

Women's social drinking patterns can be difficult to break when planning a pregnancy or when pregnant. Statistics show that 30% of Swedish females continued to drink alcohol during pregnancy. Among researchers there is a consensus about the damaging effect of heavy drinking on the fetus central nervous system. But little is known about low to moderate prenatal alcohol exposure. The Swedish National Institute of Public Health conducted this literature review to examine whether there is an association between low to moderate prenatal alcohol exposure and cognitive and socioemotional development of the child.

This report is written mainly for politicians and people working with or administrators of preventive health care. It is hoped that this report may also be of interest to non governmental organizations.

The Swedish National Institute of Public Health develops and conveys knowledge for better health.

Low dose alcohol exposure during pregnancy – does it harm?



Swedish National Institute
of **Public Health**

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A SYSTEMATIC LITERATURE REVIEW



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Preface

RECOMMENDATIONS TO pregnant women concerning alcohol consumption differ between countries. There is a consensus between scholars regarding the damaging effects of heavy drinking on the fetal central nervous systems but little is known about the effects of low to moderate prenatal alcohol.

With the child's health in focus, the Swedish National Institute of Public Health conducted this review in order to contribute to the knowledge on the association between low to moderate prenatal alcohol exposure and cognitive and socioemotional deficits in children.

This is the first review examining the association between low to moderate alcohol consumption and cognitive and socioemotional development in children. Results in this review show that half of the studies show a positive association while another half cannot demonstrate such an association. Although these results should be interpreted with caution, care professionals are recommended to advise women to abstain from alcohol consumption during or when planning pregnancy.

Sara Holmgren, Swedish National Institute of Public Health had the primary responsibility for the text. Valuable comments have been provided by Sven Bremberg, Swedish National Institute of Public Health, Claes Sundelin, former professor and child specialist at Uppsala University, and Sven Wåhlin, child specialist, and responsible for the Swedish Risk Drinking Project. A survey of the literature search was conducted by Johanna Ahnquist, Swedish National Institute of Public Health.

The formal decision to implement this review was made by Director-General Sarah Wamala.

Östersund, September, 2009

Sarah Wamala

Director-General

Swedish National Institute of Public Health

Summary

REGARDING THE PREVALENCE of prenatal alcohol exposure, statistics show that social drinking during pregnancy is relatively common, 30% of Swedish women continued to consume alcohol during pregnancy. Official recommendations for pregnant women differ between countries. However, there is a consensus among scholars that heavy drinking during pregnancy has damaging effects on the fetal central nervous system. However little is known about the effects of low to moderate doses of prenatal alcohol exposure.

With this as a background, the National Institute of Public Health conducted this literature search in order to examine the impact of low to moderate alcohol consumption on children's cognitive and socioemotional development.

Prerequisites for inclusion in the literature review: studies of representative populations, studies that adjust for socioeconomic status, studies that examine low to moderate prenatal alcohol consumption (1–4 glasses of alcohol per week) and studies that examine children between 3–16 years of age etc.

Six studies fulfilled the quality requirements and were included in this review. Results show that half of the studies show a positive association while another half cannot demonstrate such an association. However, these studies represent a total of eight analyses distributed between preschool children 3–5 years, school children 6–12 years and schoolchildren 13–16 years. These analyses show that in preschool children, 2 of 3 analyses demonstrate cognitive and socioemotional deficits. Children exposed to prenatal alcohol experience significantly more mental health problems that include hyperactivity/inattention, conduct problems, emotional problems and peer relationship problems as well as being less attentive and experiencing shorter “longest attention episodes”. Such impact was only found in 2 of 5 analyses of schoolchildren 6–16 years of age.

From a children's perspective, it is safest if the mother abstains from social drinking during pregnancy or when planning a pregnancy, since even small to moderate doses of alcohol consumption may have an impact on fetal neurobehavioral development.

Sammanfattning

Socialt drickande och effekter på foster

Många kvinnor har etablerade alkoholmönster som kan vara svåra att bryta vid en graviditet. Statistiken visar att 30 % av de svenska mödrarna fortsätter dricka alkohol under sin graviditet. Det innebär att även relativt små effekter på barnens utveckling är väsentliga ur folkhälsosynpunkt. När det gäller officiella rekommendationer till kvinnor så skiljer sig dessa åt mellan olika länder. Forskarna är eniga om att stora mängder alkoholkonsumtion skadar utvecklingen av fostrets centrala nervsystem. Effekterna av små till måttliga mängder alkoholkonsumtion diskuteras dock fortfarande av forskarna.

Med detta som bakgrund har Statens folkhälsoinstitut utfört en systematisk litteraturoversikt där syftet är att undersöka om låg till måttlig alkoholkonsumtion under graviditet påverkar barnets kognitiva och socioemotionella utveckling. Detta har utförts genom att systematiskt gå igenom forskningsartiklar inom området.

Under litteraturgenomgången har endast studier som är baserade på en representativ population och som kontrollerar för socioekonomisk status inkluderats. Övriga kriterier är att studierna möjliggör att titta på effekter av låg till måttlig alkoholkonsumtion (1-4 glas alkohol per vecka) samt att studierna undersöker barn i åldern 3 till 16 år etc.

Totalt 6 studier uppfyllde kriterierna och är därmed inkluderad i denna systematiska litteraturoversikt. Av dessa visar hälften av studierna på ett samband mellan alkoholintag under graviditet och barnets utveckling. Dessa studier representerar även totalt 8 analyser fördelade över åldersgrupperna: förskolebarn 3–5 år, skolbarn 6–12 år och skolbarn 13–16 år.

Analyserna visar att negativa effekter av prenatal alkoholexponering är tydligast i förskoleåldern. När det gäller förskolebarn 3–5 år så visar 2 av 3 analyser på att låg till måttlig alkoholkonsumtion under graviditeten kan leda till kognitiva och socioemotionella problem hos barnet. Barn utsatta för prenatal alkoholexponering uppvisar signifikant fler mentala hälsoproblem så som uppmärksamhetsstörning/hyperaktivitet, avvikande problem, emotionella problem samt relationsproblem med andra barn. När det gäller skolbarn 6–16 år visade endast 2 av 5 analyser på en sådan påverkan av prenatal alkoholexponering.

