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The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on executive function in 5-year-old children

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Abstract

Objective—To examine the effects of low to moderate maternal alcohol consumption and binge drinking in early pregnancy on children's executive functions at the age of 5 years.

Design—Follow-up study.

Setting—Neuropsychological testing in four Danish cities 2003–2008.

Population—A cohort of 1628 women and their children sampled from the Danish National Birth Cohort.

Methods—Participants were sampled based on maternal alcohol drinking patterns during early pregnancy. When the children were 5 years old, the parent and teacher forms of the Behaviour

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The findings and conclusions in this report are those of the author(s), and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure of interests
None to declare.

Contribution to authorship
USK, JB, NIL, and ELM contributed to the design of the Lifestyle During Pregnancy Study. ÅS wrote the first draft of the article, and TW and HS were responsible for the statistical analyses. All authors contributed to the interpretation of the results, and provided critical comments and revisions of the article.

Details of ethics approval
The study was approved by the DNBC Board of Directors, the DNBC Steering Committee, the regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS.

Rating Inventory of Executive Function (BRIEF) were completed by the mothers and a preschool teacher. Parental education, maternal IQ, prenatal maternal smoking, the child's age at testing, and the child's gender were considered core confounding factors. The full model also included maternal binge drinking or low to moderate alcohol consumption, maternal age, parity, maternal marital status, family home environment, postnatal parental smoking, pre-pregnancy maternal body mass index (BMI), and the health status of the child.

Main outcome measures—The BRIEF parent and teacher forms.

Results—Adjusted for all potential confounding factors, no statistically significant associations between maternal low to moderate average weekly consumption and BRIEF index scores were observed. In adjusted analyses, binge drinking in gestational week 9 or later was significantly associated with elevated Behavioural Regulation Index parent scores (OR 2.04, 95% CI 0.33–3.76), and with the risk of high scores on the Metacognitive Index assessed by the teacher (OR 2.06, 95% CI 1.01–4.23).

Conclusions—This study did not observe significant effects of low to moderate alcohol consumption during pregnancy on executive functioning at the age of 5 years. Furthermore, only weak and no consistent associations between maternal binge drinking and executive functions were observed.

Keywords

Behaviour rating inventory of executive function; binge drinking; BRIEF; executive functions; low to moderate alcohol consumption; neurodevelopmental effects; prenatal exposure

Introduction

The cognitive-behavioural effects of prenatal exposure to heavy maternal alcohol consumption are well documented.[1,2] Much less is known about the effects of low to moderate consumption during pregnancy.[3,4] As a substantial number of pregnant women drink at low to moderate levels during pregnancy, any evidence of effects on child development is important from both a clinical and a public health perspective.

Studies of low to moderate levels of maternal alcohol consumption have not provided consistent evidence concerning adverse effects. Short-term outcomes like miscarriage, stillbirth, intrauterine growth restriction, and prematurity have been shown to be associated with prenatal exposure to alcohol.[4] However, few studies of neurodevelopmental outcomes are available, even though it is possible that light maternal consumption is associated with functional and perhaps subclinical neurodevelopmental deficits. Of the few available studies addressing such long-term effects, mixed results have been obtained for global measures, such as IQ.[5–9] Studies of more specific skills suggest that exposure to moderate to heavy maternal consumption may be associated with dysfunctions in the speed and efficiency of information processing,[10] deficits in attention,[8–11] learning and working memory,[12,13] as well as executive functions.[14]

Binge drinking during pregnancy is a consumption pattern that few studies have investigated systematically.[4,15] Animal models have shown that ingesting a given dose of alcohol within

a short time period may be associated with more severe neuronal and behavioural impairment than an equal dose ingested over a longer time period.[16] In human studies, prenatal binge drinking has been associated with low verbal IQ, learning problems, poorer school performance, and an increase in delinquent behaviour, as assessed by both parents and teachers.[7,17–19]

Executive functions are defined as higher-order psychological abilities involved in goal-oriented behaviour, under conscious control.[20] Executive functions comprise several cognitive processes, including planning, organisation, and measures of self-control. Executive functions are thought to be primarily mediated by the frontal lobe of the brain.[14] Whereas some executive function abilities do not develop fully until adulthood,[21] important gains in executive functions occur between the ages of 2 and 5 years.[11] They are among the most complex cognitive functions, and may therefore be sensitive to low or moderate levels of exposure to alcohol. Deficits in executive functioning have been found consistently for children with higher levels of prenatal alcohol exposure,[14,22,23] but no previous studies have investigated associations between these functions and low to moderate prenatal alcohol exposure. Only a few, small studies have explored the effects of binge drinking on executive function and found binge drinking to be predictive of deficits in executive function in early childhood.[11,14–16]

The aim of the present study was to analyse the potential effects of low to moderate weekly alcohol consumption and binge drinking during early pregnancy on children's executive function at the age of 5 years.

