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Original article

Alcohol consumption among first-time mothers and the risk of preterm birth: a cohort study

Maria T.G. Dale PhD [a,*], Leiv S. Bakketeig PhD [a], Per Magnus PhD [a,b]

[a] Department of Genes and Environment, Norwegian Institute of Public Health, Oslo, Norway
[b] Department of Medicine, University of Oslo, Oslo, Norway

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ABSTRACT

Purpose: Our aim was to explore the association between alcohol consumption, before and during pregnancy, and the risk of preterm birth among 46,252 primiparous mothers.
Methods: We obtained information on alcohol consumption from questionnaire responses at pregnancy week 15 from the prospective, observational Norwegian Mother and Child Cohort Study. Data on preterm birth, categorized as delivery before gestation week 37, were retrieved from the Medical Birth Registry of Norway.
Results: Among the participants, 91% consumed alcohol before pregnancy and fewer than 20% reported consuming alcohol during pregnancy. The adjusted odds ratio (aOR) for preterm birth associated with prepregnancy alcohol consumption was 0.81 (95% confidence interval [CI], 0.70–0.95). We did not find a risk reduction for overall drinking during pregnancy, aOR = 1.03 (95% CI, 0.90–1.19). However, dose-response analyses showed tendencies toward adverse effects when drinking 1–3 times per month during the first 15 weeks of pregnancy, aOR = 1.51 (95% CI, 1.14–2.00).
Conclusions: We did not find any effects of alcohol consumption during pregnancy, whereas pre-pregnancy drinking was associated with reduced risk of preterm birth. Residual confounding may have influenced the risk estimates, especially before pregnancy, as nondrinkers have lower socioeconomic status and well-being than drinkers.

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Introduction

Most public health and medical authorities advise total abstinence of alcohol both during pregnancy and when contemplating pregnancy [1,2]. This advice is an invocation of the precautionary principle since existing evidence is inconclusive as to whether there is a threshold dose below which alcohol intake is safe. Overall, there are few studies that indicate adverse effects of low levels of alcohol intake [3,4], whereas there is broad consensus in the literature that abusive and heavy drinking has a teratogenic effect on the fetus, such as the risk of fetal alcohol syndrome, growth restriction, birth defects, and neurodevelopmental problems [5–7].

A concern has been that alcohol intake may increase the risk of preterm birth. Preterm birth is among the leading causes of child mortality, to which 35% of neonatal deaths on a global basis are estimated to be attributable [8,9]. In 2013, about 5.8% of all births in Norway were preterm, as defined by the World Health Organization as delivery before 37 weeks (259 days) of gestation. This rate is similar to the rest of Europe and other developed countries, where 5%–9% of all births were preterm [10,11]. From the 1990s, the chances of survival have increased because of better medical intensive care with advances such as antenatal corticosteroids, assisted ventilation, and administration of surfactant to prevent lungs from collapsing [12]. Almost in parallel with these improvements, preterm birth rates appear to increase [13]. Overall, from 1990 to 2010, there has been a 19.4% increase in the preterm birth rate in high-income countries (from 7.2% to 8.6%). The United States has a particularly high rate (12%) [8]. Better knowledge of causes and mechanisms is needed to prevent preterm birth.

Several studies on the subject of alcohol and preterm birth exist, but the findings are inconsistent. Apparently, some studies suggest that the relation between alcohol and preterm birth is J-shaped or U-shaped. A study using a Danish pregnancy cohort suggested that an intake of more than seven drinks of alcohol per week increased the risk of preterm birth [14]. Another study showed that the risk

* Corresponding author. Department of Genes and Environment, Division of Epidemiology, Norwegian Institute of Public Health, Box 4404, Nydalen, Oslo 0403, Norway. Tel.: +47-21078106; fax: +47-21078252.
E-mail address: MariaTeresaGronning.Dale@fhi.no (M.T.G. Dale).

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increased when more than 10 drinks were consumed per week [15]. However, both studies reported that lower levels of consumption might provide a small advantage as the risk of preterm birth was significantly decreased compared to nondrinkers (relative risks of 0.7–0.9) with an intake of alcohol below four drinks per week. Decreased risk at low to moderate alcohol intake was also found in a cross-sectional study by Wright et al. (1998) [16], who reported a relative risk of 0.4 (95% confidence interval [CI], 0.2–0.7) for preterm birth associated with alcohol intake in the third trimester. Looking only at induced preterm birth, Meis et al. (1997) [17] found that alcohol intake reported in gestational week 24 was associated with reduced risk (relative risk 0.34, 95% CI, 0.15–0.76). A very recent prospective cohort study by Lundsberg et al. (2015) [18] support these earlier findings, reporting reduced risk of preterm birth with low to moderate alcohol intake both during early and late pregnancy (relative risk of 0.79 and 0.60).