Från ett barnperspektiv är det säkrast att rekommendera kvinnor som försöker bli gravida och gravida kvinnor att avstå helt från socialt drickande eftersom små till måttliga mängder alkohol kan påverka fostrets neurologiska utveckling.

Introduction

The prevalence of prenatal alcohol exposure

The alcohol consumption among western women in fertile age is increasing. Social drinking may establish a drinking pattern that can be difficult to break when pregnant. In one Swedish study, 30% continued to drink alcohol during pregnancy (1). According to another study, a significant number of the American women continues with alcohol consumption during pregnancy (2). This means that even small effects on the child's development is relevant from a public health perspective.

National recommendations for pregnant women

There is no widely-applied, official recommendation for pregnant women. Depending on country, pregnant women receive different recommendations. In countries like USA and Denmark the official recommendation is strict and governments inform pregnant women or women planning pregnancy to abstain completely from alcohol intake. In Great Britain, in order to minimise the risk to the foetus, the government advises pregnant women never to drink more than one-two units of alcohol once or twice per week and avoid binge drinking. In Australia the government advises pregnant women to abstain from alcohol, but if the woman chooses to drink she should consume less than seven drinks per week, and never more than two drinks on the same day and never get tipsy (3).

Fetal alcohol spectrum disorder

There is a consensus between researchers that heavy alcohol drinking during pregnancy may lead to mild to severe fetal alcohol spectrum disorder (2, 4–6). High doses of alcohol intake cause central nervous system dysfunctions in the foetus. A central nervous system dysfunction may include neurological anomalies, delayed mental development, an alteration of cognitive functioning and behavioural problems. It may also include structural anomalies such as microcephaly or brain malformations; in addition it also has a damaging effect on morphogenesis and growth (5, 7). A study conducted on Italian schoolchildren shows that the prevalence of Fetal alcohol spectrum disorder (FASD) is about 3 percent (24).

Even low doses of prenatal alcohol exposure have been linked to adverse psychological and neurodevelopment outcomes without any structural abnormalities. This includes deficits in cognitive performance and psychosocial functioning (2).

Studies in animals indicate that consumption corresponding to 1-2 drinks a day might affect the foetus (25). Yet, findings in animal studies might not easily translate into humans. Thus, there is no consensus of the effects of low doses of alcohol. Consequently, it is vital to establish the effect of low to moderate alcohol exposure on children. Furthermore, from a public health perspective it is important to establish health effects of alcohol consumption during pregnancy. A Swedish study demonstrated long-run consequences of prenatal alcohol exposure. At the age of 30 people who had been prenatally exposed had lower educational attainments, lower earnings and higher welfare dependency rates than their peers. This result suggests that investments in early-life health may both be a more humane and a more effective way of increasing human capital accumulation in comparison with later life investments (26).

The aim

The aim of this systematic literature review is to examine the association between low to moderate prenatal alcohol exposure and cognitive and socioemotional deficits in children.

Method

The purpose of this systematic review is to synthesise results from a large number of published articles. Relevant articles on prenatal alcohol exposure were identified through search strings in databases and selection criteria. If the articles matched the selection criteria they were included. This increased opportunities to identify and include high quality articles which is important for credible conclusions.

Search method

The studies included in this review were obtained by the following literature search, see table 1. The search strings were run in the databases PubMed, Psych Info and ERIC on 22 June, 2009.

Table 1. Literature search on prenatal alcohol exposure

Search strings	Database	Number of hits
("Alcohol Drinking"[Mesh] OR alcohol*[Title/Abstract] AND ("Pregnancy Trimesters"[Mesh] OR pregnancy[Title/Abstract] OR fetal[Title/Abstract] OR prenatal[Title/abstract]) AND ("Cohort studies"[Mesh] OR cohort[Title/Abstract]))	PubMed	937
((DE "Alcohol Abuse" or DE "Alcohol Drinking Patterns" or DE "Alcohol Intoxication" or DE "Alcoholism") and (DE "Prenatal Exposure")) and (DE "Longitudinal Studies")	PsychInfo	6
(Drinking or alcohol) and KW=(Pregnancy or (Prenatal influences)) and KW=longitudinal studies	ERIC	11
KW=Drinking and KW=(Pregnancy or (Prenatal influences))	ERIC	8

A second reviewer has reviewed the search strings applied in this review.

Selection criteria

The studies were included in this review if they fulfilled the following selection criteria:

- Publication in a scientific, peer-reviewed journal.
- Examination of the offspring's cognitive and socioemotional development.
- Examination of low to moderate prenatal alcohol intake (i.e. 1-4 glasses per week or 12-48g of alcohol intake per week).
- Prospective studies.
- The study design was longitudinal, randomised or quasi-randomised controlled trials. The follow-up time of the children was between 3–16 years of age.
- The study describes their method and design. Studies that refer to other articles only are excluded.
- A control of socioeconomic status (ex. education, occupation, income) is included in the analyses, alternatively a determination of no statistical difference between the groups of no versus low alcohol intake.
- Representative population.

There is no broad consensus regarding the definition of light to moderate levels of alcohol intake (8). However, the definition of a light to moderate drinker in this review is a pregnant woman who consumes 12–48g of alcohol per week. This is equal to 1-4 standard drinks per week (AUDIT).

Since the focus is the cognitive and socioemotional development of the child, only studies that have examined children at aged 3 and above have been included. The argument behind this decision is that it is not possible to examine the effects on children at an early age since the appearance of symptoms and the development of cognitive functions mature later. The children concerned may show flaws regarding learning ability, attention and memory functions at school age (3).

High risk samples of mothers are excluded because the aim is to generalise to the wider population. Clinically diagnosed samples of children were also excluded.

Description of the studies included

The literature search on prenatal alcohol effects generated 962 articles. The abstracts of these papers were analysed. Of these, 65 articles were found to be potentially relevant and were therefore studied in full. This generated 6 articles that fulfilled the inclusion criteria.

The studies derive from US, England, Denmark, Finland and Australia. The child outcomes examined are intellectual ability, attention, memory and learning abilities, behavioural and emotional problems. Only three studies examined whether boys or girls are affected differently by prenatal alcohol consumption (9, 10, 11).

Three studies apply response categories regarding maternal alcohol intake (9, 10, 12), in addition three studies applies the AA Score which yields the average daily ounces of absolute alcohol consumed (11, 13–14). Effects of prenatal alcohol exposure can be detected from both types of alcohol intake reports.

