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To cite this version:

Marie Eliasen, Janne Schurmann Tolstrup, Anne-Marie Nybo Andersen, M Gronbæk, Jorn Olsen, et al.. Prenatal alcohol exposure and autistic spectrum disorder. International Journal of Epidemiology, 2010, 10.1093/ije/DYQ056 . hal-00583146

HAL Id: hal-00583146

https://hal.science/hal-00583146v1

Submitted on 5 Apr 2011

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OXFORD UNIVERSITY PRESS
International Journal of Epidemiology

Prenatal alcohol exposure and autistic spectrum disorder

Journal:	*International Journal of Epidemiology*
Manuscript ID:	IJE-2009-10-0883.R1
Manuscript Type:	Original Article
Key Words:	Pregnancy, Autistic Spectrum Disorder, Alcohol, Children

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Prenatal alcohol exposure and autistic spectrum disorder – A population-based prospective study of 80,552 children and their mothers

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Word count: 3,413 words (paper plus abstract).

MeSH terms: 'Pregnancy', 'Alcohol Drinking', 'Child Development Disorders, Pervasive'

Abstract

Background: To examine whether maternal alcohol intake including binge drinking (intake ≥ 5 drinks equivalent to 60g pure ethanol on a single occasion) is associated with autistic spectrum disorders (ASD) and infantile autism.

Methods: Participants were 80,552 children and their mothers enrolled in the Danish National Birth Cohort from 1996 to 2002. Alcohol consumption was obtained by self-report during pregnancy. Information on ASD was obtained from the Danish Central Psychiatry Register. Follow-up ended February 2008. Data was analysed by means of Cox regression.

Results: In total 401 children were diagnosed with ASD and 157 with infantile autism. No association was found between average alcohol consumption and ASD or infantile autism, respectively. For binge drinking, the adjusted hazard ratio (HR) for ASD was 0.72 (95% confidence interval (CI): 0.53 to 0.97) among women who binge drank once during pregnancy compared to women who did not binge drink. The corresponding HR for infantile autism was 0.61 (95% CI: 0.36 to 1.02). However, the hazard ratio for ASD was 0.84 (95% CI: 0.51 to 1.36) when restricting the analysis to first-time pregnancies conceived within 6 months of trying. No estimate was made for infantile autism due to low number of cases. No association was seen for more than one binge episode and for the timing of binge drinking.

Conclusion: Our findings do not support that a low prenatal alcohol exposure increases the risk of ASD or infantile autism. The lower risk for women who binge drank once during pregnancy is most likely non-causal.

Keywords: Pregnancy, alcohol, autistic spectrum disorders, children.

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Introduction

Autistic spectrum disorders (ASD) including infantile autism are pervasive developmental disorders characterized by qualitative impairments in social interaction and communication and stereotyped repetitive behaviour.[1] The prevalence of ASD has been increasing in the last two decades,[2] but the reason for this increase is unknown and the aetiology of ASD is still mostly unknown. A strong genetic component has been established, but also the age of the parents, psychiatric disorders, obstetrical complications, and some teratogenic factors such as thalidomide have been associated with ASD.[3-8]

Two case studies and a small follow-up study have reported higher frequency of ASD among children with foetal alcohol effects,[9-11] but a causal relation between prenatal alcohol exposure and ASD is not established. The brains of children with ASD have some similarities as do the brains of animals prenatally exposed to alcohol e.g. a decreased number of purkinje cells and reduced neuronal size compared to the normal brain.[5,12-14] Furthermore, a high prenatal alcohol exposure is associated with impaired neurodevelopment in humans.[15-18] Hence, it is possible that prenatal alcohol exposure increases the risk of ASD.

The central nervous system develops throughout the entire pregnancy, and specific functions are developed at specific time points. Prenatal alcohol exposure may therefore have time dependent effects on the foetal brain. Furthermore, the detrimental effects of alcohol also seem to depend on the achieved blood alcohol level,[12,13,17,19-25] but evidence from human studies is sparse. Previously, we have found that exposure to binge drinking (intake of larger doses of alcohol at a single occasion) in gestational week 11-16 is associated with an increased risk of neonatal seizures and epilepsy in childhood.[26] Binge drinking is a regular part of the alcohol drinking pattern among younger people in many societies, and in Norway and Denmark it has been shown that 25 and 50 %

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of pregnant women, respectively, have binge drunk once during pregnancy.[27,28] Moreover, binge drinking is increasing in the United States among both pregnant and non-pregnant women.[29]

In this study we examined whether weekly alcohol consumption, number of binge drinking episodes, as well as binge drinking during different developmental time periods is associated with the incidence of autistic spectrum disorders or infantile autism in the offspring.

