Alcohol Intake in Early Pregnancy and Risk of Attention-Deficit/Hyperactivity Disorder in Children Up to 19 Years of Age

a cohort study

Kjær Weile, Louise Katrine; Wu, Chunsen; Hegaard, Hanne Kristine; Kesmodel, Ulrik Schiøler; Henriksen, Tine Brink; Nohr, Ellen Aagaard

Published in:
Alcoholism: Clinical and Experimental Research

DOI (link to publication from Publisher):
10.1111/acer.14243

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

MRS. LOUISE KATRINE KJÆR WEILE (Orcid ID : 0000-0001-5027-5027)

PROF. ULRIK SCHIØLER KESMODEL (Orcid ID : 0000-0003-3868-106X)

Article type : Original Research Article

MRS. LOUISE KATRINE KJÆR WEILE (Orcid ID: 0000-0001-5027-5027)

Article type: Original Research Article

Title: Alcohol intake in early pregnancy and risk of Attention-Deficit Hyperactivity Disorder (ADHD) in children up to 19 years of age: a cohort study.

1. Mrs. Louise Katrine Kjær Weile[abc], MHSc.

2. Dr. Chunsen Wu[ab], PhD.

3. Dr. Hanne Kristine Hegaard[def], PhD.

4. Prof. Ulrik Schiøler Kesmodel[bfg], PhD.

5. Prof. Tine Brink Henriksen[hi], PhD.

6. Prof. Ellen Aagaard Nohr[ab], PhD.

[a]Department of Obstetrics and Gynecology, Odense University Hospital. Sdr. Boulevard 29, DK-5000 Odense C. [b]Institute of Clinical Research, University of Southern Denmark. J.B. Winsløws Vej 19, DK-5000 Odense C. [c]OPEN, Odense Patient data Explorative Network, Odense University Hospital. J.B. Winsløws Vej 9a, DK-5000 Odense C. [d]Department of Obstetrics, Copenhagen University Hospital (Rigshospitalet). Juliane Maries Vej 9, DK-2100 Copenhagen Ø. [e]The Research Unit Women's and Children's Health, Section 7821 Juliane Marie Centre, Copenhagen University Hospital (Rigshospitalet). Blegdamsvej 9, DK-2100 Copenhagen Ø. [f]Department of Clinical Medicine, Aalborg University. Søndre Skovvej 15, DK-9000 Aalborg. [g]Department of Obstetrics and Gynecology, Aalborg University Hospital. Reberbansgade 9, DK-9000 Aalborg. [h]Department of Pediatrics (Intensive Care Neonatology), Aarhus University

Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N. [i]Perinatal Epidemiology Research Unit, Department of Pediatrics, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N.
Corresponding author: Louise Katrine Kjær Weile, RM, MHSc, PhD student. Sdr. Boulevard 29, DK-5000 Odense C. Telephone: +4565415157. Email: louise.weile@rsyd.dk

Abstract

Background: Little is known about maternal alcohol intake in early pregnancy and the risk of Attention-Deficit Hyperactivity Disorder (ADHD) in the children beyond 5-years of age. We examined the association between alcohol binge drinking and weekly alcohol intake in early pregnancy and the risk of ADHD in the children followed from birth to 19 years of age.

Methods: We included 48,072 children born between 1998 and 2012, whose mothers participated in the Aarhus Birth Cohort. Maternal alcohol intake was obtained from a self-administered questionnaire completed in early pregnancy. ADHD-diagnoses were retrieved from the Danish Psychiatric Central Research Register and the Danish National Patient Register. Crude and adjusted hazard ratios (aHR) of ADHD according to alcohol binge drinking or weekly intake of alcohol were calculated using Cox regression.

Results: Compared to children of women with no binge drinking episodes, we observed an aHR for ADHD of 0.91 (95% CI 0.76-1.08), 0.73 (95% CI 0.56-0.96), and 0.77 (95% CI 0.57-1.06) among children of women reporting one, two and three or more binge drinking episodes, respectively. Among children of women drinking less than one drink per week, one drink per week, two drinks per week and three or more drinks per week, we observed an aHR for ADHD of 0.87 (95% CI 0.74-1.03), 0.63 (95% CI 0.40-0.98), 1.30 (95% CI 0.89-1.92), 0.78 (95% CI 0.38-1.59), respectively when compared to children of women not drinking on a weekly basis.

Conclusion: We found no evidence that binge drinking or low alcohol intake in early pregnancy was associated with the risk of ADHD in the children.

Keywords

Pregnancy; Binge Drinking; Low-Moderate Alcohol Consumption; ADHD diagnosis; Prenatal Exposures

Abbreviations

ADHD: Attention-Deficit Hyperactivity Disorder
aHR: Adjusted hazard ratios
BMI: Body-mass-index
CI: Confidence intervals
HR: Hazard ratio
ICD-10: International Classification of Diseases, 10th revision

Introduction

Attention-deficit-hyperactivity-disorder (ADHD) is characterized by inattention, hyperactivity, and impulsivity, and is one of the most common neurodevelopmental disorders in childhood worldwide (Polanczyk et al., 2015). The diagnostic prevalence of ADHD has tripled over the last decades (Atladottir et al., 2015), currently affecting 3% of the populations in the Nordic countries (Nylander et al., 2013, Suren et al., 2013, Madsen et al., 2015). Besides being associated with various comorbidities (e.g., autism and disruptive mood dysregulation disorder) (Biederman, 2005, Usami, 2016), ADHD has a negative impact on the quality of life in children and adolescents (Klassen et al., 2004). In the long term, children with ADHD attain poorer academic achievements, occupational rank and job performance compared to their peers (Usami, 2016). The heritable nature of ADHD is described (Biederman, 2005, Banerjee et al., 2007, Thapar et al., 2013, Sciberras et al., 2017), but 10-40% of the heritability variance may be explained by environmental exposures including perinatal risk factors (Banerjee et al., 2007, Sciberras et al., 2017).

Alcohol consumption is common among Scandinavian women of reproductive age (Stoltenberg, 2014, Jensen et al., 2017). It has been shown that one out of four Danish women of 25-34 years regularly engage in binge drinking (five or more drinks on a single occasion as defined by the Danish Health Authority (Strandberg-Larsen and Grønbæk, 1999)). Further, one out of six consume seven or more drinks per week on average, thereby exceeding the official recommendation for low-risk drinking for women (Jensen et al., 2017, Christensen et al., 2010). The proportion of Danish women drinking one drink or more per week on average in early pregnancy has decreased from 24% in 1998 to 1% in 2013 (Kesmodel et al., 2016). Still, 35-40% report binge drinking in very early pregnancy (Iversen et al., 2015, Kesmodel et al., 2016).

It is well established that high alcohol intake in pregnancy is teratogenic with the potential to cause structural malformations, and motor, cognitive and behavioral deficits in the children (Knopik et al., 2005, Riley et al., 2011). A number of observational studies focusing on binge drinking or a low-moderate alcohol intake (often defined as an intake less than six drinks per week) in early pregnancy failed to show higher risk of the core symptoms of ADHD in children up to five years of age (Kesmodel et al., 2012, Underbjerg et al., 2012, Bay et al., 2012, Skogerbo et al., 2012, Skogerbo et al., 2013). However, ADHD may not become evident or diagnosed until the child reaches an age where the expectations exceed the child's ability and resources (Kessler et al.,

2007). Recently, studies have suggested higher risk of ADHD-symptoms in children of 11-12 years exposed to alcohol in late pregnancy (Sayal et al., 2014, Furtado and Roriz, 2016, Eilertsen et al., 2017, Pagnin et al., 2018). However, only one study has examined the association between maternal alcohol consumption in early pregnancy and ADHD-symptoms in children older than five years (Rodriguez et al., 2009). Accordingly, the objective of this study was to examine the association between binge drinking or average weekly alcohol intake in early pregnancy and the risk of ADHD in the children up to 19 years of age.

