

Prenatal exposure to alcohol, and gender differences on child mental health at age seven years

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ABSTRACT

Background It remains uncertain whether exposure to lower doses of alcohol is damaging to the developing fetus. The present study aimed to investigate associations for boys and girls between prenatal exposure to binge drinking and lower doses of alcohol in pregnancy, and parent-reported behavioural and emotional development at age seven.

Methods This study used data from the Danish National Birth Cohort. Associations between cumulated alcohol exposure and binge drinking from full pregnancy and parent scores on the Strengths and Difficulties Questionnaire (SDQ) measured at age seven were investigated. The SDQ was used as continuous externalising/internalising scores, and as above/below cut-off for the specific scales of hyperactivity/inattention, conduct, emotional and peer problems. Inclusion criteria were information on alcohol exposure from three interviews, SDQ scores at age seven and being born full term (n=37 152).

Results Controlling for relevant confounders, small positive associations were observed between binge drinking and internalising (relative change in mean: 1.04–1.06), externalising scores (relative change in mean: 1.01–1.07), and conduct scores (OR 1.12 to 1.23) for boys. No associations were observed with lower doses of alcohol.

Conclusions Exposure to binge drinking is weakly associated with impaired behavioural and emotional development measured at age seven. Large differences in background characteristics were observed between the groups defined by cumulated alcohol exposure, leaving the interpretations of findings uncertain.

INTRODUCTION

Today it is recognised that prenatal exposure to large amounts of alcohol can have long-term adverse neurobehavioural consequences for the child. At the extreme end, fetal alcohol syndrome, caused by exposure to excessive amounts of alcohol in pregnancy, is characterised by growth retardation, facial abnormalities and dysfunctions of the central nervous system (CNS).¹ Evidence of CNS impairments caused by small to moderate levels of alcohol in humans, that is, <1 unit/day, has however, been less conclusive.^{2–3} Some studies have suggested subtle neuropsychological deficits later in life,^{4–6} others have not.^{7–8} Animal studies have been somewhat more conclusive and have largely found negative associations with learning, memory and social behaviour later in life.^{9–10} Most human studies concerned with alcohol intake in pregnancy distinguish between average alcohol intake (ie, low/moderate/high doses as described above) and binge drinking (most often defined as an intake of

minimum five units of alcohol on a single occasion) and the latter is generally considered to be more devastating for the developing CNS. Results from human binge-drinking studies have found negative effects on neurodevelopment including specific psychiatric disorders,¹¹ hyperactivity and inattention,¹² and IQ and delinquent behaviour,¹³ whereas others have not.^{7–8} Animal studies concerned with binge-like exposures have largely focused on brain development, and have found associations with Purkinje cell loss,¹⁴ vulnerability of developing white matter¹⁵ and neuronal reduction in the frontal cortex,¹⁶ and West and colleagues concluded that patterns of alcohol consumption that produce high blood alcohol concentration, such as binge drinking, is especially harmful to the brain of the developing fetus.¹⁷

Prenatal and postnatal brain development in males and females has been observed in animal studies to follow a somewhat different trajectory, despite no obvious anatomical differences.^{18–19} In humans, gender differences are found regarding psychopathological prevalence rates,¹⁹ different ages of onset,¹⁹ and differences in responses to psychotropic medication.¹⁹ Despite these differences, few human studies have investigated gender-specific effects of prenatal exposure to alcohol. One study concluded that exposure to <1 unit/week in early pregnancy was associated with later mental health problems in girls, but not in boys.⁵ However, another study inferred that girls as well as boys born to mothers who drank up to 1–2 drinks per week during pregnancy were not at increased risk of clinically relevant behavioural difficulties at age five compared with non-exposed children.²⁰ The aim of the present study is to investigate association between exposure to total amount of alcohol and binge drinking in full pregnancy, irrespective of the timing of the exposure, and parent-rated child behavioural and emotional development at age seven. These associations were investigated separately for boys and girls.

METHODS

Sample

Data are derived from the population-based Danish National Birth Cohort (DNBC) that comprises information on 100 418 pregnancies. The intention of the DNBC was to investigate potential associations between diverse exposures early in life and the health and development of the children from a life-course perspective.²¹ Between 1996 and 2002, pregnant women were enrolled in the cohort nationwide at their first antenatal visit. The women were approached twice in pregnancy at approximately weeks 16 and 30 and again at 6 months

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postpartum. When the offspring reached the age of seven a questionnaire regarding the child's health and development was sent to the mother. The data collection and analyses of data were, according to Danish legislation, approved by the regional ethical committee and the Data Protection Agency, respectively.

Restriction of sample

The sample for the present study was restricted to women with full information on key alcohol (average alcohol intake and binge drinking) and Strengths and Difficulties Questionnaire (SDQ) variables (hyperactivity/inattention, conduct, emotional and peer problems) and to live-born, term singletons, that is, gestational age of ≥ 37 completed weeks. This left a total of 37 152 mother-child dyads in the study.

Prenatal alcohol exposure

Alcohol exposure was assessed at three points in time from maternal self-reports: approximately in week 16 concerning pre-pregnancy and early pregnancy intake, approximately in week 30 regarding intake in the middle part of pregnancy, and 6 months postpartum concerning alcohol intake in the last part of pregnancy. The women answered separate questions regarding their weekly average intake of alcohol (beer, wine and spirits) and binge episodes, defined as an intake of five or more units of alcohol on a single occasion. Because the focus was to investigate possible associations on behavioural and emotional development with total exposure to alcohol throughout pregnancy, a single value for the cumulated intake of alcoholic drinks across the entire pregnancy was summed (figure 1). This was done by multiplying the reported intake from each interview with the number of weeks between each interview. Because the focus was to evaluate potential associations with very low exposures (ie, down to >0 –5 units of alcohol throughout pregnancy) it was decided not to divide the summed total by actual number of weeks of pregnancy. The following categories were adopted: 0, >0 –5, >5 –15, >15 –45, >45 –90 and >90 weeks. Because the >15 –45-week group was the largest, it was chosen as the reference group. When a woman reported occasions of binge drinking she was asked about the number of such episodes. The women were grouped as follows: 0, 1, 2–3, 4+ binge episodes during pregnancy.

