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ORIGINAL RESEARCH

Lifestyle in pregnancy and cryptorchidism in sons: a study within two large Danish birth cohorts

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Purpose: Cryptorchidism is the most frequent congenital malformation in boys and is associated with low sperm count, infertility and testicular cancer. Unhealthy maternal lifestyle during pregnancy such as smoking, high prepregnancy body mass index (BMI) as well as alcohol and caffeine intake may constitute possible risk factors for cryptorchidism, but results from the few previous studies are conflicting. We aimed to explore the association between maternal lifestyle factors and occurrence of cryptorchidism in sons.

Patients and methods: The Danish National Birth Cohort and the Aarhus Birth Cohort provided information on maternal lifestyle from early pregnancy. Data were linked to several Danish health registers, multiple imputation was used to handle missing data and Cox proportional hazards models were used to adjust for potential confounders.

Results: In total, 85,923 boys were included, and of them, 2.2% were diagnosed with cryptorchidism. We observed the strongest associations between maternal tobacco smoking and prepregnancy BMI and cryptorchidism. Sons of women who smoked 10–14 cigarettes/day had the highest hazard ratio (HR) for cryptorchidism (1.37; 95% CI: 1.06–1.76), and for maternal BMI ≥30 kg/m^2, the HR was 1.32 (95% CI: 1.06–1.65). Binge drinking was associated with an HR <1, if the women had one or two episodes in pregnancy (HR: 0.81; 95% CI: 0.67–0.98). Average maternal alcohol intake and caffeine intake during pregnancy were not significantly associated with a higher occurrence of cryptorchidism detected at birth or later in life.

Conclusion: Maternal tobacco smoking, overweight and obesity in pregnancy were associated with higher occurrence of cryptorchidism in boys in this study.

Keywords: alcohol, smoking, overweight, obesity, caffeine

Introduction

Cryptorchidism (undescended testis at birth) is the most common male congenital anomaly registered at birth or later.[1] The condition has been associated with an increased risk of low semen quality, infertility and testicular cancer in adulthood despite routinely corrective surgery during childhood.[2] Low birth weight and prematurity are well-documented predictors of cryptorchidism,[3] but in most cases, the cause is unidentified. Studies have indicated that the intrauterine environment and maternal factors probably have greater influence on the risk of cryptorchidism than paternal factors or genetics.[4] The multistage descent of the testes starts in early pregnancy around gestational week 8 and continues until approximately week 35 of gestation;[5] thus, maternal lifestyle and environmental exposures may interfere with normal testicular descent throughout pregnancy.[2]

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Several maternal lifestyle factors have been investigated in relation to cryptorchidism such as tobacco smoking, alcohol drinking, obesity and intake of caffeinated beverages during pregnancy.[6–35] However, most studies have been small, and results are inconsistent.

Using two large population-based cohorts, we aimed to model the association between risk of cryptorchidism and the aforementioned lifestyle factors. We hypothesized that exposure to maternal tobacco smoking, prepregnancy overweight and obesity as well as maternal intake of alcohol and caffeine would lead to a higher prevalence of cryptorchidism.

Patients and methods

Study population

The study utilized data from the Danish National Birth Cohort (DNBC) and the Aarhus Birth Cohort (ABC). The DNBC is a nationwide birth cohort that enrolled pregnant women from 1996 to 2002. All pregnant Danish-speaking women in Denmark who wanted to carry their pregnancy to term were eligible. Approximately 60% of the invited women participated and took part in four computer-assisted telephone interviews, two of them conducted during pregnancy: the earliest around gestational week 12, and then again at approximately gestational week 30.[36,37]

The ABC is an ongoing pregnancy cohort established in 1989. All pregnant women attending routine antennal care at Aarhus University Hospital, Denmark, have since 1989 been invited to participate by completing a self-administered questionnaire around the time of late first or early second trimester on lifestyle during pregnancy as well as on the medical and obstetric history. Until now, ~80% of the invited women have participated.[38,39]

For this study, we included women enrolled in the two birth cohorts, who gave birth to a live-born singleton boy from 1989 to 2012. Women were eligible if they had completed one of the prenatal interviews (DNBC) or questionnaires (ABC) and had a valid unique civil registration number. Since 1968, the Danish Civil Registration System has been assigning a unique civil registration number to all residents,[40] which is used in the health care system in Denmark. This unique identifier was used to link the data from the birth cohorts with the following national health registries: the Danish Medical Birth Register, with information regarding the pregnancy;[41] the Danish National Patient Register, with information on all diagnosis- and surgical codes for all in- and outpatient hospital contacts,[42] and the Danish Integrated Database for Labour Market Research, with information on social data.[43]

Exposure assessment

The exposures used in this study were the following maternal lifestyle factors; tobacco smoking, average alcohol intake and binge drinking, prepregnancy body mass index (BMI) as well as intake of caffeine from coffee, tea and cola beverages.

In the DNBC, this information was available from the telephone interviews. We used the first interview around gestational week 12 as the main source of exposure information. This was chosen to obtain a shorter recall period. If this information was missing, we used the information from the telephone interview around week 30.