Materials and methods

Study design, setting and participant selection

The study was based on data from the Aarhus Birth Cohort which is described in depth elsewhere (Hedegaard et al., 1993, Larsen et al., 2013). In brief, from September 1989 onward, all Danish-speaking pregnant women attending routine antenatal care at the Department of Obstetrics and Gynecology, Aarhus University Hospital, Denmark, were invited to participate in the cohort. In early pregnancy (median week 11, 5-95 percentile: 8-19), women were asked to complete a self-administered questionnaire with questions on medical and obstetric history, education and lifestyle including smoking and alcohol intake before and during pregnancy. Immediately after delivery, the attending midwife completed a structured form on the course of delivery and pregnancy outcome. The information from the delivery was validated by a research midwife prior to data entry. Until 2012, a total of 81,111 women (141,939 pregnancies) had been invited to participate in the cohort. Of these, 69,728 women (111,352 pregnancies) were enrolled, leading to a response rate of 79% of all pregnancies.

Since the establishment of the cohort, different versions of the questionnaire have been used. Thus, information on binge drinking was not available for children born prior to 2 June 1998. Therefore we restricted the population to live-born singletons born between 2 June 1998 and 31 December 2012, whose mothers consented to participate and completed a questionnaire including questions on binge drinking (n=48,072). Prior to 2000, information on average weekly alcohol intake did not allow identification of women with no weekly intake. In order to differentiate women with no weekly intake and women with an intake of less than one drink/week, we did not include information on average weekly alcohol intake on children born prior to 14 February 2000 (n=6,132). As data was linked to Danish health registries using the unique personal identification

number assigned to all Danish individuals at birth (Pedersen et al., 2006), children without a valid personal identification number were excluded (n=21).

Alcohol exposures

Our main exposure was self-reported alcohol consumption defined as binge drinking (number of episodes) and average intake of alcohol (drinks per week) in early pregnancy. In Denmark, one drink is equivalent to 12 grams of pure alcohol (Strandberg-Larsen and Grønbæk, 1999). The question on binge drinking was: *'Try to think of your entire pregnancy, including the first weeks before you knew you were pregnant. How many times have you been drinking five or more drinks on a single occasion?'*. Women were asked to report *'number of episodes'* as an integer value, or to tick in '*none'* or *'do not know/recall'*. Women reporting *'do not know/recall'* were coded as missing, and binge drinking was categorized as: *0, 1, 2, or >3 episodes*. The question on average alcohol intake was: *'How many drinks (a drink being equal to one beer, one glass of wine, or one schnapps) do you drink per week, now that you are pregnant?'.* Women were asked to report *'number of drinks per week'* as an integer value, or to tick in *'less than one drink'* or *'do not drink'*. Average weekly intake of alcohol was categorized as: *0, <1, 1, 2, >3 drinks per week.*

Time to ADHD-diagnosis

The main outcome was time to first clinical diagnosis of ADHD in the child. This information was obtained from Danish health registries. We obtained information on ADHD from the Danish National Patient Register for Psychiatry, which holds diagnoses on all psychiatric in- and outpatients since 1995 (Mors et al., 2011). In Denmark, some children with mental disorders are seen in somatic hospitals. Hence, we also retrieved ADHD diagnoses from the Danish National Patient Register, which contains diagnoses from in- and outpatient contacts since 1995 (Schmidt et al., 2015). Using the International Classification of Diseases, 10th revision (ICD-10) which was introduced in Denmark in 1994 (WHO, 1992), ADHD was defined as an ICD-10 diagnosis of F90.0-F90.2, or F90.8-F90.9. We also included F98.8, as this diagnosis is used to classify inattention without symptoms of hyperactivity in Denmark (Arngrim et al., 2013, Sundhedsstyrelsen, 2018).

Covariates

Based on a directed acyclic graph (DAG) (Williams et al., 2018), we selected a range of potential confounders a priori; maternal age at birth (*<20, 20-24, 25-29, 30-34, 35-39,* or *>40 years*), and

the following self-reported information: highest attained educational level (*none, skilled training/<3 years higher education,3-4 years higher education, >5 years or more higher education,* or *other*), pre-gestational body-mass-index (BMI) (*<18.5, 18.5-24.9, 25.0-29.9,* or *>30.0 kg/m^2*), chronic disease (*yes/no*), smoking in pregnancy (*non-smoker, cessation in pregnancy, <10 cigarettes/day,* or *>10 cigarettes/day*), parity (*nulliparous/multiparous*), and registered birth year (continuous). We also included information on maternal average alcohol intake prior to pregnancy, child's sex (*male/female*), and maternal diagnoses of mental or behavioral disorders (ICD-8: 290-315 and ICD-10: F10-F99) before the time of birth.

Statistical analyses

Cox regression was used to estimate adjusted hazard ratios (aHR) with 95% confidence intervals (95%CI) for first diagnosis of ADHD according to alcohol intake in early pregnancy. Children were followed from date of birth until the date of first diagnosis of ADHD, emigration, death or the end of follow-up (February 18, 2018), which ever came first. In Model 1, we adjusted for all predefined confounders. The reference group 'no binge drinking' included women with any weekly alcohol intake, and vice versa the reference group 'no weekly intake' included women with any binge drinking. Therefore, these analyses were mutually adjusted in Model 2 that also included the potential confounders from Model 1. Women totally abstaining from alcohol may be different from other women in the reference groups. Therefore, we replicated the analyses with 'total abstainers' (defined as women with no binge drinking episodes and no weekly intake) as a specific category. In the analysis on binge drinking, we used women with no binge drinking episodes but any weekly alcohol intake as the reference group, whereas women with no weekly alcohol intake but any binge drinking were used as reference group in the analysis on average weekly alcohol intake. In total, 28% of the women had more than one child in the cohort (n=13,440). To account for dependency between children of the same mother, analyses were clustered around mothers using robust standard errors; the "Huber Sandwich Estimator" (Williams, 2000). A two-sided p-value of less than 5% was considered statistically significant. Model assumptions were evaluated by log-log plots and Schoenfeld residuals. StataSE15.0 (StataCorp, 2017) was used for all statistical analyses.

Supplementary analyses

Model 1 and 2 were repeated by restricting to children of women without i) a diagnosis of mental or behavioral disorder prior to birth, and ii) self-reported chronic disease, and by stratifying by

child's sex. To account for the timing and duration of exposure, analyses were repeated by further adjustment for gestational age at questionnaire completion. Also, we restricted the analyses to women completing the questionnaire prior to 12 weeks gestation. To evaluate the sensitivity to missing values, all analyses were repeated using imputed datasets. Based on missing at random assumptions, missing values were imputed using multiple imputation by chained equations, performing 50 imputations (White et al., 2011). All complete variables from the models, the outcome variable, and the Nelson-Aalen estimator of H(T) were included in the imputation models (White and Royston, 2009).