Outcome measure: parent-rated SDQ

The parent version of the SDQ contains 25 items concerned with five domains of psychological adjustment: *hyperactivity/inattention*, *conduct*, *emotional*, *peer problems* and *prosocial behaviours*. Each item is scored on a 3-point Likert scale: 'not true', 'somewhat true' and 'certainly true' yielding scores between 0 and 2 for each question.^{22–24} Because the aim was to identify problem behaviours, the prosocial scale was not used. The problem scales were used as four separate scale models (ie, *hyperactivity/inattention*, *conduct*, *emotional* and *peer problems*) and as a broader model of *externalising* and *internalising* scales (combining the *hyperactivity/inattention* and *conduct* scales and the *emotional* and *peer problem* scales, respectively). The four-scale model used to identify children above 10% clinical cut-off, whereas, the two-scale model was used to

investigate mean differences between exposure groups. Both models have in the literature been found to have equally good model fits as tested by confirmatory factor analysis.²⁵ The following gender-specific cut-offs were adapted: hyperactivity/inattention (≥ 7 for boys and ≥ 6 for girls), emotional (≥ 5 for boys and girls), peer problems (≥ 3 for boys and girls) and conduct problems scores (≥ 4 for boys and girls).²⁶

Confounding factors

The following covariates were statistically controlled for: maternal cumulated smoking in pregnancy (0, >0 –100, >100 –300, >300 cigarettes); paternal smoking (yes/no), maternal and paternal education (9 years or less, 10–12 years, 13 years or more); maternal and paternal past history of psychiatric diagnosis (yes/no); and maternal well-being in pregnancy (good/somewhat good/severe problems). The maternal smoking variable was cumulated in the same way as the cumulated alcohol exposure variable (figure 1). Information on past psychiatric history and education came from the Danish registers, and the remaining variables from the structured interviews.

Statistical analyses

All analyses were carried out using SAS V9.2. The overall aim was to investigate possible associations between prenatal exposure to alcohol and parent-rated SDQ scores at age seven. The first aim was to thoroughly describe the background characteristics of the mothers in relation to their alcohol intake during pregnancy. Second, multivariate linear regressions were used to model prenatal exposure to low/moderate doses of alcohol and binge drinking and associations with continuous *externalising* and *internalising* SDQ scores. Because the distributions of SDQ scores have been found to be positively skewed²⁷ these scores were log-transformed and the outcomes thus reflect a relative change in mean. The four dichotomised problem scales (*hyperactivity/inattention*, *conduct*, *emotional* and *peer problems*) were assessed using logistic regression models with appropriate cut-offs identifying the 10% of the sample with the highest problems scores.²⁶ It was a priori decided to carry out all analyses separately for boys and girls.

To test the robustness of the results when making minor changes to the analytical strategy, we conducted the following analyses: (1) All analyses were rerun using early pregnancy exposure only. (2) Combined cumulated alcohol and binge exposure categories were constructed and all analyses were rerun with this compound exposure variable. (3) All analyses were rerun excluding the all-time abstaining women from the analyses. (4) All analyses were rerun including children born before 37 full gestational weeks. (5) All analyses were rerun excluding siblings from the analyses.

RESULTS

Background characteristics

Cumulated alcohol intake

Abstainers (0 alcoholic drinks in pregnancy) and high intakers (>90 alcoholic drinks in pregnancy) distinguish themselves from the women with a low-to-moderate intake on most characteristics (table 1). The abstainers were younger, had high

Figure 1 Timeline showing the period of which information from each interview was used.

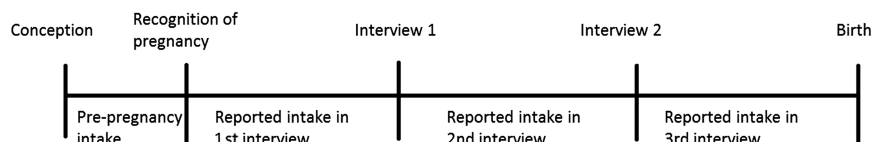


Table 1 Background characteristics across levels of cumulated exposure to alcohol and binge drinking episodes

