Published in final edited form as:
Placenta. 2014 July ; 35(7): 437–441. doi:10.1016/j.placenta.2014.04.006.

The effect of maternal prenatal smoking and alcohol consumption on the placenta-to-birth weight ratio

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Abstract

Background—Maternal influence on fetal growth is mediated through the placenta and this influence may have an implication for the offspring's long-term health. The placenta-to-birth weight ratio has been regarded as an indicator of placental function. However, few studies have examined the effect of maternal lifestyle exposures on the placenta-to-birth weight ratio. This study aims to examine the associations of maternal prenatal smoking and alcohol consumption with the placenta-to-birth weight ratio.

Methods—Data for 7945 term singletons, gestation ≥37 weeks, were selected from the Tasmanian Infant Health Survey; a 1988–1995 Australian cohort study. Placenta and birth weight were extracted from birth notification records.

Results—Maternal smoking during pregnancy was strongly associated with a 6.77g/kg higher (95% CI 4.83 to 8.71) placenta-to-birth weight ratio when compared to non-smoking mothers. Maternal prenatal smoking was associated with lower placental (β=−15.37g; 95% CI –23.43 to -7.31) and birth weights (β=−205.49g; 95% CI −232.91 to −178.08). Mothers who consumed alcohol during pregnancy had a lower placenta–to-birth weight ratio (β=−2.07g/kg; 95% CI −4.01 to −0.12) than mothers who did not consume alcohol. The associations of maternal alcohol

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consumption during pregnancy with placental and birth weight did not reach statistical significance.

Discussion—Maternal prenatal smoking and alcohol consumption may influence fetal growth by either directly or indirectly altering the function of the placenta.

Conclusions—The alteration of the *in utero* environment induced by smoking and alcohol consumption appears to affect placental and fetal growth in differing ways. Further studies are needed to elucidate the mechanism.

Keywords

Placenta; birthweight; pregnancy; maternal smoking; alcohol

INTRODUCTION

The health of a fetus is very much dependent on the environment in which it develops. More importantly, influences of the intrauterine environment during fetal growth may persist and may have an implication for the long-term health of the affected offspring. The developmental origins of adult disease hypothesis states that fetal under-nutrition at critical periods of *in utero* development results in adaptations in body structure and metabolism, leading to an increased risk of adult chronic diseases such as hypertension, diabetes, and cardiovascular disease [1].

The mother's influence on fetal growth is partly mediated through the placenta, a crucial organ for the exchange and transfer of substrates including nutrients and oxygen between mother and fetus [2]. However, the factors that determine placental size and function are still unclear. To date, epidemiological studies that have examined the effect of maternal factors on placenta have been almost entirely limited to maternal nutrition [3–5]. Although morphological studies suggest that smoking produces a decrease in size and vascularization of the placenta [6, 7], few epidemiological studies have examined the associations of maternal prenatal smoking and alcohol consumption with placental growth, and such studies have been limited by a relatively small sample size [8, 9] or the use of a dataset of a study conducted in the 1950's [10, 11].

In this study, we used data from the Tasmanian Infant Health Survey (TIHS), a large cohort study, to examine the associations between maternal prenatal cigarette smoking and alcohol consumption, and placental weight and the placenta-to-birth weight ratio which is a widely used index for assessing placental function [12–14].

METHODS

Participants

The TIHS was conducted between January 1988 and December 1995 with the primary objective of investigating the cause of Sudden Infant Death Syndrome (SIDS). Details of the study methods have been reported previously [15]. In summary, the study operated from six major obstetric hospitals in the state of Tasmania, Australia, where 93% of Tasmanian births occurred. Informed consent was obtained from the pregnant women. Infants were selected

by a locally devised scoring system identifying infants at high risk of SIDS [16]. The sample of eligible infants represented one in five Tasmanian live-births.

The composite score for the predictive model included maternal age, neonatal gender, birth weight, season of birth (March-April, May-July, and August-February), duration of second stage of labor and intention to breast feed. Infants with a score over a specific cut-off point were eligible for the study. Data including socio-demographic, obstetric and perinatal information were collected by research assistants during a hospital interview when the neonate was about 4 days old. After excluding multiple pregnancies and infants born <37 weeks of gestation, the present analysis included 7945 mothers and offspring.

