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The effects of low to moderate prenatal alcohol exposure in early pregnancy on IQ in 5-year-old children

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Abstract

Objective—To examine the effects of low to moderate maternal alcohol consumption during early pregnancy on children's intelligence (IQ) at age 5 years.

Design—Prospective 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 consumption during pregnancy. At 5 years of age, children were tested with the Wechsler Preschool and Primary Scale of

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Disclosure of interests
None to declare.

Contribution to authorship
ELM, TK, MU, JB, and USK contributed to the design of the Lifestyle During Pregnancy Study. H-LFE wrote the first draft of the article, and H-LFE, HS, TW, and JG were responsible for the statistical analyses. All authors contributed to the interpretation of the results, and made 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.

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.

Intelligence—Revised (WPPSI-R). Parental education, maternal IQ, maternal smoking in pregnancy, the child's age at testing, gender, and tester were considered core confounding factors, whereas the full model also controlled for maternal binge drinking, age, BMI, parity, home environment, postnatal smoking in the home, health status, and indicators for hearing and vision impairments.

Main outcome measures—The WPPSI-R.

Results—No differences in test performance were observed between children whose mothers reported consuming between one and four or between five and eight drinks per week at some point during pregnancy, compared with children of mothers who abstained. For women who reported consuming nine or more drinks per week no differences were observed for mean differences; however, the risks of low full-scale IQ (OR 4.6; 95% CI 1.2–18.2) and low verbal IQ (OR 5.9; 95% CI 1.4–24.9) scores, but not low performance IQ score, were increased.

Conclusions—Maternal consumption of low to moderate quantities of alcohol during pregnancy was not associated with the mean IQ score of preschool children. Despite these findings, acceptable levels of alcohol use during pregnancy have not yet been established, and conservative advice for women continues to be to avoid alcohol use during pregnancy.

Keywords

Intelligence; IQ; low to moderate alcohol consumption; neurodevelopmental effects; prenatal exposures; Wechsler primary and preschool scales of intelligence; revised

Introduction

Intellectual deficits caused by heavy prenatal exposure to alcohol are well documented, and maternal alcohol consumption during pregnancy has been suggested as a leading preventable cause of mental retardation.[1,2] Such damage is most evidently and severely manifested in fetal alcohol syndrome (FAS), characterised by growth restriction, a distinct pattern of facial features, and evidence of central nervous system dysfunction.[3] Less is known about the effects of low to moderate alcohol consumption in pregnancy on children's cognitive development. This lack of knowledge is paradoxical, as alcohol is widely used, legal and socially acceptable, and far more frequently consumed in moderate than excessive quantities.

In keeping with the general principles of teratology, a continuum of adverse effects of alcohol on pre- and postnatal development has been reported, although very few studies are available, suggesting that lighter exposure may be associated with less distinct symptoms,[4,5] or with functional rather than physical deficits.[6] Although probably more prevalent than FAS, in the absence of physical abnormalities such subclinical intellectual deficits may often remain undetected. Therefore, the potential negative effects of low to moderate alcohol consumption in pregnancy on children's cognitive development is an issue of public health concern, yet remains in need of clarification.

It has been shown fairly consistently that moderate to heavy doses of alcohol *in utero* (i.e. seven or more drinks per week) may have an impact later in life on specific cognitive skills, such as reaction time,[7] attention, memory, and learning,[8–10] in moderately exposed individuals who did not develop FAS. Studies addressing long-term effects on intelligence of light to moderate prenatal alcohol exposure, however, are scarce, and have provided mixed results.[11–16] Consequently, the existing literature allows for no firm conclusions regarding the long-term impact of low to moderate alcohol consumption in pregnancy on children's intelligence.