The sample size in the studies varies between follow-up data from 128 women to 9086 women. The attrition rate varies between 18–48 percent. One study has performed sensitivity measurements in order to examine the effects of attrition (9). This study concluded that a minor increase in the strengths of the association between <1 glass per week and the child's health outcome (9).

Results

A TOTAL OF SIX STUDIES were included in this review (9–14). These studies presented eight analyses. Of these analyses, four show a significant association between prenatal alcohol exposure and child outcome (9, 11, 14) and four do not demonstrate such association (10, 12, 13).

In these studies the children's age span varies from 3 years of age up to 16 years of age. The result is therefore divided into three age periods - preschool children 3–5 years, schoolchildren 6–12 years and schoolchildren 13–16 years, see Table 2. Some studies appear several times in table 2, since these studies examine children across childhood (9, 10).

Preschool children 3–5 years

A total of three analyses examine the outcome of prenatal alcohol exposure on preschool age children (9, 11, 12). Of these three, two report prenatal alcohol effects on children's development at 3 to 4 years of age. Children who are exposed to prenatal alcohol intake have significantly more mental health problems that include hyperactive/inattention, conduct problems, emotional problems, peer relationship problems and are less attentive and have shorter "longest attention episodes" (9, 11). The one analysis that does not report such a finding examines children's development at 4 years of age using the subscales of Griffiths test (locomotors development, personal-social development, hearing and speech, hand and eye coordination, performance tests, practical reasoning) (12).

School children 6–12 years

Two analyses examine the outcome of alcohol consumption during pregnancy on schoolchildren 6–12 years (9, 10). One claims that less than one glass of alcohol intake per week during pregnancy is associated with behavioural and emotional problems that include hyperactive/inattention, conduct problems, emotional problems, peer relationship problems in children at 81 months and at 93–108 months of age. However, this effect is only demonstrated in girls and not in boys (9). Finally, one analysis did not detect effects of alcohol exposure on children's inattention and hyperactivity at 7-8 years of age and at 10–12 years of age (10).

School children 13–16 years

Three analyses examine long-term effects of low to moderate fetal alcohol exposure on school-children in their teenage years (10, 13, 14). Of these, only one reports deficits in attention and short-term memory or more specific tasks that require more complex decision-making (14). However, there are two analyses that claim that there are no long-term effects of prenatal alcohol exposure on hyperactivity, attention and on learning and intellectual ability at 14 to 15 years of age (10, 13).

Table 2. An overview of the results of this review

Reference	Sample	Alcohol level	Pregnancy period	Child outcome	Effect
Preschool children 3-5 years					
Landesman-Dwyer (1981) US (11)	Data from 128 women	Self-report Average alcohol intake per day (calculated by the method of Jessor et al.)	Throughout the pregnancy	Behaviour at 4 years of age Focused attention, longest focused attention episode, interrupted attention episodes, no overt attention to environment, fidgeting, positive responses to parental commands	Yes Children exposed to prenatal alcohol intake are less attentive and have shorter “longest attention episodes”
Olsen (1994) Denmark (12)	N = 251 mother-child pair (in the follow-up)	Self-report Average alcohol intake per week (declared – categorical)	Throughout the pregnancy or up to the 32nd week of gestation	Child development at 42 months of age Griffiths test (motor, social, numbers, coordination, and performance)	No Trends – lower score in children exposed to alcohol in pregnancy
Sayal (2007) England (9)	Information on alcohol N = 12678 mothers (93%) 47 months N = 9086	Self-report Response categories: never, <1 glass/week, ≥1 glass/week, 1–2 glasses/day, 3–9 glasses/day, >10/day	First trimester	Behavioural and emotional problems at 47 months of age The Strengths and Difficulties Questionnaire: four symptom scales – hyperactivity/inattention, conduct problems, emotional problems, peer relationships	Yes (in girls) Less than one glass/week was linked to clinically significant mental health problems

Reference	Sample	Alcohol level	Pregnancy period	Child outcome	Effect
Schoolchildren 6–12 years					
Rodriguez (2009)	Aarhus Birth Cohort (ABC)	Self-report	Throughout the pregnancy	Inattention and hyperactivity at 7–8 years of age (NFBC) and at 10–12 years of age (ABC)	No (all cohorts)
Denmark Finland (10)	1990-92: completed child behaviour questionnaires N = 4 968 children of 8 036 children. Eligible teachers attrition = 48 percent Northern Finland Birth Cohort (NFBC) 1986: reports for 92 percent (N = 8525)	Response categories: <1, 1–4, ≥5 or more per week			
Sayal (2007)	Information of alcohol N = 12 678 mothers (93%) 47 months N = 9 086 81 months N = 8 046	Self-report	First trimester	Behavioural and emotional problems at 81-, and 93–108 months of age The Strengths and Difficulties Questionnaire: four symptom scales – hyperactivity/inattention, conduct problems, emotional problems, peer relationships	Yes (in girls) Less than one glass/week was associated with mental health problems. These effects were confirmed at 93–108 months by teacher ratings

Reference	Sample	Alcohol level	Pregnancy period	Child outcome	Effect
Schoolchildren 13–16 years					
O'Callaghan (2007) Australia (13)	8 556 women were invited to participate At 14 years N = 5 139 mothers and adolescents	Interviewed In early and late pregnancy: average alcohol intake per day	Early pregnancy and late pregnancy	Attention, learning and intellectual ability at 14 years of age	No (neither in early or late pregnancy)
Rodriguez (2009) Denmark Finland (10)	Healthy habits for two (HHT) 1984–87: around 80 % of all women participated N = 11 148 women Follow-up questionnaires on child behaviour N = 10 363 mothers. Received N = 7 844	Self-report Response categories: <1, 1-4, ≥5 or more per week	Throughout the pregnancy	Inattention and hyperactivity at 15 years of age (HHT)	No (all cohorts)
Streissguth (1994) US (14)	Screening cohort of 1 529 women Follow-up about 500 children At age 14, 82% of the original children were examined	Self-report and maternal interviews at 5th month of pregnancy Average alcohol intake per day	Throughout the pregnancy	Attention (Digit Span Subtest from the Wechsler Intelligence Scale for Children-Revised (WISC-R), the Wisconsin Card Sorting test, the Talland Letter Cancellation Test, CPT) Short-term memory (Seashore Rythm Test, Stepping Stone Maze) at 14 years of age	Yes

Note. Only analyses of children 3 to 16 years of age is included in this table. For more details of method and results of these studies, see Appendix 1.