Other studies suggest that daily drinking has an adverse effect on preterm delivery. Jaddoe et al. (2007) [19] found that an average consumption of one drink per day either during early or late pregnancy had a relative risk of 2.5 (95% CI, 0.9–6.8) for preterm birth. Another prospective study showed a dose-response risk for low and moderate intake ($\leq$0.10 oz or >0.10–0.25 oz of absolute alcohol per day) during late pregnancy and risk of preterm birth (relative risks of 2.88 and 2.96) [20]. Both studies indicate that daily alcohol intake has a risk-increasing effect and that greater the exposure the greater the risk, but no studies have found adverse effects of occasional drinking. A recent systematic review and meta-analysis by Patra et al. (2011) [4] sum up the aforementioned findings: only heavy consumption, 1.5 drinks per day and more, increased the risk of preterm birth, whereas lower levels were associated with reduced risk or no risk.

These inconsistent findings of risk at relatively high consumption levels and no risk and/or reduced risk at moderate and low levels may be due to the heterogeneity across studies, large divergence in defining and measuring alcohol consumption, and that some findings are not adjusted for important lifestyle and related socioeconomic factors [4,19–21]. Another source of confounding could be undetected differences in health-related behavior due to previous reproductive experience [21] or due to the presence of publication bias [3].

Most pregnant women in Norway either abstain from alcohol or drink occasionally. The proportion of women who are occasional drinkers may be relatively large, a recent study in Norway indicates that one in 10 women maintain light alcohol consumption during pregnancy [22]. A more solid scientific basis for advice to these women is needed and should be provided by epidemiologic cohort studies rather than studies focusing only on women with high alcohol consumption [23]. Our objective is to examine critically, in a large prospective pregnancy cohort, the effect of alcohol before and during pregnancy on preterm delivery. Studies suggesting that low levels of alcohol intake have a protective effect have been the subject of controversy—is there a biological explanation for this association or is the outcome attributed to maternal lifestyle and background variables? A major problem in this area of research is confounding by background factors such as socioeconomic status and lifestyle. We had the opportunity to control for prepregnancy drinking, as well as the drinking pattern of the spouse. Together with educational level, these two variables reveal a major part of the family's lifestyle that might have confounding effects, which allows us to identify better the alcohol-specific effects on pregnancy. This present study provides dose-response information in the drinkers versus nondrinkers analyses, making it possible to explore if low amounts of alcohol relate to preterm risk. As alcohol intake was assessed in the first trimester, prospective to the birth outcome, we avoid recall bias and under-reporting among women with adverse pregnancy outcomes. By including only singletons among primiparous births, we isolated alcohol exposure from other exposures that potentially increase the risk of preterm birth, and we captured uncontrolled confounding by previous reproductive experiences or fetal complications.

Materials and methods

Study population and data collection

This study is a subproject of the Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health [24]. MoBa is a prospective pregnancy cohort comprising all pregnant women in Norway attending routine ultrasound examinations at gestational weeks 17–18. Recruitment started in 1999 and ended in 2008, and participants were recruited to the study through a postal invitation after they have signed up for the routine ultrasound examination in their local hospital. Of the total, 40% of the invited women consented to participate, and the cohort now includes 112,768 pregnancies [25].

Questionnaires used in MoBa can be found online at http://www.fhi.no/moba-en. The record of the pregnancy and delivery in the Medical Birth Registry of Norway (MBRN) is included in the MoBa database. The information in MBRN is based on antenatal forms and data recorded at the maternity departments at delivery and during the hospital stay [26]. The present study was based on version 7 of the quality-assured data files made available in 2013. Written informed consent was obtained from all participating women, and the study has been approved by the Regional Committee for Ethics in Medical Research and the Data Inspectorate.

Variables

We defined preterm delivery as delivery before 37 weeks (259 days) of gestation. Predictions from ultrasound measures determined the outcome variable gestational age, or if this was missing, from the date of the last menstrual period. Information on maternal age at child birth was categorized as "less than 20 years," "20–24 years," "25–29 years," "30–34 years," and "35 years or more." The variables gestational age, maternal age, and child's sex were drawn from the MBRN.

Questionnaire Q1, with assessment point at gestation week 15, asks about alcohol use during the last 3 months before pregnancy and during pregnancy. The woman was asked how often she drinks alcohol with response categories "6–7 times," "4–5 times," "2–3 times," "1 time per week," "2–3 times per month," "less than once per month," or "never." There was also a question about how many units (for instance a glass of beer or a glass of wine) the mothers usually consumed on each occasion. Table 1 gives the distribution of these variables. If the woman reported to be a nondrinker before pregnancy and did not respond to the pregnancy intake question, we assumed that she was also a nondrinker during pregnancy.

