Is the association between maternal alcohol consumption in pregnancy and pre-school child behavior and emotional problems causal? Multiple approaches for controlling unmeasured confounding

Ingunn Olea Lund, PhD[1]*, Espen Moen Eilertsen, MSc[1], Line C. Gjerde, PhD[1,2], Espen Røysamb, PhD[1,2], Mollie Wood[4], Ted Reichborn-Kjennerud, MD, PhD[1,3] & Eivind Ystrom, PhD[1,2,4]

[1] The Norwegian Institute of Public health, Oslo, Norway.

[2] Section of Health, Developmental and Personality Psychology, Department of Psychology, University of Oslo, Oslo, Norway.

[3] Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

[4] PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy; & PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway.

Running head: prenatal alcohol exposure

Word count manuscript: 3407 (excl title page, abstract, key points, tables, graphs, funding, acknowledgments and references)

Declarations of interest: none

*Correspondence concerning this article should be addressed to:

Ingunn Olea Lund, Department of Mental Disorders, Norwegian Institute of Public Health, Postboks 222 Skøyen, 0213 Oslo, Norway

Phone: +47 91741188, E-mail: IngunnOlea.Lund@fhi.no / ingunnolea@gmail.com

Abstract

Background and aims: Hazardous drinking (i.e., alcohol consumption that places drinkers at risk for adverse health outcomes) during pregnancy is associated with adverse child outcomes. To address whether the associations are causal, we aimed to estimate the effect of maternal hazardous drinking during 1st trimester on offspring emotional and behavior problems throughout the preschool age. We adjust for, 1) measured confounding (e.g., smoking) 2) familial risk factors by sibling control design, and 3) non-shared environmental risk factors by using hazardous drinking the 3 months before pregnancy as an instrumental variable.

Design: Prospective cohort study. Participants were recruited between 1999-2009 at ultrasound examination offered to all pregnant women in Norway. Data was collected during the 17th and the 30th week of gestation, and when the children were 1.5, 3 and 5 years old.

Setting: Norway (1999-2015).

Participants: The sample consists of 14,639 mothers with 25 744,395 offspring siblings from the Norwegian Mother and Child Cohort Study.

Measurements: Respondents self-reported on: alcohol consumption; children's emotional problems (i.e. emotional reactive, anxiety/depression, somatic complaints) and behavioral problems (i.e. attention and aggressive behavior) throughout preschool age. We used longitudinal latent growth curve models to estimate the effect of maternal drinking during 1st trimester on offspring emotional and behavior.

Findings: Most associations were strongly reduced after controlling for both familial and measured environmental risk factors. After adjustment, exposed children were more emotionally reactive (β= 2.33; 95% CI 0.13:4.53) and had more somatic complaints (β=1.93;95%CI 0.09:3.77) at age three, but not at age five. Exposed children were less aggressive than unexposed siblings at age five (β=-2.27; 95%CI -4.02:-0.52).

Conclusions: Children exposed to hazardous drinking during 1st trimester were more emotionally reactive and had more somatic complaints at age three, but not at age five, and were less aggressive at age five compared to unexposed siblings.

Introduction

Prenatal alcohol exposure is associated with a range of adverse child outcomes (1–9), including emotional and behavior problems (10,11). Children may exhibit physically aggressive behavior, and their tendency to act out can contribute to school problems and, as they become adolescents and young adults, increased risk of, e.g. substance use problems and criminal activities (12,13). Children may also experience depression, anxiety and have somatic complaints –which are associated with psychosocial impairment (14). Thus, the short and long-term consequences of such problems can be severe for those affected; and the societal costs high (15).

The literature on prenatal alcohol exposure and child outcomes is extensive, and it is well established that heavy drinking increases the risk of severe outcomes such as fetal alcohol syndrome (FAS) and other fetal alcohol spectrum disorders (5,8,9). The literature is more ambiguous regarding effects on child behavior and emotional problems; some studies find that alcohol contributes to increased risk (7,14,16,17); others do not (18–20). A possible explanation for these discrepancies is that unmeasured confounding may obscure or inflate the observed associations, making it difficult to determine if they are truly causal. Both from a public health and a clinical perspective, knowledge about whether the relationship is causal or not is vital for prevention purposes.

Alcohol use during pregnancy is associated with disinhibited personality traits (21), and genetic factors influence both drinking behavior, behavior problems and emotional problems (22,23). The association between prenatal exposure to alcohol and child behavior and emotional problems may therefore, be confounded by common genetic factors.