In the ABC, information on maternal lifestyle came from the self-administered questionnaires. In the early period of the ABC (1989–1999), some women completed a second questionnaire in early third trimester, and if information was missing from the first questionnaire in early pregnancy, we used the information from the second. For those women who were included in both DNBC and ABC (n=3,479), we used the information from the DNBC. If data on either maternal tobacco smoking or maternal height or weight were missing from both birth cohorts, we used information from the Danish Medical Birth Register on maternal tobacco smoking (n = 230, available from 1996 to 2012) and maternal weight and height (n = 58 and n = 106, available from 2004 to 2012).

Maternal tobacco smoking

Maternal tobacco smoking during pregnancy was categorized as follows: non-smoking, stopped smoking in first trimester and 1–9, 10–14 or ≥15 cigarettes/day. Because of a higher nicotine content in other tobacco products than in cigarettes, we multiplied the numbers of cigars, cheroots and pipes by 4. "Stopped smoking" were women who reported to have smoked at the first detection of pregnancy or in very early pregnancy and did not smoke when they were interviewed (DNBC) or completed the questionnaires (ABC).

Maternal weekly alcohol intake

Maternal weekly alcohol intake during pregnancy was based on the combined average weekly intake of alcoholic beverages. One alcoholic drink was defined as one glass of wine, one bottle of beer (0.33 L) or one glass of liqueur (12.5 g alcohol/unit). The total weekly intake was categorized into 0–<1, 1–2, 3–4 and ≥5 drinks.

Maternal binge drinking

Maternal binge drinking was categorized according to the frequency of drinking five or more alcoholic drinks in one occasion, i.e., binge drinking episodes since the onset of pregnancy. We categorized the number of binge drinking episodes during pregnancy as 0, 1, 2 and ≥3 times. In ABC, questions on maternal binge drinking were not included in the early part of the cohort (1989–1998), so we limited our analysis on binge drinking in ABC to 1998 and onward.

Maternal prepregnancy BMI

Maternal prepregnancy BMI (kg/m^2) was calculated and categorized according to the World Health Organization classification: underweight: <18.5 kg/m^2, normal weight: 18.5–24.9 kg/m^2, overweight: 25–29.9 kg/m^2 and obese: ≥30 kg/m^2.[44] Outliers with excessively high or low values were recoded to missing.

Maternal caffeine intake

Maternal caffeine intake during pregnancy was based on caffeine intake from coffee, tea and cola and was categorized into 0, 1–300, 301–600 and ≥600 mg caffeine/day. We defined one cup of coffee as 100 mg of caffeine, one cup of tea as 50 mg of caffeine and 1/2 L of cola as 50 mg of caffeine according to published literature.[45,46]

Covariates

Information on covariates were either self-reported or retrieved from the Danish health registers[41] A priori, potential mediators and confounders for the five different exposures were identified by the existing literature and the use of directed acyclic graphs (DAGs).[47] In all models, we adjusted for years of education (≤9, 10–14 and ≥15 years), maternal age at birth (<25, 25–29, 30–34 and ≥35 years), parity (nulliparous and multiparous women), birth cohort (ABC or DNBC) and calendar year at birth (1989–1993, 1994–1998, 1999–2003, 2004–2008 and 2009–2012), the latter to account for the trend in the prevalence of diagnosed male genital anomalies in the Danish National Patient Register, the difference in follow-up time and the change in registration from International Classification of Diseases (ICD) version 8 to version 10 during the study period. The analyses for maternal tobacco smoking, maternal caffeine intake and maternal weekly alcohol intake and binge drinking were further adjusted for time to pregnancy (unplanned pregnancies, 0–5 months, 6–12 months and ≥12 months without assisted reproductive technology (ART) and ≥12 months with ART). The five exposures were mutually adjusted.

Outcome measures

We studied two outcomes. The first was boys with a cryptorchidism diagnosis, defined as a diagnosis of cryptorchidism according to ICD-8 (1977–1993): 75210, 75211, 75219 and ICD-10 (1994–2012): Q53. Second, we used a definition with higher positive predictive value[48] and classified boys as having cryptorchidism if they had both a diagnosis of cryptorchidism and underwent corrective surgery for cryptorchidism (orchiopexy). The Nordic classification of surgical procedures codes: KKFH00, KKFH01, KKFH10 or surgery and treatment classification of the Danish National Board of Health codes: 55640, 55600 was used to define orchiopexy.

Missing information

Missing data ranged from none for, e.g., maternal age, calendar year of birth and birth cohort, to 11.6% for maternal binge drinking (Table 1). Ignoring maternal binge drinking, 84% of the study population had complete information on all exposures, covariates and the outcomes.