Methods

Study sample

This study formed part of the Lifestyle During Pregnancy Study (LDPS), which has been described in detail elsewhere.[24] Briefly, the study is a prospective follow-up study based on a sample from the Danish National Birth Cohort (DNBC).[25] The DNBC contains information on 101,042 women and their children. Women in the DNBC were recruited in 1997–2003 at their first antenatal visit to a general practitioner (which is routinely the first contact a pregnant woman has with a healthcare practitioner). Participating women represent 60% of those invited and approximately 30% of all pregnant women in Denmark during the enrollment period.[24]

Based on information on maternal alcohol consumption, 3478 mothers with singleton pregnancies and their children were sampled from DNBC participants and invited to a follow-up when the children were between 60 and 64 months of age. Women sampled on the basis of pre-pregnancy alcohol intake were not included in the analyses presented here (n = 289), leaving 3189 women invited, of whom 1628 (51%) mother and child pairs participated in the follow-up, and only these mother and child pairs were included in the analyses.[24] Valid information on binge drinking was missing for 11 of the 1628 mothers, and consequently binge drinking analyses were conducted on 1617 mothers and their children. Data collection for the follow-up took place from September 2003 to June 2008.

Exclusion criteria were: multiple pregnancies; an inability to speak Danish; impaired hearing or vision that was likely to compromise the child's ability to perform cognitive tests; and congenital disabilities implying or likely to imply mental retardation (e.g. trisomy 21 and infantile autism).

Exposure assessment

Information on alcohol intake during pregnancy was derived from the first prenatal DNBC interview.[25] For women participating in the follow-up, the median week of gestation for completing the interview was 17 weeks (range: 7–39 weeks), and 61.6% (n = 1002) completed the interview between 14 and 20 weeks of gestation. By week 20 of gestation, 75% of women had completed the interview. During the interview women were asked about the average number of beers, glasses of wine, and glasses of spirits they currently consumed during a week, and based on this information, the total number of weekly drinks was calculated. Information on binge drinking during pregnancy included data on the number of binge episodes (defined as an intake of five or more drinks on a single occasion) and the timing (gestational week) of these episodes. These alcohol exposure questions have been shown to yield valid estimates of alcohol consumption (relative to other methods) and reliable information among pregnant Danish women.[26–28] Some women reported one or more binge episodes during the early weeks of pregnancy, although their average number of drinks per week at the time of interview was zero. These women were classified accordingly as consuming zero drinks at the time of interview, but with one or more previous binge episodes. Our definition of a drink followed the definition from the Danish National Board of Health, with one standard drink being equal to 12 g of pure alcohol. For this study low drinking was defined as the consumption of between one and four drinks per week, and moderate drinking was defined as the consumption of between five and eight drinks per week.

All mothers were sampled in strata defined by their average alcohol intake (0, 1–4, 5–8, ≥9 drinks/week) and timing of binge episodes, defined as the consumption of five or more drinks on one occasion (gestational weeks 1–2, 3–4, 5–8, 9 or later). The higher exposure categories were oversampled in an effort to ensure that all exposure categories included enough children to attain sufficient statistical power.[24] For each sample stratum the sampling probability was computed as the ratio between the number of sampled women and the total number of women available in the corresponding DNBC stratum.

Outcome measures

The Behaviour Rating Inventory of Executive Function (BRIEF) is a questionnaire for parents and teachers/preschool teachers assessing behaviours indicative of executive function in the home and daycare environment.[29,30] The BRIEF aims to evaluate a child's executive functioning behaviours in real-world settings. It is designed for a broad range of children, aged 5–18 years. The parent and teacher forms of the BRIEF each contain 86 items with eight theoretically- and empirically-derived clinical scales that measure several aspects of executive functioning: inhibit; shift; emotional control; initiate; working memory; plan/organise; organisation of materials; and monitor. Two broader indexes, the Behavioural Regulation Index (BRI) and the Metacognition Index (MI), are derived from subsets of the

clinical scales, whereas an overall score, the Global Executive Composite (GEC), is a summary measure derived from all clinical scales.[29] The BRI includes subscales of inhibit (controls impulses), shift (transitions and solves problems flexibly and appropriately for a situation), and emotional control (monitors emotional responses appropriately). The MI includes initiates (begins tasks independently), working memory (maintains information in mind during tasks in order to complete task), plan/organise (plans behaviour to reach future goals and carries out steps in a systematic manner), organisation of materials (keeps possessions and work/play spaces orderly), and monitor (self-monitors work or behaviour during and after tasks).[20] GEC scores are presented elsewhere.[31]

A translated version of the BRIEF was used (Hogrefe Psychological Publishers) with minor adjustments for preschool children, as Danish children do not enter school at age 5 years, and the preschool version of the BRIEF was not available at the start of the project. The minor adjustments were approved by the developers of the BRIEF.