Study measures

Outcomes—Placental weight was measured wet after trimming the cord and without removing the membrane and attached blood clots. Placental status was assessed using visual inspection and classified as normal, incomplete, infarcted, post mature, clots on maternal side and other abnormality. As only around 1% placentas were classified as ‘post mature’ or ‘clots on the maternal side’, we combined them with ‘other abnormality’.

Main exposures—Data on maternal prenatal cigarette smoking and alcohol consumption were collected during each trimester of pregnancy. Smoking was defined as: never smoked, smoked 1–10 cigarettes per day, smoked 11–20 cigarettes per day, and smoked 21+ cigarettes per day. Whilst alcohol consumption was defined as having consumed: no alcohol, 0–1 drinks per day, 2–3 drinks per day, 4–5 drinks per day, and 6+ drinks per day. As 97% of women who consumed alcohol during pregnancy reported drinking between 0–1 drinks per day, alcohol consumption was analyzed as a dichotomous variable (yes or no).

Covariates—The following variables were considered as covariates on the basis of possible associations with the outcomes and main exposures: components of the perinatal composite score used to determine eligibility of infants to participate in the TIHS, paternal age, maternal education, paternal education, household fortnightly income, maternal pre-pregnancy BMI (based on self-reported height and pre-pregnancy weight, kg/m^2), total pregnancy weight change (calculated as pregnancy weight prior delivery minus pre-pregnancy weight, kg), maternal passive smoking (whether or not lived with a smoker during pregnancy), parity, and gestational age of newborn (weeks).

Statistical Analysis

We used descriptive statistics to report maternal and neonatal characteristics (mean and standard deviation for continuous variables, number (%) for categorical variables). We used multivariable linear regression models to examine the associations between main exposures and outcomes. We examined residuals graphically after fitting linear regression models to check for nonlinear associations and found evidence that linear models were adequate. We considered a range of potential covariates and used change-in-estimate criterion to detect covariates which could be included in the multivariable linear regression models. Finally, we involved components of the perinatal score (with the exception of birth weight) used to determine eligibility of the infant for inclusion in the study: maternal age, neonatal gender,

season of birth (March-April, May-July, and August-February), duration of second stage of labor and intention to breast feed, and maternal education (as a proxy for maternal nutritional status and indicator of social economic status), parity, maternal pre-pregnancy BMI (kg/m^2), total pregnancy weight change (kg), maternal prenatal cigarette smoking (yes/no, except when smoking was the main exposure), maternal prenatal alcohol consumption (yes/no, except when alcohol consumption was the main exposure) and gestational age (weeks) in the multivariable linear regression models for all three outcomes (placenta-to-birth weight ratio, placental weight and birth weight). We tested for possible interactions between smoking and alcohol consumption during pregnancy with the composite eligibility score and found no indication of any interaction ($P>0.40$). All statistical analyses were performed using Stata for Windows software (Version 11.1; StataCorp LP College Station, TX USA). We considered results for statistical analyses and interaction tests as significant if $P<0.05$.

RESULTS

Table 1 shows the characteristics of the study population. Birth weight data was available for all 7945 children whilst placental weight was available for 98.6%. Over half of the women (54%) had smoked and about one third (34%) had consumed alcohol at some time during pregnancy. The average maternal pre-pregnancy BMI was $23.29 kg/m^2$ (SD 4.80) which was within the healthy range ($20–24.99 kg/m^2$) and the average total pregnancy weight change was 14.30kg (SD 6.59) which is considered to be an adequate weight gain for those with pre-pregnancy BMI between 18.5 to $24.9 kg/m^2$ [17]. Mean birth weight was 3384.78g (SD 603.20) and mean placental weight was 637.04g (SD 154.16). The status of more than half of the placentas (55%) was classified as normal at delivery.

Table 2 shows the association of specific risk factors with the placental-to-birth weight ratio, placental weight and birth weight respectively. The placental-to-birth weight ratio of infants born to mothers who smoked at any stage during their pregnancy was 6.77g/kg significantly higher (95% CI 4.83 to 8.71) than neonates of mothers who did not smoke. Maternal alcohol consumption during pregnancy was associated with a statistically significant smaller placental-to-birth weight ratio (β=−2.07g/kg; 95% CI −4.01 to −0.12) when compared to mothers who did not consume any alcohol. Other statistically significant factors associated with higher placenta-to-birth weight ratios were parity and pre-pregnancy BMI, whilst smaller ratios were associated with maternal and gestational age respectively.

