Prospective Study of Maternal Alcohol Intake During Pregnancy or Lactation and Risk of Childhood Asthma: The Norwegian Mother and Child Cohort Study

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Background: Many women drink during pregnancy and lactation despite recommendations to abstain. In animals, alcohol exposure during pregnancy and lactation influences lung and immune development, plausibly increasing risk of asthma and lower respiratory tract infections (LRTIs). Studies in humans are few.

Methods: In the Norwegian Mother and Child Cohort Study, we examined maternal alcohol intake during pregnancy and lactation in relation to risk of current asthma at 36 months (49,138 children), recurrent LRTIs by 36 months (39,791 children), and current asthma at 7 years (13,253 children). Mothers reported frequency and amount of alcohol intake each trimester and the first 3 months following delivery. We calculated adjusted relative risk (aRR), comparing children of drinkers to nondrinkers, using Generalized Linear Models.

Results: A total of 31.8% of mothers consumed alcohol during first trimester, 9.7% during second trimester, and 15.6% during third trimester. Infrequent and low-dose prenatal alcohol exposure showed a modest statistically significant inverse association with current asthma at 36 months (aRRs ~ 0.85). No association was seen with the highest alcohol intakes during the first trimester when alcohol consumption was most common. RRs of maternal alcohol intake during pregnancy with recurrent LRTIs were ~1, with sporadic differences in risk for some metrics of intake, but without any consistent pattern. For current asthma at 7 years, similar inverse associations were seen as with current asthma at 36 months but were not statistically significant. Among children breastfed throughout the first 3 months of life, maternal alcohol intake during this time was not significantly associated with any of the 3 outcomes.

Conclusions: The low levels of alcohol exposure during pregnancy or lactation observed in this cohort were not associated with increased risk of asthma or recurrent LRTIs. The slight inverse associations of infrequent or low-dose prenatal alcohol exposure with asthma may not be causal.

Key Words: Alcohol, Asthma, Breastfeeding, Pregnancy, Respiratory Tract Infections.

PUBLIC HEALTH ADVISORIES recommend that women who are pregnant or contemplating pregnancy avoid alcohol entirely (International Center for Alcohol Policies, 2009; Norwegian Health Directorate, 2005). These recommendations followed the discovery in the 1970s that high alcohol intake during pregnancy causes fetal alcohol syndrome and has been further supported by discovery of the broader range of fetal alcohol spectrum disorders (Riley et al., 2011; US Surgeon General, 2005). Similar recommendations are given to mothers who breastfeed based on the transfer of alcohol to breast milk and potential adverse influence on the breastfeeding infant (Little et al., 1989; Mennella and Beauchamp, 1991). Despite public health warnings, alcohol intake among pregnant women is common (Centers for Disease Control, 2012).

Data from animal models indicate that prenatal alcohol exposure leads to smaller, less developed lungs (Wang et al., 2007), inadequate response to neonatal hypoxic episodes (Dubois et al., 2008; Kervern et al., 2009), impaired alveolar macrophage differentiation and function (Gauthier et al., 2005b; Ping et al., 2007), reduced surfactant protein gene expression, increased oxidative stress, and altered innate immune responses, leading to increased risk of respiratory distress syndrome and respiratory infections (Gauthier et al., 2009; McGill et al., 2009; Sozo et al., 2009). Further study indicated that the increased susceptibility to infections may

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Received for publication July 8, 2013; accepted November 25, 2013.

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DOI: 10.1111/acer.12348

not persist 2 months after birth (Sozo et al., 2011). Animal studies of alcohol exposure during pregnancy or lactation have not addressed specific asthma phenotypes such as airway inflammation or hyper reactivity.

There is limited human data, mostly from adults, that alcohol intake might influence development of allergic disease (Vally and Thompson, 2003). One study reported a positive association of maternal alcohol consumption during pregnancy with total IgE measured in cord blood (Bjerke et al., 1994). With respect to asthma, 2 Danish studies found no association with prenatal alcohol exposure (Carson et al., 2012; Yuan et al., 2004), while 1 British study reported a modest inverse association of prenatal alcohol exposure with asthma at 7 years of age (Shaheen et al., 2013). Of these 3 previous studies, 1 was conducted in a high risk population of children born to mothers with asthma, while another used hospitalization for asthma as the outcome thereby excluding the majority of asthma which is less severe (Carson et al., 2012; Yuan et al., 2004). Furthermore, only 1 previous study evaluated the association of maternal alcohol intake with asthma in the offspring separately for each pregnancy trimester (Carson et al., 2012). Studies in humans also show that prenatal alcohol exposure is positively associated with severe infections leading to sepsis the first few days of life (Gauthier et al., 2004, 2005a); there are no data on lower respiratory tract infections (LRTIs). There are also no published human data on alcohol intake during lactation and risk of either of these outcomes.

Due to the persisting alcohol intake among pregnant women despite recommendation to abstain, the limited data from humans, and continued evaluation of these research questions using animal models, we examined the associations of maternal alcohol intake during pregnancy and lactation with risk of current asthma at 36 months in the Norwegian Mother and Child Cohort Study (MoBa). Because repeat episodes with LRTIs during early childhood is positively associated with asthma (Holt et al., 2010) and because 7-year follow-up information has become available on a subset of MoBa participants, recurrent LRTIs by 36 months and current asthma at 7 years were evaluated as secondary outcomes. Our study is larger than the few previous studies of maternal alcohol intake during pregnancy and risk of asthma in the offspring, providing greater power to evaluate the association with our outcomes and the low-to-moderate alcohol intake during pregnancy and lactation that persists in the population.