Discussion

Findings?

The aim of this study was to conduct a literature search to examine the association between low to moderate prenatal alcohol exposure and cognitive and socioemotional deficits in children. In this review we have shown that 4 of 8 analyses indicate cognitive and socioemotional deficits due to prenatal exposure of 1 to 4 glasses of alcohol consumption per week. In preschool children 2 of 3 analyses demonstrate effects while such effects were only found in 2 of 5 analyses of school children. The preschool children demonstrated behavioural problems and significant mental health problems which includes hyperactivity/inattention, conduct problems, emotional problems and peer relationships problems. The effects found were relatively small. The effects of prenatal alcohol exposure seems to be more difficult to establish when the children are older. One explanation might be that the exposure occurs at an early age and that the effects of different kinds of exposure generally decline with time. Due to the limited information included in these studies it was not possible to establish any dose-effect relationship. Not enough information was given to discern gender differences.

Methodological problems

Several efforts have been made to reduce possible bias in this review. In order to make sure that all relevant studies have been included several different search strings were entered in several databases in order to optimise the search. No geographical or time limitation regarding publication year has been imposed in this literature review. However if studies were indexed poorly or were not published in English they might not be included in this review. The literature search has been repeated by a second reviewer. With these efforts it is relatively certain that all the published articles in this domain have been covered.

One possible bias in these type of studies is how trustworthy the maternal self-report of alcohol intake during pregnancy really is, that is establishing the degree of exposure. Most studies faces this problem, but scholars claim that it is also associated with how close in time the self-report is to alcohol intake. Retrospective data collection of alcohol intake is more associated with underreport of the actually alcohol intake (3, 19). Therefore, only prospective studies were included in this review. Thus it is reasonable to assume that the reported alcohol intake reflects actual consumption.

There is a complex association between socioeconomic status and alcohol consumption. Low to moderate alcohol consumption is mostly linked to higher socioeconomic groups while heavy alcohol intake is associated with lower socioeconomic groups (10). Many earlier published studies on prenatal alcohol effect have been conducted on low socioeconomic samples. Studies with samples of low socioeconomic women only were excluded in this literature review for greater generalisability since social drinking is the focus here.

The causes of observed behavioural deficits in children are often difficult to establish. In addition to prenatal alcohol exposure, their behaviour has other determinants. This is one of the challenges for epidemiologic longitudinal studies. According to several authors many studies fail to control for social factors that, in addition to prenatal alcohol exposure, cause postnatal effects on children (16, 21). In the Seattle longitudinal studies, the authors have applied adjusted PLS analysis for concomitant pre and postnatal determinants of prenatal alcohol exposure. The best predictor for IQ, achievement, classroom behaviour and vigilance is parental education. Other covariates have little additional effect (15). All studies included in this review control for parental education (9–14). According to another scientist, maternal smoking and social adversity during pregnancy are independently linked to inattention and hyperactivity (10). However, the results of the studies included in this review hold after considering or adjusting for smoking (9, 11, 14). The studies are also adjusted for several other covariates, see Appendix 1 for more details.

It has also been suggested that there is a gene-environment correlation between maternal propensity for drinking alcohol during pregnancy and the offspring's predisposition for developing mental disorders (9). These are potential moderators on alcohol effects that cannot be excluded from epidemiological studies.

When it comes to limitations it should be mentioned that in the included Seattle study, mothers who had an AA score of 1.00 or higher (about 2 drinks per day) were prioritised when selected to the study. The study also contained infrequent drinkers and abstainers. This sample represents a broad range of alcohol exposure. The typical drinker based on median scores reached an AA level of 0.16 which is <1/2 a drink a day during pregnancy. Since continuous data is used, some mothers may drink above the low to moderate dose of alcohol intake that is our focus, if there is a dose-response relationship between prenatal alcohol exposure and neurobehavioral outcome it is not possible to exclude that the detrimental effects on attention and memory that has been established in this study might entirely be explained by the fact that some women were drinking above the alcohol levels of interest in this study. One advantage of this study is that the data concerning maternal alcohol intake during pregnancy was collected during a time when little was known about alcohol effects on fetuses. Consequently, it was more common to drink during pregnancy and the authors expect less reason for the mothers to minimise their reported alcohol intake. In spite of these problems this study was included since it is unlikely that more than a few women drinking more than 4 drinks a day might have been contained in the study.

Some of the studies that demonstrated effects of prenatal exposure to alcohol have collected information in a reliable manner. Thus in the Landesman-Dwyer study, naturalist observations were conducted during mealtimes, play sessions and story sessions to measure the effects of prenatal alcohol exposure (11). The principal investigator was unaware of the mothers' drinking classification during the observations. The inter-observer reliability was an average of 78 percent across codes and sessions, which is to be considered high. One advantage of this study is that the participation rates did not differ significantly regarding the drinking characteristics of the four groups of women (11).

In one of the studies there are no significant effects for higher doses of alcohol intake but less than one glass per week was associated with mental health problems. There are few mothers that drink heavily which decreases the possibility of identifying statistically significant differences; this might explain this inconsistency. The participants were informed and provided with examples to specify that 1 glass of alcohol was equivalent to 1 unit of alcohol (8g). One advantage of this study is its sensitivity analyses which examined the effects of missing data. The results show a minor increase in the strength of the link between <1 glass per week and outcomes assessed with "The strengths and difficulties questionnaire". It may be argued that the subjects that dropped out speculatively consumed more alcohol and had more problems which imply that this type of study underestimates the effect of alcohol on offspring. Furthermore, the scientists adjusted for postnatal factors such as maternal EPDS and alcohol consumption at 47 months. Since the results were only significant in girls, they imposed a stricter measurement cut-off. However the effect remained. These gender differences are unexpected because earlier research has established that boys seems to be more sensitive for central nervous system damages in comparison with girls (27). But as the authors discuss, as the results only apply to children with high levels of mental health problems it is appropriate to consider gene-environment correlation between maternal propensity to drink during pregnancy and the offspring's predisposition to developing a psychiatric disorder and the association between genes and attention-deficit/hyperactivity disorder (9).