The response categories on maternal smoking were "nonsmoker," "occasional smoker," and "daily smoker." Maternal educational attainment was categorized as "less than 12 years," "12 years," "13–16 years," and "17 years or more." The smoking variable and the information on maternal education were taken from Q1 together with variables assessing prepregnancy maternal height and weight and maternal anxiety. Prepregnancy height and body weight were used to calculate body mass index (kg/m^2) which was categorized as "less than 20," "20–24," "25–29," and "30 or more." The mothers anxiety scores range from 2 to 8 and was a sum of responses "not bothered = 1," "a little bothered = 2," "quite bothered = 3," or "very bothered = 4" on two questions on whether

Table 1
Proportions of women who drank alcohol during the 3 months before pregnancy and during pregnancy, as reported in week 15 (Q1)

Alcohol consumption	Frequency		Alcohol consumption	Amount (units) per occasion*	
	$N = 44,300$	$N = 44,300$		$N = 40,515$	$N = 4,121$
	Before pregnancy, *n* (%)	Week 0–15, *n* (%)		Before pregnancy, *n* (%)	Week 0–15, *n* (%)
Never	3040 (7.7)	35851 (80.9)			
<1 per mo	10163 (22.9)	3280 (7.4)	<1	1492 (3.7)	3111 (75.5)
1–3 per mo	16573 (37.4)	674 (1.5)	1–2	12637 (31.2)	624 (15.1)
1 per wk	8917 (20.1)	131 (0.3)	3–4	13292 (32.8)	51 (1.2)
2–3 per wk	4293 (9.7)	24 (0.1)	5–6	8444 (20.8)	34 (0.8)
4–5 per wk	463 (1.0)	4 (0.0)	7–9	3206 (7.9)	9 (0.2)
6–7 per wk	106 (0.2)	8 (0.0)	10+	782 (1.9)	6 (0.1)
No response	381 (0.9)	4328 (9.8)	No response	662 (1.6)	286 (6.9)

* Subjects who responded "never" and nonresponders to the frequency question are not included.

the woman during the past two weeks have been (1) frightened or anxious or (2) nervous and in turmoil. All questionnaire variables also include a missing category.

For the background variables (Tables 2 and 3), we included additional variables from Q1. First, social support was measured by the item "Do you have anyone other than your husband/partner that you can ask for support in a difficult situation?" and was dichotomized as "no" and "yes." Second, maternal distress was measured by the SCL-5, a shortened version of the Hopkins Symptom Checklist shown to correlate strongly with the SCL-25 index [27]. SCL-5 has five items, with four response categories from "1 = not bothered" to "4 = very bothered." A typical item was "Worrying too much about things." We scored the index as the mean of the item scores, where an average score less than 2 is considered within the normal range on the SCL-5. Third, well-being comprises five items rated on a 7-point Likert scale ranging from "1 = strongly disagree" to "7 = strongly agree." The items were phrased as follows: "in most ways my life is close to my ideal," "the conditions of my life are excellent," "I am satisfied with my life," "so far I have gotten the important things I want in life," and "if I could live my life over, I would change almost nothing." Fourth, the mother was asked if she did exercise "once a week or more" before pregnancy, and we dichotomized the responses as "no" and "yes". Fifth, we asked about folate intake and dichotomized the responses as "no" and "yes." Sixth, if the woman was previously treated for infertility, we dichotomized the responses as "no" and "yes." Finally, paternal alcohol use during the last 6 months before pregnancy and after pregnancy was asked for, and the categories were: "6–7 times," "4–5 times," "2–3 times," "1 time per week," "2–3 times per month," "less than once per month," or "never." We dichotomized the responses as "Nondrinkers" and "Drinkers."

Analytic strategy

Alcohol intake in pregnancy reported in Q1 was relatively infrequent, and the number of units consumed on each occasion was small (see Table 1). Considering the low number of heavy drinkers in pregnancy, we chose to create a simple alcohol variable (drinker or nondrinker) for two of the time periods given in Table 1 for the further analyses. In the analyses, we excluded records with missing values for the main exposure (alcohol intake in pregnancy) but included a missing category for the potentially confounding variables.

Multivariable logistic regression analyses were used to approximate crude and adjusted relative risks of preterm birth according to alcohol intake.

According to World Health Organization's *International Classification of Diseases, Tenth Revision*, the perinatal period commences after gestation week 22. As a result, earlier births were excluded in this study [28]. The number of pregnancies registered in the MBRN that had gestational length above 22 weeks and shorter than 44 weeks was 107,978. Furthermore, we wanted to isolate alcohol exposure from other exposures reported to increase the risk of