The aim of the present study was to conduct a large-scale, methodologically robust study of the potential effects on 5-year-old children's psychometric intelligence (IQ) of very low to moderate weekly alcohol intake during pregnancy, a level of alcohol consumption reflecting drinking habits that are neither uncommon nor considered socially conspicuous among Danish pregnant women.[17]

Methods

Procedures and study sample

This study formed part of the Lifestyle During Pregnancy Study (LDPS), which has been described in detail elsewhere. [18] The LDPS is a prospective follow-up based on a sample from the Danish National Birth Cohort (DNBC),[19] which is a large cohort study with information on 101 042 women and their offspring, collected by two prenatal and two postnatal telephone interviews. All women with valid information on alcohol intake were eligible. Exclusion criteria were: multiple pregnancies; an inability to speak Danish; impaired hearing or vision that was likely to compromise the ability of participants to perform the cognitive tests; and congenital disabilities that imply or are likely to imply mental retardation (e.g. trisomy 21 or infantile autism).

Participants were sampled from the DNBC in strata defined by their prenatal maternal average alcohol intake (0, 1–4, 5–8, ≥9 drinks/week), and the timing of binge episodes, defined as consuming five or more drinks on one occasion (none or at 1–2, 3–4, 5–8, or ≥9 weeks of gestation).[18] The higher exposure categories were oversampled in an effort to ensure that all exposure categories included enough children to attain sufficient statistical power; thus, the sampling probability for the ≥9 drinks/ week exposure group was 95%. Based on these predetermined levels of alcohol consumption during pregnancy, 3478 mothers with singleton pregnancies and their children were invited to participate in a follow-up study when the children were aged between 60 and 64 months. Women sampled on the basis of pre-pregnancy alcohol intake were not included in the analyses presented here (n = 289), leaving 3189 mother–child pairs invited. Of these, 1628 (51%) mother–child pairs participated in a comprehensive 3-hour assessment of cognitive ability, including tests of global and specific functions, and only these mother–child pairs were included in the analyses. The collection of the follow-up data took place from September 2003 to June 2008. Additional information on the sampling and inclusion criteria for the entire LDPS are described elsewhere.[18]

Exposure

For women participating in the follow up, the median time for completing the interview was 17 weeks of gestation (range 7–39 weeks), and 61.6% (n = 1002) completed it between 14 and 20 weeks of gestation. By 20 weeks of gestation, 75% of the women had completed the interview. Women were asked about the average number of beers, glasses of wine and glasses of spirits consumed during a week, in addition to the general alcohol question: 'how many glasses of alcohol do you drink per week?' These questions were used to calculate the average number of drinks consumed per week, and to categorise the level of exposure to alcohol. In addition to being asked about average alcohol consumption, women were asked about binge drinking in a separate question. For this study, light drinking was defined as consuming between one and four drinks per week, and moderate drinking was defined as consuming between five and eight drinks per week. Analyses of the effects of binge drinking on offspring IQ are described in a separate paper.[20] 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. The definition of a drink followed the definition from the Danish National Board of Health, with one standard drink being equal to 12 grams of pure alcohol.

Outcome measure

Intelligence was assessed with the Wechsler Primary and Preschool Scales of Intelligence—Revised (WPPSI-R).[21] The WPPSI-R is one of the most widely used, standardised measures of intelligence for children aged 3–7 years. The WPPSI-R is composed of five verbal subtests and five performance (non-verbal) subtests, from which verbal (VIQ), performance (PIQ), and full-scale (FSIQ) IQ scores are derived.

To reduce the length of the test session, we used a short form that included three verbal (arithmetic, information, and vocabulary) and three performance (block design, geometric design, and object assembly) subtests. Standard procedures were used to prorate IQs from the shortened forms of the tests.[21]

Danish WPPSI-R norms were not available at the time of the study. Consequently, Swedish norms were used to derive scaled scores and IQs.[22] Because Swedish norms were used and because of the stratified sampling according to alcohol exposure, the theoretical distribution of IQ with a mean of 100 and a standard deviation (SD) of 15 cannot necessarily be expected in this sample. This, however, will not affect internal comparisons made within the sample with respect to the effects of alcohol exposure.