We accounted for missing data by using multiple imputation.[49] This is a method widely recommended if data are missing at random (MAR);[49] data is considered to be almost MAR if the systematic difference between observed and missing values can be "explained" by the observed data, an assumption we assumed.[50] Current guidelines recommend that the number of imputations should be at least equal to the percentage of incomplete cases.[51] We fitted a multiple imputation model using chained equations and imputed 50 datasets with the following variables included in the model: maternal tobacco smoking (continuous), maternal weekly alcohol intake (categorical), maternal binge drinking (continuous), maternal prepregnancy weight and height (continuous), maternal caffeine intake (continuous), cryptorchidism, hypospadias, other malformations, maternal years of education (categorical), maternal age at birth (continuous), time to pregnancy (categorical), ART (binary), parity (categorical), nausea (binary), calendar year at birth (continuous), birth weight (continuous), gestational age (continuous) and type of cohort. Continuous variables were interval censored to ensure biologically plausible values. Binary variables were modeled using the logit function and continuous variables using the linear regression. Maternal prepregnancy weight was right skewed and transformed to approximate normality by a shifted logarithm transformation.[51]

Table 1 Distribution of maternal characteristics according to cryptorchidism among 85,923 singleton live-born boys, Denmark, 1989–2012

Characteristic	Distribution of participants, %	Cryptorchidism				Cryptorchidism – corrective surgery			
		Yes		No		Yes		No	
		n	%	n	%	n	%	n	%
Total		1,864	2.2	84,059	97.8	1,098	1.3	84,825	98.7
Smoking (cigarettes/day)									
Nonsmoker	73.8	1,289	2.0	62,117	98.0	752	1.2	62,654	98.8
Stopped smokers	9.7	211	2.5	8,118	97.5	120	1.4	8,209	98.6
1–9	8.6	180	2.4	7,229	97.6	112	1.5	7,297	98.5
10–14	4.7	110	2.7	3,946	97.3	74	1.8	3,982	98.2
≥15	2.9	66	2.6	2,450	97.4	37	1.5	2,479	98.5
Missing	0.2								
Alcohol (drinks/week)									
None to <1	70.8	1,341	2.2	59,456	97.8	792	1.3	60,005	98.7
1–2	19.7	351	2.2	16,539	97.9	197	1.2	16,693	98.7
3–4	3.9	71	2.1	3,314	97.9	44	1.3	3,341	98.7
≥5	1.6	20	1.4	1,378	98.6	15	1.1	1,383	98.9
Missing	4.0								
Binge drinking episodes (times)									
0	61.6	991	2.3	41,658	97.7	592	1.4	42,057	98.6
1	16.6	208	1.8	11,298	98.2	125	1.1	11,381	98.9
2	6.3	78	1.8	4,299	98.2	44	1.0	4,333	99.0
≥3	3.9	59	2.2	2,646	97.8	39	1.4	2,666	98.6
Missing	11.6								
Prepregnancy BMI (kg/m^2)									
<18.5	4.9	95	2.3	4,097	97.7	53	1.3	4,139	98.7
18.5–24.9	67.3	1,145	2.0	56,672	98.0	696	1.2	57,121	98.8
25–29.9	16.8	378	2.6	14,073	97.4	205	1.4	14,246	98.6
≥30	6.8	149	2.6	5,699	97.5	93	1.6	5,755	98.4
Missing	4.2								
Caffeine (mg/day)									
0	9.4	149	1.9	7,925	98.2	89	1.1	7,985	98.9
1–300	64.4	1,161	2.1	54,198	97.9	697	1.3	54,662	98.7
301–600	14.3	293	2.4	12,032	97.6	169	1.4	12,156	98.6
>600	5.5	116	2.5	4,587	97.5	68	1.5	4,635	98.6
Missing	6.4								
Age at delivery (years)									
<25	10.8	247	2.7	9,031	97.3	145	1.6	9,133	98.4
25–29	37.5	672	2.1	31,524	97.9	405	1.3	31,791	98.7
30–34	36.3	659	2.1	30,544	97.9	387	1.2	30,816	98.8
>35	15.4	286	2.2	12,960	97.8	161	1.2	13,085	98.8
Missing	0								
Parity (before this birth)									
0	48.3	979	2.4	40,492	97.6	583	1.4	40,888	98.6
≥1	51.6	885	2.0	43,498	98.0	515	1.2	43,868	98.8
Missing	0.1								
Education (years)									
Short ≤9	10.1	225	2.6	8,438	97.4	122	1.4	8,541	98.6
Medium 10–14	42.1	806	2.2	35,323	97.8	485	1.3	35,644	98.7
Long ≥15	47.2	826	2.0	39,698	98.0	488	1.2	40,036	98.8
Missing	0.7								
Time to pregnancy (months)									
0–5	50.4	889	2.1	42,424	98.0	525	1.2	42,788	98.8
6–12	12.7	240	2.2	10,695	97.8	142	1.3	10,793	98.7
≥12 without ART	5.7	121	2.5	4,796	97.5	72	1.5	4,845	98.5
≥12 with ART	5.3	108	2.4	4,453	97.6	68	1.5	4,493	98.5
Unplanned	19.2	370	2.2	16,124	97.8	226	1.4	16,268	98.6
Missing	6.6								

(*Continued*)

Table 1 (*Continued*)