Table 2
Characteristics of women according to prepregnant intake of alcohol

Background variables	Nondrinker* ($n = 3404$)	Drinker* ($n = 40,515$)	χ^2/F	$P^\dagger$
Mother				
Gestational week (mean ± SD)	39.3 ± 2.1	39.5 ± 2.0	6.9	.001
Age when child is born (mean ± SD)	27.5 ± 4.6	28.4 ± 4.4	69.3	<.0001
Education > 12 y (%)	60.8	71.7	248.3	<.0001
Smoking during pregnancy, yes (%)	5.0	8.4	47.7	<.0001
Prepregnancy BMI (mean ± SD)	23.8 ± 4.6	23.7 ± 4.3	0.8	.469
Folate, yes (%)	72.4	80.2	116.4	<.0001
Infertility, yes (%)	12.2	8.0	87.0	<.0001
Social support, yes (%)	91.4	97.8	476.3	<.0001
Exercise before pregnancy ≥ once a week (%)	75.2	83.7	124.6	<.0001
Psychological distress gestation week 18, raw score from 1 to 4 (mean ± SD)	1.3 ± 0.4	1.3 ± 0.4	6.7	.001
Well-being gestation week 18 raw score from 1–7 (mean ± SD)	5.6 ± 1.2	5.7 ± 1.1	4.3	<.014
Child				
Boys (%)	51.4	51.3	0.9	.472
Birth weight, g (mean ± SD)	3597.4 ± 597.3	3592.1 ± 580.6	0.8	.378
Father				
Drinking before pregnancy, yes (%)	99.7	99.4	3.1	.085

ANOVA = analysis of variance.

* Nondrinkers are women who reported being a nondrinker. Drinkers are women who responded to the frequency categories varying from "less than 1 per month" up to "6–7 times per week" and/or reported drinking "less than 1" up to "10 or more" units of alcohol on each occasion.

† *P* values were calculated using ANOVA for continuous variables and χ^2 test for categorical variables.

Table 3
Characteristics of women according to intake of alcohol during pregnancy

Background variables	Nondrinker* (n = 35,851)	Drinker* (n = 4121)	χ^2/F	$P^{\dagger}$
Mother				
Gestational week (mean ± SD)	39.5 ± 2.0	39.5 ± 2.0	0.6	.558
Age when child is born (mean ± SD)	28.2 ± 4.4	30.1 ± 4.4	367.1	<.0001
Education > 12 y (%)	71.1	77.6	226.9	<.0001
Drinking before pregnancy, yes (%)				
Smoking during pregnancy, yes (%)	7.5	12.0	100.7	<.0001
Prepregnancy BMI (mean ± SD)	23.7 ± 4.4	23.4 ± 3.8	17.3	<.0001
Infertility, yes (%)	8.5	6.6	43.5	<.0001
Folate, yes (%)	80.1	76.7	25.9	<.0001
Social support, yes (%)	97.4	97.9	4.1	.049
Exercise before pregnancy ≥ once a week (%)	83.1	83.3	0.1	.714
Psychological distress gestation week 18, raw score from 1 to 4 (mean ± SD)	1.2 ± 0.4	1.3 ± 0.4	51.7	<.0001
Well-being gestation week 18 raw score from 1–7 (mean ± SD)	5.7 ± 1.1	5.6 ± 1.1	50.0	<.0001
Child				
Boys (%)	51.2	51.2	0.4	.263
Birth weight, g (mean ± SD.)	3592.9 ± 580.8	3598.1 ± 57464	0.8	.376
Father				
Drinking before pregnancy, yes (%)	99.5	98.7	25.8	<.0001
Drinking during pregnancy, yes (%)	95.6	99.4	96.1	<.0001

* Nondrinkers are women who reported being a nondrinker. Drinkers are women who responded to the frequency categories varying from " less than 1 per month" up to "6-7 times per week" and/or reported drinking "less than 1" up to "10 or more" units of alcohol on each occasion.
† P values were calculated using ANOVA for continuous variables and χ^2 test for categorical variables.

preterm birth. Therefore, only cases defined as singleton births were eligible for this study (n = 104,225). To capture uncontrolled confounding by previous reproductive experiences, fetal complications and/or change of behavior after adverse pregnancy outcomes or opposite, we excluded multiparous women (57,973). The final sample consisted of a total of 46,252 primiparous mothers with singleton births (see Fig. 1).

Sensitivity analysis

To be sure that exclusion of earlier preterm births (<22 week) did not induce selection bias, we included them in a sensitivity analysis to investigate if these women were drinkers either before pregnancy (T1) or during pregnancy (T2), and if that could potentially influence our risk estimates in the primary analysis.

Furthermore, to investigate the potential impact of the nonresponse of mothers on alcohol intake during pregnancy, we performed another sensitivity analysis. We repeated the primary analysis before (T1) and during pregnancy (T2) by recoding the nonresponse of mothers as first being drinkers and later as nondrinkers. By doing this, we could separately estimate the potential largest deviations: the maximum risk effect and the maximum protective effect of alcohol consumption if the missing responses were either possible drinkers or possible nondrinkers.