Several study designs are available to address unmeasured confounding. Quasi-experimental designs using family data (24–27) are particularly compelling, as these can control for unmeasured familial risk factors (28). The maternal genome is the same across siblings; confounding by genetic risk

is therefore excluded from sibling control designs when the exposure is a maternal variable. Instrumental variables present another opportunity (29). Hazardous drinking before pregnancy is also associated with child behavioral and emotional problems (30). While this cannot be due to a direct intrauterine effect, it remains associated with these outcomes in sibling designs, where shared genetic risk factors are controlled for (31,32). This suggests that pre-conception hazardous drinking may be used as an instrumental variable - in conjunction with a sibling design to control confounding by shared maternal common causes of exposure and outcome. If the effect of prenatal exposure to maternal hazardous drinking on child behavior and emotional problems is causal, this association should be stronger than that of maternal hazardous drinking before pregnancy.

Hazardous drinking, particularly during the 1st trimester of pregnancy, is associated with an increased risk of adverse child outcomes (3,33); thus, this time-period is the focus of our study. To address whether associations represent a causal association, we estimate the effect of maternal hazardous drinking during 1st trimester on offspring behavior and emotional problems throughout the preschool age. We adjust for, 1) observed covariates, e.g., maternal smoking, 2) familial risk factors by a sibling control design and 3) non-shared environmental risk factors by using hazardous drinking in the 3 months before pregnancy as an instrumental variable.

Methods

Participants and procedures

We used data from the Norwegian Mother and Child Cohort Study (MoBa), an ongoing, prospective pregnancy cohort study (34). Participants were recruited from 1999 to 2009 at a routine ultrasound examination offered to all pregnant women in Norway at gestational week 17-18. Of the eligible women, 41% participated, and the total sample includes more than 114 000 children, 95 000 mothers,

and 75 000 fathers. Some groups of women are underrepresented in MoBa, e.g., pregnant women who are under 25 years old; women who live alone; mothers with more than two previous births; and women who smoke (35). We used data collected during the 17th and the 30th week of gestation, as well as when the children were 1.5, 3 and 5 years old. Siblings were therefore assessed at the same age. The final sample used in the present study was restricted to families with more than one birth record in MoBa: 16 310 mothers participate with more than one pregnancy, comprising a sample of 33 706 sibling children. Among these mothers, we excluded 3 683 with missing data on covariates, and 4 279 children with no outcome measures at any of the time points. Our final sample consists of 25 744 children nested within 14 639 mothers. Information was also obtained from the Medical Birth Registry of Norway (MBRN) (36).

We used version 9 of the quality-assured MoBa data files, released in 2015. All participants provided written informed consent. MoBa has been granted a license from the Norwegian Data Inspectorate, and the Regional Committee for Medical Research Ethics approved the present study.

Measures

Hazardous alcohol consumption

We used the Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) (37) to index hazardous alcohol consumption, i.e., a quantity and/or pattern of alcohol consumption that places drinkers at risk for negative health outcomes (38,39). The scale consists of 3 items summed to a total score between 0-12: Women reported how often they consumed alcohol using a scale ranging from “never” to “approximately 6-7 times per week”; their usual amount of alcohol consumption using a scale ranging from “less than 1” to “10 or more”; and frequency of binge drinking (5 or more units of alcohol per drinking occasion), using a scale ranging from “never” to “several times per week”. In MoBa, one unit is defined as “1.5 cl (12.8 g) of pure alcohol” (40). In both the 17th and the 30th week

questionnaires, the women reported alcohol use in the 3 months prior to pregnancy, and during the 1st trimester. We used the average of the two reports on pre-pregnancy and 1st trimester drinking respectively. For women, a score of 3 or more on Audit-C is often used as a cut-off for increased risk of developing alcohol-related problems (41). Also in pregnant populations, this cut-off has a high sensitivity and specificity of alcohol use disorders (42). We used this cut-off as an indicator of hazardous drinking during the 1st trimester.

Child behavior and emotional problems

Items from the Child Behavior Checklist version for preschool children (CBCL/1.5–5) were used to assess child problems in the 1.5, 3, and 5-year questionnaires (43). CBCL/1.5–5 consists of 99 items that describe child behavior in the preceding 2 months. These items constitute subscales within emotional ("emotionally reactive," "anxious/depressed," and "somatic complaints") and behavior ("attention problems" and "aggressive behavior") problems. The CBCL for older children has been validated in a Norwegian population sample (44); versions for younger children in Dutch and Danish samples (45,46). Item selection was necessary due to space restriction; selected items were based on consensus among specialists in clinical and developmental psychology. Several publications has used the instrument ,e.g. (30,40,47,48). See Table 1 for an overview over items. Mothers reported whether statements described their children on a 3-point scale: not true (1), somewhat or sometimes true (2) and very true or often true (3). There was 7%, 25%, and 49% missing data on the outcomes at 1.5, 3, and 5 years respectively. The first cohorts did not receive the five-year questionnaire , thus additional missing is not due to non-response (34).