No Danish BRIEF norms were available at the time of the study, and consequently we constructed our own Danish norms using all data available to the LDPS. A normalizing *T*-score transformation for the observed BRIEF scores was computed, with higher scores indicating more severe executive function difficulties.[32] Abnormally elevated scores suggesting clinical significance are indicated by *T*-scores of 65 (cut-off) or higher, corresponding to scores at least 1.5 SD above the mean.[29] The BRIEF is a highly reliable instrument. For the three index scores, Cronbach's α, based on the full LDPS sample, was in the range of 0.91–0.96 and 0.84–0.94 for the parent and teacher versions of the questionnaire, respectively. Thus the internal consistency of all scales was high and supported by the fact that the item-total scale correlation was below 0.30 for only one item.

Assessment was conducted at four sites located in Copenhagen, Aarhus, Odense, and Aalborg. The assessment comprised a comprehensive neuropsychological test battery, which is described in detail elsewhere.[24] Procedures were standardised in detail and carried out by ten trained psychologists blinded to the child's exposure status. While the psychologists tested the children, mothers were given an adult IQ test, answered the BRIEF parent form, and completed a questionnaire on the child's postnatal health/development, as well as parental education and lifestyle. The BRIEF teacher form was mailed to the kindergarten a few weeks before the planned test date. The BRIEF teacher form is designed to be completed by any adult who has had extended contact with the child in the kindergarten, in most cases a trained teacher. Extended contact is defined as daily contact for at least 1 month.[29,30] The completed BRIEF teacher forms were returned to the LDPS research group by mail. A maximum of two reminders were mailed to the parents and/or daycare institutions if they did not respond to the initial letter.[24]

Covariates

The following covariates were obtained in the prenatal interview and subsequently coded as follows: parity (0, 1, 2+); prenatal smoking (yes/no); and maternal pre-pregnancy body mass index [BMI; weight in kg/(height in m)^2]. At the time of the 5-year follow-up, the following variables were recorded: maternal marital status (single at either the prenatal interview or follow-up/with partner at both times); parental education in years (total duration of

education averaged for both parents, or maternal education only if information on the father was missing); an index of the quality of the postnatal home environment (suboptimal in the presence of two or more of the following adverse conditions: living with only one biological parent; changes in primary care givers; daycare for more than 8 hours a day before the age of 3 years; ≥14 days of separation from parents; breakfast irregularity; maternal depression; and maternal/paternal alcohol intake above the official recommendations from the Danish National Board of Health of 14 drinks/week for non-pregnant women or 21 for men; otherwise normal); an index of the child's health status (suboptimal in the presence of any disabilities, illness/diseases, and/or medication that has the potential to influence test performance; otherwise normal).

Maternal age was obtained from the unique Danish personal identification number, as was the gender and age of the child. Birthweight in grams and gestational age in days were obtained from the Danish Medical Birth Registry. Maternal IQ was assessed at the follow-up. Two verbal subtests (information and vocabulary) from the Wechsler Adult Intelligence Scale (WAIS) were used to assess verbal IQ,[33] and Raven's Standardised Progressive Matrices provided non-verbal IQ.[34] Raw scores of each test were standardised based on the results from the full sample, and were weighted equally in a combined score that was restandardised to an IQ scale with a mean of 100 and standard deviation (SD) of 15.

Data analysis

The number of missing values for the covariates ranged from 1 to 33. For the BRIEF parent index scores and the GEC scores, information for three children was missing, whereas information was missing in the range of 213–219 children for the BRIEF teacher index and GEC scores. Multiple imputation was used based on the following two strategies: a dedicated model for imputations, where variables were modelled from other variables thought to be most predictive of each variable (the specific equations are available upon request); and a black-box strategy where all outcome, exposure, and other covariates were used to predict missing values. For both strategies 100 completed data sets were generated. Regardless of imputation strategy, the main conclusion was unaffected, and the point estimates of the exposure parameters never differed by more than 0.5–1.0% for the BRIEF parent form, and 14.5–22.5% for the teacher form, relative to the standard error. Essentially the same results were obtained when the strategy of complete case analysis was used (i.e. when only subjects with full information on the variables needed in any given analysis were included). We report the results of the dedicated imputation strategy in this paper. All imputations were implemented with the ICE add-on command,[35] and the built-in MI ESTIMATE command in STATA 11 (StataCorp LP, College Station, TX, USA).

