Heavy prenatal alcohol exposure and obstetric and birth outcomes: a Danish nationwide cohort study from 1996 to 2018

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Summary

Background Heavy alcohol use during pregnancy can harm the fetus, but the relation to most obstetric outcomes remains unclear. We therefore aimed to describe maternal characteristics and estimate the association between heavy prenatal alcohol exposure and 22 adverse obstetric and birth outcomes.

Methods We carried out a Danish nationwide register-based historical cohort study, including all singleton births from Jan 1, 1996, to Dec 31, 2018. Births of women who had emigrated to Denmark were excluded from the study due to missing data and women who migrated within 1 year before or during pregnancy were also excluded due to loss to follow-up. Data were extracted from the Danish Medical Birth Register, the Danish National Patient Registry, the Danish National Prescription Registry, the Danish Civil Registration System, and the Population Education Register. Logistic regression models were used to estimate crude and adjusted odds ratios (ORs) of obstetric and birth outcomes. Heavy alcohol use was defined by hospital contacts for alcohol-attributable diagnoses given to the mother, her infant, or both, or maternal redeemed prescriptions for drugs to treat alcohol dependence within 1 year before or during pregnancy.

Findings Of 1 191 295 included births, 4823 (0·40%) were defined as heavily alcohol-exposed and 1 186 472 were categorised as a reference group with no identified heavy prenatal alcohol exposure. Heavy-alcohol-exposed births more often had mothers with psychiatric diagnoses (49·8% *vs* 9·6%), substance use (22·0% *vs* 0·4%), tobacco use (64·3% *vs* 15·8%), and low educational level (64·1% *vs* 17·6%) than did the reference group. For heavy-alcohol-exposed births, significantly increased adjusted ORs were found for small for gestational age (OR 2·20 [95% CI 1·97–2·45]), preterm birth (OR 1·32 [1·19–1·46]), haemorrhage in late pregnancy (OR 1·25 [1·05–1·49]), and preterm prelabour rupture of membranes (OR 1·18 [1·00–1·39]). Decreased adjusted ORs were found for postpartum haemorrhage (500–999 mL; OR 0·80 [95% CI 0·69–0·93]), gestational diabetes (OR 0·81 [0·67–0·99]), planned caesarean section (OR 0·82 [0·72–0·94]), pre-eclampsia and eclampsia (OR 0·83 [0·71–0·96]), and abnormalities of forces of labour (OR 0·92 [0·86–0·99]).

Interpretation Heavy prenatal alcohol exposure is associated with adverse obstetric and birth outcomes and high proportions of maternal low educational level, psychiatric disease, and lifestyle risk behaviours. These findings highlight a need for holistic public health programmes and policy attention on improving pre-conceptional care and antenatal care.

Funding The Obel Family Foundation, The Health Foundation, TrygFonden, Aase and Ejnar Danielsens Foundation, The North Denmark Region Health Science and Research Foundation, Holms Memorial Foundation, Dagmar Marshalls Foundation, the A.P. Møller Foundation, King Christian X Foundation, Torben and Alice Frimodts Foundation, the Axel and Eva Kastrup-Nielsens Foundation, the A.V. Lykfeldts Foundation.

Lancet Public Health 2023; 8: e28–35

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Introduction

Health protection agencies, national health authorities, and clinical guidelines advocate abstinence from alcohol during pregnancy.[1] Alcohol use among women of reproductive age is common, and globally nearly 10% of women consume alcohol during pregnancy.[2] In Denmark, prevalence of heavy prenatal alcohol consumption was estimated to be between 0·1% and 0·4% from 1995 to 2009.[3]

Heavy prenatal alcohol exposure can result in impaired fetal development[4–6] and fetal alcohol spectrum disorders,[4] and has been established as a risk factor for fetal death,[5,7] small for gestational age,[5,6] and preterm birth.[5–7] However, there is uncertainty regarding other obstetric and birth complications, and many obstetric outcomes are left unexamined. A meta-analysis with seven studies reported no association between alcohol and gestational diabetes.[8] However, the included studies

Research in context

Evidence before this study

Alcohol can interfere with normal fetal development. Heavy alcohol drinking during pregnancy is associated with small for gestational age, low birthweight, preterm birth, and fetal death. Alcohol use during pregnancy is common in many countries, but the effect of heavy alcohol drinking on most obstetric outcomes and the related maternal characteristics are less clear. We searched PubMed from inception to Dec 13, 2021, for studies investigating the association between heavy prenatal alcohol exposure and obstetric and birth conditions. The search terms were "((pregnancy OR obstetrical OR neonatal) OR (pregnanc* OR obstetric* OR neonatal*)) AND (heavy AND alcohol)" with no language restrictions. The search generated 939 studies. The identified articles predominantly investigated the association between prenatal alcohol exposure and birth outcomes. Methodological heterogeneity among studies, design limitations such as recall bias, and a wide range of publication years were observed. Thus, the extent of obstetric and birth complications related to heavy alcohol exposure is uncertain and remains to be comprehensively studied with objective, large-scale data.

Added value of this study

We used Danish nationwide registries including more than 1·1 million births to describe maternal characteristics and the association between heavy prenatal alcohol exposure and obstetric and birth outcomes. This study provides new insight into the pattern of 22 adverse obstetric and birth outcomes. Most outcomes showed an uncertain association after adjustment; these were anaemia, Apgar score of less than 7 after 5 min, emergency caesarean section, forceps or vacuum delivery, haemorrhage in early pregnancy, liver disorders, perinatal mortality, placenta praevia, placental abruption, post-partum haemorrhage (>999 mL), retained placenta and membranes, stillbirth, and uterine rupture. Our findings provide important knowledge of the profile of pregnant women with heavy alcohol use and show a strong association with maternal psychiatric disease, substance use, and tobacco use.

