Research Paper

Maternal alcohol consumption

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Key messages

Evidence of harm through exposure to alcohol *in utero* remains controversial and needs to be better understood, but risks for the offspring are far from ruled out, including the risk of attention deficit disorder with hyperactivity (ADHD).

More research is needed to address a possible dose–response relationship, effects of timing of exposure, symptom overlap between foetal alcohol syndrome disorders (FASD) and ADHD, gene–environment interaction and correlation and accounting for multiple, possibly interdependent confounding factors.

Primary care services could have an important role in screening, educating and supporting women to abstain from alcohol during pregnancy and

therewith make a major contribution to an important public health issue.

Why this matters to us

It is important to raise awareness amongst primary care professionals about the possible adverse effect of gestational exposure to alcohol on the offspring, including effects of mild to moderate maternal drinking. Unless more robust research suggests differently, risk of ADHD in the child is likely. Primary care professionals have a key role in education, prevention and early intervention and could also contribute to community-based prospective research, which is clearly needed.

ABSTRACT

Background Despite decades of research, the aetiology of attention deficit disorder with hyperactivity (ADHD) remains largely unknown. Next to a strong genetic component, increasing evidence suggests additional adverse impact of environmental factors, two of which have, although controversially, withstood meta-analysis: gestational exposure to smoking (OR 2.39) and low birth weight (OR 2.64). Several studies have investigated a possible association between prenatal exposure to alcohol and ADHD, although the matter is complicated due to foetal alcohol syndrome disorders (FASD) with ADHD-like symptoms.

Questions Can an estimate of the effect of gestational exposure to alcohol for ADHD be determined?

What is the relevance of primary care services in screening and intervention in mild to moderate drinking in pregnant women?

Method MEDLINE, Cinahl, PsychInfo, EMBASE (1995–2008) were searched for articles in English, supplemented by a manual search. Out of 23 reviewed studies, three were included in the meta-analysis; one further study was added to undertake a sub-analysis comparing severe versus mild alcohol consumption. Summary odds ratios (OR) were extracted and fixed/random-effects meta-analysis were used for combining the OR's. Heterogeneity across the studies was formally assessed using Cochran's Q.

Results An OR of 2.33 (95% CI, 1.18–4.61), ($z = 2.43$, $p = 0.02$) suggests that exposed children are

2.33 times more likely to have ADHD than non exposed children.

Discussion Our meta-analysis suggests that children exposed to alcohol during pregnancy are at risk for ADHD. However, evidence is sparse and it remains uncertain whether a causal association exists. Further research is needed into dose–response relationship, timing of exposure, influence of genetic factors involved in maternal alcohol abuse and the role of FASD in ADHD-like symptoms. If a detrimental

effect of mild to moderate drinking on the offspring is supported by stronger evidence, primary care services could have a major role in prevention and early intervention. This would be in addition to their already established role in helping heavy drinking mothers.

Keywords: attention deficit disorder with hyperactivity, gestational exposure to alcohol, prenatal risk factor, primary care services

Introduction

There is consistent evidence that genetic factors contribute to the aetiology of attention deficit disorder with hyperactivity (ADHD) with suggested rates of heritability between 60 and 91%.^{1,2} The impact of early environmental factors on a child's manifestation of ADHD is less clear. Since the 1990s research has increasingly focused on the role of environmental factors. Also, implications of gene–environment interactions and correlations for developmental psychopathology including ADHD are increasingly investigated.³ Two environmental factors that appear to be associated with ADHD have, although controversially, withstood meta-analysis: exposure to maternal smoking in pregnancy (OR 2.39)⁴ and low birth weight/prematurity (OR 2.64).⁵

Cultural factors are likely to influence the drinking behaviour of women in general and during pregnancy in particular. In the USA, between 9 and 15% of women drink alcohol at least once a month during pregnancy and ~3.5% report frequent drinking.⁶ Anonymous screening of 233 unselected antenatal clinic attendees in Sheffield, UK, revealed that 10% of women consumed up to one unit of alcohol a day and a further 1% admitted to consuming more than one unit a day.⁷

Alcohol is widely recognised as a teratogenic agent causing central nervous system (CNS) dysfunction and impaired mental functioning, including foetal alcohol syndrome disorder (FASD).⁸ FASD incorporates the core symptoms of ADHD,⁹ which makes the distinction between the two conditions difficult, and even raises the question whether they are two entities in their own right. Several studies have reported an association between prenatal alcohol exposure and ADHD, although evidence remains controversial.¹⁰

The present meta-analysis was carried out in order to arrive at a better estimate of the effect of prenatal alcohol exposure on the development of ADHD. The focus was on the maternal consumption of alcohol (not familial risk of alcoholism) and the prevalence of ADHD in the offspring. A sub-analysis investigated heavy versus mild consumption.

