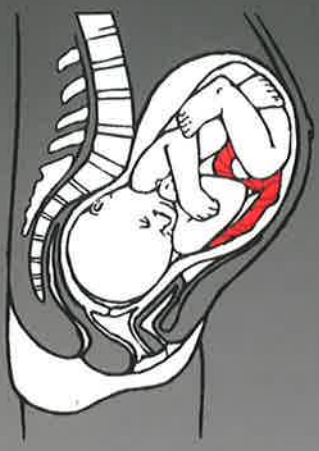
Alcohol, Pregnancy, and Child Development



Paul H. Verkerk

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P.H. Verkerk
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Stellingen
behorend bij het proefschrift
Alcohol, Pregnancy and Child Development

1. Zwangere vrouwen moeten niet meer dan één alcoholische consumptie per dag gebruiken gedurende de gehele zwangerschap.
(dit proefschrift)

2. Het gebruik van retrospectieve in plaats van prospectieve gegevens over roken en drinken tijdens de zwangerschap leidt tot minder bias dan vaak wordt verondersteld.
(dit proefschrift)

3. In tegenstelling tot wat in epidemiologie leerboeken vermeld staat kan niet-differentiële misclassificatie wel degelijk leiden tot een overschatting in plaats van een onderschatting van een effect.
(dit proefschrift)

4. Meetmethoden die het meest valide zijn in survey-onderzoek naar alcoholgebruik in een populatie zijn niet per definitie tevens de meest valide methoden in epidemiologisch onderzoek.
(dit proefschrift)

5. Bij het bepalen van de à terme datum moet meer rekening gehouden worden met de lichaamslengte van de zwangere.
(dit proefschrift)

6. Moeders die borstvoeding geven zouden, als ze alcohol willen gebruiken dit niet vóór maar juist kort ná het voeden moeten doen.
(N.a.v. Mennella et al. N Engl J Med 1991;325:981-5)

7. Bij screeningsprogramma's is continue evaluatie en terugkoppeling van de resultaten naar uitvoerders essentieel voor de handhaving en verbetering van de kwaliteit van het programma.

8. In epidemiologie onderwijs moet meer aandacht besteed worden aan vooringenomenheid van de onderzoeker als oorzaak van bias.

9. Nog steeds wordt algemeen aangenomen dat verschillen tussen PKU-patiënten en de algemene populatie pas na de geboorte optreden. De bevindingen dat PKU-patiënten een lager geboortegewicht en vaker een aangeboren hartafwijking hebben, maken dat hierbij op zijn minst vraagtekens geplaatst moeten worden.
(N.a.v. Verkerk et al. J Pediatr 1991;119:282-3 en Verkerk et al. Arch Dis Child 1994;71:114-8)

10. Lage respons bij een onderzoek komt voor een belangrijk deel voort uit slechte communicatie.

11. Voorstanders van loting bij de selectie van studenten wijzen met name op de matig voorspellende waarde van schoolcijfers. Dit is inconsequent aangezien zij zelf voorstander zijn van een selectieprocedure die volstrekt geen voorspellende waarde heeft.

12. De door Commissies Medische Ethiek vereiste zinsneden zoals "Deelname aan het onderzoek is natuurlijk geheel vrijwillig en hoewel wij hopen op uw medewerking, is het te allen tijde mogelijk van verdere deelname af te zien." kunnen tot zodanige non-response leiden dat het ethisch niet meer verantwoord is het onderzoek uit te voeren.

13. Een goede docent onderscheidt zich van een slechte docent door het vermogen een sfeer te creëren waarin ook 'domme' vragen gesteld kunnen worden.

14. Alcohol vormt een afrodisiacum voor vrouwen, maar juist niet voor mannen.
(N.a.v. Eriksson et al. Nature 1994;369:711.)

Leiden, 20 november 1996
Paul H. Verkerk

ALCOHOL, PREGNANCY, AND CHILD DEVELOPMENT

PROEFSCHRIFT

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Voor Andrea

CONTENTS

Chapter 1. Introduction

Fetal alcohol syndrome

In the saga of Samson an angel appears to the hero's mother before she is pregnant and cautions:

> Behold now, thou art barren, and bearest not: but thou shalt conceive, and bear a son.
> Now therefore beware, I pray thee, and drink not wine nor strong drink, and eat not any unclean thing.

Judges 13:3-4

This biblical passage is often cited as proof that the ancient Hebrews were already aware of the fact that alcohol may have a deleterious effect on the fetus. However, in an excellent review on the various epochs of the history of the fetal alcohol syndrome Abel points out what the real meaning of this excerpt is.[1] The angel is not warning Samson's mother for the teratogenic effects of alcohol but makes it clear that Samson is predetermined to live the ascetic life of a Nazirite. In the next verse (Judges 13:5) it is stated: "... for the child shall be a Nazirite unto God from the womb ... ". The pledge of the Nazirites prohibited those who took it, from the use of intoxicants, from cutting their hair and from touching dead bodies. Samson was predestined to become a Nazirite from the moment of his conception ("from the womb").

There are more passages in the ancient and medieval world where there seems to be a prerecognition of the deleterious effects of alcohol on the fetus. According to Abel in all these passages the drinking habits of the father are considered to be harmful for the developing child. An awareness that drinking of the mother during pregnancy may be related with birth defects came into place not until the end of the 19th century. But the evidence at that time was not considered very convincing. Not the drinking habits of the parents but social and constitutional factors in which alcoholic parents differed from non-alcoholic parents were regarded as the real cause.

The first detailed description of the offspring of excessively drinking parents appeared in 1968.[2] In this French study Lemoine et al described the following remarkable features in 127 children born to alcoholic parents, especially to alcoholic mothers:

"*Quatre points nous ont particulièrement frappés chez ces enfants:*
- un faciès très particulier;
- une hypotrophie staturo-pondérale considérable;
- une grande fréquence de malformations;
- des perturbations psycho-motrices."

Since the report was published in French it did not receive much attention. Unaware of this French study Jones et al reported comparable results.[3-5] Jones was also the first to use the term "fetal alcohol syndrome". The studies of Lemoine and Jones were case reports. The authors could, thus, not refute the criticism that the cause of the defects was not the alcohol use but other factors related to alcoholism. However, these studies led to widespread attention for the possible dangers of drinking during pregnancy and to new research in this area.

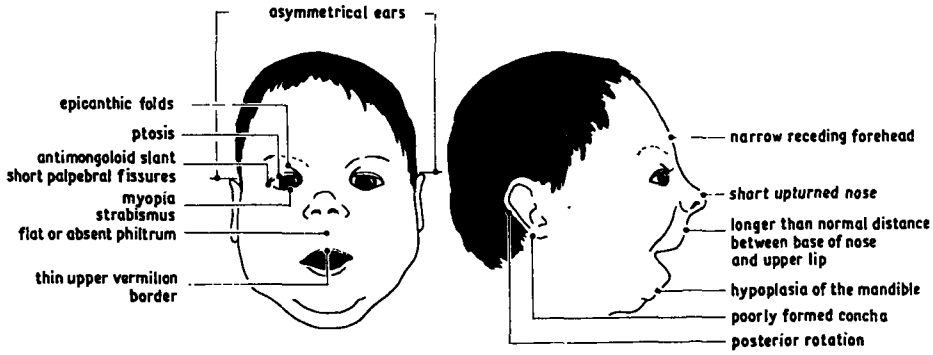
A diagnosis of fetal alcohol syndrome (FAS) can be made when the patient has signs of abnormality in each of the following three categories:[6]
- a characteristic facial dysmorphology (including short palpebral fissures, elongated midface, a long and flattened philtrum, thin upper lip, and flattened maxilla) (see figure 1);
- prenatal and/or postnatal growth retardation (below the 10th percentile in weight and/or length or height after correction for gestational age);
- central nervous system involvement (including neurological abnormality, developmental delay, behavioral dysfunction or deficit, intellectual impairment and/or structural abnormalities, such as microcephaly (head circumferences below third percentile) or brain malformations found on imaging studies or autopsy).

Available studies show that not all alcoholic mothers will give birth to an infant with FAS. Estimates range from 1 to 10 percent.[7,8] This suggests that alcohol use alone is not a sufficient cause and that other factors such as (illicit) drugs may also play a role. Unfortunately, the study of such factors has received little attention in the literature. Alcohol is not specific in producing the facial dysmorphology considered typical for FAS.[9] Maternal phenylketonuria, the use of certain drugs and perhaps any teratogen to which the fetus is exposed at specific moments during pregnancy may lead to a FAS-phenotype. Pregnant mothers with phenylketonuria, who are not on a strict diet, have offspring that is exposed to high levels of phenylalanine during pregnancy. These infants

often have a facial appearance that resembles that of FAS. Interestingly, as in children with FAS, children of mothers with untreated phenylketonuria have frequencies of growth retardation, microcephaly and mental retardation that are greatly increased over those in the normal population.[10] Furthermore, drugs such as hydantoins and toluene abuse can also produce the phenotype of FAS.[11] Animal research even suggests that any teratogen exposure during the gastrulation stage of embryogenesis results in craniofacial, brain and eye defects corresponding to those noted in severe forms of FAS.[9] The naming of the syndrome may cause that it is unlikely that FAS will be reported in the absence of alcohol use during pregnancy.[9] Thus, some women who have drunk considerably during pregnancy may have a child with a FAS-phenotype and will be considered to have child with FAS, although their drinking behaviour was not the cause of this phenotype. This will result in an overestimation of the prevalence of FAS.

The world-wide prevalence of FAS is estimated to be 1.9 per 1000 live births.[7] However, prevalence rates vary considerably, depending on study site. The best available estimate of FAS in the Netherlands is provided by the Dutch centers of the European Registration of Congenital Anomalies and Twins (EUROCAT). Their estimate is one case per 231.000 live births.[12] This low prevalence rate may be caused by the fact that registration takes place on a voluntary basis, and because parents have to give permission to supply their data to be entered into the registration.

Figure 1 Facial features of the fetal alcohol syndrome[13,14]



Experimental studies

Alcoholics are very different from non-alcoholics in many respects, such as for instance addiction to other drugs, smoking and nutritional status. To identify the effects of alcohol per se on the fetus in alcoholics will, therefore, be very difficult if not impossible. Researchers have developed animal models to study the effects of alcohol on the fetus. These models provide an opportunity for very carefully controlled experiments. Animal models in alcohol research have been able to duplicate virtually all reported effects found in humans.[1] These effects range from gross morphological defects at one extreme to subtle cognitive and behaviourial dysfunctions on the other end.[15] These studies support the hypothesis that alcohol use is the causal factor in FAS. Dose and pattern of alcohol intake as well as duration and period of exposure may play a role in the size of effects. Peak blood alcohol levels seem to be more important than the total dose of alcohol consumed. Thus, high levels in a short time period may cause more harm than a low level during a longer period, despite the fact that the total amount of alcohol may be the same.[15] Animal research has shown that birth defects are related to critical periods for specific aspects of fetal development. In the period of organogenesis (first trimester) exposure to alcohol may lead to gross morphological defects. When exposure to alcohol takes place in a later period of gestation when the brain is undergoing rapid growth (second and third trimester), behaviourial deficits are commonly observed.[15]

A limitation of animal research is that it is questionable whether the results can be generalized to humans. However, the teratogenic effects of alcohol have not only been found in animals such as mice and rats, but also in animals that resemble humans more closely such as nonhuman primates.[16]

Mechanisms

Because of its solubility in water and fat, alcohol readily diffuses across all cell membranes and is distributed equally throughout all body tissues in proportion to their tissue water content.[1] It also rapidly crosses the placenta and equilibrates between the mother and the fetus.[15] That alcohol passes the placenta quickly was also demonstrated in an experimental study in 12 pregnant women who were their own controls.[17] Consumption of two glasses of white wine led to a reduction in fetal breathing movements after 15-30 minutes.

In a review on the pathophysiological events underlying alcohol teratogenesis Schenker mentioned three main, non-exclusive, mechanisms.[15] These are (1) fetal hypoxia, (2) excess formation of certain prostaglandins, and (3) a direct effect of alcohol on developing cells, especially of the central nervous system, altering net protein synthesis, neuronal membrane composition and/or neuronal process formation, and production of neurotrophic factors needed for cell growth and interaction. Hypoxia may be caused by

a compromised blood flow to the placenta. A moderate dose of alcohol will lead to a rapidly reversible collapse of umbilical vessels in pregnant monkeys.[18] However, this effect could not be detected in a study with six pregnant women.[19] Prostaglandins are critically involved in all stages of pregnancy from implantation through initiation of labour, as well as in normal fetal growth and development. Furthermore, they play a role in the regulation of placental blood flow. Alcohol has been shown to interact with prostaglandins in various body tissues and could thus be an important factor in alcohol teratogenesis. Alcohol has a direct effect on developing as well as on mature cells. Thiamine malnutrition can cause brain damage in alcoholics, but alcohol per se can also cause direct neuronal damage in cerebral cortex which, in turn, can contribute to cognitive impairment.[20]

Research questions

The combined evidence from animal models as well as from observations made in infants of alcoholic mothers strongly supports the hypothesis that alcohol and its metabolite acetaldehyde can be teratogenic in humans. Current estimates place the human fetus at risk for the physical signs of the FAS if maternal drinking during pregnancy is six drinks or more per day.[21] Animal studies have found that many of the teratogenic actions of alcohol are dose-dependent.[15] Therefore, moderate levels of alcohol intake during pregnancy may also be harmful for the developing human fetus. If there are any effects of moderate levels, they are likely to be subtle in the individual case. However, from a public health point of view these subtle effects may be considerable, and could even be more important than the effects of excessive drinking since moderate drinking is much more prevalent.

The main aim of this thesis is to test the hypothesis that moderate drinking during pregnancy has a deleterious effect on fetal development. Moderate drinking will be defined as drinking in the range of one drink per week to two drinks per day. We performed several epidemiological studies to test this hypothesis. In some of these studies information on alcohol intake during pregnancy was collected after the birth of the baby. Since cases may report exposure information differently from controls, we examined the magnitude of this bias (Part I). Unfortunately, specific biological alcohol markers do not exist. Therefore, the quantification of alcohol consumption in our studies was based on self reports of the participating women. There is ample evidence that self reports may be prone to considerable underestimation. We, therefore, examined how underestimation may distort effect estimates (Part I).

Infants with FAS have a reduction in birthweight that persists after correction for gestational age (small for gestational age). Furthermore, infants with FAS are often born

preterm.[1] The relationship between these outcomes and moderate alcohol consumption will be examined in Part II.

The most important outcome of infants with FAS is impairment of the central nervous system. This may involve cognitive deficits, neurological deficits such as motor and coordination problems, as well as behaviourial problems such as hyperactivity and sleep disturbances.[1] These outcomes can only be measured in studies with sufficient follow-up time. Studies with a long follow-up time have the advantage that subtle aspects of cognitive development can also be measured. Cognitive development is also influenced by environmental factors. The relative contribution of these factors is larger at older ages compared to younger ages. Unfortunately, these environmental factors are difficult to measure in an observational study. Therefore, a disadvantage of a long follow-up period is the potential bias introduced by these factors. Another disadvantage of a long follow-up time compared to a short follow-up time is that loss to follow-up will be greater. In order to take both issues into account we chose to assess child development at several ages: in the first two years of life, at the age of 5 years and at the age of 15 years.

The following research questions were formulated:

1. Does the method of retrospectively collecting information on alcohol exposure lead to a bias of effect estimates?
2. What is the effect of underreporting of alcohol intake on effect estimates?
3. What is the relationship of moderate alcohol consumption during pregnancy to birthweight and gestational age?
4. What is the relationship between moderate alcohol consumption during pregnancy and psychomotor development as well as child behaviour in the first two years of life?
5. What is the relationship between moderate alcohol consumption during pregnancy and IQ, hyperactivity and motor development at 5 years of age?
6. What is the relationship between moderate alcohol consumption during pregnancy and IQ, hand coordination, attention deficits, behaviourial problems (e.g. hyperactivity) and memory at 15 years of age?

Outline of this thesis

Research questions 1 and 2 will be discussed in Part I (Misclassification of alcohol), research question 3 will be discussed in Part II (Alcohol and direct pregnancy outcomes) and research questions 4, 5 and 6 will be discussed in Part III (Alcohol and long-term outcomes). Part IV will present a general discussion and a summary of the findings.

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PART I

MISCLASSIFICATION OF ALCOHOL

Chapter 2. Differential misclassification of alcohol and cigarette consumption by pregnancy outcome

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International Journal of Epidemiology 1994; 23: 1218-25.

Abstract

Background: The validity of the results of studies using retrospectively collected information on exposures is often criticized, because cases may report differently from controls even if their true exposure status is the same. This study was performed to quantify the extent to which this effect (differential misclassification) may occur for alcohol and cigarette consumption by pregnancy outcome.
Methods: Prospective as well as retrospective information on alcohol and cigarette consumption was collected for 2806 mothers resident in all 12 provinces of the Netherlands, who gave birth between 1978 and 1979. Changes in mean reported consumption and changes from user to non-user based on retrospective and prospective information were compared for cases and controls. This was done by calculating absolute differences (retrospective minus prospective) in reported consumption and by calculating "misclassification odds ratios". Further, conventional odds ratios based on retrospective information were compared with those based on prospective information. Outcome measures were stillbirth, small for gestational age (SGA), congenital malformations, preterm birth and low birthweight.
Results: The only statistically significant result was found for smoking and SGA. Mothers with an SGA child retrospectively reported a higher number of cigarettes smoked than they had prospectively, more so than mothers of a control child. However, the odds ratios of the relation between SGA and smoking based on prospective and retrospective information, respectively, were virtually the same.
Conclusions: Our results suggest that information bias is unlikely to have a large influence on effect estimates in studies using retrospective information on alcohol and cigarette consumption.

Introduction

In case-control and cross-sectional studies data on past exposures are often obtained by interviewing respondents. It is generally agreed that this retrospective approach may lead to information bias, because of differential misclassification of exposure status with respect to outcome.[1] In a study of etiologic factors for congenital malformations mothers with a malformed infant may for instance be more likely to search for explanations for the disease and may, therefore, be more likely to remember certain past events than mothers with a healthy infant. This is referred to as recall bias. It may cause a harmless exposure to be wrongly identified as a risk factor. Socially unacceptable behaviour, such as smoking and drinking during pregnancy, is likely to be underreported by cases as well

as controls. However, if mothers of a malformed infant are more likely to deny these exposures than mothers of a normal child, this could lead to deflation of the risk estimates. Not blinding interviewers for outcome status may also lead to information bias. Interviewers may be more inclined to collect precise exposure information for cases than for controls. This form of information bias is called observer bias.
Although such differential misclassification is a potential threat for the validity of a study there are only limited data available on the extent to which it may occur.[2] This paper discusses the extent to which differential misclassification of alcohol and cigarette consumption by pregnancy outcome may occur.

Methods

Between September 1978 and November 1979, TNO Prevention and Health performed in collaboration with the Dutch Midwifery Society a study which main aim was to assess the quantity of cigarettes and alcohol used during pregnancy and their effects on pregnancy outcome.[3] Further, factors that influence a woman's choice of breast or bottle feeding were studied. At that time the Dutch Midwifery Society had about 500 practising member of whom 317 agreed to participate. The 317 midwives were living in all of the 12 provinces of the Netherlands. Data were collected with standardized questionnaires. The study population consisted of the first 12 Dutch speaking women who consecutively attended the midwives for their second antenatal visit. The study population is of low risk, since Dutch midwives only provide care to women who have an uncomplicated pregnancy and delivery. The women are from all social classes. However, based on the health insurance data it can be concluded that women of lower social class are somewhat overrepresented. The percentage of sick-fund and private insured women was respectively 83% and 17%, whereas in the general population at that time these percentages were 70% and 30%. Information about cigarette and alcohol consumption was obtained during pregnancy (prospective information) as well as after delivery (retrospective information).

Prospective information
Subjects were interviewed at the second antenatal visit (at approximately the 18th week of pregnancy). They were asked about the number of cigarettes they smoked and the number of alcoholic drinks they consumed, on average, at the time of the interview. They were also questioned about their smoking and drinking behaviour before pregnancy. After the interview was completed the questionnaire was to be sent to the TNO Institute.

Retrospective information

After delivery, the women were again interviewed by the midwife (approximately on the fifth day post delivery) and were asked what they had been drinking and smoking, on average, during the last three months of their pregnancy. Further, information was obtained about their smoking behaviour before pregnancy. Information on alcohol consumption before pregnancy was unfortunately not obtained. The phrasing of the retrospective questions and prospective questions on alcohol and smoking was the same. The interviewers were not blinded with regard to the outcome.

The women were asked about the number of drinks they used. The type of drink was not recorded, but from other studies it is known that in the Netherlands the majority of women drink either wine or beer.[7] In the Netherlands, a standard glass of wine contains 12 ml and a standard glass of beer 12.5 ml of alcohol[2], which is equal to 9.6 g and 10 g of pure alcohol, respectively. Therefore, each drink was considered to contain 10g of pure alcohol. The amount of alcohol consumed in grams per week was calculated. Gestational age was calculated by date of last menstrual period in completed weeks and, for a small percentage of cases, by clinical assessment.

Pregnancy outcome variables were stillbirth, preterm birth (< 37 completed weeks), low birthweight (< 2500 g), small for gestational age (SGA) and congenital malformations. SGA was defined as a birthweight under the 10th percentile standardised for gestational age, sex and parity according to Dutch reference values.[3]

Statistical analysis

Changes in retrospective and prospective information were compared for cases (stillbirth, small for gestational age, congenital malformations, preterm birth and low birthweight) and controls in two ways. First, for each subject, the difference between the retrospectively and prospectively obtained information on cigarette and alcohol consumption during pregnancy was calculated in number of cigarettes per day or grams of alcohol per week consumed. We then tested whether these differences (retrospective minus prospective) were statistically significantly different between cases and controls. For this analysis we used a non-parametric statistical test (Mann-Whitney test). A limitation of this analysis is that it obscures changes from drinker to non-drinker (and vice versa) and changes from smoker to non-smoker (and vice versa) in retrospective versus prospective collected data. In a second analysis we, therefore, also compared these changes for cases and controls with the help of a "misclassification odds ratio". The misclassification odds ratio for drinking is defined as follows. First, the misclassification odds is calculated for cases:

the frequency of women who reported drinking according to prospectively obtained information and not drinking according to retrospectively obtained information

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the frequency of women who reported not drinking according to prospectively obtained information and drinking according to retrospectively obtained information

Then, the same odds is calculated for controls. The ratio of these odds (odds for cases is the numerator and odds for controls is the denominator) provides the misclassification odds ratio. A misclassification odds ratio greater than 1 indicates that cases are retrospectively more inclined to deny their drinking (or smoking) behaviour than controls. A limitation of this analysis is that its power to detect a difference in reporting behaviour between cases and controls is smaller than in the first analysis. An example may illustrate this point. Let us assume that cases are retrospectively more inclined to underestimate their smoking or drinking behaviour, but are not denying that they smoked or drinked. The first analysis could detect this change in reporting behaviour, whereas the second analysis could not.
To increase the power to detect changes in reporting between cases and controls we defined, in both analyses, as controls only those women who had none of the abovementioned adverse pregnancy outcomes.

Further, we also compared odds ratios for pregnancy outcome for prospectively and retrospectively collected information on alcohol and cigarette consumption in the conventional way used in etiologic research. In these analysis the outcomes stillbirth and congenital malformations were combined to avoid empty cells.
All reported p-values are two-tailed.

Results

Response and maternal characteristics
Prospectively as well as retrospectively collected information on alcohol and cigarette consumption was available for 2806 (81 percent) of the 3447 women enroled in the study. The average age of the 2806 women was 25.5 years (SD 3.7). Of the women, 3.3% were younger than 20 years and 1.4% were over 40 years. The percentage of primiparae was 46%; 4.8% had only primary education and 1.4% completed a graduate training.

Differences in cigarette consumption

The average number of cigarettes smoked during pregnancy as reported in the after pregnancy interview was 0.6 (SE 0.1) higher than reported in the interview that took place during pregnancy. These changes were not statistically significantly different for cases and controls, with the exception of SGA (table 1). For mothers with an SGA child the change (retrospective minus prospective) in cigarette consumption was 1.1 (SE 0.3), whereas the change in the mothers of the controls was 0.6 (SE 0.1). None of the misclassification odds ratios were statistically significant.

The average number of cigarettes smoked before pregnancy as reported in the after-delivery interview was 0.5 (SE 0.1) lower than reported in the interview that took place during pregnancy (table 2). These changes were not statistically significantly different for cases and controls. The misclassification odds ratios also, were not statistically significant.