Implications of all the available evidence

Heavy alcohol use during pregnancy is a high-risk behavior associated with maternal vulnerability and adverse obstetric and birth outcomes, which endanger both maternal and fetal health. The association between heavy alcohol exposure and both small for gestational age and preterm birth is marked, both of which are precursors of infant morbidity and mortality. Protecting maternal and children´s health begins pre-conceptionally. Heavy alcohol use during pregnancy and the associated risks require immediate action and persistent attention in antenatal planning, in addition to intervention at all levels.

had contrary results.[8] Another meta-analysis of placenta-related outcomes found increased odds for placental abruption, but no association with placenta praevia.[9] Most of the included studies investigating placenta-related outcomes relied on maternal self-reported information on alcohol consumption and some studies did not include a thorough analysis of potential confounders.[9] Furthermore, one study identified an association between low or moderate alcohol exposure and placenta accreta, while another study found no association between heavy alcohol exposure and pre-eclampsia.[9]

Maternal risk factors for obstetric and birth outcomes are multidimensional. Alcohol use during pregnancy has been related to risk behaviours such as co-use of substances and tobacco, both of which can affect obstetric and birth outcomes.[10] Furthermore, maternal age, parity, and concurrent maternal somatic and psychiatric diseases are examples of risk factors for adverse obstetric and birth outcomes.

The existing evidence is based on studies with varying sample size and range of publication years and evidence based on a more contemporary population with access to modern antenatal care strategies is scarce. We therefore aimed to: (1) investigate the association between heavy prenatal alcohol exposure and a wide range of obstetric and birth outcomes within a nationwide cohort, thus allowing for a broad insight; and (2) describe maternal characteristics of heavy alcohol users.

Methods

Study design and participants

This historical cohort study is based on Danish nationwide registries.[11] The Danish welfare system offers pregnant women free antenatal care, including three general practitioner visits, four midwife visits, and ultrasound scans in gestational weeks 13–14 and 18–20. Our study population comprised singleton births from Jan 1, 1996, to Dec 31, 2018. We excluded births of women who emigrated to Denmark due to a large proportion of missing data and women who migrated within 1 year before or during pregnancy due to loss to follow-up (appendix p 2). In accordance with the General Data Protection Regulation, approval to use the data sources for research purposes was granted by the data institute in the Capital Region of Denmark (approval number: P-2019-280). In Denmark, ethical committee approval or patient consent are not required for register-based studies.

See Online for appendix

Procedures

All residents in Denmark receive a unique Civil Personal Registration number for administrative purposes (eg, for contact with the health-care system).[12,13] We linked each

birth record to the mother using this Civil Personal Registration number and relevant register data.

We obtained data from the Danish Medical Birth Register concerning date of birth, stillbirth, fetal sex, gestational age, birthweight, Apgar score, and maternal data on age at birth, parity, tobacco use, and body-mass index (BMI) at the first antenatal care visit.[14] The Danish National Patient Registry contains information on hospital admissions since 1977, and outpatient and inpatient hospital contacts since 1995.[15] From this registry we obtained data on outpatient and inpatient hospital contacts, diagnosis codes according to the International Classification of Diseases (8th Revision and 10th Revision [ICD-10]), and surgical procedure codes according to the Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures.[16] Information on redeemed prescriptions from Danish pharmacies was extracted from the Danish National Prescription Registry according to the Anatomical Therapeutic Chemical codes.[17] We obtained data on ethnicity based on the participants' own or parents' country of birth from the Danish Civil Registration System.[12] Data on maternal highest educational level at delivery was extracted from the Population Education Register.[18] The data were collected continuously at the time of use of health-care services and directly transferred into the registers used. The Danish registries have been validated, previously described in detail, and are generally of high quality and completeness.[13]

Heavy prenatal alcohol exposure was our primary interest. As a proxy measure, we used pharmacological treatment of alcohol dependence and clinically recognised conditions, by definition, caused directly by alcohol use, defined as the presence of one or more of the following criteria: (1) maternal contact with a hospital with a 100% alcohol-attributable diagnosis within 1 year before or during pregnancy; (2) redeemed prescription for drugs to treat maternal alcohol dependence within 1 year before or during pregnancy; (3) a prenatal alcohol-related diagnosis given to the child after their birth (appendix p 6). The 100% alcohol-attributable diagnoses cover acute and chronic conditions according to pre-existing lists selected by experts on alcohol and based on previous evidence.[19,20] Pregnant women were systematically screened for alcohol use at the first antenatal care visit. If excessive use was reported, the woman was referred to hospital and given a 100% alcohol-attributable diagnosis. Exposure within 1 year before the index pregnancy was included as pre-pregnancy drinking has been shown as a strong predictor of pregnancy drinking.[21] An Australian study showed that about 51% of mothers had a recorded alcohol-attributable diagnosis both before and during pregnancy.[22] The pregnancy period was estimated by subtracting recorded gestational age at birth from the date of birth. Ultrasound pregnancy dating has, before 2005, been performed in weeks 17–18 and since 2005 in weeks 11–14 by measurement of biparietal diameter, including crown–rump length since 2008.[23] Missing data on gestational age was replaced with 40 weeks' gestation.