Testing took place in four major cities in Denmark (Copenhagen, Odense, Aalborg, and Aarhus). Test procedures were standardised in detail and carried out by 10 trained psychologists blinded to the exposure status of the child. Tester differences were taken into account by the inclusion of an indicator variable in the statistical analyses.

Covariates

Information on the following variables was obtained from the prenatal telephone interview and subsequently coded as shown in parenthesis: prenatal binge drinking episodes (yes/no), parity (0, 1, ≥2), prenatal maternal smoking (yes/ no), and maternal pre-pregnancy body mass index [BMI; weight in kg/(height in m)^2].

A questionnaire administered at the 5-year follow-up provided information on the following variables: maternal marital status (single, either at the prenatal interview or at follow-up/ married or cohabitating); parental education in years (total duration, averaged for both parents or, if information on the father was unavailable, maternal education only); an index of the quality of postnatal family/home environment (dichotomised as normal/suboptimal in the presence of two or more of the following adverse conditions: living with only one biological parent; changes in primary care givers; day care for more than 8 hours/day before the age of 3 years; ≥14 days of separation from parents; breakfast irregularity; maternal depression; and maternal and paternal alcohol intake above the official recommendations from the Danish National Board of Health at the time of follow-up); dichotomised child health status (presence of major medical conditions or regular use of prescription medications that might influence test performance, including: epilepsy, syndromes [e.g. neurofibromatosis type 1], congenital toxoplasmosis and hypothyroidism; and medicines for asthma and allergy, attention deficit hyperactivity disorder, epilepsy and respiratory conditions); postnatal parental smoking (yes if at least one of the parents smoked in the home, no if otherwise); hearing (normal/impaired); and vision (normal/ impaired).

Maternal IQ was assessed at the follow-up examination. Two verbal subtests (information and vocabulary) from the Wechsler Adult Intelligence Scale (WAIS) were used to assess verbal IQ,[23] and the Raven's Standard Progressive Matrices provided non-verbal IQ.[24] 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 an SD of 15.

Maternal age was obtained from the Danish Civil Registration System, as were the gender and age of the child. Birthweight (grams) and gestational age (days) were obtained from the Danish Birth Registry.

Data analysis

All statistical analyses were conducted with stata 11 (StataCorp LP, College Station, TX, USA), and were weighted by sampling probabilities with robust variance estimation.[25] Statistical tests were two-tailed and declared significant at the 5% level. Estimates are accompanied by 95% confidence intervals.

The number of missing values in each of the variables ranged from two to 33, with eight missing values on FSIQ. Missing values were imputed based on the following two strategies: a dedicated model for imputations, for which variables were modelled from the other variables considered to be most predictive (specific equations are available upon request); and by a black-box strategy, for which all variables were used to predict missing values. For both strategies 100 completed data sets were generated. Regardless of imputation strategy, the main conclusions were not affected and point estimates of the exposure parameters did not differ by more than 0.6% relative to standard error. All conclusions were maintained when a complete case analysis was conducted (*n* = 1549). The results of the dedicated imputation strategy are reported. All imputations were performed with the ice add-on command and the built-in mi estimate command of stata 11.[26]

Associations between alcohol exposure categories (0, 1–4, 5–8, ≥9 drinks/week) and the continuous FSIQ, VIQ, and PIQ outcome scores were estimated using multiple linear regression. Parental education, maternal IQ, maternal smoking in pregnancy, the child's age at testing, the child's gender, and tester 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: parity, maternal marital status, maternal age and BMI, maternal binge drinking in pregnancy, family/home environment, parental postnatal smoking, the child's health status, and hearing and vision abilities. Birthweight and gestational age were considered to be potential mediators of the effects of alcohol exposure, and consequently were not included in these main analyses.

The three IQ dichotomised outcomes were analysed using the sample mean minus one SD as cut-off for below-average FSIQ, VIQ, and PIQ. Because logistic regressions were used in these analyses odds ratios are reported, with the category above the cut-off used as the reference group.