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Methods

Study population

The Danish National Birth Cohort (DNBC) is a population-based cohort of pregnant women and their offspring approved by the Danish Scientific Ethical Committees.[30] The women were recruited from March 1996 to November 2002 through their first antenatal visit with their general practitioner. Around 50 % of all practitioners in Denmark participated and around 60 % of those invited returned a signed consent form and thereby consented to be telephone-interviewed twice during pregnancy, around pregnancy week 17 (quartile 14-20) and pregnancy week 32 (quartile 30-34). English translations of the interviews are available at www.dnbc.dk.

Of all enrolled pregnancies (n=100,418), we limited our analyses to women who gave birth to a live-born singleton and completed the first interview (n=86,783). We excluded women with incomplete information on binge drinking (n=330), women with missing information on gestational age at the first interview (n=878) as well as women for whom the discrepancy between the self-reported gestational age and the information recorded in the National Discharge Registry exceeded one week (n=4441) as one of the main exposures in this study was gestational timing of binge drinking. Furthermore, we excluded women with lacking information on the covariates included in the regression models (n=580) and children who were unidentifiable in the National Central Personal Register (n=2) probably due to a coding error of their personal id number. Hereby 80,552 children and their mothers were eligible for the analyses.

Alcohol consumption

In the first interview, the women were asked to report the number of drinks of beer, wine, and spirits per week they on average consumed while being pregnant. One drink was defined as one bottle of beer (0.33L), one glass of wine, or one glass of spirits, and in Denmark the alcohol content

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for each type of drink is roughly the same and equivalent to approximately 12 g of pure alcohol. Women who reported to consume less than one drink per week of these beverages were assigned the numeric value of ½ drink per week. The weekly intake of beer, wine, and spirits were added up to a total and before doing any analyses categorized into the groups: 0, ½-1½, 2-3½ and 4 or more drinks per week. In analyses with too few cases, the two last groups were combined into one group: 2 or more drinks per week.

Information on binge drinking was obtained by asking the women how many times and when in pregnancy they had consumed five or more alcoholic drinks on a single occasion since the onset of pregnancy, defined as the first day of the last menstrual period. Information on binge drinking during the period from onset of pregnancy to the first interview was given in the first interview, while information from the second interview, if available, was used to describe binge drinking in the period between the two interviews. We categorized number of binge episodes into 0, 1, 2 and 3 or more episodes. For the analyses of the timing of binge drinking we classified the pregnancy into different fetal developmental time periods and categorized binge drinking as 'yes' versus 'no' in the preconceptional period (pregnancy weeks 0-2), the fertilization and implementation period (weeks 3-4), the embryonic period (weeks 5-10), the early fetal period (weeks 11-16), and the mid fetal period (weeks 17-30), respectively. The classification was set before doing the analyses and was defined as detailed as the number of exposed permitted.

Identification of ASD and infantile autism

Using the civil registry number, which is unique to every Danish citizen, diagnoses of ASD or infantile autism on the children were identified through linkage to the Danish Psychiatric Central Register.[31] The registry contains information about all contacts to psychiatric inpatient and outpatient facilities since 1995 and contacts are diagnosed according to the International

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Classification of Diseases, Tenth Edition (ICD-10).[2] The children were classified as having ASD if they were diagnosed with one of the following ICD-10 codes: Infantile autism (F84.0), atypical autism (F84.1), Asperger's syndrome (F84.5), or pervasive developmental disorder not otherwise specified (F84.8 and F84.9), and classified as having infantile autism if they were diagnosed with the ICD-10 code F84.0. The children classified as having infantile autism were therefore a subset of those classified as having ASD.

Covariates

Based on the existing literature, we made an a priori decision to adjust for maternal age (<25, 25-29, 30-34, 35-39, ≥40 years), paternal age (father unidentified, <25, 25-29, 30-34, 35-39, 40-44, ≥45 years), smoking habits during pregnancy (non-smoker, stopped smoking before time of the interview, 1-10, 11 or more cigarettes per day), self-reported maternal history of psychiatric disorder (affective disorders, nervous conditions, psychosis), household occupational position (higher-grade professionals, middle-grade professionals, skilled workers, unskilled workers, students, unemployed for more than one year), and parity (0, 1, 2 or more children).[27,29,32-35] Information on the covariates was obtained from the first interview.