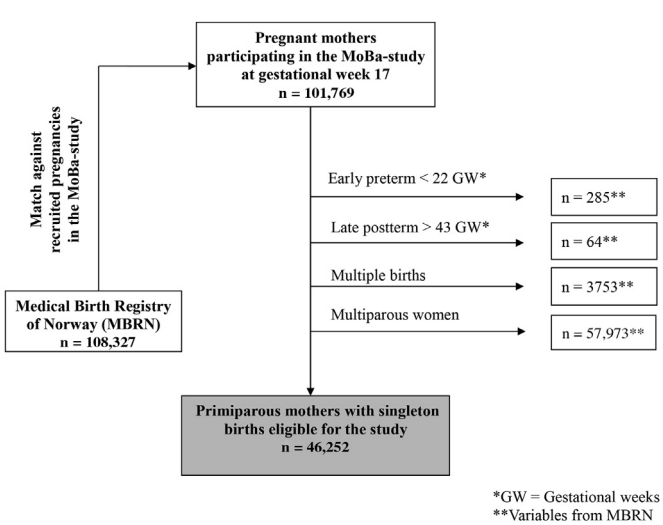

Fig. 1. Flow diagram displaying exclusion criteria for the final study population. *GW = Gestational weeks. **Variables from MBRN.

Covariates

Factors that could potentially influence maternal alcohol use and risk of preterm delivery were identified as confounders. The following covariates were included: Maternal age at delivery, years of education, pre-pregnancy body mass index, smoking, exercise before pregnancy, and paternal drinking before pregnancy.

The analyses were computed with PASW software, version 22.0, (SPSS Inc., Chicago, IL).

Results

Characteristics of the study population

Alcohol consumption before and during pregnancy was measured by a general questionnaire sent out in gestational week 15, Q1, with a response rate of 94.9%. In this version, the total sample sizes were 101,769 for Q1 and 108,327 for the MBRN, but after excluding multiparous women, plural births, and births before gestation week 22, and after gestation week 43, it was reduced to 46,252 (see flow chart concerning excluded cases for details).

Nondrinkers and drinkers differed on several background variables, dependent on the two measurement times. Women drinking before pregnancy were more likely to be older, smokers, have higher education, take folic acid during pregnancy, experienced more social support, exercised more before pregnancy, and they reported less treatment due to infertility when compared with nondrinkers before pregnancy (see Table 2).

Women drinking during pregnancy shared the same background variables as nondrinking women during pregnancy when it comes to age, smoking, and education. On the other hand, it was less likely that they reported taking folic acid supplements, and they experienced lower well-being, and they reported more treatment due to infertility when compared to nondrinkers during pregnancy. They also experienced more psychological distress had lower body mass index, and their partners were more likely to drink when compared to nondrinkers during pregnancy (see Table 3).

Table 4
Number and prevalence (percent) of preterm births (<37 weeks), and crude odds ratios and aORs according to self-reported alcohol intake before pregnancy (T1) and the first 15–17 weeks of pregnancy (T2) for 46,252 pregnancies in the Norwegian Mother and Child Cohort Study

First-time mothers and preterm birth (T1 alcohol before pregnancy)					
Exposure	N of births	N of cases	Percent	cOR	aOR[*]
Nondrinker T1[†]	3404	236	6.93	1.0	1.0
Drinker T1[†]	40,515	2338	5.77	0.82 (0.72–0.94)[‡]	0.81 (0.70–0.95)[‡]
<1 per mo	10,163	629	6.19	0.89 (0.76–1.03)	0.85 (0.71–1.01)
1–3 per mo	16,573	989	5.97	0.85 (0.74–0.99)[‡]	0.85 (0.72–1.00)[§]
1 per wk	8917	486	5.45	0.77 (0.66–0.91)[‡]	0.76 (0.64–0.92)[‡]
2–3 per wk	4293	210	4.89	0.69 (0.57–0.84)[‡]	0.66 (0.53–0.83)[‡]
4–5 per wk	463	19	4.10	0.57 (0.36–0.93)[‡]	0.58 (0.34–0.99)[‡]
6–7 per wk	106	5	4.71	0.67 (0.27–1.65)	0.61 (0.22–1.71)
No response	381	24	6.23	0.90 (0.52–1.39)	1.45 (0.80–2.63)
First-time mothers and preterm birth (T2 alcohol during first 15 wk)					
Exposure	N of births	N of cases	Percent	cOR	aOR[‖]
Nondrinker T2[†]	35,851	2104	5.87	1.0	1.0
Drinker T2[†]	4121	242	5.87	1.00 (0.87–1.15)	1.03 (0.90–1.19)
<1 per mo	3280	180	5.49	0.93 (0.80–1.09)	0.97 (0.82–1.13)
1–3 per mo	674	55	8.16	1.43 (1.08–1.89)[‡]	1.51 (1.14–2.00)[‡]
≥1 per wk	167	7	3.82	0.70 (0.33–1.50)	0.71 (0.33–1.52)
No response	4328	252	6.18	0.99 (0.87–1.14)	0.99 (0.86–1.14)

[*] Adjusted for maternal age, educational attainment, smoking before pregnancy, prepregnancy BMI, exercise before pregnancy and paternal drinking before pregnancy.
[†] Nondrinkers are women who reported being a nondrinker. Drinkers are women who responded to the frequency categories varying from " less than 1 per month" up to "6–7 times per week" and/or reported drinking "less than 1" up to "10 or more" units of alcohol on each occasion.
[‡] $P < .05$.
[§] Borderline statistically significant.
[‖] Adjusted for drinking before pregnancy, maternal age, educational attainment, smoking before pregnancy, pre-pregnancy BMI and paternal drinking before pregnancy.