Outcomes and covariates

We examined 22 outcomes. Three outcomes were analysed with exclusion of stillbirths: (1) Apgar score of less than 7 after 5 min (Apgar <7/5), which was a proxy for perinatal asphyxia. Recorded Apgar scores contained errors in 1996; therefore we used data from 1997 to 2018. (2) Small for gestational age was a composite of the diagnosis SGA (ICD-10: P05·1) or a birth weight of less than 2 standard deviations (SDs) below the mean for gestational age according to the ultrasound-based reference curve commonly used in Denmark.[24] Gestational age of less than 25+0 weeks or more than 42+6 weeks, and extreme small for gestational age curve values (SD +/–4 from the mean) were excluded to avoid misclassification (appendix p 10). (3) Preterm birth was a composite of the diagnosis preterm infant (ICD-10: P07.3, P07.2) or gestational age of less than 37 weeks. In Denmark, livebirth is defined as any signs of life after complete expulsion or extraction from the uterus, irrespective of pregnancy duration.[25] Stillbirth was defined as pregnancy loss or death at or after 28 weeks before 2004, and from 2004, as pregnancy loss or death at or after 22 weeks' gestation.[25] Perinatal mortality was defined as stillbirth and death within 7 days after birth. Gestational diabetes was diagnosed at a risk factor-based screening by a 75 g oral glucose challenge test with a 2-h venous or capillary plasma glucose of 9·0 mmol/L or higher. Pre-eclampsia was defined as systolic blood pressure of 140 mm Hg or higher and diastolic blood pressure of 90 mm Hg or higher, accompanied by proteinuria (≥0·3 g/day or ≥1+[20 mg/dl] on a urine dipstick). Haemorrhage in early pregnancy was defined as bleeding before 11 weeks and 6 days of gestation, and haemorrhage in late pregnancy was defined as bleeding from 12 completed weeks onwards. Postpartum haemorrhage was defined as 500–999 mL and more than 999 mL of blood loss within 24 h after delivery. Blood loss estimation was measured by volume, as has been standard procedure since 2012. Preterm pre-labour rupture of membranes (PPROM) was defined as rupture of membranes before labour before 37 weeks. Anaemia was defined as haemoglobin concentrations of less than 110 g/l and approximately 6·8 mmol/l in the first trimester and less than 105 g/l and approximately 6·5 mmol/l in the second and third trimesters. Emergency caesarean section was performed within 8 h after a decision was made that it was required, and planned caesarean section scheduled 8 hours after the decision. Any use of vacuum or forceps during delivery was evaluated as a composite endpoint. Abnormalities of forces of labour included hypertonic uterine dysfunction, labour dystocia, labour weakness, and failed induction of labour. Uterine rupture included both incomplete and

	Total (n=1 191 295)	Reference group (n=1 186 472)	Heavy-alcohol-exposed group (n=4823)
Fetal sex*			
Female	578 179/1 188 503 (48·6%)	575 862/1 183 704 (48·6%)	2317/4799 (48·3%)
Male	610 324/1 188 503 (51·4%)	607 842/1 183 704 (51·4%)	2482/4799 (51·7%)
Maternal age, years			
12–19	15 929 (1·3%)	15 437 (1·3%)	492 (10·2%)
20–29	541 300 (45·4%)	538 781 (45·4%)	2519 (52·2%)
30–39	602 756 (50·6%)	601 118 (50·7%)	1638 (34·0%)
40–49	31 275 (2·6%)	31 101 (2·6%)	174 (3·6%)
50–61	35 (<0·1%)	35 (<0·1%)	0
Ethnicity			
Danish	1 169 365 (98·2%)	1 164 603 (98·2%)	4762 (98·7%)
Other	21 930 (1·8%)	21 869 (1·8%)	61 (1·3%)
Parity			
Nulliparous	548 039 (46·0%)	545 106 (45·9%)	2933 (60·8%)
Parous (1)	444 358 (37·3%)	443 382 (37·4%)	976 (20·2%)
Parous (>1)	198 898 (16·7%)	197 984 (16·7%)	914 (19·0%)
Maternal chronic somatic diseases†	133 503 (11·2%)	132 582 (11·2%)	921 (19·1%)
Maternal psychiatric diseases‡	116 551 (9·8%)	114 147 (9·6%)	2404 (49·8%)
Substance use§	5294 (0·4%)	4231 (0·4%)	1063 (22·0%)
ISCED			
Primary and lower secondary	211 445 (17·7%)	208 353 (17·6%)	3092 (64·1%)
Upper secondary	486 393 (40·8%)	485 112 (40·9%)	1281 (26·6%)
Short cycle tertiary and Bachelor's degree or equivalent	357 126 (30·0%)	356 764 (30·1%)	362 (7·5%)
Master's degree or equivalent and Doctoral degree or equivalent	136 331 (11·4%)	136 243 (11·5%)	88 (1·8%)
Tobacco use¶	157 185/989 909 (16·0%)	154 627/979 930 (15·8%)	2558/3979 (64·3%)
Missing	36 292/989 909 (3·6%)	36 109/979 930 (3·7%)	183/3979 (4·6%)
BMI‖			
Underweight (<18·5 kg/m²)	28 842/702 084 (4·1%)	28 563/699 138 (4·1%)	279/2946 (9·5%)
Normal (18·5–24·9 kg/m²)	441 637/702 084 (62·9%)	439 790/699 138 (62·9%)	1847/2946 (62·7%)
Overweight (25·0–29·9 kg/m²)	149 645/702 084 (21·3%)	149 130/699 138 (21·3%)	515/2946 (17·5%)
Obese (30·0–34·9 kg/m²)	59 726/702 084 (8·5%)	59 509/699 138 (8·5%)	217/2946 (7·4%)
Obese (>34·5 kg/m²)	22 234/702 084 (3·2%)	22 146/699 138 (3·2%)	88/2946 (3·0%)
Missing	46 293/748 377 (6·2%)	46 038/745 176 (6·2%)	255/3201 (8·0%)