Ethical approval

The study was approved by the Danish Data Protection Agency (j.nr. 2012-41-1084, j.nr. 2012-58-0018) and the Danish Patient Safety Authority for research purposes (FSEID-00003175).

Results

The median gestational age at completion of the questionnaire was 11 weeks (5-95 percentile range: 8-19). Information on binge drinking was available for 42,862 children (11% missing). Restricted to questionnaires completed after inclusion of the abstention category for average weekly alcohol intake, information on average weekly alcohol intake was available for 41,049 children (2% missing). Women with no information on binge drinking or average weekly alcohol intake were less likely to have attained >5 years higher education compared to women, who provided this information. Also, they more often abstained from alcohol prior to pregnancy, were more likely to smoke in pregnancy, and less likely to have planned their pregnancy. Women with no information on binge drinking were more likely to have a diagnosis of a mental or behavioral disorder prior to birth than women with missing data on binge drinking. The opposite was observed among women with missing information on average alcohol intake (data not shown in table).

Characteristics of study population

The characteristics of the study population according to self-reported alcohol consumption in early pregnancy are presented in Table 1. Compared to women with any binge drinking in early pregnancy, women who did not binge were older, and had a lower average alcohol intake prior to pregnancy. Also, they were more likely to be non-smokers and multiparous. Compared to women

with any average weekly alcohol intake, women with no weekly intake were younger, had a higher BMI, and more often had a diagnosis of a mental or behavioral disorder prior to birth. They had a lower average alcohol intake prior to pregnancy, and were more likely to be non-smokers and multiparous. The lowest alcohol exposures were seen in the late period of the cohort (Table 1).

The median follow-up time was 12 years, ranging from birthday to a maximum of 19 years and eight months. Overall, 3% (n=1,346) of the children had a diagnosis of ADHD, and one fourth of the diagnosed children (n=369) were female. While 12% of the children with an ADHD-diagnosis had a mother with a diagnosis of a mental or behavioral disorder prior to birth, this applied to 8% of the children not diagnosed with ADHD (data not shown in table).

Association between alcohol consumption in early pregnancy and the risk of ADHD

The associations between binge drinking and ADHD are presented in Table 2. The highest risk of ADHD was observed among children of women who reported no binge drinking, and a significantly lower risk of ADHD was observed among children of women reporting two binge drinking episodes (aHR 0.73 95% CI 0.56-0.96). Restricting analyses to children of women without mental or behavioral disorders prior to birth (Table 2), and to children of women without chronic disease only changed estimates marginally (data not shown).

The associations between average alcohol intake and ADHD are presented in Table 3. There was no clear pattern with association measures pointing in various directions. However, compared to children of women with no weekly alcohol intake, children of women reporting one drink per week had a significantly lower risk of ADHD (aHR 0.63 95% CI 0.40-0.98). Results among children of women without mental or behavioral disorders prior to birth (Table 3), and among children of mothers without chronic disease were comparable to those within the entire study population (data not shown).

The results from the analyses including total abstainers as a separate category are presented in Table 4. Compared to children of women not binge drinking, children of total abstainers seemed to have a higher risk of ADHD (aHR 1.17 95% CI 0.99-1.39). Similarly, higher risk of ADHD was indicated for children of total abstainers compared to children of women with no weekly alcohol intake (aHR 1.12 95% CI 0.93-1.34) (Table 4). In all analyses, we observed no significant differences according to sex of the children. Adjusting for gestational age at questionnaire

completion had marginal effect on risk estimates, whereas restriction to children of women completing the questionnaire prior to 12 weeks of gestation slightly attenuated results towards entity (supplemental Table S1). This was especially pronounced for children of women with >3 binge drinking episodes (aHR 1.00; 95% CI 0.68-1.46), and for children of women with a weekly intake of two (aHR 1.19; 95% CI 0.72-1.99), or >3 drinks (aHR 0.89; 95% CI 0.36-2.20). Results from the analyses of imputed data sets were comparable to the results from the analyses of complete cases only.

Discussion

Main results and previous studies

In this study, we observed no association between binge drinking and average weekly alcohol intake in early pregnancy and the risk of ADHD in children up to 19 years of age. Lower risks of ADHD were indicated with binge drinking or average weekly alcohol intake up to one drink per week, but we expect these patterns to represent residual or unmeasured confounding.

In relation to maternal alcohol intake in early pregnancy, our results are in agreement with several studies on this topic (Kesmodel et al., 2012, Underbjerg et al., 2012, Bay et al., 2012, Skogerbo et al., 2012, Skogerbo et al., 2013) that did not observed any significant or systematically higher risk of core symptoms of ADHD. In these studies, the functional domains of ADHD were measured with several different tools (e.g., the Strengths and Difficulties Questionnaire, the Behavior Rating Inventory of Executive Functions, and the Test of Everyday Attention for Children at Five). Similar, a study including children from Aarhus Birth Cohort born between 1990 and 1992 did not show higher risk of parent- or teacher-rated ADHD-symptoms according to average weekly alcohol intake at the age of 7-15 years (Rodriguez et al., 2009). However, there is a growing body of evidence more consistently suggesting mildly higher risk of parent- or teacher-rated ADHD-symptoms among children exposed to maternal alcohol drinking in the second or third trimester, or throughout pregnancy (Sayal et al., 2014, Niclasen et al., 2014, Furtado and Roriz, 2016, Eilertsen et al., 2017, Pagnin et al., 2018).

There may be different explanations for the abovementioned differences of findings according to the timing of the maternal alcohol intake. Firstly, although the opposite has been found in experimental animal studies (Bonthius and West, 1990, Schneider et al., 2011, Valenzuela et al., 2012, Schambra et al., 2017), it is possible that isolated episodes of binge drinking and low average weekly alcohol intake in early pregnancy do not affect the development of the human fetal brain. Secondly, the majority of women drinking alcohol in early pregnancy cease to drink, or decreases alcohol consumption after pregnancy recognition, and only few continue or even increase their intake (McCormack et al., 2017, Pryor et al., 2017, Strandberg-Larsen et al., 2008). Studies on alcohol intake in late pregnancy may therefore reflect an accumulated effect of alcohol, with the possibility to affect the neurodevelopment of the fetus more profoundly. Thirdly, the difference of findings may also be explained by different characteristics of women included in the individual studies. Whereas the studies on maternal alcohol intake throughout pregnancy or late in

pregnancy have been carried out in different countries (i.e., England, Denmark, Brazil, and Norway), studies on maternal alcohol intake in early pregnancy have primarily been based on data from Danish women. It is well established that alcohol drinking is a common part of Danish social interaction, and the majority of Danes drink in social contexts in contrast to drinking alone (Bloomfield et al., 2008, Grønkjær et al., 2009, Seid et al., 2016). Although the Danish Health Authority recommends alcohol abstention in pregnancy, some alcohol intake in pregnancy is apparently socially accepted (Kesmodel and Kesmodel, 2011, Kesmodel and Urbute, 2019). Further, in Denmark drinking in early pregnancy is not associated with social adversity (Strandberg-Larsen et al., 2008, Rodriguez et al., 2009). As such, it is possible that all studies on maternal alcohol intake in early pregnancy including ours to some degree may be confounded by the 'healthy-drinker-effect' (Kesmodel, 2018).