Association between alcohol exposure categories and the continuous BRI, MI, and GEC outcome scores were estimated using multiple linear regression. In the analyses of maternal average alcohol consumption, binge drinking was included as a potential confounding factor (based on preliminary analyses coded as yes/no in the statistical analysis), whereas the maternal average number of drinks per week during pregnancy was included as a potential confounding factor in the analyses of effects of binge drinking (coded 0, 1–4, 5–8, ≥9 drinks/week). Separate analyses were performed for the effect of binge drinking as a

dichotomous variable (yes/no), number of binge episodes (continuous, coded as 0, 1, 2, ≥3), and timing of binge drinking (none, gestational weeks 1–2, 3–4, 5–8, ≥9, multiple timings). Parental education, maternal IQ, prenatal maternal smoking, the child's age at testing, and the child's gender were considered core confounding factors, and were included as covariates in a separate model. In addition, the final model included the following potential confounding factors: maternal binge drinking or maternal average consumption; maternal age; parity; maternal marital status; family home environment; postnatal parental smoking; pre-pregnancy maternal body mass index (BMI); and the health status of the child. Birthweight and gestational age were considered as potential mediators of the effect of alcohol exposure, and consequently were not included in the main analyses.

The clinical cut-off for the BRIEF is a *T*-score of 65 (1.5 SD above the mean), but for cognitive tests, 1 SD below the mean has been used as the cut-off for low scores in the LDPS. Consequently, supplementary logistic regression analyses for the two index scores and the GEC were conducted using the sample mean plus both 1 SD and 1.5 SD as cut-offs for potential deficits on the BRI, MI, and GEC, and using the category below the cut-off as the reference group. Very few children born to mothers that consumed ≥9 drinks per week scored above the cut-off, and consequently this group was collapsed with the group of mothers that consumed between 5–8 drinks per week in these analyses.

Potential interactions were tested in supplementary analyses: interactions between average consumption and binge drinking, as well as interactions of alcohol exposure variables with gender, parental education, and smoking during pregnancy. In addition, correlations between the BRI, MI, and GEC for the parent and the teacher forms, and correlations between the same scales, across the parent and teacher forms, were explored. Finally, *T*-scores on the clinical BRIEF scales were analysed using linear regression models adjusting for core and potential confounding factors.

All statistical analyses were conducted in STATA 11 (StataCorp LP, College Station, TX, USA), and weighted by sampling probabilities. All statistical tests were two-sided and determined significant at a level of 5%. All estimates are accompanied by 95% confidence intervals.

Results

Sample characteristics across levels of average maternal alcohol intake and number of binge episodes in pregnancy are presented elsewhere.[36,37] Notably, the women reporting no alcohol consumption during a typical week were significantly younger, and they were also significantly more likely to be primiparous, less likely to be smokers, and less likely to have suboptimal family/home conditions. Smoking and suboptimal family/home conditions were more frequent among women who consumed five or more drinks per week.[36] Women without binge drinking episodes were significantly older, less likely to be primiparous, had significantly higher BMIs, were less likely to be smokers, had a lower average alcohol intake, and had significantly lower IQ compared with bingers.[37] Binge drinking in gestational week 9 or later was associated with high maternal age, single mother status,

suboptimal home index, low education, low IQ, and pre- and postnatal smoking (data not shown). No substantial differences were seen between participants and nonparticipants.

Results for low-moderate alcohol intake

The results for the BRI and MI indexes are presented in Table 1. A statistically significant effect was observed for parent-rated MI in unadjusted and core confounding factor adjusted analyses. This effect was small (less than one-third SD), but indicated a significant increase in scores (i.e. lower executive functioning) for children of mothers consuming ≥9 drinks per week. The estimated increase remained unchanged, but became non-significant when adjusted for all potential confounding factors.

Supplementary logistic regression analyses of the dichotomised BRIEF scores showed no association with maternal alcohol consumption for cut-off at a *T*-score of 65 or at 1.5 SD above the mean. This was also the case for cut-off at a *T*-score of 60 (1.0 SD above the mean).

Supplementary analyses of the clinical parent and teacher scales showed no statistically significant association with alcohol exposure when adjusting for all potential confounding factors.

Tests of interactions of average alcohol consumption with prenatal maternal binge drinking, as well as interactions with gender, parental education, and smoking, were conducted. Only the interaction between level of education and average alcohol consumption on the teacher BRI ($P = 0.04$) was significant. Stratified analyses showed a non-significant trend towards lower BRI scores (and better executive functioning) for the children of mothers with a low level of education who consumed ≥9 drinks per week (data not shown).

Results for binge drinking

For mean BRI and MI scores and risk of high *T*-scores, we found no systematic or statistically significant associations between a dichotomised binge variable (data not shown) or number of binge episodes and executive function in any BRIEF index (Table 2). The number of binge episodes reported in early pregnancy did not vary with time of interview.