Table 1 Cigarette consumption (in cig/day) during pregnancy, reported during pregnancy (prospective) and after delivery (retrospective), differences in this information, changes from smoker to non-smoker and vice versa, and misclassification odds ratio by pregnancy outcome, among subjects from the Netherlands, 1978 - 1979

Pregnancy outcome		Prospective reporting		Retrospective reporting		Retrospective reporting minus prospective reporting		pro-spective smoker and retro-spective non-smoker	pro-spective non-smoker and retro-spective smoker	misclassification odds ratio (ad/bc)
		consumption	smokers	consumption	smokers	consumption				
	N	mean (SE)	n (%)	mean (SE)	n (%)	mean (SE)	p-value^	a	b	OR (95% CI)
Cases										
Stillbirth	10	4.7 (1.3)	6 (60)	6.4 (2.1)	6 (60)	1.7 (0.9)	0.20	0	0	-
Small for gestational age	323	6.7 (0.4)	216 (67)	7.8 (0.5)	215 (67)	1.1 (0.3)	0.001	11	10	0.9 (0.4 - 2.3)
Congenital malformations	40	4.5 (1.0)	18 (45)	5.5 (1.3)	19 (48)	1.1 (0.9)	0.99	1	2	0.4 (0.0 - 4.8)
Preterm birth	102	4.7 (0.6)	55 (54)	4.6 (0.6)	52 (51)	-0.1 (0.4)	0.26	7	4	1.5 (0.4 - 5.3)
Low birth weight	74	7.0 (0.8)	49 (66)	7.5 (0.9)	46 (62)	0.5 (0.5)	0.70	6	3	1.7 (0.4 - 7.0)
Controls										
None of the abovementioned adverse outcomes	2320	3.6 (0.1)	980 (42)	4.2 (0.1)	967 (42)	0.6 (0.1)		c 87	d 74	1

^ comparing the differences in retrospectively and prospectively collected data for cases and controls

Table 2 Cigarette consumption (in cig/day) before pregnancy, reported during pregnancy (prospective) and after delivery (retrospective), differences in this information, changes from smoker to non-smoker and vice versa, and misclassification odds ratio by pregnancy outcome, among subjects from the Netherlands, 1978 - 1979

Pregnancy outcome		Prospective reporting		Retrospective reporting		Retrospective reporting minus prospective reporting		pro-spective smoker and retro-spective non-smoker	pro-spective non-smoker and retro-spective smoker	misclassification odds ratio (ad/bc)
		consumption	smokers	consumption	smokers	consumption				
	N	mean (SE)	n (%)	mean (SE)	n (%)	mean (SE)	p-value^	a	b	OR (95% CI)
Cases										
Stillbirth	10	9.7 (2.9)	6 (60)	10.3 (3.1)	6 (60)	0.6 (0.8)	0.69	0	0	-
Small for gestational age	323	11.9 (0.6)	240 (74)	11.3 (0.6)	234 (72)	-0.6 (0.4)	0.90	11	5	1.2 (0.4 - 3.6)
Congenital malformations	40	7.7 (1.4)	23 (58)	8.1 (1.7)	22 (55)	0.4 (1.2)	0.79	2	1	1.1 (0.1 - 12.2)
Preterm birth	102	9.0 (0.9)	67 (66)	8.8 (1.0)	64 (63)	-0.2 (0.6)	0.79	4	1	2.2 (0.2 - 19.9)
Low birth weight	74	12.2 (1.2)	55 (74)	12.0 (1.3)	56 (76)	-0.2 (0.7)	0.78	1	2	0.3 (0.0 - 3.1)
Controls										
None of the abovementioned adverse outcomes	2320	7.1 (0.2)	1218 (53)	6.6 (0.2)	1162 (50)	-0.5 (0.1)		c 123	d 67	1

^ comparing the differences in retrospectively and prospectively collected data for cases and controls

Differences in alcohol consumption

The average amount of alcohol consumption during pregnancy as reported in the after-delivery interview was 4.1 g (SE 0.7) higher than reported in the interview that took place during pregnancy (table 3).

These changes were not statistically significantly different for cases and controls. The misclassification odds ratios also, were not statistically significant.

Differences in prospective and retrospective information on alcohol consumption before pregnancy could not be calculated, because this information was only collected prospectively.

Table 3 Alcohol consumption (in gram/wk) during pregnancy, reported during pregnancy (prospective) and after delivery (retrospective), differences in this information, changes from drinker to non-drinker and vice versa and misclassification odds ratio by pregnancy outcome, among subjects from the Netherlands, 1978 - 1979

Pregnancy outcome		Prospective reporting		Retrospective reporting		Retrospective reporting minus prospective reporting		pro-spective smoker and retro-spective non-smoker	pros-pective non-smoker and retro-spective smoker	misclassification odds ratio (ad/bc)
		consumption	smokers	consumption	smokers	consumption				
	N	mean (SE)	n (%)	mean (SE)	n (%)	mean (SE)	p-value^	a	b	OR (95% CI)
Cases										
Stillbirth	10	7.3 (3.3)	5 (50)	9.0 (3.4)	6 (60)	1.7 (2.8)	0.74	0	1	-
Small for gestational age	323	17.3 (3.2)	164 (51)	19.4 (3.1)	164 (51)	2.0 (1.9)	0.24	49	49	1.2 (0.8 - 1.8)
Congenital malformations	40	7.8 (2.8)	17 (43)	16.4 (5.9)	20 (50)	8.7 (5.6)	0.75	4	7	0.7 (0.2 - 2.4)
Preterm birth	102	12.2 (2.2)	53 (52)	15.2 (3.1)	47 (46)	3.0 (3.4)	0.14	16	10	1.9 (0.9 - 4.3)
Low birth weight	74	13.4 (3.3)	35 (47)	13.0 (3.1)	32 (43)	-0.4 (4.1)	0.08	16	13	1.5 (0.7 - 3.1)
Controls										
None of the abovementioned adverse outcomes	2320	13.2 (0.6)	1191 (51)	17.5 (0.8)	1252 (54)	4.3 (0.7)		c / 299	d / 360	1

^ comparing the differences in retrospectively and prospectively collected data for cases and controls

Odds ratios based on prospective information and on retrospective information

There were no large differences between most of the odds ratios based on prospectively and retrospectively collected exposure information and pregnancy outcome (table 4, 5 and 6). The largest difference was found for alcohol consumption of more than 50 g per week and outcome stillbirth and/or congenital malformations. The tables on which these odds ratios were based showed that the prevalences of stillbirth and/or congenital malformations in the prospectively determined reference group of abstainers and the retrospectively determined reference group of abstainers were virtually the same. The prevalence of this outcome in the group who drank more than 50 g per week based on retrospective information (5/270=1.9 percent) was almost twice as high as the prevalence in the alcohol group based on prospectively collected information (2/192=1.0 percent). However, these prevalences were not statistically significantly different (Fisher's exact test, p=0.38).

Table 4 Odds ratios for different pregnancy outcomes and cigarette consumption before pregnancy, based on information collected during pregnancy (prospective) and on information collected after delivery (retrospective), among subjects from various parts of the Netherlands, 1978 - 1979

Pregnancy outcome	Cigarette consumption (cig/day)	Prospective reporting	Retrospective reporting
		OR (95% CI)	OR (95% CI)
Stillbirth and/or Congenital malformations	0	1	1
	1-10	1.10 (0.53 - 2.27)	1.09 (0.53 - 2.23)
	>10	1.15 (0.59 - 2.23)	1.18 (0.61 - 2.31)
Small for gestational age	0	1	1
	1-10	1.99 (1.45 - 2.73)	1.97 (1.44 - 2.69)
	>10	3.04 (2.29 - 4.03)	3.12 (2.36 - 4.13)
Preterm birth	0	1	1
	1-10	1.43 (0.86 - 2.38)	1.52 (0.93 - 2.48)
	>10	1.68 (1.06 - 2.66)	1.50 (0.94 - 2.41)
Low birthweight	0	1	1
	1-10	1.45 (0.73 - 2.87)	2.47 (1.32 - 4.60)
	>10	3.11 (1.79 - 5.40)	3.10 (1.74 - 5.55)

Table 5 Odds ratios for different pregnancy outcomes and cigarette consumption during pregnancy, based on information collected during pregnancy (prospective) and on information collected after delivery retrospective), among subjects from various parts of the Netherlands, 1978 - 1979

Pregnancy outcome	Cigarette consumption (cig/day)	Prospective reporting	Retrospective reporting
		OR (95% CI)	OR (95% CI)
Stillbirth and/or Congenital malformations	0	1	1
	1-10	1.22 (0.67 - 2.24)	1.31 (0.70 - 2.46)
	>10	0.76 (0.26 - 2.19)	1.06 (0.45 - 2.48)
Small for gestational age	0	1	1
	1-10	2.48 (1.91 - 3.23)	2.39 (1.82 - 3.13)
	>10	3.38 (2.42 - 4.74)	3.45 (2.54 - 4.68)
Preterm birth	0	1	1
	1-10	1.49 (0.98 - 2.27)	1.38 (0.90 - 2.13)
	>10	1.23 (0.64 - 2.34)	1.10 (0.61 - 1.98)
Low birthweight	0	1	1
	1-10	2.01 (1.18 - 3.43)	1.73 (1.01 - 2.97)
	>10	3.56 (1.92 - 6.61)	2.68 (1.49 - 4.80)

Table 6 Odds ratios for different pregnancy outcomes and alcohol consumption during pregnancy, based on information collected during pregnancy (prospective) and on information collected after delivery (retrospective), among subjects from various parts of the Netherlands, 1978 - 1979

Pregnancy outcome	Alcohol consumption (gram/week)	Prospective reporting	Retrospective reporting
		OR (95% CI)	OR (95% CI)
Stillbirth and/or Congenital malformations	0	1	1
	1-50	0.77 (0.43 - 1.39)	0.93 (0.51 - 1.70)
	>50	0.52 (0.12 - 2.19)	1.05 (0.40 - 2.80)
Small for gestational age	0	1	1
	1-50	0.93 (0.73 - 1.19)	0.84 (0.65 - 1.07)
	>50	1.34 (0.87 - 2.05)	1.15 (0.78 - 1.69)
Preterm birth	0	1	1
	1-50	1.06 (0.71 - 1.60)	0.71 (0.46 - 1.08)
	>50	0.86 (0.36 - 2.03)	0.88 (0.44 - 1.74)
Low birthweight	0	1	1
	1-50	0.85 (0.53 - 1.38)	0.63 (0.38 - 1.04)
	>50	0.91 (0.35 - 2.33)	0.81 (0.36 - 1.82)

Discussion

Our results suggest that the impact of information-bias on effect estimates is limited. However, some limitations of our study have to be taken into account.

One limitation was that the prospectively obtained information on alcohol and cigarette consumption during pregnancy did not refer to exactly the same time period as the retrospectively obtained information. The prospective information was referring to mid pregnancy and the retrospective information was referring to the last three months of pregnancy. In our opinion this is not a problem in the present analysis, since it is unlikely that a woman with an adverse pregnancy outcome would change her alcohol or cigarette consumption in a different way than a woman with a normal outcome. One exception may be smoking in relation to SGA and low birthweight. Smoking has a pronounced effect on fetal growth. The rate of fetal growth is particularly high in the last trimester. If fetal growth is mostly affected during the last trimester, one would expect that mothers who increase their cigarette consumption during pregnancy are more likely to have an SGA child than mothers who decrease their cigarette consumption during pregnancy. Therefore, the statistically significant result we found for differences in retrospectively and prospectively obtained information on smoking between mothers with a SGA child and those without an SGA child (table 1) may be due to a true increase of number of cigarettes smoked. Although this result was statistically significant, the resulting bias in the effect estimates is negligible, as can be seen in table 5.

A second limitation is that women may have reported at the second interview in the same way as they did during the first interview, since they were aware that this information had been asked before. The same may be true for the midwife. In other words: would there not have been a first interview, then women with an adverse outcome may perhaps have been more inclined to change their reporting behaviour. Thus, our finding that differential misclassification has only a limited effect on effect estimates, may be due to an underestimation of the true amount of differential misclassification. On the other hand, almost half a year passed between the first and second interview. Because of this long period would it seem unlikely that many women will still remember the exact amount of cigarettes and alcohol they reported to have consumed at the first interview.

In this study we have examined the effect of information bias on effect estimates. Information bias is the combined effect of recall bias and observer bias. Observer bias can occur when interviewers are not blinded for outcome status as was the case in our study. Thus, a third limitation of our study is that the effects of recall bias and observer bias could not be analyzed separately. Our results, therefore, cannot show that both the effects of recall bias and of observer bias are limited. Both biases could, theoretically, act in an opposite direction and counterbalance each other's effects. For instance, mothers

of a case child may be more inclined to underestimate their exposure compared with mothers of a control child while, on the other hand, interviewers may be more inclined to get accurate exposure information from mothers of a case child than from mothers of a control child.

Our results are in agreement with most of the studies on this subject.[7-11] One study by Werler et al found evidence for recall bias for some exposures when the recall of mothers with a malformed infant and mothers of nonmalformed infants were compared with information in medical records.[12] Another study by Feldman et al found that women with adverse outcome tended to postnatally report a "milder" degree of alcohol consumption than had really occurred, more so than did women with a normal outcome.[13] The results of our study, together with the combined evidence of other studies mentioned, however, suggest that effect estimates of studies using retrospective data may be less biased than is often assumed.

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Chapter 3. The impact of alcohol misclassification on the relationship between alcohol and pregnancy outcome

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Abstract

Underreporting, more than overreporting, is a problem in studies of the effects of alcohol consumption using self-reported data. Numerical examples illustrate that in studies of the effect of alcohol, nondifferential misclassification of alcohol consumption due to underreporting may lead to a bias away from the null value. It may also cause a true threshold level for alcohol to appear as a dose-response relationship. It is shown that the effect of misclassification on effect estimates will depend on the true frequency of abstainers in the studied population.

Introduction

In studies of the effects of alcohol consumption accurate measurement of alcohol intake is a major concern. With no specific biological alcohol marker, the quantification of alcohol consumption depends on self-report. It is generally agreed that self-report of alcohol use will lead to considerable underestimation.[1]

Self-reports are probably unreliable in detecting problem drinkers.[2] However, in a recent study that evaluated methods of measuring *moderate* drinking, it was concluded that in prospective epidemiological studies self-administered questionnaires can produce effective estimates of alcohol consumption over prolonged periods of time.[3] In the general population underreporting is likely to be most prominent in excessive drinkers, since this behaviour is socially not acceptable. Moderate drinking during pregnancy, though, may be equally unacceptable since it is perceived to be dangerous to the fetus. It is, therefore, likely that during pregnancy even moderate drinkers may underreport.

In this chapter, we give some examples of the bias introduced because of misclassification of drinking status, using a hypothetical prospective study of a possible association between alcohol intake and a given disorder. In a prospective study, misclassification of alcohol consumption will most likely be the same for cases and non-cases (nondifferential misclassification), at least for primigravidae.
It is generally believed that nondifferential misclassification will lead to a bias towards the null value.[4,5] We will show that this may not be the case, using as an example the effects of alcohol on birthweight. Examination of the effect of different levels of misclassification may give a better idea about the extent to which estimates of association may be biased.

The model

Our hypothetical study group consists of 1000 women-child pairs. Alcohol consumption is categorized in four levels (none, mild, moderate, heavy). For reasons of simplicity we will assume that there are no confounding variables. We will discuss the effect of three levels of underreporting (minor, intermediate, major), two levels of overreporting (none and minor) and two distributions of alcohol intake (40% abstainers and 10% abstainers). Minor overreporting is defined as 5% of moderate drinkers being misclassified as heavy drinkers, 2% of mild drinkers as heavy drinkers, 5% of mild drinkers as moderate drinkers and no misclassification of abstainers to any level of drinking (table 1). Table 2 presents the definitions of underreporting.

Table 1 Definitions of minor overreporting

True level	-> reported level	%
moderate	-> heavy	5
mild	-> heavy	2
abstainer	-> heavy	0
mild	-> moderate	5
abstainer	-> moderate	0
abstainer	-> mild	0

Table 2 Definitions of minor, intermediate and major underreporting

True level	-> reported level	minor %	intermediate %	major %
heavy	-> moderate	60	60	5
heavy	-> mild	30	30	40
heavy	-> abstainer	0	5	50
moderate	-> mild	60	60	40
moderate	-> abstainer	0	30	55
mild	-> abstainer	0	60	95

Table 3 shows the unbiased and the biased mean birthweights for the different alcohol categories with minor underreporting and no overreporting, for respectively a true dose-response (I) and a true threshold effect (II). As is shown, due to reporting bias birthweight means in the mild and moderate drinking groups are reduced, changing a true threshold level into a spurious dose-response relationship.

Table 3 Examples of the effect of minor underreporting and no overreporting of alcohol consumption on the relationship between alcohol and birthweight in a situation of a true dose-response relationship (I) and a true threshold level (II)

Type of relationship	Distribution of alcohol consumption (%)				Birthweight (g)			
	unbiased		minor underreport		unbiased		minor underreport	
	n	(%)	n	(%)	mean	difference	mean	difference
I. Dose-response								
Reported consumption								
none	400	(40)	400	(40)	3400	0	3400	0
mild	400	(40)	490	(49)	3300	-100	3276	-124
moderate	100	(10)	100	(10)	3200	-200	3140	-260
heavy	100	(10)	10	(1)	3100	-300	3100	-300
II. Threshold								
Reported consumption								
none	400	(40)	400	(40)	3400	0	3400	0
mild	400	(40)	490	(49)	3400	0	3382	-18
moderate	100	(10)	100	(10)	3400	0	3220	-180
heavy	100	(10)	10	(1)	3100	-300	3100	-300

See table 2 for definition of minor underreporting

When there is a true dose-response relationship and drinkers are classified as abstainers, as in our examples of intermediate and major underreporting, the birthweight means in all the drinking categories are more likely to be biased toward the null value (see I in table 4). A true threshold level, however, is again likely to appear as a dose-response relationship. When a true dose-response relationship exists, the bias introduced by even major underreporting seems to be limited, at least for the intermediate categories.

The distribution of drinking status in a population may modify the effect of bias introduced by misclassification. When the number of true abstainers is large, the estimate of the mean birthweight in this group will be less affected by misclassifications of drinkers as abstainers. Because nondrinkers are the reference group this will also influence the differences in mean birthweight (compare I and II in table 4).

When there is a considerable underreporting even minor overreporting will lead to substantial bias toward the null value (compare I and III in table 4). Since overreporting will undo some of the effects of underreporting the estimates of the distribution of

alcohol consumption are somewhat less biased. This will not necessarily affect other variables associated with alcohol consumption in the same way.

Table 4 Examples of the effect of moderate and heavy underreporting of alcohol consumption on the relationship between alcohol and birthweight in a situation of no overreporting and many abstainers (see I), no overreporting and few abstainers (see II) and very mild overreporting and many abstainers (see III)

Alcohol-intake	Distribution of alcohol consumption (%)			Difference in means (g) (unbiased dose-response)			Difference in means (g) (unbiased threshold)		
	unbiased	underreporting		unbiased	underreporting		unbiased	underreporting	
		intermediate	major		intermediate	major		intermediate	major
I. No overreporting, many abstainers									
none	40.0	67.5	88.5	0	0	0	0	0	0
mild	40.0	25.0	10.0	-100	-101	-148	0	- 34	-103
moderate	10.0	7.0	1.0	-200	-239	-178	0	-255	-133
heavy	10.0	0.5	0.5	-300	-253	-228	-300	-298	-283
II. No overreporting, few abstainers									
none	10.0	46.5	75.0	0	0	0	0	0	0
mild	40.0	43.0	22.0	-100	- 63	-80	0	- 18	-35
moderate	40.0	10.0	2.5	-200	-154	-91	0	-177	-40
heavy	10.0	0.5	0.5	-300	-194	-171	-300	-297	-280
III. Very mild overreporting, many abstainers									
none	40.0	67.5	88.5	0	0	0	0	0	0
mild	40.0	22.2	7.2	-100	-107	-194	0	-38	-150
moderate	10.0	8.5	2.5	-200	-200	-68	0	-210	-43
heavy	10.0	1.8	1.8	-300	-137	-111	-300	-81	-66

See table 1 and 2 for definitions of intermediate and major underreporting and minor overreporting

Discussion

Our examples show that depending on the amount of underreporting, overreporting and the true distribution of drinking habits in a population, various spurious associations may appear. Even biases away from the null value are likely to occur. Although not widely appreciated, the possibility that nondifferential misclassification may lead to biases away from the null value has been described before.[3,4]

Because underreporting more than overreporting seems to be the main problem in alcohol research, a true threshold level of alcohol might appear as a dose-response relationship.

Studies that claim to have found a dose-response relationship of alcohol on pregnancy outcome should therefore be interpreted cautiously.[8-10]

On the other hand, certain combinations of under- and overestimation may change a true dose-response level into a spurious threshold level of effect. In fact, any result may arise from nondifferential misclassification.

In the absence of overreporting even considerable underreporting seems to have a limited impact on the effect estimates, especially when the number of abstainers is large. In a situation of considerable underreporting even a small amount of overreporting may introduce a large bias toward the null value.

It is generally believed that the best measure for alcohol intake is detailed information on the drinking pattern of the week before the interview (from now on referred to as measure A). This measures was also used in most of the participating countries of the EUROMAC study. Studies in which mothers are asked about their average alcohol consumption during a longer period of time during pregnancy (measure B) are considered less precise. Measure B was used in Dundee, the Netherlands and Roubaix.

The amount of underestimation may be greater for measure B than for A, since many women may not realize the exact amount of alcohol they consume, unless they are asked to recall very carefully their drinking behaviour. However, measure A is more likely to result in some overreporting than measure B. The drinking habits during one week of pregnancy may not be representative for the actual intake during pregnancy because many women do not drink alcohol regularly. If, for example, a woman had two social events during which she used alcohol in the week before the interview, whereas she normally had only one such event in a month, her alcohol intake would be considerably overestimated. When women are asked about their drinking habits during a longer period of time it seems less likely that they will give an overreported estimate even if they had recently had more social events than usual.

Although the amount of underreporting may be less when using A as compared to B, it may still be considerable, due to forgetfulness, underreporting of the exact amount of levels that are considered socially acceptable and a week unrepresentative of the average intake.

If the objective of a study is to assess the distribution of alcohol intake in a population, measure A may be preferable. If the objective is to assess the effect of alcohol on *outcome* it is not obvious that measure A is preferable to measure B. This can be shown from data in Table 4. Let us assume that measure A leads to intermediate underreporting with minor overreporting and measure B leads to major underreporting with no overreporting. Suppose the true distribution of alcohol consumption contains many abstainers so that there are 40% nondrinkers, 40% mild drinkers, 10% moderate drinkers and 10% heavy drinkers. Using measure A this distribution would be: 67.5%, 22.2%,

8.5% and 1.8%, respectively (column 2, section III of Table 4). Using measure B the distribution would be 88.5%, 10.0%, 1.0% and 0.5%, respectively (column 3, section 1 of Table 4). When both distributions are subsequently compared with the true distribution, measure A provides the least distorted estimates.

Now compare the effect estimates of alcohol on the differences in birthweight using measures A and B. Assuming many abstainers and a dose-response relationship, the true estimates of the differences in birthweight are 0 g (referent category), -100 g (mild drinking) and -300 g (heavy drinking). Using measure A the effect estimates are 0 g, -107 g, -200 g and -137 g. Using measure B the estimates are 0 g, -148 g, -178 g, and -228 g. The two intermediate levels are best predicted by measure A. The estimate of the highest level, however, is best predicted by measure B.

The likelihood of detecting an effect of alcohol on the fetus may be enhanced by avoiding misclassification of drinkers as abstainers. Since it is socially more acceptable for women to drink when they are not pregnant, a true abstainer level may more reliably be obtained from women reporting themselves as abstainers before and during pregnancy. Women who report having quit drinking may, thus, be categorized as ex-drinkers.

In the examples presented in the chapter we focused on the effect of underreporting on the effect estimates. Other factors which may lead to further misclassification are:

- for certain outcomes critical exposure periods may exist;
- all mothers may not have the same vulnerability to alcohol due to differences in their ability to metabolize it;
- the blood alcohol level may be a better predictor than the dose.

We have discussed only reporting bias. Observational studies are however vulnerable to many kinds of bias. Some can be overcome by using a prospective design with examination of the newborn by a person who is unaware of maternal alcohol consumption. Inadequate or lack of adjustment for confounding variables and measurement errors of confounders and pregnancy outcome are other potential sources of bias.[11] All these possibilities need to be considered before interpreting the results of studies of the effect of maternal drinking on pregnancy outcome.

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PART II

ALCOHOL AND DIRECT PREGNANCY OUTCOMES

Chapter 4. The effect of moderate maternal alcohol consumption on birthweight and gestational age in a low risk population

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Abstract

We analyzed the relationship between moderate maternal alcohol consumption during pregnancy and both birthweight corrected for gestational age and preterm delivery in 3447 women. Information on alcohol consumption in the first and second trimester was obtained during mid pregnancy and information about third trimester drinking was obtained a few days after delivery.

After adjustment for possible confounders we found that for most women alcohol consumption was unrelated to birthweight corrected for gestational age and preterm delivery. However, in the subgroup of women smoking 20 cigarettes or more a day, drinking more than 120 g alcohol a week in early pregnancy was associated with a 7.2% (95% CI 0.2% to 14.2%) decrease in birthweight.

We conclude that the effect of alcohol use on birthweight corrected for gestational age and gestational age is limited. However, in women who smoke heavily, a reported consumption of about 2 drinks or more a day in early pregnancy may be an additional risk factor for impaired fetal growth.

Key words: pregnancy, alcohol consumption, birthweight, preterm delivery

Introduction

The first description in the medical literature of characteristic malformations in children of alcoholic mothers appeared in 1968.[16] These characteristics were described as the fetal alcohol syndrome (FAS) by Jones et al.[12] The syndrome is characterized by fetal growth retardation, developmental delay and facial abnormalities. Since then, much research has been performed concerning the effects of prenatal alcohol exposure in humans and animals.[20] It is now widely accepted that heavy drinking has adverse effects on the human fetus].[1] The results of studies investigating the effects of social drinking on pregnancy outcome, however, are conflicting.[23,26] Some studies have detected an adverse effect on birthweight [6,17] gestational age[24], the risk of congenital malformations[2,7] and the risk of spontaneous abortion[21], whereas others have not.[10,14,18] One study even showed a beneficial effect of alcohol use on birthweight.[9]

Some studies may have failed to detect an effect due to the method of alcohol measurement, failure to take into consideration the relevant developmental period during which exposure should occur in order to have an effect and the possibility of effect modification by smoking and lack of statistical power. In some studies it was found that smokers who drink may be particularly at risk for having a growth retarded child .[5,19,25]

We describe the results of a study which had a higher power to detect a possible detrimental effect of alcohol on pregnancy outcome than many others. There are a number of reasons why we believe this is the case. First, our study was performed in a low risk population, which limits random variation in outcome measures. Second, the sample size was large and the group contained a high percentage of alcohol drinking mothers. Third, we considered in the analysis as non-exposed only those mothers that reported to be non-drinkers before and during pregnancy, thus designing a group which was very unlikely to have been contaminated by drinkers. Fourth, since the effect of alcohol on different outcomes may be dependent on gestational age, alcohol use was measured for each trimester. Outcome measures were restricted to those for which the statistical power was sufficiently high, namely birthweight corrected for gestational age and preterm delivery.