MATERIALS AND METHODS

Study Population

MoBa recruited pregnant women between 1999 and 2008, at approximately 18 weeks gestation, and has been described in detail (Magnus et al., 2006; Nilsen et al., 2009). Participants signed a written informed consent. Mothers could participate with more than 1 pregnancy resulting in 90,680 mothers and 108,859 children. Children not successfully linked to the Medical Birth Registry of Norway (n = 614) and children from multiple births (n = 3,801) were not eligible for analysis. The analysis of current asthma at 36 months included the 49,138 singletons whose mothers completed follow-up questionnaires at 18, 22, and 30 gestational weeks and when the child was 6 and 36 months of age. The analysis of recurrent LRTIs by 36 months included the 39,791 of the 49,138 children in the analysis of current asthma at 36 months, who also had follow-up information from the 18 months questionnaire. Among the 49,138 children in the analysis of current asthma at 36 months, we had data from the 7-year questionnaire on 13,253 children among the 19,576 who had reached 7 years. Questionnaires are available online (Norwegian Institute of Public Health, 2005). The Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research approved this study.

Exposure

Alcohol intake was queried on questionnaires returned at 18 and 30 gestational weeks, and when the child was 6 months. Mothers reported frequency of drinking and average number of drinks per time at all time points, while frequency of periodic binge drinking (defined as drinking 5 or more drinks per sitting) was reported at 18 and 30 gestational weeks. On the 18 gestational week questionnaire, the mother reported alcohol intake up to that time. At 30 gestational weeks, the mother reported alcohol intake during 3 periods: 0 to 12 weeks, 13 to 24 weeks, and 25+ weeks. When the child was 6 months, the mother reported alcohol intake during the last 3 months of pregnancy and the first 3 months following delivery. Where the mother had reported alcohol intake for the same time period in 2 consecutive questionnaires, we used the highest reported value.

We created exposure variables for frequency of alcohol intake in the first, second, and third trimesters (never, less than once a month, and once a month or more), average number of drinks per time each trimester (none, <1, 1 to 2, 3 to 4, and 5+ for first trimester; none, <1 and 1+ for second and third trimesters) and total number of drinks consumed throughout pregnancy (none, 1 to 2, 3 to 10, and 11+). Frequency of periodic binge drinking (defined as drinking 5 or more drinks per sitting) was only evaluated as an exposure during first trimester (categorized as never, less than once a month, and once a month or more), as too few mothers reported this in the second and third trimesters. Maternal alcohol intake during lactation was categorized according to maternal frequency of drinking during the first 3 months following delivery (none, less than once a month, 1 to 3 times per week, more than 3 times per week), average number of drinks per time the first 3 months following delivery (none, <1, 1 to 2, 3 to 4, and 5+), total drinks consumed the first 3 months following delivery (none, 1 to 2, 3 to 10, 11+) and alcohol intake during and after pregnancy (none, during pregnancy only, after pregnancy only, during and after pregnancy).

Outcome

The primary outcome was current asthma at 36 months, based on maternal "yes" in response to a question about current asthma in combination with reported use of an inhaled asthma medication in the past 12 months on the 36-month questionnaire. Inhaled asthma medications included maternal report of inhaled glucocorticoids and/or beta-2 agonists. These are the primary medications for treatment of asthma in young children in Norway. A secondary outcome was recurrent LRTIs by 36 months, categorized as 3 or more LRTIs during the first 36 months of life (Ten Brinke et al., 2005). LRTIs included maternal report of pneumonia, bronchitis, and/or respiratory syncytial virus when the child was 6 and 18 months, and maternal report of pneumonia and/or bronchitis at 36 months. Mothers reported frequency

of LRTIs during the following periods of the child's life: up to 6 months, between 6 and 18 months, and between 18 and 36 months. Current asthma at 7 years was classified based on maternal "yes" in response to the child having experienced asthma symptoms in the past year in combination with maternal report that the child had used a medication for asthma in the past 12 months on the 7-year questionnaire.

Covariates

Based on the literature review, factors that could potentially influence maternal alcohol intake and subsequent risk of asthma and LRTIs were identified as potential confounders. We included the following covariates: maternal age at delivery, parity, years of education, income, pre-pregnancy body mass index (BMI; weight (kg)/height $(m)^2$; classified according to WHO guidelines [World Health Organization, 2011]), smoking during pregnancy, folate supplement intake during pregnancy, maternal history of asthma, breastfeeding (evaluated for both the first 3 months and the first 6 months of the child's life), and maternal smoking when the child was 6 and 36 months. We classified breastfeeding into none, any, and all months. Adverse pregnancy outcomes were not included as covariates because they could be on the causal pathway between maternal alcohol intake and early childhood respiratory disorders (Jaakkola et al., 2006; Odendaal et al., 2009; Patelarou et al., 2009; Patra et al., 2011).