Sibling comparison and instrumental variable

We adjusted for variables stable across pregnancies with the sibling comparison and used maternal hazardous drinking during the last 3 months before pregnancy as an instrumental variable. Sibling comparison allows us to compare outcomes within siblings who are exposed to different patterns of maternal drinking during 1st trimester; but who have similar familial background and environment. The persistence of the observed effect estimate in the instrumental variable analysis provides additional evidence that the observed association is causal, e.g., not due to confounding. Figure 1 illustrates our instrumental variable approach on within sibling pair effects. Three assumptions define instrumental variables : one, the instrument (hazardous alcohol consumption before pregnancy) is associated with the exposure of interest (hazardous alcohol consumption during pregnancy). Two, no uncontrolled common causes of the exposure and outcome are associated with the instrument. Three, the instrument has no direct effect on the outcome of interest; i.e., maternal hazardous drinking is independent of child behavior, given the measured covariates and shared confounders. Within siblings of the same mothers, shared unmeasured familial confounding is controlled by design, so although the instrumental variable assumptions are not formally testable, it is likely that these assumptions hold.

Covariates

We included the following potential confounders that can vary across pregnancies, and are not likely consequences of current hazardous alcohol consumption or alcohol use disorders from the MBRN: Parity, and from MoBa Q1: unplanned pregnancy, daily smoking, and pre-pregnancy abstinence from alcohol.

Insert Figure 1 about here

Analyses

We used a graded response item response theory model (GRM-IRT) to model the syndromal scales of the CBCL; this is a confirmatory factor analysis for ordinal items using a logit link function. Hence, each response category of each item has a separate threshold, and each item has a single slope (i.e., factor loading). To improve interpretability, we used the CBCL standard of the T-score (SD of 10) and fixed the variance at the first time point to this value. The variances at 3 and 5 years were freely estimated. We used a latent growth curve to model the scales across time. This approach allows for repeated measures of outcomes (i.e. emotional and behavioral problems) while having a single time-invariant exposure (i.e. hazardous drinking during pregnancy). By reducing development across time into a growth curve, it is possible to estimate the effect at each time point while retaining all outcome observations for those who might have missing data. This maximizes statistical power to reduce the risk for a type II error and the risk for bias due to missing data under the "missing at random assumption. The growth curve had its' random intercept set to 1.5 years, a random slope, and a fixed quadratic slope (49). To model changes in latent means and variances across time, we set the thresholds for each response category and factor loadings for each item to equal across time. See Table 1 for an overview of standardized factor loadings for all items at all time-points. We calculated the effect at each time point as estimated by the parameters in the latent growth curve model. Further, we rescaled the effect sizes from T-scores (β_T) to odds ratios (OR) via logits by using the standard deviation of the logistic response variable $\left(e^{\frac{\beta_T}{10}\sqrt{\frac{\pi^2}{3}}}\right)$ (50). The OR are presented in a supplement table.

We regressed the latent intercept and slopes of the growth curves on the hazardous drinking measures and the covariates in three steps. First, we adjusted for the covariates. Second, we group

mean centered the hazardous drinking measures to perform sibling control analyses. Third, we included group mean centered hazardous drinking three months before pregnancy as an instrumental variable by regressing hazardous drinking during pregnancy on hazardous drinking before pregnancy in a structural equation model. We used the default sandwich estimator of Mplus 7.31 to correct for dependent observations in the sibling data. We used Full Information Maximum Likelihood (FIML), e.g., all available information was used to estimate the model.

Insert Table 1 about here

Results

Table 2 illustrates characteristics of women who participated in the MoBa study with two or more pregnancies. The mean age at recruitment was 30 years, and the majority of the pregnancies were planned (83.2%). About half (49.7%) reported hazardous drinking 3 months before pregnancy; only 2.49% did so during the 1st trimester. Only 6 % reported daily smoking during pregnancy.