Alcohol group n	Full sample 37 152	Cumulated alcohol exposure (total number of alcohol-containing units in entire pregnancy)						Binge drinking (number of binge episodes in entire pregnancy)			
		0 3910	>0–5 6739	>5–15 7156	>15–45 9929	>45–90 6091	>90 3327	0 25 692	1 6833	2–3 3779	4+ 848
Age (M)*	30.7	29.7	29.9	30.4	30.8	31.4	32.7	30.8	30.3	30.4	31.1
Age (P)*	32.5	31.6	31.6	32.1	32.4	33.2	34.7	32.6	32.0	32.1	33.0
Unplanned pregnancy† (%)	22.1	24.3	19.7	21.4	21.3	23.9	24.9	19.4	25.4	31.1	36.2
Time to pregnancy‡ (%)	26.4	28.1	27.9	26.9	25.1	25.2	26.4	27.0	25.9	23.7	24.9
Fertility treatment§ (%)	5.7	5.6	6.5	6.2	5.3	5.6	5.0	7.0	3.3	2.4	1.9
Married (no)¶ (%)	2.0	3.3	1.9	2.1	1.6	1.7	2.2	1.7	1.9	3.0	6.4
<i>Education (%)</i>											
Mandatory (M)**	6.8	14.6	8.4	6.5	4.7	4.7	5.4	7.0	6.1	6.5	8.1
University (M)**	15.8	6.8	11.6	14.1	17.6	21.1	22.9	15.1	16.5	18.8	16.9
Mandatory (P)**	12.2	20.9	14.2	12.2	10.0	9.2	10.0	12.4	11.3	11.9	14.0
University (P)**	16.4	7.8	12.7	15.3	18.1	21.0	22.5	16.0	17.2	17.5	17.2
<i>Contact with psychiatric system (%)</i>											
Prepregnancy (M)††	2.5	4.0	2.9	2.1	2.1	2.3	2.4	2.4	2.2	3.1	4.0
Prepregnancy (P)††	1.7	2.5	1.9	1.6	1.3	1.6	1.9	1.6	1.9	1.9	2.4
<i>Maternal lifestyle factors in pregnancy</i>											
Binge drinking‡‡ (%)	30.9	10.1	19.3	28.1	34.3	42.7	52.7	0	100	100	100
Cumulated alcohol intake §§ (%)	33.2	0	2.7	9.8	28.5	64.6	140.8	27	38	55	93
Cumulated smoking ¶¶ (%)	53 (22.8)	85 (28.1)	54 (21.5)	51 (21.2)	43 (20.3)	46 (23.3)	67 (28.8)	47 (18.9)	59 (27.8)	74 (34.7)	122 (47.5)
Partner smoking*** (%)	27.8	34.8	27.5	27.1	25.5	26.6	30.2	26.2	29.7	32.0	39.2
Coffee† (%)††	41.4	31.9	30.6	26.9	43.0	51.3	63.7	40.0	42.3	45.0	56.5
Vitamins*** (%)	84.9	83.1	85.9	86.5	85.1	84.3	81.9	85.2	84.7	84.6	80.2
Fish oil*** (%)	4.9	4.7	4.9	5.0	4.6	4.8	5.4	4.8	4.8	5.1	6.0
Fish eating (never)*** (%)	3.2	6.5	4.1	3.1	2.5	1.9	1.5	3.2	3.0	3.0	2.6
BMI‡‡‡ (%)	30.3	41.1	35.2	31.4	27.9	24.7	22.6	31.2	28.7	28.2	25.1
Cola§§§ (%)	15.1	23.2	16.2	15.0	13.4	12.7	13.4	15.0	15.3	15.7	16.3, NS
TV¶¶¶ (%)	20.0	27.7	23.4	20.4	18.3	16.6	14.8	19.3	20.8	22.6	25.2
Tenant**** (%)	25.7	28.6	26.6	26.6	25.0	25.2	22.1	23.8	28.5	31.9	34.4
Exercise†††† (%)	25.7	18.6	22.7	25.3	27.6	29.5	28.1	24.9	26.5	29.2	26.4
<i>Child characteristics</i>											
Sex (boys) (%)	51.0	51.4	50.6	51.7	50.9	50.7	50.9	51.2	50.8	50.1	50.7
Birth weight‡‡‡‡ (%)	3654	3636	3660	3656	3655	3658	3643	3659	3651	3632	3596
SGA (%)	8.6	9.2	8.7	8.5	8.2	8.0	9.8	8.3	9.0	9.3	12.2
GA	281.5	280.6	281.3	281.3	281.6	282.0	282.6	281.3	281.9	282.0	282.6
Psychiatric diagnosis§§§§ (%)	1.3	1.6	1.3	1.4	0.8	1.1	1.2	1.3	1.0	1.4	1.5

Virtually all intergroup differences are statistically significant at $p > 0.0001$ level and thus not reported in the table.

*Age at birth.

†Fully or partly unplanned pregnancy.

‡Time to pregnancy (≥ 6 months).

§Fertility treatment—yes.

¶Married or cohabiting with the child's biological father 6 months postpartum.

**Register-based information on educational level in year 2010.

††Register-based information on contact with the psychiatric system.

‡‡Binge drinking—yes.

§§Maternal cumulated alcohol intake in pregnancy.

¶¶Cumulated smoking in pregnancy (smoking in pregnancy—yes).

***Maternal intake of alcohol in the last part of pregnancy.

†††Maternal intake of coffee in pregnancy—yes.

‡‡‡Prepregnant BMI outside normal range. BMI normal range: 18.5–24.99.

§§§Intake of ≥ 1 L of cola per week.

¶¶¶Television watching ≥ 2 h/day in the last part of pregnancy.

****Tenant, homeless or live with parents.

††††Maternal exercise in last part of pregnancy.

‡‡‡‡Birth weight in grams.

§§§§Child contact with the psychiatric system before the age of seven.

BMI, Body Mass Index; SGA, small for gestational age; GA, gestational age; M, maternal; P, paternal.

frequencies on psychiatric variables, more likely to drink cola, watch television, smoke cigarettes, have a prepregnancy Body Mass Index (BMI) outside the normal range and they were the least educated. Of the otherwise abstainers, 10.1% reported at least one binge episode in pregnancy. Because of the large

sample size, highly statistically significant differences ($p > 0.0001$) were observed for virtually all variables and are thus not reported here.

The women with the highest alcohol intake (>90 drinks) were the oldest, the most well educated, most likely to drink

coffee and do exercise. They had high smoking frequencies, but were the least likely to watch television, drink cola and have a prepregnancy BMI outside the normal range; 52.7% reported binge drinking in pregnancy. The frequencies for the low-to-moderate exposure groups were generally in-between these two extreme groups and appeared rather similar on most characteristics.