In supplementary analyses, raw scores of each individual WPPSI-R subtest were examined with linear regression models adjusted for core and potential confounding factors. Furthermore, potential interactions with alcohol exposure were assessed for gender, parental education, maternal binge episodes and smoking during pregnancy. For all continuous covariates potential quadratic associations with the IQ outcomes were tested. No significant nonlinear associations were observed.

Results

Table 1 presents sample characteristics. Notably, women reporting no alcohol consumption during a typical week were younger, and were more likely to be primiparous than the women in the three alcohol consumption categories. Smoking and suboptimal family/home conditions were more frequent among women who reported consuming five or more drinks per week. Children of abstaining mothers were less likely to show impaired vision or hearing on the test day. No notable differences were seen between participants and non-participants (Table 2).

WPPSI-R

Means (SDs) for the three IQ scales across all exposure groups were 105.5 (12.9) for FSIQ, 104.8 (10.9) for VIQ, and 105.0 (16.2) for PIQ. The effects of consuming between one and four drinks per week and between five and eight drinks per week on FSIQ were close to zero, both before and after adjustment, whereas an intake of nine or more drinks per week was associated with a decrement of 5.5 FSIQ points compared with the reference group (95% CI −13.88 to 2.86), when adjusted for potential confounding factors. However, the sample in the latter exposure category was very small (n = 20), resulting in wide confidence intervals (Table 3). An effect of consuming nine or more drinks per week was also observed for VIQ. No significant trends were observed across levels of average alcohol intake (Table 3).

The logistic regression analyses of the dichotomised IQs showed no association with an intake of between one and eight drinks per week (Table 4). For an intake of nine or more drinks per week we found an unadjusted OR of 2.5 (95% CI 0.9–7.0) for an FSIQ lower than one SD below the mean. When adjustment was made for core and potential confounding factors, this marginally significant association became significant, and the OR increased to 4.6 (95% CI 1.2–18.2). Furthermore, there was a significantly increased risk of a low VIQ associated with exposure to nine or more drinks per week, compared with the reference group, with an unadjusted OR of 3.1 (95% CI 1.1–8.7). This difference became more pronounced and remained statistically significant in the fully adjusted model (OR 5.9; 95% CI 1.4–24.9), and after adjustment for gestational age and birthweight. Again, this exposure group was small and had wide confidence intervals. There were no significant differences in the odds of low PIQ between any of the exposure categories and the reference group, but the magnitude of the effect was comparable with that of VIQ. No significant trends were observed across levels of average alcohol intake (Table 4).

The supplementary analyses showed no effects of alcohol exposure on the raw scores of the WPPSI-R subtests. Tests of interactions with gender, parental education, prenatal maternal binge drinking, and smoking were insignificant. Adjustment for gestational age and birthweight did not change the results for any of the analyses.

Discussion

In the present study, no statistically significant effects were found for low to moderate consumption of alcohol during pregnancy for children's IQ at age 5 years. The consumption of higher levels of alcohol (i.e. ≥9 drinks/week) was associated with a decrease of about six IQ points, corresponding to approximately 0.5 of a standard deviation, although this decrease was not statistically significant.

When IQ was analysed as a dichotomous variable, significant adjusted ORs for below-average FSIQ and VIQ scores were observed for the higher exposure category, whereas there were no significant associations between alcohol exposure at any level and a risk of low PIQ.

The present findings are consistent with previous studies addressing the effects on intelligence of very low levels of alcohol *in utero*, although studies of this kind are sparse. O'Callaghan et al.[27] found no significant effects of less than one drink per day at age 14 years on outcomes from the Wide Range Ability Scale—Revised or Raven's Standard Progressive Matrices Test in 3731 children. Likewise, Alati et al.[16] reported no differences in IQ, as measured with the Wechsler Intelligence Scale for Children—III, in 4332 8- year-old children of mothers with an average intake of up to seven drinks per week, compared with children of mothers who abstained. In a recent study Kelly et al.[15] examined the effects of very low levels of alcohol in more than 11 000 5-year-old children, and found no effects on scores of three subscales of the British Ability Scale in children born to mothers who consumed up to two drinks per week or per occasion during pregnancy, compared with nonexposed children. Findings from the present study are consistent with our findings in multivariate analyses reported elsewhere,[25] with previous studies and with studies of other neurodevelopmental outcomes.[28,29] To our knowledge, to date no study has shown any effects of very light drinking, i.e. consuming less than one drink per day, on child intelligence scores.

