Alcohol intake in early pregnancy and spontaneous preterm birth

a cohort study

Weile, Louise Katrine Kjaer; Hegaard, Hanne Kirstine; Wu, Chunsen; Tabor, Ann; Wolf, Hanne Trap; Kesmodel, Ulrik Schiøler; Henriksen, Tine Brink; Nohr, Ellen Aagaard

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MRS. LOUISE KATRINE KJÆR WEILE (Orcid ID : 0000-0001-5027-5027)

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MRS. LOUISE KATRINE KJÆR WEILE (Orcid ID: 0000-0001-5027-5027)

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1. Mrs. Louise Katrine Kjær Weile[abc], MHSc.
2. Dr. Hanne Kirstine Hegaard[def], PhD.
3. Dr. Chunsen Wu[ab], PhD.
4. Prof. Ann Tabor[def], Doctor of Medical Sciences.
5. Dr. Hanne Trap Wolf[g], Master of Medical Sciences.
6. Prof. Ulrik Schiøler Kesmodel[hi], PhD.
7. Prof. Tine Brink Henriksen[jk], PhD.
8. Prof. Ellen Aagaard Nohr[ab], PhD.

[a]Department of Obstetrics and Gynecology, Odense University Hospital. Sdr. Boulevard 29, DK-5000 Odense C.

[b]Institute of Clinical Research, University of Southern Denmark. J.B. Winsløws Vej 19, DK-5000 Odense C.

[c]OPEN, Odense Patient data Explorative Network, Odense University Hospital. J.B. Winsløws Vej 9a, DK-5000 Odense C.

[d]Department of Obstetrics, Copenhagen University Hospital (Rigshospitalet). Juliane Maries Vej 9, DK-2100 Copenhagen Ø.

[e]The Research Unit Women's and Children's Health, Juliane Marie Centre, Copenhagen University Hospital (Rigshospitalet). Tagensvej 22, DK-2200 Copenhagen N.

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[f] Department of Clinical Medicine, University of Copenhagen. Blegdamsvej 3b, DK-2200 Copenhagen N.

[g]Department of Obstetrics and Gynecology, Hvidovre University Hospital. Kettegård Alle 30, DK -2650 Hvidovre.

[h]Department of Clinical Medicine, Aalborg University. Søndre Skovvej 15, DK-9000 Aalborg.

[i]Department of Obstetrics and Gynecology, Aalborg University Hospital. Reberbansgade 9, DK-9000 Aalborg

[j] Department of Pediatrics (Intensive Care Neonatology), Aarhus University Hospital. Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N.

[k]Perinatal Epidemiology Research Unit, Department of Pediatrics, Aarhus University Hospital. Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N.

Corresponding author:

Mrs. Louise Katrine Kjær, RM, MHSc, PhD student. Sdr. Boulevard 29, DK-5000 Odense C.

Telephone: +4565415157. Email: louise.weile@rsyd.dk

Abstract

Background: Limited research has addressed whether maternal alcohol intake in early pregnancy increases the risk of spontaneous preterm birth. In the current study, we examined how alcohol binge drinking and weekly alcohol intake in early pregnancy were associated with spontaneous preterm birth in a contemporary cohort of Danish women.

Methods: We included 15,776 pregnancies of 14,894 women referred to antenatal care at Copenhagen University Hospital, Denmark, between 2012 and 2016. Self-reported alcohol intake in early pregnancy was obtained from a web-based questionnaire completed prior to the women's first visit at the department. Information on spontaneous preterm birth was extracted from the Danish Medical Birth Register. Adjusted hazard ratios (aHR) with 95% confidence intervals (CI) of spontaneous preterm birth according to self-reported alcohol binge drinking and weekly intake of alcohol in early pregnancy were derived from Cox regression.

Results: Women reporting one, two and >3 binge drinking episodes had an aHR for spontaneous preterm birth of 0.88 (95% CI 0.68-1.14), 1.34 (95% CI 0.98-1.82), and 0.93 (95% CI 0.62-1.41), respectively, compared to women with no binge drinking episodes. Women who reported an intake of >1 drink per week on average had an aHR for spontaneous preterm birth of 1.09 (95% CI 0.63-1.89) compared to abstainers. When restricting to nulliparous women or cohabiting women with >3 years higher education, this estimate was 1.28 (95% CI 0.69-2.40) and 1.20 (95% CI 0.67-2.15), respectively.

Conclusion: We found no evidence that maternal alcohol intake in early pregnancy was associated with a higher risk of spontaneous preterm birth, neither for alcohol binge drinking nor for a low average weekly intake of alcohol.

Keywords:

Pregnancy; Binge Drinking; Low-Moderate Alcohol Consumption; Spontaneous Preterm Birth; Prenatal Alcohol Exposure

Abbreviations:

aHR:	Adjusted hazard ratios
BMI:	Body-mass-index
CI:	Confidence intervals
HR:	Hazard ratio
MAR:	Missing at random
PPROM:	Preterm premature rupture of membranes

Introduction

Preterm birth, defined as birth prior to 37 completed weeks of gestation, is one of the strongest predictors for mortality and morbidity in infancy and early childhood (Liu et al., 2016, Costeloe et al., 2000, Stephens et al., 2016, Luu et al., 2017). Globally, 11% of all livebirths are preterm with variations from 18% in some African countries to 5% in the Scandinavian countries (Blencowe et al., 2012). The etiology of preterm birth has been studied intensively without any convincing breakthrough to reduce the frequency (Purisch and Gyamfi-Bannerman, 2017, Blencowe et al., 2012). However, interpretation of preterm rates is complicated, and while rates of spontaneous preterm birth are decreasing, iatrogenic preterm birth rates are increasing (Lucovnik et al., 2016, Ananth and Vintzileos, 2006, Moutquin, 2003). Still, in both American and European populations, 65-75% of all preterm deliveries have spontaneous onset (Lucovnik et al., 2016, Ananth and Vintzileos, 2006, Moutquin, 2003).

