1159	66.7	34.4	47.4	2.63	32.64
Smoker in pregnancy	876	23.1	58.9	41.0	89.47	50.73
Smoker before and after (not during pregnancy)	297	10.2	6.7	11.5	7.89	16.63
			$\chi^2 = 313.130$; $P = .001$			
Birth weight, kg	2362					
>3.50	993	43.9	34.8	37.5	35.9	41.09
3.01-3.50	905	37.9	38.0	40.0	33.33	38.93
≤3.00	464	18.2	27.2	22.5	30.77	19.98
			$\chi^2 = 10.286$; $P = .24$			
Maternal marital status	2340					
Married	1876	87.5	67.8	77.2	56.41	73.71
Cohabiting	216	5.9	8.9	13.9	20.51	12.37
Single	248	6.5	23.3	8.9	23.08	13.92
			$\chi^2 = 96.587$; $P<.001$			
Maternal education	2346					
Beyond high school	415	19.1	18.5	21.2	12.82	15.81
Completed high school	1527	64.6	58.7	61.2	64.10	66.63
Did not complete high school	404	16.3	22.8	17.5	23.08	17.56
			$\chi^2 = 8.682$; $P = .37$			
Maternal depression at 14-y follow-up	2356					
Not depressed	2135	92.1	91.3	88.6	84.62	89.22
Depressed	221	7.9	8.7	11.4	15.38	10.78
			$\chi^2 = 7.206$; $P = .12$			
Maternal anxiety at 5-y follow-up	2348					
Not anxious	1943	83.4	83.7	86.1	71.79	82.00
Anxious	405	16.6	16.3	13.9	28.21	18.00
			$\chi^2 = 4.734$; $P = .31$			
Internalizing symptoms at age 14 y	2344					
Normal	2152	92.4	86.8	92.5	92.31	91.52
Case	192	7.6	13.2	7.5	7.69	8.48
			$\chi^2 = 3.686$; $P = .45$			
Externalizing symptoms at age 14 y	2344					
Normal	2083	90.8	85.7	88.8	76.92	87.28
Case	261	9.2	14.3	11.2	23.08	12.72
			$\chi^2 = 13.549$; $P = .009$			

*Because of rounding, percentages may not total 100. No specific quantity of alcohol was mentioned in the questionnaire, but current guidelines estimate approximately 10 g per standard drink.

†This category includes prenatal and postnatal alcohol exposure.

sis on the weighted sample, we found that our results were the same as those presented herein.

COMMENT

Ours is the first study, to our knowledge, to support evidence of a specific contribution of alcohol exposure during pregnancy to both early and late onset of alcohol disorders at age 21 years.[7] In addition to the work by Baer and colleagues,[6,7] we were also able to explore the confounding effects of maternal smoking over the child's life course by using the same analytical procedure as that used for maternal alcohol exposure. We found that maternal smoking during pregnancy attenuated the association between in utero alcohol exposure and alcohol disorders in youth but did not confound it, suggesting that a com-

Table 4. Multivariable Associations Between Maternal Alcohol Use Over Time and Onset of Alcohol Disorders at Age 21 Years*

	% Reporting	Early Onset			Late Onset		
		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Maternal alcohol use over time†							
≤2 Glasses	50.0	1	1	1	1	1	1
≥3 Glasses in early pregnancy	3.8	3.93 (2.21-6.97)	3.04 (1.68-5.50)	2.95 (1.62-5.36)	3.37 (1.80-6.28)	3.37 (1.78-6.37)	3.29 (1.74-6.24)
≥3 Glasses in late pregnancy	3.9	1.78 (0.93-3.41)	1.42 (0.73-2.75)	1.35 (0.69-2.63)	1.86 (0.95-3.62)	1.70 (0.86-3.38)	1.67 (0.84-3.31)
≥3 Glasses during both pregnancy periods	1.7	3.45 (1.50-7.95)	2.40 (0.91-6.34)	2.49 (1.06-5.85)	2.60 (1.00-6.74)	2.46 (0.93-6.53)	2.43 (0.91-6.44)
≥3 Glasses but not during pregnancy	40.7	1.20 (0.90-1.60)	0.94 (0.68-1.28)	0.94 (0.68-1.28)	1.57 (1.17-2.09)	1.55 (1.13-2.10)	1.52 (1.12-2.07)

*Of the 2555 offspring who completed the Composite International Diagnostic Interview–computerized version at age 21 years, 333 (13.0%) met *DSM-IV* criteria for early onset of an alcohol disorder (onset between ages 13 and 17 years) and 307 (12.0%) for late onset (onset between ages 18 and 21 years); 1915 (75.0%) met no criteria for a disorder. Data are expressed as odds ratio (95% confidence interval) unless otherwise indicated. Model 1 is adjusted for sex; model 2, for sex, smoking over time, birth weight, gestational age, maternal education, age, and marital status at the antenatal visit; and model 3, all items adjusted for in model 2 plus maternal anxiety at the 5-year follow-up and maternal depression and child behavior at the 14-year follow-up. The fully adjusted analysis was conducted on 2138 participants with complete data at all phases.