Characteristic	Distribution of participants, %	Cryptorchidism				Cryptorchidism – corrective surgery			
		Yes		No		Yes		No	
		n	%	n	%	n	%	n	%
Cohort									
DNBC	53.7	1,076	2.3	45,089	97.7	627	1.4	45,538	98.6
ABC	46.3	788	2.0	38,970	98.0	471	1.2	39,287	98.8
Missing	0								
Calendar year of birth									
1989–1993	7.7	218	2.8	7,523	97.2	129	1.7	7,612	98.3
1994–1998	17.3	368	2.5	14,525	97.5	192	1.3	14,701	98.7
1999–2003	55.4	1,080	2.3	46,482	97.7	640	1.4	46,922	98.7
2004–2008	10.8	155	1.7	9,125	98.3	106	1.1	9,174	98.9
2009–2012	7.5	43	0.7	6,404	99.3	31	0.5	6,416	99.5
Missing	0								

Abbreviations: BMI, body mass index; ART, assisted reproductive technology; DNBC, Danish National Birth Cohort; ABC, Aarhus Birth Cohort.

Data analyses

Cryptorchidism is by definition present at birth but may not be diagnosed at birth; the condition may thus be diagnosed at any time during childhood.[3,52] By the end of follow-up (December 31, 2012), not all boys in the DNBC and the ABC were of the same age. To account for this variation in follow-up time, we used a Cox proportional hazards model, with the boy's age as the underlying time axis. The boys entered the risk set at birth and were followed until their age at diagnosis of cryptorchidism, death, emigration from Denmark, or the end of follow-up, whichever came first. Crude and adjusted hazard ratios (HRs) with 95% CI for cryptorchidism according to the different maternal lifestyle factors were estimated. Since the cohorts included siblings, the CIs were calculated using robust standard errors with the mother as cluster identifier. The proportional hazards assumption was verified by visual inspection of log-minus-log plots. Overall statistical significance for each exposure variable was tested using the Wald test or a test for linear trend.

We performed the following subanalyses. First, a subanalysis on the association between paternal smoking and cryptorchidism was conducted to investigate potential familial confounding. Second, we carried out a subanalysis, restricting our study population to DNBC that holds information on nausea, because women with coffee aversion and nausea are probably more likely to lower their coffee intake. Further, it has been proposed that nausea is an indicator of viability of the fetus, reflecting a healthy hormone balance in the pregnancy.[76] Third, we fitted a multiple imputation model with 100 datasets and compared the results to the main analysis using 50 datasets to check the validity of our imputation model. We compared the main result with results from a complete case analysis, and finally, we performed separate analyses in the two cohorts. Data were analyzed using STATA version 11.2 at Statistics Denmark with encrypted identification numbers and no contact with individuals. The study was approved by the Danish Data Protection Agency (No. 2013-41-1964).

Results

From the DNBC, 46,165 live-born singleton boys born from 1996 to 2003 and from the ABC 39,758 live-born singleton boys born from 1989 to 2012 were included in this study. This added up to a final study population of 85,923 mother–son pairs. Of them, 1,864 (2.2%) boys were diagnosed with cryptorchidism (1,076 from the DNBC and 788 from the ABC), and 1,098 (59%) of them underwent corrective surgery (627 from the DNBC and 471 from the ABC). The mean (range) follow-up time was 12 years (range 0–23 years).

Table 1 lists distribution of the five exposures and relevant covariates according to cryptorchidism with and without corrective surgery. The following appeared to be more frequent among mothers of boys with cryptorchidism: tobacco smoking, overweight and obesity, caffeine intake during pregnancy, maternal age <25 years at birth and short education, nulliparity, time to pregnancy of >12 months with and without ART and giving birth between 1989 and 1993.

Table 2 presents the adjusted HRs of cryptorchidism according to the maternal lifestyle factors of interest. We observed associations between maternal tobacco smoking and maternal prepregnancy BMI and occurrence of cryptorchidism.

We observed higher HR for cryptorchidism with higher exposure to maternal tobacco smoking during pregnancy, and compared to the unexposed, boys of mothers who smoked 10–14 cigarettes/day had the highest HRs for cryptorchidism

Table 2 HRs for cryptorchidism according to maternal smoking, weekly alcohol intake, binge drinking, prepregnancy BMI and caffeine intake during pregnancy among 85,923 singleton live-born boys, Denmark 1989–2012[a]