Alcohol consumption is a modifiable lifestyle factor. In the Scandinavian countries, alcohol drinking is increasing among women of childbearing age (Stoltenberg, 2014, Jensen et al., 2017). Currently, 13-18% of Danish women between 25 and 34 years of age drink seven drinks or more per week (one drink being equal to 12 grams of pure alcohol), while 23-25% regularly consume five drinks or more on a single occasion (binge drinking as defined by the Danish Health Authority (Strandberg-Larsen and Grønbæk, 1999)). Although, the majority of women cease or decrease alcohol consumption once they recognize that they are pregnant (Strandberg-Larsen et al., 2008, McCormack et al., 2017, Pryor et al., 2017), 35-40% of Danish women engage in binge drinking in very early pregnancy (Iversen et al., 2015, Kesmodel et al., 2016). From a public health perspective, it is urgent to clarify potential detrimental effects of maternal alcohol consumption in early pregnancy.

A meta-analysis based on data collected between 1974 and 2006 showed no association between maternal alcohol intake up to 1.5 drinks per day and preterm birth (Patra et al., 2011). A number of studies published after this meta-analysis including two large cohorts found that any alcohol intake was associated with higher risk of preterm birth (Salihu et al., 2011, Miyake et al., 2014, Nykjaer et al., 2014, Aliyu et al., 2010). However, other recent studies found no association (Meyer-Leu et al., 2011, McCarthy et al., 2013, Cooper et al., 2013, Dale et al., 2016, Lundsberg et al., 2015, Smith et al., 2015, Sbrana et al., 2016, Baron et al., 2017, Strandberg-Larsen et al., 2017), and one study indicated lower risk among drinkers compared to non-drinkers (Pfinder et al., 2013) which is in accordance with previous studies suggesting an apparently beneficial effect of a low to moderate alcohol intake (Kesmodel et al., 2000, Albertsen et al., 2004, Jaddoe et al., 2007). It has been discussed if these findings may be due to residual confounding (the healthy-drinker-effect) caused by the inability to adjust for lifestyle and socioeconomic factors (Bailey and Sokol, 2011, Henderson et al., 2007a, Henderson et al., 2007b, Patra et al., 2011, Pfinder et al., 2013). Further, it has been suggested that the general inconsistency of findings may be due to the heterogeneity across studies in terms of measuring and defining alcohol consumption, and measuring gestational age (Bailey and Sokol, 2011, Henderson et al., 2007a, Henderson et al., 2007b, Patra et al., 2011). A meta-analysis recently concluded that the evidence on the role of light drinking in pregnancy compared to abstinence is limited for most neonatal outcomes including preterm birth (Mamluk et al., 2017).

Preterm birth can be categorized as spontaneous or iatrogenic. Spontaneous preterm birth is characterized by exaggerated inflammatory response and dysregulation of the immune system (Voltolini et al., 2013). Alcohol in early pregnancy may predispose to spontaneous preterm birth by causing impaired trophoblast invasion (Kalisch-Smith et al., 2016), and placental development (Burd et al., 2007) subsequently altering the levels of prostaglandins, progesterone (Bocking et al., 1993, Lee and Wakabayashi, 1985, Ahluwalia et al., 1992), and inflammatory cytokines (Lohsoonthorn et al., 2007, Catov et al., 2007). Further, alcohol may affect the susceptibility to infections due to impaired immune-response (Zheng et al., 2017, Mastrogiannis et al., 2014, Szabo and Saha, 2015). In contrast, iatrogenic preterm birth reflects an underlying maternal or fetal pathology, prompting a medically induced delivery of the child or a cesarean section. Inherently, pathologies will only result in a preterm birth if a clinician evaluates that the advantages of delivery outweigh the disadvantages of awaiting the spontaneous course.

Few studies have focused on spontaneous preterm birth in relation to maternal alcohol consumption (Kramer et al., 1992, Adams et al., 1995, Peacock et al., 1995, Harlow et al., 1996, McCarthy et al., 2013, Baron et al., 2017, Kesmodel et al., 2000, Aliyu et al., 2010). While most of these studies found no association, one study reported higher risk of spontaneous preterm birth among women with an intake of 10 or more drinks per week (Kesmodel et al., 2000). Furthermore, one study of more than one million singleton pregnancies found that any alcohol intake was associated with a higher risk of preterm birth, and that the excess risk for spontaneous preterm birth with any alcohol intake was higher than the excess risk for iatrogenic preterm birth (Aliyu et al., 2010).

It has also been speculated if binge drinking episodes rather than total alcohol exposure may interfere with fetal development and the pregnancy outcome (Pierce and West, 1986). Nonetheless, the literature on binge drinking and preterm birth is sparse and inconclusive (Henderson et al., 2007b, O'Leary et al., 2009, Meyer-Leu et al., 2011, McCarthy et al., 2013, Cooper et al., 2013), and only one study focused on the risk of spontaneous preterm birth (McCarthy et al., 2013).