Given the heritability of ADHD (Biederman, 2005, Banerjee et al., 2007, Thapar et al., 2013, Sciberras et al., 2017) and the fact that a child's resilience in mental health is highly associated with the mental health of the primary caregiver (Rutten et al., 2013, Hauck et al., 2013), it is plausible that children of women with ADHD or other mental or behavioral disorders may have a higher a priori risk of ADHD than other children. In our population, women with mental or behavioral disorders prior to birth less frequently reported binge drinking or drinking on a weekly basis than women without such diagnoses. It is plausible that women with mental diseases deliberately abstain from alcohol, as alcohol may exaggerate their symptoms, or as health care providers may encourage women in medical treatment not to drink. Also, as alcohol drinking in Denmark is a highly social behavior, and as women with mental or behavioral disorders may be less enticed by social interaction, it is reasonable to assume that these women less often than other women engage in situations in which alcohol drinking is common or even expected. On the other hand, we cannot exclude that women with mental or behavioral disorders are more aware of the negative connotations of alcohol drinking and therefore more likely to underreport or even deny alcohol intake which would have introduced differential misclassification potentially masking a true association. However, in the analyses restricted to women without mental or behavioral disorders prior to birth associations were attenuated towards the null-hypothesis, and we do not expect a true association to be masked. Optimally we should have accounted for maternal ADHD and not just any mental or behavioral disorder, but due to the time period in which the mothers grew up, it is likely that the disorder was undetected or classified as other mental disorders, and in

our population only 1% of the mothers had a diagnosis of ADHD. Thus, some of the indicated protective effect of the prenatal alcohol exposure may be explained by maternal mental health.

Due to our formulations of the alcohol questions, the binge drinking question captured all episodes until questionnaire completion, whilst the question average weekly alcohol intake only reflected consumption after recognition of the pregnancy only. Thereby, in the supplementary analyses including 'total abstainers' as a separate category, the reference group of women with no weekly alcohol intake are likely to represent the regular, socially accepted drinkers who cease drinking after recognition of pregnancy. It is more complicated to interpret, the reference group of women with no binge drinking episodes when separating the total abstainers. However, as children of total abstainers seemed to have higher risks of ADHD when compared to children of women without binge drinking and children of women with no average weekly alcohol intake, one may infer that in a Danish setting, children of total abstainers have a higher risk of ADHD presumably due to the maternal characteristics related to total alcohol abstinence. This elucidates the importance of considering total abstainers as a specific group when investigating the potential risk of prenatal alcohol exposure.

The gestational age at questionnaire completion varied quite widely in our population. Whereas additional control for gestational age had marginal effect, restriction to children of mothers completing the questionnaire prior to 12 weeks gestation attenuated estimates towards the null. As one may assume that the information about alcohol consumption in early pregnancy collected in the first trimester was more precise due to a better recall, these findings weaken the indications of a protective effect of alcohol consumption in early pregnancy. However, it should be noted that in these analyses, the sample was halved resulting in broader confidence intervals.

Strengths and limitations

Our study was based on a sample of 48,072 children from the Aarhus Birth Cohort, which is a community-based data-collection with a high response rate. The number of missing questionnaire information was generally low. Although one-tenth of the women did not provide information on binge drinking, our supplementary analyses using imputed datasets did not indicate that missing values affected our effect estimates. Using data from Danish registers ensured that only migration could cause loss to follow-up, and the frequency of ADHD was comparable to those reported in other Nordic register studies (Madsen et al., 2015, Suren et al., 2013, Nylander et al., 2013). The

children in our cohort were born between 1998 and 2012, hereby not being followed for an equal amount of time. However in Denmark, most children with ADHD are diagnosed by the age of 12 years (Pottegard et al., 2012), and when we analyzed children below versus above the age of 12 years, we found comparable results.

There are also limitations to our design. Firstly, the prenatal alcohol exposures were based on self-administered questionnaires. In lack of valid biomarkers, there is no valid gold standard for measuring the validity of self-reported alcohol intake, and often methods yielding the highest intake are considered the most valid (Kesmodel, 2005). In pregnant women, self-administered questionnaires have been shown to result in slightly lower frequencies of both binge drinking (Kesmodel and Frydenberg, 2004) and average weekly alcohol intake (Kesmodel and Olsen, 2001) than other methods (e.g. diaries) which may have affected our estimates. Presuming that an association actually exists, denial of alcohol consumption may increase the risk of the unexposed children (Kesmodel, 2018), and in our study this would have led to an overestimation of the risk of ADHD among children of women not binge drinking and women with no weekly intake. Secondly, ADHD may be slightly underestimated in our study, as we did not have information on redeemed prescriptions of central stimulants (i.e. methylphenidate and atomoxetine) which can be used to identify cases of ADHD treated in private psychiatric practices not obliged to report to the national registers (Madsen et al., 2018, Christensen et al., 2019). Thirdly, participants were enrolled over a 14 years period. Within this period, the proportion of women with any weekly alcohol intake declined markedly, whilst the occurrence of binge drinking among Danish pregnant women was relatively constant. Therefore, although controlling for birth year of the child, we cannot exclude residual confounding as the factors associated with alcohol drinking in the early study period may be different than those in the late study period. Further, except from birth year all confounders were based on self-report, and some misclassification may have occurred; it is likely that variables such as highest attained educational level and height may be overestimated, whereas variables such as weight and smoking may be underestimated. Even though capturing a wide range of diseases, chronic disease was dichotomized, and we cannot exclude some residual confounding. However, results did not change when excluding all women with a chronic disease. Overall, the results on binge drinking were less sensitive to adjustment for confounders than the results on average weekly alcohol intake, but we cannot exclude that this may be due to

unmeasured - and yet unknown - factors intertwined with binge drinking in early pregnancy and ADHD in the children.

Our results may be generalizable to cultural settings where maternal alcohol intake in early pregnancy is socially accepted, and where access to healthcare is free of charge.

Conclusion

Our findings were most compatible with a small protective association between low maternal alcohol intake in early pregnancy and the risk of ADHD in children followed from birth to 19 years, but results are likely to be confounded by health-related factors. However, the absence of a positive dose-response association implies that low maternal alcohol intake in early pregnancy is not a risk factor for ADHD in the children.

Funding

Louise Katrine Kjær Weile the Department of Obstetrics and Gynecology at Odense University Hospital, the Faculty of Health Sciences at University of Southern Denmark, and the Region of Southern Denmark (J.nr. 15/50963). The study was further supported by the Danish Midwives Association, the Beckett Foundation, and Odense University Hospital. The Aarhus Birth Cohort has been funded by Aarhus University Research Foundation, The Tryg Foundation, and the Danish Council for Independent Research, Medical Science.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

Arngrim T, Brødsgaard M, Christensen PB, Dalsgaard S, Geoffroy MB, Jacobsen TB, Jørgensen MB, Nørbak H, Toft T, Warrer T. Dansk Psykiatrisk Selskab (Danish Psychiatric Society). Retningslinjer for diagnostik og behandling af ADHD hos voksne. Available at: http://dpsnet.dk/wp-content/uploads/2014/12/2013-11-29_retningslinjer_adhd_ok.pdf. Accessed February 7, 2019.