Characteristic	Distribution of participants, %	Cryptorchidism				Cryptorchidism – surgery			
		Cases, %	Crude HR	aHR	95% CI	Cases, %	Crude HR	aHR	95% CI
Smoking (cigarettes/day)[b]									
Nonsmoker	73.8	2.0	1.00	1.00	Reference	1.2	1.00	1.00	Reference
Stopped smokers	9.7	2.5	1.22	1.19	(1.03–1.38)	1.4	1.19	1.16	(0.96–1.41)
1–9	8.9	2.5	1.12	1.07	(0.91–1.25)	1.5	1.17	1.15	(0.93–1.41)
10–14	4.7	2.7	1.21	1.13	(0.92–1.39)	1.8	1.40	1.37	(1.06–1.76)
≥15	2.9	2.6	1.18	1.09	(0.84–1.42)	1.5	1.13	1.11	(0.78–1.57)
Test for trend				1.01	(1.00–1.02)			1.02	(1.00–1.03)
Wald test[b]					p=0.17				p=0.10
Alcohol (drinks/week)[c]									
None to <1	74.1	2.2	1.00	1.00	Reference	1.3	1.00	1.00	Reference
1–2	20.1	2.1	0.87	0.89	(0.79–1.00)	1.2	0.83	0.85	(0.73–1.00)
3–4	4.1	2.1	0.92	0.91	(0.71–1.16)	1.3	0.96	0.96	(0.70–1.30)
≥5	1.7	1.4	0.71	0.69	(0.44–1.08)	1.1	0.90	0.87	(0.52–1.45)
Test for trend				0.91	(0.84–0.99)			0.93	(0.83–1.03)
Wald test[c]					p=0.10				p=0.27
Binge drinking episodes (times)[c]									
None	66.3	2.2	1.00	1.00	Reference	1.3	1.00	1.00	Reference
1	21.2	1.7	0.85	0.83	(0.71–0.96)	1.0	0.87	0.81	(0.67–0.98)
2	8.2	1.6	0.85	0.80	(0.64–1.01)	1.0	0.82	0.74	(0.54–1.00)
≥3	4.3	2.1	1.01	0.92	(0.71–1.20)	1.4	1.11	0.96	(0.69–1.34)
Test for trend				0.94	(0.89–1.00)			0.94	(0.87–1.02)
Wald test[c]					p=0.03				p=0.05
BMI (kg/m^2)[d]									
<18.5	5.3	2.3	1.11	1.08	(0.88–1.33)	1.3	1.03	1.00	(0.76–1.32)
18.5–24.9	69.9	2.0	1.00	1.00	Reference	1.2	1.00	1.00	Reference
25–29.9	17.9	2.6	1.31	1.33	(1.18–1.49)	1.4	1.17	1.18	(1.01–1.38)
≥30	7.0	2.6	1.29	1.29	(1.09–1.54)	1.6	1.33	1.32	(1.06–1.65)
Wald test[d]				1.02	(1.01–1.03)			1.01	(1.00–1.03)
Test for trend					p=0.00				p=0.03
Caffeine (mg/day)[e]									
None	9.4	1.9	0.98	0.97	(0.81–1.15)	1.1	0.99	0.94	(0.75–1.18)
1–300	67.6	2.1	1.00	1.00	Reference	1.3	1.00	1.00	Reference
301–600	16.9	2.4	1.07	1.06	(0.93–1.21)	1.4	1.02	1.02	(0.85–1.21)
>600	6.1	2.6	1.09	1.06	(0.87–1.30)	1.5	1.06	1.02	(0.79–1.33)
Wald test[e]				1.00	(1.00–1.00)			1.00	(1.00–1.00)
Test for trend					p=0.77				p=0.96

Notes: [a]50 imputed sets. [b]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and alcohol intake, maternal prepregnancy BMI and time to index pregnancy. [c]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and smoking, maternal prepregnancy BMI and time to index pregnancy. [d]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and alcohol intake and maternal smoking during pregnancy. [e]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' alcohol intake and smoking, maternal prepregnancy BMI and time to index pregnancy.

Abbreviations: HR, hazard ratio; BMI, body mass index; aHR, adjusted hazard ratio.

(HR: 1.37; 95% CI: 1.06–1.76). Sons of mothers who stopped smoking in early pregnancy also had a slightly higher HR of cryptorchidism (HR: 1.16; 95% CI: 0.96–1.41). For maternal BMI, we observed a dose–response-like association. Sons of obese mothers (BMI: ≥30 kg/m^2) had the highest HR for cryptorchidism (HR: 1.32; 95% CI: 1.06–1.65). Maternal weekly alcohol intake during pregnancy was not associated with cryptorchidism. However, one or two binge-drinking episodes during pregnancy were associated with a slightly lower HR for cryptorchidism in sons compared with no binge drinking. Finally, maternal caffeine intake during pregnancy was not associated with cryptorchidism. Results from analyses of all diagnosed boys with cryptorchidism were similar to those verified by surgery.

The subanalysis on the association between paternal smoking and cryptorchidism, showed no association (data

not shown). Adjusting for nausea did not change the results on the association between caffeine intake during pregnancy and cryptorchidism (data not shown). Furthermore, we checked the robustness of the multiple imputation model and found similar results when imputing 100 datasets instead of 50 datasets (data not shown). The results of the complete case analyses were similar to our main results as presented (Table S1). Finally, stratifying by type of birth cohorts gave only small differences in the results. However, the association between prepregnancy obesity and risk of cryptorchidism was stronger in ABC compared with DNBC, and binge drinking was only associated with decreased risk in DNBC (Table S2).

Discussion

In this large population-based study; maternal tobacco smoking during pregnancy and prepregnancy overweight and obesity were associated with a higher occurrence of cryptorchidism in sons. Our results indicated no associations between weekly alcohol consumption or caffeine intake during pregnancy and cryptorchidism at the levels consumed in these cohorts. Counterintuitively, one to two binge drinking episodes were associated with HRs <1 for cryptorchidism, which could be a chance finding.