Statistical Analyses

We examined the associations of maternal alcohol intake during pregnancy with current asthma at 36 months, recurrent LRTIs by 36 months, and current asthma at 7 years. Among children breastfed throughout the first 3 months of life, we evaluated associations of maternal alcohol intake the first 3 months following delivery, in addition to alcohol intake both during and after pregnancy, with asthma and recurrent LRTIs (n = 30,030 for analysis of current asthma at 36 months, n = 24,430 for analysis of recurrent LRTIs by 36 months and n = 8,335 for analysis of current asthma at 7 years). We used Generalized Linear Models, specifying a binary outcome distribution and a log-link function (i.e., log binomial regression), calculating relative risk (RR), and 95% confidence intervals (CI), comparing children of drinkers to those of nondrinkers. Robust cluster variance estimation was employed to account for siblings. Multivariable regression models were used to calculate adjusted RR (aRR) adjusting for all covariates identified. Covariates were categorized as indicated in Table 1 and entered using dummy variables. There were 8 to 17% of observations missing information on 1 or more covariates in the multivariable analyses. Therefore, we used multiple imputation by chained equations, imputing 10 data sets, to evaluate any influence of missing covariate information on the associations (Sterne et al., 2009). Sensitivity analyses were conducted excluding mothers who did not drink alcohol the last 3 months before pregnancy. We evaluated multiplicative interaction by maternal smoking on the associations of maternal alcohol intake with the outcomes of interest. We further evaluated multiplicative interaction by preterm delivery (<37 gestational weeks) on the association of maternal alcohol intake the first 3 months following delivery with the outcomes of interest. To evaluate whether selection bias due to participating mothers in MoBa not responding to follow-up questionnaires might have influenced the observed associations, we used inverse probability weighting (Hernan et al., 2004; Sheikh, 2007). Weights were created based on the probability of having the necessary follow-up information to be included in the respective analyses among eligible MoBa children. All analyses were conducted using STATA version 12 (Stata Corporation, College Station, TX).

RESULTS

A total of 31.8% of mothers consumed alcohol during first trimester, 9.7% during second trimester, and 15.6% during third trimester. Among mothers who consumed alcohol first trimester, 68.9% consumed alcohol less than once a month and 80.8% consumed an average of 2 or fewer drinks per time. Only 7.7% of mothers consumed 11 drinks or more throughout pregnancy. Mothers with the highest alcohol consumption (11 or more drinks throughout pregnancy) were more likely to be older, smokers, have higher parity, have higher education, have higher income, and normal BMI, and less likely to take folic acid supplements, as compared to nondrinkers and those who consumed less (Table 1). Mothers with the highest alcohol intake during pregnancy were also more likely to smoke when the child was 6 or 36 months and less likely to breastfeed throughout the first 6 months of the child's life (Table 1).

Current asthma at 36 months was reported for 5.8% of children. Examining frequency of drinking each trimester, children of mothers who drank less than once per month and children of mothers who drank once per month or more had lower risk of asthma relative to nondrinkers (Table 2). For average number of drinks per time during the first trimester, the RR of asthma was reduced in the 2 lowest consumption categories (<1 drink, aRR 0.90 [95% CI: 0.81, 1.00], 1 to 2 drinks aRR 0.82 [95% CI: 0.71, 0.94]), but not in the 2 higher categories (3 to 4 drinks aRR 1.13 [95% CI: 0.93, 1.36], 5+ drinks aRR 0.98 [95% CI: 0.78, 1.22]; Table 2). Frequency of periodic binge drinking during first trimester (consuming 5 drinks or more per sitting) was not associated with asthma at 36 months. Among children breastfed throughout the first 3 months of life, maternal alcohol intake the first 3 months following delivery was not associated with asthma at 36 months (Table 3).

Recurrent LRTIs by 36 months were reported for 4.4% of children. Most associations of maternal alcohol intake during pregnancy with recurrent LRTIs were ~1.0, with sporadic modest increases in risk, but without dose–response (Table 4). For example, for average number of drinks per time during first trimester, the aRR for 3 to 4 drinks was 1.28 (95% CI: 1.01, 1.61), but for 5+ drinks the aRR was 0.90 (95% CI: 0.65, 1.23; Table 4), when compared with none. The association of binge drinking once a month or more first trimester with recurrent LRTIs was aRR 0.73 (95% CI: 0.53, 1.00; Table 4). Among children breastfed throughout the first 3 months of life, maternal alcohol intake during the first 3 months following delivery was not associated with recurrent LRTIs (Table S1).

Current asthma at 7 years was reported for 5.2% of children. Overall, the observed associations of maternal alcohol intake during pregnancy with current asthma at 7 years were similar to what was seen for current asthma at 36 months but not statistically significant (Table S2). Among children breastfed throughout the first 3 months of life, maternal alcohol intake the first 3 months after delivery was not statis-

Table 1. Maternal Characteristics by Total Number of Drinks Consumed During Pregnancy (N = 49,138)