Statistics

Data were analysed by means of Cox regression models with the children's age in days as underlying time variable, using SAS, 9.1 (SAS Institute Inc, Cary, NC). The children were followed from the date of birth until the date of diagnosis with ASD, death, emigration, or the end of follow up (February 10, 2008), whichever came first. Robust standard errors were calculated to account for the dependency between children with siblings in the study (n=4943). The number of weeks with information on binge drinking was included in the strata-statement in all analyses on binge drinking

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to account for the fact that the women were interviewed in different pregnancy weeks and subsequent had information on binge drinking from different spans of pregnancy. The proportional hazard assumption was examined for average alcohol consumption and binge drinking by plotting the negative logarithm of the estimated survival function against survival time (age) and by including an interaction term between age and average alcohol consumption and binge drinking, respectively, in the models. No sign of violation of the proportional hazards assumption was seen.

Initially, we estimated crude and adjusted hazard ratios for ASD and infantile autism according to average alcohol consumption and the number of binge episodes during pregnancy in separate models as well as in one combined model. Furthermore, the hazard ratios for ASD according to the timing of binge episodes were estimated by including the time periods for binge drinking simultaneously into one model. The association between the timing of binge drinking and infantile autism was not investigated due to the lack of statistical power. Eight percent of the binge drinkers did not report the timing of at least one of their binge episodes. We imputed the missing information on timing by use of a probability distribution of when in pregnancy binge drinking occurred based on the existing data on timing of binge drinking. For example, if a woman was interviewed in pregnancy week 14 and reported two binge episodes, with the first episode in pregnancy week 4 and the timing of the second was missing, the second episode was defined to be between week 4 and 14. The probability distribution was made dependent on whether the pregnancy was recognized before pregnancy week 4, 4-8, 8-12, after week 12, or unknown. The imputation procedure was repeated five times. The presented estimates are the average of the estimates, and the used standard errors are based on the variation both within and between the imputations.[36]

To examine the robustness of the obtained results, the analyses were restricted to primiparous women, who conceived within six months of trying (n=19,253). Hereby we attempted to avoid bias

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arising from selective change in behaviours related to the women's previous reproductive experience or prolonged waiting time to pregnancy.[37] Furthermore, we restricted the analyses to women who had complete information on the time of binge episodes (n=78,881) and to the first enrolled pregnancies (n=75,609). The restrictions were only made on the analyses for ASD due to the limited number of cases of infantile autism.

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Results

Out of the 80,552 pregnant women, 401 gave birth to a child diagnosed with ASD and 157 to a child diagnosed with infantile autism. The average age of the children at the time of diagnosis was 4.9 years for ASD and 4.1 years for infantile autism. At the end of follow up the children were between 4.6 and 10.3 years, with an average age of 7.4 years.

Almost half of the women reported an average weekly intake of at least half a standard alcoholic drink (45%), and approximately one fourth of the women reported at least one episode of binge drinking during pregnancy (table 1). Binge drinking most often occurred before the pregnancy was recognized. Only 5.4 % of all the women reported binge drinking subsequent to pregnancy recognition. Other characteristics of the women are described in table 1.

(Table 1 here)

Women who reported an average alcohol consumption of ½-1½, 2-3½, or 4 or more drinks per week during pregnancy had a risk of having a child diagnosed with ASD or infantile autism similar to what was found for women who reported no average alcohol consumption during pregnancy (table 2). Women who reported binge drinking once during pregnancy had an adjusted hazard ratio (HR) for having a child with ASD of 0.72 (95 % confidence interval (CI): 0.53 to 0.97) compared to women who reported no episodes of binge drinking during pregnancy. One episode of binge drinking was also associated with a lower hazard of infantile autism when compared to no binge drinking (HR: 0.61; 95% CI: 0.36 to 1.02). For two or more binge episodes the hazard ratios for ASD and infantile autism were around 1 compared with no binge drinking. Adjustment for parental age, smoking habits, self-reported maternal history of psychiatric disorder, household socio-occupational position, and parity let only to minor changes of the estimates (table 2).