Therefore, to fill in the gaps within the overall topic of maternal alcohol consumption and the risk of preterm birth, we examined the association between binge drinking in early pregnancy and spontaneous preterm birth. Further, we examined the association with average weekly alcohol in early pregnancy by comparing light drinking to abstinence, and benefited from a contemporary cohort with rich data on socioeconomic and health-related factors.

Materials and methods

Study design and population

The study was a cohort study comprising all pregnant women referred for antenatal care at the Department of Obstetrics, Copenhagen University Hospital (Rigshospitalet), Denmark between September 16, 2012, and October 31, 2016. The cohort has been described in detail elsewhere (Iversen et al., 2015). Rigshospitalet serves as a primary birth facility for the inner city of Copenhagen and as a tertiary referral center. As pregnant women with a known alcohol related disorder are referred to a specialized unit at Hvidovre University Hospital, Denmark, they were not included in this cohort. Prior to the first antenatal visit at the department, all women received a link by e-mail to a web-based questionnaire which was used to obtain the medical history for the woman's medical record as part of normal antenatal care. The following information was obtained by the questionnaire: medical and obstetric history, education and lifestyle before and during pregnancy including smoking, use of recreational drugs, physical activity and alcohol consumption. In case of no response, a reminder was automatically e-mailed twice.

In the study period, 20,282 pregnancies were identified (See flowchart in Figure 1). After excluding pregnancies with miscarriage prior to questionnaire completion (n=992), the overall response rate was 91% (n=19,290). In Denmark, a personal identification number is uniquely assigned to all inhabitants at the time of birth or upon immigration and ensures unambiguous linkage to all Danish registries. Using the women's personal identification number, information from the questionnaire was linked to data from the Danish Medical Birth Register, which contains information on pregnancy and delivery reported from each hospital contact for all livebirths and stillbirths after gestational week 22 (Bliddal et al., 2018). In woman completing more than one questionnaire due to several pregnancies during the study period, questionnaire data was linked to the correct delivery using information on the date of last menstrual period, due date, or booking date. If these variables were missing or erroneous, these pregnancies were excluded (n=1,663). Finally, we excluded pregnancies without a registered delivery (abortion, miscarriage, or emigration after questionnaire completion) (n=1,181), leaving 16,446 successfully linked records. For the purpose of the current study, we excluded multiple pregnancies (n=571) and observations with missing information on gestational age at birth (n=99), leaving 15,776 pregnancies of 14,894 women.

Alcohol exposures

The main exposures were self-reported binge drinking (number of episodes) and average weekly intake of alcohol (drinks per week) in early pregnancy (median gestational age at questionnaire completion: 10 weeks, 5-95 percentile range: 7-14 weeks). In accordance with the definition of the Danish Health Authority, a standard drink was equivalent to 12 grams of pure alcohol (Strandberg-Larsen and Grønbæk, 1999). The question on binge drinking was phrased: '*The following question concerns your entire pregnancy including the first weeks when you were unaware that you were pregnant. How many times have you been drinking 5 or more drinks on a single occasion?'* The question on weekly intake of alcohol in pregnancy was: *'How many units (one unit corresponds to 1 beer, 1 glass of wine or 4 cl. of spirits) do you drink per week, now that you are pregnant?'* Both number of binge drinking episodes and drinks per week were reported as an integer value. For binge drinking, women were also able to tick *'do not know/recall'*. Preliminarily, binge drinking was categorized as 0, 1, 2, 3, 4, or >5 episodes. Because the risk of spontaneous preterm birth did not increase in accordance with increasing number of binge drinking episodes and because numbers were small in the highest categories, we chose to combine >3 binge drinking episodes into one category in order to perform meaningful analyses. Women ticking *'do not know/recall'* were coded as missing. Average weekly intake of alcohol was categorized as: *0* or *>1 drink per week*.

Spontaneous preterm birth

The primary outcome was time to spontaneous preterm birth defined as the delivery of a live-born child after spontaneous onset of labor or PPROM prior to 37 weeks and 0 days gestation. From the Danish Medical Birth Register, we retrieved information on gestational age at birth. Approximately 94% of all Danish pregnant women have an ultrasound scan including an estimation of the due date based on the fetal crown-rump length between 11 and 13 weeks gestation (Kopp et al., 2017). Induction procedures in pregnancy (*yes/no*), and diagnoses of PPROM (ICD-10 O42) (*yes/no*) were also based on information from the Danish Medical Birth Register. As an overall approach, preterm births were classified as spontaneous when no induction procedure was registered. However in Denmark, pregnancies presenting with PPROM without a subsequent spontaneous labor are managed actively (induction or elective cesarean section) after 34 weeks of gestation (Barbosa et al., 2017). Therefore, preterm births with a PPROM-diagnosis were also classified as spontaneous regardless of further registration of induction procedures.