Among women who stopped smoking in early pregnancy, we observed risks of cryptorchidism similar to women smoking one to nine cigarettes during pregnancy, which may reflect the importance of the early prenatal exposure to tobacco smoking, where the fetus is more vulnerable. On the other hand, it could also indicate that these women actually were heavy smokers before pregnancy and share characteristics with smokers. In a subanalysis, we found no association between paternal smoking and cryptorchidism, but the association was strengthened when both parents smoked compared to maternal smoking alone. This could indicate that the sons were exposed to more passive smoking. It could also suggest that these women smoke to a larger extent and exposed the fetus for a longer period or more extensively than those women with a nonsmoking partner. Smoking is thought to induce hypoxia in the fetus caused by the vasoconstrictive effects of nicotine[55] but contains thousands of other potentially toxic chemicals[56] and is also associated with deficient or altered androgen signaling.[57] Although the majority of existing literature does not support an association between smoking and cryptorchidism,[8,9,12–14,17,19,23–25,27–31,34,35] our results are consistent with five previous studies,[7,11,22,26] including those of a large Danish pregnancy cohort study by Jensen et al[22] that also found a higher risk among sons exposed to >10 cigarettes/day.

Alcohol consumption during pregnancy is suspected to modify sex hormone levels in utero, which are essential for the descent of the testes.[58] However, our results point toward a lower occurrence of cryptorchidism among sons of mothers who reported binge drinking during pregnancy. A majority of previous studies reported no association between weekly alcohol intake and cryptorchidism.[9,11,12,17,19,21,25,26,28,29,32,35] A few studies have suggested a higher risk among binge drinkers[21,32] and yet others have observed a dose–response-like relationship with weekly alcohol consumption during pregnancy.[13,15] A meta-analysis by Zhang et al[33] indicated a lower risk of cryptorchidism in sons of pregnant women with low-to-moderate alcohol intake, whereas more than five drinks per week was associated with a higher risk. Our findings for binge drinking could be due to chance, selection bias, information bias or uncontrolled confounding, which is likely, as women binge drinking before versus after recognition of pregnancy have previously been shown to differ on other maternal characteristics in DNBC.[59] Separating the two cohorts showed that the HR between binge drinking and cryptorchidism was only <1 in DNBC, indicating that the women in this cohort may be healthier.[60]

Maternal overweight and obesity during pregnancy are associated with aberrant glycemic control and a less healthy nutritional status of the pregnant women.[61] It has previously been associated with other congenital anomalies.[62] In case of cryptorchidism, results have been mixed with some showing an association, whereas others not.[6,9,10,12,14,16,18,23–26,31,33,34,63] A recent register-based Swedish study by Arendt et al,[63] including 1,055,705 boys, found results similar to ours regarding cryptorchidism and obesity.

High caffeine consumption during pregnancy has previously been associated with pregnancy complications[64] and fetal death.[65] Maternal caffeine intake could result in disturbed development of the fetus because of uteroplacental vasoconstriction due to rise in maternal serum catecholamine levels and reduced blood flow to the placenta.[66] However, we found no indication to support an effect of caffeine on the risk of cryptorchidism. Only three case–control studies with a small sample size have explored the relation between maternal caffeine levels and cryptorchidism with different results.[9,20,28]

The discrepancies in previous studies on maternal lifestyle and cryptorchidism in boys could be caused by differences in ascertainment of cryptorchidism. We have classified boys with cryptorchidism using both registration

of diagnosis and corrective surgery from the Danish National Patient Registry, which has been shown to have a high positive predictive value.[48]

The present study provides sufficient power to investigate our hypotheses, although some exposures only had few highly exposed. In addition to the high number of participants, another major strength of this study was the detailed prospectively collected information on lifestyle factors and potential confounding factors from the two Danish birth cohorts. Thus, we were able to adjust for several potential confounders, yet residual confounding or confounding from unknown factors cannot be ruled out. For instance, we did not have information about diet and nutrition, and nutritional deficiencies may well be a potential confounder. We were to some extent limited by lack of information on coffee aversion and nausea in ABC, and therefore, we restricted a subanalysis to DNBC that holds information on nausea. These analyses gave results comparable to our main results.

In both the DNBC and the ABC, the participation rate was ~60% and 80%, and we used the Danish health care registers with negligible loss to follow-up. Selection bias due to nonparticipation at inclusion in both cohorts cannot be rejected but is probably not a major problem because of the early inclusion prior to the end point registration of genital anomalies or other pregnancy outcomes. Yet, participation may be associated with both the exposure and potential factors directly linked to cryptorchidism, such as time to pregnancy or prior congenital malformations. We assume that this will only be of minor importance.[60] Furthermore, our imputed model yielded results similar to the complete case analysis. We only included live-born singleton boys, which could be a potential selection problem often referred to as live–birth bias.[67] The lifestyle factors are all associated with a higher risk of fetal death,[65,68–70] and among fetal deaths, the occurrence of congenital abnormalities is high.[71] If the most highly exposed fetuses died before birth, it could theoretically have biased our results toward the null. However, cryptorchidism is a milder congenital malformation unrecognized before birth; we therefore consider this to be a minor issue.