This is further strengthened by the significant effect on VIQ associated with higher levels of alcohol consumption, when IQ was analysed as a binary outcome. Wilford and co-workers, for example, found a predicted decrement in child IQ at age 10 years of 1.9 points associated with increasing alcohol consumption from no alcoholic drink to one alcoholic drink per day.[13] This result, however, was restricted to an African-American subgroup (n = 337) and not observed among Caucasian children. Streissguth et al.[30] found a decrement of four IQ points in 482 4-year-old children exposed to three drinks per day or more. A similiar effect was found at a follow-up of the same cohort at age 7 years;[12] at age 14 years, however, effects on IQ were no longer present.[9]

Other studies have found no associations between childhood IQ and various levels of alcohol exposure.[2,14,31]

Diverse categorisations of alcohol exposure do complicate the comparison of previous studies. However, previous reports of effects of heavier alcohol exposure on mean IQ and neurobehavioural outcomes suggest that the absence of statistically significant effects in this study looking for very subtle neurodevelopmental changes is likely to reflect the low statistical power from the small sample size, particularly for the moderate drinking group, even though imputation methods were used to maximise the sample size and power. Although initial calculations indicated that the present sample size should be sufficient, with a previously calculated minimum detectable RR of 1.5, 1.7, and 3.5, for the low (1–4 drinks/week), moderate (5–8 drinks/week), and high (≥9 drinks/week) categories, respectively, the final sample size may still not have been adequate for more subtle effects.

The present study has important methodological strengths lacking in many previous studies, in particular the large sample of children with very low exposure compared with previous studies, and the inclusion of critical confounding factors, especially maternal IQ and parental education. These variables were associated with alcohol consumption patterns in this study, and are known to be strong predictors of child IQ. For example, Alati et al.[16] found parental education alone to account for 19% of the variance in child IQ, whereas prenatal parental alcohol and tobacco use accounted for only 4%. Yet, many previous studies of prenatal alcohol exposure and IQ did not adjust for both of these confounding factors,[12,32] leaving a high risk of substantial residual confounding.[33] Furthermore, this study was conducted in a relatively homogeneous upper middle-class population, which effectively eliminates confounding from important sociodemographic or socioeconomic factors that have plagued many previous studies.

Some limitations of the study should be noted, however. Although the assessment of consumption levels in this study was contemporary (thus reducing recall bias), variation in the date of interview during pregnancy (7–39 weeks of gestation) may dilute any impact on neurodevelopment, if in fact the effect was sensitive to a specific time period in gestation. Furthermore, drinking habits (especially in pregnancy) are associated with psychological, behavioural, and social mechanisms, many of which may also predict cognitive development. Such complexity can be captured only partially in a statistical model, leaving the risk of some degree of residual confounding, even when including a broad range of potential confounding factors.

Both the reliability of cognitive assessment and, in particular, the stability of intelligence test scores in general are quite low in children aged 4–5 years.[34] For the WPPSI-R, reliability coefficients for the present age group for the three IQ scores are very high (0.90–0.96), but are low for the individual subtests (0.49–0.80).[22] Also, long-term effects cannot necessarily be predicted from findings in early childhood, in that early deficits may grow to become more pronounced during childhood. However, the effects of alcohol on IQ observed in early childhood have been found to be insignificant at follow-ups in later childhood and adolencence. [35] This may speak against the likelihood of a future follow-up of our sample to show effects of low-level maternal alcohol consumption on general intelligence. Finally, participation bias is always a concern in studies that assess children. Although the 51% participation rate for this study is quite good for studies of this nature, the possibility remains that the mothers of children who were not functioning at age level may have declined to participate.