(Table 2 here)

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Women with one or more binge episodes in pregnancy weeks 0-2, 3-4, 5-10, and 17-30 had basically a similar hazard of having a child with ASD as women who did not binge drink in the same period (table 3). However, binge drinking in pregnancy weeks 11-16 yield a hazard ratio above 1 compared to non-binge drinking, but the confidence interval still included 1 (adjusted HR: 1.32; 95% CI: 0.65 to 2.68). Adjustment for potential covariates, average alcohol consumption and the number of binge episodes did not change the estimates much.

(Table 3 here)

The lower hazard ratio for ASD associated with one binge episode increased to 0.84 (95 % CI: 0.51 to 1.36) in the analyses restricted to primiparous women who conceived within six months of trying (table 4). Restriction to women with complete information on the time of binge episodes and restriction to the first enrolled pregnancies did not change the estimates essentially.

(Table 4 here)

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Discussion

In this large population-based cohort study we found no positive associations between ASD and infantile autism and average alcohol consumption, number, or timing of binge episodes during pregnancy. Binge drinking once during pregnancy was associated with a lower risk of having a child with ASD which could be a chance finding or be confounded. Women with a high risk of reproductive failure may modify their drinking behaviour in subsequent pregnancies. If reproductive failures or prolonged waiting time to pregnancy are associated with increased risk of ASD, and if the study does not fully adjust for the underlying causes of these reproductive failures or prolonged waiting time, confounding will be present. The increasing of the hazard ratio for one binge episode when restricting the analysis to primiparous women who conceived within six months of trying may indicate that confounding is present in the analyses of the total population.

We have not adjusted for ethnicity, which has been shown to be associated with both ASD and alcohol consumption.[6,29,38] However, availability to take part in interviews hold in Danish was a condition for participating in the study, hence we expected only few non-Danish born women not well integrated in the Danish society to be included in the study. Consequently, we assume that our findings are not likely to be confounded by ethnicity.

The analyses on the timing of binge drinking may indicate a possible susceptible period for binge drinking in weeks 11-16. However, the confidence interval included 1 and it may very well be a chance finding. The results were based on only ten cases which limits the statistical power. Hence, further investigations on the potential effects of the timing of binge drinking are needed to make further conclusions.

The present study is to our knowledge the first to examine the association between moderate to light prenatal alcohol exposure and ASD. A suggested higher prevalence of ASD among children with fetal alcohol effects and fetal alcohol syndrome found in two case studies and a small follow-

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up study may be explained by excessive prenatal exposure to alcohol or by other factors associated with a heavy drinking pattern that could be of importance.[9-11] Our study does not rule out that heavy alcohol intake may cause ASD or that alcohol exposure in short time windows may play a role as we do not have the data to rule out such effects.

The detrimental effects of alcohol may depend on the maximal blood alcohol concentration that is achieved during a drinking occasion.[12,13,17,19-25] If so, our results would be conservative estimates of this association since binge drinking is not an accurate measure of the maximal blood alcohol concentration because the amount of time that is spend during drinking differs. However, information on the pace of drinking was not given and we could not address this point any further.

Our study has several strengths including its size and linkage to nationwide registries ensuring almost complete follow-up. Other strengths include the measurement of alcohol consumption during pregnancy with validated questionnaires, both including beverage-specific average alcohol consumption and repeated measures of the number and timing of binge drinking episodes.[22,39,40] Moreover, the setting of the study in a culture where alcohol consumption among women is more socially accepted than in many other countries makes the social desirability of underreporting less likely, and thereby probably makes the data more reliable. However, we do expect pregnant women to underreport their alcohol consumption to some extent.[39] This would probably bias the estimates towards the null value, as we do not expect the misclassification of alcohol consumption to be associated with the risk of having a child with ASD since the alcohol intake was collected in pregnancy.

We expect that some children with ASD and infantile autism were not diagnosed even though the validity of infantile autism in the Danish Psychiatric Central Register is presumed to be high.[41] Some of the children fulfilling the criteria for ASD may not have been diagnosed because of less

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severe behavioural problems that do not lead to contact with the psychiatric hospitals, which are the only places in Denmark where ASD is diagnosed, except for one private diagnostic service which does not report to the Danish Psychiatric Central Register.[2] The conservative estimate of the incidence of ASD may have biased the results, but the direction of the bias is unknown. However, mothers with extensive alcohol consumption might be less likely to seek psychiatric help for their children as extensive alcohol consumption has been associate with reduced ability to assess the mental development of the child.[42] A differential misclassification might therefore be present which could mask a positive association between alcohol consumption and ASD. However, we expect that only few women with extensive alcohol consumption participated in the study. Furthermore, the women with a moderate alcohol consumption in our study had a higher than average education and socio-occupational position.[28] The possible misclassification is therefore expected to be of minor importance.