Consistent with previous knowledge, the birth weight of neonates born to mothers who smoked was significantly lower (β= −205.49g; 95% CI −232.91 to −178.08) when compared to non-smoking mothers, whilst maternal prenatal smoking was also associated with a significant reduction in placental weight but the magnitude of the reduction was much smaller (β= −15.37g; 95% CI -23.43 to −7.31) than for birth weight. The linear regression model that included placental weight accounted for 20% of the variation in birth weight (β= 2.06; 95% CI 1.98 to 2.13, R^2 value changed from 0.45 to 0.65 after adding placental weight in the model; data not shown). Alcohol consumption and placental weight were negatively associated but the association did not reach statistical significance. Birth weight on the other

hand, was positively associated with alcohol consumption but again did not reach statistical significance.

We examined the possible interactive effects of maternal prenatal smoking and alcohol consumption on birth weight, placental weight and the placental weight to birth weight ratio but no interaction was observed (P=0.94, 0.76 and 0.87, respectively. data not shown).

We further examined the associations between timing and amount of prenatal smoking and any alcohol consumption during pregnancy on the placenta-to-birth weight ratio and the placental and birth weights respectively (Table 3). Compared to mothers who did not smoke, in any trimester an increase in the number of cigarettes smoked in that trimester was associated with a statistically significant higher placenta-to-birth weight ratio ($P<0.001$). The greatest increase was found in those who smoked 21 or more cigarettes particularly during the second trimester (β=10.59 g/kg; 95% CI 7.18 to 14.01) however estimates were similar across trimesters. Consuming alcohol during the first two trimesters of pregnancy was associated with a modest but significantly smaller placenta-to-birth weight ratio (β= −2.60 g/kg, −2.13 g/kg respectively).

The association between placental weight and the amount of smoking was found to be negative across all trimesters however, this was statistically significant in trimesters one and three for mothers who smoked <21 cigarettes per day and in trimester two for mothers who smoked between 11–20 cigarettes per day. Neonates born to smoking mothers had placental weights that ranged from 5.14g to 18.83g lighter than non-smoking mothers. Consistent with current knowledge, we were able to show that regardless of amount, smoking during pregnancy had a very strong negative association with birth weight. The magnitude of the estimate was slightly lower for mothers who smoked between 1–10 cigarettes per day during pregnancy but was similar across the trimesters for amounts greater than10 cigarettes per day (β ranged from −180.83g to −233.33g). Alcohol consumption during pregnancy was negatively associated with placental weight but positively associated with birth weight although these associations were not statistically significant.

In sensitivity analysis that included only women with placentas classified as ‘normal’ at delivery, we examined whether the state of the placenta played a significant role in the reported associations of smoking and alcohol consumption with relative placental weight. The directions of the associations for the placenta-to-birth weight ratio, the placental weight and birth weight were similar to those reported in Table 3 (data not shown).

DISCUSSION

In this large cohort of mothers and offspring, we found that maternal prenatal cigarette smoking was strongly associated with a significantly larger placenta-to-birth weight ratio, smaller placental weight and significantly lower birth weight. The magnitude of the association for the placenta-to-birth weight ratio was similar across trimesters with the largest effect observed in mothers who smoked 21 or more cigarettes per day. Maternal prenatal alcohol consumption had a relatively small but significant effect on reducing the

placenta-to-birth weight ratio. There was however, no evidence for an association of alcohol consumption with placental or birth weight.

Our findings in relation to smoking and the placenta-to-birth weight ratio is consistent with a previous study conducted by *Williams et al* [8]. Such findings appeared to support the hypothesis that smoking produces a direct effect on placenta structure and function, resulting in a decrease in vascularisation that may lead to fetal hypoxia and consequently result in a reduction in both absolute placental and fetus weight. In turn, poorer function may cause the placenta to grow relative to fetal weight so that it can provide more nutrition and oxygen to the fetus [18, 19].