Methods

The study was performed between September 1978 and November 1979.[13] The main objectives were to assess the quantity of cigarettes and alcohol used during pregnancy and their effects on pregnancy outcome. Further, factors that influence a woman's choice of breast or bottle feeding were studied. Data were collected by 317 midwives practising in various regions of the Netherlands. In the Netherlands midwives provide care to women at low risk for pregnancy complications. Only Dutch speaking women were considered eligible for the study.

At mid pregnancy (approximately 18 weeks) demographic data were obtained and the women were asked how many alcoholic drinks they drank on average at that time (second trimester drinking) and what they drank on average in the three months before pregnancy. Since a woman often does not realize that she is pregnant until a number of weeks after conception, we considered prepregnancy drinking as an indicator for drinking in the first trimester. A few days after delivery the women were asked what they drank on average in the last three months of pregnancy (third trimester drinking). The type of drink was not recorded, but from other studies it is known that in the Netherlands the majority of women drink either wine or beer.[8] In the Netherlands, a standard glass of wine contains 12 ml and a standard glass of beer 12.5 ml pure alcohol[11], 9.6 g and 10 g of alcohol, respectively. Therefore, we considered each drink to contain 10 g of pure alcohol. We calculated the amount of alcohol in grams per week.

Outcome measures were birthweight ratio and preterm delivery. Gestational age was mainly (99%) calculated by date of last menstrual period in completed weeks. For a few (1%) cases gestational age based on clinical assessment was used to maximise the

number of observations in the analysis. Birthweight ratio was calculated as the ratio of observed birthweight to expected mean birthweight corrected for gestational age, sex and parity (0, 1+) from the Dutch standards by Kloosterman[15] according to the method of Bland et al.[4] This method of correction for gestational age is preferable to the commonly used method of regression of birthweight on gestational age. The last method is questionable, because of the non-linear relationship of mean birthweight to gestational age and the relationship between the mean and the standard deviation of birthweight.[4] The birthweight ratio, however, has a mean and standard deviation independent of gestational age.

Efforts were made to obtain outcome information on all children not delivered by the midwife who did the interview in mid pregnancy due, for instance, to removal or referral to an obstetrician.

Univariate analysis comprised chi square tests. We also used multivariate modelling techniques to control for possible confounding factors. Least squares linear regression analysis was used in the analysis of birthweight ratio. Linear regression analysis was not considered appropriate to analyze gestational age, due to the skewed distribution. We, therefore, dichotomised gestational age into preterm birth (< 37 completed weeks) or term birth and used logistic regression to adjust for possible confounding factors. To avoid dubious linearity assumptions, all continuous independent variables in the models were categorized. To measure first trimester alcohol consumption women were categorized into abstainers, 1-50 g/wk, 51-120 g/wk and >120 g/wk users. To measure second and third trimester alcohol consumption women were categorized into abstainers, ex-drinkers, 1-50 g/wk, 51-120 g/wk and >120 g/wk users. In the analysis with birthweight ratio, adjustment was made for smoking (non-smoker, ex-smoker, 1-9 cig/day, 10-19 cig/day, ≥20 cig/day), smoking by the husband (yes, no), education (special, primary, secondary, tertiary), employment (yes, no), maternal age (<20, 20-34, >34) and marital status (married, unmarried). In the analysis of preterm birth, we adjusted for smoking, education, employment, maternal age and marital status.

Results

Response

Gestational age was known in 85% of women and the birthweight ratio could be calculated in 83% of eligible cases. One of the main reasons for loss to follow-up was referral to an obstetrician (table 1). However, first and second trimester alcohol consumption of all women lost to follow-up was comparable with alcohol consumption of those eligible for analysis (table 2). The same results were found when the subgroup of

women lost to follow-up due to referral to an obstetrician was compared with those eligible for analysis.

Table 1 Sample size and response

	No	(%) of women
Completed first interviews		3447
Excluded		54
Twin birth	17	
Induced abortion	2	
Miscarriage	35	
Eligible		3393 (100)
More ≥ 1 outcome variable known		2901 (85)
Lost		492 (15)
Referral to obstetrician	281	
Non infant related	90	
Unknown	121	

Table 2 Alcohol consumption before and during mid pregnancy of women included in the study compared with all women lost to follow-up and lost due to referral to an obstetrician

Alcohol consumption	Lost to follow up					
	No		Yes			
	n	(%)	All		Referred to an obstetrician	
			n	(%)	n	(%)
First trimester						
Abstainer	633	(22)	118	(24)	63	(22)
1- 50 g/wk	1627	(56)	256	(52)	140	(50)
51-120 g/wk	367	(13)	71	(14)	47	(17)
>120 g/wk	274	(9)	47	(10)	31	(11)
Total	2901	(100)	492	(100)	281	(100)
p-value^			0.37^		0.12^	
Second trimester						
Abstainer	633	(22)	118	(24)	63	(22)
Ex-drinker	789	(27)	128	(26)	71	(25)
1- 50 g/wk	1276	(44)	218	(44)	128	(46)
51-120 g/wk	144	(5)	15	(3)	9	(3)
>120 g/wk	59	(2)	13	(3)	10	(4)
Total	2901	(100)	492	(100)	281	(100)
p-value^			0.27^		0.29^	
Third trimester						
Abstainer	524	(19)				
Ex-drinker	783	(28)				
1- 50 g/wk	1226	(44)				
51-120 g/wk	169	(6)				
>120 g/wk	101	(4)				
Total	2803	(100)				

^ compared to women not lost to follow up

Birthweight ratio

Table 3 presents the coefficients of the regression analysis of the main effect models without and with confounders. The coefficients of these analyses reflect the differences in birthweight ratio between alcohol users and abstainers. After multiplication with 100 these can be interpreted as percentage differences in birthweight. All differences were close to zero and not statistically significant. The largest difference was found for second trimester alcohol consumption of 51 g to 120 g: -1.1%. Since an average boy born after 40 weeks to a primiparous woman weights about 3470 g in the Netherlands[15], this level of drinking would lead to a decrease in birthweight from 3470 to 3432 g (-38 g). Adding an interaction term for smoking and drinking to the main effects models did not result in a statistically better fit. However, since this may be due to lack of power, we also inspected the results of an analysis of birthweight ratio by alcohol, separately for each smoking stratum. The only statistically significant adjusted difference we found was in the group of mothers smoking 20 cigarettes or more (table 4). In this smoking stratum the adjusted difference in birthweight ratio between mothers who consumed more than 120 g alcohol per week in the first trimester and abstainers was -7.2% (95% confidence interval -14.2% to -0.2%).

Table 3 Regression coefficients for different levels of maternal alcohol consumption on birthweight ratio and differences in adjusted birthweight

Alcohol consumption	n	Coefficient		Difference in adjusted birthweight@ (in g)
		unadjusted	adjusted^ (95% CI)	
First trimester				
Abstainers (ref)	615	0	0	0
1- 50 g/wk	1580	0.002	-0.005 (-0.016 to 0.007)	-17
51-120 g/wk	359	0.009	0.004 (-0.012 to 0.020)	14
>120 g/wk	262	-0.007	-0.003 (-0.021 to 0.015)	-10
Second trimester				
Abstainers (ref)	615	0	0	0
Ex-drinkers	764	-0.001	-0.005 (-0.018 to 0.008)	-17
1- 50 g/wk	1238	0.006	-0.002 (-0.014 to 0.010)	-7
51-120 g/wk	141	-0.015	-0.011 (-0.033 to 0.012)	-38
>120 g/wk	58	-0.004	0.009 (-0.025 to 0.042)	31
Third trimester				
Abstainers (ref)	517	0	0	0
Ex-drinkers	774	0.005	0.002 (-0.012 to 0.016)	7
1- 50 g/wk	1209	0.006	0.003 (-0.010 to 0.016)	10
51-120 g/wk	167	-0.008	-0.006 (-0.027 to 0.016)	-21
>120 g/wk	99	-0.024	-0.010 (-0.036 to 0.017)	-35

^ Adjusted for smoking, smoking of the husband, education, employment, maternal age and marital status
@ for an average boy of 40 weeks gestational age born to a primiparous woman in the Netherlands

Table 4 Regression coefficients of first trimester maternal alcohol consumption on birthweight ratio and differences in adjusted birthweight in women smoking 20 cigarettes or more

Alcohol consumption	n	Coefficient		Difference in adjusted birthweight@ (in g)
		unadjusted	adjusted^ (95% CI)	
Abstainers (ref)	31	0	0	0
1- 50 g/wk	49	-0.012	-0.016 (-0.071 to 0.040)	-56
51-120 g/wk	10	0.063	0.054 (-0.032 to 0.140)	187
>120 g/wk	20	-0.056	-0.072 (-0.142 to -0.002)*	-250

^ and @ see footnote to table 3
* $p < 0.05$

Preterm birth

Compared to abstainers, the rate of preterm birth was lower in all categories of alcohol use with the exception of drinking 51 to 120 g per week in the first trimester (table 5). However, none of these differences was statistically significant.

Table 5 Frequencies and unadjusted and adjusted odds ratios of preterm birth by maternal alcohol consumption

Alcohol Consumption	Preterm birth n/N (%)	Odds Ratios unadjusted	adjusted^ (95% CI)
First trimester			
Abstainers (ref)	31/633 (4.9)	1	1
1- 50 g/wk	59/1627 (3.6)	0.73	0.71 (0.45 to 1.11)
51-120 g/wk	20/367 (5.4)	1.12	1.05 (0.58 to 1.89)
>120 g/wk	10/274 (3.6)	0.74	0.65 (0.31 to 1.36)
Second trimester			
Abstainers (ref)	31/633 (4.9)	1	1
Ex-drinkers	28/789 (3.5)	0.71	0.65 (0.38 to 1.11)
1- 50 g/wk	53/1276 (4.2)	0.84	0.82 (0.52 to 1.30)
51-120 g/wk	6/144 (4.2)	0.84	0.79 (0.32 to 1.94)
>120 g/wk	2/59 (3.4)	0.68	0.60 (0.14 to 2.60)
Third trimester			
Abstainers (ref)	25/524 (4.8)	1	1
Ex-drinkers	30/783 (3.8)	0.80	0.76 (0.44 to 1.32)
1- 50 g/wk	37/1226 (3.0)	0.62	0.60 (0.35 to 1.01)
51-120 g/wk	7/169 (4.1)	0.86	0.77 (0.32 to 1.83)
>120 g/wk	3/101 (3.0)	0.61	0.54 (0.16 to 1.85)

^ Adjusted for smoking, education, employment, maternal age and marital status

Discussion

The results suggest that alcohol in general is not related to a decrease in birthweight or gestation. The only statistically significant relationship found was an association between first trimester alcohol consumption and birthweight in the subgroup of women smoking 20 cigarettes or more per day. In this subgroup, the average birthweight ratio of women consuming more than 120 g alcohol per week was 7.2% lower than that of abstainers. For an average boy born after 40 weeks to a primiparous women this would imply a decrease of 250 g, additional to the effect of smoking on birthweight. This should be interpreted cautiously, however. Since we made many comparisons a chance finding can not be ruled out. Another reason that may explain this finding is residual confounding

of smoking. However, since in this subgroup of smokers the average cigarette consumption (23 per day) in abstainers was only slightly lower compared with mothers drinking 120 g or more per week (25 cigarettes per day) this form of bias is probably not the explanation for the large difference. Further, in a number of other studies comparable results were found. Wright et al found a synergistic effect of alcohol and smoking and the risk for delivering a baby on or below the 10th centile.[25] Drinking around the time of conception seemed to contribute to the effect. The same synergistic effect was also found in another study[5], in which the difference in birthweight ratio in smokers who consumed 100 g alcohol or more and smokers who did not drink was comparable with our finding. In non-smokers no detrimental effect was found. Olsen et al found that average alcohol consumption during the first 36 weeks of gestation of 120 g a week or more was associated with a reduction of birthweight of 40 g in non-smokers and of 200 g in smokers.[19]

We could not detect an effect of alcohol consumption on preterm birth, even in the group of women that reported a consumption of more than 120 g per week (about 2 drinks per day). If anything, our results suggest a lower prevalence of preterm birth in mothers who drank alcohol. Shiono et al found a lower prevalence of preterm birth in women drinking less than one drink in early pregnancy and a higher prevalence of preterm birth in women drinking daily.[22] In other studies a detrimental effect was only found in women consuming two drinks or more a day.[18,22,24] It thus seems unlikely that an intake below two drinks a day has an effect on gestational age.

Failure to find an effect of alcohol use on outcome measures is often attributed to misclassification. There are two reasons why this is not likely to be the case in our study. First, alcohol use is generally underestimated, which implies that the true consumption at a certain level will in fact be higher than the reported consumption. Second, in our analysis we used as reference group only those women, who reported that they drank neither before nor during pregnancy. Since, it is socially more acceptable for women to drink when they are not pregnant, we believe that we thus achieved a "clean" abstainer group.

A limitation of our study is that third trimester alcohol was measured after birth and may, therefore, be subject to differential misclassification, because of recall bias and/or interviewer bias. It should be noted that even in studies in which third trimester alcohol consumption was measured before delivery this form of bias may be present, since the mother may already know whether her child has serious growth retardation at that time.

We conclude that the effect of moderate alcohol consumption on birthweight corrected for gestational age and gestational age is limited. However, heavy smokers who report drinking two drinks or more a day in early pregnancy may be at higher risk for having a growth retarded child compared to heavy smokers who do not drink.

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Chapter 5. Social class, ethnicity and other risk factors for small for gestational age and preterm delivery in the Netherlands

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Abstract

Social class and ethnicity are important risk factors for small for gestational age and preterm delivery in many countries. This study was performed to assess whether this is also the case in the Netherlands, a country with a high level of social security, relatively small income differences and easy access to medical care for all its inhabitants. Other riskfactors that were taken into account were smoking, drinking, occupation, age and height.

Information was collected by interview in the first three weeks of life of 2027 (response 97%) live born singletons born in the period from April 1988 to October 1989 in the study area.

After adjustment for possible confounding factors very low social class was significantly associated with reduced birthweight (-4.0%; 95% CI -7.4% to -0.7%), but not with preterm delivery (OR 2.09; 95% CI 0.67 to 6.48) compared to high social class. The adjusted birthweight of Turkish infants (2.7%; 95% CI -1.1% to 6.5%) and the adjusted birthweight of infants from Surinam or the Antilles (-1.6%; 95% CI -5.5% to 2.1%) were not significantly different compared to infants of Dutch mothers. After adjustment the frequency of preterm birth was lower in Turkish infants, but not significantly (OR 0.22; 95% CI 0.04 to 1.10), whereas the frequency of preterm birth in infants from Surinam or the Antilles was significantly higher (OR 2.51; 95% CI 1.04 to 6.08) compared to Dutch infants. Of the other factors the main riskfactors were smoking (negatively related with birthweight) and maternal age. Mothers of 40 years and older had an increased risk (OR 5.53 (95% CI 1.72 to 17.77) of preterm delivery compared to mothers of 20 to 29 years. After adjustment higher maternal height was significantly associated with higher birthweight, but also with a decreased risk of preterm delivery.

We conclude that in the Netherlands infants of very low social class are at increased risk for low birthweight for gestational age and that a background from Surinam or the Antilles is associated with an increased risk for preterm delivery. Taller mothers do not only have heavier infants, but these infants also appear to be less often premature. Older mothers are at increased risk for preterm delivery.

Keywords: birthweight, preterm birth, social class, ethnicity, riskfactors

Introduction

Low birthweight remains the major determinant of infant mortality and is important in relation to infant morbidity.[1] It is now widely acknowledged that causality of low birthweight is "multifactorial", with smoking as the major preventable risk factor.[2,3] In many countries social class and ethnicity are also important riskfactors for low birthweight.[2,4,5]

The Netherlands are a country with a high level of social security, relatively small income differences and easy access to high quality medical care for all its inhabitants resulting in one of the lowest infant mortality rates in the world.[6] Because of this high standard of living one may expect that social class is not an important riskfactor for low birthweight in the Netherlands. To our knowledge only one study has been performed in the Netherlands that has tried to determine the relationship between social class and birthweight.[7] It was found that infants of mothers with a low level of education weighed 276 g less than infants of mothers with a high level of education, however no adjustment had been made for important confounding factors such as maternal smoking. Only one study performed in the Netherlands has addressed the relationship between ethnicity and low birthweight.[8] Other riskfactors for low birthweight we were interested in, and which were considered to be possible underlying causes of eventual social class and/or ethnic differences in low birthweight were maternal smoking, drinking, height, occupation and age.

The group of low birthweight babies consists of children born after a short gestation and/or babies that are small for gestational age. Since fetal growth and preterm delivery do not have the same etiologic background these outcomes were studied separately.

Methods

The data were derived from a large population based study conducted in the Netherlands: the Social Medical Survey of Children attending Child Health Clinics (SMOCC). Detailed information about the study design can be found elsewhere.[9] In short: the study population included all live-born infants of mothers who, at the time of birth, were living in the catchment areas of 21 child health clinics during the period from April 1st 1988 to October 31st 1989. Data were collected by interview with a standardised questionnaire by a trained nurse from the Health Clinic at the mother's home which for most children took place in the first three weeks after delivery. Data on birthweight were obtained from the delivery report of the midwife or gynaecologist or, if not available, by questioning the mother. Gestational age was calculated by last menstrual period. In the few cases in

which the expected date of delivery was not known we used gestational age as estimated by obstetrical clinical assessment of the infant after birth.

Birthweight is mainly influenced by gestational age. Other important determinants are sex of the child and parity. Since one of the objectives of this study was to examine factors that may influence fetal growth, other than gestational age, sex and parity, we corrected for these variables. This was done by calculating the ratio of observed birthweight to expected mean birthweight for gestational age (in completed weeks), sex and parity (primiparous, multiparous) from the tables of Kloosterman[10], according to the method of Bland et al.[11] This "birthweight ratio" was used as outcome variable in the analysis. This method to control for gestational age is preferable to the commonly used method of regression of birthweight on gestational age. The latter method is questionable, because of the non-linear relationship of mean birthweight to gestational age and the relationship between the mean and the standard deviation of birthweight.[11] The birthweight ratio however, has a mean and standard deviation independent of gestational age.

As proxy for social class we used level of education of the mother, which was categorized as: very low (special education and primary education), low (junior vocational training and lower secondary general education), middle (senior vocational training and higher secondary general education), high (vocational colleges and university education) and unknown. Ethnicity was defined by country of origin of the mother and categorized into Dutch, Turkish, Suriname/Antilles and otherwise. The mothers were asked how many cigarettes they had smoked on average per day during the pregnancy and what number of alcoholic drinks they drank on average per week while pregnant. Maternal height was measured in centimetres. Occupation was defined as having work outside the house for 2 or more days per week. Maternal age was calculated in completed years at the date of delivery.

Linear regression analysis was used to assess the relationship between the risk factors and birthweight ratio. Gestational age was dichotomised into preterm (less than 37 completed weeks) and not preterm since residuals were not normally distributed in a linear regression analysis with gestational age in days as dependent variable. In the analysis of preterm delivery we used logistic regression analysis.

Results

Response

A total of 2151 children were born in the region of the participating Health Clinics during the study period (table 1). For 2092 (97%) of these valid questionnaires were obtained. For the present analyses we considered only singleton births (n=2027).

Table 1 Sample size and response

No of eligible children		2151 (100%)
Completed interviews		2092 (97%)
Singleton^		2027
Twin		65
Lost		59 (3%)
Preventive medical control elsewhere	22	
Removal	7	
Refused	25	
Other	5	

^ Analyses based on these 2027 observations

Birthweight ratio

Table 2 presents the unadjusted and adjusted coefficients of the regression analysis. The coefficients of these analyses reflect the differences in birthweight ratio between a certain category and the reference category. After multiplication by 100 these coefficients can be interpreted as percentage differences in birthweight.

After adjustment for the other factors in table 2 very low social class was associated with a decrease of 4.0% (p=0.02) in birthweight compared to mothers of high social class. According to Dutch reference values an average boy and girl born after 40 weeks to a primiparous woman weigh about 3466 g and 3340 g, respectively. A decrease of 4.0% in birthweight would in these examples imply a decrease of 139 g and 134 g, respectively. Infants of non-Dutch ethnicity had a lower birthweight ratio than Dutch children, however after adjustment for the other factors in table 2 these associations disappeared.

With the exception of the highest smoking category, the more the mothers smoked the less their infant weighed. Taller mothers had heavier infants. Consuming up to 7 alcoholic drinks per week was not associated with a decrease in birthweight compared with non-drinkers. In the group of mothers who consumed more than 7 drinks per week, however, a sharp decrease occurred (-7.2%; p=0.07).

Table 2 Unadjusted and adjusted regression coefficients for birthweight ratio^ in relation to social class, ethnicity, smoking, alcohol consumption, occupation, age and height

Risk factor	No. mothers	Unadjusted coefficient (95% confidence interval)	Adjusted@ coefficient (95% confidence interval)
Social class			
very low	108 (5)	-0.067 (-0.095 to -0.038)*	-0.040 (-0.074 to -0.007)*
low	905 (45)	-0.014 (-0.031 to 0.002)	-0.003 (-0.020 to 0.015)
middle	644 (32)	-0.003 (-0.021 to 0.014)	0.001 (-0.016 to 0.019)
high (ref)	330 (16)	0	0
unknown	40 (2)	-0.056 (-0.099 to -0.013)*	-0.013 (-0.065 to 0.039)
Ethnicity			
Dutch (ref)	1798 (89)	0	0
Turkish	67 (3)	-0.038 (-0.070 to -0.005)*	0.027 (-0.011 to 0.065)
Suriname/ Antilles	45 (2)	-0.037 (-0.076 to 0.002)	-0.017 (-0.055 to 0.021)
Other	117 (6)	-0.026 (-0.051 to -0.001)*	-0.002 (-0.029 to 0.024)
Smoking (cig/day)			
0 (ref)	1498 (74)	0	0
1-5	203 (10)	-0.016 (-0.035 to 0.003)	-0.014 (-0.033 to 0.005)
6-10	162 (8)	-0.053 (-0.074 to -0.032)*	-0.051 (-0.072 to -0.030)*
11-15	82 (4)	-0.086 (-0.116 to -0.057)*	-0.079 (-0.107 to -0.050)*
>15	80 (4)	-0.045 (-0.074 to -0.015)*	-0.047 (-0.076 to -0.018)*
Alcohol (drinks/week)			
0 (ref)	1497 (74)	0	0
1	432 (21)	0.006 (-0.008 to 0.021)	0.001 (-0.014 to 0.015)
2-7	86 (4)	0.009 (-0.020 to 0.038)	0.003 (-0.025 to 0.032)
>7	10 (0)	-0.079 (-0.162 to 0.003)	-0.072 (-0.152 to 0.007)
Occupation			
no (ref)	1377 (68)	0	0
yes	650 (32)	-0.002 (-0.015 to 0.010)	-0.009 (-0.022 to 0.003)
Age			
15-19	30 (1)	-0.039 (-0.087 to 0.009)	-0.011 (-0.058 to 0.036)
20-29 (ref)	1119 (55)	0	0
30-34	662 (33)	-0.001 (-0.014 to 0.012)	-0.002 (-0.015 to 0.010)
35-39	190 (9)	-0.004 (-0.024 to 0.017)	-0.002 (-0.022 to 0.018)
40-44	23 (1)	0.053 (-0.002 to 0.108)	0.044 (-0.009 to 0.097)
Height (cm)			
<160	184 (9)	-0.050 (-0.070 to -0.029)*	-0.047 (-0.068 to -0.026)*
160-169 (ref)	933 (47)	0	0
170-179	792 (40)	0.044 (0.032 to 0.056)*	0.043 (0.031 to 0.055)*
>180	95 (5)	0.091 (0.064 to 0.118)*	0.082 (0.055 to 0.109)*

^ birthweight ratio is the ratio of observed birthweight to expected mean birthweight corrected for gestational age, sex and parity

@ for the other variables in the table

* $p<0.05$

Preterm birth

Compared with high social class all other categories had a higher risk of preterm birth, however none were statistically significant (table 3). After adjustment the frequency of preterm birth was lower in Turkish infants (OR=0.22; p=0.07), but higher in infants from Surinam and the Antilles (OR=2.51; p=0.04) compared to Dutch infants.

Smoking was not associated in a dose-response relationship with preterm birth. When smoking was entered as a dichotomous variable into the model the adjusted odds ratio was 1.50 (95% CI 0.97 to 2.32; p=0.07). Higher alcohol intake seemed to be associated with a lower frequency of preterm birth. The adjusted odds ratio of using 2 drinks or more per week was 0.15 (p=0.07) compared to abstainers. After adjustment mothers of 40 years and older had a higher frequency of preterm birth compared to mothers who were 20 to 29 years old (OR=5.53; p=0.004). Maternal height appeared to be related with preterm delivery in a dose-response relationship. To avoid dubious linearity assumptions we first entered maternal height as a categorical variable into the model. The coefficients of the different height categories indicated that a linear association was a reasonable description of the relationship between the log(odds) of preterm delivery and height. Height was therefore also entered as a continuous variable into the model. After adjustment for other factors it appeared that every increase of 10 cm in height was associated with a 0.61-fold (95% CI 0.44 to 0.83) decreased risk of preterm delivery.