Binge drinking

The women in the four binge-drinking groups did not differ as markedly as the cumulated alcohol exposure groups. However, the 4+ binge group did stand: they were more likely to have been in contact with the psychiatric system, to smoke, drink coffee and alcohol, but less likely to have a prepregnancy BMI outside the normal range. All four binge groups had similar educational levels. Statistical differences were observed between the binge exposure groups, however, not on as many variables and not as highly significant as the cumulated exposure groups.

Prenatal alcohol exposure and continuous scores

From the adjusted model, no associations were observed between low/moderate doses of alcohol in pregnancy and the parent-rated SDQ *externalising* and *internalising* scores at age seven (table 2). However, an apparent protective association was found for the high-exposure group (>90). Small, but statistically significant, elevated risks were found between binge drinking and *internalising* (relative change in mean: 1.03–1.07) and

externalising scores (relative change in mean: 1.01–1.07) for boys. No associations were observed for girls.

Prenatal alcohol exposure and above cut-off SDQ scores

Cumulated alcohol exposure

From the adjusted model, no overall association with any of the four problem scales appear (*hyperactivity/inattention*, *conduct*, *emotional* and *peer problems*) (table 3). However, few significant associations opposite to the expected direction were present for the abstaining (0) group for boys: *peer problems* (OR 1.21 (CI 1.03 to 1.43)); and for girls: for *conduct* (OR: 1.17 (CI 1.00 to 1.37)), and *peer problems* (OR: 1.40 (CI 1.15 to 1.71)), and for the high-exposure group (>90) for boys for *hyperactivity/inattention* (OR: 0.79 (CI 0.65 to 0.96)) and *emotional* (OR: 0.71 (CI 0.59 to 0.85)), and for girls *emotional* (OR: 0.82 (CI 0.69 to 0.98)).

Binge drinking

From the adjusted model in table 3 it appears that binge drinking, overall, was associated with above clinical cut-off conduct scores (OR: 1.12 to 1.23) but only for boys. No dose-response effects were present, that is, no increased OR was found with increased exposure to binge episodes. No associations were observed for girls.

Sensitivity analyses

Alcohol consumption, in the literature, is most often defined from early pregnancy intake only. In order to make the analyses

Table 2 Relative change in mean between cumulated alcohol exposure and binge drinking in pregnancy, and continuous SDQ externalising and internalising scores at age seven

Exposure categories	Boys		Girls	
	Unadjusted Univariable relative change in mean	Adjusted Multivariable relative change in mean (95% CI)	Unadjusted Univariable relative change in mean	Adjusted Multivariable relative change in mean (95% CI)
SDQ externalising scores at age seven and cumulated alcohol exposure in full pregnancy				
0	1.10	1.02 (0.98 to 1.06)	1.06	0.99 (0.95 to 1.03)
>0–5	1.01	0.98 (0.95 to 1.01)	1.00	0.97 (0.94 to 1.01)
>5–15	1.00	0.98 (0.95 to 1.01)	0.99	0.97 (0.94 to 1.00)
>15–45	1	1	1	1
>45–90	0.98	0.98 (0.95 to 1.02)	0.97	0.98 (0.94 to 1.01)
>90+	0.95	0.95 (0.91 to 0.99)	1.00	0.99 (0.95 to 1.04)
SDQ internalising scores at age seven and cumulated alcohol exposure in full pregnancy				
0	1.08	1.03 (0.99 to 1.08)	1.09	1.03 (0.98 to 1.07)
>0–5	1.04	1.02 (0.98 to 1.06)	1.01	0.99 (0.96 to 1.03)
>5–15	1.03	1.02 (0.99 to 1.06)	1.02	1.01 (0.97 to 1.04)
>15–45	1	1	1	1
>45–90	0.99	0.99 (0.96 to 1.03)	0.96	0.97 (0.94 to 1.01)
>90+	0.93	0.92 (0.88 to 0.97)	0.97	0.97 (0.92 to 1.01)
SDQ externalising scores at age seven and binge drinking exposure in full pregnancy				
0	1	1	1	1
1	1.04	1.04 (1.01 to 1.07)	1.02	1.02 (0.99 to 1.05)
2–3	1.08	1.07 (1.04 to 1.11)	1.03	1.03 (0.99 to 1.07)
4+	1.05	1.01 (0.94 to 1.09)	1.10	1.07 (0.99 to 1.15)
SDQ internalising scores at age seven and binge drinking exposure in full pregnancy				
0	1	1	1	1
1	1.03	1.04 (1.00 to 1.07)	1.01	1.01 (0.98 to 1.04)
2–3	1.04	1.04 (1.00 to 1.08)	1.00	1.01 (0.97 to 1.05)
4+	1.08	1.06 (0.98 to 1.15)	1.01	0.97 (0.90 to 1.05)

Adjusted model; adjusted for the following confounders: parental smoking, parental education, parental prepregnancy psychiatric diagnoses and maternal psychological well-being in pregnancy.
SDQ, Strengths and Difficulties Questionnaire.

Table 3 Cumulated alcohol exposure and binge drinking in pregnancy and SDQ hyperactivity/inattention, conduct, emotional and peer problem scores above clinical cut-off at age seven