Finally, I will end this discussion with four general questions. Firstly – is it possible to establish how large the impact of alcohol exposure is on children? Unfortunately, it is not possible to give a uniformed statement about effect sizes in this review, because the results in the publications are described using different measurements. In Sayal et als study, the Strengths and Difficulties Questionnaire is being used, resulting in an OR of 1.79 at child age 93–108 months (9). Other publications display the results as coefficients (α , β), number of episodes, etc. (see appendix 1 for more details). Secondly, another common question is whether one drink means the same for all women. Only one publication specifies that they have used examples to specify how much one glass of alcohol was equal to in units or in grams. Although the other included publications are providing less detail regarding the questionnaires or interviews, it is reasonable to assume that examples have been used in these studies as well. Thirdly, when it comes to the validity of the outcome

variables, all publications have used well known measurements or they account for high inter-observer reliability. Fourthly, what do we know about the women who did not participate or dropped out? The answer is that we don't know much, but it is more likely that these women drink more and possibly have more problems than not. Previous studies have shown that the drop-out rate is higher among individuals with higher levels of alcohol consumption (28–29). In that case the result in this review might be underestimated. The included publications have established that even small to moderate doses of alcohol consumption may have an impact on children's cognitive and socioemotional development.

Conclusion

FROM A CHILD PERSPECTIVE, it is safest if the mother abstains from alcohol consumption during pregnancy or when planning a pregnancy. As this literature review demonstrates, even small to moderate doses of alcohol intake might exert a negative affect on children. Children exposed to prenatal alcohol intake may show a significant increase of cognitive and socioemotional problems.

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20. Linnet KM, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: Review of the current evidence. *Am Psychiatry* 2003;160:1028-40.
21. Wright J, Toplis P, Waterson J. Alcohol and the fetus. *Br Hosp Med* 1983;March: 260-6.
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29. Leifman H. The measurement of alcohol-related social problems in Sweden. *J Subst Abuse* 2000;12(1-2):197-212.

Appendix 1. More detailed description of studies included

Reference	Alcohol level	Method	Effect
Landesman-Dwyer (1981)	Smokers and non smokers were divided into moderate drinkers and occasional or non-drinkers	Combination of interview, questionnaire, and naturalistic observation (15 minutes during mealtime and play session and 10 minutes during stories session in the home setting. The outcome was coded every 10 seconds. Assessment 3 hour * 8 times)	Examined behaviourally at age 4 (focused attention, longest focused attention episode, interrupted attention episodes, no overt attention to environment, fidgeting, positive responses to parental commands)
US (11)	Maternal drinking: Average alcohol intake per day AA and QFV Score (the lowest score is 0 = abstainer and the highest is 4 = heavy drinker) Average moderate drinker mean = 0.45 oz No one reported binge drinking of four drinkers per day	Interobserver reliability averaged 78% Maternal education level is not significant between groups Covariates for birth order (proxy for parent-child interactions, child development) Covariates for total HOME score were temperament scores and behavioural observations Independent variables in addition to alcohol intake: smoking, child's gender, birth weight	ANCOVA Mealtime: Number of interrupted focused attention episodes $F(1,127)=5.31, p=0.02$, longest focused attention episodes $F(1,127)=4.37, p=0.03$, not attending to objects or persons $F(1,127)=3.86, p=0.05$, and positive responses to parental commands $F(1,127)=4.59, p=0.03$ Children exposed to moderate prenatal alcohol intake are less attentive and have shorter "longest attention episodes" Boys showed more fidgety behaviour than girls $F(1,127)=6.73, p=0.01$ No significant main or interaction effects of smoking Story time: tendency Gender interactions: no overt attention to the environment $F(1,127)=7.84, p=0.01$

Reference	Alcohol level	Method	Effect
Olsen (1994) Denmark (12)	Average consumption of 5 drinks or more/wk in the first trimester were recruited Average intake of alcohol: >1 drink/wk; 1-4 drinks/wk; 5-9 drinks/wk; 10+ drinks/wk Binge drinking: 0; 1-4 times; 5+ times; Father's average intake	1:1 matched pregnant women (similar age and expected time of delivery) 164 x 2 women were recruited N = 251 mother-child pair (in the follow-up) Attrition: 44 children, original 295 children at the second follow-up Effects of child development at 18 and 42 months Control for mother and fathers school education, type of residence, smoking in pregnancy	No (including binge drinking) At 42 months – Griffiths test (motor, social, numbers, coordination, and performance) Trends – lower score in children exposed to alcohol in pregnancy

Reference	Alcohol level	Method	Effect
Sayal (2007) England (9)	Self-report (postal questionnaire at 18 week's gestation) Low level (<1 drink per week) Response categories: never, <1 glass/week, ≥1 glass/week, 1–2 glasses/day, 3–9 glasses/day, >10/day	The Avon Longitudinal Study of Parents and Children (ALSPAC) Information of alcohol N = 12 678 mothers (93%) 47 months N = 9 086 81 months N = 8 046 Controls for maternal age, smoking, cannabis use, illicit drug use, parity, highest maternal education, own home, currently married, maternal depression, gestational age, ethnicity, gender, birth weight Sensitivity analyses examined the effects of missing data. There was a minor increase in the strength of the association between <1 glass/wk and SDQ scores. Control for postnatal factors such as maternal EPDS and alcohol consumption at 47 months followed, and stricter SDQ cut off. Result only statistically significant in girls	Yes (in girls) The Strengths and Difficulties Questionnaire: four symptom scales – hyperactivity/inattention, conduct problems, emotional problems, peer relationships which are summed to provide a total score, and a prosocial behaviour scale At age 47 months Multivariable OR Parent SDQ <1 glass = 1.48 (1.05-2.10) At age 81 months Multivariable OR Parent SDQ <1 glass = 1.62 (1.10-2.38) At age 93-108 months Multivariable OR Teacher SDQ <1 glass = 1.79 (1.06-3.00) Less than one glass/week was associated with high total SDQ scores in girls at 47 months, and 81 months, that is independently linked to clinically significant mental health problems. These effects were confirmed at 93–108 months by teacher ratings