Data are n (%) or n/N (%). ISCED=International Standard Classification of Education. BMI=body-mass index. *The distribution of fetal sex excludes stillbirths. †Maternal chronic somatic disease registered within 10 years before birth. ‡Maternal psychiatric disease registered within 2 years before birth. §Maternal substance use registered 1 year before or during pregnancy. ¶The distribution of tobacco is only available for 1999–2018. ‖The distribution of BMI is only available for 2004–18.

Table: **Baseline characteristics**

complete type. Retained placenta and membranes comprised conditions indicating manual removal, placenta accrete vera without deep invasion of the myometrium, and placental percreta with visible growth through the uterine wall. Furthermore, we examined placental abruption, placenta praevia, and liver disorders related to pregnancy. Additional ICD-10 and surgical procedure codes outcome definitions are listed in the appendix (p 7).

Maternal psychiatric disease was defined by the diagnosis: mental disorders complicating pregnancy, childbirth, and the puerperium (ICD-10: O99·3B) during pregnancy or conditions within the ICD-10 chapter Mental and behavioural disorders (F20-F99) within 2 years before delivery to ensure current illness. Maternal chronic somatic disease was defined by a chronic condition, as reported by Jølving and colleagues,[26] within 10 years before delivery (appendix p 8). Prenatal exposure to substance was defined by hospital contact for substance-attributable diagnoses (appendix p 9) given to the newborn or the mother within 1 year before or during pregnancy. Parity was categorised according to status before the index birth as 0, 1, and more than 1 (multiparous). Missing data on parity was replaced with counts of recorded before the index birth for each woman in the Danish Medical Birth Register.[14] We used maternal highest-achieved educational level at delivery as a proxy for socioeconomic status and categorised levels into five groups according to the International Standard Classification of Education (appendix p 9).[27] Births with missing educational information were coded as primary and lower secondary. Tobacco use was based on self-reported information given at the first antenatal care visit, which was systematically registered from 1999 to 2018. Pre-pregnancy BMI was systematically registered from 2004 to 2018. BMI outside the range of 14 to 60 kg/m² or less was excluded in order to avoid misclassification. All outcomes were examined in births with available data.

Statistical analysis

Maternal characteristics for each birth were summarised using counts and percentages, and differences were tested with χ^2 tests. Logistic regression models with robust standard errors were performed to estimate crude and adjusted ORs with 95% CIs for each outcome, according to heavy prenatal alcohol exposure yes versus no. Robust standard errors were used to account for correlations between births by mothers contributing to study data with more than one birth.[28] Outcomes were adjusted for the following potential confounders: maternal age, parity, maternal psychiatric and chronic somatic diseases, substance use, and highest attained educational level. Outcomes concerning liveborn infants were further adjusted for fetal sex. BMI (<18·5, 18·5–24·9, 25·0–29·9, 30·0–34·9, >34·5 kg/m²), education (primary and lower secondary, upper secondary, short cycle tertiary and Bachelor's degree or equivalent, or Master's degree or equivalent and Doctoral degree or equivalent), parity (nulliparous, multiparous),

and ethnicity (Danish, other) were entered in models as categories, and age as a continuous variable. All confounders were selected before analyses. Sensitivity analyses were done by repeating the aforementioned logistic regression model using four modified exposure definitions: (1) heavy alcohol exposure restricted in time to only during pregnancy; (2) mothers with a chronic alcohol-attributable condition; (3) mothers with an acute alcohol-attributable diagnosis; (4) restriction to nulliparous. Maternal characteristics were additionally described. Furthermore, in sensitivity analyses, we added the potential confounders tobacco use from 1999 to 2018 and BMI from 2004 to 2018. All analyses were carried out as complete-case analyses and performed with R software (version 3.6.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analyses, data interpretation, or writing of the report.

Results

Of 1 407 689 Danish singleton births in 1996–2018, 1 191 295 were deemed eligible after exclusion of women who had emigrated and loss to follow-up. Of these, 4823 (0·4%) were identified to have had heavy prenatal alcohol exposure and 1 186 472 were categorised as a reference group without identified prenatal heavy alcohol exposure. Further details of selection of the study population are shown in the appendix (p 2).