Covariates

A directed acyclic graph (Williams et al., 2018, Howards, 2018b) was used to select the following self-reported confounders a priori; maternal age (years), cohabitation status (*cohabiting/living alone*), highest attained educational level (*none, skilled training, <3 years of higher education, 3-4 years of higher education, and >5 years of higher education*), pre-gestational body mass index (BMI) based on self-reported height and weight (kg/m^2), recreational drug use prior to pregnancy (*yes/no*), physical activity in pregnancy (*<1, 1-5, and >5 hours/week*), smoking in pregnancy (*yes/no*), parity (*nulliparous/multiparous*), and assisted reproductive technology in the current pregnancy (*yes/no*). Based on the most prevalent chronic disease categories among Danish pregnant women (hypertension, heart disease, lung disease including asthma, diabetes mellitus, thyroid disorders, rheumatoid arthritis and psychiatric disorder) (Jolving et al., 2016), self-reported chronic disease (*yes/no*) was also included as a confounder. Finally, for descriptive statistics and sensitivity analyses, we included gestational age at questionnaire completion, self-reported information on ethnicity, smoking and average weekly intake of alcohol prior to pregnancy, and previous preterm birth.

Statistical analyses

The risk of spontaneous preterm birth according to binge drinking or weekly intake of alcohol in early pregnancy was estimated as crude and adjusted hazard ratios (aHR) with 95% confidence intervals (CI) using Cox regression analyses with gestational days as the underlying time scale. Follow-up started at gestational day 154 (22 weeks and 0 days gestation) and ended at the time of spontaneous preterm birth, stillbirth, birth after induction or elective cesarean section, or at gestational day 259 (37 weeks and 0 days gestation), which ever came first. In Model 1, binge drinking and weekly intake of alcohol were adjusted for all confounders defined *a priori*. In Model 2, analyses of binge drinking were further adjusted for weekly intake of alcohol, and vice versa. Because 882 women contributed with two or more births, robust standard errors were estimated using the "Huber Sandwich Estimator" (Williams, 2000). Model assumptions were evaluated based on log-log plots and Schoenfeld residuals. Statistical significance was defined as a two sided p-value of 0.05. StataIC15.0 (StataCorp, 2017) was used for all statistical analyses.

We carried out a number of supplementary analyses to test the robustness of our findings. It has previously been suggested that women with an underlying increased obstetric risk may be more prone to abstain from alcohol in subsequent pregnancies (Henderson et al., 2007a). Hence, to eliminate the risk of confounding by previous pregnancy experience, we repeated the analyses in a sub-sample of nulliparous women. To reduce the risk of confounding by social class, analyses were also repeated within a sub-sample of cohabiting women who had attained an educational level including academic training which in Denmark applies to all higher educations of at least three years duration. In order to assess the overall impact of binge drinking compared to non-binge drinking, we repeated analyses where any binge drinking in pregnancy was collapsed into one category. To narrow the timing of exposure, analyses were repeated in women completing the questionnaire prior to 10 weeks gestation. As alcohol metabolism may differ by ethnicity, we repeated analyses further adjusting for maternal ethnicity. Analyses were also carried out for early spontaneous preterm birth (prior to 32 weeks and 0 days gestation) and for any preterm birth (any delivery prior to 37 weeks and 0 days gestation). The potential influence of missing information on the results was investigated by repeating analyses in imputed datasets. Based on missing at random assumptions (MAR), incomplete exposure variables and covariates were imputed using multiple imputation by chained equations generating 50 copies of the dataset for both primary and secondary outcome variables (White et al., 2011). All covariates from the analytic models, the outcome variables, the Nelson-Aalen estimator of H(T), and additional variables including PPROM, and induction procedures were included as explanatory variables in the imputation models (White and Royston, 2009, White et al., 2011). The assumption for MAR is untestable and might be violated if women that binge drink might be more likely not to report the information due to the risk of social stigmatizing. Therefore, we conducted an additional sensitivity analysis assuming different scenarios for the distribution of binge drinking among women with missing information on binge drinking.

Ethical approval

The study was approved by the Danish Patient Safety Authority for research purposes (J.no. 3-3013-2203/1/), Sundhedsdatastyrelsen (FSEID: 00003415 and FSEID: 00003189) and the Danish Data Protection Agency (I-Suite nr.: 05846. ID nr.: RH-2017-285).

Results

In 37% of the pregnancies, women reported binge drinking (range: 1-37 episodes), and in 3% of the pregnancies, women reported to consume >1 drink per week (range: 1-9 drinks per week). Cross-tabulation between average weekly and binge drinking is presented in the supplementary Table S1. Totally, 3.6% (n=562) of the 15,776 births were defined as spontaneous preterm including 0.6% (n=93) early spontaneous preterm births. Any preterm occurred in 4.3% (n=681) of the deliveries.

Study characteristics according to self-reported alcohol consumption in early pregnancy are presented in Table 1. Compared to women not binge drinking, women reporting binge drinking were younger, less likely to have chronic diseases, and more likely to have a higher weekly alcohol intake and to use recreational drugs prior to pregnancy. They were more likely to be physically active, to smoke in pregnancy, to be nulliparous and to conceive spontaneously, and less likely to have had a previous preterm birth. Compared to women with no weekly alcohol intake, women who reported an intake were older, more likely to cohabite, to have a higher educational level, and less likely to have chronic diseases. They were more likely to have a higher weekly alcohol intake and to use recreational drugs prior to pregnancy, to be physically active and to smoke in pregnancy (Table 1).

Overall, missing values of covariates included in the models ranged between 0-5% (Table 1). However, for 1,756 pregnancies (11%), data on binge drinking was missing, and for 1,180 (7%), data on weekly intake of alcohol was missing. A total of 1,148 (7%) had missing data for both binge drinking and weekly alcohol, and 1,788 (11%) had missing on either of these variables. Compared to women with complete information on binge drinking, women without this information had a lower educational level and a higher weekly alcohol intake prior to pregnancy. They were less physically active and more often conceived spontaneously. Except from having a lower educational level, women with missing information on weekly alcohol intake were comparable to women who provided this information.