Characteristic	No drinks N = 27,735 (%)	1 to 2 drinks N = 4,587 (%)	3 to 10 drinks N = 7,007 (%)	11 or more drinks N = 3,304 (%)
Maternal age at delivery				
<25	10.1	6.7	5.1	6.3
25 to 29	35.4	33.2	29.1	24.0
30 to 34	39.0	42.6	44.1	41.0
35 and older	15.5	17.5	21.7	28.7
Maternal parity				
Primiparous	47.6	51.9	50.2	49.2
1	35.1	31.9	32.5	31.8
2	13.6	13.3	14.0	14.9
3 or more	3.7	2.9	3.3	4.2
Maternal education				
Less than high school	5.3	3.6	3.0	3.8
High school	27.4	20.2	21.1	23.9
Up to 4 years of college	44.3	44.4	44.6	40.1
More than 4 years of college	23.0	32.0	31.3	32.3
Maternal income				
<200,000 NOK	26.9	21.7	20.2	21.5
200,000 to 399,000 NOK	62.3	62.1	62.9	58.8
400,000 NOK or more	10.9	16.2	16.9	19.6
Maternal pre-pregnancy body mass index				
Underweight (<18.5)	2.9	2.8	2.9	2.6
Normal weight (18.5 to 24.9)	65.1	69.8	70.0	70.9
Overweight (25 to 29.9)	22.3	19.7	20.4	20.7
Obese (≥30)	9.7	7.7	6.8	5.8
Maternal smoking during pregnancy				
No	93.8	93.9	93.2	87.2
Occasionally	1.1	1.5	2.0	3.5
Daily	5.1	4.6	4.8	9.4
Folate intake during pregnancy				
No	11.4	9.5	11.7	13.4
Only first trimester	25.8	23.8	23.7	21.3
Only after first trimester	7.4	7.5	7.7	9.4
Both first trimester and after	55.4	59.2	57.0	56.0
Maternal asthma				
No	92.6	92.5	93.3	93.0
Yes	7.4	7.5	6.7	7.0
Breastfeeding 0 to 6 months[a]				
None	2.7	1.8	2.1	1.7
Any	51.0	52.4	54.5	59.5
All months	46.3	45.8	43.4	38.8
Mother smoking when the child is 6 or 36 months				
No	86.0	84.5	81.8	72.5
Occasionally	3.8	5.6	7.0	9.4
Daily	10.2	9.9	11.3	18.2

[a]Children defined as having received any breastfeeding were those who had been given at least some breast milk the first 6 months of life but who had also been given another source of milk. Children defined as being breastfed all months were those who had been given breast milk each month during the first 6 months of the child's life and who had not been given any other source of milk.

tically significantly associated with asthma at 7 years (Table S3).

The complete case and multiple imputation analyses yielded similar results. Sensitivity analyses limited to children of mothers who had consumed alcohol the last 3 months before pregnancy did not change the results. There was no indication of an interaction by maternal smoking on the associations of maternal alcohol intake during pregnancy or lactation with any of the respiratory outcomes of interest (p-values for interaction >0.1). There was no indication of an interaction by preterm delivery on the association of maternal alcohol intake during lactation with any of the respiratory outcomes of interest (p-value for interaction >0.1). Results of inverse probability weighting did not provide evidence that selection bias due to missing questionnaire follow-up data influenced the associations examined (Tables 2–4).

DISCUSSION

Overall, we observed no appreciable association between maternal alcohol intake during pregnancy and lactation with current asthma at 36 months and 7 years, with a modest inverse association of infrequent and low-dose alcohol intake during pregnancy with current asthma at 36 months. The association between maternal alcohol intake during pregnancy and lactation with recurrent LRTIs by 36 months was also overall null, with sporadic differences in risk for some

Table 2. Association of Maternal Alcohol Intake During Pregnancy with Current Asthma at 36 Months of Age ($N = 49,138$)

Exposure	*n*	Freq. asthma	Crude RR (95% CI)	aRR (95% CI)[a]	aRR (95% CI)[b]	aRR (95% CI)[b,c]
Frequency of drinking first trimester						
Never	32,663	6.1	1	1	1	1
Less than once a month	10,507	5.4	0.89 (0.81, 0.98)	0.91 (0.83, 1.01)	0.92 (0.84, 1.01)	0.91 (0.82, 1.00)
Once a month or more	4,741	5.0	0.82 (0.72, 0.94)	0.86 (0.75, 0.99)	0.88 (0.77, 1.00)	0.86 (0.75, 0.99)
Frequency of drinking second trimester						
Never	39,530	5.9	1	1	1	1
Less than once a month	2,969	5.0	0.84 (0.71, 0.99)	0.83 (0.70, 1.00)	0.88 (0.75, 1.03)	0.87 (0.74, 1.03)
Once a month or more	1,268	4.4	0.74 (0.57, 0.97)	0.78 (0.60, 1.03)	0.78 (0.60, 1.02)	0.77 (0.58, 1.02)
Frequency of drinking third trimester						
Never	41,061	6.0	1	1	1	1
Less than once a month	5,125	4.9	0.82 (0.72, 0.93)	0.83 (0.73, 0.95)	0.84 (0.74, 0.96)	0.84 (0.73, 0.95)
Once a month or more	2,489	4.5	0.75 (0.62, 0.90)	0.78 (0.64, 0.95)	0.80 (0.66, 0.97)	0.80 (0.66, 0.97)
Number of drinks per time first trimester						
None	32,663	6.1	1	1	1	1
<1	7,901	5.2	0.85 (0.76, 0.94)	0.90 (0.81, 1.00)	0.90 (0.81, 1.00)	0.88 (0.79, 0.98)
1 to 2	4,310	4.8	0.78 (0.68, 0.91)	0.80 (0.69, 0.93)	0.82 (0.71, 0.94)	0.82 (0.71, 0.96)
3 to 4	1,593	6.6	1.08 (0.89, 1.31)	1.12 (0.92, 1.37)	1.13 (0.93, 1.36)	1.11 (0.92, 1.35)
5 or more	1,307	6.2	1.01 (0.82, 1.26)	0.97 (0.77, 1.21)	0.98 (0.78, 1.22)	0.94 (0.75, 1.19)
Number of drinks per time second trimester						
None	39,530	5.9	1	1	1	1
<1	3,510	4.8	0.82 (0.70, 0.96)	0.83 (0.71, 0.98)	0.84 (0.72, 0.98)	0.82 (0.70, 0.96)
1 to 2 or more	1,131	4.9	0.83 (0.64, 1.08)	0.85 (0.64, 1.11)	0.87 (0.68, 1.12)	0.89 (0.68, 1.16)
Number of drinks per time third trimester						
None	41,061	6.0	1	1	1	1
<1	5,067	4.9	0.81 (0.71, 0.92)	0.83 (0.72, 0.95)	0.85 (0.74, 0.96)	0.84 (0.73, 0.96)
1 to 2 or more	2,765	4.7	0.78 (0.65, 0.92)	0.79 (0.66, 0.95)	0.78 (0.66, 0.93)	0.79 (0.65, 0.94)
Total drinks entire pregnancy						
None	27,735	6.1	1	1	1	1
1 to 2	4,587	5.7	0.93 (0.82, 1.06)	0.96 (0.85, 1.10)	0.97 (0.85, 1.10)	0.96 (0.84, 1.10)
3 to 10	7,007	4.9	0.80 (0.71, 0.90)	0.84 (0.74, 0.94)	0.84 (0.74, 0.95)	0.83 (0.73, 0.95)
11 or more	3,304	5.0	0.82 (0.70, 0.96)	0.83 (0.70, 0.98)	0.84 (0.72, 0.98)	0.84 (0.71, 0.98)
Frequency of binge drinking first trimester						
Never	41,188	5.8	1	1	1	1
Less than once a month	5,364	6.0	1.04 (0.93, 1.16)	1.06 (0.94, 1.19)	1.06 (0.95, 1.19)	1.06 (0.95, 1.20)
Once a month or more	1,619	5.5	0.95 (0.77, 1.17)	0.96 (0.77, 1.19)	0.97 (0.79, 1.20)	0.94 (0.76, 1.16)