Exposure categories	Boys		Girls	
	Unadjusted Univariable OR	Adjusted Multivariable OR (95% CI)	Unadjusted Univariable OR	Adjusted Multivariable OR (95% CI)
SDQ hyperactivity/inattention scores at age seven and cumulated alcohol exposure in full pregnancy				
0	1.42	1.13 (0.96 to 1.32)	1.39	1.12 (0.95 to 1.32)
>0–5	1.10	1.02 (0.88 to 1.17)	1.05	0.97 (0.84 to 1.12)
>5–15	0.98	0.94 (0.81 to 1.08)	0.93	0.89 (0.76 to 1.03)
>15–45	1	1	1	1
>45–90	1.02	1.05 (0.90 to 1.21)	0.83	0.84 (0.71 to 0.98)
>90+	0.80	0.79 (0.65 to 0.96)	0.99	0.94 (0.78 to 1.14)
SDQ conduct scores at age seven and cumulated alcohol exposure in full pregnancy				
0	1.34	1.08 (0.94 to 1.24)	1.47	1.17 (1.00 to 1.37)
>0–5	1.14	1.05 (0.93 to 1.18)	1.02	0.93 (0.81 to 1.07)
>5–15	0.96	0.89 (0.79 to 1.01)	0.92	0.87 (0.76 to 1.00)
>15–45	1	1	1	1
>45–90	1.03	1.06 (0.94 to 1.20)	1.02	1.05 (0.91 to 1.20)
>90+	0.88	0.86 (0.73 to 1.02)	0.89	0.89 (0.74 to 1.06)
SDQ emotional scores at age seven and cumulated alcohol exposure in full pregnancy				
0	1.24	1.08 (0.93 to 1.25)	1.10	0.96 (0.82 to 1.12)
>0–5	1.15	1.08 (0.95 to 1.23)	1.04	0.99 (0.87 to 1.13)
>5–15	1.12	1.10 (0.97 to 1.25)	0.98	0.96 (0.84 to 1.09)
>15–45	1	1	1	1
>45–90	0.94	0.95 (0.83 to 1.09)	0.84	0.86 (0.75 to 0.99)
>90+	0.73	0.71 (0.59 to 0.85)	0.82	0.82 (0.69 to 0.98)
SDQ peer problems scores at age seven and cumulated alcohol exposure in full pregnancy				
0	1.45	1.21 (1.03 to 1.43)	1.75	1.40 (1.15 to 1.71)
>0–5	1.11	1.05 (0.90 to 1.21)	1.11	1.01 (0.84 to 1.21)
>5–15	1.04	1.00 (0.86 to 1.15)	1.11	1.05 (0.87 to 1.26)
>15–45	1	1	1	1
>45–90	0.89	0.91 (0.78 to 1.06)	1.02	1.04 (0.85 to 1.26)
>90+	0.93	0.92 (0.76 to 1.12)	0.89	0.83 (0.64 to 1.07)
SDQ hyperactivity/inattention scores at age seven and binge drinking exposure in full pregnancy				
0	1	1	1	1
1	1.15	1.16 (1.02 to 1.30)	1.11	1.11 (0.98 to 1.25)
2–3	1.16	1.16 (0.99 to 1.35)	1.21	1.14 (0.97 to 1.33)
4+	1.18	1.06 (0.77 to 1.43)	1.32	1.14 (0.83 to 1.54)
SDQ conduct scores at age seven and binge drinking exposure in full pregnancy				
0	1	1	1	1
1	1.11	1.14 (1.03 to 1.27)	0.94	0.93 (0.82 to 1.05)
2–3	1.22	1.23 (1.08 to 1.40)	0.95	0.93 (0.80 to 1.09)
4+	1.20	1.12 (0.86 to 1.45)	1.02	0.89 (0.65 to 1.21)
SDQ emotional scores at age seven and binge drinking exposure in full pregnancy				
0	1	1	1	1
1	1.18	1.17 (1.05 to 1.31)	1.12	1.11 (0.99 to 1.24)
2–3	1.11	1.10 (0.96 to 1.27)	1.08	1.13 (0.98 to 1.30)
4+	1.33	1.20 (0.90 to 1.56)	1.03	0.90 (0.66 to 1.21)
SDQ peer problem scores at age seven and binge drinking exposure in full pregnancy				
0	1	1	1	1
1	1.03	1.07 (0.94 to 1.21)	1.11	1.14 (0.98 to 1.32)
2–3	1.12	1.15 (0.98 to 1.35)	1.07	0.98 (0.80 to 1.20)
4+	1.15	1.11 (0.80 to 1.50)	1.13	0.93 (0.60 to 1.38)

Adjusted model; adjusted for the following confounders: parental smoking, parental education, parental past history of contact with psychiatric system and maternal well-being in pregnancy.

SDQ, Strengths and Difficulties Questionnaire.

from the present study comparable with the remaining literature, the analyses were replicated with average alcohol intake in the early part of pregnancy as the exposure variable. The total sample added up to 37 152 pregnancies and was defined as

follows: 0, >0–2, >2–4 and >4 units/week. The results of the analyses for the average alcohol intake in early part of pregnancy revealed significant associations for boys opposite to the expected direction, that is, the higher the intake the lower score

Table 4 Relative change in mean between cumulated alcohol exposure and binge drinking in early part of pregnancy, and continuous SDQ externalising and internalising scores at age seven

Exposure categories	Boys		Girls	
	Unadjusted Univariable relative change in mean	Adjusted Multivariable relative change in mean (95% CI)	Unadjusted Univariable relative change in mean	Adjusted Multivariable relative change in mean (95% CI)
SDQ externalising scores at age seven and average alcohol intake in early part of pregnancy				
0	1	1	1	1
>0–2	0.96	0.98 (0.96 to 1.00)	0.98	1.00 (0.98 to 1.02)
>2–4	0.94	0.96 (0.91 to 1.01)	1.00	1.01 (0.96 to 1.07)
>4+	1.04	1.00 (0.90 to 1.11)	1.14	1.07 (0.96 to 1–20)
SDQ internalising scores at age seven and average alcohol intake in early part of pregnancy				
0	1	1	1	1
>0–2	0.94	0.95 (0.92 to 0.97)	0.96	0.98 (0.96 to 1.00)
>2–4	0.89	0.90 (0.85 to 0.95)	0.94	0.97 (0.91 to 1.02)
>4+	0.87	0.85 (0.75 to 0.95)	0.98	0.94 (0.84 to 1.05)
SDQ externalising scores at age seven and binge drinking exposure in early part of pregnancy				
0	1	1	1	1
1	1.04	1.04 (1.01 to 1.07)	1.00	1.02 (0.99 to 1.05)
2–3	1.05	1.05 (1.00 to 1.09)	1.02	1.02 (0.98 to 1.07)
4+	1.04	0.96 (0.88 to 1.06)	1.03	1.09 (0.99 to 1.19)
SDQ internalising scores at age seven and binge drinking exposure in early part of pregnancy				
0	1	1	1	1
1	1.04	1.04 (1.01 to 1.08)	1.00	1.01 (0.98 to 1.04)
2–3	1.05	1.06 (1.01 to 1.11)	1.02	1.04 (0.99 to 1.08)
4+	1.04	1.02 (0.93 to 1.13)	1.03	1.01 (0.91 to 1.11)