†No specific quantity of alcohol was mentioned in the questionnaire, but current guidelines estimate approximately 10 g per standard drink.

mon mechanism may underlie the effect of both exposures on the brain's natural reward circuitry.[16]

In addition to the findings of Baer et al, our study points to a more specific timing of the in utero effect, such that exposure in early pregnancy was a stronger predictor than exposure in late pregnancy. We also found that exposure to maternal alcohol consumption during the developmental years was associated with later onset of alcohol disorders, which reflects a possible contribution of genetic or childhood and adolescence environmental exposures (or both) to alcohol use.

Our findings support a biological contribution to the origin of alcohol disorders[12] and suggest that greater attention should be given to the role of the programming effect of in utero alcohol exposure to the development of alcohol disorders in adulthood.[14,15] The effects of alcohol exposure in both early and late pregnancy on the increased and earlier acceptance of ethanol in offspring have been consistently found in animal studies.[9,11] In humans, the results of ultrasonography performed on pregnant women revealed a dose-response relationship between frontal cortex size in the fetus and maternal alcohol consumption, suggesting that alcohol-associated changes in the fetal brain are already apparent before birth.[27] In adult humans and in many animals, specific drugs appear to act by modifying the natural reward circuitry of the brain.[16] This circuit involves the mesolimbic dopamine system, with dopamine-producing neurons in its ventral tegmental area connecting to cells in the nucleus accumbens.[16] In addition, prenatal alcohol exposure may exert long-term effects on the hypothalamus and/or pituitary-adrenal axis, and this may be responsible for increased alcohol intake in adult offspring.[28,29]

Genetic predisposition may confound the associations we found. However, when we excluded cases with sibling and paternal alcohol problems, we found the strength of the associations to be of the same magnitude as those reported in Table 4, suggesting no attenuation of the biological effect of maternal drinking in pregnancy on alcohol disorders in offspring.

Our results should be seen in the context of some limitations. First, our assessment of maternal alcohol consumption does not accurately match current screening measures, which include the assessment of quantity, frequency, and variability over a specific period.[30] Our study had only limited capacity to assess the frequency of alcohol consumption. Our findings suggest that, compared with less frequent exposure, in utero exposure to 3 or more glasses consumed as frequently as a few times a month is associated with double the risk of both early- and late-onset alcohol disorders in youth. In our main analysis, the effect of alcohol exposure appeared to be stronger earlier in pregnancy; however, limited information on the frequency of intake precludes more detailed identification of when the effect may occur. Future studies with more accurate measures of the frequency and variability of maternal alcohol use in pregnancy are needed to further our understanding of the contribution of different patterns of in utero alcohol exposure to the development of alcohol disorders in youth. Other longitudinal data with repeated measures of alcohol exposure at different gestation periods are also needed to replicate our results and to ascertain whether the risk is greater during a specific point in gestation.

Finally, the ability to adequately account for genetic heritability and/or environmental influences is always problematic. Although we used all of the measures available in the study and excluded individuals who may have been at risk of other familial environmental or genetic influences and still found the effects to be robust, we cannot exclude the possibility that drinking patterns in other family members and/or peers has an influence during early adolescence. Such information may have modified our findings.

The loss to follow-up in our cohort was considerable. This analysis was conducted on a subsample of the initial birth cohort for whom data on the CIDI-Auto were available. Because these 2555 individuals represent only 35.4% of the 7223 offspring in the original birth cohort, the loss to follow-up is such that it may introduce bias in our results. If the patterns of maternal alcohol use and alcohol

disorders in youth were less prevalent among those lost to follow-up, our results would overestimate the association between maternal substance use and their offspring's alcohol use at age 21 years. It is also worth noting that patterns of maternal alcohol consumption in pregnancy did not differ between those lost to follow-up and those retained in the study. This indicates that loss to follow-up was not related to our primary exposure variable and predictor of interest, and that attrition is unlikely to have introduced bias in our results. To further explore this possibility, we attached inverse probability weighting to subjects included in the analyses to restore the representation of those lost to follow-up. As in previous studies stemming from the same cohort,[17] we found little difference between the weighted and nonweighted results, suggesting that attrition is unlikely to have substantively biased our findings in either direction.

The strength of this study is in its longitudinal nature. This large population-based birth cohort study is one of the few studies to prospectively examine the association of maternal alcohol consumption at several time points and alcohol problems in youth, taking into account a number of important potential confounders. In addition, it is the first study, to our knowledge, to assess youth alcohol problems according to *DSM-IV* criteria for alcohol disorders.[18,31] Similar studies with improved capacity to assess comprehensive family drinking patterns, paternal alcohol use, and peer influences are needed to confirm the biological effect we found between maternal alcohol use in pregnancy and the development of alcohol disorders in youth.

Our study supports a developmental role in some instances of alcohol disorders.[14,15] Fetal exposure to alcohol consumption of 3 or more glasses per occasion, in addition to and beyond genetic heritability and environmental factors, may play an important role in the causal pathway that leads to alcohol disorders in adulthood.

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Correspondence: Rosa Alati, PhD, School of Population Health, The University of Queensland, First Floor, Public Health Building, Medical School, Herston, Queensland 4006, Australia (r.alati@sph.uq.edu.au).
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