Table 3 Frequencies, unadjusted and adjusted odds ratios for preterm birth in relation to social class, ethnicity, smoking, alcohol consumption, occupation, age and height

Risk factor	Preterm birth		Unadjusted odds ratio (95% confidence interval)	Adjusted@ odds ratio (95% confidence interval)
	n/N	(%)		
Social class				
very low	7/108	(6)	1.84 (0.70 to 4.79)	2.09 (0.67 to 6.48)
low	57/905	(6)	1.78 (0.94 to 3.63)	1.44 (0.72 to 2.87)
middle	29/644	(5)	1.25 (0.63 to 2.48)	1.16 (0.57 to 2.37)
high (ref)	12/330	(4)	1	1
unknown	3/40	(8)	1.45 (0.44 to 4.79)	1.01 (0.11 to 9.22)
Ethnicity				
Dutch (ref)	97/1798	(5)	1	1
Turkish	2/67	(3)	0.54 (0.13 to 2.24)	0.22 (0.04 to 1.10)
Suriname/ Antilles	7/45	(16)	3.23 (1.41 to 7.42)*	2.51 (1.04 to 6.08)*
Other	2/117	(2)	0.31 (0.07 to 1.25)	0.25 (0.06 to 1.13)
Smoking (cig/day)				
0 (ref)	70/1498	(5)	1	1
1-5	12/203	(6)	1.28 (0.68 to 2.41)	1.27 (0.66 to 2.43)
6-10	15/162	(9)	2.08 (1.16 to 3.73)*	1.96 (1.07 to 3.59)*
11-15	5/82	(6)	1.32 (0.52 to 3.38)	1.23 (0.47 to 3.22)
>15	5/80	(6)	1.36 (0.53 to 3.47)	1.35 (0.52 to 3.55)
Alcohol (drinks/week)				
0 (ref)	87/1497	(6)	1	1
1	19/432	(4)	0.75 (0.45 to 1.24)	0.80 (0.47 to 1.36)
2-7	1/86	(1)	0.17 (0.02 to 1.24)^	0.15 (0.02 to 1.15)^
>7	0/10	(0)		
Occupation				
no (ref)	72/1377	(5)	1	1
yes	36/650	(6)	1.06 (0.70 to 1.60)	1.10 (0.71 to 1.72)
Age				
15-19	2/30	(7)	1.18 (0.27 to 5.05)	0.84 (0.18 to 3.85)
20-29 (ref)	64/1119	(6)	1	1
30-34	27/662	(4)	0.70 (0.44 to 1.11)	0.76 (0.47 to 1.23)
35-39	10/190	(5)	0.92 (0.46 to 1.82)	1.10 (0.54 to 2.25)
40-44	4/23	(17)	3.47 (1.15 to 10.50)*	5.53 (1.72 to 17.77)*
Height (cm)				
<160	17/184	(9)	1.84 (1.03 to 3.27)*	2.00 (1.07 to 3.75)*
160-169(ref)	49/933	(5)	1	1
170-179	37/792	(5)	0.88 (0.57 to 1.37)	0.85 (0.55 to 1.33)
>180	3/95	(3)	0.59 (0.18 to 1.92)	0.59 (0.18 to 1.98)

@ adjusted for the other variables in the table

^ categories of 2-7 and > 7 drinks/week combined because of empty cells

* $p < 0.05$

Discussion

This is the first study performed in the Netherlands in which a large number of possible risk factors were studied for their independent effect on birthweight for gestational age and on preterm delivery. The main findings were that very low social class is a riskfactor for impaired fetal growth and that mothers of Suriname or the Antilles have a higher risk for preterm delivery compared to Dutch mothers.

In the Netherlands the standard of living is very high and access to high quality medical care is possible for all inhabitants. The fact that in this country social class is a riskfactor, even after adjustment for several possible confounders, indicates that it will be very difficult to eradicate these social class differences in other countries. Of course social class can not be in itself a cause of impaired fetal growth. Factors which were not controlled for in the analysis, such as infections, nutrition, maternal vascular diseases[12], may account for the social class differences in birthweight.

Compared with whites, blacks, Asians and Hispanics have been found to have babies that are of lower birthweight and to have babies that are more often preterm, even after adjustment for confounding variables.[4,5,8,13] In our study differences between ethnic groups in birthweight disappeared after correction. However, in the analysis of preterm birth we found that the risk was increased for infants of Suriname or the Antilles compared to Dutch infants even after adjustment. There is some evidence that genetic factors may play a causal role in these ethnic differences, but that non-genetic maternal factors are probably of more importance.[5]

Besides the well-known detrimental effect of smoking on birthweight, there also seemed to be a negative effect of alcohol on birthweight in mothers who drank more than 7 drinks a week. However, statistical significance was not reached (p=0.08), maybe because of low statistical power. In some other studies, alcohol has also been found to be harmful for fetal growth beyond a certain threshold level.[14,15] In our study drinking two glasses or more per week seemed to be associated with a decreased risk of preterm birth, although statistical significance was not reached (p=0.07). Shiono et al also reported a decreased risk of preterm delivery, but only in mothers who drank less than one glass a day.[13] Others found no relationship between moderate drinking and preterm delivery[16], or only a detrimental effect for women consuming two drinks or more a day.[17] These results suggest that drinking one glass per day has no effect on birthweight and gestational age.

It has been well documented that maternal height is associated in a dose-response relationship with birthweight. But our findings, as well as those of others[8], also indicate that maternal height is associated in a dose-response relationship with preterm birth. Taller mothers had less often a preterm delivery. These findings suggest that taller

women have a later physiological term date, which may have consequences for the clinical management of post-term pregnancies.
We found that women aged 40 years or more have an increased risk for preterm delivery, whereas no adverse effect could be detected of higher maternal age on birthweight. An explanation for the higher frequency of preterm delivery could be that in the group of the older women the proportion of women with poor reproductive history, which may be associated with adverse pregnancy outcome, is higher than in young women. Unfortunately, we do not have information concerning history of infertility in our sample. In two studies in which such information was available a deleterious effect of older maternal age on low birthweight and preterm delivery could not be detected.[18,19]
Since this study is of a retrospective design, the relationships between smoking and drinking and birthweight should be interpreted cautiously. It is possible that interviewers tried to get better data on exposure status in cases with growth retardation than in cases with normal birthweight. This could lead to a bias away from the null value. On the other hand, one could argue that mothers of small babies may be more inclined to underestimate their drinking and smoking habits, which would have an opposite effect. An important advantage of our study is the fact that it is population based and that the response was very high. Selection bias is therefore very unlikely to have occurred.
We conclude that despite the high standard of living in the Netherlands very low social class remains a riskfactor for low birthweight for gestational age. Further, infants of mothers from Surinam or the Antilles are at increased risk for preterm delivery compared with Dutch infants.

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PART III

ALCOHOL AND LONG-TERM OUTCOMES

Chapter 6. Use of alcohol, cigarettes or psychofarmaca during pregnancy and child development and behaviour in the first two years of life

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Submitted

Abstract

Objective
To examine the relationship between moderate maternal alcohol consumption, smoking and psychofarmaca use during pregnancy on child development and child behaviour in the first two years of life.

Design
Population based cohort study.

Setting
Child Health Clinics in the Netherlands

Participants
The study population consisted of all 2027 live-born singleton between April 1, 1988 to October 31, 1989 of mothers who, at the time of birth, were living in the catchment areas of 21 Child Health Clinics in the Netherlands.

Outcomes
Child development in the first two years of life and child behaviour in the first year of life.

Main results
Maternal alcohol consumption was negatively associated with communication and social behaviour ($p<0.01$). Infants of mothers who used psychofarmaca had an adjusted z-score on gross motor function that was on average 0.65 ($p<0.05$) points lower compared with control infants. Furthermore, psychofarmaca use was associated with more frequent crying of the infant in the first year of life ($p=0.05$).

Conclusions
Psychofarmaca use and moderate alcohol consumption during pregnancy may be associated with lower developmental scores in the first two years of life. No such relationship could be detected for smoking during pregnancy.

Key words: pregnancy, alcohol, smoking, psychofarmaca, child development, child behaviour.

Introduction

Description of the Fetal Alcohol Syndrome (FAS) has led to awareness that excessive drinking during pregnancy may lead to fetal growth retardation, fetal morphological abnormalities and developmental delay.[1] Furthermore, infants with FAS seem to be more often hyperactive and they sleep less and more restless when they sleep compared to other children.[2] The description of FAS also contributed to the notion that exposure during pregnancy may not only lead to morphological abnormalities but may also lead to behaviourial disturbances.

The frequency of moderate drinking during pregnancy is much higher than excessive drinking. Therefore, even if the effects of moderate prenatal drinking on the developing fetus would be small this could still be a major public health issue. However, little is known about the effects of lower levels of drinking during pregnancy.[3] Some studies found a detrimental effect on child development[4,5], some could not detect such a relationship.[6] A recent large multicentre trial even found that infants of mothers who had used moderate amounts of alcohol had higher developmental scores compared with mothers who did not drink.[7]

Women who drink may also be more likely to use other substances during pregnancy.[3] Smoking during pregnancy has a well documented negative effect on fetal growth[8], but it may also have an effect on brain development as has been shown in animal research.[9] In some human epidemiological studies this effect could be confirmed[10], whereas in others it could not.[11] Two recent studies also suggest a harmful effect of psychofarmaca use during pregnancy on child development.[12,13] However, the results of these two studies may be biased since no adjustment was made for other potential confounders such as alcohol use, smoking and socio-economic status.

The aim of this study was to examine the independent effect of moderate alcohol consumption, smoking and psychofarmaca use during pregnancy on child development and child behaviour in the first two years of life.

Methods

Population

The Social Medical Survey of Children attending Child Health Clinics (SMOCC) is a population based study in which data on 2151 infants in the Netherlands have been collected. The study has been described in detail elsewhere.[14,15] In short: the study population included all infants that were live-born between April 1, 1988 to October 31,

1989 of mothers who, at the time of birth, were living in the catchment areas of 21 Child Health Clinics.

Exposure

Demographic data and exposure information were collected by interview. A standardised questionnaire was administered by a trained nurse from the child health clinic at the mother's home within the first three weeks after delivery. The mothers were asked how many cigarettes they had smoked on average per day during pregnancy, what number of alcoholic drinks they drank on average per week while pregnant and which medicines they had been taking. As psychofarmaca we considered benzodiazepines and its derivatives (e.g. diazepam, flurazepam, lorazepam).

Psychomotor development

Psychomotor development was assessed by child health physicians using the Gesell test adapted for Dutch children (the revised Van Wiechentest.[16]) The revised Van Wiechentest is the standard test that is being used at child health clinics in the Netherlands. Many of its items are comparable with those of the Bayley Scales of Infant Development.[17] Thus, all participating child health physicians were familiar with it. However, to minimise inter-observer variability, the participating physicians received a special training before the study started. To avoid bias they were not informed of the goal of the present study. Infants were tested nine times during the first two years of life: at the age of one month, two months, three months, six months, nine months, twelve months, fifteen months, eighteen months and twenty-four months. The test covers five functions of development: gross motor (e.g. 'walks without support'), fine motor (e.g. 'builds tower of three blocks'), adaptation (e.g. 'plays with his/her hands'), communication (e.g. 'uses sentences of two words') and social behaviour (e.g. 'imitates other persons'). At each interval five to six items are assessed. The test is designed in such a way that at least 90% of children can perform the items belonging to a certain interval.[15] Normally, only items belonging to the appropriate age interval are tested, but for this study the items belonging to the next interval were assessed as well. The completion of items belonging to the appropriate age interval compared to the children present at that interval varied from 76.0% to 99.3% (average 96.3%), whereas for items belonging to the next interval completion varied from 62.4% to 93.2% (average 81.8%). In the first two years of life, differentiation between fine motor function and adaptation as well as differentiation between communication and social behaviour is difficult. Therefore, these four functions were combined into two functions. For each child three developmental indices (gross motor, fine motor/adaptation and communication/social behaviour) were calculated by giving one point for each item scored and dividing the sum of these points by the total number of items ("appropriate"

items as well as items of the next interval) registered at the nine assessments. Indices were only calculated when at least 10 items for a developmental function had been assessed. The distribution of the indices were skewed to the left. To obtain a more normal distribution the indices were raised to the square. To facilitate interpretation we then transformed the squared indices into a z-score. This was done by calculating the mean and standard deviation of an index in all infants. This mean score was subsequently subtracted from each infant's index and divided by that standard deviation. In this approach items with missing values are excluded. Besides lack of time, one of the reasons that item scores are missing may be the fact that the test is aborted when the child fails to perform some items. In that case, missingness is related to ability level and excluding missing items will overestimate the true ability level. In case exposed infants have more missing items than unexposed infants, this could bias the effect estimates. We applied multiple imputation to obtain estimates of development that correct for undesirable nonresponse effects.[18] The appendix describes the approach in more detail.

Child behaviour

At each interval, except at the interval at the age of two months, parents were asked by the child health physician if their child cried more than they had expected before they were pregnant and if their child did sleep well. A child was considered to cry frequently if a positive answer was given to that question on at least two of the five assessments in the first year of life of the infant. To maximise the contrast between frequent crying and not frequent crying we excluded 444 infants from the analysis of whom the mothers gave a positive answer at only one interval. To minimise the number of missing values we considered infants who were present at least three intervals not to be frequent criers when the parents had given a negative answer at these three assessments. In the same way we defined 'difficult sleeping behaviour'.

Confounders

As possible confounders we considered level of education of the mother, age of the mother, ethnicity of the mother, occupation of the mother, parity, type of feeding and child's sex. Level of education was categorized as: very low (special education and primary education), low (junior vocational training and lower secondary general education), middle (senior vocational training and higher secondary general education) and high (vocational colleges and university education). Maternal age was calculated in completed years at the date of delivery and was categorized into 15 to 24 years, 25 to 29 years, 30 to 34 years and 35 to 44 years of age. Ethnicity was defined by country of origin and categorized into Dutch, Turkish, Suriname/Antilles and other. Occupation was defined as having paid work outside the house for two or more days per week. Parity

was categorized into 4 categories (0, 1, 2 or 3 or more children before this child). Type of feeding was defined by status at the age of four weeks of the child and categorized into three categories (formula only, breast-fed only, or breast fed combined with formula-milk).

Statistical analysis

Univariate testing comprised anova, chi-square tests and Fisher's Exact tests were appropriate. All independent variables were coded into indicator variables. To assess the overall contribution of a variable to a model we compared the model with the indicator variables with the model without the alcohol indicator variables. In the linear regression analyses the partial F-test was used. In the logistic regression analyses the difference in -2 log likelihood of the two models (i.e. the improvement chi-square test or likelihood ratio test) was calculated. All statistical tests were two sided.

Results

Response and population

A total of 2151 children were liveborn in the catchment area of the participating child health clinics during the study period. For 2092 (97%) of these, valid questionnaires on demographic data and exposure information were obtained. The response at the 9 different intervals varied from 93% to 83%. For the present analyses we selected only singleton births (n=2027). No developmental indices could be calculated for 92 singletons, leaving data from 1935 (95%) singleton children for analysis.

The frequency of abstainers and non-smokers was 74% (table 1). Use of psychofarmaca was reported by 1% of the women. Almost 90% of the women were of Dutch origin.

Table 1 Characteristics of the study group

Variable	n	%
Exposures		
Alcohol (drinks/week)		
0	1427	(74)
1	416	(22)
2-7	82	(4)
>7	9	(0)
Smoking (cig/day)		
0	1440	(74)
1-5	197	(10)
6-10	150	(8)
11-15	76	(4)
>15	71	(4)
Use of psychofarmaca		
no	1922	(99)
yes	13	(1)
Education of mother		
unknown	30	(2)
very low	102	(5)
low	867	(45)
medium	615	(32)
high	321	(17)
Ethnicity		
Dutch	1720	(89)
Turkish	64	(3)
Suriname/Antilles	41	(2)
Other	110	(6)

Gross motor function (table 2)

A statistically significant relationship was found between gross motor function and psychofarmaca use (table 2). Infants of mothers who had used psychofarmaca had an adjusted z-score on gross motor function that was on average 0.65 ($p<0.05$) points lower compared with control infants.

After adjustment the z-scores on gross motor function of infants of mothers who smoked 6-10 cigarettes per day was 0.19 ($p<0.05$) points higher than the z-score of non-smokers. However, the overall improvement of the fit was not improved when we added all four smoking indicator variables to the model with the other variables ($F=1.52$, $df=4$, $p=0.19$). Therefore, this relationship may be a chance finding. Alcohol was not related with gross motor function.

Table 2 Unadjusted and adjusted differences in z-scores for gross motor function in relation to maternal alcohol consumption, smoking and use of psychofarmaca during pregnancy

Exposure	df	F	Unadjusted difference (SE)	df	F	Adjusted[@] difference (95% CI)
Alcohol drinks/wk)	3	0.05		3	0.58	
0 (ref)			0			0
1			-0.02 (0.06)			-0.07 (-0.18 to 0.04)
2-7			0.03 (0.11)			-0.02 (-0.25 to 0.20)
>7			-0.01 (0.35)			0.18 (-0.47 to 0.83)
Smoking (cig/day)	4	0.44		4	1.52	
0 (ref)			0			0
1-5			-0.02 (0.08)			-0.01 (-0.16 to 0.14)
6-10			0.11 (0.09)			0.19 (0.02 to 0.36)*
11-15			0.02 (0.12)			0.11 (-0.12 to 0.35)
>15			0.05 (0.12)			0.11 (-0.13 to 0.35)
Use of psycho-farmaca	1	5.18*		1	5.35*	
no (ref)			0			0
yes			-0.65 (0.29)*			-0.65 (-1.19 to -0.10)*

@ for the other variables in the table as well as infant's sex, maternal education, ethnicity, occupation, age and parity

* $p<0.05$

Fine motor function and adaptation (table 3)

No significant relationships were found between smoking and psychofarmaca use on the one hand and fine motor function and adaptation on the other hand (table 3). After adjustment the z-scores were in all three drinking levels lower compared with the z-scores of non-drinkers. Only the z-score in women who had drunk 1 glass per week was statistically significant. However, we considered this relationship to be a chance finding, since the overall fit of the model was not improved when all three drinking indicator variables were added to the model with the other variables.

Table 3 Unadjusted and adjusted differences in z-scores for fine motor function and adaptation in relation to maternal alcohol consumption, smoking and use of psychofarmaca during pregnancy

Exposure	df	F	Unadjusted difference (SE)	df	F	Adjusted@ difference (95% CI)
Alcohol (drinks/wk)	3	0.24		3	1.68	
0 (ref)			0			0
1			-0.03 (0.06)			-0.13 (-0.24 to -0.02)*
2-7			0.06 (0.11)			0.00 (-0.22 to 0.23)
>7			-0.13 (0.35)			-0.02 (-0.67 to 0.63)
Smoking (cig/day)	4	0.32		4	0.36	
0 (ref)			0			0
1-5			-0.05 (0.08)			-0.02 (-0.17 to 0.13)
6-10			-0.06 (0.09)			-0.00 (-0.17 to 0.16)
11-15			-0.08 (0.12)			0.02 (-0.17 to 0.13)
>15			0.04 (0.12)			0.14 (-0.10 to 0.38)
Use of psycho-farmaca	1	1.95		1	1.80	
no (ref)			0			0
yes			-0.40 (0.28)			-0.37 (-0.91 to 0.17)

@ see table 2
* $p<0.05$

Communication and social behaviour (table 4)

After adjustment we found a statistically significant improvement of the fit when we added the alcohol indicator variables to the model with as outcome variable communication and social behaviour ($F=5.35$, $df=3$, $p=0.001$) (table 4). All three alcohol indicator variables had a negative sign indicating that children of mothers who drank during pregnancy had lower scores on 'communication and social behaviour' than children of mothers who did not drink. However, a clear dose response relationship was not present. Smoking 6-10 cigarettes per day was associated with a higher z-score compared to non-smoking. Since the overall fit of the model was not increased by adding the four smoking indicator variables to the model this result may be a chance finding.

Table 4 Unadjusted and adjusted differences in z-scores for communication and social behaviour in relation to maternal alcohol consumption, smoking and use of psychofarmaca during pregnancy

Exposure	df	F	Unadjusted difference (SE)	df	F	Adjusted[@] difference (95% CI)
Alcohol (drinks/wk)	3	1.55		3	5.35**	
0 (ref)			0			0
1			-0.12 (0.06)*			-0.22 (-0.33 to -0.11)**
2-7			-0.04 (0.11)			-0.06 (-0.28 to 0.16)
>7			-0.22 (0.36)			-0.11 (-0.77 to 0.56)
Smoking (cig/day)	4	1.29		4	1.96	
0 (ref)			0			0
1-5			-0.08 (0.08)			-0.05 (-0.19 to 0.10)
6-10			0.14 (0.09)			0.20 (0.03 to 0.36)*
11-15			-0.06 (0.12)			0.06 (-0.16 to 0.29)
>15			0.11 (0.13)			0.17 (-0.07 to 0.40)
Use of psycho-farmaca	1	2.28		1	1.63	
no (ref)						0
yes			-0.44 (0.29)			-0.36 (-0.90 to 0.19)

@ see table 2
* p<0.05; ** p<0,01

Multiple imputation

When we reanalysed the relation between the exposures and the developmental indices after we had used multiple imputation, similar results were found for most coefficients (results are shown in the appendix). However, in this analysis the coefficients denoting smoking 6-10 cigarettes were not significantly associated with gross motor function and with communication and social behaviour. On the other hand the use of psychofarmaca was significantly associated with a lower outcome on communication and social behaviour (adjusted difference -0.58; p<0.05).

Behaviour (table 5 and 6)

The only statistically significant relationship found was between psychofarmaca use during pregnancy and frequent crying (table 5). Adding this variable to the model with the other exposures and confounders resulted in a decrease in deviance of 3.84 (df=1, p=0.05). Infants of mothers that used psychofarmaca cried more often than control infants.

Table 5 Frequencies, percentages and results of logistic regression analysis on frequent crying in the first year of life

Exposure	df	Chi-square	n/N' (%)	unadjusted odds ratio	df	Change in deviance	adjusted@ odds ratio (95% CI)
Alcohol (drinks/wk)	2^	0.9			2	1.4	
0 (ref			97/1088 (9)	1			1
1			30/326 (9)	1.0			1.1 (0.7 to 1.8)
2-7			8/59 (14)	1.4			1.6 (0.7 to 3.7)
>7			0/6 (0)	-^			-^
Smoking (cig/day)	4	5.5			4	7.1	
0 (ref)			97/1092 (9)	1			1
1-5			20/161 (12)	1.5			1.5 (0.9 to 2.6)
6-10			10/121 (8)	0.9			0.9 (0.4 to 1.7)
11-15			2/59 (3)	0.4			0.3 (0.1 to 1.3)
>15			6/46 (13)	1.5			1.4 (0.6 to 3.6)
Use of psycho-farmaca	-	- $			1	3.8*	
no (ref)			132/1469 (9)	1			1
yes			3/10 (30)	4.3			5.0 (1.0 to 21.8)*

* $p \leq 0.05$

@ see table 2

^ Categories >7 and 2-7 were collapsed into one category to avoid cells with expected frequency < 5 and to avoid empty cells

\# 444 infants were excluded to increase contrast between groups (see methods)

$ Fisher's Exact test p=0.055 (chi-square not calculated because of cell with minimum expected frequency < 5)

Table 6 Frequencies, percentages and results of logistic regression analysis on difficult sleeping behaviour in the first year of life

Exposure	df	Chi-square	n/N' (%)	unadjusted odds ratio	df	Change in deviance	adjusted@ odds ratio (95% CI)
Alcohol (drinks/wk)	2^	1.3			3	3.3	
0 (ref)			94/1151 (9)	1			1
1			34/340 (10)	1.2			1.3 (0.8 to 2.0)
2-7			6/73 (8)	1.0			0.9 (0.4 to 2.2)
>7			2/8 (25)	3.7			3.9 (0.7 to 21.1)
Smoking (cig/day)	4	3.3			4	2.6	
0 (ref)			105/1175 (9)	1			1
1-5			17/161 (11)	1.2			1.1 (0.6 to 2.0)
6-10			7/126 (6)	0.6			0.6 (0.3 to 1.4)
11-15			3/56 (5)	0.6			0.6 (0.2 to 2.1)
>15			4/54 (7)	0.8			0.8 (0.3 to 2.4)
Use of psycho-farmaca	-	- $			-	- &	
no (ref)			136/1559 (9)	1			1
yes			0/13 (0)	-			- &

@ see table 2
^ Categories >7 and 2-7 were collapsed into one category to avoid cells with expected frequency < 5
& Variable not entered into the model, because of empty cell
# 339 infants were excluded to increase contrast between groups (see methods)
$ Fisher's Exact test p=0.3 (chi-square not calculated because of cell with minimum expected frequency < 5)

Discussion

We found that moderate maternal alcohol consumption and psychofarmaca use during pregnancy was associated with lower psychomotor development of the infant in the first two years of life. Use of psychofarmaca was also associated with more crying of the infant in the first year of life.

Experimental studies using animal models have also shown an effect of alcohol use as well as psychofarmaca use on brain development.[2,19,20] Furthermore, negative relationships between alcohol use and psychofarmaca use on the one hand and child development on the other hand have also been found in other epidemiological studies in humans.[4,12,13,21] Especially the relationship between psychofarmaca use and child development appeared to be strong in our study. Infants of mothers who used psychofarmaca had a z-score on gross motor function that was on average 0.7 points lower compared with control infants. However, this estimate has a wide confidence interval due to the small number of

mothers reporting psychofarmaca use. Laegreid et al also found a retarded gross motor development in infants of mothers who had used psychofarmaca.[12] They found this effect to be present at the ages of 6 and 10 months, but at the age of 18 months gross motor function was nearly normal.

Our results suggest that even a moderate intake of one drink per week (the equivalent of 10 grams per week) may have a negative effect on child development. However, this result must be interpreted very cautiously, for three reasons. First, the effect may be due to underreporting of alcohol consumption. It has been shown that underreporting may lead to a bias away from the null value for intermediate categories of exposure.[22] Therefore, it is possible that drinking one glass per week is in fact not harmful but may appear to be harmful due to misclassification of heavier drinkers in this exposure category. Second, an important aspect that should be considered before concluding that an association is causal, is consistency.[23] In most other studies of maternal alcohol consumption and child development a detrimental effect has only been shown above 150 to 200 grams (15 to 20 drinks) per week.[5,24] Recently, we completed a follow-up study of this same cohort at the age of five years. At the age of five years we were unable to detect a detrimental effect of alcohol on IQ as well as on the four functions of the Denver Developmental Screening Test (unpublished observations). We did, however, find that an average consumption of more than seven drinks per week was associated with an increased risk of having a child with attention-deficit hyperactivity disorder. Third, we would have been inclined to consider the relationship between one drink per week and developmental outcome more convincing when a clearer dose-response relationship had been found. For instance, consuming one drink per week was associated with a decrease in z-score of 0.22 points for 'communication and social behaviour', whereas drinking 2-7 drinks per week was associated with a decrease of only 0.06 points. For these reasons we are not convinced that a consumption of only one drink may have a detrimental effect on child development. Based on the current evidence we would recommend pregnant women to restrict their consumption to not more than one drink per day throughout pregnancy.