The association between maternal prenatal cigarette smoking and low birth weight has been well established in epidemiological studies [20–26]. However, there is limited evidence regarding the association between smoking and placental weight, although the available evidence supports the inference that there is a negative association [8–11, 27]. Of the five previous studies that have examined the association between smoking and placental weight, four studies reported a negative association [9–11, 27], although only one reached statistical significance [27]. The lack of statistical evidence may be partly due to selection bias, insufficient power resulting from small sample size or relatively low prevalence of smoking among pregnant mothers in the study population.

Findings from our study showed that the association between an increase in the number of cigarettes smoked and lower placental weight was statistically significant. Such a negative association is consistent with morphological research on human placentas showing smoking during pregnancy could affect placental cell proliferation and differentiation and increase the rate of placental cell death [21, 28].

Several studies have consistently found that maternal prenatal alcohol consumption was negatively associated with birth weight [29, 30]. While, few studies have examined the association between alcohol consumption and placental weight and function and there is currently inconsistent evidence to indicate whether such an association actually exists. One study found no effect of maternal alcohol consumption during pregnancy on placental weight [9]. Another study conducted among women in an alcohol treatment program reported a decreased placental weight in regular users of alcohol during pregnancy based on univariate analysis [31]. In our multivariable analysis, we found significantly negative associations of maternal prenatal alcohol consumption with placenta-to-birth weight ratio. However, the associations with birth weight and placental weight did not reach statistical significance. This lack of statistical significance may partly reflect a lack of heterogeneity of alcohol exposure in our sample.

Whilst the exact mechanisms underlying alcohol-induced placental and fetal damage have not been fully delineated, it is well established that alcohol passes freely through the placenta to the fetus. In a review article on the human placenta, *Burd et al* concluded that maternal alcohol consumption impaired placental growth, resulted in vasoconstriction and increased perfusion pressure [32]. For the unborn child, alcohol affects how the placenta transfers important nutrients for growth and interferes with the ability of the fetus to receive

sufficient oxygen and nourishment. In addition, studies have suggested that prenatal alcohol consumption disrupts the normal functioning of both the maternal and the fetal endocrine systems and may disturb the normal maternal-fetal endocrine balance [33]. Such effects of alcohol could in part explain the smaller placenta-to-birth weight ratio.

Our study has several strengths. First, it involved a large sample size and relatively high prevalence of mothers who reported prenatal cigarette smoking to increase statistical power. Second, data for maternal smoking has been validated in a subset of the cohort using urinary cotinine assays [34]. Third, we were able to adjust for covariates relating to maternal adiposity and parity which were associated with birth weight.

The limitations of our study should also be considered. First, our cohort was recruited on the basis of specific eligibility criteria which make the results less generalizable to a general population. However, other data that have been examined indicate that results from this sample reflect population-wide changes [35]. In addition, we have adjusted for most factors used to select the participants, although we could not completely rule out the possibility of residual selection bias. Second, the information of the length of the cord trimmed before the placenta was weighed is not available and it may result in some measurement error in placental weight. However, such error is likely to be non-differential to the factors studied and thus may only lead the associations to null if it exists. Nevertheless, the mean placental weight in our study is similar to another study also conducted in Australia [8]. Third, as data on the number of cigarettes smoked was collected as an interval, we were unable to fully explore the possibility of a dose-dependent association between the number of cigarettes smoked and the magnitude of change in the placenta-to-birth weight ratio. Forth, our data on alcohol intake is relatively low, with only 3% of mothers consuming more than one alcoholic drink per day, which could partly be explained by under-reporting, a common phenomenon in alcohol assessment [36]. Fifth, we had no data on placental microstructure or nutrient transport function to fully elucidate the underlying mechanism.

Our findings showed that cigarette smoking and alcohol consumption during pregnancy affect the placenta-to-birth weight ratio in opposing ways with smoking being associated with a larger ratio whilst alcohol with a smaller ratio. This may reflect a difference in the mechanisms by which each exposure influences fetal growth either directly or indirectly by altering the development, structure and function of the placenta. Further prospective studies and experimental studies are needed to elucidate the role of *in utero* influences such as smoking and alcohol consumption on the development and function of the placenta and consequently the health and viability of the fetus.