In general, misclassification, in particular under-reporting, cannot be excluded in studies of exposures during pregnancy. Compared with other studies, the under-reporting in this study may be reduced because Danish pregnant women in general do not consider the consumption of small quantities of alcohol during pregnancy to be problematic. [17] Even so, the apparent threshold effect of nine or more drinks per week in this study could not be explained by under-reporting, and in the case of under-reporting, the actual threshold would be higher. An artifact of using separate questions for average weekly alcohol consumption and binge consumption in this study must also be noted. Over 66% of women in this study who reported no weekly alcohol consumption also reported at least one binge episode, and over 77% of women who consumed between one and four drinks per week reported a binge episode. Future studies will need to take this possibility into account in interview design so that such non-mutual exclusivity is avoided.

No significant association between maternal intake of low to moderate levels of alcohol and child intelligence were observed in this large-scale study, despite adjustment for maternal intelligence and a wide set of covariates. This finding is consistent with the few previous studies examining the effects of low to moderate doses of alcohol *in utero* on intelligence. It should be noted, however, that on average the exposure levels reported in this study represent 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 (one or two drinks per week) or, at most, levels of less than one drink per day.

Although these findings suggest that occasional small quantities of alcohol consumption may not pose serious issues for later neurodevelopment, alcohol is a known teratogen at higher, daily intake levels, with no established safe level of consumption during pregnancy. Thus, the most conservative advice for women is not to drink alcohol during pregnancy to avoid any possibility of adverse effects.

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Table 1

Sample characteristics across levels of average maternal alcohol intake in pregnancy, Denmark, 2003–2008*

	Average number of drinks per week					***P***
	0	**1–4**	**5–8**	**≥9****	**Total**	
Number of participants	758	675	175	20	1628	
Sampling fraction (median, 10th/90th percentiles)	8.0 (1.5/49.6)	5.5 (1.2/22.8)	65.6 (34.3/76.5)	95.0 (57.9/95.0)	9.7 (1.5/49.6)	
Median number of drinks per category	0	1	5	10	n.a.	
Timing of interview, gestational week (median, 10th/90th percentiles)	16.0 (12.0/23.0)	17.0 (13.0/24.0)	17.0 (13.0/24.0)	17.5 (12.0/26.0)	17.0 (13.0/24.0)	0.02
Family characteristics						
Maternal age, years (mean ± SD)	29.8 ± 4.3	31.4 ± 4.1	33.1 ± 4.4	35.7 ± 4.7	30.9 ± 4.4	<0.01
Parity						
0 (%)	56.5	49.2	29.7	15.0	50.1	0.02
1 (%)	30.2	31.7	41.7	40.0	32.2	
2+ (%)	13.3	19.1	28.6	45.0	17.8	
Maternal BMI, kg/m^2 (median, 10th/90th precentiles)	22.7 (19.5/29.1)	22.6 (19.6/28.4)	22.5 (19.9/27.7)	21.6 (18.0/29.4)	22.6 (19.6/28.7)	0.18
Maternal marital status***						
Single (%)	12.9	11.9	9.9	5.0	12.1	0.68
Parental education, years (median, 10th/90th percentiles)	12.5 (11.0/16.0)	13.0 (11.0/16.0)	13.0 (11.0/16.5)	13.0 (11.3/16.8)	13.0 (11.0/16.0)	0.40
Family/home index						
Suboptimal (%)****	18.0	17.2	25.4	35.0	18.7	0.03
Maternal IQ (mean ± SD)	98.8 ± 15.1	101.2 ± 14.6	100.7 ± 15.7	101.8 ± 13.8	100.0 ± 15.0	0.73
Maternal smoking in pregnancy						
Smokers (%)	31.7	27.9	40.6	60.0	31.4	<0.01
Parental postnatal smoking						
Smokers (%)	30.4	31.0	39.4	55.0	31.9	<0.001
Maternal binge drinking in pregnancy (%)*****	66.4	77.3	57.1	40.0	69.6	<0.01
Child characteristics						
Sex						
Male (%)	49.5	53.5	57.1	50.0	52.0	0.41
Age at testing, years (median, 10th/90th percentile)	5.2 (5.1/5.3)	5.2 (5.1/5.3)	5.2 (5.1/5.3)	5.3 (5.2/5.3)	5.2 (5.1/5.3)	0.15
Birthweight, grams	3601.6 ± 525.2	3618.8 ± 511.3	3559.3 ± 484.6	3416.3 ± 572.5	3601.9 ± 516.1	0.11