Methods

A systematic review and meta-analysis were conducted in line with best practice guidelines on the synthesis of observational epidemiological data.¹¹

The relevant studies were identified and agreed upon through discussion by the first and last author via independent systematic searches of electronic databases including PsycINFO, MEDLINE, EMBASE and Cinahl, covering the period from 1995 until February 2008. An additional hand search of reference lists of primary and review articles was carried out. *A priori* inclusion criteria were defined to select only cross-sectional, case-control and cohort epidemiological studies published in English. They had to have examined the relationship between prenatal alcohol exposure and subsequent ADHD (fulfilling diagnostic criteria in accordance with DSMIII/IV or ICD9/10) using some comparison or control group. The attrition rate had to be less than 30%.

Out of 23 studies only three met the selection criteria and were included for the overall meta-analysis. In a sub-analysis two studies were comparable in terms of heavy versus mild prenatal alcohol consumption. Summary odds ratios (OR), with corresponding 95% confidence intervals (CI), were extracted. Where adjusted values were not presented, we used unadjusted OR's, or calculated an unadjusted value from given frequencies. The data extracted from each study was reviewed independently by the first and the second author to minimise error. Inter-rater agreement was 92% and disagreement was resolved through discussion. Fixed-effects and random-effects meta-analyses were used to combine the OR's. Heterogeneity across studies was formally assessed using Cochran's Q, although we were aware that, due to the small number of studies involved, this test had low power. The statistics package Stata was used in all analyses.

Results

Analysis A: association between gestational exposure to alcohol and child ADHD

Three studies that met the inclusion criteria provided sufficient data to calculate an OR (Table 1). In one study we calculated an OR of 4, (95% CI 1.34, 12.04).¹² The authors described that prenatal alcohol use was determined using a median split i.e. those in the top half of consumption versus those in the bottom half of consumption.

Gestational exposure to alcohol, diagnosis of ADHD and possible confounding factors were assessed via standardised interviews and psychometric instruments. The influence of potential confounders was examined in all studies, though these did not always involve the same variables. Multivariate analyses of confounding variables were used to produce adjusted estimates.

The studies were selected for a random-effects meta-analysis to calculate the OR's. All three studies showed increased rates of ADHD in children exposed to alcohol during pregnancy, compared with children not exposed, although this association disappeared in one study¹² when accounting for familiarity of alcoholism. The pooled OR was statistically significant: OR = 2.33 (95% CI, 1.18–4.61; $z = 2.43$, $p = 0.02$) (Figure 1). The test for heterogeneity was not significant ($Q = 2.64$, $p = 0.27$). The possibility of publication bias was not assessed due to the small number of studies involved.

Analysis B: association between heavy vs mild gestational consumption of alcohol and child ADHD

Our searches produced two studies that could be included on the basis of comparing heavy vs mild prenatal alcohol consumption, using the mild exposure group as controls. The demographic data from the samples involved are presented in Table 2.

The Swedish study¹⁵ included a high percentage of children with FASD. No accounting for relevant confounders such as IQ or foster placement was undertaken. The second study¹⁴ has been described above. The pooled OR was statistically significant, OR = 2.28 (95% CI, 1.03–5.02; $z = 2.04$, $p = 0.04$; Figure 2). The test for heterogeneity was not significant ($Q = 0.06$, $p = 0.81$), although we were aware of the very small sample size, and therefore of the reduced value of the test. The results were identical for fixed and random models.

Discussion

To our knowledge, this review represents the first meta-analysis attempting to add to the existing sparse evidence. Our main findings are: 1. Children who have been exposed to alcohol *in utero* are 2.33 times more likely to have ADHD than non-exposed children. 2. Children who have been exposed to heavy consumption of alcohol *in utero* are 2.27 times more likely to have ADHD than children exposed to mild consumption. The differences are statistically significant.