Effect of alcohol and risk of preterm birth

In this dataset, the prevalence of preterm birth was 5.9% (2729 of 46252). The median length of gestation was 40 weeks for both drinkers during pregnancy and nondrinkers, whereas the mean gestational length was 39.47 weeks (SD = 2.03) for both groups. The mean pregnancy length for prepregnancy drinkers was 39.48 (SD = 2.02), whereas it was 39.34 (SD = 2.12) for nondrinkers (F = 13.4, 1 degrees of freedom, $P < .001$). The mean pregnancy length for drinkers during pregnancy was 39.50 (SD = 2.02) and 39.47 (SD = 2.03) for nondrinkers (F = 1.2, 1 degrees of freedom, $P = .281$).

Overall, alcohol consumption was not associated with preterm birth risk. Table 4 lists a statistically significant tendency toward lower risk of preterm birth of prepregnancy drinking (adjusted odds ratio [aOR] = 0.81, 95% CI = 0.70–0.95). When we analyzed the dose-response relationship, we found that the risk decreased when the average frequency in consumption increased. A similar association was not found among women who reported drinking during early pregnancy aOR = 1.03 (95% CI = 0.90–1.19).

Table 5 shows the same tendency: when women who reported being drinking either before pregnancy or during the first 15 gestation weeks were analyzed together with subjects who reported drinking in both periods, the risk of preterm birth was significantly reduced for women who reported drinking before pregnancy. But not after pregnancy, with nondrinkers as the reference (aOR = 0.80, 95% CI = 0.68–0.94).

Potential effect of very early preterm birth and nonresponse on alcohol intake

In this data set (after exclusion of multiple births and parity), 93 children were born before gestation week 22 and eligible to be included in the sensitivity analysis. These extra cases increased the total number of preterm births from 2474 to 2567 at T1 and from 2346 to 2439 at T2. When we explored the potential impact of nonresponse mothers, the total number of drinkers increased from 40,515 to 40,896 and from 3404 to 3785 for nondrinkers at T1. At T2, the total number of drinkers increased from 4121 to 8449 and from 35,851 to 40,179 for nondrinkers. As Table 6 shows, our findings in the main analysis remained the same after exploring the potential impact of very early preterm birth and the nonresponse of mothers. When we included very early preterm births in the analysis, the estimates were in line with our previous results both before pregnancy (aOR = 0.84, 95% CI = 0.73–0.96) and during pregnancy (aOR = 1.03, 95% CI = 0.90–1.18).

When we included mothers with nonresponse in the analysis and recoded them as being drinkers, the odds for preterm birth were unchanged with no risk for prepregnancy drinking (aOR = 0.82, 95%

Table 5
Prevalence of preterm birth and crude (cOR) and adjusted (aOR) odds ratios (with 95% confidence interval (CI)) according to alcohol intake before pregnancy and during first 15 weeks of gestation in 46, 252 pregnancies from the Norwegian Mother and Child Cohort Study

First-time mothers and preterm birth (T1 and T2)						
Drinking before pregnancy[*]	Drinking 0–15 wk[*]	No of births	No of cases	Prevalence	cOR	aOR[†]
No	No	3160	235	4.18	1.0	1.0
Yes	No	30,523	1862	4.14	0.82 (0.71–0.94)[‡]	0.80 (0.68–0.94)[‡]
Yes	Yes	3857	239	3.63	0.83 (0.69–1.00)[§]	0.83 (0.66–1.03)

[*] Women who report being drinking either before pregnancy or during the first 15 gestation weeks were analyzed together with subjects who report drinking in both periods.
[†] Adjusted for maternal age, educational attainment, smoking before pregnancy, prepregnancy BMI, and paternal drinking before pregnancy.
[‡] $P < .05$.
[§] Borderline statistically significant.

CI = 0.70–0.97) and drinking during pregnancy (aOR = 0.95, 95% CI = 0.85–1.07). The estimates remained stable showing no risk of preterm birth associated with alcohol consumption when we recoded nonresponse as nondrinkers at T1 (aOR = 0.80, 95% CI = 0.69–0.94) and T2 (aOR = 1.01, 95% CI = 0.86–1.17).

Discussion

The message from this study is somewhat complex. Our finding that alcohol consumption during the last 15 weeks before pregnancy was associated with reduced risk of preterm birth, whereas drinking during pregnancy was not is intuitively difficult to make sense of.