With respect to the timing of binge drinking, we found no association between binge drinking in gestational weeks 1–8 and BRIEF index scores (Table 2). However, binge drinking in gestational week 9 or later was associated with significantly increased means in unadjusted and adjusted analyses of parent BRI (adjusted increase 2.04, 95% CI 0.33–3.76). Results for the teacher version were not significant. For both the parent and teacher versions, the mean MI was significantly increased only in the unadjusted analyses, but not in any of the adjusted analyses.

The adjusted logistic regression analyses of the dichotomised BRIEF scores showed no significantly elevated risk of BRI parent or BRI teacher scores above the 1.5 SD cut-off. The dichotomised MI parent scores were unrelated to the timing of binge drinking, but for the MI teacher version a significantly elevated risk of scores above the cut-off was observed in both unadjusted and adjusted analyses of binge drinking in gestational week 9 or later (OR

2.06, 95% CI 1.01–4.23, with adjustment for potential confounding factors). No other significant associations between binge drinking and BRIEF scores above the cut-off were observed. Similar results were obtained for analyses based on the 1.0 SD above the mean cut-off.

Supplementary analyses were conducted on the BRIEF clinical scales. For the parent version, the clinical scales for inhibit and emotional control showed significantly elevated scores for children of women who reported binge drinking in gestational week 9 or later, even after adjustment for core and potential confounding factors. When adjusting for all potential confounding factors no other significant associations with binge drinking were observed for the clinical scales.

Tests of interactions of binge drinking with prenatal maternal average alcohol consumption, as well as with gender, parental education, and smoking, were not statistically significant.

Intercorrelations among BRIEF scores

Weighted correlations between BRI, MI, and GEC for teacher and parent versions were explored. For the BRIEF parent version, the correlation between BRI and MI was 0.78, the correlation between BRI and GEC was 0.92, and the correlation between MI and GEC was 0.96. For the BRIEF teacher version the correlation between BRI and MI was 0.78, the correlation between BRI and GEC was 0.92, and the correlation between MI and GEC was 0.96. Additionally, the correlations across the BRIEF parent and teacher versions for BRI, MI, and GEC were analysed. The correlation between BRI parent and BRI teacher was 0.28, the correlation for MI parent and MI teacher was 0.27, and the correlation for GEC parent and GEC teacher was 0.28.

Discussion

The present study examined the potential effects of low to moderate prenatal alcohol exposure and binge drinking on executive function of children at the age of 5 years. No statistically significant effects were found for low to moderate weekly consumption levels during early pregnancy. Children of mothers consuming moderately high levels of alcohol (i.e. ≥9 drinks/week) did show significantly increased parent-rated MI scores, indicating executive functioning difficulties. This finding was observed in both unadjusted and core confounding factor adjusted analyses. For binge drinking we found no consistent associations between binge drinking during early pregnancy and child executive function. There was a tendency towards elevated point estimates for the children of women reporting binge drinking in gestational week 9 or later, but the significance estimates varied between the parent and the teacher versions, and between the BRI and the MI scores.

Based on the LDPS sample, similar results have been observed for the GEC index, intelligence, and attention.[31,36,37] Furthermore, when the BRIEF results were analysed as a dichotomous variable, few statistically significant results were observed for the index scores or the clinical scales.

There are a number of previous reports of effects of heavy alcohol exposure on executive function and neurobehavioural outcomes,[14,22,23] but studies evaluating the effects of very low quantities of alcohol are rare. To our knowledge, none of the few studies available to date show any effects of very light or occasional drinking on executive function in children. A recent study examined the effects of very low quantities of alcohol in more than 11,000 5-year-old children, and found no significant effects on performance for three subscales of the British Ability Scale (which encompasses some aspects of executive functioning) among children exposed to six drinks or less per week, or among children exposed to binges of six or more drinks per occasion, compared with non-exposed children.[6] These results are consistent with the findings of the present study.

A possible limitation of our study is the age of the child at assessment. Although important development in executive function occurs between 2 and 5 years of age, adult-level abilities are only reached on some executive function tasks during adolescence.[21] Thus, it is possible that some long-term effects on executive functions can only be detected later in life. Although the BRIEF is a highly reliable instrument, the derived scores are based on possibly biased parent and teacher ratings, and it is a concern that the bivariate correlations between the corresponding index scores of the parent and teacher versions were low, in the range of 0.27–0.28. Thus, scores on the two versions of the BRIEF clearly reflect different aspects of the child's neurocognitive functioning.

As with all active participation studies, the potential differences between those who agreed to participate and those who did not must be considered. Although the 51% participation rate for this study is quite good for studies of this nature, the possibility remains that mothers of children who were not functioning at age level on executive functioning, or any other neurocognitive skill, might have been more likely to decline to participate. Finally, in studies with null effects, a lack of sufficient statistical power must be considered, especially when potential subtle effects are investigated. In this study, the groups with moderate consumption, of between 5–8 drinks per week, and with the consumption of ≥9 drinks per week may have been particularly under-powered by small sample sizes.