Figure 1 Random effects meta-analysis – plot of studies included in estimate of the pooled OR of the effect of maternal alcohol consumption during pregnancy on child diagnosis of ADHD. Diagnostic criteria used were based on DSM III/IV. An increased OR for ADHD existed among cases exposed to alcohol *in utero* ($z = 2.43$; $p = 0.02$). Fixed effects analysis: Pooled estimate = 2.37, 95% CI (1.34, 4.22), $z = 2.95$, $p = 0.003$. The test for heterogeneity was not significant ($p = 0.27$). CI is illustrated by the error bars. The size of the data marker corresponds to the weight of that study.

Table 1 Studies investigating the association between ADHD and maternal drinking during pregnancy, included in pooled OR analysis A.

Study	Design	Exposure	No Exposure	OR	95% CI	Age (years)	Gender	Confounders addressed	Comment
Mick <i>et al</i> , 2002, USA ¹³	Case control, retrospective	GEA <i>n</i> =19	No GEA <i>n</i> =503, matched	2.5	(1.14, 5.48)	6–17	Mixed	Familial psychopathology, maternal age at birth, socioeconomic status (SES), conduct disorder (CD) in child	Hospital based sample
Hill <i>et al</i> , 2000, USA ¹²	Cohort, prospective	NA (no absolute figures)	NA (no absolute figures)	4.0	(1.33, 12.05)	8–18	Mixed	SES, parental smoking, parental antisocial personality disorder	Selected sample based on familial risk of alcoholism, follow up 4 years
Knopik <i>et al</i> , 2005, USA ¹⁴	Sequential cohort, prospective	GEA <i>n</i> =1068	No GEA <i>n</i> =2804	0.97	(0.26,3.63)	13–19	Female	Maternal education, low birth weight, familial risk for alcohol dependence	Community based sample, follow up 4 years

GEA: gestational exposure to alcohol; ASPD: antisocial personality disorder

Table 2 Studies investigating the association between ADHD and heavy vs non heavy maternal drinking during pregnancy

Study	Design	Exposure	No Exposure	OR	95% CI	Age (years)	Gender	Confounders	Comment
Knopik <i>et al</i> , 2005, USA ¹⁴	Sequential cohort study, prospective	Heavy GEA <i>n</i> =140	No GEA, <i>n</i> =928	2.20	(0.95,5.09)	13–19	Females	Maternal education, LBW, familial risk for alcohol dependence	Community based sample
Aronson <i>et al</i> , 1997, Sweden ¹⁵	Cohort study, prospective	Moderate to severe GEA <i>n</i> =19	Mild GEA <i>n</i> =5	3.00	(0.28,31.64)	11–14	Mixed	Not made explicit	Outpatient clinic based sample, follow up 14 years

GEA: gestational exposure to alcohol; DAMP: deficits in attention, motor control and perception

However, given that studies are few and mostly not specifically designed to address the research question, it is not possible to know whether the observed association is real or spurious; and if real, whether the exposure is causal for ADHD. It is hoped that future research will be able to shed some light on the effects of alcohol consumption during pregnancy.

The review raises a number of interesting points for discussion.