Atladottir HO, Gyllenberg D, Langridge A, Sandin S, Hansen SN, Leonard H, Gissler M, Reichenberg A, Schendel DE, Bourke J, Hultman CM, Grice DE, Buxbaum JD, Parner ET (2015) The increasing prevalence of reported diagnoses of childhood psychiatric disorders: a descriptive multinational comparison. European child & adolescent psychiatry 24**:**173-183.

Banerjee TD, Middleton F, Faraone SV (2007) Environmental risk factors for attention-deficit hyperactivity disorder. Acta paediatrica (Oslo, Norway : 1992) 96**:**1269-1274.

Bay B, Stovring H, Wimberley T, Denny CH, Mortensen EL, Eriksen HL, Kesmodel US (2012) Low to moderate alcohol intake during pregnancy and risk of psychomotor deficits. Alcoholism, clinical and experimental research 36**:**807-814.

Biederman J (2005) Attention-deficit/hyperactivity disorder: a selective overview. Biological psychiatry 57**:**1215-1220.

Bloomfield K, Grittner U, Rasmussen HB, Petersen HC (2008) Socio-demographic correlates of alcohol consumption in the Danish general population. Scandinavian journal of public health 36**:**580-588.

Bonthius DJ, West JR (1990) Alcohol-induced neuronal loss in developing rats: increased brain damage with binge exposure. Alcoholism, clinical and experimental research 14**:**107-118.

Christensen AI, Davidsen M, Ekholm O, Hansen SE, Holst M, Juel K. Sundhedsstyrelsen (The Danish Health Authority). Den nationale sundhedsprofil 2010 – Hvordan har du det? Available at: https://www.sst.dk/~/media/0486203C9CB34BB581139CE461BD98D7.ashx. Accessed February 20, 2019.

Christensen J, Pedersen LH, Sun Y, Dreier JW, Brikell I, Dalsgaard S (2019) Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs With Risk for Attention-Deficit/Hyperactivity Disorder in Offspring. JAMA network open 2**:**e186606.

Eilertsen EM, Gjerde LC, Reichborn-Kjennerud T, Orstavik RE, Knudsen GP, Stoltenberg C, Czajkowski N, Roysamb E, Kendler KS, Ystrom E (2017) Maternal alcohol use during pregnancy and offspring attention-deficit hyperactivity disorder (ADHD): a prospective sibling control study. International journal of epidemiology 46**:**1633-1640.

Furtado EF, Roriz ST (2016) Inattention and impulsivity associated with prenatal alcohol exposure in a prospective cohort study with 11-years-old Brazilian children. European child & adolescent psychiatry 25**:**1327-1335.

Grønkjær M, Vinther_Larsen M, Curtis T, Grønbæk M, Nørgaard M (2009) Alcohol use in Denmark: A descriptive study on drinking contexts. Addiction Research & Theory Volume 18, 2010.

Hauck Y, Allen S, Ronchi F, Faulkner D, Frayne J, Nguyen T (2013) Pregnancy experiences of Western Australian women attending a specialist childbirth and mental illness antenatal clinic. Health care for women international 34**:**380-394.

Hedegaard M, Henriksen TB, Sabroe S, Secher NJ (1993) Psychological distress in pregnancy and preterm delivery. BMJ (Clinical research ed.) 307**:**234-239.

Iversen ML, Sorensen NO, Broberg L, Damm P, Hedegaard M, Tabor A, Hegaard HK (2015) Alcohol consumption and binge drinking in early pregnancy. A cross-sectional study with data from the Copenhagen Pregnancy Cohort. BMC pregnancy and childbirth 15**:**327.

Jensen HAR, Davidsen M, Ekholm O, Christensen AI. Sundhedsstyrelsen (The Danish Health Authority). Danskernes sundhed. Den nationale sundhedsprofil 2017. Available at: https://www.sst.dk/da/udgivelser/2018/danskernes-sundhed-den-nationale-sundhedsprofil-2017. Accessed February 20, 2019.

Katusic SK, Barbaresi WJ, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ (2005) Psychostimulant treatment and risk for substance abuse among young adults with a history of attention-deficit/hyperactivity disorder: a population-based, birth cohort study. Journal of child and adolescent psychopharmacology 15**:**764-776.

Kesmodel U (2005) Self-reported Intake of Alcohol: Methods and Approaches, in Comprehensive Handbook of Alcohol Related Pathology, Vol. 3, Comprehensive Handbook of Alcohol Related Pathology (PREEDY VR, WATSON RR eds), pp 1367-1382, Elsevier Ltd., Oxford, United Kingdom.

Kesmodel U, Frydenberg M (2004) Binge drinking during pregnancy--is it possible to obtain valid information on a weekly basis? American journal of epidemiology 159**:**803-808.

467 Kesmodel U, Olsen SF (2001) Self reported alcohol intake in pregnancy: comparison between four
468 methods. Journal of epidemiology and community health 55**:**738-745.
469 Kesmodel US (2018) Information bias in epidemiological studies with a special focus on
470 obstetrics and gynecology. Acta obstetricia et gynecologica Scandinavica 97**:**417-423.
471 Kesmodel US, Bertrand J, Stovring H, Skarpness B, Denny CH, Mortensen EL (2012) The effect
472 of different alcohol drinking patterns in early to mid pregnancy on the child's intelligence,
473 attention, and executive function. BJOG : an international journal of obstetrics and
474 gynaecology 119**:**1180-1190.
475 Kesmodel US, Kesmodel PS (2011) Alcohol in pregnancy: attitudes, knowledge, and information
476 practice among midwives in Denmark 2000 to 2009. Alcoholism, clinical and experimental
477 research 35**:**2226-2230.
478 Kesmodel US, Petersen GL, Henriksen TB, Strandberg-Larsen K (2016) Time trends in alcohol
479 intake in early pregnancy and official recommendations in Denmark, 1998-2013. Acta
480 obstetricia et gynecologica Scandinavica 95**:**803-810.
481 Kesmodel US, Urbute A (2019) Changes in drinking patterns, attitudes towards and knowledge
482 about alcohol consumption during pregnancy in a population of pregnant Danish women.
483 Alcoholism, clinical and experimental research.
484 Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB (2007) Age of onset of
485 mental disorders: a review of recent literature. Current opinion in psychiatry 20**:**359-364.
486 Klassen AF, Miller A, Fine S (2004) Health-related quality of life in children and adolescents who
487 have a diagnosis of attention-deficit/hyperactivity disorder. Pediatrics 114**:**e541-547.
488 Knopik VS, Sparrow EP, Madden PA, Bucholz KK, Hudziak JJ, Reich W, Slutske WS, Grant JD,
489 McLaughlin TL, Todorov A, Todd RD, Heath AC (2005) Contributions of parental
490 alcoholism, prenatal substance exposure, and genetic transmission to child ADHD risk: a
491 female twin study. Psychological medicine 35**:**625-635.
492 Larsen PS, Kamper-Jorgensen M, Adamson A, Barros H, Bonde JP, Brescianini S, Brophy S,
493 Casas M, Charles MA, Devereux G, Eggesbo M, Fantini MP, Frey U, Gehring U,
494 Grazuleviciene R, Henriksen TB, Hertz-Picciotto I, Heude B, Hryhorczuk DO, Inskip H,
495 Jaddoe VW, Lawlor DA, Ludvigsson J, Kelleher C, Kiess W, Koletzko B, Kuehni CE,
496 Kull I, Kyhl HB, Magnus P, Momas I, Murray D, Pekkanen J, Polanska K, Porta D,
497 Poulsen G, Richiardi L, Roeleveld N, Skovgaard AM, Sram RJ, Strandberg-Larsen K,
498 Thijs C, Van Eijsden M, Wright J, Vrijheid M, Andersen AM (2013) Pregnancy and birth