As with any study of teratogenic effects, limitations in exposure measurement must be acknowledged. In this study, information on average alcohol use reflects the specific time of enrollment into the DNBC (which varied from gestational week 7 to gestational week 39). Any interaction of timing with exposure, as well as with the specific neurodevelopmental skills of executive functioning, may have been diluted if either were sensitive to a specific time period in gestation, as reflected by the time of exposure interview. If, for example, the damaging effects of alcohol depend on the maximal blood concentration, the number and timing of binge drinking episodes would be only indirect estimates of such exposure. The blood concentration depends not only on the volume of alcohol consumed, but also on the duration of drinking as well as the blood volume and speed of enzymatic breakdown. Thus, our estimates of a relationship between binge drinking and executive function are likely to be conservative estimates of any associations. Furthermore, our results suggest that the damage caused by maternal binge drinking may depend on the timing of the alcohol intake, but no further stratification was possible from gestational week 9 onwards. If harmful effects of binge drinking occur mainly later in pregnancy (i.e. in the late second or third trimester),

when the growth and development of the central nervous system is rapid, our study could not assess such risk. Finally, for average consumption, the exposure represents the lower tail of the distribution for the low and moderate consumption categories, suggesting that these findings are more in line with occasional weekly drinking (of one or two drinks per week) or, at most, levels of less than one drink per day.

Even so, the LPDS has important strengths compared with many previous studies, in particular the large sample consisting of a relatively middle-class homogenous population of women who are generally not stigmatised for consuming small quantities of alcohol during pregnancy. In addition, the LPDS includes a wide range of potential confounding factors. None of the previous studies of alcohol and executive function adjusted for all of the confounding factors used in this study. In particular we controlled for maternal IQ and parental education, which are the most important confounding factors, leaving a high risk of substantial residual confounding in many previous studies.

In general, information bias, in particular misclassification because of under-reporting, is a possibility in all studies of alcohol consumption during pregnancy, as reliable biomarkers are currently not available. Compared with other studies, under-reporting in this study may be reduced, both because we used methods shown to yield valid and reliable information among Danish pregnant women,[15,26–28,38] and because the consumption of small quantities of alcohol during pregnancy was generally not considered to be problematic in Denmark during the time of data collection.

The lack of statistically significant findings suggests that any true effects of low to moderate alcohol consumption and maternal binge drinking on executive function may be subtle, and difficult to detect with current measures of neurodevelopment, such as the BRIEF. A null effect always raises the possibility that the study design and the chosen measures were not sensitive enough to detect a true effect. In spite of failing to detect consistent effects on executive functioning in this study, low and moderate maternal alcohol consumption and binge drinking may compromise other aspects of cognitive development. Despite the negative findings, additional large-scale studies (with concomitant statistical power) that further investigate the possible effects that minimal alcohol use during pregnancy may have on children are important from a public health perspective.

Even though this study observed no consistent effects of low to moderate levels of prenatal alcohol exposure on executive functioning at the age of 5 years, and only unsystematic and insignificant associations were found for binge drinking, alcohol is a known teratogen, and safe levels of alcohol use during pregnancy have not yet been established. Consequently, women should be advised that it is safest to abstain from using alcohol when pregnant. Concerns regarding the small quantities women may consume occasionally in social situations are best addressed with their primary health provider.

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Table 1

Associations between maternal low to moderate alcohol intake in pregnancy and offspring mean BRIEF index scores*

Average no. drinks/ week in pregnancy	Crude			Adjusted for core confounding factors**		Adjusted for potential confounding factors***	
	Mean score	Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI
Parent-rated BRIEF BRI**							
0	49.27	Reference		Reference		Reference	
1–4	49.86	0.59	(−0.94; 2.13)	0.78	(−0.71; 2.28)	0.97	(−0.53; 2.47)
5–8	49.47	0.20	(−2.66; 3.06)	−0.09	(−3.00; 2.82)	−0.19	(−2.94; 2.56)
≥9*****	50.05	0.78	(−2.36; 3.93)	0.85	(−2.05; 3.75)	1.45	(−1.76; 4.67)
*P******		0.87		0.73		0.52	
Parent rated BRIEF MI**							
0	49.10	Reference		Reference		Reference	
1–4	50.12	1.02	(−0.53; 2.57)	1.23	(−0.26; 2.73)	1.35	(−0.15; 2.86)
5–8	50.21	1.11	(−1.92; 4.13)	0.51	(−2.61; 3.63)	0.15	(−2.75; 3.05)
≥9*****	52.17	3.07	(0.20; 5.93)	2.87	(0.04; 5.70)	2.87	(−0.48; 6.23)
*P******		0.16		0.15		0.17	
Teacher rated BRIEF BRI**							
0	50.19	Reference		Reference		Reference	
1–4	49.88	−0.31	(−1.89; 1.27)	−0.24	(−1.80; 1.32)	−0.15	(−1.74; 1.44)
5–8	49.42	−0.77	(−3.15; 1.61)	−1.13	(−3.53; 1.26)	−1.22	(−3.70; 1.25)
≥9*****	47.64	−2.55	(−7.42; 2.33)	−2.66	(−7.70; 2.38)	−2.24	(−7.53; 3.05)
*P******		0.73		0.62		0.68	
Teacher rated BRIEF MI**							
0	49.94	Reference		Reference		Reference	
1–4	50.09	0.15	(−1.37;1.66)	0.26	(−1.22; 1.74)	0.29	(−1.20; 1.78)
5–8	50.60	0.65	(−1.74;3.05)	0.04	(−2.29; 2.36)	−0.27	(−2.73; 2.19)
≥9*****	47.66	−2.29	(−6.86;2.29)	−2.53	(−7.38;2.32)	−2.59	(−7.99; 2.82)
*P******		0.72		0.77		0.77	