In case an exposure is categorized into two levels such as psychofarmaca use in our study every form of non-differential misclassification will lead to a bias toward the null value. Therefore, the actual effect of psychofarmaca use on development may be even greater than we have found in our study.

We could not confirm the relationship between child development and maternal smoking as has been reported in seven to eleven year old children [25] and in three to four year old children.[10] Perhaps the effects of smoking on development are too subtle to be detected in the first two years of life. On the other hand two other studies in which children of 10 to 12 years of age were studied were also unable to detect such a relationship.[11,26]

Furthermore, a recent large study that used a biomarker of cigarette exposure (cotinine) also failed to show a relationship between smoking during pregnancy and developmental outcome at the age of 5 years.[27] This would suggest that smoking is unlikely to have a considerable effect on psychomotor development.

Our study had several advantages compared to other studies. Our study was population based and had a very high response. Thus, selection bias seems unlikely. Recall bias is unlikely to have occurred since the exposures were registered before child development and child behaviour were assessed. Furthermore, interviewer bias is unlikely to have occurred, because the child health physicians that assessed developmental outcome were not informed of the purpose of this study.

In an observational study such as ours, confounding can never be excluded. Especially, the relationship between psychofarmaca use and child development, but also the relationship between alcohol and child development, may be due to confounders such as rearing pattern. Perhaps mothers who use psychofarmaca or who drink do not stimulate their infants as much as mothers who do not use psychofarmaca or who do not drink. Furthermore, the relationship between frequent crying and psychofarmaca may also be biased. This behaviour was based on the perceptions of the mother of her infant. It is possible that mothers who use psychofarmaca are bothered more by the crying of their infants than mothers who do not use psychofarmaca. Future studies on psychofarmaca should, therefore, try to take into account differences in rearing patterns and should also measure the quantity as well as the timing of these drugs during pregnancy. Furthermore, the medical indication for psychofarmaca use should be registered. For instance a causal effect may be considered less likely to exist, if the relationship shows to be much weaker in mothers who use these drugs only as a sleeping drug compared with mothers who use them as tranquillizers.

We conclude that psychofarmaca use and moderate alcohol consumption during pregnancy may be associated with lower developmental scores in the first two years of life. No such relationship could be detected for smoking during pregnancy.

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Chapter 7. Prenatal alcohol consumption and child development and child behaviour at five years of age

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Abstract

Objective
To examine the relationship between moderate alcohol consumption during pregnancy and child development as well as child behaviour at 5 years of age.

Design
Population based cohort study.

Setting
21 child health clinics in the Netherlands

Subjects
The study population consisted of 564 children (response 92%). The sample was taken from a larger population based cohort study in such a way that heavier drinkers were overrepresented. The children were born between April 1, 1988 and October 31, 1989 of mothers who were living in the catchment areas of the 21 participating child health clinics in the Netherlands. At follow-up the average age of the children was 5.4 years (SD 0.4).

Main outcome measures
IQ, attention-deficit hyperactivity disorder (ADHD) and motor development were measured with use of a questionnaire administered by the parents.

Results
Women with an average consumption of more than a drink per day during pregnancy had an increased risk of having a child with ADHD compared with non-drinkers (relative risk 11.9; 95% CI 2.0-44.4). No relationship could be detected between alcohol consumption and IQ or motor development.

Conclusions
Alcohol consumption during pregnancy of more than a drink per day may be associated with an increased risk of having a child with ADHD.

Key words
Pregnancy, alcohol, child development, child behaviour, attention-deficit hyperactivity disorder

Introduction

Numerous studies have shown that severe abuse of alcohol during pregnancy may lead to the fetal alcohol syndrome (FAS).[1] Besides growth retardation and specific congenital malformations children with FAS are mainly known to have central nervous system manifestations such as intellectual deficits, hyperactivity and attention deficits as well as delayed motor development.[1-4]

Moderate drinking during pregnancy is much more prevalent than heavy drinking. Therefore, at a population level the effects of moderate drinking may have major public health implications even when the effects at an individual level would be small. Whether moderate alcohol use during pregnancy is harmful to the fetus has been unclear until now. Several studies indicate that a consumption of two or more drinks per day may affect fetal growth as well as child development, whereas the findings for alcohol consumption below this level are inconsistent.[5] Part of the explanation may be that most of these studies have been performed in children of two years or younger. At these ages subtle effects of alcohol on cognitive and emotional development may be difficult to measure. We, therefore, performed a follow-up study of 5 years. Goal of the study was to investigate the relationship between moderate alcohol consumption during pregnancy and IQ, attention-deficit hyperactivity disorder and motor development.

Methods

Population

The Social Medical Survey of Children Attending Child Health Clinics (SMOCC) is a population based study that has been described in detail elsewhere.[6] In short: the study population included all 2151 infants live-born between April 1, 1988 to October 31, 1989 of mothers who, at the time of birth of their child, were living in the catchment areas of 21 child health clinics. A standardised questionnaire was administered by a trained nurse from the child health clinic at the mother's home within the first three weeks after delivery. Demographic data and exposure information were collected of 2092 (97%) infants. Alcohol consumption was measured by asking the mothers what they drank on average during pregnancy. The infants were seen at several occasions up until their second birthday at the Child Health Clinic. At the last occasion the parents were asked to participate in a follow-up study which would take place around the fifth birthday of their child.

Selection of study sample

For this study a selection was made of the original 2092 participating infants. We excluded: (1) infants of whom the mother language of both parents was not Dutch, (2) infants whose mother and/or father were not born in Europe, (3) infants of whom the mother and/or father had attended special education or only primary education, (4) mothers who reported the use of illegal drugs, (5) twins and (6) infants with Down syndrome. These exclusions were made to achieve a more homogenous sample with respect to variables that may influence development of the child, thus increasing the precision of the study. An additional reason to exclude parents with a low education and parents whose native language was not Dutch, was to ensure that parents would understand the self-administered questionnaire. Of the remaining 1649 infants, the mothers of 1454 (88%) agreed to participate in a follow-study at the age of about five years. Of these 1454, a stratified sample by alcohol, education of the mother and age of the infant was taken. All mothers who drank two or more drinks per week were included. Mothers who drank less were sampled in such a way that approximately 50% were abstainers and 30% drank about one drink per week. Age of child and education of mother are important predictors of child development. To minimise random error and to avoid confounding we, therefore, ensured that the age distribution of infants and the distribution of maternal education was comparable for drinkers and abstainers in the final sample. This final sample consisted of 610 children.

Outcomes

All outcomes were assessed with a self-administered questionnaire that was sent to the parents in 1994. Parents were not informed about the exact goal of this study to avoid bias. We used an IQ-test that was standardized for Dutch children of an age between 4.5 and 6.5 years.[7] The test consists of three subtests. One in which children have to reproduce five figures (square, triangle, cross, trapezium and a kite), one in which children have to draw a person and one in which children have to give the meaning of a list of 13 words. Parents were asked to write down literally what meaning their child gave of the words. The test was subsequently scored according to a protocol by two research assistants who were blinded with respect to the alcohol status of the mother. Attention-deficit hyperactivity disorder (ADHD) was based on DSM-III-R criteria.[8,9] This questionnaire consists of 14 items such as: "has difficulty in concentrating on a task or play". Each item was rated on a 4 point score ranging from 0 (not at all) to 3 (very often) by the parents. When a child had at least 8 positive items (score $\geq$ 2) it was considered to have ADHD. A disadvantage of dichotomizing an outcome is that information will be lost. Therefore, we also constructed a continuous attention-deficit hyperactivity

variable. This was done by calculating for each child the sum of the 14 items. After a log transformation this variable was approximately normally distributed. For ease of interpretation we transformed this log(sumscore) into a z-score. This was done by calculating the mean and standard deviation of the log(sumscore) in all infants. Then this mean was subtracted from each infant's individual score and divided by that standard deviation.

The Denver Developmental Screening Test was used to assess the functions: gross motor, fine motor-adaptive, language and personal-social.[10] A child was considered to have a delay in one of these four functions if it could not pass an item at an age at which 75% of children can. The 75th centile was based on Dutch reference values.[11]

The questionnaire was first pre-tested in four families who were observed while completing the questionnaire. This led to some minor adjustments. We then further tested the questionnaire by sending it to 10 families in which both parents had a low education (junior vocational training or lower secondary general education). Nine of these parents completed the questionnaire and were interviewed by phone. Only one family refused to participate. These pilot studies showed that parents understood the questions and that children enjoyed to participate. The questionnaire took about one hour to complete. To diminish the inclination of parents to give too optimistic a view of their children's performance we stressed at several places in the questionnaire that it is perfectly normal for a child not to be able to perform on all items. The parents were also instructed that motivating their child was allowed, but giving advice or helping the child was not allowed.

Response

A high response is essential in order to avoid bias. Effect estimates of the relation between maternal alcohol consumption and child development will for instance be biased toward the null value, if heavy drinkers with children with developmental problems would be less motivated to participate than heavy drinkers with normal children. To achieve a high response we used some techniques that are being used in professional mail surveys.[12] First, we spent some time in developing a questionnaire that could easily be completed by parents. Second, the questionnaire was sent with an accompanying letter that was personal (e.g. personally signed), short, gave the purpose of the study (parents were informed that we were interested to know how their child had developed and that we would compare these results with data we had collected previously). As an incentive we included a balloon for the child. After about two weeks we sent a reminder (without questionnaire) and after 6 weeks we sent another questionnaire. Non-responders were then contacted by telephone. The new address of parents who were moved was found with the help of the municipal administration or by asking the former neighbours.

Confounders

As possible confounders we considered age of the mother, smoking and use of psychofarmaca during pregnancy, occupation of the mother, parity, child's sex, and type of feeding. Although level of education of the mother and child's age are not confounders because of our sampling procedure, we included these variables too in the models to increase precision of the effect estimates.

Level of education was categorized as: low (junior vocational training and lower secondary general education), middle (senior vocational training and higher secondary general education) and high (vocational colleges and university education). Maternal age was calculated in completed years at date of delivery and was categorized into 15 to 24 years, 25 to 29 years, 30 to 34 years and 35 to 44 years of age. Occupation was defined as having paid work outside the home for two or more days per week. Parity was categorized into two categories (primi- and multiparous). Type of feeding was defined by status at the age of four weeks of the child and categorized into three categories (formula only, breast-fed only, or breast fed substituted with formula-milk).

Statistical analysis

In the univariate analyses analysis of variance, chi square and likelihood ratio tests were used when appropriate. To adjust for confounders linear regression analysis was used in the analysis with IQ, and logistic regression analysis was used in the analysis with the dichotomous outcome variables. The parameters of the logistic regression model correspond to odds ratios. However, the odds ratio is not always the most preferable measure, since it can differ considerably from the relative risk, especially in situations where disease is not rare. When appropriate we, therefore, also calculated an average adjusted relative risk. This was done with the help of the coefficients of the logistic regression model. First, we calculated the risks predicted by the logistic regression model in the situation that all children would not be exposed to alcohol. Next, the risks were calculated for the situation were all children would be exposed to alcohol. By dividing these risks we calculated for each child the individual relative risk. Due to the properties of the logistic regression model these relative risks differ between children. Therefore, the average of these relative risks was calculated as a summary measure of the adjusted relative risk for our population. The 95% confidence limits were calculated in the same way, except that we replaced the coefficient denoting alcohol with the coefficient plus 1.96 times the standard error and minus 1.96 times the standard error.

Alcohol was coded into three indicator variables denoting alcohol consumption in the ranges of 1, 2-7 and >7 drinks per week. If the mother was a non-drinker all three variables were coded 0. To assess the overall contribution of alcohol to a model we

compared the model with the alcohol indicator variables to the model without the alcohol indicator variables. In the linear regression analyses the partial F-test was used. In the logistic regression analyses the difference in -2 log likelihood of the two models (i.e. the improvement chi-square test or likelihood ratio test) was calculated. All statistical tests were two sided.

Results

Response and population characteristics

Of 564 (92%) of the 610 infants sampled, an eligible questionnaire was received. As a result of the sampling scheme, the distribution of maternal education and age of the child was comparable for different levels of alcohol consumption (table 1). The mean age of the mothers was 30.0 years (SD 3.9) and the mean age of the children was 5.4 years (SD 0.4). Mothers who drank alcohol during pregnancy were older (p=0.001) and were more often smokers (p=0.08). Mothers who drank two or more drinks per week were more often multiparous than women who drank less (p=0.04). Only 6 mothers reported to have drunk more than 7 drinks per week. The exact alcohol intake of these 6 mothers is not known. However, there were no signs that they were alcoholics. All 6 had a stable relationship.

Table 1 Study characteristics by alcohol consumption during pregnancy

Characteristic	Alcohol consumption (drinks per week)			
	0 (N=305)	1 (N=187)	≥2 (N=72)	total (N=564)
Means (SD)				
Maternal age (yrs)*	29.7 (3.9)	29.9 (3.8)	31.6 (3.8)	30.0 (3.9)
Infant's age (yrs)	5.4 (0.4)	5.3 (0.4)	5.4 (0.4)	5.4 (0.4)
Count (%)				
Maternal smoking during pregnancy^				
yes	48 (16)	44 (24)	16 (22)	108 (19)
no	257 (84)	143 (76)	56 (78)	456 (81)
Maternal occupation				
yes	120 (39)	78 (42)	35 (49)	233 (41)
no	185 (61)	109 (58)	37 (51)	331 (59)
Maternal education				
low	92 (30)	57 (30)	21 (29)	170 (30)
medium	106 (35)	70 (37)	25 (35)	201 (36)
high	107 (35)	60 (32)	26 (36)	193 (34)
Parity*				
primiparous	133 (44)	92 (49)	23 (32)	248 (44)
multiparous	172 (56)	95 (51)	49 (68)	316 (56)
Feeding pattern				
Breast	169 (55)	112 (60)	44 (61)	325 (58)
Breast/Formula	21 (7)	16 (9)	6 (8)	43 (8)
Formula	115 (38)	59 (32)	22 (31)	196 (35)

^ $p<0.10$; * $p<0.05$

IQ

Mean IQ of the children was 108 (SD 15) (table 2). Children whose mothers had the highest level of education, had an average IQ of 110, whereas children whose mothers had the lowest education had an average IQ of 105 (table 2). After adjustment for confounders children of mothers with the highest alcohol levels had an average IQ that was one point lower than that of children whose mothers were abstainers (table 3). This difference was not statistically significant, however.

Table 2 Mean IQ (SD) stratified by maternal alcohol consumption during pregnancy and maternal education

Alcohol (drinks/wk)	Maternal education (in years)			
	low	medium	high	total
0	104 (16)	107 (16)	111 (13)	108 (15)
1	108 (13)	109 (15)	109 (13)	108 (14)
≥2	101 (17)	106 (14)	111 (15)	106 (15)
total	105 (15)	108 (16)	110 (13)	108 (15)
F-value (df)	1.78 (2)	0.38 (2)	0.80 (2)	0.52 (2)
p-value	0.17	0.69	0.45	0.60

Table 3 Regression coefficients of linear regression analysis for alcohol consumption during pregnancy on IQ

Alcohol consumption (drinks/wk)	Unadjusted coefficient (95% CI)	Adjusted^ coefficient (95% CI)
0 (ref)	0	0
1	0.6 (-2.1 to 3.3)	0.1 (-2.6 to 2.7)
2-7	-1.4 (-5.4 to 2.5)	-1.4 (-5.3 to 2.6)
>7	-2.1 (-14.1 to 10.0)	-1.0 (-12.6 to 10.7)
F-value (df)	0.35 (3)	0.18 (3)
p-value	0.79	0.91

^ adjusted for level of education of the mother, age of the mother, smoking and psychofarmaca use during pregnancy, occupation of the mother, parity, child's sex and age, and type of feeding

Attention deficit and hyperactivity disorder

A diagnosis of ADHD was made in 26 (4.6%) of the 564 children. After adjustment for confounders, alcohol appeared to be related with ADHD (p=0.07) (table 4). Mothers who drank more than 7 drinks per week had 11.9 times (95% confidence interval 2.0 to 44.4) more often a child with ADHD than mothers who did not drink (adjusted OR 16, 95% confidence interval 2 to 124). The relative risk in the group of mothers who had drunk 2-7 drinks per week was also increased compared to the non-drinking mothers, although not statistically significant (RR 2.5, 95% confidence interval 0.8 to 7.1). Comparable results were found in the analysis in which the continuous measure of attention deficit

and hyperactivity was used. Children of mothers who drank more than 7 drinks per week had on average a z-score that was 0.83 higher (95% confidence interval 0.06 to 1.60) than that of children of abstainers. A higher z-score indicates more attention deficit and hyperactivity problems. In contrast with the dichotomous measure of ADHD, this analysis showed no increase in the scores of mothers who had drunk 2 to 7 drinks per week compared with mothers who had not drunk.

Table 4 Frequencies, percentages and odds ratios of alcohol consumption during pregnancy and attention-deficit hyperactivity disorder (ADHD) as well as differences in z-scores of attention-deficit hyperactivity

	ADHD			differences in z-scores of attention-deficit and hyperactivity	
Alcohol consumption (drinks/wk)	n/N (%)	Unadjusted relative risk	Adjusted^ relative risk (95% CI)	difference unadjusted	difference adjusted^ (95% CI)
0 (ref)	12/305 (4)	1	1	0	0
1	7/187 (4)	0.9	1.3 (0.5 to 3.4)	-0.06	-0.05 (-0.23 to 0.13)
2-7	5/66 (8)	2.0	2.5 (0.8 to 7.1)	-0.17	-0.17 (-0.43 to 0.09)
>7	2/6 (33)	12.2	11.9 (2.0 to 44.4)**	0.82	0.83 (0.06 to 1.60)*
	LR=6.83@ (df=3) p=0.08		LR=7.10 (df=3) p=0.07	F=2.00) (df=3) p=0.11	F=2.17 (df=3) p=0.09

^ see table 3

* p<0.05; ** p<0.01

@ LR = likelihood ratio

Denver Developmental Screening Test

None of the four functions of the Denver Developmental Screening Test was statistically significantly related with alcohol use (table 5).

Table 5 Frequencies, percentages and adjusted^ odds ratios of the four functions of the denver developmental screening test by alcohol consumption during pregnancy

	Delay in							
	Gross motor		Fine motor - adaptive		Language		Personal - social	
Alcohol consumption (drinks/wk)	n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)
0 (ref)	79/297 (27)	1	70/303 (23)	1	18/302 (6)	1	27/304 (9)	1
1	49/186 (26)	1.1 (0.7 1.7)	34/187 (18)	0.7 (0.5 1.2)	8/187 (4)	0.7 (0.3 1.6)	13/187 (7)	0.8 (0.4 1.6)
2-7	23/66 (35)	1.6 (0.9 3.0)	13/66 (20)	0.7 (0.4 1.5)	6/65 (9)	1.5 (0.5 4.0)#	6/65 (9)	0.9 (0.3 2.1)
>7	2/6 (33)	1.1 (0.2 6.6)	2/6 (33)	1.5 (0.3 8.8)	0/6 (0)	-#	1/6 (17)	2.1 (0.2 25.5)
LR@ (df)	2.0 (3)	2.1 (3)	2.3 (3)	2.2 (3)	1.7 (2#)	1.9 (2#)	1.1 (3)	1.1 (3)
p	0.6	0.6	0.5	0.5	0.4	0.4	0.8	0.8

^ see table 3

\# categories 2-7 and >7 collapsed into one category to avoid empty cells

@ LR = likelihood ratio

Discussion

The main finding of our study is that an average consumption of more than a drink per day during pregnancy may be associated with an increased risk of having a child with attention-deficit hyperactivity disorder (ADHD). No relationship was found between alcohol on the one hand and child's IQ and motor development on the other hand.
Many studies have reported a strong relationship between ADHD and excessive drinking.[1] One would assume that in studies of moderate drinking during pregnancy this would be considered an important outcome measure. However, only two cohort studies with a sufficiently long follow-up period have addressed this question. In a four year follow-up study, Landesman-Dwyer et al found more attention deficits in children of mothers who drank on average 0.45 oz (about one drink) per day, compared with children of mothers who drank less.[12] Attention measures were derived from direct observations at the home of the child. In another cohort study, attention was measured in 4 year old as well as 7 year old children in a laboratory setting with the help of a computer-controlled vigilance task.[14,15] This study showed a dose-response relationship on some of the outcome measures: higher amounts of alcohol consumption were related to more attentional problems. Furthermore, experimental studies in which animals were prenatally exposed to alcohol suggest that their offspring have difficulty in inhibiting their behaviour.[1] Some of these experiments also showed a dose-response relationship. This combined evidence suggests that a moderate consumption of more than one drink per day may be causally related to hyperactivity. ADHD is one of the major behaviourial problems in children. Motivation of pregnant women to consume less then one drink per day may, therefore, have considerable impact at population level.
In our study IQ as well as motor development do not appear to be related with an average alcohol intake of up to one drink per day. Since the number of mothers who reported to drink more than a drink per day was small, no conclusions can be drawn with regard to higher quantities of alcohol intake. This finding is in line with the conclusions of a recent review of the literature on this subject as well as a recent study performed in preschool children.[16,17] In these reports no evidence was found for a detrimental effect of alcohol of less than 150 gram per week (about two drinks per day) on mental and motor development.
Misclassification of alcohol is often mentioned as a serious threat to the validity of the results of a study. With no specific biological marker, the quantification of alcohol consumption has to be based on self-reported data. It is generally agreed that self-reporting may lead to considerable underestimation.[18] In a prospective study such as ours the amount of underreporting of alcohol is likely to be the same for mothers who have children with developmental delay as well as mothers who have normal children. It has

been shown that in such situations effect estimates of intermediate categories of exposure are likely to be biased away from the null value (inflated) and that there will be only a small bias toward the null value (deflation) for the effect estimate of the highest exposure level.[19] Therefore, underestimation of alcohol seems unlikely to explain the fact that we did not find a relationship between alcohol levels of up to a drink per day and development of the child.

The fact that we used a self-administered questionnaire to measure development of the child in our study may have had some disadvantages, but may also have had some advantages. Disadvantage may be the fact that parents might have been inclined to give too optimistic a view of their child's performance. Since most items were very straightforward, it seems unlikely that this has led to much misclassification. Advantage of using a questionnaire may be a much higher response rate than may have been achieved in a situation where parents have to accompany their child to a research laboratory or where they have to be visited by an interviewer. In our study, the response was 92% whereas comparable studies did not even achieve 70%.[17,20] Another advantage is that children, especially at the age of 5 years, are likely to be more at ease and more cooperative with their parents, which will lead to less biased results than when they were tested by an unknown interviewer.

The advice on alcohol drinking that is being given to pregnant women varies from country to country. In the United States pregnant women are recommended to refrain from drinking any alcohol, whereas in Germany there are no government or official recommendations.[21] Based on our study and on other studies on this subject the best possible recommendations are probably given in Britain. The British government advises pregnant women that drinking one or two units once or twice a week is unlikely to affect fetal development.

We conclude that drinking up to one drink per day during pregnancy does not seem to have an important effect on child development. A consumption of more than a drink per day may be associated with a higher risk of having a child with ADHD.

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Chapter 8. Maternal drinking during pregnancy and child development: results of a 15 year follow-up study

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Submitted

Abstract

Objective
To examine the relationship between moderate alcohol consumption during pregnancy and child development at 15 years of age.

Design
Follow-up study.

Setting
77 midwifery practices in the Netherlands.

Subjects
The study population consisted of 168 children born in 1978 or 1979 (response 80%). A sample was taken from a large cohort study in such a way that women drinking relatively heavily during pregnancy were overrepresented.

Main outcome measures
IQ, behaviourial problems, attentional problems, memory and hand coordination.

Results
Children of women with an average consumption of about one drink per day during the second and third trimester of pregnancy did not differ in IQ from children of women who did not drink during pregnancy (difference in IQ 0.0 points; 95% CI -3.9 to 3.8 points). Furthermore, no clear relationship could be detected between alcohol consumption and the other outcomes.

Conclusions
We conclude that consumption of about one drink per day during pregnancy is unlikely to have an important deleterious effect on the development of the fetus.

Key words
Pregnancy, alcohol, child development, child behaviour

Introduction

Severe abuse of alcohol during pregnancy may lead to the fetal alcohol syndrome (FAS).[1] Children with FAS are growth retarded, have specific congenital malformations and have central nervous system manifestations such as intellectual deficits, hyperactivity and attention deficits.[1-4]

Whether moderate drinking is harmful as well is still a matter of debate. The most consistent finding is that consumption of two or more drinks per day may be detrimental to fetal growth as well as child development, whereas the findings with respect to alcohol consumption below this level are inconsistent.[5] Part of the explanation may be that most of these studies have been performed in children who are two years of age or younger. At these ages subtle effects of alcohol on cognitive and emotional development may be difficult to measure. To study the effects of prenatal alcohol consumption on brain development is important, however, since animal research of the effects of alcohol on the fetus suggests that central nervous system dysfunction can occur at lower levels of alcohol exposure than growth retardation will. Until now, only one prospective epidemiological study has been performed in which adolescents have been tested.[6] This study found a dose-response relationship between alcohol consumption during pregnancy and adolescent attention and memory. A threshold level and, thus, a safe level of consumption could not be detected in this study.

Another limitation of many of the studies of maternal drinking on fetal development is that they were performed at a time when alcohol was considered to be an important health risk for the developing fetus. Women who, despite the fact that they know it may affect their child, drink during pregnancy may differ in a number of factors from non-drinking women. They may have for instance a more negative attitude towards their child than non-drinking mothers. This could result in a less stimulating environment for their child. Since such factors are difficult to measure in an epidemiological study this could lead to biased results. In our study, data on alcohol consumption, were collected between 1978 and 1979. At this time moderate drinking during pregnancy was not considered to be harmful in the Netherlands.

Aim of our study was to investigate the relationship between moderate alcohol consumption during pregnancy and development at 15 years of age.