Maternal alcohol intake and spontaneous preterm birth

The associations between binge drinking and spontaneous preterm birth are presented in Table 2. When compared to deliveries of women not binge drinking, we found the highest risk of spontaneous preterm birth among women with two binge drinking episodes (aHR 1.34, 95% CI 0.98-1.82). No association was found between spontaneous preterm birth and one binge drinking episode (aHR 0.88, 95% CI 0.68-1.14) or >3 binge drinking episodes (aHR 0.93, 95% CI 0.62-1.41). Compared to women not binge drinking, any binge drinking was not associated with a higher risk of spontaneous preterm birth (aHR 1.00, 95% CI 0.81-1.23). Restriction to nulliparous women, indicated results in line with those observed in the main analysis: aHR 0.87 (95% CI 0.64-1.18), aHR 1.37 (95% CI 0.97-1.93), and aHR 0.93 (95% CI 0.60-1.45) for one, two and >3 binge drinking episodes, respectively. Similarly, the results among cohabiting women with >3 years of higher education were comparable to the main analysis: aHR 0.76 (95% CI 0.56-1.04), aHR 1.28 (95% CI 0.89-1.85), and aHR 1.07 (95% CI 0.69-1.66) for one, two and >3 binge drinking episodes, respectively (Table 2). Compared to women not binge drinking, women with two binge drinking episodes had twice the risk of early spontaneous preterm birth (aHR 2.27, 95% CI 1.13-4.43). No association was observed between early spontaneous preterm birth and one binge drinking episode (aHR 1.56, 95% CI 0.88-2.75), and >3 binge drinking episodes (aHR 0.58, 95% CI 0.14-2.47), but only three early spontaneous preterm births were observed in the latter exposure group. The aHRs for any preterm birth among those reporting one, two or >3 binge drinking episodes were: 0.99 (95% CI 0.79-1.24), 1.31 (95% CI 0.98-1.74), and 0.97 (95% CI 0.67-1.41), respectively. Thus, the risk estimates for any preterm birth according to binge drinking were comparable to the estimates on spontaneous preterm birth.

Table 3 shows the associations between weekly intake of alcohol and spontaneous preterm birth. We observed no association between average weekly alcohol intake and spontaneous preterm birth (aHR 1.09, 95% CI 0.63-1.89). Restricting to nulliparous women and cohabiting women with >3 years of higher education, estimates remained not statistically significant but moved further away from null: aHR 1.28 (95% CI 0.69-2.40) and aHR 1.20 (95% CI 0.67-2.15), respectively (Table 3). Only one early spontaneous preterm birth was observed among women with an intake of >1 drink per week, and the risk of early spontaneous preterm birth according to average weekly alcohol intake was not estimated. The aHRs for any preterm birth among women with an intake of >1 drink per week was 1.18 (95% CI 0.73-1.91), and thereby comparable to the risk of spontaneous preterm birth.

Restriction to women completing the questionnaire prior to 10 weeks gestation changed the direction of the association for the risk of spontaneous preterm birth among women with >3 binge drinking episodes (aHR 1.25, 95% CI 0.71-2.20), while all other associations were only slightly strengthened and remained not statistically significant. Results were robust to further adjustment for maternal ethnicity. All results from the imputed datasets were comparable to complete case analyses (Table S2 and S3), and the additional sensitivity analysis of binge drinking produced comparable results (Table S4).

Discussion

Main findings and previous studies

In this contemporary cohort of Danish pregnant women, we found no evidence for an association between binge drinking or average weekly alcohol intake in early pregnancy and spontaneous preterm birth. Although elevated risks were indicated for women with two binge drinking episodes, we suggest that these findings were due to chance, as no consistent pattern of associations was found across number of binge drinking episodes, and as estimates were imprecise.

To our knowledge, the association between binge drinking and spontaneous preterm birth has only previously been examined by McCarthy et al. (2013). This study comprising 5,628 pregnancies indicated lower risk of spontaneous preterm birth for women who reported one or >2 binge drinking episodes in early pregnancy compared to abstainers: OR 0.68 (95% CI 0.23-2.06) and OR 0.90 (95% CI 0.70-1.16) (McCarthy et al., 2013). However, using a definition of binge drinking equivalent to an intake of >48 grams of pure alcohol, results were not completely comparable to ours: we defined binge drinking as an intake of >60 grams. Thus, the literature on binge drinking and preterm birth is sparse with imprecise results and inconsistent directions of findings. Further, as the definition of binge drinking varies widely across studies, comparisons are difficult.