Baseline characteristics of the study population are presented in the table. Heavily alcohol-exposed mothers were more often younger than 30 (3011 [62·4%] of 4823 *vs* 554 218 [46·7%] of 1 186 472), underweight (279 [9·5%] of 2946 *vs* 28 563 [4·1%] of 699 138), nulliparous (2933 [60·8%] of 4823 *vs* 545 106 [45·9%] of 1 186 472), and more often showed psychiatric (2404 [49·8%] of 4823 *vs* 1 141 147 [9·6%] of 1 186 472) and chronic (921 [19·1%] of 4823 *vs* 132 582 [11·2%] of 1 186 472) somatic diseases, substance (1063 [22·0%] of 4823 *vs* 4231 [0·4%] of 1 186 472) and tobacco use (2558 [64·3%] of 3979 *vs* 154 627 [15·8%] of 979 930), and a low educational level (3092 [64·1%] of 4823 *vs* 208 353 [17·6%] of 1 186 472) compared with the reference group (table 1). We found the same characteristics in subgroups of alcohol-exposed mothers (appendix pp 11–14), with the exception of mothers with alcohol exposure restricted to during pregnancy (appendix p 11) and a chronic alcohol-attributable condition (appendix p 12), who were more often adolescent mothers, and nulliparous or multiparous compared with the reference group. Chronic alcohol-attributable conditions were associated with the highest proportion of maternal psychiatric diseases (55·9%) compared with the other subgroups (appendix pp 11, 13–14). Mothers with alcohol exposure restricted to during pregnancy (appendix p 11) had a low educational level (67·1%), high amounts of substance use (34·6%) and tobacco use (71·8%), age older than 39 years (4·9%) and, together with nulliparous women (appendix pp 14) the highest proportion of underweight (9·4–9·9%). Mothers with an acute alcohol-attributable diagnosis had the highest proportion of births during adolescence (17·0%), nulliparous births (71·9%), and maternal chronic somatic diseases (20·6%; appendix p 13).

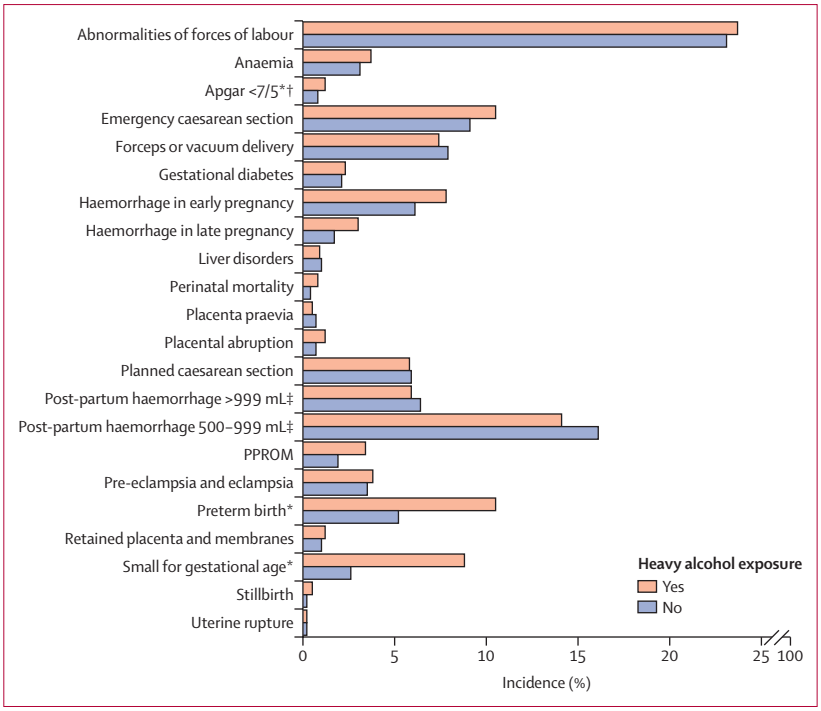

***Figure 1*: Incidences of obstetric and birth outcomes among births with heavy alcohol exposure compared with the reference group**

Apgar <7/5=Apgar score of less than 7 after 5 min. PPROM=preterm pre-labour rupture of membranes. *Incidences excluded stillbirths and missing data. †The distribution of Apgar scores were available for 1997–2018. ‡The distribution of post-partum haemorrhage data were available for 2012–18. Further details regarding counts and numbers are presented in the appendix (pp 2, 10).

Incidences of obstetric and birth outcomes are presented in figure 1 and the appendix (p 10). The incidence of perinatal mortality, very and moderate to late preterm birth, small for gestational age, and stillbirth were at least twice as high for alcohol-exposed births as for the reference group. The unadjusted and adjusted ORs from the logistic regression analysis are presented in figure 2. Alcohol exposure was significantly associated with increased adjusted ORs for small for gestational age (OR 2·20 [95% CI 1·97–2·45]), preterm birth (OR 1·32 [1·19–1·46]), haemorrhage in late pregnancy (OR 1·25 [1·05–1·49]), and PPROM (OR 1·18 [1·00–1·39]). Furthermore, we found significantly decreased adjusted ORs for postpartum haemorrhage 500–999 mL (OR 0·80 [95% CI 0·69–0·93]), gestational diabetes (OR 0·81 [0·67–0·99]), planned caesarean section (OR 0·82 [0·72–0·94]), pre-eclampsia and eclampsia (OR 0·83 [0·71–0·96]), and abnormalities of forces of labour (OR 0·92 [0·86–0·99]). In the unadjusted analysis, significantly increased ORs were additionally