Reference	Alcohol level	Method	Effect
Rodriguez (2009)	Self-report	Three cohorts with varying alcohol consumption	No (all cohorts)
Denmark	Categories: <1, 1-4, ≥5 or more/wk	Recruited via government-run antenatal health services	Inattention and hyperactivity (the core of ADHD symptoms)
Finland		Nordic Network on ADHD f	One exception ABC teacher p<0.1 after adjusted model
(10)		Aarhus Birth Cohort (ABC) 1990-92: completed child behaviour questionnaires N = 4 968 children of 8036 children. Eligible teacher attrition = 48 percent	
		Northern Finland Birth Cohort (NFBC) 1986: Reports for 92 percent (N = 8525)	
		Healthy habits for two (HHT) 1984-87: around 80 percent of all women participated N = 11 148 women. Follow-up questionnaires on child behaviour N = 10363 mothers. Received N = 7 844	
		At age 10-12 years old (ABC); 7-8 years old (NFBC); 15 years old (HHT)	
		Examined drinking, social adversity, smoking, and attrition across cohorts	
		Model 1: unadjusted Model 2: smoking, social adversity, birth weight and gestational age The model were conducted separately by gender	

Reference	Alcohol level	Method	Effect
O'Callaghan (2007) Australia (13)	In early pregnancy: on average 0.146 oz AA per day (1/3 glass per day or 2 glasses per week) Late pregnancy: 0.074 oz AA per day (1/7 glass/day or 1 glass/ wk)	Mater-University of Queensland Study of Pregnancy 8556 women were invited to participate At 14 years N = 5139 mothers and adolescents Control for maternal BMI, smoking, social risk score, low maternal education, maternal age, single parent status or low income in pregnancy or at 14 years of age	No (neither in earlier or late pregnancy) Attention, learning and intellectual ability at 14 years of age
Streissguth (1994) US (14)	Self-report and mater- nal interviews at 5th months of pregnancy AA Score QFV Score Typical drinker during pregnancy reported: AA mean = 0.32 AA median = 0.16 (<1/2 a drink/day) Prior pregnancy or recognition of preg- nancy and during pregnancy	The Seattle Longitudinal Prospective Study on Alcohol and Pregnancy Representative sample of the women in Seattle Screening cohort of 1529 women Follow-up about 500 children At age 14, 82% of the original children were examined Control for maternal nutrition, use of drugs and medica- tions, SES, education, mother-child interactions, major life stresses in household, child accidents, hospitalisations and illnesses, educational experiences of child etc.	Yes Attention and short-term memory at age 14 PLS: 13 alcohol scores and 52 attention/memory scores Sum of squares of each column is 1.00 AA during $\alpha = -0.22$ (the binge scores ADOCC, QFV, MAX, and BINGE have the highest salience $\alpha =$ between -0.38 too -0.27) Strongest association with prenatal alcohol exposure: CPT (reaction time) $\beta =$ range from 0.20 to 0.27 Talland (letter cancellation) $\beta = -0.25$ for total correct both capitals and spaces Stepping stone maze $\beta = 0.21$ for number of trials to first success See table 4 in the article for more details Fluctuating attentional states, problems with response inhibition and spatial learning

Note. Only effects significant at $p \leq 0.05$ are viewed
Only analyses of children over 3 years of age are included

Appendix 2. Excluded studies

Excluded studies	Reason why excluded
Alati R, Macleod J, Hickman M, Sayal K, May M, Smith G, et al. Intrauterine exposure to alcohol and tobacco use and childhood IQ: findings from a parental-offspring comparison within the Avon longitudinal study of parents and children. <i>Pediatr Res</i> 2008;64:659-66.	Incorrect dose of alcohol intake. 1–6 glasses per week. Mean change in IQ per increase in alcohol categories. No description on average alcohol intake
Alvik A, Heyerdahl S, Haldorsen T, Lindemann R. Alcohol use before and during pregnancy: a population-based study. <i>Acta Obstet Gynecol</i> 2006:1-7.	Incorrect focus – prevalence
Aronson M, Hagberg B. Neuropsychological disorders in children exposed to alcohol during pregnancy: A follow-up study of 24 children to alcoholic mothers in Göteborg, Sweden. <i>Alcohol Clin Exp Res</i> 1998;22:321-24.	Not a representative sample. Alcoholic mothers
Aronson M, Hagberg B, Gillberg C. Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: a follow-up study. <i>Dev Med Child Neurol</i> 1997;39:583-87.	Not a representative sample. Alcoholic women
Autti-Rämö I. Twelve-year follow-up of children exposed to alcohol in utero. <i>Dev Med Child Neurol</i> 2000;42:406-11.	Not a representative sample. Heavy drinkers and special clinic
Autti-Rämö I, Autti T, Korkman M, Kettunen S, Salonen O, Valanne L. MRI findings in children with school problems who had been exposed prenatally to alcohol. <i>Dev Med Child Neurol</i> 2002;44:98-106.	Not a representative sample. Special clinic? Small sample
Autti-Rämö I, Korkman M, Hilakivi-Clarke L, Lehtonen M, Halmesmäki, E, Granström ML. Mental development of 2-year-old children exposed to alcohol in utero. <i>J Pediatr</i> 1992;120:740-46.	Not a representative sample. Clinic for alcohol consuming pregnant women
Bachman JG, et al. Smoking, drinking, and drug use in young adulthood: The impacts of new freedoms and new responsibilities. <i>Research monographs in adolescence (RMA)</i> 1997:241 pp	Incorrect focus. Prevalence
Barr HM, Bookstein FL, O'Malley KD, Connor PD, Huggins JE, Streissguth AP. Binge drinking during pregnancy as a predictor of psychiatric disorders on the structured clinical interview for DSM-IV in young adult offspring. <i>Am J Psychiatry</i> 2006;163:1061-1065.	Oversampled for heavier drinkers. Incorrect focus - binge drinking
Brookes KJ, Mill J, Guindalini C, Curran S, Xu X, Knight J, chen CK, Huang YS, Sethna V, Taylor E, Chen W, BreenG, Asherson P. A common Haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. <i>Arch Gen Psychiatry</i> 2006;63:74-81.	Children with ADHD
Caruso K, ten Bensel R. Fetal alcohol syndrome and fetal alcohol effects. <i>Clinical & Health Affairs</i> 1993;76:25-29.	Not a representative sample