While other studies examining the association between average weekly alcohol intake and spontaneous preterm birth found no association (Kramer et al., 1992, Adams et al., 1995, Peacock et al., 1995, Harlow et al., 1996, McCarthy et al., 2013), the largest study observed higher risks of spontaneous preterm birth for women drinking 1-2, 3-4, and >5 drinks per week at delivery compared to abstainers: OR 1.16 (95% CI 1.10-1.23), OR 1.97 (95% CI 1.73-1.24), and OR 2.10 (95% CI 1.84-2.39) (Aliyu et al., 2010). Kesmodel et al. (2000) also reported a higher risk of spontaneous preterm birth among women drinking >10 drinks per week) in the first trimester compared to women drinking <1 drink per week (unadjusted RR 3.22, 95% CI 1.07-9.67). Previous studies have indicated a U-shaped association between average weekly alcohol intake and both spontaneous preterm birth (Kesmodel et al., 2000, McCarthy et al., 2013) and any preterm birth (Kesmodel et al., 2000, Albertsen et al., 2004, Jaddoe et al., 2007, Strandberg-Larsen et al., 2017) with the lowest risks seen at an intake of 1-6 drinks per week compared to an intake of less than one drink per week. It has been suggested that the apparently beneficial effect of small doses of alcohol may be due to confounding by the 'healthy-drinker-effect'. This may appear if drinking in small amounts is associated with a healthier lifestyle, or if women with chronic diseases are more likely to abstain from alcohol than healthy women (Strandberg-Larsen et al., 2008, Strandberg-Larsen et al., 2017, Kesmodel, 2018, Howards, 2018a, Howards, 2018b). In order to reduce the risk of unmeasured confounding by education, life-style and medical/obstetric history, we chose to study a homogeneous population with a high educational level, and further restricted the analyses to nulliparous women or cohabiting women with >3 years higher education. Regrettably, we were unable to examine higher levels of weekly alcohol intake, or to investigate the shape of a potential association as an intake of two or more drinks per week was reported in less than 0.5% of the included pregnancies. However, all adjusted point estimates indicated higher - albeit small and not statistically significant - risks of both spontaneous preterm birth and any preterm birth in pregnancies of women with a weekly alcohol intake compared to women with no weekly alcohol intake.

Strengths and limitations

The study was based on questionnaire data from nearly 16,000 pregnancies with a high response rate and almost complete follow-up in Danish registers. The level of alcohol consumption observed was comparable to drinking levels reported by other current Danish data collections (Backhausen et al., 2014, Petersen et al., 2015). Also, the frequency of preterm birth in our study population was comparable to national figures for the period 2013-2017 (Sundhedsdatastyrelsen, 2017). In general, the number of missing values was low, and women with missing information on binge drinking differed only slightly from those providing this information. Supplementary analyses of imputed data and sensitivity analysis did not suggest that results were influenced by missing values, and selection bias due to missingness may be regarded as a small problem.

The alcohol exposures were based on self-reported information collected as part of the women's medical records, and due to potential stigma, women consuming alcohol may have denied or under-reported their actual intake (Bailey and Sokol, 2011). Further, information on alcohol was obtained by self-administered questionnaires which are known to underestimate alcohol intake compared to diaries and interviews (Kesmodel and Olsen, 2001, Kesmodel and Frydenberg, 2004). Also, questions on alcohol were global which may yield lower alcohol intake than beverage specific questions (Bailey and Sokol, 2011). As information about alcohol exposures was determined before the delivery of the child, we expect any misclassification to be non-differential. Typically, non-differential misclassification of a dichotomized exposure variable leads to bias towards the null-hypothesis, whereas the mechanisms are harder to predict in an exposure variable with three or more categories (Kesmodel, 2018). Average weekly alcohol was dichtomized, and for binge drinking, we had findings close to null when dichotomizing the exposure. Thus, for both exposures, non-differential misclassification may have masked an association in both directions.

We did not have information about timing of exposure, and the gestational age at questionnaire completion varied between 7-14 weeks gestation (5-95% percentile range), meaning that early pregnancy was quite broadly defined. Further, as a result of the question formulations, binge drinking reflected the whole period of early pregnancy, whilst average weekly alcohol intake only captured consumption at the time of questionnaire completion after referral to antenatal care. Typically, women cease or restrict alcohol consumption when recognizing pregnancy (Strandberg-Larsen et al., 2008, McCormack et al., 2017, Pryor et al., 2017). Accordingly, our measure of average weekly alcohol intake may on average be lower than women's actual weekly alcohol intake in the whole period of early pregnancy.

Gestational age at birth was based on ultrasound examination in early pregnancy. In lack of the precise time of conception, this method is considered quite reliable (Wilcox, 2010). However, as both induction procedures (Langhoff-Roos, 2003) and diagnoses of PPROM (Nohr et al., 2007) are slightly underreported in the Danish Medical Birth Register. a small number of spontaneous preterm births may have been affected by non-differential misclassification. As the pathophysiological mechanisms initiating spontaneous labor in the case of intrauterine death possibly differ from those initiating spontaneous preterm livebirth, stillbirths were censored at the time of birth. Also, the outcome measure did not capture fetal death prior to the start of follow-up. If alcohol consumption may impair fetal survival, we may thereby have underestimated the potentially harmful effect of alcohol due to survival bias.

Our data allowed us to adjust for a large number of confounders. Still, we cannot exclude residual or unobserved confounding. In Denmark, the use of recreational drugs is illegal, and smoking during pregnancy is discouraged. It is therefore likely that the use of these substances may be underreported, whilst socially desirable variables such as physical activity may have been overreported. It has previously been shown, that a positive association between alcohol and preterm birth disappeared in distressed women (Pfinder et al., 2013). We were unable to adjust for maternal distress, and our results may be confounded by maternal distress. Also, it has been suggested that some women may be more susceptible to adverse effects during pregnancy than other (Bailey and Sokol, 2011). Hence, our estimates may also be affected by unobserved genetic confounding.