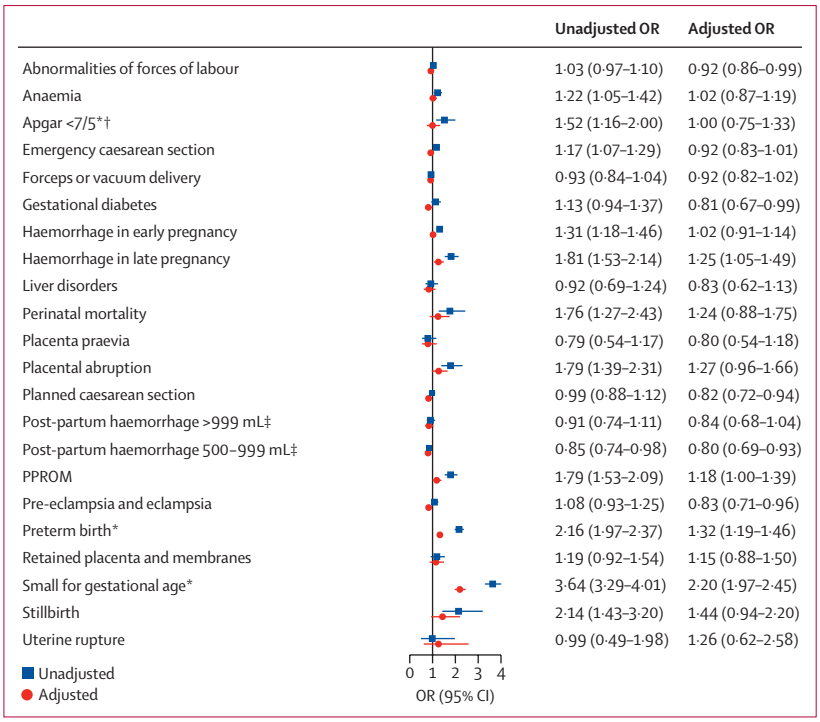

***Figure 2*: Association between heavy alcohol exposure and obstetric and birth outcomes**
ORs were adjusted for maternal age, parity, maternal chronic somatic and psychiatric disease, substance use, and educational level. Apgar <7/5=Apgar score of less than 7 after 5 min. OR=odds ratio. PPROM=preterm pre-labour rupture of membranes. *Analyses excluded stillbirths and missing data. †The distribution of Apgar scores were available for 1997–2018. ‡The distribution of post-partum haemorrhage data were available for 2012–18. Further details are presented in the appendix (p 2).

observed for anaemia, Apgar <7/5, emergency caesarean section, haemorrhage in early pregnancy, perinatal mortality, placental abruption, and stillbirth, but attenuated following adjustment for potential confounders (figure 2).

Overall, results from the adjusted main and sensitivity analyses of women with alcohol exposure restricted to during pregnancy, with chronic alcohol use, and nulliparous women were comparable with the exception of significantly decreased ORs for abnormalities of forces of labour, and for nulliparous forceps or vacuum delivery (appendix p 3). Acute alcohol-attributable diagnosis was associated with stillbirth, but not small for gestational age, preterm birth, and PPROM after adjustment (appendix p 3). Results of the sensitivity analyses with tobacco and BMI were comparable with the main analyses (appendix pp 4–5).

Discussion

This study showed that heavy prenatal alcohol exposure was associated with small for gestational age, preterm birth, haemorrhage in late pregnancy, and PPROM after adjustment for potential confounders. By contrast, a negative association was found for gestational diabetes, post-partum haemorrhage 500–999 mL, planned caesarean section, pre-eclampsia and eclampsia, and abnormalities of forces of labour. Abnormalities of forces of labour, anaemia, haemorrhage in early and late pregnancy, post-partum haemorrhage, caesarean section, forceps or vacuum delivery, liver disorders, PPROM, and uterine rupture are, to our knowledge, novel findings that have not previously been reported.

Maternal heavy alcohol use is associated with substantial clustering of lifestyle health risks such as tobacco use and substance use, and psychiatric diseases reflecting maternal vulnerability. Whether alcohol leads to risk behaviour or vice versa is unknown. We found that heavy alcohol exposure was negatively associated with gestational diabetes; however, a previously published meta-analysis (including seven observational studies) concluded no association, nonetheless the included studies found contradictory results and levels of alcohol consumption unclear.[8]

Our findings of increased odds for PPROM and haemorrhage in late pregnancy were expected, as they are precursors of preterm birth. Although our definition of preterm birth included both spontaneous preterm labour and induced labour, the increased OR of PPROM and reduced OR of pre-eclampsia and planned caesarean section suggest that preterm birth was mainly triggered by spontaneous preterm labour. The decreased association for planned caesarean section might be related to the higher incidence of PPROM (3·4% *vs* 1·9%) and possibly increased surgical risk factors in heavy-alcohol-exposed individuals; hence doctors might be less likely to suggest caesarean section as mode of delivery. The negative association for post-partum haemorrhages 500–999 mL was unexpected and might be partly related to the higher incidence of placental abruption (1·2% *vs* 0·7%) resulting in immediate treatment, which possibly prevents post-partum haemorrhage.

Salihu and colleagues[5] assessed the biological mechanisms of alcohol in placental and fetal development by examining the effect of prenatal alcohol exposure on the risk of placenta-associated syndromes defined as the occurrence of either placental abruption, placenta praevia, pre-eclampsia, small for gestational age, preterm birth, or stillbirth. They identified an association for placenta-associated syndromes, but no association with preeclampsia or placenta praevia in sensitivity analyses.[5]

We found no association for haemorrhage in early pregnancy, placenta praevia, placental abruption, post-partum haemorrhage >999 mL, stillbirth, perinatal mortality, and retained placenta and membranes after adjustment. The association for pre-eclampsia and eclampsia was negative, as shown in sensitivity analyses including tobacco and BMI as potential confounders despite slightly attenuated estimates.