499 cohort resources in europe: a large opportunity for aetiological child health research.
500 Paediatric and perinatal epidemiology 27:393-414.
501 Levy S, Katusic SK, Colligan RC, Weaver AL, Killian JM, Voigt RG, Barbaresi WJ (2014)
502 Childhood ADHD and risk for substance dependence in adulthood: a longitudinal,
503 population-based study. PloS one 9:e105640.
504 Madsen KB, Ersboll AK, Olsen J, Parner E, Obel C (2015) Geographic analysis of the variation in
505 the incidence of ADHD in a country with free access to healthcare: a Danish cohort study.
506 International journal of health geographics 14:24.
507 Madsen KB, Ravn MH, Arnfred J, Olsen J, Rask CU, Obel C (2018) Characteristics of
508 undiagnosed children with parent-reported ADHD behaviour. European child & adolescent
509 psychiatry 27:149-158.
510 McCormack C, Hutchinson D, Burns L, Wilson J, Elliott E, Allsop S, Najman J, Jacobs S, Rossen
511 L, Olsson C, Mattick R (2017) Prenatal Alcohol Consumption Between Conception and
512 Recognition of Pregnancy. Alcoholism, clinical and experimental research 41:369-378.
513 Mors O, Perto GP, Mortensen PB (2011) The Danish Psychiatric Central Research Register.
514 Scandinavian journal of public health 39:54-57.
515 Niclasen J, Nybo Andersen AM, Teasdale TW, Strandberg-Larsen K (2014) Prenatal exposure to
516 alcohol, and gender differences on child mental health at age seven years. Journal of
517 epidemiology and community health 68:224-232.
518 Nylander L, Holmqvist M, Gustafson L, Gillberg C (2013) Attention-deficit/hyperactivity disorder
519 (ADHD) and autism spectrum disorder (ASD) in adult psychiatry. A 20-year register
520 study. Nordic journal of psychiatry 67:344-350.
521 Pagnin D, Zamboni Grecco ML, Furtado EF (2018) Prenatal alcohol use as a risk for attention-
522 deficit/hyperactivity disorder. European archives of psychiatry and clinical neuroscience.
523 Pedersen CB, Gotzsche H, Moller JO, Mortensen PB (2006) The Danish Civil Registration
524 System. A cohort of eight million persons. Danish medical bulletin 53:441-449.
525 Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA (2015) Annual research review: A
526 meta-analysis of the worldwide prevalence of mental disorders in children and adolescents.
527 Journal of child psychology and psychiatry, and allied disciplines 56:345-365.
528 Pottegard A, Bjerregaard BK, Glintborg D, Hallas J, Moreno SI (2012) The use of medication
529 against attention deficit hyperactivity disorder in Denmark: a drug use study from a
530 national perspective. European journal of clinical pharmacology 68:1443-1450.

Pryor J, Patrick SW, Sundermann AC, Wu P, Hartmann KE (2017) Pregnancy Intention and Maternal Alcohol Consumption. Obstetrics and gynecology 129:727-733.

Riley EP, Infante MA, Warren KR (2011) Fetal alcohol spectrum disorders: an overview. Neuropsychology review 21:73-80.

Rodriguez A, Olsen J, Kotimaa AJ, Kaakinen M, Moilanen I, Henriksen TB, Linnet KM, Miettunen J, Obel C, Taanila A, Ebeling H, Jarvelin MR (2009) Is prenatal alcohol exposure related to inattention and hyperactivity symptoms in children? Disentangling the effects of social adversity. Journal of child psychology and psychiatry, and allied disciplines 50:1073-1083.

Rutten BP, Hammels C, Geschwind N, Menne-Lothmann C, Pishva E, Schruers K, van den Hove D, Kenis G, van Os J, Wichers M (2013) Resilience in mental health: linking psychological and neurobiological perspectives. Acta psychiatrica Scandinavica 128:3-20.

Sayal K, Heron J, Draper E, Alati R, Lewis SJ, Fraser R, Barrow M, Golding J, Emond A, Davey Smith G, Gray R (2014) Prenatal exposure to binge pattern of alcohol consumption: mental health and learning outcomes at age 11. European child & adolescent psychiatry 23:891-899.

Schambra UB, Lewis CN, Harrison TA (2017) Deficits in spatial learning and memory in adult mice following acute, low or moderate levels of prenatal ethanol exposure during gastrulation or neurulation. Neurotoxicology and teratology 62:42-54.

Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT (2015) The Danish National Patient Registry: a review of content, data quality, and research potential. Clinical epidemiology 7:449-490.

Schneider ML, Moore CF, Adkins MM (2011) The effects of prenatal alcohol exposure on behavior: rodent and primate studies. Neuropsychology review 21:186-203.

Sciberras E, Mulraney M, Silva D, Coghill D (2017) Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence. Current psychiatry reports 19:1.

Seid AK, Hesse M, Bloomfield K (2016) 'Make it another for me and my mates': Does social capital encourage risky drinking among the Danish general population? Scandinavian journal of public health 44:240-248.

Skogerbo A, Kesmodel US, Denny CH, Kjaersgaard MI, Wimberley T, Landro NI, Mortensen EL (2013) The effects of low to moderate alcohol consumption and binge drinking in early

pregnancy on behaviour in 5-year-old children: a prospective cohort study on 1628 children. BJOG : an international journal of obstetrics and gynaecology 120**:**1042-1050.

Skogerbo A, Kesmodel US, Wimberley T, Stovring H, Bertrand J, Landro NI, Mortensen EL (2012) The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on executive function in 5-year-old children. BJOG : an international journal of obstetrics and gynaecology 119**:**1201-1210.

StataCorp (2017) Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, in Series Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

Stoltenberg C. Folkehelseinstituttet (Norwegian Institute of Public Health). Folkehelserapporten 2014. Helsetilstanden i Norge. Available at: https://brage.bibsys.no/xmlui/handle/11250/277374. Accessed February 20, 2019.

Strandberg-Larsen K, Grønbæk M. Sundhedsstyrelsen (The Danish Health Authority). Graviditet og alkohol. Forebyggelse og sundhedsfremme 1999/5. Available at: https://www.sst.dk/da/sundhed-og-livsstil/graviditet-og-foedsel/information-til-gravide/~/media/D1B054A249ED4CF6A3689BE420546D72.ashx. Accessed February 20, 2019.

Strandberg-Larsen K, Rod Nielsen N, Nybo Andersen AM, Olsen J, Gronbaek M (2008) Characteristics of women who binge drink before and after they become aware of their pregnancy. European journal of epidemiology 23**:**565-572.

Sundhedsstyrelsen (2018) Sundhedsstyrelsen (Danish Health Authority). National klinisk retningslinje for udredning og behandling af ADHD hos børn og unge., in Series Sundhedsstyrelsen (Danish Health Authority). National klinisk retningslinje for udredning og behandling af ADHD hos børn og unge.