Adjusted model; adjusted for the following confounders: parental smoking, parental education, parental prepregnancy psychiatric diagnoses, and maternal psychological well-being in pregnancy.
SDQ, Strengths and Difficulties Questionnaire.

with *internalising* (table 4) and *emotional* scores (table 5). The binge-drinking variable was defined as 0, 1, 2–3 and 4 episodes in the early part of pregnancy, and these subanalyses revealed no consistent significant associations with any of the outcomes. However, significant associations were observed in the expected direction for boys for the 1 and 2–3 exposure groups *externalising* and *internalising* scores (table 4). No associations were observed for girls.

The cumulated alcohol estimates and the number of binge episodes were combined appropriately into six exposure groups (n=37 152) and the analyses were rerun with this combined measure as the exposure variable. The analyses of the combined alcohol measure revealed no associations with the SDQ internalising and externalising scores. For the four problem scales, the high-exposure group almost consistently had the most extreme estimates, but in the expected and unexpected directions.

The analyses were further rerun where all-time abstainers were excluded from the analyses, and where exposure was defined from first early pregnancy intake only (n=32 733). No important differences were found between these analyses and the analyses excluding prepregnancy abstaining women. Likewise, the analyses were rerun including non-term-born babies (n=38 421), and rerun excluding siblings from the analyses (n=35 635). These results were all virtually identical to the main analyses presented above.

DISCUSSION

After controlling for a wide range of confounding factors, the main analyses revealed statistically significant, positive associations between exposure to binge drinking in pregnancy and internalising, externalising and conduct scores at age seven for boys, but not for girls. The findings are somewhat contradictory

to another study that inferred that prenatal exposure to alcohol is more damaging to girls.⁵ However, these authors actually hypothesised that any associations would be more readily detectable in boys, and further concluded that their finding might be chance.⁵ Another study investigating associations between exposure to smoking in pregnancy and conduct disorder in childhood, did find associations for boys only.²⁸ Thus, it may be that the brain development trajectory for boys is somewhat more vulnerable to prenatal exposures than girls.^{18 19}

No associations were observed between lower doses of alcohol and any of the outcomes. On the contrary, the main analyses revealed the poorest mental health outcomes for children of abstainers, but most advanced outcomes for children of the high intakers. Very large differences on background characteristics were observed between the groups defined on the basis of cumulated alcohol exposure. The high intakers were older, and much more well educated than the abstainers who were the least educated, the ones with the highest frequencies of mental disorders and poorest lifestyles habits. These characteristics may well be mentally protective for the high-exposed children but disadvantageous for the unexposed children.^{29 30} The expectedly large positive impact of the home environments of the well educated may mask the potential small negative effects of being exposed to low doses of alcohol. This has similarly been inferred in a study by Kelly where the odds of behavioural problems in children of never drinkers were similar to those of children exposed to high levels.²⁰ For the binge groups, the distribution of covariates were less variable, and the results will, all other things being equal, be less confounded.

The sensitivity analyses defining alcohol exposure from early pregnancy, rather than full pregnancy, revealed a linear trend in the opposite of expected direction for *internalising* scores, that

Table 5 Average alcohol exposure and binge drinking in early part of pregnancy and SDQ hyperactivity/inattention, conduct, emotional and peer problem scores above clinical cut-off at age seven