Only around 30 % of all pregnant women in Denmark during the study period participated in the DNBC (60 % of those invited), and thereby selection bias is possible.[30] Pilot tests have shown that the main reasons for non-participation were lack of time and interest.[30] It is likely that alcohol consumption during pregnancy influenced the participation, but as the risk of ASD was not known beforehand, we assume that participation was not associated with ASD. Hence, it is believed that our results are not highly influenced by selection bias. However, selection bias could occur if women with a high alcohol intake who suffered from ASD were less likely to accept the invitation, since the offspring of these mothers would have a higher probability of having ASD. Such a selection could mask an association when family history of ASD was not adjusted for.

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In conclusion, we did not find that average alcohol consumption, frequency or timing of binge drinking episodes during pregnancy were associated with the risk of having a child with ASD or infantile autism for women drinking light to moderate. ASD is a rare condition and despite this large cohort study, the results were limited by statistical power.

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Key messages

- The average alcohol consumption, frequency or timing of binge drinking episodes during pregnancy were not found to be associated with the risk of having a child with ASD or infantile autism for women drinking light to moderate.
- Further studies are needed to rule out any effect of prenatal alcohol exposure on ASD and infantile autism especially for women drinking heavier and for high blood alcohol concentration in short time windows.
- When studying the effects of prenatal alcohol exposure it is important to include binge drinking and the timing of the binge drinking episodes.

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Acknowledgements

This work was supported by grants from the Danish Ministry of Health, the Danish National Board of Health, the Health Insurance Foundation, and the National Institute of Public Health, University of Southern Denmark. The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of major grant from this foundation. Additional support for the Danish National Birth Cohort was obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation.

Conflicts of interests

All authors declare that they have no conflicts of interest and no financial interest of the manuscript.

Guarantor and references

Katrine Strandberg-Larsen is the guarantor for the paper. Katrine Strandberg-Larsen and Marie Eliasen have checked the references for accuracy and completeness.

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Table 1 Maternal and paternal characteristics according to alcohol consumption during pregnancy

	Total N (%)	**Maternal age** (Years) Median (10th; 90th percentile)	**Paternal age** (Years) Median (10th; 90th percentile)	**Maternal smokers**[a] (%)	**Maternal psychiatric disorder**[b] (%)	**Middle or higher grade professionals** (%)	**Primiparous** (%)
Total population	80,552 (100)	30 (25; 36)	32 (27;39)	25.5	7.7	55.2	46.8
Average alcohol consumption							
Drinks per week							
0	44,493 (55.2)	29 (24; 35)	32 (26; 40)	26.0	8.1	51.1	49.4
½-1½	26,663 (33.1)	30 (25; 36)	33 (27; 39)	23.3	7.1	59.3	45.3
2-3½	7,708 (9.6)	31 (26; 37)	34 (28; 41)	27.6	7.2	63.9	40.6
4+	1,688 (2.1)	33 (27; 38)	35 (29; 43)	38.3	10.7	60.5	33.0
Binge drinking							
Number of episodes							
0	59,609 (74.0)	30 (25; 36)	33 (27; 39)	22.3	7.5	55.2	43.4
1	13,037 (16.2)	29 (25; 35)	32 (26; 39)	30.2	7.7	55.6	54.3
2	4,699 (5.8)	29 (24; 35)	32 (26; 39)	37.8	8.2	53.8	60.4
3+	3,207 (4.0)	30 (24; 36)	32 (27; 40)	47.6	12.0	55.4	61.6
Timing of binge episodes [b]							
Binge drinking at least once in the specific period							
Weeks 1-2	6,635 (8.2)	29 (25; 35)	32 (27; 39)	35.3	8.6	58.1	62.3
Weeks 3-4	11,785 (14.6)	29 (25; 35)	32 (27; 39)	34.0	8.0	57.6	61.1
Weeks 5-10 [c]	5,610 (7.0)	29 (24; 36)	32 (26; 40)	39.9	9.9	50.8	55.8
Weeks 11-16 [c]	1,248 (1.6)	30 (24; 37)	33 (26; 41)	49.6	12.9	41.6	40.8
Weeks 17-30 [c]	1,441 (2.5)	30 (24; 37)	33 (27; 41)	47.8	13.5	42.6	37.3

[a] Smoked at some time during pregnancy.
[b] By self-report
[c] Pregnancy weeks measured from first day in last menstrual period.
[d] In these three last periods respectively 4, 2,579, and 23,471 women are treated as missing due to completing the last interview before the end of the specific time period.