Excluded studies	Reason why excluded
Chapman K, Tarter RE, Kirischi L, Cornelius MD. Childhood neurobehavior disinhibition amplifies the risk of substance use disorder: Interaction of parental history and prenatal alcohol exposure. <i>J Dev Behav Pediatr</i> 2007;28:219-24.	Only boys were recruited
Coles CD. Fetal alcohol exposure and attention: moving beyond ADHD. <i>Alcohol Res Health</i> 2001;25:199-203.	Incorrect focus. FAS, FAE and ADHD
Coles CD, Brown RT, Smith IE, Platzman KA, Erickson S, Falek A. Effects of prenatal alcohol exposure at school age. I. Physical and cognitive development. <i>Neurotoxicol Teratol</i> 1991;13:357-67.	Not a representative sample
Coles CD, Smith IE, Falek A. Prenatal alcohol exposure and infant behavior: Immediate effects and implications for later development. <i>Adv Alcohol Subst Abuse</i> 1987;6:87-105.	Not a representative sample. Low SES women
Connor PD, Sampson PD, Bookstein FL, Barr HM, Streissguth AP. Direct and indirect effects of prenatal alcohol damage on executive function. <i>Dev Neuropsychol</i> 2000;18:331-54.	Clinical group FAS and FAE
Connor PD, Sampson PD, Streissguth AP, Bookstein FL, Barr HM. Effects of prenatal alcohol exposure on fine motor coordination and balance: A study of two adult samples. <i>Neuropsychologica</i> 2006;44:744-51.	Incorrect outcome
Connor PD, Streissguth AP, Sampson PD, Bookstein FL, Barr HM. Individual differences in auditory and visual attention among fetal alcohol-affected adults. <i>Alcohol Clin Exp Res</i> 1999;23:1395-402.	Small sample n = 11 adult patients with FAS or FAE
Disney ER, Iacono W, McGue M, Tully E, Legrand L. Strengthening the case: prenatal alcohol exposure is associated with increased risk for conduct disorder. <i>Pediatrics</i> 2008;122:e1225-e1230.	Incorrect independent variable. Non drinkers vs drinkers (≥ 1 drink coded positive as drinking during pregnancy)
Dónofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Rathouz PJ, Lahey BB. Causal inferences regarding prenatal alcohol exposure and childhood externalizing problems. <i>Arch Gen Psychiatry</i> 2007;64:1296-304.	No information on doses (measure alcohol intake for each additional day)
Faden VB, Graubard, BI. Maternal substance use during pregnancy and developmental outcome at age three. <i>J Subst Abuse</i> 2000; 12:329-340.	Insufficient information on alcohol doses
Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. <i>Neurotoxicol Teratol</i> 2004;26:521-32.	Not a representative sample. Lower socioeconomic status
Goldschmidt L, Richardson GA, Stoffer DS, Geva D, Day NL. Prenatal alcohol exposure and academic achievement at age six: A nonlinear fit. <i>Alcohol Clin Exp Res</i> 1996;20:763-70.	Not a representative sample. Lower socioeconomic status

Excluded studies	Reason why excluded
Heller J, Anderson HR, Bland JM, Brooke OG, Peacock JL, Stewart CM. Alcohol in pregnancy: patterns and association with socio-economic, psychological and behavioural factors. <i>Br J Addict</i> 1988;83:541-51.	Incorrect focus – prevalence
Holzman C, Paneth N, Little R, Pinto-Martin J, the Neonatal brain hemorrhage study team. Perinatal brain injury in premature infants born to mothers using alcohol in pregnancy. <i>Pediatrics</i> 1995;95:66-73.	Incorrect focus – brain injury in premature infants
Howell KK, Lynch ME, Platzman KA, Smith GH, Coles CD. Prenatal alcohol exposure and ability, academic achievement, and school functioning in adolescence: A longitudinal followup. <i>J Pediatr Psychol</i> 2006;31:116-26.	Not a representative sample. 265 low SES adolescents
Hunt E, Streissguth AP, Kerr B, Carmichael Olson H. Mothers' alcohol consumption during pregnancy: Effects on spatial-visual reasoning in 14-year-old children. <i>American Psychological Society</i> 1995;6:339-42.	Incorrect focus
Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R. Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. <i>Alcohol Clin Exp Res</i> 2004;28:1732-45.	Incorrect independent variable. Moderate-to-heavily exposed children
Jacobson JL, Jacobson SW, Sokol RJ, Martier SS, Ager JW, Kaplan-Estrin MG. Teratogenic effects of alcohol on infant development. <i>Alcohol Clin Exp Res</i> 1993;17:174-83.	Not a representative sample. Lower socioeconomic class
Kelly Y, Sacker A, Gray R, Kelly J, Wolke D, Quigley MA. Light drinking in pregnancy, a risk for behavioural problems and cognitive deficits at 3 years of age?. <i>Int J Epidemiol</i> 2008;1: 1-12.	Retrospective data collection of alcohol intake during pregnancy
Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, Waldron M, Martin NG. Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design. <i>Psychol Med</i> 2006;36:1461-71.	Incorrect focus
Korkman M, Hilakivi-Clarke LA, Autti-Rämö I, Fellman V, Granström M-L. Cognitive impairments at two years of age after prenatal alcohol exposure or perinatal asphyxia. <i>Neuropediatrics</i> 1994;25:101-5.	Incorrect independent level. Heavy alcohol exposure? Small sample n =60
Larroque B, Kaminski M. Prenatal alcohol exposure and development at preschool age: Main results of a French study. <i>Alcohol Clin Exp Res</i> 1998;22:295-03.	Mainly of low SES. Heavy drinkers are overrepresented in the sample. Incorrect doses
Larroque B, Kaminski M, Dehaene P, Subtil D, Delfosse MJ, Querleu D. Moderate prenatal alcohol exposure and psychomotor development at preschool age. <i>Am J Public Health</i> 1995;85:1654-61.	Mainly of low SES. Heavy drinkers are overrepresented in the sample. Incorrect doses