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* The clinical scales form two indexes: the Behavioural Regulation Index (BRI) and the Metacognition Index (MI).

** Parental education, maternal IQ, prenatal maternal smoking, age at testing, and gender of child.

*** Parental education, maternal IQ, prenatal maternal smoking, binge drinking, maternal age, parity, prenatal and postnatal marital status, postnatal parental smoking, maternal pre-pregnancy BMI, gender of child, age at testing, health status on the day of testing, and family/home environment.

**** The number of children in each exposure category was 758, 675, 175, and 20 for the 0, 1–4, 5–8, and ≥9 drinks/week categories, respectively.

***** Range: 9–14 drinks/week.

****** *P* value for the hypothesis of no difference in BRIEF scores across levels of average alcohol intake.

Table 2

Associations between maternal binge drinking in pregnancy and offspring mean BRIEF index scores*

	Crude			Adjusted for core confounding factors**		Adjusted for potential confounding factors***	
	Mean score	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Number of binge drinking episodes in pregnancy** **Parent rated BRIEF BRI**							
0	49.32	Reference	–	Reference	–	Reference	–
1	50.20	0.88	(−0.42; 2.17)	1.06	(−0.23; 2.36)	0.92	(−0.36; 2.31)
2	50.07	0.75	(−0.98; 2.48)	1.12	(−0.63; 2.87)	1.20	(−0.54; 2.95)
≥3*****	49.90	0.53	(−1.68; 2.73)	0.86	(−1.38; 3.10)	0.62	(−1.58; 2.83)
*P*****			0.61		0.40		0.45
Number of binge drinking episodes in pregnancy** **Parent rated BRIEF MI**							
0	49.41	Reference	–	Reference	–	Reference	–
1	49.98	0.57	(−0.74; 1.88)	0.70	(−0.60; 2.00)	0.62	(−0.68; 1.93)
2	50.73	1.32	(−0.51; 3.15)	1.60	(−0.24; 3.45)	1.86	(−0.07; 3.67)
≥3*****	48.86	−0.55	(−2.88; 1.79)	−0.49	(−2.89; 1.91)	−0.61	(−2.97; 1.76)
*P*****			0.40		0.25		0.18
Number of binge drinking episodes in pregnancy** **Teacher rated BRIEF BRI**							
0	49.95	Reference	–	Reference	–	Reference	–
1	49.89	−0.06	(−1.39; 1.27)	0.12	(−1.20; 1.45)	0.06	(−1.27; 1.38)
2	50.02	0.07	(−1.66; 1.79)	0.28	(−1.50; 2.07)	0.36	(−1.46; 2.17)
≥3*****	49.67	−0.29	(−2.42; 1.85)	−0.21	(−2.41; 1.98)	−0.40	(−2.65; 1.85)
*P*****			0.99		0.98		0.94
Number of binge drinking episodes in pregnancy** **Teacher rated BRIEF MI**							
0	49.89	Reference	–	Reference	–	Reference	–
1	49.66	−0.23	(−1.53; 1.06)	0.10	(−1.38; 1.18)	0.05	(−1.33; 1.24)
2	50.20	0.31	(−1.39; 2.00)	0.51	(−1.22; 2.24)	0.83	(−0.94; 2.60)
≥3*****	49.22	−0.66	(−2.85; 1.52)	−0.75	(−2.95; 1.46)	−0.62	(−2.89; 1.65)