We expect some degree of misclassification and recall bias; however, we consider it likely to be mostly non-differential, as information on lifestyle factors was collected in early pregnancy by telephone interviews in DNBC and self-administered questionnaires in ABC.

A large Norwegian cohort study comparing self-reported smoking status and plasma cotinine concentrations revealed that self-reported smoking is a valid marker for tobacco exposure in utero.[72] Further, to evaluate the validity of our tobacco smoking information, we corroborated the well-known reduction in birth weight with increasing levels of tobacco smoking during pregnancy.[53] Boys exposed to 15 or more cigarettes per day on average had 292 grams (95 % CI: −318; −266) lower birth weight than sons of non-smokers. Information on maternal alcohol intake may to some extent be underreported[73,74] due to the widespread consensus that alcohol consumption during pregnancy may damage the fetus. However, interviews and questionnaires have been shown to be reliable methods to collect information on the overall distribution of alcohol consumption in pregnant Danish women.[73] In addition, body weight tends to be underreported, and there might also be some degree of misclassification in our data.[75] We consider information about caffeine consumption not to be underreported, mainly because intake of coffee, tea and cola during pregnancy is widely accepted in Denmark. In addition, we were able to include caffeine exposure not only from tea and coffee consumption but also from intake of cola. Caffeine content depends highly on types of coffee, tea and cola and brewing methods. Unfortunately, this type of data was unavailable.

This study benefits from the use of two large birth cohorts, and by virtue of the study strengths and limitations, we believe that these findings are rather valid and may apply to other populations. Future studies could, if possible, look at siblings with different in utero exposure to limit the unmeasured time stable confounding.

Conclusion

In this large population-based cohort study, maternal tobacco smoking during pregnancy and maternal prepregnancy obesity were associated with an increased occurrence of cryptorchidism in sons, while alcohol or caffeine intake was not.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 HRs for cryptorchidism according to maternal smoking, weekly alcohol intake, binge drinking, prepregnancy BMI and caffeine intake during pregnancy among 85,923 singleton live-born boys, Denmark, 1989–2012 (Complete case)

Characteristic	Distribution of participants, %	Cryptorchidism – diagnosis				Cryptorchidism – surgery			
		Cases, %	Crude HR	aHR	95% CI	Cases, %	Crude HR	aHR	95% CI
Smoking (cigarettes/day)[a]									
Complete observations[a]	84.2								
Nonsmoker	73.8	2.0	1.00	1.00	Reference	1.2	1.00	1.00	Reference
Stopped smokers	9.7	2.5	1.22	1.20	(1.02–1.41)	1.4	1.19	1.19	(0.97–1.47)
1–9	8.6	2.4	1.10	1.13	(0.95–1.34)	1.5	1.17	1.21	(0.97–1.52)
10–14	4.7	2.7	1.21	1.26	(1.01–1.57)	1.8	1.40	1.58	(1.21–2.06)
≥15	2.9	2.6	1.18	1.00	(0.73–1.36)	1.5	1.13	0.90	(0.59–1.39)
Wald test					*p*=0.06				*p*=0.01
Alcohol (drinks/week)[b]									
Complete observations[b]	84.2								
None to <1	70.8	2.2	1.00	1.00	Reference	1.3	1.00	1.00	Reference
1–2	19.7	2.2	0.88	0.92	(0.81–1.04)	1.2	0.84	0.88	(0.74–1.04)
3–4	3.9	2.1	0.93	0.81	(0.61–1.07)	1.3	0.97	0.93	(0.66–1.30)
≥5	1.6	1.4	0.71	0.73	(0.45–1.17)	1.1	0.90	0.83	(0.47–1.47)
Wald test					*p*=0.17				*p*=0.47
Binge drinking episodes(times)[b]									
Complete observations[b]	82.7								
None	61.6	2.3	1.00	1.00	Reference	1.4	1.00	1.00	Reference
1	16.6	1.8	0.85	0.83	(0.71–0.98)	1.1	0.86	0.79	(0.64–0.96)
2	6.3	1.8	0.85	0.79	(0.62–1.01)	1.0	0.80	0.67	(0.49–0.93)
≥3	3.9	2.2	1.03	0.92	(0.69–1.22)	1.4	1.14	0.94	(0.66–1.33)
Wald test					*p*=0.05				*p*=0.02
Prepregnancy BMI (kg/m^2)[c]									
Complete observations[c]	86.5								
<18.5	4.9	2.3	1.12	1.08	(0.86–1.36)	1.3	1.03	0.98	(0.73–1.33)
18.5–24.9	67.3	2.0	1.00	1.00	Reference	1.2	1.00	1.00	Reference
25–29.9	16.8	2.6	1.33	1.33	(1.17–1.51)	1.4	1.19	1.18	(1.00–1.40)
≥30	6.8	2.6	1.30	1.26	(1.05 –1.52)	1.6	1.34	1.30	(1.02–1.64)
Wald test					*p*=0.00				*p*=0.06
Caffeine (mg/day)[d]									
Complete observations[d]	84.2								
None	9.4	1.9	0.98	0.96	(0.80–1.16)	1.0	0.98	0.95	(0.75–1.21)
1–300	64.4	2.1	1.00	1.00	Reference	1.3	1.00	1.00	Reference
400–600	14.3	2.4	1.05	1.08	(0.93–1.24)	1.4	1.01	1.03	(0.85–1.24)
>600	5.5	2.5	1.06	1.11	(0.90–1.37)	1.5	1.04	1.11	(0.85–1.45)
Wald test					*p*=0.59				*p*=0.85

Notes: [a]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and alcohol intake, maternal prepregnancy BMI and time to index pregnancy. [b]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and smoking, maternal prepregnancy BMI and time to index pregnancy. [c]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and alcohol intake and maternal smoking during pregnancy. [d]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' alcohol intake and smoking, maternal prepregnancy BMI and time to index pregnancy.