Insert table 2 about here

Table 3 shows the results from the regression analysis of child behavior and emotional problems for AUDIT scores 1, 2 and ≥ 3. Hazardous alcohol consumption during pregnancy (≥ 3) was associated with all forms of emotional or behavior problems in unadjusted analyses. In the analyses adjusted for measured confounders, hazardous drinking during the 1st trimester was still associated with all forms of problems at one or more time points. Adjusting for maternal risk factors stable across pregnancies by sibling control markedly reduced the associations. However, in the sibling control instrumental variable analysis children exposed to hazardous drinking during pregnancy had more emotionally

reactive problems (β= 2.33; 95% CI 0.13:4.53) and somatic complaints (β =1.93;95%CI 0.09:3.77) at three years. These effects were no longer evident at five years ((β= -0.04;95%CI. -4.02:3.94) and (β=-0.64; 95%CI.-3.11:1.83), respectively). For an instrument to be included, it must be associated with the exposure of interest. The standardized effect ±S.E. of the instrumental variable on the category 1, 2, and 3 of the exposure was 0.044±0.008, 0.134±0.009, and 0.175±0.010 (all $p < 0.001$). After adjusting for factors shared by siblings and pre-pregnancy drinking using the instrumental variable sibling control design, we found no associations between maternal hazardous drinking during pregnancy and offspring behavioral (i.e., inattention and aggression) problems. There was one exception: in the final adjusted model, children exposed to hazardous drinking during pregnancy were less likely to have aggression problems (β =-2.27;95%CI -4.02:-0.52). Readers that would like to see OR, please see supplement table.

Insert Table 3 about here

Discussion

The main finding was that maternal hazardous drinking during the 1st trimester initially seemed to be associated with all forms of behavior and emotional problems, but only a few effects remained associated after sibling control instrumental variable analysis. Exposed children were more emotionally reactive and had more somatic complaints at age three - but no longer at age five. Further, at age five they were less aggressive. After accounting for unmeasured confounding using sibling control and instrumental variable analysis, exposure to 1st trimester hazardous drinking was not at any time point associated with anxiety/depression or attention problems compared to no

exposure. While our findings do not rule out a causal effect of exposure to 1st trimester hazardous drinking on some child emotional and behavior problems, most associations seem confounded by time-invariant familial risk factors shared by siblings born of the same mother. The findings underscore the importance of applying multiple methods to explore the causal relationship that may underlie the associations in observational studies.

Previous studies on the effect of prenatal exposure to alcohol on child behavior and emotional problems have provided mixed results. Some studies have found an association (7,14,16,17,51); others have not (18–20). Our findings do not rule out a causal effect between exposure to 1st trimester hazardous drinking and increased somatic complaints, increased emotional reactivity and fewer problems with aggression when children are five years old. Other associations i.e., on anxious/depressed, and attention problems disappeared after sibling control - suggesting that associations between l drinking during pregnancy and some child emotional and behavioral outcomes are likely driven by genetic or shared environmental confounding. For instance, drinking during pregnancy may be a proxy for maternal behavior problems. This is in line with previous studies, which have shown that disinhibited personality is related to drinking during pregnancy (21); hazardous drinking before pregnancy is associated with maternal emotional and behavior problems (30), and a children-of-twins study found that common familial risk factors confounded transmission of risk between parental behavior problems and child emotional problems (52).

To the best of our knowledge, only one other study has addressed prenatal exposure to alcohol and child behavior problems using sibling control (51). Their results indicate a causal effect of prenatal exposure to alcohol on conduct problems, but not on attention/impulsivity problems. Their finding of a lack of association with attention problems is in line with ours. In contrast, while our study also suggests an effect on aggression problems at five– and their study showed an effect on conduct

problems – the findings point in opposite directions. Our finding suggests less aggression problems in children prenatally exposed to hazardous drinking, and their study suggested more conduct problems. Some differences between the studies should be noted. First, they investigated behavior problems in children in a different age range, namely, 4-11-year-old children, versus 1.5, 3 and 5 years-olds in our study. Second, their respondents provided information about drinking during pregnancy retrospectively; respondents in our study provided information about drinking before and during the 1st trimester during pregnancy (51).

We are not aware of other studies that have explored prenatal exposure to alcohol and child emotional problems using sibling control. Our findings suggest that increased risk of emotional problems, i.e. emotional reactivity and somatic complaints from exposure to 1st-trimester hazardous drinking are transient.