Contrary to our results, previous studies identified an association between heavy alcohol exposure and stillbirth.[5,7] The studies were based on maternal self-reported alcohol consumption and controlled for potential confounders, but substance use and psychiatric

and somatic diseases were not included. However, we found stillbirth associated with an acute alcohol-attributable diagnosis. Acute alcohol-attributable versus chronic alcohol-attributable diagnoses represent different drinking patterns. However, baseline characteristics were generally comparable. We found five outcomes negatively associated with alcohol; however, prenatal alcohol consumption is not considered beneficial.

A strength of this study is the nationwide population-based design and large sample size. Furthermore, the Danish tradition of extensive data collection of its population allowed adjustment for several potential confounders. Although a distinction in quantity and type of tobacco use and substance use would be preferable, such a distinction was not possible. Nonetheless, recall bias and co-use of substances seem probable. However, despite the free antenatal care and a general high health status in Danish pregnant women, residual confounding cannot be excluded—heavy alcohol use indicates a maternal vulnerability possibly related to clustering of adversities, which can impact stress and other lifestyle factors that perhaps affect obstetric and birth outcomes.[21] Furthermore, some women with heavy alcohol use might not participate in antenatal care, leading to unrecognised obstetric complications such as gestational diabetes, pre-eclampsia, anaemia, and light haemorrhage. Anaemia and light haemorrhage can also be handled by the general practitioner, resulting in a possible under-estimation of our findings. Moreover, results might be more pronounced in populations with less health-care access. Another limitation is the high incidence for some outcomes preventing the interpretation of ORs as relative risks.

The observational unit of births instead of pregnancies was a limitation. Prenatal alcohol exposure is a risk factor for pregnancy loss and we found a higher incidence of stillbirths among heavy-alcohol-exposed pregnancies than in the reference group. Hence, pregnancy loss as well as therapeutic terminations represents competing risk. Thus, the remaining cohort might represent more robust pregnancies, which potentially can result in underestimation of risks attributable to prenatal heavy alcohol exposure.

Alcohol consumption during pregnancy has declined substantially in Denmark.[29] Our results were generated based on any hospital contact with 100% alcohol-attributable diagnosis given to the mother or child and maternal alcohol treatment as an objective proxy measure with the potential to include individuals that would not self-report heavy alcohol use. Recall bias was avoided. However, our estimates did not account for non-identified alcohol-attributable diseases. Misclassification could bias the reference group. Nonetheless, we consider misclassification to have a minor effect on results from the large reference group.

A further limitation was lack of information on timing, quantity, frequency, and type of alcohol consumed, which might vary from none to daily heavy alcohol use, potentially underestimating the obstetric and birth outcomes on average. However, several births met more than one inclusion criterion. Furthermore, 37% of women in alcohol treatment were observed with heavy alcohol exposure restricted to during pregnancy, and additionally 481 (10%) births exclusively met the exposure inclusion criterion of an alcohol-related diagnosis given to the child, of which 141 (29%) had fetal alcohol syndrome. Overall, we consider the exposed cohort to represent pregnancies experiencing the utmost alcohol-related health consequences, which might be underestimated in this study.

Despite the health-promoting efforts of the Danish free antenatal care programme, our results emphasise a need for attention to pre-conceptional health and prenatal alcohol exposure. Our results highlight maternal heavy alcohol use as part of a complex lifestyle. Prenatal alcohol exposure remains an urgent public health problem, which seems not to be remedied without a holistic approach targeting detection, prevention, and intervention towards women in a vulnerable position in life. In accordance with our knowledge of fetal alcohol spectrum disorders,[4] our results show that prenatal alcohol exposure is particularly harmful to fetal health—especially small for gestational age and preterm birth, which are both precursors of infant morbidity and mortality.

In conclusion, heavy prenatal alcohol exposure is associated with adverse obstetric and birth outcomes and higher proportions of maternal low educational level, psychiatric disease, and lifestyle risk behaviors. However, alcohol consumption is common in many countries.[2] Our exposed group represents women and their children personally experiencing the most adverse alcohol-related consequences. This highlights a need for attention and a holistic approach towards prenatal alcohol exposure starting with pre-conceptional care for everyone.

Contributors

MB, CT-P, BMH, USK, KS-L, and TL conceptualised and designed the analysis; MB and CT-P verified the underlying data and did the data analysis; MB and JMW created the figures. All authors interpreted the results. MB wrote the first draft of the manuscript. All authors revised the work critically for intellectual content and approved the final version of the work to be published; all authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. TL, CT-P, and MB were responsible for project administrative and material support. USK, CT-P, BMH, and KS-L supervised the study. MB and CT-P have accessed and verified the underlying data. All authors confirm that they had access to the data and accept responsibility for the decision to submit for publication.

Declaration of interests

CT-P reports grants for studies from Bayer and Novo Nordisk unrelated to the current study. All other authors declare no competing interests.

Data sharing

The nationwide and highly sensitive data used were made available only within the highly protected environment of the research facilities in the

state organisation Statistics Denmark. Inquiries about secure access to data under conditions stipulated by the Danish Data Protection Agency should be directed to the corresponding author. The authors of this paper are authorised and willing to discuss such requests with international colleagues.