1. A large female twin cohort study¹⁴ found that ADHD was more likely in girls whose mothers reported frequent heavy alcohol use during pregnancy. Non-shared environmental factors accounted for ca. 14% of the total variance in ADHD liability, both before and after controlling for prenatal and parental risk factors, suggesting that much of the genetic influence on the risk for ADHD remains unexplained. No evidence of significant gene-environment interaction was observed. The authors concluded that prenatal and parental risk factors appear to combine with genetic risk, rather than interact with it. This suggests that prenatal and parental risk factors may not be important moderators of genetic influences on risk after all (i.e. much of the associations between these variables and ADHD may be indirect). Genetic confounding could be a part of or even the only explanation of the statistical association seen.
2. One study¹² found that gestational exposure to alcohol was a significant risk for child ADHD after adjusting for SES and parental antisocial personality disorder. The association was no longer statistically significant once familial loading for alcohol dependence was accounted for. This suggests that
- the two factors (prenatal exposure to alcohol and familial risk) are correlated and are not independent predictors of ADHD. The generalisability of the study's results is limited due to small sample size and selection bias, since the subjects were children of parents with a substance use problem.¹² A possible explanation for the study's finding might be that maternal alcohol consumption acted as a form of self medication to cope with the psychopathology linked to their own ADHD, and therefore be a proxy variable for the genetic risk of child ADHD.
3. Alcohol consumption is common and frequently part of the modern lifestyle, but the degree ranges widely from mild over moderate use to harmful use or dependency. Most studies in the field have focused on the effects of heavy drinking. Although all studies included in our review involved heavy drinking during pregnancy, they differed in relation to the definition of dose, frequency and timing of exposure. There is a need to systematically address this issue in future research, although design of such studies might raise ethical concern, especially when looking at mild to moderate consumption.
4. A further difficulty is the disentanglement for possible multiple confounders. It is likely that the population under investigation is also predisposed to numerous other risk factors, some of which are already known to be associated with ADHD. Smoking, low birth weight, maternal stress during pregnancy, low SES, poor diet, maternal age at birth, poor parenting, foster placements, parental psychopathology, sex, age, race, ethnicity and IQ are all factors that would need to be accounted for. Some of above factors may be inter-correlated rather than independent.

Figure 2 Random effects meta-analysis – plot of studies included in estimate of the pooled OR of the effect of heavy maternal alcohol consumption during pregnancy on child diagnosis of ADHD vs mild alcohol consumption. Diagnostic criteria used were based on DSM III/IV. An increased OR for ADHD existed among cases exposed to heavy vs mild alcohol consumption *in utero* ($z = 2.04$; $p = 0.04$). The test for heterogeneity was not significant, although due to very small sample size this is of little value. The results are the same for fixed and random models. Pooled estimate = 2.28, 95% CI (1.03, 5.02), $z = 2.04$, $p = 0.04$. CI is illustrated by the error bars. The size of the data marker corresponds to the weight of that study.

5. Alcohol is recognised as a teratogenic agent causing CNS dysfunction and impaired mental functioning including FASD. Given the symptom overlap with ADHD¹⁶, a question arises whether ADHD in the context of gestational exposure to alcohol is an entity in its own right or on a spectrum of FASD. The similarity in presentation of ADHD and the ADHD-like behavioural component of FASD suggests that alcohol may also play a role in the aetiology of ADHD. One study⁹ compared performance of alcohol-exposed and non-exposed children with ADHD and found qualitative differences on measures of focused and sustained attention. Children with FASD performed least well on encoding and shift aspects of attention. Further research investigating the qualitative differences between the two conditions is clearly needed.

Limitations

The small number of studies included clearly reduces the power of our meta-analysis. In addition methodological problems of the studies involved limit the interpretation and generalisation of their results, including selection bias, recall bias and small sample sizes. A large cohort sample is especially needed when the putative outcome is rare or the effect small. Case-control studies are particularly susceptible to recall bias due to retrospective data collection and confounding.¹³ In observational designs quality assessment is less well defined than in randomised controlled trials. Self-reports of exposure levels in all studies allowed for recall bias. All data were collected in the USA and Sweden. International data is needed and cultural sensitivity should be considered. Further dichotomising alcohol consumption into abstainers vs any alcohol intake during pregnancy may be too crude. It may hide a true association, as well as hinder the detection of a possible dose-response effect or a threshold value.¹⁰

Our review highlights the clear need for more rigorous prospective studies. In line with increasing evidence it may be possible to develop more efficient clinical screening methods and interventions. Public health recommendations could be changed accordingly including possible advice of abstinence. Since 1981, agencies in the United States have consistently recommended, that women who are pregnant are advised not to drink alcoholic beverages and alcohol-containing products should carry a health warning.¹⁷ This is not the case to date in the UK. The most recent National Institute for Health and Clinical Excellence (NICE) clinical guidelines on antenatal care 2008 recommend that women should avoid alcohol in the first three months if possible. If a woman chooses to drink alcohol, she should be advised to drink no more than

1–2 UK units once or twice a week.¹⁸ Primary care services are in a key position to reinforce public health recommendations and make a positive contribution through education, prevention, support and intervention in a behaviour that could present a modifiable risk factor for a common psychiatric condition of childhood.

ETHICAL APPROVAL

None sought

CONFLICTS OF INTEREST

None

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