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Table 2 Crude and adjusted hazard ratios for ASD and infantile autism according to alcohol consumption during pregnancy.

	ASD			Infantile autism		
Exposure	Cases	HR† (95 % CI)	HR‡ (95 % CI)	Cases (%)	HR† (95 % CI)	HR‡ (95 % CI)
Average alcohol consumption						
Drinks per week						
0	237	1 (ref.)	1 (ref.)	92 (0.2)	1 (ref.)	1 (ref.)
½-1½	119	0.83 (0.67-1.04)	0.84 (0.68-1.05)	45 (0.2)	0.81 (0.57-1.16)	0.79 (0.56-1.13)
2-3½	36	0.87 (0.62-1.24)	0.86 (0.60-1.23)	17 (0.2)	1.06 (0.63-1.77)	0.98 (0.58-1.65)
4 +	9	0.97 (0.50-1.90)	0.91 (0.46-1.80)	3 (0.2)	0.84 (0.27-2.66)	0.71 (0.22-2.30)
Binge drinking						
Episodes						
0	303	1 (ref.)	1 (ref.)	125 (0.2)	1 (ref.)	1 (ref.)
1	51	0.74 (0.55-1.00)	0.72 (0.53-0.97)	17 (0.1)	0.61 (0.37-1.02)	0.61 (0.36-1.02)
2	31	1.33 (0.84-1.77)	1.16 (0.80-1.68)	7 (0.2)	0.69 (0.32-1.49)	0.68 (0.32-1.46)
3+	16	0.91 (0.55-1.50)	0.80 (0.48-1.34)	8 (0.3)	1.16 (0.57-2.37)	1.04 (0.48-2.22)

† Crude
‡ Adjusted for maternal age, paternal age, smoking habits, self-reported maternal history of psychiatric disorder, household socio-occupational position, and parity

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Table 3 Crude and adjusted hazard ratios for ASD according to timing of binge drinking episodes.

	ASD		
Timing of episodes	Cases	HR† (95 % CI)	HR‡ (95 % CI)
Weeks 0-2			
0	370	1 (ref.)	1 (ref.)
1+	31	0.94 (0.65-1.36)	0.90 (0.62-1.31)
Weeks 3-4			
0	380	1 (ref.)	1 (ref.)
1+	51	0,83 (0.61-1.12)	0.79 (0.58-1.07)
Weeks 5-10			
0	372	1 (ref.)	1 (ref.)
1+	29	1.02 (0.67-1.56)	0.99 (0.65-1.52)
Missing [a]	0	-	-
Weeks 11-16			
0	379	1 (ref.)	1 (ref.)
1+	10	1.40 (0.71-2.78)	1.32 (0.65-2.68)
Missing [a]	12	-	-
Weeks 17-30			
0	249	1 (ref.)	1 (ref.)
1+	8	1.05 (0.52-2.15)	1.02 (0.49-2.11)
Missing [a]	144	-	-

† Crude
‡ Adjusted for maternal age, paternal age, smoking habits, self-reported maternal history of psychiatric disorder, household socio-occupational position, and parity
[a] Missing indicates women who had no information on binge drinking in the weeks investigated due to last interview before the specific week

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Table 4 Adjusted hazard ratios for ASD and infantile autism according to alcohol consumption during pregnancy for first-time pregnant women who waited less than six months to become pregnant (N=19,253)

	ASD		
	Cases	HR† (95 % CI)	HR‡ (95 % CI)
Average alcohol consumption			
Drinks per week			
0	62	1 (ref.)	1 (ref.)
½-1½	28	0.82 (0.52-1.28)	0.85 (0.55-1.34)
2+	15	1.46 (0.83-2.57)	1.49 (0.84-2.66)
Binge drinking			
Episodes			
0	68	1 (ref.)	1 (ref.)
1	20	0.91 (0.55-1.49)	0.92 (0.56-1.53)
2	10	1.11 (0.58-2.15)	1.08 (0.57-2.04)
3+	7	1.08 (0.50-2.36)	1.00 (0.44-2.28)

† Crude
‡ Adjusted for maternal age, paternal age, smoking habits, self-reported maternal history of psychiatric disorder, household socio-occupational position, and parity

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