Acknowledgments

We would like to thank Jette Meelby, Academic Health Librarian, for valuable information-gathering for our study. This study was supported by The Obel Family Foundation, The Health Foundation, TrygFonden, Aase and Ejnar Danielsens Foundation, The North Denmark Region Health Science and Research Foundation, Holms Memorial Foundation, Dagmar Marshalls Foundation, A.P. Møller og Hustru Chastine Mc-Kinney Møllers Foundation, Kong Christian den Tiendes Fond, Torben and Alice Frimodts Foundation, Tømrermester Axel Kastrup-Nielsen & Hustru Eva Kastrup-Nielsens Memorial Foundation, and Grosserer A.V. Lykfeldts og Hustrus Foundation.

References

1 Schölin L. Prevention of harm caused by alcohol exposure in pregnancy: rapid review and case studies from member states. 2016. https://apps.who.int/iris/handle/10665/329491 (accessed Sept 28, 2022).

2 Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. *Lancet Glob Health* 2017; **5:** e290–99.

3 Petersen GL, Kesmodel US, Strandberg-Larsen K. Alkoholforbrug blandt gravide og kvinder i den fertile alder i Danmark. 2015. https://www.sst.dk/-/media/Udgivelser/ 2015/Alkoholforbrug-blandt- gravide-og-kvinder-i-den-fertile- alder-i-Danmark_160315. ashx?la= da&hash= D1B41F1E20516A1626BF7C49A6DE13 E13AA1B375 (accessed Sept 28, 2022).

4 Hoyme HE, Kalberg WO, Elliott AJ, et al. Updated clinical guidelines for diagnosing fetal alcohol spectrum disorders. *Pediatrics* 2016; **138:** 20154256.

5 Salihu HM, Kornosky JL, Lynch O, et al. Impact of prenatal alcohol consumption on placenta-associated syndromes. *Alcohol* 2011; **45:** 73–79.

6 Patra J, Bakker R, Irving H, et al. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA): a systematic review and meta-analyses. *BJOG* 2011; **118:** 1411–21.

7 Bailey BA, Sokol RJ. Prenatal alcohol exposure and miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome. *Alcohol Res Health* 2011; **34:** 86–91.

8 Hu SL, He BT, Zhang, RJ. Association between maternal alcohol use during pregnancy and gestational diabetes mellitus: a meta-analysis. *Int J Diabetes Dev Ctries* 2021; **41:** 189–95.

9 Steane SE, Young SL, Clifton VL et al. Prenatal alcohol consumption and placental outcomes: a systematic review and meta-analysis of clinical studies. *Am J Obstet Gynecol* 2021; **225:** 607.e1–22.

10 May PA, Gossage JP. Maternal risk factors for fetal alcohol spectrum disorders: not as simple as it might seem. *Alcohol Res Health* 2011; **34:** 15–26.

11 Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011; **39:** 12–16.

12 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014; **29:** 541–49.

13 Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019; **11:** 563–91.

14 Bliddal M, Broe A, Pottegård A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register. *Eur J Epidemiol* 2018; **33:** 27–36.

15 Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; **7:** 449–90.

16 The Nordic Medico-Statistical Committee. Classification of surgical procedures. https://norden.diva-portal.org/smash/get/diva2:970547/FULLTEXT01.pdf (accessed Sept 28, 2022).

17 Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: the Danish National Prescription Registry. *Int J Epidemiol* 2017; **46:** 798–798f.

18 Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011; **39:** 91–94.

19 Eliasen M, Becker U, Grønbæk M, et al. Alcohol-attributable and alcohol-preventable mortality in Denmark: an analysis of which intake levels contribute most to alcohol's harmful and beneficial effects. *Eur J Epidemiol* 2014; **29:** 15–26.

20 Centers for Disease Control and Prevention. Alcohol-related ICD codes. 2020. https://www.cdc.gov/alcohol/ardi/alcohol-related-icd-codes.html (accessed Sept 28, 2022).

21 Skagerström J, Chang G, Nilsen P. Predictors of drinking during pregnancy: a systematic review. *J Womens Health (Larchmt)* 2011; **20:** 901–13.

22 O'Leary CM, Halliday J, Bartu A, D'Antoine H, Bower C. Alcohol-use disorders during and within one year of pregnancy: a population-based cohort study 1985–2006. *BJOG* 2013; **120:** 744–53.

23 Skalkidou A, Kullinger M, Georgakis MK, Kieler H, Kesmodel US. Systematic misclassification of gestational age by ultrasound biometry: implications for clinical practice and research methodology in the Nordic countries. *Acta Obstet Gynecol Scand* 2018; **97:** 440–44.

24 Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr* 1996; **85:** 8430–38.

25 Sundhedsstyrelsen. Vejledning om kriterier for levende-og dødfødsel mv. 2005. https://www.sst.dk/da/udgivelser/2005/~/media/93C011AB599D483B976237969F082523.ashx (accessed Sept 28, 2022).

26 Jølving LR, Nielsen J, Kesmodel US, Nielsen RG, Beck-Nielsen SS, Nørgård BM. Prevalence of maternal chronic diseases during pregnancy—a nationwide population based study from 1989 to 2013. *Acta Obstet Gynecol Scand* 2016; **95:** 1295–304.

27 United Nations Educational, Scientific and Cultural Organization. International Standard Classification of Education ISCED 2011. 2012. http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf. (accessed Sept 28, 2022).

28 Huber P J. "The Behavior of Maximum Likelihood Estimates under Nonstandard Conditions", proceedings of the fifth Berkeley symposium on mathematical statistics and probability 1967; **5.1:** 221–33.

29 Strandberg-Larsen K, Andersen AN, Kesmodel US. Unreliable estimation of prevalence of fetal alcohol syndrome. *Lancet Glob Health* 2017; **5:** e6.