Notably, we did not observe an overall effect on preterm birth among alcohol drinkers during pregnancy. Instead, the dose-response analyses showed tendencies toward adverse effects when drinking 1–3 times per month during the first trimester. This finding is not in accordance with the two Danish prospective studies of alcohol exposure during pregnancy and preterm birth that report a J-shaped relationship between the dose of alcohol and the risk of preterm birth, indicating that moderate drinking during pregnancy is protective [11,12]. An important contrast to these aforementioned studies is that the participants of MoBa report very low alcohol consumption. We had no possibility of studying the effects of alcohol intake above four drinks per week.

Another essential difference between this study and the two Danish studies is that the risk reduction was observed for drinking before pregnancy. Our results suggest a protective dose-response effect of prepregnancy alcohol consumption. Women who consumed alcohol 4–5 times per week had a lower risk (aOR = 0.58) than women drinking less than once per month (aOR = 0.85). This reduced risk with prepregnancy drinking has previously been reported in a review by Patra et al. (2011) [4]. On the other hand, their review showed a dose-response relationship between preterm birth and prenatal drinking, with no effect at an average of 1.5 drinks per day and monotonically increased risk with higher consumptions.

Cloner and Rezkalla (2007) [29] pose the question "To drink or not to drink" in their review of the benefits of low to moderate consumption alcohol. One might suggest that a more relevant question is about the labeling "To be a drinker or a nondrinker?" rather than the alcohol consumption by itself. We assume that a possible and more intuitive explanation can be that differences in socioeconomic status, health-related behavior, and physical and psychological well-being between drinkers and nondrinkers influence the risk estimates.

Interestingly, alcohol consumption among women in northern Europe and the United States has increased during the last decades as alcohol has become more integrated into everyday life. The alcohol consumption in Norway has increased by 40 percent over the last two decades, with the highest growth among well-educated and high-income women [30]. In most western cultures, the use of alcohol is the norm, and abstinence is associated with social deviance [31,32]. A relevant Norwegian population-based study shows that people with low alcohol consumption are at higher risk of depression and anxiety compared with moderate drinkers, and the abstainers have the highest risk of experiencing these negative mental health consequences [32].

This tendency has previously been described as the "healthy drinker effect." Healthy women tend to drink more than women with chronic diseases [15,18]. However, perhaps a broader term such as the "higher well-being effect" is more appropriate, as intake of alcohol appears to be associated with healthful lifestyle, higher education, and better social network.

In this study, we identified several significant differences in background variables between drinkers and nondrinkers. Drinkers overall appear to have higher education, be more social and have a higher score on well-being. Not surprisingly, the differences are most

Table 6
Sensitivity analyses with number and prevalence (percent) of preterm births (<37 weeks), and crude (cOR) and adjusted (aOR) odds ratios according to self-reported alcohol intake before pregnancy (T1) and the first 15–17 weeks of pregnancy (T2) including very preterm births (>22) and the nonresponse of mothers on alcohol intake in the main analysis

First-time mothers and preterm birth (T1 alcohol before pregnancy)					
Exposure	N of births	N of cases	Percent	cOR	aOR*
Including very early preterm birth (<22, n = 88)					
Nondrinker T1†	3411	243	7.12	1.0	1.0
Drinker T1†	40,596	2419	5.96	0.83 (0.72–0.95)‡	0.84 (0.73–0.96)‡
Including nonresponse as drinkers (n = 381)					
Nondrinker T1	3404	236	6.93	1.0	1.0
Drinker T1	40,896	2362	5.78	0.82 (0.72–0.95)‡	0.82 (0.70–0.97)‡
Including nonresponse as nondrinkers (n = 381)					
Nondrinker T1	3785	260	6.87	1.0	1.0
Drinker T1	40,515	2338	5.77	0.83 (0.73–0.95)‡	0.80 (0.69–0.94)‡
First-time mothers and preterm birth (T2 alcohol during first 15 wk)					
Exposure	N of births	N of cases	Percent	cOR	aOR§
Including very early preterm birth (<22, n = 81)					
Nondrinker T2	35,919	2172	6.05	1.0	1.0
Drinker T2	4134	255	6.17	1.02 (0.89–1.17)	1.03 (0.90–1.18)
Including nonresponse as drinkers (n = 4328)					
Nondrinker T1	35,851	2104	5.12	1.0	1.0
Drinker T1	8449	494	5.85	0.97 (0.90–1.10)	0.95 (0.85–1.07)‡
Including nonresponse as nondrinker (n = 4328)					
Nondrinker T1	40,179	2356	5.86	1.0	1.0
Drinker T1	4121	242	5.87	1.00 (0.87–1.15)	1.01 (0.86–1.17)‡

* Adjusted for maternal age, educational attainment, smoking before pregnancy, prepregnancy BMI, exercise before pregnancy and paternal drinking before pregnancy.
† Nondrinkers are women who reported being a nondrinker. Drinkers are women who responded to the frequency categories varying from " less than 1 per month" up to "6–7 times per week" and/or reported drinking "less than 1" up to "10 or more" units of alcohol on each occasion.
‡ $P < .05$.
§ Adjusted for drinking before pregnancy, maternal age, educational attainment, smoking before pregnancy, prepregnancy BMI and paternal drinking before pregnancy.