	Boys		Girls	
	Unadjusted Univariable OR	Model 1 Multivariable OR (95% CI)	Unadjusted Univariable OR	Model 1 Multivariable OR (95% CI)
SDQ hyperactivity/inattention scores at age seven and average alcohol intake in early part of pregnancy				
0	1	1	1	1
>0–2	0.86	0.91 (0.82 to 1.00)	0.89	0.94 (0.85 to 1.04)
>2–4	0.81	0.84 (0.66 to 0.95)	0.94	0.99 (0.78 to 1.25)
>4+	1.04	0.94 (0.59 to 1.44)	1.24	1.02 (0.63 to 1.58)
SDQ conduct scores at age seven and average alcohol intake in early part of pregnancy				
0	1	1	1	1
>0–2	0.87	0.93 (0.86 to 1.01)	0.90	0.97 (0.88 to 1.06)
>2–4	0.88	0.92 (0.75 to 1.12)	0.74	0.80 (0.62 to 1.01)
>4+	1.29	1.22 (0.84 to 1.73)	1.44	1.33 (0.87 to 1.96)
SDQ emotional scores at age seven and average alcohol intake in early part of pregnancy				
0	1	1	1	1
>0–2	0.80	0.83 (0.76 to 0.91)	0.88	0.92 (0.84 to 1.00)
>2–4	0.68	0.71 (0.56 to 0.88)	0.78	0.81 (0.64 to 1.01)
>4+	0.59	0.56 (0.33 to 0.99)	1.05	0.94 (0.60 to 1.42)
SDQ peer problems scores at age seven and average alcohol intake in early part of pregnancy				
0	1	1	1	1
>0–2	0.80	0.84 (0.76 to 0.93)	0.86	0.93 (0.82 to 1.06)
>2–4	0.73	0.75 (0.58 to 0.96)	0.83	0.92 (0.67 to 1.23)
>4+	0.91	0.87 (0.53 to 1.37)	1.32	1.10 (0.61 to 1.84)
SDQ hyperactivity/inattention scores at age seven and binge drinking exposure in early part of pregnancy				
0	1	1	1	1
1	1.12	1.13 (1.00 to 1.28)	1.11	1.11 (0.98 to 1.26)
2–3	1.06	1.07 (0.89 to 1.28)	1.17	1.11 (0.92 to 1.33)
4+	0.99	0.80 (0.51 to 1.21)	1.22	1.12 (0.74 to 1.63)
SDQ conduct scores at age seven and binge drinking exposure in early part of pregnancy				
0	1	1	1	1
1	1.07	1.10 (0.99 to 1.23)	0.96	0.96 (0.84 to 1.08)
2–3	1.13	1.16 (0.99 to 1.35)	0.92	0.91 (0.75 to 1.08)
4+	1.08	1.02 (0.72 to 1.43)	1.08	0.99 (0.67 to 1.43)
SDQ emotional scores at age seven and binge drinking exposure in early part of pregnancy				
0	1	1	1	1
1	1.15	1.15 (1.02 to 1.29)	1.09	1.10 (0.98 to 1.24)
2–3	1.14	1.16 (0.98 to 1.36)	1.15	1.21 (1.03 to 1.41)
4+	1.26	1.17 (0.82 to 1.64)	1.28	1.13 (0.78 to 1.59)
SDQ peer problem scores at age seven and binge drinking exposure in early part of pregnancy				
0	1	1	1	1
1	1.03	1.07 (0.94 to 1.22)	1.02	1.07 (0.91 to 1.26)
2–3	1.10	1.18 (0.98 to 1.41)	1.01	0.97 (0.76 to 1.22)
4+	0.93	0.84 (0.53 to 1.28)	1.30	1.13 (0.68 to 1.77)

Adjusted model; adjusted for the following confounders: parental smoking, parental education, parental past history of contact with psychiatric system and maternal well-being in pregnancy.

SDQ, Strengths and Difficulties Questionnaire.

is, the higher average intake, the lower (and thus more favourable) scores. Two explanations could account for these differences. The first is, that the differences are real because early pregnancy exposure and full pregnancy exposure are associated with different observable behaviours at age seven. Another possible explanation is that the results are due to unmeasured and residual confounding. Large intergroup differences in characteristics were observed for the groups defined on the basis of full pregnancy exposure on key covariates, for example, age, education, psychiatric difficulties and lifestyle factors. It is very likely that the pattern in covariates observed on the basis of full pregnancy exposure (as reported in table 1) and the pattern that

would be observed for the groups defined on the basis of early pregnancy exposure differs. One study did report large differences on lifestyle and sociodemographic factors of women who binge drank before and after they become aware of their pregnancy.³¹ In other words, the characteristics, along with other unmeasured confounding variables such as IQ, attachment style and personality could be mentally protective for the high-exposed children, but disadvantageous for the unexposed children. It is today well known that the quality of the mother–child relationship has lasting consequences for a wide range of developmental cognitive and mental health outcomes.³² Infants who develop a secure attachment style have a better emotional

regulation, higher self-esteem, and develop more coping skills that, in turn, makes them better able to handle stressful or challenging situations and lowers the risk for poorer mental health outcomes later in life. On the other hand, insecurely attached children are at greater risk for poor mental health outcomes.^{32 33} Thus, different home environments create different conditions for the developing brain. Because the home environment has such great impact on brain development, a potential damaging effect of being exposed to a small amount of alcohol is masked. Further, because the distribution of covariates in the binge-exposure groups were less variable compared to the cumulated alcohol-exposure groups, less confounding will mask potential associations in the binge-exposure groups.

Strengths and limitations

The tremendous size of the sample and the use of well-established outcome measure are obvious advantages of the present study. Also, exposure from full pregnancy was used, rather than just from early pregnancy. The construction of the cumulated alcohol measure can, on the other hand, also be considered a limitation as it may include some misclassification. However, the strong linear trends for many of the covariates validate the method. The use of self-reported alcohol intake, as well as SDQ outcome measures, can also be considered a limitation, and we cannot rule out interdependence between these self-reported measures. Finally, the timing of the exposure has been ignored in the present study. Other studies have demonstrated that ignoring this factor can mask potential associations of low and moderate prenatal alcohol exposure and fetal effects.³⁴

What is known on this subject

Prenatal exposure to high levels of alcohol is known to be associated with childhood mental health problems. Evidence of mental health problems caused by small to moderate levels of alcohol has, however been less conclusive.

What this study adds

Binge drinking is weakly associated with behavioural and emotional development at age seven. Large differences in background characteristics were observed between the groups defined by cumulated alcohol exposure, that is, low-moderate doses of alcohol, leaving these interpretations of findings uncertain.