Abbreviations: HR, hazard ratio; BMI, body mass index; aHR, adjusted hazard ratio.

Table S2 HRs for cryptorchidism according to maternal smoking, weekly alcohol intake, binge drinking, prepregnancy BMI and caffeine intake in ABC and the DNBC among 85,923 singleton live-born boys, Denmark, 1989–2012 (Complete case stratified by birth cohort)

Characteristic	DNBC (n = 46,165)					ABC (n = 39,758)				
	Distribution of participants		Crude HR	aHR	95% CI	Distribution of participants		Crude HR	aHR	95% CI
	Total, %	Cases, %				Total, %	Cases, %			
Smoking (cigarettes/day)[a]										
Nonsmoker	74.4	1.3	1.00	1.00	Reference	73.1	1.1	1.00	1.00	Reference
Stopped smokers	9.1	1.6	1.29	1.26	(0.97–1.63)	10.4	1.3	1.07	1.09	(0.77–1.54)
1–9	9.0	1.5	1.15	1.16	(0.88–1.54)	8.2	1.6	1.20	1.29	(0.89–1.86)
10–14	4.6	2.1	1.64	1.66	(1.19–2.32)	4.9	1.6	1.14	1.43	(0.91–2.25)
≥15	2.9	1.5	1.18	0.99	(0.59–1.65)	3.0	1.4	1.07	0.75	(0.34–1.66)
	0.1					0.5				
Alcohol (drinks/week)[b]										
None to <1	70.9	1.4	1.00	1.00	Reference	70.6	1.2	1.00	1.00	Reference
1–2	24.4	1.2	0.86	0.88	(0.72–1.07)	14.1	1.1	0.79	0.90	(0.65–1.24)
3–4	3.6	1.3	0.94	0.88	(0.55–1.40)	4.4	1.3	1.01	1.01	(0.61–1.66)
≥5	1.0	1.3	0.88	0.96	(0.43–2.15)	2.3	1.0	0.91	0.73	(0.32–1.66)
	0.1					8.6				
Binge drinking episodes (times)[b]										
None	74.8	1.4	1.00	1.00	Reference	35.1	1.2	1.00	1.00	Reference
1	16.0	1.1	0.78	0.74	(0.58–0.94)	17.9	1.0	1.06	0.98	(0.66–1.44)
2	5.6	1.0	0.67	0.57	(0.37–0.88)	7.8	1.1	1.07	0.93	(0.55–1.55)
≥3	3.5	1.5	1.04	0.93	(0.61–1.42)	4.8	1.4	1.34	1.02	(0.54–1.92)
	0.2					34.4				
Prepregnancy BMI (kg/m²)[c]										
<18.5	4.3	1.5	1.12	1.08	(0.74–1.57)	5.5	1.1	0.94	0.85	(0.51–1.41)
18.5–24.9	64.2	1.3	1.00	1.00	Reference	70.9	1.1	1.00	1.00	Reference
25–29.9	18.4	1.5	1.11	1.10	(0.90–1.36)	14.9	1.4	1.32	1.36	(1.03–1.81)
≥30	7.7	1.6	1.21	1.21	(0.91–1.61)	5.7	1.6	1.59	1.54	(1.01–2.34)
	5.3					2.9				
Caffeine (mg/day)[d]										
0	6.6	1.4	1.01	1.03	(0.74–1.42)	12.6	1.0	0.92	0.87	(0.61–1.24)
1–300	70.0	1.3	1.00	1.00	Reference	57.9	1.2	1.00	1.00	Reference
301–600	16.1	1.5	1.08	1.07	(0.85–1.35)	12.3	1.3	0.91	0.96	(0.69–1.33)
>600	7.1	1.4	1.06	1.08	(0.78–1.48)	3.5	1.5	1.01	1.23	(0.75–2.03)
	0.1					13.6				

Notes: [a]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and alcohol intake, maternal prepregnancy BMI and time to index pregnancy. [b]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and smoking, maternal prepregnancy BMI and time to index pregnancy. [c]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' caffeine intake and alcohol intake and maternal smoking during pregnancy. [d]Adjusted for maternal years of education, maternal age at delivery, parity, calendar year, cohort, mothers' alcohol intake and smoking, maternal prepregnancy BMI and time to index pregnancy.

Abbreviations: HR, hazard ratio; BMI, body mass index; ABC, Aarhus Birth Cohort; DNBC, Danish National Birth Cohort; aHR, adjusted hazard ratio.