aRR, adjusted relative risk.

Multivariable analyses adjusted for maternal age at delivery, maternal education, maternal parity, maternal pre-pregnancy body mass index, maternal income, maternal smoking during pregnancy, maternal folate intake during pregnancy, maternal asthma, breastfeeding up to 6 months of age, and maternal smoking when the child is 6 and/or 36 months.

[a]Complete case analyses. Between 8 and 17% of observations had missing information on 1 or more of covariates in the multivariable analyses.

[b]Multiple imputation analyses. Multiple imputation of covariates in multivariable analyses conducted using chained equations. A total of 10 imputed data sets generated. Total number of observations in all multivariable analyses is 49,138.

[c]Inverse probability weighting. Inverse probability weighting conducted to examine whether selection bias due to mothers not returning the necessary questionnaires to be included in the current analysis could have influenced the observed associations. Weights were generated based on the probability of having the necessary follow-up information among all eligible children in the Norwegian Mother and Child Cohort Study.

metrics of intake of maternal alcohol intake during pregnancy, but without a consistent pattern.

There are few human data on maternal alcohol intake during pregnancy and risk of asthma in the offspring. A population-based Danish study reported no association of maternal alcohol intake during pregnancy with hospitalization for asthma in the offspring (307 asthma cases; Yuan et al., 2004). Findings from a different Danish study of 411 term children born to mothers with a history of asthma found no association of maternal alcohol intake during pregnancy with wheezing, asthma, or neonatal lung function in the offspring (Bisgaard et al., 2009; Carson et al., 2012). Similar to our findings, a slight inverse association of maternal alcohol intake during pregnancy and childhood asthma was observed in a British birth cohort with a sample size of about 7,600 in most analyses (Shaheen et al., 2013). Like these previous human studies, our larger study found no increased risk of asthma in relation to modest prenatal alcohol exposure. We were further able to show that maternal alcohol intake during lactation showed no association with childhood asthma.

Two human studies have suggested that prenatal alcohol exposure might increase the risk of severe infections leading to sepsis during the first few days of life (Gauthier et al., 2004, 2005a), but they did not isolate respiratory infections. We did not find consistent evidence that prenatal alcohol exposure was positively associated with recurrent LRTIs by 36 months. This might be because of the modest prenatal alcohol exposure in the current study, or because the increased risk of infections might be transient as suggested by some animal data (McGill et al., 2009; Sozo et al., 2011). We are not aware of any prior human studies of maternal

Table 3. Association of Maternal Alcohol Intake During Breastfeeding with Current Asthma at 36 Months of Age Among Children Breastfed Between 0 and 3 Months of Age (N = 30,030)