Methodological considerations

The literature on prenatal exposure to alcohol and child behavior and emotional problems carries various shortcomings. First, studies based on clinical samples, e.g., pregnant women in treatment for alcohol problems, typically only provide information about the association between prenatal exposure to high levels of alcohol and child outcomes (53). Second, many studies are small and may lack sufficient power to detect differences (54). Third, few studies control for unmeasured familial risk factors (28). The current study does not suffer such methodological shortcomings and is the first to use a sibling design to study prenatal exposure to alcohol during the 1st trimester and a broad range of child behavior and emotional problems. The sibling design allowed for controlling for unmeasured familial risk factors, and by including pre-pregnancy drinking within the sibling design as an instrumental variable, we could adjust for environmental risk factors that may be present close to

conception. Another major advantage was the large sample size - thus, a lack of statistically significant associations after adjusting for confounding in several steps point to actual lack of associations, rather than a lack of power. Other strengths are the prospective data collection and the general population sample of pregnant women. Further, by using FIML to handle missing data, all cases with data on at least one outcome time-point is included, under the Missing At Random assumption. However, the large proportion of missing data makes the current findings less certain. The use of a validated measurement tool for assessing maternal drinking (37,41); that women were asked twice about both pre-pregnancy and 1st-trimester drinking is another advantage, as is the high consistency regardingo how often and how much they drank.

Several limitations should be considered. First, the MoBa participation rate may have resulted in a selection bias; some groups are underrepresented, e.g., women who smoke and do not live with a partner (35). However, previous studies suggest that differences between the MoBa sample and the general pregnant population in Norway are small (35,55,56). Further, the current study was not concerned with estimates of prevalence, but with the identification of associations between exposures and outcomes. Insistence on "representative samples" in such studies is neither necessary nor necessarily desired (57,58). Second, in similar studies without a sibling-control design self-reported measures may suffer from social desirability bias, and hence result in underreporting of "bad behavior", e.g., alcohol consumption during pregnancy. Importantly, in the current study, such social desirability bias in the maternal reporter is controlled for by design in having repeated assessments from the same mother. Third, the use of short-scales of CBCL is not optimal with regards to construct validity. However, a recent study shows a high correlation between the short-scales and the original CBCL (59). Fourth, we only have maternal reports on child problems; it would be preferable to also

have information from other sources, e.g., from kindergarten teachers. However, any systematic rating bias related to maternal report is adjusted for in the sibling control analysis. Fifth, our sibling design increases the standard error of the estimates. Further, in within-pair estimates, the attenuation of associations due to random measurement error in exposure is higher; and therefore weaker than unpaired associations even if confounding is not an issue (60).

Despite these limitations, sibling studies are a useful approach to study whether certain associations are causal; particularly when, as in our study, they are combined with other study designs (60).

Conclusion

After accounting for confounding factors, exposure to 1st trimester hazardous drinking was associated with increased risk of temporary emotional reactivity and somatic complaints; reduced risk of aggression at five; but no risk difference for anxiety/depression or attention problems. It seems unlikely that the effect of exposure to 1st trimester hazardous drinking on child emotional and behavior problems represents a causal relationship. The study demonstrates the importance of applying multiple methods when investigating if associations in observational studies reflect a causal relationship. Importantly, maternal alcohol use during pregnancy may still be hazardous for other child outcomes. Our study should therefore not be taken to imply that drinking during pregnancy is safe.

Acknowledgments

The Norwegian Research Councils Health Sciences and Biology Program supported this work (Grant no. 231105).

The MoBa study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research (NIH/NIEHS, contract no N01-ES-75558; NIH/NINDA, grant no.1 UO1 NS 047537-01 and grant no. 2 Uo1 NS 047537-06A1). We are grateful to the families who participated in this ongoing cohort study.