	Average number of drinks per week					*P*
	0	**1–4**	**5–8**	**≥9[**]**	**Total**	
Gestational age, days (median, 10th/90th percentiles)	281.0 (267.0/293.0)	282.0 (269.0/293.0)	282.0 (268.0/292.0)	277.0 (261.0/294.0)	281.0 (267.0/293.0)	0.59
Health status						
Condition/medicine (%)[******]	3.2	2.5	6.3	5.0	3.3	0.32
Hearing abilities						
Impaired (%)	3.6	5.9	4.0	15.0	4.7	0.05
Vision abilities						
Impaired (%)	2.5	2.7	4.6	10.0	2.9	0.04

* Based on unweighted data. *P*-values based on weighted analyses.

** Range 9–14 drinks/week.

*** Single if single either in pregnancy or at follow-up (at 60–64 months postpartum).

**** Defined as a score on at least two of the following items: child living with both biological parents; changes in care giving; daycare of >8 hours/day before the age of 3 years; 14+ days of separation from parents; irregular breakfast meals; maternal depression; high maternal or paternal alcohol use.

***** Defined as the consumption of five drinks or more on one occasion.

****** Medical conditions or regular medications that may influence test performance.

Table 2

Maternal and child characteristics of participants and non-participants, Denmark, 2003–2008

	Participants	Questionnaire only*	Non-participants	Total
Number of participants	1628	140	1421	3189
Sampling fraction (median, 10th/90th percentiles)	9.7 (1.5/49.6)	9.7 (1.2/34.3)	8.0 (1.5/49.6)	8.0 (1.5/49.6)
Timing of interview, gestational week (median, 10th/90th percentiles)	17.0 (13.0/24.0)	18.0 (13.0/23.0)	17.0 (13.0/24.0)	17.0 (13.0/24.0)
Maternal characteristics				
Age, years (mean ± SD)	30.9 ± 4.4	30.5 ± 4.7	30.2 ± 4.6	30.6 ± 4.5
Prenatal marital status				
Single (%)	3.0	1.4	3.1	3.0
Parity				
0 (%)	50.1	52.9	48.6	49.5
1 (%)	32.2	31.4	33.4	32.7
2+ (%)	17.8	15.7	17.9	17.7
BMI, kg/m^2 (median, 10th/90th percentiles)	22.6 (19.6/28.7)	22.7 (19.5/28.0)	23.0 (19.4/30.0)	22.8 (19.5/29.1)
Smoking in pregnancy				
Smokers (%)	31.4	30.0	35.3	33.1
Binge drinking in pregnancy (%)**	69.6	63.6	65.4	67.5
Alcohol intake during pregnancy				
0 (%)	46.6	40.0	51.4	48.4
1–4 (%)	41.5	47.1	38.1	40.2
5–8 (%)	10.7	12.1	9.9	10.4
≥9 (%)***	1.2	0.7	0.6	0.9
Child characteristics				
Sex				
Male (%)	52.0	49.3	51.4	51.6
Birthweight, grams (mean ± SD)	3601.9 ± 516.1	3586.4 ± 524.3	3542.4 ± 558.7	3574.7 ± 536.5
Gestational age at birth, days (median, 10th/90th percentiles)	281.0 (267.0/293.0)	281.0 (265.0/292.0)	281.0 (264.0/293.0)	281.0 (266.0/293.0)

*This subsample completed a parent questionnaire, but did not participate in cognitive testing.