Acknowledgments

We thank the staff involved in the fieldwork of the TIHS. We especially thank all the participants in this study who made this investigation possible. The TIHS was funded by the National Health and Medical Research Council of Australia, US National Institutes of Health (grant 001 HD28979-01A1), Tasmanian State Government, Australian Rotary Health Research Fund, Sudden Infant Death Syndrome Research Foundation, National Sudden Infant Death Syndrome Council of Australia, Community Organisations' support programme of the Department of Human Services and Health, Zonta International, Wyeth Pharmaceuticals, and Tasmanian Sanatoria After-Care Association. NW is supported by the ‘Laurie Cox’ Fellowship. CS is supported by the Australian National Health and Medical Research Council Early Career Public Health Fellowship (1013538). GT, CS, AP, ALP, and TD are supported by the Victorian Government’s Operational Infrastructure Support Program.

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Highlights

- We explore the effect of maternal lifestyle exposures on the placenta-to-birth weight ratio.
- We use data for 7945 term singletons from the Tasmanian Infant Health Survey; a cohort study.
- Maternal prenatal smoking strongly increases the placenta-to-birth weight ratio.
- Maternal prenatal alcohol consumption decreases the placenta–to-birth weight ratio.
- The in *utero* influences of smoke and alcohol affect placenta and fetal growth in differing ways.

Table 1

Maternal and neonatal characteristics of participants of the TIHS cohort included in the analysis [a]

Maternal characteristics	N=7945	Range
Age, years	23.25±4.11	13.39 to 44.75
Education		
Primary school	1548 (20)	
High school	4934 (62)	
Completed secondary	1048 (13)	
Tertiary	358 (4.5)	
Parity		
First born	3628 (46)	
Second born	2659 (34)	
Third born	1152 (15)	
Forth born	362 (4.6)	
Fifth^{+} born	133 (1.7)	
Any cigarette smoking during pregnancy (yes, no)	4282 (54)	
1st trimester		
Nil	3796 (48)	
1–10 cigarettes/day	1739 (22)	
11–20 cigarettes/day	1659 (21)	
21^{+} cigarettes/day	666 (9.0)	
2nd trimester		
Nil	4047 (51)	
1–10 cigarettes/day	1609 (20)	
11–20 cigarettes/day	1597(20)	
21^{+} cigarettes/day	677 (9.0)	
3rd trimester		
Nil	4084 (51)	
1–10 cigarettes/day	1587 (20)	
11–20 cigarettes/day	1512 (19)	
21^{+} cigarettes/day	748 (10)	
Any alcohol consumption during pregnancy (yes, no)	2662 (34)	
1st trimester	2286 (29)	
2nd trimester	2092 (26)	
3rd trimester	2054 (26)	
Pre-pregnancy BMI, kg/m^2	23.29±4.80	13.87 to 52.16
Pregnancy weight change, kg	14.30±6.59	−23 to 45
Neonatal Characteristics		
Gender, male	5815 (73)	
Gestational age, weeks	39.64±1.25	37 to 44
Birth weight, grams	3384.78±603.20	1470 to 5845

Maternal characteristics	**N=7945**	**Range**
Placental weight, grams	637.04±154.16	175 to 1400
Placenta-to-birth weight ratio, g/kg	188.63± 33.88	69.07 to 392.67
Placental status		
Normal	4311 (55)	
Incomplete	429 (5.5)	
Infarction	138 (1.8)	
Other status (post mature, clots on maternal side and other abnormality)	2940 (38)	

[a]Characteristics reported as: mean ± standard deviation for continuous variables and number (%) for categorical variables

Table 2

Factors associated with the placenta-to-birth weight ratio, placental weight and birth weight