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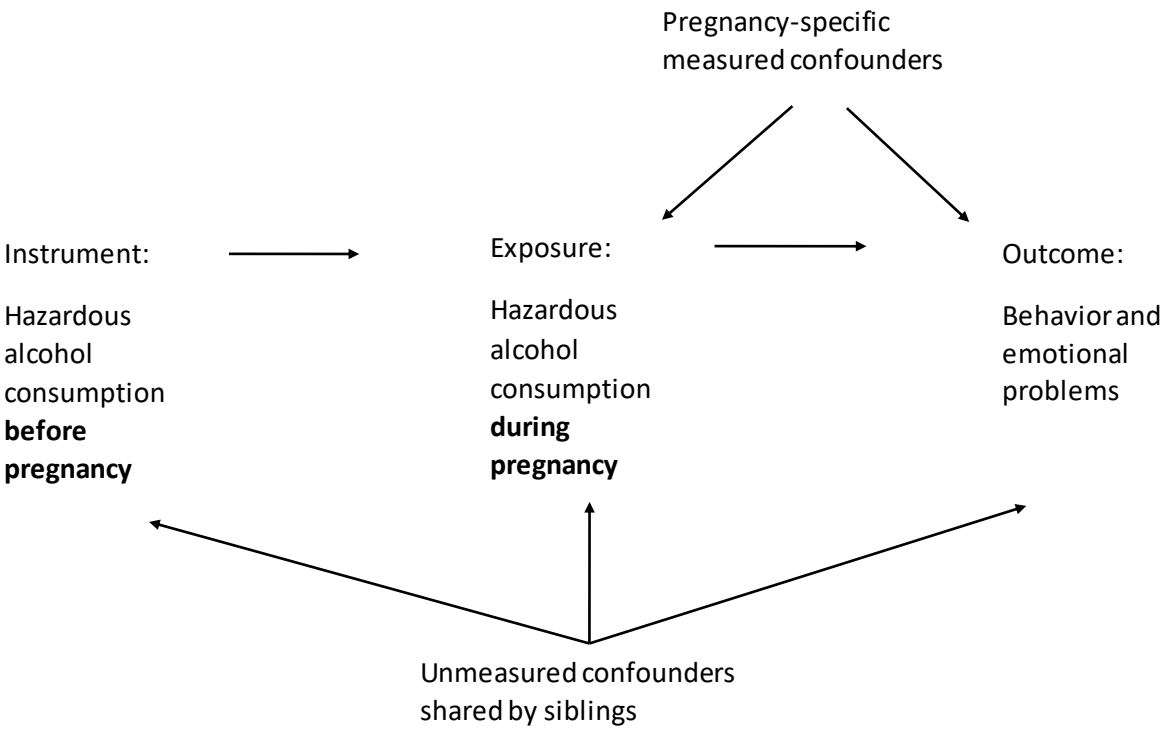
Figure 1.



Instrumental variable approach on within sibling pair effects. We assume that the instrument is associated with the exposure of interest, but have no direct effect on the outcome.

Table 1. Standardized factor loadings for items from the child behavior checklist (CBCL) included in the MoBa questionnaires at 1.5, 3 and 5 years.

	1.5 years	3 years	5 years
Emotional problems			
Emotionally Reactive			
Disturbed by any change in routine	0.82	0.83	0.89
Sudden changes in moods or feelings		0.29	
Anxious/depressed			
Clings to adults or too dependent	0.60	0.66	0.76
Feelings are easily hurt			0.51
Gets too upset when separated from parents	0.53	0.59	0.70
Nervous, high strung, or tense			0.77
Self-conscious or easily embarrassed			0.53
Too fearful or anxious	0.51	0.57	0.68
Unhappy, sad or depressed			0.62
Somatic complaints			
Constipated, doesn't move bowels		0.30	
Doesn't eat well	0.75	0.74	0.79
Stomach aches or cramps (without medical cause)		0.31	0.35
Vomiting, throwing up (without medical cause)		0.41	0.45
Behavior problems			
Attention problems			
Can't concentrate, can't pay attention for long	0.62	0.68	0.78
Can't sit still, restless or overactive	0.68	0.74	0.83
Poorly coordinated or clumsy		0.28	0.37
Quickly shifts from one activity to another	0.61	0.68	0.78
Aggressive behavior			
Can't stand waiting, wants everything now		0.77	0.79
Defiant	0.53	0.51	0.54
Demands must be met immediately		0.88	0.90
Doesn't seem to feel guilty after misbehaving	0.24	0.23	0.24
Gets in many fights	0.38	0.32	0.35
Hits others	0.40	0.34	0.36
Punishment doesn't change his/her behavior	0.37	0.32	0.34

Table 2. Characteristics of the 25 744 pregnancies within 14 639[a] mothers from the Norwegian Mother and Child Cohort study.