The study was conducted in a cohort of Danish pregnant women living in the uptake area of Copenhagen University Hospital, thereby representing a Scandinavian capital city. Our results may be generalizable to women with a high educational level and in cultural settings where alcohol drinking is common and socially accepted. Our population did not include women treated for alcohol use disorders in relation to pregnancy, and our findings cannot be generalized to populations where heavy drinking in pregnancy is common. Further, the study population consisted of 95% women with European origin and findings may not be generalizable to other geographical regions.

Conclusion

We found no association between maternal alcohol intake in early pregnancy and spontaneous preterm birth, neither for alcohol binge drinking nor for a low weekly alcohol intake.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Table 1: Characteristics according to self-reported alcohol consumption in early pregnancy; Copenhagen University Hospital, Denmark, 2012-2016.

	Total	Average intake (drinks/week)		Binge drinking (number of episodes)			
	Total	0	>1	0	1	2	>3
	n=15,776 n (%)	n=14,151 %	n=445	n=8,875 %	n=2,950	n=1,270	n=925
Age, mean years (SD)*	32.0 (4.4)	31.9 (4.4)	33.5 (4.0)	32.3 (4.5)	31.5 (4.0)	31.3 (4.1)	31.1 (3.9)
Cohabitation status (cohabiting)	14,511 (92.7)	(92.9)	(93.4)	(93.3)	(93.5)	(91.8)	(92.0)
Highest attained educational level							
>5 years higher education	7,773 (52.1)	(52.2)	(64.0)	(53.2)	(53.8)	(53.0)	(52.4)
3-4 years higher education	4,620 (31.0)	(31.0)	(24.9)	(30.3)	(31.6)	(29.5)	(30.1)
<3 years higher education	1,003 (6.7)	(6.8)	(3.9)	(6.7)	(5.5)	(7.4)	(6.7)
Skilled training	516 (3.5)	(3.4)	(3.2)	(3.3)	(2.9)	(4.0)	(4.4)
None	997 (6.7)	(6.6)	(3.9)	(6.5)	(6.2)	(6.2)	(6.4)
Pre-gestational BMI, mean kg/m^2 (SD)	22.5 (3.7)	22.5 (3.6)	22.2 (2.9)	22.5 (3.8)	22.4 (3.4)	22.4 (3.2)	22.3 (3.1)
Chronic disease (yes)*	1,703 (10.8)	(10.9)	(7.6)	(12.1)	(9.3)	(8.1)	(6.9)
Average alcohol intake prior to pregnancy							
Abstainer	3,799 (26.1)	(26.9)	(1.6)	(37.6)	(9.9)	(4.5)	(2.1)
1-3 drinks/week	6,492 (44.6)	(45.0)	(30.0)	(46.1)	(52.2)	(32.2)	(21.3)
4-6 drinks/week	2,766 (19.0)	(18.5)	(33.4)	(12.3)	(26.5)	(33.8)	(32.8)
>7 drinks/week	1,509 (10.4)	(9.6)	(35.0)	(4.0)	(11.4)	(26.4)	(43.8)
Recreational drugs prior to pregnancy (yes)	845 (5.4)	(5.2)	(12.4)	(3.1)	(6.4)	(10.9)	(16.1)
Physical activity in pregnancy*							
0 hours/week	7,400 (46.9)	(46.9)	(39.6)	(48.4)	(43.5)	(40.2)	(43.7)
1-5 hours/week	4,406 (27.9)	(27.9)	(32.6)	(27.1)	(30.2)	(30.1)	26.5)
>6 hours/week	3,970 (25.2)	(25.2)	(27.9)	(24.1)	(26.3)	(29.7)	(29.8)
Smoking in pregnancy (yes)	225 (1.5)	(1.4)	(4.4)	(1.4)	(0.8)	(1.6)	(2.1)
Parity (nulliparous)	9,612 (61.0)	(61.3)	(57.3)	(54.7)	(67.1)	(76.8)	(81.9)
Previous preterm birth (yes)	445 (2.9)	(2.9)	(2.1)	(3.5)	(2.1)	(1.9)	(1.4)

Assisted reproductive technology (yes)	1,708	(11.1)	(11.3)	(9.0)	(16.6)	(3.3)	(2.0)	(1.8)

Abbreviations: Body-mass-index (BMI). *Complete data. Missing data: cohabitation status (n=127), highest attained educational level (n=867), pre-gestational BMI (n=41), average alcohol intake prior to pregnancy (n=1,210), recreational drugs prior to pregnancy (n=261), smoking in pregnancy (n=525), parity (n=16), previous preterm birth (n=504), and assisted reproductive technology (n=416).

Table 2: Hazard ratios for spontaneous preterm birth (prior to 37 gestational weeks and 0 days) according to binge drinking in early pregnancy; Copenhagen University Hospital, Denmark, 2012-2016.