Methods

Population

The 2-4-6 study is a cohort study that has been described in detail elsewhere.[7,8] Between September 1978 and November 1979 each of 317 midwives throughout the Netherlands contributed their first 12 Dutch speaking pregnant women for a second antenatal visit to the study population. The main objectives were to assess the quantity of cigarettes and alcohol used during pregnancy and the effects on direct pregnancy outcome. Further, factors that influence a woman's choice of breast or bottle feeding were studied. Women were interviewed at the second antenatal visit, four days after birth and six weeks after birth. All information was collected with standardised questionnaires. This information was sent anonymously to our Institute. At that time it was not intended to carry out a follow-up study at the age of 15 years. In 1993, to find out whether such a follow-up study would be feasible with respect to a sufficient number of children, we sent a short questionnaire to the midwives who had participated in the original study. Of the 317 midwives 77 replied that they still possessed the names and addresses of the women they had contributed to the 2-4-6 study and that they were willing to participate in a follow-up study. In many circumstances a low response rate may be a serious threat for the validity of the results. However, not in this case. It seems very unlikely that willingness to participate of the midwife could have a relation with alcohol intake of "their" pregnant mothers as well as with the outcome of the children. We then selected 224 children in such a way that children of women who drank relatively large amounts of alcohol during pregnancy were overrepresented. Children with Down syndrome were excluded. With date of birth of mother and child as well as birthweight and sex of the child the midwives were able to identify the children we had selected. Because of privacy reasons the midwives could not sent the names and addresses to our Institute but had to contact the parents and children for consent themselves. For various reasons related to a variety of personal circumstances a small group of midwives did not attempt to contact "their" 14 children. The final sample, thus, consisted of 210 children.

Alcohol exposure

In 1978 and 1979 at the second antenatal visit (approximately 18 weeks of gestation) demographic data were obtained and the women were asked how many alcoholic drinks they drank on average at that time (second trimester drinking) and what they drank on average in the three months before pregnancy. Since a woman often does not realize that she is pregnant until a number of weeks after conception, we considered prepregnancy drinking as an indicator for drinking in the first trimester. Four days after delivery the women were asked what they had been drinking, on average, during the last three months

of pregnancy (third trimester drinking). The type of alcohol beverage was not recorded, but from other studies it is known that in the Netherlands the majority of women drink either wine or beer.[9] In the Netherlands, a standard glass of wine and beer contains 10 g of alcohol. Especially exposures in the second and third trimester of gestation are likely to lead to behaviourial deficits because of the rapid growth and development of the brain.[10] We, therefore, considered average alcohol intake during this period most likely to be related to child outcome. However, a more deleterious effect of alcohol exposure in the first trimester has also been reported [11], whereas in another study a more deleterious effect of alcohol exposure later in pregnancy was found.[12] Therefore, we also considered alcohol exposure during each trimester separately.

Outcome measures

Outcome measures were chosen on the basis of findings in children with FAS and on the basis of the effects of alcohol in animal models.[1,13] Furthermore, we had decided the total time necessary to perform all tests should not exceed 2.5 hour. The following outcomes were defined: IQ, short term memory, long term memory, concentration, hand coordination and behaviour. IQ was measured with a Dutch version of the WAIS-test.[14] Short term memory was based on the digit span subtest of the WAIS in which test persons have to repeat a number of digits forward and backward. Long term memory was based on the number of recollected words of a subtest of the WAIS after two hours. Concentration was measured with the Bourdon-Vos test.[15] This test consists of a sheet of paper (size A4) with 33 lines. Each line consists of 24 spots and a spot either consists of 3, 4 or 5 dots. The test person has to mark all the spots that consist of 4 dots. This test provides three outcomes. The first is a measure of information processing. This measure is based on the average time needed to complete a line. The second is a measure of concentration fluctuation. This measure is the standard deviation of the average time needed per line. The third is a measure of precision. This measure is based on the number of errors made. Hand coordination was based on the spiral test.[16] This test consists of a sheet of paper (size A4) on which two spirals has been printed. Each spiral has a distance of one centimetre between the lines. The test person has to draw a line as quickly as possible from the end of the spiral to the mid point without touching the spiral. The score consists of the time needed to perform the test in seconds added with three seconds for each time a line is touched and five seconds for each time a line has been passed. The dominant as well as the non-dominant hand was tested twice. Outcome measure was the average score of these four measurements. Behaviour was measured with a Dutch version of the Child Behaviour Checklist (CBCL).[17] With the CBCL, a total behavioral problem score, an internalizing behavioral problem score and an externalizing behavioral problem score can be calculated. We also construed a hyperactivity index

based on items 8 ("Can not concentrate") and 10 ("can not sit quietly, restless, overactive") of the CBCL. Furthermore, the CBCL includes a question on type of school the child is following. Tests were performed by five trained interviewers who were not informed about the past drinking pattern of the mother. We anticipated that the long time period that had passed since the original study combined with the fact that children at the age of fifteen years are in general not very motivated to undergo an IQ-test, may lead to a low response rate. To avoid this we took the following measures. First, for convenience of the adolescents and the parents the examination was performed at their own home. Second, adolescents that participated in the IQ-test received fl 50,- ($ 30,-). Third, in case the IQ-test was refused the midwife should ask whether the parents and child were willing to participate in a limited examination. This would consist of sending the CBCL, the spiral test and the concentration test to the parents. This was carried out by the midwife. The parents were instructed to fill in the CBCL and to test their child. Subsequently the forms could be sent to our institute. For this examination the child would receive fl 25,-. We had planned that in case parents and/or child would refuse this examination as well, the midwife would ask the type of school the child was following.

Confounding variables

As possible confounders we considered variables that are related with outcome and exposure as well as variables that most likely are only related with outcome. Adjustment for the last mentioned variables may lead to an increased precision of the effect estimates.

As possible confounders we considered: education of the mother, education of the father, job status of the father, type of health insurance, maternal age at birth, maternal smoking during pregnancy, occupation of the mother, parity, child's sex, type of feeding of the child in the first six weeks of life and family environment. Type of health insurance (private or sick fund) is being used as proxy measure for income. Mothers who drink alcohol during pregnancy may have a different child rearing style than mothers who do not drink. Therefore, family environment was measured with a Dutch version of the Family Adaptability and Evaluation Scales.[18,19] This test measures adaptability and cohesion of the family. Despite the fact that we used trained interviewers there were statistically significant inter-observer differences with respect to the IQ-scores of the children that they had tested. Thus, the interviewer was considered as a separate variable. We also included in the analysis of hand coordination and concentration a separate variable indicating whether the interviewer or the parents had performed the test.

Statistical analysis

Distributions of all outcome measures were inspected. Outcome measures that were not normally distributed (concentration fluctuation as well as precision score of the Bourdon-Vos test) were transformed into a normally distributed variables with help of a log transformation or were recoded into a dichotomous variable (hyperactivity, long term memory).

In the Netherlands children follow five different levels of secondary education depending on their intellectual abilities. Children at the lowest level have an average IQ of 95 points, whereas children at the highest level have an average IQ of about 125 points. Between each level the difference in average IQ is about 7 points. This strong relationship between level of education and IQ was used to estimate IQ in children with missing IQ data but of whom level of education was known. The estimated IQ was based on the relationship between IQ and level of education in children of which we had both information (conditional mean imputation).

To adjust for confounders, linear regression analysis was used with continuous outcome variables and logistic regression analysis was used with dichotomous outcome variables.

Results

Response and study characteristics

Information about one or more outcomes was collected for 168 of the 210 (80%) children of which in 139 children an IQ-test had been performed (table 1). No significant differences in maternal alcohol consumption were found between participating children and children that were lost to follow-up.

Of the 168 women 105 (63%) reported no alcohol use in the second and third trimester. In this period the average alcohol consumption in the group of women who were categorized as drinkers (n=63), was 70 g per week (SD 38; range 21 to 150 g/wk), which is equal to one drink per day or 0.4 oz per day. Women who used alcohol had received a higher education and were older than women who did not drink during pregnancy (table 2).

Table 1 Sample size, response and average maternal alcohol consumption during pregnancy

	n	(%)	average alcohol consumption (in g/wk)
Children approached	210	(100)	
Loss of follow-up	42	(20)	
Moved and new address unknown	20		26
died	1		0
refusal	21		23
≥ 1 outcome variable known	168	(80)	
All outcome information	139		27
All outcome information except IQ-test	15		21
Only type of school	14		25

Table 2 Study characteristics by maternal alcohol consumption in the second and third trimester

Characteristic	non-drinker (n=105)	drinker (n=63)	total (N=168)
Means (SD)			
Maternal age (yrs)***	26.3 (4.1)	28.5 (3.3)	27.1 (4.0)
Child's age (yrs)	15.5 (0.3)	15.5 (0.3)	15.5 (0.3)
Child's birthweight (g)	3447 (479)	3431 (468)	3441 (474)
Count (%)			
Maternal smoking during pregnancy (in cig/day)			
0	62 (59)	32 (51)	94 (56)
1-10	27 (26)	20 (32)	47 (28)
>10	16 (15)	11 (17)	27 (16)
Maternal education (yrs)***			
6	9 (9)	2 (3)	11 (7)
7-12	83 (79)	36 (57)	119 (71)
>12	13 (12)	25 (40)	38 (23)
Parity			
primiparous	49 (47)	24 (38)	73 (43)
multiparous	56 (53)	39 (62)	95 (57)
Feeding pattern			
Formula	38 (36)	18 (29)	56 (33)
Breast/Formula	28 (27)	23 (37)	51 (30)
Breast	39 (37)	22 (35)	61 (36)

* p<0.05; ** p<0.01; *** p<0.001

IQ

Mean IQ in our study population was 109 (SD 13). After adjustment for confounding variables, the combined group of children of drinkers in the second and third trimester had an IQ that was on average 0.1 (95% CI -4.6 to 4.4) points lower than the IQ of

children of non-drinkers. Furthermore, no relationship was found between different levels of alcohol consumption and child's IQ in any trimester (table 3). After adjustment, the IQ of children of mothers who drank more than 100 grams per week in the second and third trimester was 0.2 points (95% CI -7.1 to 7.5) higher than the IQ of children with mothers who did not drink.

Of 27 children level of education was known but IQ had not been measured. For these children IQ was estimated to be equal to the average IQ of the type of school they attended. These 27 children were added to the group of 139 children with a measured IQ and the analyses were repeated. In this analysis the adjusted difference in IQ in children of women who drank during the second and third trimester was equal (0.0; 95% CI -3.9 to 3.8) compared to children of women who did not drink at that time. A result that is comparable to the result found in the 139 children with a measured IQ.

Table 3 Differences in total IQ in relation to maternal alcohol consumption during pregnancy in 139 children at the age of fifteen years

Alcohol (in g/wk)	Average during 2nd and and 3rd trimester			1st trimester		2nd trimester		3d trimester	
	n	unadjusted difference (SE)	adjusted difference (SE)	n	adjusted difference (SE)	n	adjusted difference (SE)	n	adjusted difference (SE)
0 (ref)	83	0	0	43	0	83	0	88	0
1-49	25	4.1 (2.8)	0.2 (2.9)	46	-2.1 (2.5)	23	1.7 (3.1)	20	2.1 (2.1)
50-99	19	1.4 (3.2)	-0.6 (3.2)	23	-2.8 (3.1)	24	-1.5 (2.8)	22	-1.5 (3.0)
≥100	12	7.1 (3.9)	0.2 (3.7)	27	-3.0 (3.0)	9	0.6 (4.2)	9	2.8 (4.1)

Other outcomes

The total behavioral problem score, information processing and hand coordination were not related to average maternal alcohol consumption in the second and third trimester of pregnancy (table 4). For all three outcomes displayed in table 4, a positive difference indicates a less favourable result compared to the reference group, whereas a negative difference indicates a more favourable outcome.

Furthermore, no relationships could be detected between alcohol consumption on the one hand and the internalizing behavioral problem score, the externalizing behaviourial problem score, hyperactivity problems, concentration fluctuation, precision and short term

memory on the other hand (see appendix). Long term memory was the only outcome in which statistically significant relationships were detected. Children of mothers that consumed 1-49 g/wk during the second trimester (OR 0.2; 95% CI 0.0 to 0.7) and children of mothers that consumed $\geq$ 100 g/wk (OR 0.1; 95% CI 0.0 to 0.8) in the third trimester had a better long term memory compared to children of non-drinking mothers.

Table 4 Adjusted differences in total behavioral problem score, information processing and hand coordination in relation to average maternal alcohol consumption in the second and third trimester of pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	n	Total behavioral problem score (in t-scores)	Information processing (in s)	Hand coordination (in s)
0 (ref)	95	0	0	0
21-49	25	3.0 (2.3)	-0.8 (0.4)	-1.2 (0.9)
50-99	21	0.1 (2.5)	-0.3 (0.5)	-0.3 (0.9)
$\geq$100	13	0.8 (3.2)	-0.1 (0.6)	-1.2 (1.2)

Discussion

Our study failed to find a clear relationship between moderate alcohol consumption during pregnancy and several outcome measures that are considered to be sensitive for the effects of alcohol on the fetus. Children with mothers who, on average, drank one alcoholic consumption per day had an IQ that was equal to that of children whose mothers did not drink. The 95% confidence interval was -3.9 to 3.8 points, indicating that our results are compatible with a maximum decrease in IQ of 3.9 and a maximum increase in IQ of 3.8 points. Thus, the effect of one drink per day is unlikely to have a large impact on child's IQ. The only statistically significant relationship we found was a better long term memory in children of mothers who had consumed alcohol, compared to the long term memory of children of non-drinking mothers. This result is considered to be a chance finding, since there is no biologically plausible explanation for this relationship and many comparisons were made in our study, which increases the likelihood of at least one chance finding.

The Seattle Longitudinal Prospective Study on Alcohol and Pregnancy is the only epidemiological study known to us with a follow-up time that is almost as long as the follow-up time in our study.[6] In the Seattle study, children were tested at the age of fourteen years. The design of the Seattle study is comparable to that of our study. Contrary to our study, the Seattle study did find a deleterious effect of alcohol consumption during pregnancy on attention and memory. An explanation may be that alcohol has a deleterious effect on attention and memory, but that this effect is only present at an alcohol consumption above 2 drinks per day. In our study most participants consumed less than this amount. Since the Seattle study had almost three times as many participants and included more "heavy" drinkers than our study, it had more statistical power to find an effect. This explanation may seem to be in contrast with the fact that in the Seattle study a dose-dependent relationship was found between alcohol and attention/memory deficits. However, misclassification of alcohol consumption due to underreporting can lead to a bias away from the null value for intermediate categories of exposure.[20] This phenomenon may cause a true threshold level for alcohol (e.g. higher than 2 drinks per day) to appear as a dose-response relationship.

Our finding that one drink per day is unlikely to have an effect on child's IQ is in agreement with a recent review of the literature as well as with a recent study from France on this subject.[21,22] In this review no evidence was found for a detrimental effect of alcohol of less than 150 grams per week (about two drinks per day). The French study showed that consumption of 1.5 oz (about three drinks) or more per day during pregnancy was associated with a decrease of 7 IQ-points in 155 children tested at the age of about 4.5 years.[22] A British study found even that alcohol consumption before and after pregnancy was significantly related to better motor performance and mental performance at age 18 months.[23] However, this British study could not detect a significant relationship between child development and alcohol consumption during pregnancy.

Limitation of our study is that we do not have information on binge drinking. Animal research into the effects of alcohol on the fetus suggests that peak blood alcohol levels better predict fetal outcome than total dose.[24] Thus, drinking seven drinks once a week may be more harmful than drinking one drink per day. Another limitation is the fact that we had no information on illicit drug use during pregnancy. However, it is unlikely that not adjusting for this factor will have obscured a relationship between drinking and child development. First, the number of pregnant women who use such drugs is likely to be very small and, thus, could not have a large impact on the results. In a recent study in pregnant women from the Netherlands, only 0.1% reported the use of such drugs.[25] Second, use of such drugs is likely to be positively related with alcohol use and

negatively correlated with child development. Thus, not adjusting for illicit drug is more likely to lead to spuriously unfavourable estimates of the relationship between alcohol and child outcome. Finally, a limitation of a long follow-up time may be that influence of postnatal factors on child development is larger than when a short follow-up time is used. In case these postnatal factors are not related to alcohol consumption the effect will be an increase in "background noise" (random variation) of the outcome measures, thus decreasing the power to detect a true effect. In case these postnatal factors are related to alcohol consumption, an additional effect will be bias of the effect estimates due to confounding, unless adequate adjustment is possible. Although we have adjusted for important postnatal factors such as parental education and family environment this may correct only partially for the complexities involved in child development. IQ and behaviour especially are likely to be influenced by postnatal factors. However, outcomes such as hand coordination and memory are less likely to be influenced by postnatal factors. In our study they were not negatively associated with moderate drinking.

Our study had several advantages compared to other studies. First, the information on alcohol exposure was collected in a period that moderate drinking during pregnancy was, in the Netherlands, not considered to be harmful for the fetus. Nowadays moderate drinking during pregnancy is generally considered not to be socially acceptable. Therefore, reporting of alcohol consumption during pregnancy at that time may have been more in agreement with the actual drinking pattern than the reporting of alcohol consumption during pregnancy would be today. Second, our study was performed in a population of women who all received adequate antenatal care and who had a low risk of pregnancy complications. In the Netherlands women with a high risk for complications are referred to an obstetrician. A low risk of pregnancy complications will limit random variation in the outcome measures and will increase precision of the effect estimates. Third, in a population of women who receive adequate antenatal care, the number of women with alcohol problems is likely to be small. Women with an alcohol problem are considered to be more inclined to deny their alcohol intake which will lead to an underestimation of the effects of alcohol on child development. Fourth, an advantage of our long follow-up time is that we could study outcomes such as hand coordination, information processing and memory, that are more difficult to assess in young children. Fifth, alcohol consumption was measured separately per trimester, allowing us to assess whether there are specific time-windows in which alcohol may be more deleterious.

Advice on alcohol drinking during pregnancy varies from country to country.[26] In the United States the advice is that pregnant women should abstain from alcohol, whereas in Britain the advice is that pregnant women should limit drinking to no more than one

or two units once or twice a week. We would favour the British advice, since it is more in agreement with current scientific evidence and it is less likely to cause unnecessary feelings of guilt and concern.

We conclude that consumption of about one drink per day during pregnancy is unlikely to have an important deleterious effect on the fetus.

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PART IV

GENERAL DISCUSSION AND SUMMARY

Chapter 9. General discussion

The main aim of this thesis was to investigate whether moderate alcohol consumption in the range of one drink per week to two drinks per day during pregnancy has a deleterious effect on the fetus. This relationship was investigated in two separate cohort studies. First, the major results and conclusions of these studies will be discussed. Next, comments will be made on the clinical implications of the findings. Finally, suggestions for further analyses will be presented.

Major results

Two cohort studies, the "2-4-6-study" and the "SMOCC-study", were used to answer the research questions. The 2-4-6-study was started in the late seventies and the SMOCC-study in the late eighties. In the SMOCC-study, outcome information on child development was collected at birth as well as during the first two years of life and at the age of 5 years. In the 2-4-6-study, child outcome was assessed at birth and at the age of 15 years. The long follow-up period allowed us to investigate the association between alcohol and a wide range of developmental outcomes. Before I will discuss the results of the 2-4-6 and the SMOCC-study I will comment on some methodological issues with respect to misclassification of alcohol consumption.

Misclassification of alcohol (Part I: chapter 2 and 3)
Self-reported alcohol consumption was measured retrospectively as well as prospectively in both studies. In which way retrospectively collected information on drinking may influence effect estimates was examined in chapter 2 of this thesis. The validity of the results of studies using retrospectively collected information on exposures is often criticized, with the argument that cases may report differently from controls even if their true exposure status is the same. Therefore, we tried to determine to what extent this effect occurred for alcohol consumption by pregnancy outcome. No statistically significant differences could be detected when prospectively collected information on alcohol consumption was compared with retrospectively collected information by pregnancy outcome. We, therefore, concluded that effect estimates based on retrospectively collected alcohol information are unlikely to be very biased in our material.

In the 2-4-6 and in the SMOCC-study, information on alcohol consumption was based on self-reports. It is generally agreed that self-reports lead to considerable underestimation of actual alcohol intake. We, therefore, attempted to ascertain to what extent underreporting may influence effect estimates of exposure in our data (chapter 3). Several text books on epidemiology claim that nondifferential misclassification of exposure will invariably lead to a bias towards the null value. In chapter 3 we showed nonetheless, that nondifferential misclassification of alcohol consumption due to underreporting can in some situations, lead to a bias away from the null value for intermediate categories of exposure. This phenomenon may cause a true threshold level for alcohol to appear as a dose-response relationship. This important finding can have two implications for the interpretation of the results of epidemiological studies in which alcohol intake is based on self reports. First, finding an association between alcohol and an outcome at an intermediate category of exposure may in fact be due to bias. In reality there may be no relationship at all at that level of exposure. If one is unaware of this phenomenon, recommendations on alcohol drinking may be made that are in fact too strict. Second, not finding an association at an intermediate category of alcohol exposure is more likely to be a reflection of reality and less probable to be due to bias.

Alcohol and direct pregnancy outcomes (Part II: chapter 4 and 5)

We were unable to detect an independent relationship between alcohol and birthweight corrected for gestational age in the 2-4-6-study. However, in the subgroup of women smoking 20 cigarettes or more a day, alcohol consumption of more than 12 drinks per week in early pregnancy was associated with a 7.2% (95% CI 0.2% to 14.2%) decrease in birthweight. In the SMOCC-study, a relationship between alcohol and birthweight was found that was of "borderline" significance. The birthweight of children whose mothers drank more than 7 drinks per week was 7.2% (95% CI -0.7% to 15.2%; p=0.07) lower than that of children whose mothers did not drink. Unfortunately, in the SMOCC-study the exact amounts of alcohol that mothers reported has not been collected. It is conceivable that mothers in the SMOCC-study who reported to drink more than 7 drinks per week in fact consumed more than 14 drinks per week. If indeed this is the case, this particular finding is in agreement with the results of the 2-4-6-study. In the 2-4-6-study, no independent effect of alcohol could be demonstrated in the range of 7 to 14 drinks per week, despite the fact that a considerable number of women reported to drink this amount. Furthermore, other studies seem to indicate consistently lower birthweight only among children born to mothers drinking more than 14 drinks per week.[1] In the SMOCC-study, we were unable to demonstrate the synergistic effect of alcohol and smoking on birthweight as found in the 2-4-6-study.

In the 2-4-6-study, a trend was found towards a lower rate of preterm birth in women

who reported alcohol use. However, none of these differences was statistically significant. In the SMOCC-study we also found a trend towards a lower rate of preterm birth. Women who reported to consume 2 drinks or more per week less often suffered a preterm delivery (p=0.07) than abstainers. Shiono et al also reported a decreased risk of preterm delivery, but only in mothers who drank less than one glass a day.[2] Historically, alcohol infusions have been used as a means of postponing premature labour. It was assumed that alcohol decreased uterine contractions by exhibiting an inhibitory effect on oxytocin release from the pituitary gland.[3] Based on this theory, a chronic low dosage of alcohol may have an effect on oxytocin release as well and could, thus, decrease the preterm delivery rate. However, the evidence for a causal relationship is not very strong. A number of other authors were unable to demonstrate a relationship between moderate alcohol consumption and preterm delivery.[1]

Alcohol and long-term outcomes (Part III: chapter 6, 7, 8)

In tables 1, 2 and 3 a summary is presented of the effect estimates of the associations between alcohol and the long-term outcomes studied. To facilitate interpretation, effect estimates in which alcohol is deleterious for child development are underlined. Underlining does not indicate whether the relationship was statistically significant. Effect estimates that do not show an effect or even a "beneficial" effect of alcohol on child development are not underlined. Of the relationships in table 1, 2 and 3 30 out of 58 have been underlined. In other words, about half of the effect estimates are associated with a negative outcome for the child. Of the 58 relationships only three showed to be statistically significantly related with alcohol consumption:

- Children of mothers who reported a consumption of one drink per week had a lower score on 'communication and social behaviour' compared to those of non-drinkers (table 1 and chapter 6).
- Children of mothers who reported a consumption of one drink per week had a lower score on 'fine motor and adaptation' compared to those of non-drinkers (table 1 and chapter 6).
- Children of mothers who reported a consumption of more than 7 drinks per week had more often attention-deficit hyperactivity disorder (ADHD) compared to those of non-drinkers (table 2 and chapter 7).

Thus, two detrimental effects were found with sensorimotor outcomes as well as one detrimental effect on child behaviour at the age of five years.