Excluded studies	Reason why excluded
Lumeng JC, Cabral HJ, Cannon TH, Frank DA. Pre-natal exposures to cocaine and alcohol and physical growth patterns to age 8 years. <i>Neurotoxicol Teratol</i> 2007;29:446-57.	Incorrect focus. Outcome weight, height, and head circumference
Milotová M, Riljak V, Jandová K, Bortelová J, Maresová D, Pokorný J, Langmeier M. Changes of hippocampal neurons after perinatal exposure to ethanol. <i>Physiol Res</i> 2008;57:275-82.	Incorrect focus – structural changes
Newman NM, Correy JF. Effects of alcohol in pregnancy. <i>Med J Aust</i> 1980;2:5-10.	A non systematic review. Out of date
Nordberg L, Rydelius P-A, Zetterström R. Children of alcoholic parents: health, growth, mental development and psychopathology until school age. Result from a prospective longitudinal study of children from the general population. <i>Acta Pædiatr Suppl</i> 1993;387:1-24.	Not a representative sample. Alcoholic women
Nulman I, Rovet J, Kennedy D, Wasson C, Gladstone J, Fried S, Koren G. Binge alcohol consumption by non-alcoholdependent women during pregnancy affects child behaviour, but not general intellectual functioning; a prospective controlled study. <i>Arch Womens Ment Health</i> 2004;7:173-81.	Incorrect focus – binge alcohol consumption
Olson HC, Streissguth AP, Sampson PD, Barr HM, Bookstein FL, Thiede K. Association of prenatal alcohol exposure with behavioral and learning problems in early adolescence. <i>J Am Acad Child Adolesc Psychiatry</i> 1997;36:1187-94.	Incorrect dose of alcohol consumption
Peterson J, Kirchner HL, Xue W, Minnes S, Singer LT, Bearer CF. Fatty acid ethyl esters in meconium are associated with poorer neurodevelopmental outcomes to two years of age. <i>J Pediatr</i> 2008;152:788-92.	Not a representative sample
Plant ML. Drinking in pregnancy and fetal harm: Results from a Scottish prospective study. <i>Midwifery</i> 1986;2:81-85.	Incorrect focus. Birth abnormalities
Rasmussen C. Executive functioning and working memory in fetal alcohol spectrum disorder. <i>Alcohol Clin Exp Res</i> 2005;29:1359-67.	A non systematic review
Rosett HL, Weiner L. Alcohol and pregnancy: A clinical perspective. <i>Ann Rev Med</i> 1985;36:73-80.	A non systematic review
Russell M, Czarnecki DM, Cowan R, McPherson E, Mudar PJ. Measures of maternal alcohol use as predictors of development in early childhood. <i>Alcohol Clin Exp Res</i> 1991;15:991-1000.	Incorrect dose of alcohol consumption
Sampson PD, Streissguth AP, Barr HM, Bookstein FL. Neurobehavioral effects of prenatal alcohol: Part II. Partial Least Squares Analysis. <i>Neurotoxicol Teratol</i> 1989;11:477-491.	Refers to earlier studies
Streissguth AP, Barr HM, Martin DC. Maternal alcohol use and neonatal habituation assessed with the Brazelton scale. <i>Child Dev</i> 1983;54:1109-18.	Incorrect age – newborn infants

Excluded studies	Reason why excluded
Streissguth AP, Barr HM, Martin DC. Alcohol exposure in utero and functional deficits in children during the first four years of life. Mechanism of alcohol damage in utero 1984;176-96.	Symposium Incorrect dose of alcohol consumption
Streissguth AP, Barr HM, Sampson PD. Moderate prenatal alcohol exposure: Effects on child IQ and learning problems at age 7 1/2 years. Alcohol Clin Exp Res 1990;14:662-69.	Incorrect dose of alcohol consumption. Poor description of doses
Streissguth AP, Barr HM, Sampson PD, Darby DC, Martin DC. IQ at age 4 in relation to maternal alcohol use and smoking during pregnancy. Dev Psychol 1989;25:3-11.	Incorrect dose of alcohol consumption. The cut-off is about 3 drinks per day or 1.5 oz
Streissguth AP, Barr HM, Sampson PD, Parrish-Johnson JC, Kirchner GL, Martin DC. Attention, distraction and reaction time at age 7 years and prenatal alcohol exposure. Neurobehav Toxicol Teratol 1986;8:717-25.	Incorrect dose of alcohol consumption
Streissguth AP, Bookstein FL, Sampson PD, Barr HM. Neurobehavioral effects of prenatal alcohol: Part III. PLS analyses of neuropsychologic test. Neurotoxicol Teratol 1989;11:493-507.	It is not possible to deduce the doses of alcohol we are interested in
Streissguth AP, Martin DC, Barr HM. The Seattle longitudinal prospective study on alcohol and pregnancy. Neurobehav Toxicol Teratol 1981;3:223-33.	Description of the Seattle longitudinal study
Streissguth AP, Sampson PD, Olson HC, Bookstein FL, Barr HM, Scott M, Feldman J, Mirsky AF. Maternal drinking during pregnancy: Attention and short-term memory in 14-year-old offspring – A longitudinal prospective study. Alcohol Clin Exp Res 1994;18:202-18.	Incorrect dose of alcohol consumption
Van Der Leeden M, Van Dongen K, Kleinhout M, Phaff J, De Groot CJ, De Groot L, Hesselings PB. Infants exposed to alcohol prenatally: outcome at 3 and 7 months of age. Ann Trop Paediatr 2001;21:127-34.	Not a representative sample. Low SES area. Small sample n = 29 exposed children
Walpole I, Zubrick S, Pontré J, Lawrence C. Low to moderate maternal alcohol use before and during pregnancy, and neurobehavioural outcome in the newborn infant. Dev Med Child Neurol 1991;33:875-83.	Incorrect age (newborn infant)
Willford JA, Leech SL, Day NL. Moderate prenatal alcohol exposure and cognitive status of children at age 10. Alcohol Clin Exp Res 2006;30:1051-1059.	Not a representative sample. Lower SES class
Willford JA, Richardson GA, Leech SL, Day NL. Verbal and visuospatial learning and memory function in children with moderate prenatal alcohol exposure. Alcohol Clin Exp Res 2004;28:497-507.	Not a representative sample. Lower SES class
Wright JT, Barrison I, Toplis PJ, Waterson J. Alcohol and the fetus. Br J Hosp Med 1983; March:260-66.	A not a systematic review