Factors	Placenta-to-birth weight ratio (g/kg) β (95% CI)[b]	Placental weight (g) β (95% CI) [b]	Birth weight (g) β (95% CI) [b]
Maternal age, years	−0.48 (−0.75, −0.21)*	−8.52 (−9.65, −7.39)**	−35.68 (−39.51, −31.85)**
Maternal education	−0.39 (−1.74, 0.96)	6.03 (0.43, 11.64)*	41.94 (22.95, 60.93)**
Parity	1.36 (0.18, 2.55)*	26.39 (21.48, 31.31)**	119.19 (102.51, 135.87)**
Any prenatal cigarette smoking (yes, no)	6.77 (4.83, 8.71)**	−15.37 (−23.43, −7.31)**	−205.49 (−232.91, −178.08)**
Any prenatal alcohol consumption (yes, no)	−2.07 (−4.01, −0.12)*	−4.09 (−12.14, 3.96)	14.32 (−12.99, 41.63)
Pre-pregnancy BMI, kg/m^2	0.71 (0.50, 0.91)**	7.14 (6.30, 7.97)**	25.03 (22.20, 27.85)**
Total pregnancy weight change, kg	−0.07 (−0.21, 0.08)	3.70 (3.09, 4.31)**	21.04 (18.95, 23.13)**
Gender of infant, female	1.75 (−0.42, 3.92)	−58.63 (−67.63, −49.62)**	−339.97 (−370.55, −309.39)**
Gestational age, weeks	−3.34 (−4.10, −2.58)**	23.47 (20.31, 26.63)**	181.46 (170.73, 192.18)**

[b] β-coefficient and 95% confidence interval for linear regression model adjusted for components of perinatal score except for birth weight (maternal age, neonatal gender, season of birth, duration of second stage labor and intention to breast feed), maternal education, infant parity, maternal pre-pregnancy BMI, total pregnancy weight change, any prenatal cigarette smoking, any prenatal alcohol consumption, and gestational age.

* $P<0.05$,

** $P<0.001$

Placenta. Author manuscript; available in PMC 2015 July 01.

Table 3

Role of maternal cigarette smoking and alcohol consumption during pregnancy on the placenta-to-birth weight ratio, placental weight and birth weight

Factors	Placenta-to-birth weight ratio (g/kg) β (95% CI)[C]	Placental weight (g) β (95% CI)[C]	Birth weight (g) β (95% CI)[C]
1st trimester			
Smoking			
Nil	Ref	Ref	Ref
1–10 cigarettes/day	4.84 (2.55, 7.12)**	−15.19 (−24.84, −5.54)*	−180.83 (−214.32, −147.34)**
11–20 cigarettes/day	7.40 (4.99, 9.80)**	−16.40 (−26.58, −6.23)*	−226.14 (−261.37, −190.92)**
21+ cigarettes/day	8.64 (5.34, 11.94)**	−13.09 (−27.05, 0.87)	−231.66 (−280.05, −183.28)**
Any alcohol consumption (yes, no)	−2.60 (−4.49, −0.70)*	−5.77 (−13.80, 2.26)	8.19 (−19.62, 36.01)
2nd trimester			
Smoking			
Nil	Ref	Ref	Ref
1–10 cigarettes/day	7.41 (5.09, 9.74)**	−9.18 (−19.04, 0.67)	−196.76 (−230.90, −162.63)**
11–20 cigarettes/day	7.24 (4.81, 9.67)**	−18.83 (−29.15, −8.50)**	−233.04 (−268.59, −197.50)**
21+ cigarettes/day	10.59 (7.18, 14.01)**	−5.37 (−19.88, 9.13)	−233.33 (−283.41, −183.26)**
Any alcohol consumption (yes, no)	−2.13 (−4.08, −0.19)*	−4.39 (−12.61, 3.83)	13.00 (−15.46, 41.46)
3rd trimester			
Smoking			
Nil	Ref	Ref	Ref
1–10 cigarettes/day	7.73 (5.39, 10.06)**	−11.26 (−21.17, −1.35)*	−211.65 (−245.92, −177.38)**
11–20 cigarettes/day	7.93 (5.46, 10.40)**	−14.21 (−24.73, −3.68)*	−222.23 (−258.42, −186.03)**
21+ cigarettes/day	9.81 (6.54, 13.07)**	−5.14 (−19.00, 8.72)	−222.55 (−270.38, −174.72)**
Any alcohol consumption (yes, no)	−0.56 (−1.21, 0.09)	−1.77 (−4.52, 0.97)	0.31 (−9.18, 9.81)

[C]β-coefficient and 95% confidence interval for linear regression model adjusted for components of perinatal score except for birth weight (maternal age, neonatal gender, season of birth, duration of second stage labor and intention to breast feed), maternal education, infant parity, maternal pre-pregnancy BMI, total pregnancy weight change, any prenatal cigarette smoking (except when smoking was the main exposure), any prenatal alcohol consumption (except when alcohol consumption was the main exposure), and gestational age.

*$P<0.05$,

** $P<0.001$