Table 1 Relationship between child development at the age of 1 to 24 months and average maternal alcohol consumption during pregnancy in the SMOCC-study (Chapter 6)

	Adjusted differences in z-scores (95% CI)			Adjusted odds ratios (95% confidence interval)	
Alcohol (drinks per week)	fine motor/ adaptation	gross motor	communication/ social behaviour	difficult sleeping behaviour	frequent crying
0 (ref)	0	0	0	1	1
1	-0.1 (-0.2 to -0.0)*	-0.1 (-0.2 to 0.0)	-0.2 (-0.3 to -0.1)**	1.3 (0.8 to 2.0)	1.1 (0.7 to 1.8)
2-7	0.0 (-0.2 to 0.2)	-0.0 (-0.3 to 0.2)	-0.1 (-0.3 to 0.2)	0.9 (0.4 to 2.2)	1.6 (0.7 to 3.7)
>7	-0.0 (-0.7 to 0.6)	0.2 (-0.5 to 0.8)	-0.1 (-0.8 to 0.6)	3.9 (0.7 to 21.1)	-^

* $p<0.05$; ** $p<0.01$
^ Categories >7 and 2-7 were collapsed into one category to avoid empty cells
Remark: effect estimates in which alcohol is deleterious for child development are underlined

Table 2 Relationship between child development at the age of 5 years and average maternal alcohol consumption during pregnancy in the SMOCC-study (Chapter 7)

	adjusted differences (95% CI)	Adjusted odds ratios (95% confidence interval)				
Alcohol (drinks per week)	IQ	attention-deficit hyperactivity disorder	fine motor/ adaptation	gross motor	language	Personal/ social
0 (ref)	0	1	1	1	1	1
1	0.1 (-2.6 to 2.7)	1.3 (0.5 to 3.7)	0.7 (0.5 to 1.2)	1.1 (0.7 to 1.7)	0.7 (0.3 to 1.6)	0.8 (0.4 to 1.6)
2-7	-1.4 (-5.3 to 2.6)	2.6 (0.8 to 8.5)	0.7 (0.4 to 1.5)	1.6 (0.9 to 3.0)	1.5 (0.5 to 4.0)	0.9 (0.3 to 2.1)
>7	-1.0 (-12.6 to 10.7)	16.2 (2.1 to 124.3)*	1.5 (0.3 to 8.8)	1.1 (0.2 to 6.6)	-^	2.1 (0.2 to 25.5)

* $p<0.05$
^ Categories >7 and 2-7 were collapsed into one category to avoid empty cells
Remark: effect estimates in which alcohol is deleterious for child development are underlined

Table 3 Relationship between child development at the age of 15 years and average maternal alcohol consumption during the second and third trimester of pregnancy in the 2-4-6-study (Chapter 8)

	Adjusted differences (SE)							Adjusted odds ratios (95% confidence interval)	
Alcohol (drinks per week)	IQ	behaviour problems	information processing	concentration fluctuation	precision	hand coordination	short term memory	long term memory	hyperactivity
0 (ref)	0	0	0	0	0	0	0	1	1
2-4	0.2 (2.9)	3.0 (2.3)	-0.8 (0.4)	-0.2 (0.3)	0.1 (0.3)	-1.2 (0.9)	0.3 (0.9)	0.4 (0.1 to 1.2)	1.1 (0.4 to 3.6)
5-9	-0.6 (3.2)	0.1 (2.5)	-0.3 (0.5)	-0.4 (0.3)	0.1 (0.3)	-0.3 (0.9)	1.1 (1.0)	0.7 (0.2 to 2.8)	0.3 (0.1 to 1.3)
10-15	0.2 (3.7)	0.8 (3.2)	-0.1 (0.6)	0.2 (0.3)	0.0 (0.4)	-1.2 (1.2)	1.1 (1.2)	0.5 (0.1 to 2.6)	1.0 (0.2 to 4.6)

Remark: effect estimates in which alcohol is deleterious for child development are underlined

Whether the relationship between one drink per week and the two sensorimotor outcomes may be considered causal will largely depend on the a priori assumptions made with respect to the relationship between alcohol and child development. If one considers it to be quite possible that even very moderate amounts of alcohol can have an effect on child development then weak evidence may be considered as further support. If one considers it less probable that such very low amounts of alcohol can have a measurable effect on child development, then strong evidence is needed to change this opinion. Based on the literature my a priori view was more in agreement with the latter statement. There are several reasons why I am still not convinced that as little as one drink per week may have a deleterious effect on child development. First, an important aspect that should be considered before concluding an association is causal, is consistency.[4] When the effect estimates in tables 1, 2 and 3 are compared the most striking feature is their lack of consistency. Almost half of the effect estimates are in the direction of a "beneficial" effect of alcohol on child development and the other half are in the direction of a "deleterious" effect. Further, although we did not find a significant "beneficial" effect of average drinking in the second and third trimester and child development, we did find such an effect when second and third trimester drinking was analyzed separately. Drinking in the range of one to four drinks per week during the second trimester

appeared to be "beneficial" for long term memory (chapter 8). Therefore, I would not rule out the possibility that the statistically significant results we found may be chance findings, due to the fact that many comparisons were made. Second, I would be more convinced that a detrimental effect of one drink per week on child development as found in the SMOCC-study may be causal, when this relationship would also be present in the 2-4-6-study. The 2-4-6-study has some advantages compared with the SMOCC-study (see also the discussion in chapter 8). One of the advantages is that in the 2-4-6-study the information on alcohol exposure was collected in a period that moderate drinking during pregnancy was not considered to be harmful for the fetus. In the late eighties, moderate drinking was generally considered not be socially acceptable. Therefore, reporting of alcohol consumption during pregnancy in the late seventies may have been more in agreement with the actual drinking pattern than the reporting of alcohol consumption during pregnancy would be today. Third, I would have been inclined to consider the relationship between one drink per week and the two developmental outcomes in the first two years of life more convincing when they would have shown a clearer dose-response relationship. For instance, consuming one drink per week was associated with a decrease in z-score of 0.2 points for 'communication and social behaviour', whereas drinking 2-7 drinks per week was associated with a decrease of only 0.1 points. Finally, as I discussed before, it can not be excluded that the relationship between a consumption of one drink per week and child development is biased away from the null value due to underreporting of alcohol consumption.

I consider the relationship between a consumption of more than seven drinks per week and attention-deficit hyperactivity disorder (ADHD) at the age of 5 years to be the finding that is most likely to be causal (table 2). This relationship was very strong and strong relationships are less likely to be caused by bias. Furthermore, ADHD is one of the prominent features of children with FAS. An argument against the fact that this finding may be causal is lack of consistency. At the age of 15 years no relationship could be detected between alcohol on the one hand and hyperactivity and measures of attentional capacities on the other hand. However, this may be related to the nature of ADHD. In many cases, this disorder is usually apparent by age 3 and symptoms often disappear around puberty.[5] Thus, a relationship between alcohol use and ADHD may be more likely to be detected at the age of 5 than at the age of 15 years. Interestingly, in the first two years a rather strong relationship seemed to exist, though it was not significant, between a consumption of more than seven drinks per week and difficult sleeping behaviour (table 1). As mentioned before, in the SMOCC-study the exact amounts of alcohol that mothers reported has not been collected. Therefore, we do not know how much alcohol those mothers consumed who reported to drink more than 7 drinks per week.

Conclusions

The main aim of this thesis was to investigate whether moderate alcohol consumption in the range of one drink per week to two drinks per day during pregnancy has a deleterious effect on the fetus. I conclude that a consumption of one drink per day or less is unlikely to have a clinically relevant effect on child development. Larger amounts may be harmful, especially with respect to the development of ADHD, but due to the limitations of our data it is not possible to assess at what levels these effects occur. The answers to the research questions formulated in chapter 1 are as follows:

Research question 1
Does the method of retrospectively collecting information on alcohol exposure lead to a bias of effect estimates (Chapter 2)?
Our results suggest that it is unlikely that large differences exist in self reports of alcohol between mothers with an unfavourable pregnancy outcome and mothers with a "normal" outcome. Thus, retrospectively collected information on alcohol is unlikely to lead to considerable bias of effect estimates.

Research question 2
What is the effect of underreporting of alcohol intake on effect estimates (Chapter 3)?
Underreporting may lead to a bias away from the null value for intermediate categories of exposure. Further, it may cause a true threshold level for alcohol to appear as a dose-response relationship.

Research question 3
What is the relationship of moderate alcohol consumption during pregnancy to birthweight and gestational age (Chapter 4 and 5)?
We were unable to detect an independent effect of alcohol in the range of 1 to 7 drinks per week on birthweight. However, in women who smoke heavily, a consumption of about 12 drinks or more per week in early pregnancy may be an additional risk factor for impaired fetal growth. Moderate alcohol consumption may be associated with a decreased risk of preterm delivery.

Research question 4
What is the relationship between moderate alcohol consumption during pregnancy to psychomotor development and child behaviour in the first two years of life (Chapter 6)?
Alcohol consumption of about 1 drink per week was found to be negatively associated with communication and social behaviour. No relationship could be detected between alcohol and child behaviour.

Research question 5
What is the relationship between moderate alcohol consumption during pregnancy and IQ, hyperactivity and motor development at 5 years of age (Chapter 7)?
Women who consumed more than 7 drinks per week during pregnancy had an increased risk of having a child with ADHD compared to women who did not drink. No relationship could be detected between alcohol consumption on the one hand and IQ as well as the four functions of the Denver Developmental Screening Test on the other hand.

Research question 6
What is the relationship between moderate alcohol consumption during pregnancy and IQ, hand coordination, attention deficits and child behaviourial problems (e.g. hyperactivity) and memory at 15 years of age (Chapter 8)?
No relationships could be detected between alcohol consumption on the one hand and IQ, hand coordination, attention deficits, behaviourial problems and short term memory on the other hand. Children of mothers who consumed alcohol had better long term memory than those of non-drinkers.

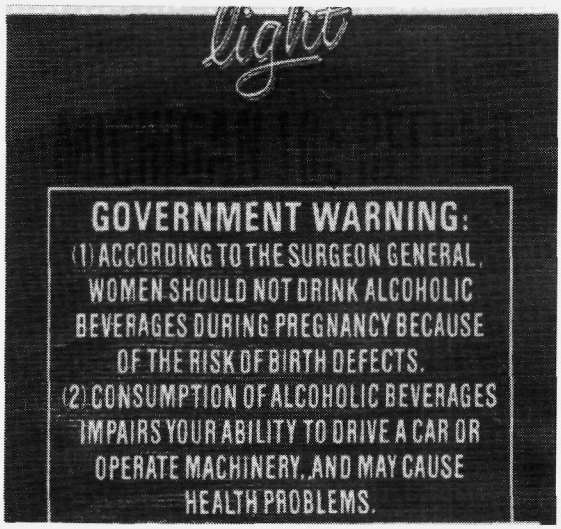
Implications for clinical practice

In the previous section, the evidence for a deleterious effect of moderate alcohol consumption on child development has been presented from a scientific viewpoint. The evidence has been discussed independent of the clinical consequences. From a scientific viewpoint no definite answer can be given to the question what levels of alcohol are safe and what levels are not safe. It should be realised that all scientific work is incomplete and is liable to be upset or modified by advancing knowledge.[4]

Obstetricians, general practitioners and midwives can not always wait for more answers to emerge. They are being confronted daily with questions from their patients as to what amount of alcohol consumption during pregnancy can be considered safe. In formulating implications for clinical practice of the results of this thesis, it is not only the scientific evidence that should be taken into consideration. The advantages and disadvantages of certain types of advice should be weighed as well. In some countries abstinence from alcohol is considered to be the best solution (figure 1).[6] In a recent Dutch article the same advice was given.[7] In my opinion, these guidelines are not based on clear evidence. Furthermore, this type of advice may have negative consequences as well. A number of women who have drunk moderately during pregnancy will give birth to an abnormal

child, whose abnormalities are, in reality, not associated with their drinking behaviour. The fact that they had drunk despite the advice not to drink, may cause unnecessary feelings of guilt and concern. Based on the results of this thesis as well as on the evidence in the literature I would recommend pregnant women to restrict their consumption to not more than one drink per day throughout pregnancy.

Figure 1 Label of a beer bottle from the USA



Further analyses

Only a small percentage of alcoholic mothers will give birth to an infant with FAS. This suggests that alcohol use alone is not a sufficient cause and that other factors such as (illicit) drugs and genetic susceptibility may also play a role. Until now the study of such factors has received little attention in the literature. These factors may identify a subgroup of women that are at higher risk of having a child with an unfavourable outcome even when they drink only moderate amounts of alcohol. Recently McCarver-May et al found some evidence that genetic diversity in the enzymes responsible for alcohol metabolism may be of importance.[8] They found that heavy drinking during pregnancy ($\geq$ 0.5 oz absolute alcohol per day) was associated with decreased birthweight, decreased head circumference and lower Bayley mental index (MDI) scores ($p<0.05$). When considered simultaneously with the presence of heavy drinking and birthweight, the presence of the

ADH2*3 allele in the mother and in the infant were each associated with higher MDI scores (p=0.03).

Until now most of the attention for the deleterious effects of alcohol on offspring has been focused on drinking of the mother. However, animal research has shown that paternal drinking may also have negative consequences for the child. Recently, Bielawski and Abel found that male rats that were exposed to alcohol were more likely to have offspring with congenital malformations than rats that were not exposed.[9] Therefore, in future studies more attention should be paid to the effects of paternal drinking on infant development.

Finally, in further studies the long-term effects of alcohol on infant growth should be assessed. One experimental study has shown that alcohol consumption before breast feeding has an immediate effect on feeding behaviour of infants.[10] Infants of mothers who had drunk orange juice containing alcohol (0.3 g per kilogram of body weight) drunk less milk than infants of mothers who had drunk only orange juice (average 120 ml vs. 156 ml) (p<0.001). Whether this immediate effect of alcohol on breast feeding may result in long term effects such as growth retardation is unknown.

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SUMMARY

Chapter 1 presents a short review of the Fetal Alcohol Syndrome. The rationale to evaluate the relationship between moderate alcohol consumption during pregnancy and child outcome is explained.

Chapter 2. The validity of the results of studies using retrospectively collected information on exposures is often criticized, with the argument that cases may report differently from controls even if their true exposure status is the same. We studied to what extent this effect occurred for alcohol consumption by pregnancy outcome, since in some of our analyses alcohol was collected retrospectively. No statistically significant differences could be detected when prospectively collected information on alcohol consumption was compared to retrospectively collected information by pregnancy outcome.

Chapter 3. In both our studies information on alcohol consumption was based on self-reports. It is generally agreed that self-reports will lead to considerable underestimation of actual alcohol intake. We, therefore, attempted to ascertain to what extent underreporting may influence effect estimates of exposure in our data. Many text books on epidemiology claim that nondifferential misclassification of exposure will always lead to a bias toward the null value. We show nonetheless that nondifferential misclassification of alcohol consumption due to underreporting may lead to a bias away from the null value for intermediate categories of exposure. We also showed that the method of measuring alcohol consumption that is based on detailed information on the drinking pattern of the week before the interview may not be the best method in an epidemiological study. This approach is often advocated by alcohol researchers. Collecting information on average alcohol consumption during a longer period of time may lead to less biased results in an epidemiological study, especially in countries were alcohol is not drunk on a regular basis.

Chapter 4. In a study performed in the late seventies (the 2-4-6-study), no independent effect of alcohol on birthweight could be detected. However, in the subgroup of women smoking 20 cigarettes or more a day, drinking more than 120 g alcohol (12 drinks) a week in early pregnancy was associated with a 7.2% (95% CI 0.2% to 14.2%) decrease in birthweight. Further, no relationship between alcohol and preterm delivery could be detected.

Chapter 5. In a study performed in the late eighties (the SMOCC-study) no independent effect of alcohol on birthweight could be detected in the range of 1 to 7 drinks per week. In the group of mothers who consumed more than 7 drinks per week (n=10), however, a sharp decrease occurred (-7.2%; p=0.07). A synergistic effect between alcohol and smoking on birthweight was not found. A lower prevalence of preterm birth was found in mothers who consumed 2 drinks or more per week compared to the prevalence of preterm birth in mothers who did not drink (odds ratio 0.15, p=0.07).

Chapter 6. In a follow-up study in children in the range of one to 24 months (SMOCC study) maternal alcohol consumption was found to be negatively associated with communication and social behaviour (p<0.01). Even children of mothers who consumed only one drink per week during pregnancy had lower scores than children of mothers who did not consume alcohol during pregnancy (difference in z-score -0.2; 95% CI -0.3 to -0.1). No relationship could be detected between alcohol on the one hand and gross motor function, fine motor function/adaptation and child behaviour (sleeping behaviour and crying) on the other hand.

Chapter 7. In a follow-up study in children at the age of 5 years (SMOCC study) we found that mothers who consumed more than 7 drinks per week during pregnancy had an increased risk of having a child with ADHD compared to mothers who consumed no alcohol (RR 11.9; 95% CI 2.0 to 44.4). No relationship could be detected between alcohol consumption on the one hand and IQ as well as the four functions of the Denver Developmental Screening Test (gross motor, fine motor/adaptive, language and personal/social) on the other hand.

Chapter 8. In a follow-up study in children at the age of 15 years (2-4-6 study) no relationship could be detected between alcohol consumption in the range of 1 to 15 drinks per week on the one hand and IQ, behaviourial problems, attentional problems, short term memory and hand coordination at the age of 15 years on the other hand. Children of mothers who consumed 1 to 49 grams per week during the second trimester (OR 0.2; 95% CI 0.0 to 0.7) and children of mothers who consumed 100 grams per week or more (OR 0.1; 95% CI 0.0 to 0.8) in the third trimester had a better long term memory compared to children of non-drinking mothers.

In **chapter 9** the findings of our studies are discussed. Based on our results and the evidence in the literature we would advise pregnant women to drink not more than one drink per day throughout pregnancy.

SAMENVATTING

Hoofdstuk 1 geeft een beknopt literatuuroverzicht over het Foetaal Alcohol Syndroom. Tevens wordt uiteengezet waarom de relatie tussen matig alcoholgebruik tijdens de zwangerschap en de ontwikkeling van het kind is onderzocht.

Hoofdstuk 2. Als bezwaar tegen epidemiologische studies waarin gebruik wordt gemaakt van retrospectief verzamelde expositie-gegevens wordt vaak genoemd dat de resultaten vertekend zijn als gevolg van informatiebias. Deze bias ontstaat wanneer cases anders rapporteren dan controles over hun expositie, zelfs wanneer er in werkelijkheid geen verschil bestaat in expositie. In enkele van onze analyses is gebruik gemaakt van retrospectief verzamelde alcoholgegevens. Vervolgens is nagegaan wat de mate van vertekening is, die als gevolg van deze bias kan optreden. Hierbij is gebruik gemaakt van het feit dat we in één van onze studies zowel beschikten over prospectief als retrospectief verzamelde gegevens over alcoholgebruik bij zwangeren. In deze studie konden geen statistisch significante verschillen gevonden worden tussen retrospectief en prospectief verzamelde gegevens tussen moeders met een ongunstige zwangerschapsuitkomst en moeders met een normale zwangerschapsuitkomst.

Hoofdstuk 3. In al onze analyses is gebruik gemaakt van alcoholgegevens die verzameld zijn met behulp van een interview. Algemeen wordt aangenomen dat deze methode leidt tot aanzienlijke onderrapportage van het werkelijke alcoholgebruik. Daarom is nagegaan wat de effecten van onderrapportage op onze uitkomsten kunnen zijn. In veel epidemiologische leerboeken staat vermeld dat niet-differentiële misclassificatie altijd leidt tot een bias naar de nulwaarde (onderschatting van het effect). Aangetoond werd dat niet-differentiële misclassificatie echter wel degelijk kan leiden tot een overschatting van het effect. Onderrapportage kan namelijk leiden tot een bias weg van de nulwaarde, zelfs indien onderrapportage niet gerelateerd is aan de ziekte-uitkomst (niet-differentiële misclassificatie). Tevens werd aannemelijk gemaakt dat het meten van alcoholgebruik gedurende de week voorafgaand aan het interview niet de beste methode is in een epidemiologisch onderzoek. Deze methode wordt vaak aanbevolen door onderzoekers. Meten van alcoholgebruik gedurende een langere periode zou weleens tot minder vertekening kunnnen leiden van de schattingen van het effect, met name in landen waar het drinken van alcohol geen gewoonte is.

Hoofdstuk 4. In een onderzoek dat eind jaren zeventig (de 2-4-6 studie) werd uitgevoerd, kon geen onafhankelijke relatie aangetoond worden tussen alcohol en geboortegewicht. In de subgroep van vrouwen die meer dan 20 sigaretten per dag rookten werd wel een relatie gevonden tussen alcohol in het begin van de zwangerschap en geboortegewicht. Vrouwen die veel rookten en meer dan 12 glazen per week dronken hadden kinderen

met een geboortegewicht dat gemiddeld 7,2% (95% BI 0,2% tot 14,2%) lichter was dan het geboortegewicht van vrouwen die veel rookten maar niet dronken. Een relatie tussen alcohol en vroeggeboorte kon niet aangetoond worden.

Hoofdstuk 5. In een onderzoek dat eind jaren tachtig werd uitgevoerd (de SMOCK-studie) kon geen onafhankelijke relatie aangetoond worden tussen alcoholgebruik van 1 tot 7 glazen per week en geboortegewicht. Vrouwen die meer dan 7 glazen per week dronken tijdens de zwangerschap (n=10) hadden echter kinderen die beduidend lichter (7,2%) waren dan kinderen van moeders die niet hadden gedronken. Roken leek de relatie tussen alcohol en geboortegewicht niet te beïnvloeden in dit onderzoek. Moeders die twee of meer glazen per week dronken hadden minder vaak een vroeggeboorte dan moeders die niet dronken (odds ratio 0,15; p=0.07).

Hoofdstuk 6. In een prospectieve studie werd nagegaan hoe de relatie is tussen alcoholgebruik tijdens de zwangerschap enerzijds en de psychomotore ontwikkeling en het gedrag bij kinderen op de leeftijd van één tot 24 maanden anderzijds. Alcoholgebruik was gerelateerd aan een ongunstigere score op communicatie en sociaal gedrag (p<0,01). Zelfs kinderen waarvan de moeder slechts één glas per week had gedronken hadden lagere scores dan kinderen waarvan de moeder niet had gedronken. Er kon geen relatie aangetoond worden tussen alcohol aan de ene kant en grove motoriek, fijne motoriek/adaptatie en gedrag van het kind aan de andere kant.

Hoofdstuk 7. In een prospectieve studie bij kinderen op de leeftijd van vijf jaar werd een relatie gevonden tussen alcoholgebruik tijdens de zwangerschap en hyperactiviteit bij het kind. Vrouwen die meer dan 7 glazen per week dronken tijdens de zwangerschap hadden 12 (95% BI 2 tot 44) keer zo vaak een kind met hyperactiviteit als vrouwen die niet hadden gedronken. Alcoholgebruik leek niet gerelateerd te zijn aan IQ, grove motoriek, fijne motoriek/adaptatie, taal of sociaal gedrag.

Hoofdstuk 8 beschrijft de resultaten van een prospectieve studie naar de relatie tussen drinken tijdens de zwangerschap (1 tot en met 15 glazen per week) en de ontwikkeling bij kinderen die gevolgd zijn vanaf de geboorte tot en met de leeftijd van 15 jaar. In dit onderzoek kon geen relatie aangetoond worden tussen alcoholgebruik aan de ene kant en IQ, gedrag, aandacht, korte termijn geheugen en hand coördinatie aan de andere kant. Kinderen waarvan de moeder 1 tot 5 glazen per week dronk in het tweede trimester en kinderen waarvan de moeder meer dan 10 glazen per week dronk in het derde trimester hadden een beter lange-termijn geheugen, dan kinderen waarvan de moeder niet dronk tijdens de zwangerschap.

In **hoofdstuk 9** worden de bevindingen van de hiervoor genoemde studies besproken. Op basis van onze resultaten en die van anderen wordt zwangeren aangeraden niet meer dan één alcoholische consumptie per dag te gebruiken gedurende de gehele zwangerschap.

APPENDIX

Figure 1 Alcohol consumption during pregnancy by maternal age among subjects in the Netherlands in 1978-1979 (2-4-6-study) and in 1988-1989 (SMOCC-study)

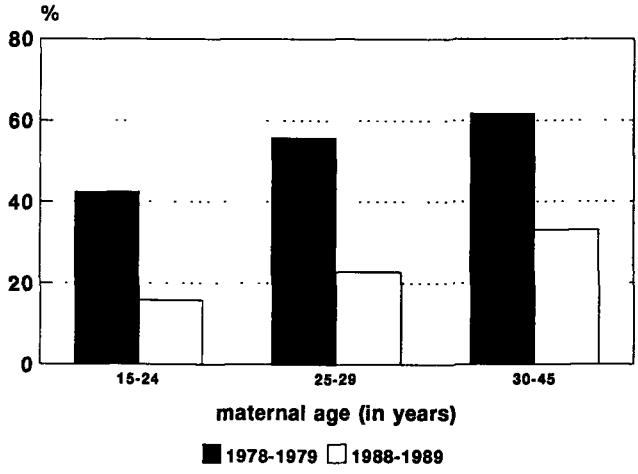
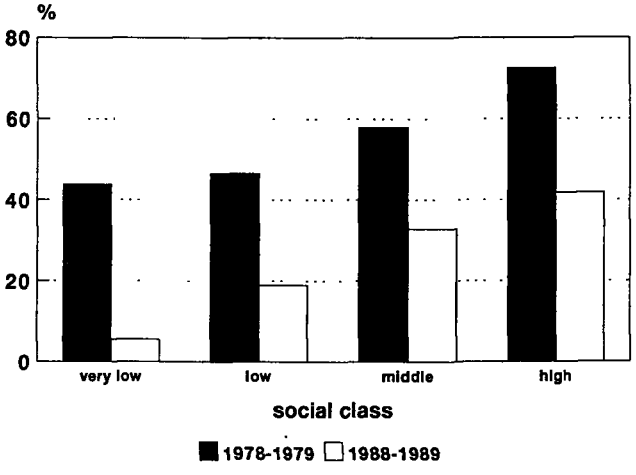


Figure 2 Alcohol consumption during pregnancy by social class among subjects in the Netherlands in 1978-1979 (2-4-6-study) and in 1988-1989 (SMOCC-study)



Chapter 5

Interaction of alcohol and smoking in the relationship with small for gestational age?

Several studies found a synergistic effect of alcohol and smoking for birthweight. We, therefore, assessed whether this effect could also be detected in the SMOCC-study. Adding an interaction term alcohol.smoking to the basic model described in table 2 did not result in a significant better fit (p=0.52). Nevertheless we examined the interaction in more detail. We included in the basic model separate alcohol effects in three different catgeories of smokers (0, 1-10 and >10 cig/day) (table 4). The lowest mean birthweight was found in the children of mothers who smoked more than 10 cigarettes per day. However, because of the large standard error there was not enough evidence to conclude that there may be a synergistic effect of alcohol and smoking for birthweight.