The entire study population (n=15,776)

				Crude (n=14,020)	**Model 1*** (n=12,570)			**Model 2**** (n=12,542)		
Binge drinking	SPTB	Gestational days x 10^3	IR/10,000	HR	aHR	95% CI		aHR	95% CI	
0 episodes	316	924	3.4	1	1			1		
1 episode	93	307	3.0	0.88	0.89	0.69	1.16	0.88	0.68	1.14
2 episodes	58	132	4.4	1.29	1.34	0.99	1.83	1.34	0.98	1.82
>3 episodes	29	97	3.0	0.88	0.94	0.62	1.41	0.93	0.62	1.41

Nulliparous women (n=9,612)

				Crude (n=8,558)	**Model 1*** (n=7,719)			**Model 2**** (n=7,703)		
Binge drinking	SPTB	Gestational days x 10^3	IR/10,000	HR	aHR	95% CI		aHR	95% CI	
0 episodes	200	504	4.0	1	1			1		
1 episode	63	206	3.1	0.77	0.87	0.64	1.19	0.87	0.64	1.18
2 episodes	49	101	4.9	1.23	1.38	0.97	1.94	1.37	0.97	1.93
>3 episodes	25	79	3.2	0.80	0.95	0.61	1.47	0.93	0.60	1.45

Cohabiting women with >3 years higher education (n=11,574)

				Crude (n=10,475)	**Model 1*** (n=9,936)			**Model 2**** (n=9,916)		
Binge drinking	SPTB	Gestational days x 10^3	IR/10,000	HR	aHR	95% CI		aHR	95% CI	
0 episodes	225	691	3.3	1	1			1		
1 episode	60	234	2.6	0.78	0.78	0.57	1.06	0.76	0.56	1.04
2 episodes	36	96	3.8	1.16	1.29	0.89	1.86	1.28	0.89	1.85
>3 episodes	23	71	3.2	1.00	1.09	0.70	1.69	1.07	0.69	1.66

Abbreviations: Spontaneous preterm birth (SPTB), hazard ratio (HR), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, education, chronic disease, BMI, recreational drugs, physical activity, smoking, parity, and assisted reproductive technology. **Adjusted for maternal age, education, chronic disease, BMI, recreational drugs, physical activity smoking, parity, assisted reproductive technology and average weekly alcohol intake in early pregnancy.

Table 3: Hazard ratios for spontaneous preterm birth (prior to 37 gestational weeks and 0 days) according to average weekly alcohol intake in early pregnancy; Copenhagen University Hospital, Denmark, 2012-2016.

The entire study population (n=15,776)

				Crude (n=14,596)	**Model 1*** (n=13,068)			**Model 2**** (n=12,542)		
Average intake	SPTB	Gestational days x 10^3	IR/10,000	HR	aHR	95% CI		aHR	95% CI	
0 drinks/week	506	1473	3.4	1	1			1		
>1 drinks/week	16	46	3.5	1.00	1.07	0.63	1.81	1.09	0.63	1.89

Nulliparous women (n=9,612)

Average intake	SPTB	Gestational days x 10^3	IR/10,000	Crude (n=8,920) HR	Model 1* (n=8,023) aHR	95% CI		Model 2** (n=7,703) aHR	95% CI	
0 drinks/week	345	901	3.8	1	1			1		
>1 drinks/week	12	26	4.6	1.19	1.15	0.61	2.15	1.28	0.69	2.40

Cohabiting women with >3 years higher education (n=11,574)

Average intake	SPTB	Gestational days x 10^3	IR/10,000	Crude (n=10,843) HR	Model 1* (n=10,276) aHR	95% CI		Model 2** (n=9,916) aHR	95% CI	
0 drinks/week	346	1092	3.2	1	1			1		
>1 drinks/week	13	37	3.5	1.10	1.23	0.70	2.16	1.20	0.67	2.15

Abbreviations: Spontaneous preterm birth (SPTB), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, education, chronic disease, BMI, recreational drugs, physical activity, smoking, parity, and assisted reproductive technology. **Adjusted for maternal age, education, chronic disease, BMI, recreational drugs, physical activity smoking, parity, assisted reproductive technology and binge drinking in early pregnancy.

Table legends

Table 1: Characteristics according to self-reported alcohol consumption in early pregnancy; Copenhagen University Hospital, Denmark, 2012-2016.
Abbreviations: Body-mass-index (BMI). *Complete data. Missing data: cohabitation status (n=127), highest attained educational level (n=867), pre-gestational BMI (n=41), average alcohol intake prior to pregnancy (n=1,210), recreational drugs prior to pregnancy (n=261), smoking in pregnancy (n=525), parity (n=16), previous preterm birth (n=504), and artificial reproductive technology (n=416).

Table 2: Hazard ratios for spontaneous preterm birth (prior to 37 gestational weeks and 0 days) according to binge drinking in early pregnancy; Copenhagen University Hospital, Denmark, 2012-2016.
Abbreviations: Spontaneous preterm birth (SPTB), hazard ratio (HR), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, education, chronic disease, BMI, recreational drugs, physical activity, smoking, parity, and assisted reproductive technology. **Adjusted for maternal age, education, chronic disease, BMI, recreational drugs, physical activity smoking, parity, assisted reproductive technology and average weekly alcohol intake in early pregnancy.

Table 3: Hazard ratios for spontaneous preterm birth (prior to 37 gestational weeks and 0 days) according to average weekly alcohol intake in early pregnancy; Copenhagen University Hospital, Denmark, 2012-2016.
Abbreviations: Spontaneous preterm birth (SPTB), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, education, chronic disease, BMI, recreational drugs, physical activity, smoking, parity, and assisted reproductive technology. **Adjusted for maternal age, education, chronic disease, BMI, recreational drugs, physical activity smoking, parity, assisted reproductive technology and binge drinking in early pregnancy.

Figure 1: Inclusion of study population, Copenhagen University Hospital 2012-2016.