	Crude			Adjusted for core confounding factors**		Adjusted for potential confounding factors***	
	Mean score	Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI
*P*******		0.85		0.76		0.65	
Timing of binge drinking episodes in pregnancy** (gestational week) Parent rated BRIEF BRI**							
No binge drinking	49.32	Reference	–	Reference	–	Reference	–
1–2	49.31	−0.01	(−1.61; 1.58)	0.40	(−1.21; 2.00)	0.06	(−1.57; 1.70)
3–4	49.90	0.58	(−1.03; 2.19)	0.93	(−0.69; 2.56)	0.99	(−0.62; 2.59)
5–8	50.52	1.20	(−0.44; 2.84)	1.45	(−0.18; 3.07)	1.18	(−0.73; 2.78)
≥9*******	51.69	2.37	(0.68; 4.06)	2.00	(0.28; 3.71)	2.04	(0.33; 3.76)
Multiple timings	50.53	1.21	(−0.57; 2.99)	1.33	(−0.48; 3.13)	1.22	(−0.58; 3.02)
*P*****		0.08		0.23		0.19	
Timing of binge drinking episodes in pregnancy** (gestational week) Parent rated BRIEF MI**							
No binge drinking	49.41	Reference	–	Reference	–	Reference	–
1–2	49.95	0.54	(−1.04; 2.13)	0.92	(−0.68; 2.51)	0.71	(−0.93; 2.35)
3–4	49.79	0.38	(−1.27; 2.03)	0.66	(−0.99; 2.30)	0.82	(−0.83; 2.46)
5–8	50.11	0.70	(−0.89; 2.29)	0.94	(−0.64; 2.53)	0.77	(−0.82; 2.35)
≥9*******	51.28	1.87	(0.21; 3.52)	1.29	(−0.39; 2.97)	1.09	(−0.61; 2.78)
Multiple timings	50.02	0.61	(−1.33; 2.54)	0.54	(−1.41; 2.50)	0.52	(−1.45; 2.49)
*P*******		0.40		0.72		0.84	
Timing of binge drinking episodes in pregnancy** (gestational week) Teacher rated BRIEF BRI**							
No binge drinking	49.95	Reference	–	Reference	–	Reference	–
1–2	49.61	−0.34	(−1.97; 1.29)	−0.05	(−1.69; 1.58)	−0.23	(−1.87; 1.40)
3–4	49.75	−0.20	(−1.87; 1.47)	0.06	(−1.63; 1.72)	0.16	(−1.52; 1.84)
5–8	50.52	0.57	(−1.18; 2.31)	0.94	(−0.85; 2.65)	0.70	(−1.05; 2.45)
≥9*******	51.05	1.10	(−0.60; 2.80)	0.95	(−0.81; 2.67)	0.78	(−0.99; 2.54)
Multiple timings	49.69	−0.26	(−2.01; 1.48)	−0.29	(−2.08; 1.53)	−0.39	(−2.21; 1.59)
*P*****		0.63		0.74		0.82	
Timing of binge drinking episodes in pregnancy** (gestational week) Teacher rated BRIEF MI**							
No binge drinking	49.89	Reference	–	Reference	–	Reference	–

	Crude			Adjusted for core confounding factors**		Adjusted for potential confounding factors***	
	Mean score	Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI
1–2	49.93	0.04	(−1.55; 1.63)	0.31	(−1.28; 1.90)	0.36	(−1.23; 1.95)
3–4	49.01	−0.88	(−2.53; 0.76)	−0.68	(−2.31; 0.96)	−0.42	(−2.06; 1.22)
5–8	50.27	0.38	(−1.30; 2.07)	0.69	(−1.00; 2.37)	0.63	(−1.07; 2.34)
≥9*******	51.65	1.76	(0.07; 3.46)	1.39	(−0.31; 3.08)	1.03	(−0.69; 2.76)
Multiple timings	49.89	−0.00	(−1.72; 1.72)	−0.11	(−1.85; 1.64)	0.08	(−1.73; 1.89)
*P*****		0.17		0.36		0.73	

* The clinical scales form two indexes: the Behavioural Regulation Index (BRI) and the Metacognition Index (MI).

** Parental education, maternal IQ, prenatal maternal smoking, age at testing, and gender of child.

*** Parental education, maternal IQ, prenatal maternal smoking, prenatal maternal average alcohol intake, maternal age, parity, prenatal and postnatal marital status, postnatal parental smoking, maternal pre-pregnancy BMI, gender of child, age at testing, health status, and family/home environment.

**** Of the 1617 mothers, 1122 reported one or more binge drinking episodes. The range was 3–12 episodes. The number of children in each category was 495, 783, 225, and 114 for 0, 1, 2, and 3+ episodes, respectively. The number of children in each timing category was 495, 237, 261, 216, 234, and 174.

***** Range: 3–12 episodes.

****** *P* value for the hypothesis of no difference in BRIEF scores across levels of binge drinking.

******* Range: 9–14 drinks/week.