pronounced before pregnancy, since during pregnancy total alcohol abstinence is highly recommended, and therefore, the socioeconomic difference between drinkers and nondrinkers decreases at that measurement time. Consequently, it is very likely that studies like our study, measuring the association between the mothers' self-reported alcohol intake and preterm risk, also indirectly measures the impact of maternal social resources and well-being by assessing several factors that accompany both alcohol and the risk of preterm birth. The fact that adverse social circumstances are associated with the risk of preterm birth underscores the complexity of factors and mechanisms involved in understanding the association between alcohol consumption and potential adverse birth effects [9,33]. In this sense, if alcohol consumption was the only significant predictor and explanation for our results, the exposure should display the same risk estimates during early pregnancy, and not only be associated with reduced preterm risk when measured before pregnancy.

If there is a biological explanation for this association, the mechanisms are uncertain. One possible explanation of the results is similar causal pathways as for the association between alcohol and cardiovascular disease. Studies have found protective effects of alcohol on the vascular endothelium, resulting in increased angiogenesis, and reduced risk of inflammation and infections [33]. However, as already mentioned, this protective effect does not pertain in our study when women report drinking during pregnancy.

Strengths of this study include a large population sample of first-time mothers with only singleton births, with relevant data on a number of covariates and background variables that permitted adjustment for important confounders. Alcohol exposure was assessed in the first trimester prospective to the birth outcome, avoiding potential systematic errors due to under-reporting and recalls bias. Our relatively large cohort of mothers should enable identification of variations in maternal attributes, and a study of recruitment bias in MoBa by Nilsen et al. (2009) [34] concludes that exposure-outcome associations are not biased.

However, this cohort study suffers from several limitations that might have affected the validity of our findings. As with other questionnaire studies, some caution is required when interpreting self-reported measures. Mothers' responses may be affected by social desirability and other response biases. Women who believe that they should not drink any alcohol during pregnancy may under-report alcohol intake, and cause a potential source of error by misclassification toward inclusion of drinkers in the nondrinker category. Such misclassification may lead to a bias toward the null value in the estimate of the effects of alcohol consumption during pregnancy on preterm birth.

Moreover, drinking before pregnancy were assessed retrospectively and is potentially subject to recall bias and under-reporting especially if mothers discover any complications during early pregnancy. For this purpose, we performed a sensitivity analysis on the potential impact of the nonresponding mothers and mothers with births before gestation week 22, to see if these groups could induce selection bias. However, the effect estimates in the cohort analyses remained unchanged. If under-reporting were present in the self-reported alcohol consumption, the effect estimates should have been underestimated.

A relevant substudy of the MoBa cohort explored the risk of underestimates with variables linked to social desirability. They found that self-reported smoking status during pregnancy had a sensitivity of 82% and a specificity of 99% against plasma cotinine concentrations, signifying that self-reported smoking is a valid measure in the MoBa cohort [35]. This could suggest that reporting bias is not the explanation for our results, especially before pregnancy, as there is no established stigma attached to prepregnancy drinking in Norway and most of mothers in the cohort (91%) report to drink alcohol.

Another possible source of error is that the timing of conception and alcohol consumption may overlap. Other studies have shown that when women are asked about their alcohol consumption before pregnancy, they might report consumption before pregnancy recognition and therefore include early pregnancy [36,37].

An important limitation is that even if potentially confounding variables are included in the data set, residual confounding cannot be ruled out: The list of potential confounders is extensive, and it is impossible to control for all. Finally, two factors in our study raise an important question of the representativeness of the sample. First, the missing rate is high, and the women who did not participate might have a different exposure-outcome relation than those who did participate. Second, given that we only included primiparous women with singleton births, our findings are limited to represent women at low risk. Hence, our conclusions might not provide any guidance to other pregnant women. Consequently, we suggest that further studies should explore the effects of alcohol consumption among different groups of women.

Conclusions

We cannot conclude from our study that alcohol intake is of benefit to the fetus. More research is needed to understand the causal pathways. The health of the fetus may be affected in many complex ways by alcohol, and any beneficial effect on reduced risk of preterm birth may as well be outweighed by other risks. This question will be investigated further in MoBa by looking at neurodevelopmental outcomes. Furthermore, the protective effect of prepregnancy alcohol consumption, also seen in other studies, can reflect a biological mechanism where gene–environment interactions have a part to play and that may lead to better prevention of preterm birth after more detailed clinical and experimental studies have explored the possible underlying mechanisms.

As this effect was not present during pregnancy, we further suggest that any direct positive effects of prepregnancy drinking can be explained by differences in socioeconomic background variables that we have not been able to control for. More importantly, our data suggest that women drinking during pregnancy are not at lower risk of having a preterm birth. Instead, there might be a slight inverse risk that warrants the existing recommendations against any maternal alcohol intake during pregnancy.

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