Suren P, Bakken IJ, Lie KK, Schjolberg S, Aase H, Reichborn-Kjennerud T, Magnus P, Oyen AS, Svendsen BK, Aaberg KM, Andersen GL, Stoltenberg C (2013) Differences across counties in the registered prevalence of autism, ADHD, epilepsy and cerebral palsy in Norway. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 133**:**1929-1934.

Thapar A, Cooper M, Eyre O, Langley K (2013) What have we learnt about the causes of ADHD? Journal of child psychology and psychiatry, and allied disciplines 54**:**3-16.

Underbjerg M, Kesmodel US, Landro NI, Bakketeig L, Grove J, Wimberley T, Kilburn TR, Svaerke C, Thorsen P, Mortensen EL (2012) The effects of low to moderate alcohol

consumption and binge drinking in early pregnancy on selective and sustained attention in 5-year-old children. BJOG : an international journal of obstetrics and gynaecology 119:1211-1221.

Upadhyaya HP, Rose K, Wang W, O'Rourke K, Sullivan B, Deas D, Brady KT (2005) Attention-deficit/hyperactivity disorder, medication treatment, and substance use patterns among adolescents and young adults. Journal of child and adolescent psychopharmacology 15:799-809.

Usami M (2016) Functional consequences of attention-deficit hyperactivity disorder on children and their families. Psychiatry and clinical neurosciences 70:303-317.

Valenzuela CF, Morton RA, Diaz MR, Topper L (2012) Does moderate drinking harm the fetal brain? Insights from animal models. Trends in neurosciences 35:284-292.

Welsh JW, Knight JR, Hou SS, Malowney M, Schram P, Sherritt L, Boyd JW (2017) Association Between Substance Use Diagnoses and Psychiatric Disorders in an Adolescent and Young Adult Clinic-Based Population. The Journal of adolescent health : official publication of the Society for Adolescent Medicine 60:648-652.

White IR, Royston P (2009) Imputing missing covariate values for the Cox model. Statistics in medicine 28:1982-1998.

White IR, Royston P, Wood AM (2011) Multiple imputation using chained equations: Issues and guidance for practice. Statistics in medicine 30:377-399.

WHO WHO (1992) Klassifikation af sygdomme. Systematisk del. 10. revision. (International Statistical Classification of Diseases and Health Related Problems), in Series Klassifikation af sygdomme. Systematisk del. 10. revision. (International Statistical Classification of Diseases and Health Related Problems) (SCIØLER G, MOSBECH J eds), Sundhedsstyrelsen (The Danish Health Authority), Munksgaard.

Williams RL (2000) A note on robust variance estimation for cluster-correlated data. Biometrics 56:645-646.

Williams TC, Bach CC, Matthiesen NB, Henriksen TB, Gagliardi L (2018) Directed acyclic graphs: a tool for causal studies in paediatrics. Pediatric research.

Table 1: Characteristics according to self-reported alcohol consumption in early pregnancy; Aarhus Birth Cohort, Denmark, 1998-2012.

			Binge drinking (number of episodes)				Average alcohol intake (drinks/week)				
Maternal and child characteristics, n (%)	Total (n=48,072)		0 (n=27,264)	1 (n=9,038)	2 (n=3,964)	>3 (n=2,596)	0 (n=27,279)	<1 (n=10,974)	1 (n=1,427)	2 (n=964)	>3 (n=405)
Age at birth*											
<20 years	866	(1.8)	(1.5)	(0.9)	(1.3)	(1.7)	(2.2)	(0.5)	(0.2)	(0.3)	(1.0)
20-24 years	5,596	(11.6)	(10.5)	(10.5)	(11.3)	(13.8)	(13.5)	(6.6)	(5.1)	(3.6)	(4.2)
25-29 years	19,030	(39.6)	(37.2)	(45.2)	(46.3)	(46.2)	(39.8)	(40.2)	(34.9)	(34.2)	(26.4)
30-34 years	13,872	(28.9)	(30.6)	(28.9)	(27.1)	(25.3)	(27.3)	(33.1)	(36.7)	(35.9)	(30.1)
35-39 years	7,443	(15.5)	(17.2)	(12.8)	(12.3)	(11.4)	(14.7)	(17.1)	(18.9)	(21.4)	(30.1)
>40 years	1,265	(2.6)	(3.0)	(1.7)	(1.6)	(1.6)	(2.5)	(2.5)	(4.1)	(4.6)	(8.1)
Highest attained educational level											
None	7,696	(17.8)	(17.2)	(15.9)	(18.8)	(22.2)	(19.4)	(13.4)	(12.8)	(11.1)	(14.1)
Skilled training/<3 years higher education	9,058	(21.0)	(19.9)	(22.1)	(22.2)	(20.7)	(19.5)	(21.2)	(16.6)	(21.7)	(20.7)
3-4 years higher education	15,338	(35.5)	(35.5)	(37.6)	(36.9)	(34.0)	(35.3)	(37.6)	(36.0)	(35.3)	(33.7)
>5 years higher education	9,113	(21.1)	(22.9)	(20.4)	(18.5)	(19.3)	(20.7)	(24.2)	(31.2)	(28.1)	(26.4)
Other	1,986	(4.6)	(4.4)	(4.1)	(3.6)	(3.8)	(5.0)	(3.5)	(3.4)	(3.8)	(5.2)
Pre-gestational BMI											
<18.5 kg/m2	2,232	(4.8)	(5.0)	(3.8)	(3.6)	(4.2)	(4.9)	(4.2)	(3.9)	(3.6)	(5.8)
18.5-24.9 kg/m2	33,439	(71.3)	(71.1)	(72.7)	(75.2)	(76.3)	(69.6)	(74.8)	(78.1)	(77.6)	(79.1)
25.0-29.9 kg/m2	7,999	(17.1)	(16.6)	(17.3)	(16.4)	(14.8)	(17.4)	(16.0)	(15.0)	(15.1)	(11.3)

>30.0 kg/m2	3,229	(6.9)	(7.3)	(6.1)	(4.9)	(4.7)	(8.0)	(5.0)	(2.9)	(3.8)	(3.8)
Chronic disease (yes)	5,218	(11.4)	(11.7)	(10.6)	(8.8)	(9.9)	(11.8)	(10.0)	(9.7)	(10.4)	(11.9)
Mental or behavioural disorder (yes)*	3,869	(8.0)	(8.1)	(7.1)	(7.2)	(9.1)	(10.0)	(5.9)	(5.1)	(5.8)	(7.9)
Average alcohol intake prior to pregnancy											
<1 drink/week	21,855	(53.3)	(63.9)	(39.0)	(22.5)	(11.3)	(65.1)	(36.9)	(0.6)	(1.1)	(1.5)
1-2 drinks/week	6,550	(16.0)	(16.4)	(20.4)	(15.5)	(8.6)	(13.7)	(21.8)	(22.4)	(12.8)	(0.0)
3-4 drinks/week	5,592	(13.6)	(11.2)	(19.4)	(22.1)	(17.2)	(10.1)	(19.5)	(33.5)	(20.5)	(12.0)
5-9 drinks/week	5,245	(12.8)	(7.2)	(17.3)	(29.3)	(36.5)	(8.7)	(16.9)	(33.0)	(44.4)	(39.3)
>10 drinks/week	1,727	(4.2)	(1.3)	(3.9)	(10.6)	(26.4)	(2.4)	(4.9)	(10.5)	(21.1)	(47.1)
Smoking in pregnancy											
Non-smoker	38,095	(79.9)	(86.1)	(76.2)	(68.3)	(60.7)	(82.2)	(79.7)	(79.8)	(73.7)	(61.3)
Cessation in pregnancy	5,247	(11.0)	(6.9)	(14.9)	(20.8)	(24.9)	(10.1)	(12.1)	(13.1)	(15.0)	(12.8)
<10 cigarettes/day	2,601	(5.5)	(4.1)	(5.6)	(7.6)	(9.5)	(4.6)	(5.4)	(5.6)	(6.8)	(13.3)
>10 cigarettes/day	1,726	(3.6)	(2.8)	(3.3)	(3.2)	(4.9)	(3.1)	(2.8)	(1.4)	(4.5)	(12.8)
Planned pregnancy (yes)*	35,823	(74.5)	(77.9)	(77.1)	(72.4)	(64.1)	(74.9)	(77.1)	(76.5)	(75.6)	(65.9)
Parity (nulliparous)*	24,896	(51.8)	(45.4)	(57.0)	(66.2)	(75.7)	(53.9)	(48.0)	(47.2)	(46.1)	(41.7)
Child's gender (male)*	24,670	(51.3)	(51.1)	(51.5)	(52.9)	(50.9)	(51.1)	(51.9)	(51.0)	(50.3)	(52.6)