Exposure	n	Freq. asthma	Crude RR (95% CI)	aRR (95% CI)[a]	aRR (95% CI)[b]	aRR (95% CI)[b,c]
Frequency of drinking when the child is aged 0 to 3 months						
None	16,535	5.7	1	1	1	1
Less than once a month	6,449	5.3	0.93 (0.83, 1.05)	1.00 (0.87, 1.14)	0.99 (0.87, 1.12)	1.00 (0.87, 1.13)
1 to 3 times per week	3,653	5.0	0.88 (0.75, 1.02)	0.99 (0.83, 1.18)	0.96 (0.81, 1.13)	0.98 (0.82, 1.16)
More than 3 times per week	1,549	4.8	0.84 (0.67, 1.06)	0.96 (0.75, 1.24)	0.95 (0.75, 1.20)	0.94 (0.73, 1.20)
Number of drinks per time when the child is aged 0 to 3 months						
None	16,535	5.7	1	1	1	1
<1	3,367	5.0	0.89 (0.76, 1.05)	1.00 (0.84, 1.19)	0.99 (0.84, 1.17)	0.98 (0.83, 1.17)
1 or 2	7,742	5.0	0.89 (0.79, 1.00)	0.95 (0.84, 1.09)	0.96 (0.84, 1.09)	0.97 (0.85, 1.10)
3 or 4	662	5.6	0.99 (0.72, 1.37)	1.05 (0.75, 1.46)	0.98 (0.71, 1.35)	1.02 (0.73, 1.42)
5 or more	385	6.1	1.08 (0.73, 1.62)	1.09 (0.71, 1.68)	1.04 (0.70, 1.54)	1.00 (0.66, 1.51)
Total drinks consumed when the child is aged 0 to 3 months						
None	16,535	5.7	1	1	1	1
1 to 2	2,026	5.1	0.90 (0.74, 1.10)	0.99 (0.79, 1.23)	1.01 (0.83, 1.24)	0.99 (0.81, 1.22)
3 to 10	7,891	5.1	0.91 (0.81, 1.02)	1.00 (0.88, 1.14)	0.97 (0.86, 1.10)	0.99 (0.87, 1.12)
11 or more	1,524	5.2	0.91 (0.73, 1.14)	0.98 (0.76, 1.26)	1.05 (0.84, 1.32)	1.07 (0.85, 1.36)
Alcohol intake during and after pregnancy						
No alcohol intake during or after pregnancy	11,672	5.7	1	1	1	1
Alcohol intake during pregnancy only	3,737	5.5	0.95 (0.82, 1.11)	1.09 (0.91, 1.32)	0.95 (0.81, 1.11)	0.93 (0.79, 1.10)
Alcohol intake after pregnancy only	4,779	5.6	0.98 (0.85, 1.13)	1.14 (0.96, 1.35)	1.02 (0.89, 1.18)	1.02 (0.88, 1.19)
Alcohol intake during and after pregnancy	6,959	4.7	0.82 (0.72, 0.94)	0.91 (0.76, 1.07)	0.87 (0.76, 0.99)	0.87 (0.76, 1.00)

aRR, adjusted relative risk.

Multivariable analyses adjusted for maternal age at delivery, maternal education, maternal parity, maternal pre-pregnancy body mass index, maternal income, maternal smoking during pregnancy, maternal folate intake during pregnancy, maternal asthma, alcohol intake during pregnancy, and maternal smoking when the child is 6 and/or 36 months.

[a]Complete case analyses. Between 8 and 17% of observations had missing information on 1 or more of covariates in the multivariable analyses.

[b]Multiple imputation analyses. Multiple imputation of covariates in multivariable analyses conducted using chained equations. A total of 10 imputed data sets generated. Total number of observations in all multivariable analyses is 30,030.

[c]Inverse probability weighting. Inverse probability weighting conducted to examine whether selection bias due to mothers not returning the necessary questionnaires to be included in the current analysis could have influenced the observed associations. Weights were generated based on the probability of having the necessary follow-up information among all eligible children in the Norwegian Mother and Child Cohort Study.

alcohol intake during breastfeeding and risk of early childhood LRTIs.

The slight inverse association of prenatal alcohol exposure with asthma we identified may not be causal as it was seen at very low intakes levels. Although we considered a large number of covariates, and the crude and adjusted measures of associations were similar, unmeasured confounding by maternal characteristics related to low levels of alcohol intake that are difficult to assess may have influenced our results. Sensitivity analysis excluding children of mothers who did not consume alcohol the last 3 months before pregnancy yielded similar results. The modest inverse association of infrequent and low-dose alcohol intake during pregnancy with current asthma at 36 months was therefore apparently not due to an abstainer effect. Notably, women who reported the highest alcohol intake during pregnancy in MoBa were older, more educated and were more likely to be normal weight, which is similar to the characteristics of mothers who had the highest alcohol consumption in the British study (Shaheen et al., 2013). Similar to the pattern in our study, the Danish National Birth Cohort reported that binge drinking before a woman was aware that she was pregnant was more common among women with higher education and occupational status (Strandberg-Larsen et al., 2008). These women might reflect a group of more confident mothers who might be less likely to report that their child has asthma for the same presentation of symptoms that would cause another mother to bring the child to a doctor and thus get labeled with this diagnosis. However, these are only speculations that cannot be addressed using the current data. In the recent British study, a Mendelian randomization analysis based on alcohol dehydrogenase (*ADH*)*1B* genotype supports our assertion that the slight inverse association observed in that study, similar to ours, is unlikely to be causal (Shaheen et al., 2013). The authors also conclude based on this genetic analysis that they were unlikely to have missed a positive association with maternal alcohol intake due to bias. We do not have the genotype information to repeat this analysis in our data.

In adults, alcohol intake has been showed to have a j-shaped association with lung function (Sisson et al., 2005; Tabak et al., 2001). A modest alcohol intake has therefore been associated with better lung function. Despite this beneficial association with low-dose alcohol intake in adults, we remain cautious in our interpretation of the observed inverse association of infrequent and low-dose prenatal alcohol exposure with asthma development.

Like all studies, our study has limitations. Knowing the recommendations not to consume alcohol during pregnancy or lactation, women may underreport alcohol intake.