Contributors JN: JN conceptualised and designed the study, carried out the initial analyses, drafted the initial manuscript, approved the final manuscript as submitted, and is the guarantor of the paper. A-MNA: AMNA coordinated and supervised data collection, helped with the analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. TWT: TWT helped with the analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. KS-L: KSLA helped with the analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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REFERENCES

- 1 Calhoun F, Warren K. Fetal alcohol syndrome: historical perspectives. *Neurosci Biobehav Rev* 2007;31:168–71.
- 2 Gray R, Henderson J. Review of the fetal effects of prenatal alcohol exposure. National Perinatal Epidemiology Unit, University of Oxford, 2007.
- 3 Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. *BJOG* 2007;114:243–52.
- 4 Kapil Sayal, Jon Heron, Jean Golding, *et al.* Prenatal alcohol exposure and gender differences in childhood mental health problems: a longitudinal population-based study. *Pediatrics* 2007;119:426–34.
- 5 Sayal K, Heron J, Golding J, *et al.* Prenatal alcohol exposure and gender differences in childhood mental health problems: a longitudinal population-based study. *Pediatrics* 2007;119:e426–34.
- 6 Jacobson JL, Jacobson SW. Effects of prenatal alcohol exposure on child development. *Alcohol Res Health* 2002;26:282–6.
- 7 Skogerbo A, Kesmodel US, Wimberley T, *et al.* The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on executive function in 5-year-old children. *BJOG* 2012;119:1201–10.
- 8 Underbjerg M, Kesmodel US, Landro NI, *et al.* The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on selective and sustained attention in 5-year-old children. *BJOG* 2012;119:1211–21.
- 9 Schneider ML, Moore CF, Adkins MM. The effects of prenatal alcohol exposure on behavior: rodent and primate studies. *Neuropsychol Rev* 2011;21:186–203.
- 10 Valenzuela CF, Morton RA, Diaz MR, *et al.* Does moderate drinking harm the fetal brain? Insights from animal models. *Trends Neurosci* 2012;35:284–92.
- 11 Barr HM, Bookstein FL, O'Malley KD, *et al.* Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring. *Am J Psychiatry* 2006;163:1061–5.
- 12 Sayal K, Heron J, Golding J, *et al.* Binge pattern of alcohol consumption during pregnancy and childhood mental health outcomes: longitudinal population-based study. *Pediatrics* 2009;123:e289–96.
- 13 Bailey BN, Aney-Black V, Covington CY, *et al.* Prenatal exposure to binge drinking and cognitive and behavioral outcomes at age 7 years. *Am J Obstet Gynecol* 2004;191:1037–43.
- 14 Idrus NM, Napper RM. Acute and long-term Purkinje cell loss following a single ethanol binge during the early third trimester equivalent in the rat. *Alcohol Clin Exp Res* 2012;36:1365–73.
- 15 Watari H, Born DE, Gleason CA. Effects of first trimester binge alcohol exposure on developing white matter in fetal sheep. *Pediatr Res* 2006;59(4 Pt 1):560–4.
- 16 Burke MW, Palmour RM, Ervin FR, *et al.* Neuronal reduction in frontal cortex of primates after prenatal alcohol exposure. *Neuroreport* 2009;20:13–17.
- 17 West JR, Goodlett CR, Bonthius DJ, *et al.* Manipulating peak blood alcohol concentrations in neonatal rats: review of an animal model for alcohol-related developmental effects. *Neurotoxicology* 1989;10:347–65.
- 18 Goodlett CR, Johnson TB. Temporal windows of vulnerability within the third trimester equivalent: why "knowing when" matters. In: Hannigan JH, Goodlett CR, Spear LP, Spear NE, eds. *Alcohol and alcoholism: effects on brain and development*. Mahwah, NJ: L. Erlbaum Associates, 1999:59–91.
- 19 Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev* 2003;27:3–18.
- 20 Kelly YJ, Sacker A, Gray R, *et al.* Light drinking during pregnancy: still no increased risk for socioemotional difficulties or cognitive deficits at 5 years of age? *J Epidemiol Community Health* 2012;66:41–8.
- 21 Olsen J, Melbye M, Olsen SF, *et al.* The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health* 2001;29:300–7.
- 22 Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry* 1997;38:581–6.
- 23 Goodman R, Scott S. Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: is small beautiful? *J Abnorm Child Psychol* 1999;27:17–24.
- 24 Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry* 2001;40:1337–45.

- 25 Niclasen J, Skovgaard AM, Andersen AM, *et al.* A confirmatory approach to examining the factor structure of the Strengths and Difficulties Questionnaire (SDQ): a large scale cohort study. *J Abnorm Child Psychol* 2013;41:355–65.
- 26 Niclasen J. SDQ Danish cut off scores: 5–7-year-olds. 18-12-2012. Ref Type: Internet Communication
- 27 Niclasen J, Teasdale TW, Andersen AM, *et al.* Psychometric properties of the Danish strength and difficulties questionnaire: the SDQ assessed for more than 70,000 raters in four different cohorts. *PLoS One* 2012;7:e32025.
- 28 Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Arch Gen Psychiatry* 1998; 55:721–7.
- 29 Levitt P. Structural and functional maturation of the developing primate brain. *J Pediatr* 2003;143(4 suppl):S35–S45.
- 30 Sroufe LA. Attachment and development: a prospective, longitudinal study from birth to adulthood. *Attach Hum Dev* 2005;7:349–67.
- 31 Strandberg-Larsen K, Rod NN, Nybo Andersen AM, *et al.* Characteristics of women who binge drink before and after they become aware of their pregnancy. *Eur J Epidemiol* 2008;23:565–72.
- 32 Bowlby J. Research into the origins of delinquent behaviour. *Br Med J* 1950;1:570–3.
- 33 Ainsworth MD, Bell SM. Attachment, exploration, and separation: illustrated by the behavior of one-year-olds in a strange situation. *Child Dev* 1970;41:49–67.
- 34 O'Leary CM, Bower C, Zubrick SR, *et al.* A new method of prenatal alcohol classification accounting for dose, pattern and timing of exposure: improving our ability to examine fetal effects from low to moderate alcohol. *J Epidemiol Community Health* 2010;64:956–62.

Corrections

Niclasen J, Nybo Andersen AM, Teasdale TW, *et al.* Prenatal exposure to alcohol, and gender differences on child mental health at age seven years. *J Epidemiol Community Health* 2014;**68**:224–32. The first author's name was published incorrectly as J Niclasen. The correct name should be Janni Niclasen.



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