Mean age at gestational week 17/18 in years (SD)	29.97 (4.1)
Parity (%)	
0	10 637 (41.3)
1	10 850 (42.2)
2	3 358 (13)
3	668 (2.6)
4 or more	231 (0.9)
Unplanned pregnancy (%)	
No	21 414 (83.2)
Yes	4 330 (16.8)
Daily smoking during pregnancy (%)	
No	24 189 (94)
Yes	1 555 (6)
Pre-pregnancy abstinence from alcohol (%)	
No	24 905 (96.7)
Yes	839 (3.3)
Hazardous alcohol consumption	
During the 1st trimester[b] (%)	
No	25 102 (97.5)
Yes	642 (2.5)[c]
During the 3 months prior to pregnancy[b] (%)	
No	12 959 (50.3)
Yes	12 785 (49.7)

[a]Within the MoBa, 16 310 mothers participate with more than one pregnancy, comprising a sample of 33 706 sibling children. Among these mothers, we excluded 3 683 with missing data on covariates, and 4 279 children with no outcome measures at any of the time points. This left us with a final sample of 25 744 children nested within 14 639 mothers. [b]Hazardous drinking was defined as scoring 3 or more on AUDIT-C. cAmong the 642 children exposed to hazardous drinking during the first trimester, 440 (69%) had siblings who were unexposed to hazardous drinking during pregnancy.

Table 3. Results from latent growth analyses on the effect of maternal hazardous drinking during pregnancy on child emotional and behavior problems.

	Unadjusted									Model 1: Adjusted								
	1.5y			3y			5y			1.5y			3y			5y		
	β	95%CI		β	95%CI		β	95%CI		β	95%CI		β	95%CI		β	95%CI	
Emotional problems																		
Emotionally Reactive																		
AUDIT = 1	-0.10	-0.79	0.58	1.04	0.19	1.89	0.72	-0.43	1.86	-0.19	-0.94	0.55	0.79	0.09	1.49	0.32	-0.88	1.52
AUDIT = 2	0.41	-0.58	1.39	1.18	0.07	2.28	0.94	-0.70	2.58	0.31	-0.76	1.38	0.72	-0.28	1.71	0.25	-1.51	2.01
AUDIT >= 3	0.71	-0.72	2.14	3.25	1.60	4.90	2.54	0.18	4.90	0.24	-1.33	1.80	2.46	1.11	3.81	1.55	-0.81	3.92
Anxious/depressed																		
AUDIT = 1	-0.56	-1.07	-0.04	0.56	0.06	1.06	2.04	1.16	2.92	-0.61	-1.14	-0.08	0.40	-0.11	0.91	1.74	0.85	2.63
AUDIT = 2	0.70	-0.04	1.43	1.18	0.46	1.89	1.82	0.54	3.09	0.62	-0.13	1.37	0.83	0.10	1.56	1.10	-0.21	2.41
AUDIT >= 3	1.61	0.58	2.63	2.61	1.57	3.64	3.94	2.02	5.86	1.19	0.13	2.25	1.87	0.81	2.92	2.78	0.82	4.73
Somatic complaints																		
AUDIT = 1	-0.25	-0.86	0.35	0.70	0.16	1.25	0.74	-0.04	1.52	0.66	-0.11	1.42	0.28	-0.30	0.85	0.68	-0.14	1.50
AUDIT = 2	0.25	-0.63	1.12	1.02	0.22	1.83	0.80	-0.33	1.93	0.43	-0.68	1.54	0.18	-0.67	1.02	0.54	-0.65	1.73
AUDIT >= 3	2.03	0.80	3.27	3.76	2.64	4.87	1.64	0.02	3.26	1.66	0.09	3.22	2.50	1.33	3.66	1.17	-0.54	2.89
Behavior problems																		
Attention problems																		
AUDIT = 1	0.69	0.24	1.15	0.92	0.36	1.47	1.76	0.88	2.63	0.44	-0.03	0.90	0.64	0.07	1.21	1.41	0.51	2.30
AUDIT = 2	1.47	0.82	2.12	1.87	1.07	2.67	1.90	0.65	3.15	0.89	0.22	1.56	1.19	0.37	2.01	1.13	-0.16	2.41
AUDIT >= 3	3.11	2.14	4.07	2.79	1.67	3.91	4.09	2.29	5.90	2.21	1.22	3.21	1.72	0.58	2.86	2.73	0.90	4.57
Aggressive behavior																		
AUDIT = 1	1.01	0.48	1.55	1.31	0.91	1.71	0.89	0.32	1.45	1.13	0.60	1.67	1.19	0.78	1.59	0.79	0.22	1.36
AUDIT = 2	2.21	1.45	2.98	1.74	1.16	2.32	0.90	0.07	1.74	2.35	1.57	3.12	1.50	0.91	2.09	0.68	-0.18	1.54
AUDIT >= 3	3.14	4.19	1.87	2.72	1.87	3.57	1.94	0.77	3.10	3.09	1.99	4.18	2.21	1.40	3.01	1.53	0.35	2.71

Model 1 adjusted for observed covariates: maternal smoking. Model 2 adjusted for familial risk factors by a sibling control design. Model 3 adjusted for non-shared environmental risk factors by using hazardous drinking in the three months prior to pregnancy as an instrumental variable.