**Defined as the consumption of five drinks or more on one occasion.

***Range 9–14 drinks/week.

Table 3

Associations between maternal alcohol intake in pregnancy and offspring mean WPPSI-R scores, Denmark, 2003–2008

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
FSIQ							
0	104.9	Reference	–	Reference	–	Reference	–
1–4	105.9	1.0	−1.1; 3.1	0.5	−1.4; 2.3	0.6	−1.2; 2.5
5–8	104.3	−0.6	−3.5; 2.3	−0.5	−3.4; 2.4	−0.4	−3.2; 2.4
≥9	98.5	−6.4	−14.6; 1.9	−6.6	−14.8; 1.6	−5.5	−13.8; 2.8
*P****		0.27		0.37		0.47	
VIQ							
0	104.3	Reference	–	Reference	–	Reference	–
1–4	105.6	1.3	−0.4; 3.0	0.8	−0.8; 2.4	0.9	−0.6; 2.4
5–8	104.0	−0.3	−2.8; 2.1	−0.7	−3.2; 1.9	−0.3	−2.7; 2.0
≥9	100.5	−3.9	−11.3; 3.6	−4.5	−11.8; 2.7	−3.3	−10.9; 4.3
P		0.26		0.37		0.48	
PIQ							
0	104.3	Reference	–	Reference	–	Reference	–
1–4	104.8	0.4	−2.2; 3.1	0.1	−2.2; 2.4	0.2	−2.1; 2.6
5–8	103.6	−0.7	−4.6; 3.2	−0.2	−3.7; 3.4	−0.2	−3.8; 3.4
≥9	96.8	−7.6	−15.8; 0.6	−7.3	−15.8; 1.3	−6.4	−14.7; 1.8
P		0.29		0.42		0.48	

* Parental education, maternal IQ, prenatal maternal smoking, the child's gender and age, and tester.

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

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

Table 4

Associations between maternal alcohol intake in pregnancy and below-average offspring WPPSI-R scores (less than one SD below the mean), Denmark, 2003–2008

	Crude		Adjusted for core confounding factors*		Adjusted for potential confounding factors**	
Average no. drinks/week in pregnancy	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**
FSIQ						
0	Reference	–	Reference	–	Reference	–
1–4	1.0	0.6; 1.4	1.0	0.6; 1.5	1.1	0.7; 1.8
5–8	0.9	0.5; 1.7	0.9	0.4; 2.0	1.1	0.5; 2.4
≥9	2.5	0.9; 7.0	3.7	1.0; 12.9	4.6	1.2; 18.2
*P******	0.30		0.24		0.18	
VIQ						
0	Reference		Reference		Reference	
1–4	0.8	0.5; 1.3	0.9	(0.5; 1.4)	0.9	0.5; 1.5
5–8	1.0	0.5; 2.1	1.2	(0.5; 2.6)	1.3	0.6; 2.8
≥9	3.1	1.1; 8.7	5.0	(1.3; 18.7)	5.9	1.4; 24.9
P	0.08		0.08		0.08	
PIQ						
0	Reference		Reference		Reference	
1–4	0.9	0.6; 1.3	0.9	0.6; 1.4	1.0	0.6; 1.5
5–8	1.3	0.7; 2.4	1.2	0.6; 2.5	1.2	0.6; 2.6
≥9	2.0	0.7; 5.9	2.3	0.7; 7.5	2.7	0.8; 9.4
P	0.39		0.47		0.41	

[*] Parental education, maternal IQ, prenatal maternal smoking, the child's sex and age, and tester.

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

[***] *P*-value for the hypothesis of no difference in OR for IQ below the sample mean minus one SD across levels of average alcohol intake.