Table 4. Association of Maternal Alcohol Intake During Pregnancy with Recurrent Lower Respiratory Tract Infections (LRTIs) by 36 Months of Age (N = 39,791)

Exposure	n	Freq. recurrent LRTIs	Crude RR (95% CI)	aRR (95% CI)[a]	aRR (95% CI)[b]	aRR (95% CI)[b,c]
Frequency of drinking first trimester						
Never	26,311	4.4	1	1	1	1
Less than once a month	8,645	4.6	1.03 (0.92, 1.16)	1.04 (0.92, 1.17)	1.05 (0.94, 1.18)	0.99 (0.86, 1.14)
Once a month or more	3,863	3.7	0.84 (0.71, 1.00)	0.88 (0.73, 1.06)	0.86 (0.72, 1.03)	0.79 (0.64, 0.97)
Frequency of drinking second trimester						
Never	31,694	4.3	1	1	1	1
Less than once a month	2,620	4.9	1.15 (0.96, 1.38)	1.12 (0.93, 1.35)	1.15 (0.96, 1.37)	1.11 (0.90, 1.36)
Once a month or more	1,134	5.1	1.19 (0.91, 1.55)	1.16 (0.87, 1.53)	1.15 (0.88, 1.49)	1.19 (0.88, 1.60)
Frequency of drinking third trimester						
Never	32,862	4.4	1	1	1	1
Less than once a month	4,383	4.5	1.03 (0.89, 1.20)	1.03 (0.88, 1.21)	1.02 (0.88, 1.20)	0.97 (0.81, 1.15)
Once a month or more	2,190	4.4	1.01 (0.82, 1.24)	1.01 (0.81, 1.25)	0.99 (0.80, 1.23)	1.02 (0.80, 1.29)
Number of drinks per time first trimester						
None	26,311	4.4	1	1	1	1
<1	6,495	4.4	1.00 (0.88, 1.13)	0.99 (0.86, 1.13)	1.02 (0.90, 1.16)	0.98 (0.83, 1.15)
1 to 2	3,588	4.0	0.89 (0.74, 1.06)	0.93 (0.78, 1.12)	0.93 (0.78, 1.11)	0.93 (0.75, 1.16)
3 to 4	1,299	5.3	1.20 (0.94, 1.53)	1.29 (1.01, 1.66)	1.28 (1.01, 1.61)	1.18 (0.88, 1.58)
5 or more	1,037	4.0	0.90 (0.66, 1.22)	0.96 (0.71, 1.31)	0.90 (0.65, 1.23)	0.83 (0.55, 1.23)
Number of drinks per time second trimester						
None	31,694	4.3	1	1	1	1
<1	3,042	5.1	1.21 (1.02, 1.42)	1.20 (1.01, 1.42)	1.18 (0.99, 1.40)	1.16 (0.95, 1.41)
1 to 2 or more	1,017	4.5	1.05 (0.78, 1.41)	1.01 (0.74, 1.38)	1.00 (0.75, 1.33)	1.02 (0.72, 1.46)
Number of drinks per time third trimester						
None	32,862	4.4	1	1	1	1
<1	4,294	4.6	1.04 (0.89, 1.21)	1.05 (0.90, 1.23)	1.03 (0.89, 1.20)	0.97 (0.82, 1.15)
1 to 2 or more	2,444	4.4	1.00 (0.82, 1.21)	0.99 (0.81, 1.22)	0.94 (0.77, 1.15)	0.94 (0.75, 1.18)
Total drinks entire pregnancy						
None	22,217	4.4	1	1	1	1
1 to 2	3,690	4.2	0.97 (0.82, 1.15)	0.93 (0.78, 1.11)	0.98 (0.82, 1.17)	0.91 (0.74, 1.11)
3 to 10	5,881	4.6	1.05 (0.92, 1.20)	1.10 (0.96, 1.27)	1.07 (0.93, 1.22)	1.03 (0.87, 1.22)
11 or more	2,784	3.8	0.88 (0.72, 1.08)	0.89 (0.73, 1.10)	0.88 (0.73, 1.07)	0.85 (0.67, 1.08)
Frequency of binge drinking first trimester						
Never	33,449	4.4	1	1	1	1
Less than once a month	4,313	4.5	1.02 (0.88, 1.18)	1.07 (0.92, 1.25)	1.05 (0.91, 1.22)	1.07 (0.88, 1.29)
Once a month or more	1,247	3.2	0.72 (0.53, 0.99)	0.76 (0.55, 1.05)	0.73 (0.53, 1.00)	0.66 (0.45, 0.99)

aRR, adjusted relative risk.

Multivariable analyses adjusted for maternal age at delivery, maternal education, maternal parity, maternal pre-pregnancy body mass index, maternal income, maternal smoking during pregnancy, maternal folate intake during pregnancy, maternal asthma, breastfeeding up to 6 months of age, and maternal smoking when the child is 6 and/or 36 months.

[a]Complete case analyses. Between 8 and 17% of observations had missing information on 1 or more of covariates in the multivariable analyses.

[b]Multiple imputation analyses. Multiple imputation of covariates in multivariable analyses conducted using chained equations. A total of 10 imputed data sets generated. Total number of observations in all multivariable analyses is 39,791.

[c]Inverse probability weighting. Inverse probability weighting conducted to examine whether selection bias due to mothers not returning the necessary questionnaires to be included in the current analysis could have influenced the observed associations. Weights were generated based on the probability of having the necessary follow-up information among all eligible children in the Norwegian Mother and Child Cohort Study.