Table 4 Adjusted^ regression coefficients (SE) for birthweight ratio by maternal alcohol consumption and smoking habit

Alcohol (in drinks/wk)	Smoking (in cig/day)		
	0	1-10	>10
	coeff. (SE)	coeff. (SE)	coeff. (SE)
0 (ref)	0	0	0
1	0.006 (0.008)	-0.020 (0.016)	-0.012 (0.026)
>1	-0.007 (0.016)	0.037 (0.036)	-0.037 (0.042)

^ Adjusted for social class, ethnicity, maternal occupation, maternal age and maternal height

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The presence of missing data complicates the computation of the psycho-motor development indices. Let Y_{ij} be a 0-1 score indicating whether child i passes test j (1) or not (0). The proportion of passed items, $p_i = \Sigma Y_{ij} / k$, is used as an ability score for gross motor function. There are k = 47 gross motor items, but many scores are missing. 2A simple work-around is to base the calculations on the available data only, that is, on $p_i = \Sigma Y_{ij} / k_i$, where k_i is the number of observed items for child i. Though simple, this approach is not satisfactory because the reason that a score is missing is likely to be related to the score itself. In practice, tests are often aborted if the child fails a couple of times. The available data approach does not account for this phenomenon and will tend to overestimate the true ability level.

A better alternative is to use multiple imputation.[18,28] Briefly, multiple imputation produces m complete data sets. Each is analyzed by the complete data method, after which the m results are pooled into a final estimate. Suppose that X_i represents a row vector of background factors (ethnicity, child's sexe, level of education of the mother, parity, maternal age, gestational age birthweight) of individual i, and that Z_i is the child's age (in days) at which test j is taken. Assuming that the missing data are Missing at Random (MAR), imputations for Y_{ij} are created using the logistic regression model:

$$p(Y_{ij} = 1) = 1 / (1 + \exp(-(X_i\beta + Z_{ij}\gamma + Y_{i,j-1}\phi_1 + Y_{i,j-2}\phi_2 + Y_{i,j-3}\phi_3))), \qquad j=1,..,47,$$

where the probability that child i passes test j depends on a function of age, background factors, and scores of the preceding three tests. After estimating the parameters from the cases with known Y_{ij}, the covariates are used to multiply impute the missing scores, as in Rubin.[18]

Since X_i, Z_{ij} and $Y_{i,j-1}$ also contain missing data the actual imputations are created in several substeps. First, X_i and Z_{ij} are multiply imputed five times by the Gibbs sampling algorithm as proposed in Rubin and Schafer.[29] Next, the logistic model is applied to create multiple imputations for j = 1 (where $Y_{i,j-1}$, $Y_{i,j-2}$ and $Y_{i,j-3}$ are temporarily omitted from the model), then create imputations for j=2 conditional on the completed data for $Y_{i,j-1}$, and so on to j=47. Finally, the developmental score of child i is computed as $Y_i = \Sigma\Sigma Y_{ijm} / mk$.

Table 7 Unadjusted and adjusted differences in z-scores for gross motor function in relation to maternal alcohol consumption, smoking and use of psychofarmaca during pregnancy based on exclusion of missing developmental items (A) and on multiple imputation (B)

Exposure	Unadjusted difference (SE)		Adjusted@ difference (SE)	
	A (SE)	B (SE)	A (SE)	B (SE)
Alcohol (drinks/week)				
0 (ref)	0	0	0	0
1	-0.02 (0.06)	-0.01 (0.06)	-0.07 (0.06)	-0.07 (0.06)
2-7	0.03 (0.11)	-0.13 (0.11)	-0.02 (0.12)	-0.16 (0.12)
>7	-0.01 (0.35)	-0.15 (0.35)	0.18 (0.33)	-0.07 (0.33)
Smoking (cig/day)				
0 (ref)	0	0	0	0
1-5	-0.02 (0.08)	0.03 (0.08)	-0.01 (0.08)	0.03 (0.08)
6-10	0.11 (0.09)	-0.02 (0.09)	0.19 (0.09)*	0.02 (0.09)
11-15	0.02 (0.12)	-0.05 (0.12)	0.11 (0.12)	0.03 (0.12)
>15	0.05 (0.12)	-0.01 (0.12)	0.11 (0.12)	-0.01 (0.12)
Use of psychofarmaca				
no (ref)	0	0	0	0
yes	-0.65 (0.29)*	-0.71 (0.28)*	-0.65 (0.28)*	-0.55 (0.28)*

@ for the other variables in the table as well as infant's sex, maternal education, ethnicity, occupation, age and parity

* $p<0.05$

Table 8 Unadjusted and adjusted differences in z-scores for fine motor function and adaptation in relation to maternal alcohol consumption, smoking and use of psychofarmaca during pregnancy based on exclusion of missing developmental items (A) and multiple imputation (B)

Exposure	Unadjusted difference (SE)		Adjusted@ difference (SE)	
	A (SE)	B (SE)	A (SE)	B (SE)
Alcohol (drinks/week)				
0 (ref)	0	0	0	0
1	-0.03 (0.06)	-0.02 (0.06)	-0.13 (0.06)*	-0.11 (0.06)
2-7	0.06 (0.11)	-0.06 (0.11)	0.00 (0.11)	-0.12 (0.12)
>7	-0.13 (0.35)	-0.20 (0.35)	-0.02 (0.33)	-0.12 (0.33)
Smoking (cig/day)				
0 (ref)	0	0	0	0
1-5	-0.05 (0.08)	-0.01 (0.08)	0.02 (0.08)	0.02 (0.08)
6-10	-0.06 (0.09)	-0.13 (0.09)	-0.00 (0.09)	-0.08 (0.09)
11-15	-0.08 (0.12)	-0.13 (0.25)	0.02 (0.12)	-0.04 (0.12)
>15	0.04 (0.12)	0.02 (0.12)	0.14 (0.12)	0.10 (0.12)
Use of psychofarmaca				
no (ref)	0	0	0	0
yes	-0.40 (0.28)	-0.62 (0.28)*	-0.37 (0.28)	-0.43 (0.28)

@ see table 7

* $p<0.05$

Table 9 Unadjusted and adjusted differences in z-scores for communication and social behaviour in relation to maternal alcohol consumption, smoking and use of psychofarmaca during pregnancy based on exclusion of missing developmental items (A) and multiple imputation (B)

Exposure	Unadjusted difference (SE)		Adjusted@ difference (SE)	
	A (SE)	B (SE)	A (SE)	B (SE)
Alcohol (drinks/week)				
0 (ref)	0	0	0	0
1	-0.12 (0.06)*	-0.09 (0.06)	-0.22 (0.06)**	-0.18 (0.06)**
2-7	-0.04 (0.11)	-0.18 (0.11)	-0.06 (0.11)	-0.18 (0.11)
>7	-0.22 (0.36)	-0.23 (0.35)	-0.11 (0.34)	-0.11 (0.34)
Smoking (cig/day)				
0 (ref)	0	0	0	0
1-5	-0.08 (0.08)	-0.03 (0.08)	-0.05 (0.08)	-0.02 (0.08)
6-10	0.14 (0.09)	0.03 (0.09)	0.20 (0.08)*	0.08 (0.08)
11-15	-0.06 (0.12)	-0.14 (0.12)	0.06 (0.12)	-0.03 (0.12)
>15	0.11 (0.13)	0.07 (0.13)	0.17 (0.12)	0.12 (0.12)
Use of psychofarmaca				
no (ref)	0	0	0	0
yes	-0.44 (0.29)	-0.70 (0.29)*	-0.36 (0.28)	-0.58 (0.28)*

@ see table 7

* $p<0.05$; ** $p<0.01$

Table 5 Differences in total IQ in relation to maternal alcohol consumption during pregnancy in 139 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	43	0	0
1-49	46	-1.8 (2.7)	-2.1 (2.5)
50-99	23	1.1 (3.3)	-2.8 (3.1)
≥100	27	2.2 (3.1)	-3.0 (3.0)
Second trimester			
0 (ref)	83	0	0
1-49	23	6.2 (2.9)*	1.7 (3.1)
50-99	24	1.0 (2.9)	-1.5 (2.8)
≥100	9	5.3 (4.4)	0.6 (4.2)
Third trimester			
0 (ref)	88	0	0
1-49	20	6.9 (3.1)*	2.1 (2.1)
50-99	22	3.4 (3.0)	-1.5 (3.0)
≥100	9	6.1 (4.3)	2.8 (4.1)
Average of 2nd and 3d trimester			
0 (ref)	83	0	0
1-49	25	4.1 (2.8)	0.2 (2.9)
50-99	19	1.4 (3.2)	-0.6 (3.2)
≥100	12	7.1 (3.9)	0.2 (3.7)

* $p<0.05$

Table 6 Differences in total IQ in relation to maternal alcohol consumption during pregnancy in 139 children by available case method (AC) and in 166 children by conditional mean imputation (CMI)@ at the age of fifteen years

Alcohol (in g/wk)	n		Unadjusted difference (SE)		Adjusted difference (SE)	
	AC	CMI	AC	CMI	AC	CMI
First trimester						
0 (ref)	43	57	0	0	0	0
1-49	46	53	-1.8 (2.7)	-1.0 (2.3)	-2.1 (2.5)	-1.1 (2.1)
50-99	23	25	1.1 (3.3)	0.7 (2.9)	-2.8 (3.1)	-3.1 (2.8)
≥100	27	31	2.2 (3.1)	2.3 (2.7)	-3.0 (3.0)	-2.9 (2.6)
Second trimester						
0 (ref)	83	104	0	0	0	0
1-49	23	24	6.2 (2.9)*	6.8 (2.7)*	1.7 (3.1)	2.7 (2.7)
50-99	24	25	1.0 (2.9)	0.9 (2.6)	-1.5 (2.8)	-1.7 (2.5)
≥100	9	13	5.3 (4.4)	3.9 (3.5)	0.6 (4.2)	0.1 (3.3)
Third trimester						
0 (ref)	88	108	0	0	0	0
1-49	20	23	6.9 (3.1)*	6.6 (2.7)*	2.1 (2.1)	2.7 (2.8)
50-99	22	22	3.4 (3.0)	3.5 (2.8)	-1.5 (3.0)	-1.1 (2.7)
≥100	9	13	6.1 (4.3)	3.2 (3.5)	2.8 (4.1)	0.3 (3.4)
Average of 2nd and 3d trimester						
0 (ref)	83	103	0	0	0	0
1-49	25	26	4.1 (2.8)	4.7 (2.6)	0.2 (2.9)	0.9 (2.6)
50-99	19	22	1.4 (3.2)	0.7 (2.8)	-0.6 (3.2)	-0.7 (2.7)
≥100	12	15	7.1 (3.9)	5.4 (3.3)	0.2 (3.7)	-0.8 (3.2)

@ of 27 children with available school type but missing IQ-data mean IQ was imputed of the the relationship between IQ and school type of 138 children with available data on both IQ and school type

* $p<0.05$

Table 7 Differences in verbal IQ in relation to maternal alcohol consumption during pregnancy in 139 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	43	0	0
1-49	46	-3.0 (2.8)	-2.6 (2.6)
50-99	23	1.0 (3.4)	-3.0 (3.2)
≥100	27	1.1 (3.2)	-3.1 (3.0)
Second trimester			
0 (ref)	83	0	0
1-49	23	6.3 (3.0)*	1.2 (3.2)
50-99	24	1.0 (3.0)	-1.8 (2.8)
≥100	9	3.6 (4.5)	0.7 (4.3)
Third trimester			
0 (ref)	88	0	0
1-49	20	5.6 (3.2)	-0.8 (3.4)
50-99	22	3.2 (3.1)	-0.7 (3.1)
≥100	9	6.3 (4.5)	0.9 (4.2)
Average of 2nd and 3d trimester			
0 (ref)	83	0	0
1-49	25	3.6 (3.0)	-0.8 (3.0)
50-99	19	2.0 (3.3)	0.2 (3.2)
≥100	12	5.9 (4.0)	-0.7 (3.8)

* $p<0.05$

Table 8 Differences in performal IQ in relation to maternal alcohol consumption during pregnancy in 139 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	43	0	0
1-49	46	-0.0 (2.6)	-1.4 (2.6)
50-99	23	0.7 (3.2)	-2.6 (3.3)
≥100	27	3.0 (3.0)	-2.4 (3.1)
Second trimester			
0 (ref)	83	0	0
1-49	23	4.6 (2.9)	2.3 (3.3)
50-99	24	0.7 (2.8)	-1.4 (2.9)
≥100	9	6.1 (4.3)	0.4 (4.4)
Third trimester			
0 (ref)	88	0	0
1-49	20	7.1 (3.0)*	5.4 (3.4)
50-99	22	2.9 (2.9)	-1.8 (3.1)
≥100	9	4.5 (4.2)	4.9 (4.2)
Average of 2nd and 3d trimester			
0 (ref)	83	0	0
1-49	25	3.5 (2.8)	0.8 (3.0)
50-99	19	0.2 (3.1)	-1.9 (3.3)
≥100	12	7.1 (3.7)	1.9 (3.9)

* $p<0.05$

Table 9 Differences in total behavior problem score (in t-scores) in relation to maternal alcohol consumption during pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	50	0	0
1-49	51	-1.6 (2.0)	-0.1 (2.0)
50-99	24	-0.7 (2.5)	3.7 (2.6)
≥100	29	-1.6 (2.4)	0.1 (2.4)
Second trimester			
0 (ref)	95	0	0
1-49	23	1.2 (2.4)	3.4 (2.4)
50-99	24	-0.8 (2.3)	0.7 (2.4)
≥100	12	-3.0 (3.1)	-0.6 (3.3)
Third trimester			
0 (ref)	100	0	0
1-49	22	-2.1 (2.4)	1.7 (2.5)
50-99	22	-0.6 (2.4)	-0.1 (2.7)
≥100	10	-0.6 (3.4)	2.4 (3.3)
Average of 2nd and 3d trimester			
0 (ref)	95	0	0
1-49	25	1.5 (2.3)	3.0 (2.3)
50-99	21	-1.7 (2.5)	0.1 (2.5)
≥100	13	-2.2 (3.0)	0.8 (3.2)

Table 10 Differences in internalizing behavioral problem score (in t-scores) in relation to maternal alcohol consumption during pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	50	0	0
1-49	51	-0.4 (2.1)	1.0 (2.0)
50-99	24	0.7 (2.6)	5.0 (2.6)
≥100	29	-0.8 (2.4)	0.0 (2.4)
Second trimester			
0 (ref)	95	0	0
1-49	23	0.1 (2.4)	2.0 (2.5)
50-99	24	-1.0 (2.4)	0.4 (2.5)
≥100	12	-1.9 (3.2)	-0.7 (3.3)
Third trimester			
0 (ref)	100	0	0
1-49	22	-3.3 (2.4)	-0.1 (2.5)
50-99	22	-0.5 (2.4)	-0.0 (2.8)
≥100	10	-1.1 (3.4)	1.0 (3.4)
Average of 2nd and 3d trimester			
0 (ref)	95	0	0
1-49	25	1.1 (2.3)	2.2 (2.4)
50-99	21	-2.1 (2.5)	-0.2 (2.6)
≥100	13	-2.2 (3.1)	-0.4 (3.3)

Table 11 Differences in externalizing behavioral problem score (in t-scores) in relation to maternal alcohol consumption during pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	50	0	0
1-49	51	-1.2 (1.9)	0.5 (1.9)
50-99	24	-2.4 (2.4)	1.6 (2.4)
≥100	29	-1.5 (2.3)	0.2 (2.2)
Second trimester			
0 (ref)	95	0	0
1-49	23	0.4 (2.3)	2.2 (2.3)
50-99	24	0.1 (2.2)	1.8 (2.3)
≥100	12	-5.1 (3.0)	-2.3 (3.0)
Third trimester			
0 (ref)	100	0	0
1-49	22	-2.9 (2.3)	0.9 (2.3)
50-99	22	-0.4 (2.3)	0.2 (2.5)
≥100	10	-0.2 (3.2)	2.8 (3.1)
Average of 2nd and 3d trimester			
0 (ref)	95	0	0
1-49	25	0.6 (2.2)	2.1 (2.2)
50-99	21	-1.3 (2.4)	0.3 (2.4)
≥100	13	-2.8 (2.9)	0.4 (3.0)

Table 12 Differences in hand coordination (in seconds) in relation to maternal alcohol consumption during pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	50	0	0
1-49	51	0.6 (0.7)	0.8 (0.7)
50-99	24	-1.3 (0.9)	-0.8 (1.0)
≥100	29	-0.7 (0.8)	-0.5 (0.9)
Second trimester			
0 (ref)	95	0	0
1-49	23	-1.0 (0.8)	-0.8 (0.9)
50-99	24	-1.5 (0.8)	-1.1 (0.9)
≥100	12	-0.4 (1.1)	-0.1 (1.2)
Third trimester			
0 (ref)	100	0	0
1-49	22	-0.8 (0.8)	-0.8 (0.9)
50-99	22	-1.3 (0.8)	-1.1 (1.0)
≥100	10	-0.8 (1.2)	-0.6 (1.2)
Average of 2nd and 3d trimester			
0 (ref)	95	0	0
1-49	25	-1.2 (0.8)	-1.2 (0.9)
50-99	21	-0.8 (0.8)	-0.3 (0.9)
≥100	13	-1.3 (1.1)	-1.2 (1.2)

Table 13 Differences in information processing in relation to maternal alcohol consumption during pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	50	0	0
1-49	51	-0.5 (0.4)	-0.5 (0.4)
50-99	24	-0.2 (0.5)	-0.3 (0.5)
≥100	29	-0.7 (0.5)	-0.5 (0.5)
Second trimester			
0 (ref)	95	0	0
1-49	23	-0.5 (0.5)	-0.8 (0.5)
50-99	24	-0.2 (0.5)	-0.5 (0.5)
≥100	12	-0.6 (0.6)	0.2 (0.6)
Third trimester			
0 (ref)	100	0	0
1-49	22	-0.8 (0.5)	-0.7 (0.5)
50-99	22	-0.7 (0.5)	-0.7 (0.5)
≥100	10	0.6 (0.6)	0.6 (0.6)
Average of 2nd and 3d trimester			
0 (ref)	95	0	0
1-49	25	-0.6 (0.4)	-0.8 (0.4)
50-99	21	-0.3 (0.5)	-0.3 (0.5)
≥100	13	-0.2 (0.6)	-0.1 (0.6)

Table 14 Differences in concentration fluctuation (in z-scores) in relation to maternal alcohol consumption during pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	50	0	0
1-49	51	-0.4 (0.2)*	-0.2 (0.2)
50-99	24	-0.2 (0.2)	0.1 (0.3)
≥100	29	-0.5 (0.2)*	-0.4 (0.3)
	F=2.23; df=3,150; p=0.09		
Second trimester			
0 (ref)	95	0	0
1-49	23	-0.4 (0.2)	-0.2 (0.3)
50-99	24	-0.3 (0.2)	-0.4 (0.3)
≥100	12	0.0 (0.3)	0.2 (0.3)
Third trimester			
0 (ref)	100	0	0
1-49	22	-0.6 (0.2)**	-0.5 (0.3)
50-99	22	-0.4 (0.2)	-0.3 (0.3)
≥100	10	0.1 (0.3)	0.1 (0.3)
	F=2.87; df=3,150; p=0.04		
Average of 2nd and 3d trimester			
0 (ref)	95	0	0
1-49	25	-0.4 (0.2)	-0.2 (0.3)
50-99	21	-0.4 (0.2)	-0.4 (0.3)
≥100	13	0.1 (0.3)	0.2 (0.3)

* $p<0.05$; ** $p < 0.01$

Table 15 Differences in precision (in z-scores) in relation to maternal alcohol consumption during pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	50	0	0
1-49	50	-0.2 (0.2)	-0.2 (0.2)
50-99	23	-0.1 (0.3)	0.1 (0.3)
≥100	27	-0.0 (0.2)	0.1 (0.3)
Second trimester			
0 (ref)	94	0	0
1-49	22	-0.0 (0.2)	0.1 (0.3)
50-99	23	0.0 (0.2)	0.1 (0.3)
≥100	11	-0.0 (0.3)	0.1 (0.4)
Third trimester			
0 (ref)	99	0	0
1-49	22	-0.2 (0.2)	-0.1 (0.3)
50-99	22	-0.1 (0.2)	-0.0 (0.3)
≥100	7	0.0 (0.4)	-0.0 (0.4)
Average of 2nd and 3d trimester			
0 (ref)	94	0	0
1-49	25	0.1 (0.2)	0.1 (0.3)
50-99	20	-0.2 (0.2)	0.1 (0.3)
≥100	11	0.1 (0.3)	0.0 (0.4)

Table 16 Differences in short term memory in relation to maternal alcohol consumption during pregnancy in 139 children at the age of fifteen years

Alcohol (in g/wk)	n	Unadjusted difference (SE)	Adjusted difference (SE)
First trimester			
0 (ref)	43	0	0
1-49	46	-1.0 (0.7)	-1.2 (0.8)
50-99	23	0.6 (0.9)	-0.0 (1.0)
≥100	27	0.1 (0.8)	-0.5 (0.9)
Second trimester			
0 (ref)	83	0	0
1-49	23	1.1 (0.8)	0.6 (0.9)
50-99	24	0.6 (0.8)	0.5 (0.9)
≥100	9	2.3 (1.2)	1.9 (1.3)
Third trimester			
0 (ref)	88	0	0
1-49	20	0.9 (0.8)	0.5 (1.0)
50-99	22	1.3 (0.8)	0.9 (1.0)
≥100	9	1.8 (1.2)	1.7 (1.3)
Average of 2nd and 3d trimester			
0 (ref)	83	0	0
1-49	25	0.8 (0.8)	0.3 (0.9)
50-99	19	0.9 (0.8)	1.1 (1.0)
≥100	12	1.9 (1.0)	1.1 (1.2)

Table 17 Long term memory in relation to maternal alcohol consumption during pregnancy in 139 children at the age of fifteen years

Alcohol in g/wk)	No. words remembered < P50		Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
	n/N	(%)		
First trimester				
0 (ref)	24/43	(56)	1	1
1-49	20/46	(43)	0.6 (0.3 to 1.4)	0.6 (0.2 to 1.8)
50-99	10/23	(43)	0.6 (0.2 to 1.7)	0.5 (0.1 to 1.9)
≥100	13/27	(48)	0.7 (0.3 to 1.9)	0.6 (0.2 to 2.3)
Second trimester				
0 (ref)	42/83	(51)	1	1
1-49	4/23	(17)	0.2 (0.1 to 0.7)**	0.2 (0.0 to 0.7)*
50-99	15/24	(63)	1.6 (0.6 to 4.1)	0.7 (0.2 to 2.5)
≥100	6/9	(67)	2.0 (0.5 to 8.3)	1.2 (0.2 to 8.0)
				LR-test=7.93, df=3, p=0.047
Third trimester				
0 (ref)	46/88	(52)	1	1
1-49	8/20	(40)	0.6 (0.2 to 1.6)	0.4 (0.1 to 1.5)
50-99	11/22	(50)	0.9 (0.4 to 2.3)	0.4 (0.1 to 1.6)
≥100	2/9	(22)	0.3 (0.1 to 1.3)	0.1 (0.0 to 0.8)*
				LR-test=6.44, df=3, p=0.09
Average of 2nd and 3d trimester				
0 (ref)	42/83	(51)	1	1
1-49	9/25	(36)	0.5 (0.2 to 1.4)	0.4 (0.1 to 1.2)
50-99	10/19	(53)	1.1 (0.4 to 2.9)	0.7 (0.2 to 2.8)
≥100	6/12	(50)	1.0 (0.3 to 3.3)	0.5 (0.1 to 2.6)

LR=Likelihood-ratio test

* p<0.05; ** p < 0.01

Table 18 Hyperactivity in relation to maternal alcohol consumption during pregnancy in 154 children at the age of fifteen years

Alcohol (in g/wk)	Hyperactivity		Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
	n/N	(%)		
First trimester				
0 (ref)	20/50	(40)	1	1
1-49	16/51	(31)	0.7 (0.3 to 1.6)	0.9 (0.4 to 2.5)
50-99	6/24	(25)	0.5 (0.2 to 1.5)	0.8 (0.2 to 2.9)
≥100	9/29	(31)	0.7 (0.3 to 1.8)	1.0 (0.3 to 3.2)
Second trimester				
0 (ref)	35/95	(37)	1	1
1-49	6/23	(26)	0.6 (0.2 to 1.7)	0.8 (0.2 to 2.8)
50-99	8/24	(33)	0.9 (0.3 to 2.2)	0.9 (0.3 to 2.9)
≥100	2/12	(17)	0.3 (0.1 to 1.7)	0.3 (0.0 to 1.7)
Third trimester				
0 (ref)	38/100	(38)	1	1
1-49	4/22	(18)	0.4 (0.1 to 1.2)	0.3 (0.1 to 1.4)
50-99	7/22	(32)	0.8 (0.3 to 2.0)	0.9 (0.3 to 3.1)
≥100	2/10	(20)	0.4 (0.1 to 2.0)	0.6 (0.1 to 3.6)
Average of 2nd and 3d trimester				
0 (ref)	35/95	(37)	1	1
1-49	9/25	(36)	1.0 (0.4 to 2.4)	1.1 (0.4 to 3.6)
50-99	3/21	(14)	0.3 (0.1 to 1.0)	0.3 (0.1 to 1.3)
≥100	4/13	(31)	0.8 (0.2 to 2.7)	1.0 (0.2 to 4.6)

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CURRICULUM VITAE

Paulus Hendrikus Verkerk werd op 24 oktober 1960 geboren te Losser. In 1979 behaalde hij het eindexamen VWO B aan het Twents Carmellyceum te Oldenzaal. Aansluitend startte hij met de studie geneeskunde aan de Rijksuniversiteit te Groningen, waar hij in 1984 het doctoraal examen en in 1987 het artsexamen haalde (bijvak aan de Faculteit der Wiskunde en Natuurwetenschappen: inleiding informatica). Van 1987 tot 1988 werkte hij als wetenschappelijk medewerker bij de Vakgroep Sociale Geneeskunde en Epidemiologie van de Rijksuniversiteit Groningen (hoofd: Prof.Dr. R. van der Lende). Vanaf 1988 werkt hij als wetenschappelijk medewerker bij TNO Preventie en Gezondheid te Leiden bij de Divisie Collectieve Preventie (hoofd: Dr. A. Dijkstra) in de sector Jeugd (hoofd: Prof. Dr. S.P. Verloove-Vanhorick).

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* related to this thesis