Birthyear*										
1998-2002	15,199	(31.6)	(27.2)	(31.2)	(34.7)	(36.7)	(15.7)	(29.6)	(38.8)	(45.4)	(52.3)
2003-2007	17,476	(36.4)	(37.1)	(36.6)	(35.5)	(37.1)	(38.2)	(49.1)	(47.7)	(47.3)	(39.0)
2008-2012	15,397	(32.0)	(35.6)	(32.1)	(29.8)	(26.2)	(46.1)	(21.3)	(13.6)	(7.3)	(8.6)

Abbreviations: Body-mass-index (BMI). *Complete data. Missing data: highest attained educational level (n=4,881), BMI (n=1,173), chronic disease (n=2,142), average alcohol intake prior to pregnancy (n=7,103), and smoking in pregnancy (n=403).

Table 2: Hazard ratios for Attention Deficit Disorder according to binge drinking in early pregnancy; Aarhus Birth Cohort, Denmark, 1998-2012.

General study population

Binge drinking	ADHD	Person-years x 10^3	IR/10,000	**Crude** (n=42,862)	**Model 1*** (n=38,136)		**Model 2**** (n=33,529)	
				HR	aHR	95% CI	aHR	95% CI
0 episodes	741	313	2.4	1	1		1	
1 episode	249	108	2.3	0.95	0.91	(0.77 - 1.06)	0.91	(0.76 - 1.08)
2 episodes	101	49	2.1	0.85	0.80	(0.64 - 1.01)	0.73	(0.56 - 0.96)
>3 episodes	68	32	2.1	0.84	0.79	(0.61 - 1.03)	0.77	(0.57 - 1.06)

Children of mothers without mental or behavioral disorder prior to birth

Binge drinking	ADHD	Person-years x 10^3	IR/10,000	**Crude** (n=36,451)	**Model 1*** (n=32,787)		**Model 2**** (n=28,802)	
				HR	aHR	95% CI	aHR	95% CI
0 episodes	530	265	2.0	1	1		1	
1 episode	190	94	2.0	0.99	0.91	(0.76 - 1.09)	0.91	(0.74 - 1.11)
2 episodes	78	42	1.9	0.89	0.89	(0.70 - 1.15)	0.82	(0.61 - 1.11)
>3 episodes	53	27	2.0	0.94	0.87	(0.64 - 1.18)	0.89	(0.63 - 1.26)

Abbreviations: Attention Deficit Disorder (ADHD), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, and birth year. **Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, birth year, and average weekly alcohol intake.

Table 3: Hazard ratios for Attention Deficit Disorder according to average weekly alcohol intake in early pregnancy; Aarhus Birth Cohort, Denmark, 2000-2012.

General study population

Average intake	ADHD	Person-years x 10^3	IR/10,000	**Crude** (n=41,049)	**Model 1*** (n=35,359)		**Model 2**** (n=33,529)	
				HR	aHR	95% CI	aHR	95% CI
0 drinks/week	709	282	2.5	1	1		1	
<1 drink/week	279	135	2.1	0.74	0.84	(0.72 - 0.98)	0.87	(0.74 - 1.03)
1 drink/week	24	19	1.3	0.44	0.55	(0.35 - 0.86)	0.63	(0.40 - 0.98)
2 drinks/week	34	13	2.6	0.89	1.12	(0.77 - 1.63)	1.30	(0.89 - 1.92)
>3 drinks/week	12	5	2.2	0.74	0.77	(0.41 - 1.46)	0.78	(0.38 - 1.59)

Children of mothers without mental or behavioral disorder prior to birth

Average intake	ADHD	Person-years x 10^3	IR/10,000	**Crude** (n=34,552)	**Model 1*** (n=30,234)		**Model 2**** (n=28,802)	
				HR	aHR	95% CI	aHR	95% CI
0 drinks/week	493	230	2.1	1	1		1	
<1 drink/week	222	119	1.9	0.77	0.85	(0.71 - 1.02)	0.88	(0.73 - 1.06)
1 drink/week	19	17	1.1	0.45	0.57	(0.35 - 0.92)	0.64	(0.39 - 1.05)
2 drinks/week	27	12	2.3	0.93	1.14	(0.76 - 1.73)	1.29	(0.84 - 1.97)
>3 drinks/week	10	5	2.2	0.87	0.99	(0.50 - 1.94)	1.08	(0.53 - 2.20)

Abbreviations: Attention Deficit Disorder (ADHD), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, and birth year. **Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, birth year, and binge drinking.

Table 4: Hazard ratios for Attention Deficit Disorder according to binge drinking and average weekly alcohol intake in early pregnancy (total abstainers included as a separate category); Aarhus Birth Cohort, Denmark, 1998-2012.

General study population

Binge drinking	ADHD	Person-years x 10^3	IR/10,000	**Crude** (n=42,862) HR	**Model 1*** (n=38,136) aHR	95% CI
Total abstainers†	443	176	2.5	1.40	1.17	(0.99 - 1.39)
0 episodes††	298	137	2.2	1	1	
1 episode	249	108	2.3	1.15	0.99	(0.82 - 1.19)
2 episodes	101	49	2.1	1.02	0.87	(0.68 - 1.12)
>3 episodes	68	32	2.1	1.01	0.86	(0.65 - 1.15)

Average intake	ADHD	Person-years x 10^3	IR/10,000	**Crude** (n=41,049) HR	**Model 1*** (n=35,359) aHR	95% CI
Total abstainers†	443	176	2.5	1.04	1.12	(0.93 - 1.34)
0 drinks/week †††	266	107	2.5	1	1	
<1 drink/week	279	135	2.1	0.76	0.90	(0.74 - 1.10)
1 drink/week	24	19	1.3	0.46	0.59	(0.37 - 0.94)
2 drinks/week	34	13	2.6	0.91	1.20	(0.81 - 1.78)
>3 drinks/week	12	5	2.2	0.76	0.83	(0.43 - 1.58)

Abbreviations: Attention Deficit Disorder (ADHD), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, and birth year. †n=17,249 ††n=10,015 †††n=10,030