However, 1 study found that average alcohol consumption during pregnancy could be obtained by self-report through questionnaires with reasonable validity when compared to a daily diary (Kesmodel and Olsen, 2001). In MoBa, we had the opportunity to examine the consistency of maternal report of alcohol intake. For example, comparing maternal report of alcohol intake during third trimester, which was reported both at 30 gestational weeks and when the child was 6 months, we saw that 78% reported the same amount of alcohol intake in a consecutive questionnaire. Furthermore, any underreporting would need to be conditional upon the child's risk of developing the respiratory outcomes of interest to bias the results. Our ability to evaluate maternal alcohol intake during breastfeeding might be weakened, as women might time their alcohol intake when they know it will be several hours until next feeding, in order to reduce exposure to the child. We have no information on the timing of alcohol intake relative to breastfeeding.

We recognize the limitation of questionnaire-based outcomes. Asthma classification at 36 months is likely to be influenced by wheezing symptoms due to LRTIs. However, the prevalence of current asthma at 36 months in MoBa (5.8%) is lower than the prevalence of an early childhood wheezing episode (40.8%). This suggests that the diagnosis of asthma is not being applied indiscriminately to children with early wheezing. We also note that among children who have information from the 7-year follow-up, 42.7% of children whose mothers reported asthma at 36 months still had current asthma at 7 years. We have also previously demon-

strated that mothers report that the child took asthma medications at age 7 in MoBa had high validity when compared to the records of filling a prescription for asthma medication in the Norwegian Prescription Registry (Furu et al., 2011). Furthermore, maternal report of LRTIs is also likely to be subject to misclassification. Mothers were not asked about doctor diagnosis. They were asked about hospital admission for LRTIs, but we could not determine how many infections resulted in the child being admitted to a hospital across the various questionnaires because of the possibility of double counting. Thus we could not use these variables to identify recurrent LRTIs. In addition, by limiting the outcome to hospitalized LRTIs, we would have missed episodes which were likely to be LRTIs but less severe and thus managed by primary care physicians. Another concern is whether the mother is able to distinguish between upper respiratory tract infections and LRTIs. Based on maternal report, 97.9% of children had 3 or more colds in the first 36 months, 10% of children had 3 or more throat infections in the first 36 months, while 16.4% had 3 or more ear infections in the first 36 months. As only 4.4% of children had 3 or more LRTIs, this suggests that maternal report of LRTIs is capturing something more severe/rare than common upper respiratory tract infections. We did not have information about use of antibiotics for LRTIs. However, use of antibiotics would only cover bacterial infections, and because many LRTIs are viral in origin (Mermond et al., 2012), it might not be advisable to use this restriction in the definition of this classification. Finally, because of the prospective data collection, any outcome misclassification is not likely to be differential by maternal alcohol intake and would therefore likely bias the results towards the null.

Another limitation is potential bias due to loss to follow-up. In the current study, mothers of children with the necessary follow-up information at 36 months were older, had a lower parity, higher education, and were more likely to consume alcohol during the first trimester. However, using inverse probability weighting (Hernan et al., 2004; Sheikh, 2007), we show that the likelihood of severe selection bias is low, as the nonweighted and weighted associations were similar (Tables 2–4). In addition, we have previously reported that the prevalence of prescriptions for asthma medication at age 7 were comparable among children in MoBa whose mothers completed the 7-year questionnaire and those who did not (Furu et al., 2011).

Strengths of the current study include a large population-based sample, prospective data collection, consideration of a numerous covariates, opportunity to examine trimester specific and breastfeeding exposure windows, the use of multiple imputation to avoid potential bias due to missing data, and the use of inverse probability weighting to evaluate selection bias.

In conclusion, we found no consistent evidence that maternal alcohol intake during pregnancy or lactation increased the risk of asthma or LRTIs in the offspring. The observed slight inverse association of infrequent and low-dose prenatal alcohol exposure with asthma is most likely noncausal. These results suggest that the levels of alcohol intake during pregnancy or lactation that persist in the population despite health recommendations to abstain are not contributing to the high rates of childhood asthma seen in many high income countries. However, there are other outcomes for which even low levels of prenatal alcohol exposure have been implicated (Andersen et al., 2012; Patra et al., 2011; Valenzuela et al., 2012), and thus these results do not imply that existing recommendations against alcohol intake during pregnancy and breastfeeding should be modified. Nonetheless, these data might provide some reassurance to mothers of children who develop asthma, who might have consumed a small amount of alcohol during pregnancy.

ACKNOWLEDGMENTS

The authors are grateful to all the families participating in the ongoing Norwegian Mother and Child Cohort Study. The Norwegian Mother and Child Cohort Study is supported by NIH (NIH/NIEHS contract number N01-ES-75558, NIH/NINDS grant no.1 UO1 NS 047537-01 and grant no.2 UO1 NS 047537-06A1) and the Norwegian Research Council/FUGE (grant number 151918/S10). MCM is also supported by the Norwegian Extra-Foundation for Health and Rehabilitation (grant number 2011.2.0218). This research was supported in part by the Intramural Program of the National Institutes of Health, National Institute of Environmental Health Sciences.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Association of maternal alcohol intake during breastfeeding with recurrent lower respiratory tract infections by 36 months among children breastfed between 0 and 3 months of age (N = 24,430).

Table S2. Association of maternal alcohol intake during pregnancy with current asthma at 7 years of age (n = 13,253).

Table S3. Association of maternal alcohol intake during breastfeeding with asthma at age 7 among children breastfed between 0 and 3 months of age (N = 8,335).