Table 3. Results from latent growth analyses on the effect of maternal hazardous drinking during pregnancy on child emotional and behavior problems (continued).

	Model 2: Sibling control									Model 3: Sibling and instrumental variable control								
	1.5y			3y			5y			1.5y			3y			5y		
	β	95%CI		β	95%CI		β	95%CI		β	95%CI		β	95%CI		β	95%CI	
Emotional problems																		
Emotionally Reactive																		
AUDIT = 1	0.48	-0.65	1.62	-0.05	-1.06	0.97	-1.43	-3.24	0.38	0.30	-0.88	1.49	0.18	-0.87	1.23	-1.42	-3.35	0.51
AUDIT = 2	-0.02	-1.67	1.64	0.14	-1.35	1.63	-2.20	-4.93	0.52	-0.20	0.19	-0.59	0.11	-1.43	1.64	-2.31	-5.23	0.61
AUDIT >= 3	0.52	-1.79	2.84	1.75	-0.40	3.90	-0.67	-4.48	3.14	0.21	-0.20	0.62	2.33	0.13	4.53	-0.04	-4.02	3.94
Anxious/depressed																		
AUDIT = 1	-0.54	-1.32	0.24	-0.22	-0.93	0.48	0.20	-1.14	1.53	-0.69	-1.44	0.06	-0.12	-0.81	0.57	0.65	-0.67	1.96
AUDIT = 2	0.74	-0.42	1.89	-0.14	-1.15	0.87	-1.32	-3.28	0.63	0.69	-0.42	1.79	0.03	-0.96	1.02	-0.85	-2.77	1.07
AUDIT >= 3	0.89	-0.72	2.51	-0.18	-1.67	1.31	-1.61	-4.59	1.37	0.79	-0.77	2.34	0.01	-1.45	1.46	-1.03	-3.94	1.88
Somatic complaints																		
AUDIT = 1	0.65	-0.35	1.65	-0.07	-0.97	0.83	-0.94	-2.25	0.37	0.55	-0.41	1.50	-0.04	-0.91	0.82	-0.79	-2.07	0.49
AUDIT = 2	-0.38	-1.85	1.09	-0.32	-1.68	1.04	-0.77	-2.65	1.11	-0.15	-1.56	1.25	-0.05	-1.34	1.24	-0.89	-2.73	0.96
AUDIT >= 3	0.22	-2.01	2.45	1.76	-0.17	3.70	-0.46	-3.03	2.11	0.77	-1.34	2.88	1.93	0.09	3.77	-0.64	-3.11	1.83
Behavior problems																		
Attention problems																		
AUDIT = 1	-0.21	-0.87	0.45	-0.43	-1.28	0.42	-0.42	-1.77	0.94	-0.09	-0.73	0.56	-0.30	-1.14	0.53	-0.28	-1.61	1.06
AUDIT = 2	-0.15	-1.08	0.79	-0.11	-1.35	1.13	-0.96	-2.89	0.97	-0.29	-1.21	0.62	-0.09	-1.30	1.12	-0.97	-2.89	0.95
AUDIT >= 3	-0.64	-2.05	0.76	0.43	-1.31	2.17	-2.53	-5.36	0.29	-0.25	-1.63	1.13	-0.49	-2.19	1.20	-2.15	-4.93	0.63
Aggressive behavior																		
AUDIT = 1	0.11	-0.66	0.87	0.14	-0.45	0.72	-0.56	-1.40	0.29	-0.06	-0.81	0.68	0.07	-0.51	0.64	-0.55	-1.38	0.28
AUDIT = 2	1.10	-0.04	2.24	0.63	-0.18	1.45	-1.01	-2.26	0.24	0.79	-0.30	1.88	0.38	-0.42	1.18	-1.26	-2.49	-0.03
AUDIT >= 3	0.37	-1.12	1.87	0.29	-0.94	1.51	-2.36	-4.14	-0.58	0.53	-0.94	2.00	0.45	-0.74	1.65	-2.27	-4.02	-0.52

Model 1 adjusted for observed covariates: maternal smoking. Model 2 adjusted for familial risk factors by a sibling control design. Model 3 adjusted for non-shared environmental risk factors by using hazardous drinking in the three months prior to pregnancy as an instrumental variable.