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Hyperemesis gravidarum and the risk of childhood cancer – A case-control study in Denmark

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ABSTRACT

Objective: Only a few studies have reported on the association between hyperemesis gravidarum and the risk of childhood cancer. We examined possible associations in this population-based study in Denmark.
Methods: Pediatric cancer cases (n = 6420) were ascertained from the Denmark Cancer Registry among children born between 1977 and 2013. Twenty-five controls were matched to each case by sex and birth date from the Central Person Registry (n = 160500). Mothers with hyperemesis gravidarum were ascertained from the National Patient Register. The risk of childhood cancer was estimated using conditional logistic regression. In a separate analysis, we examined pregnancy prescription of antinauseant medications, ascertained from the National Pharmaceutical Register, to determine associations with childhood cancers.
Results: In Denmark, hyperemesis gravidarum was associated with an increased risk of childhood cancer [all types combined; Odds Ratio (OR) = 1.43, 95% confidence interval (CI) 1.12, 1.81; n = 73 exposed cases). Hyperemesis gravidarum was also associated with an increased risk of neuroblastoma (OR = 2.52, 95% CI 1.00, 6.36; n = 5 exposed cases), acute lymphoblastic leukemia (OR = 1.63, 95% CI 0.98, 2.72; n = 16 exposed cases), and non-Hodgkin's lymphoma (OR = 2.41, 95% CI 0.95, 6.08; n = 5 exposed cases). We observed no childhood cancer risk increase from antinauseant prescriptions (OR = 1.05, 95% CI 0.84, 1.30; n = 91 exposed cases).
Conclusion: Our results are suggestive of an association between hyperemesis gravidarum and the overall cancer risk in offspring, particularly for neuroblastoma. Mothers with hyperemesis gravidarum should be closely monitored and receive appropriate treatment during pregnancy.

1. Introduction

Hyperemesis gravidarum is severe nausea and persistent vomiting during pregnancy, sometimes necessitating hospital admission and treatment [1]. It is prevalent in about 2–3% of pregnant women and can result in weight loss, dehydration, electrolyte disturbance, acid-base imbalance, and nutritional deficiency [2]. Hyperemesis gravidarum typically occurs between the 4th and 10th week of pregnancy and subsides by the 20th week, but it may persist throughout pregnancy [1]. Although the etiology is unclear, several mechanisms have been proposed as risk factors for hyperemesis gravidarum, including multiple gestation, hydatidiform mole, hormonal or endocrine disorders, gastrointestinal infection, higher gravidity, and underweight [1,3–5], while smoking appears negatively associated [6].

Most studies have shown that hyperemesis gravidarum is associated with intrauterine growth restriction, placenta abruption, preterm birth, and small for gestational age [2,7,8]. Other complications reported in offspring of mothers with severe hyperemesis gravidarum include Wernicke's encephalopathy [9], rhabdomyolysis, central pontine myelinolysis, and vasospasm of cerebral arteries [10]. These complications result from nutritional deficiencies and electrolyte disturbances. Intrauterine exposures of the fetus to undernutrition and electrolyte imbalance may lead to long-lasting effects on immune function, blood pressure, insulin, and cholesterol metabolism and may affect fetal

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growth and neurodevelopment or contribute to diseases in later life [11].

Prenatal exposures often influence the risk of specific childhood cancers [12]. In line with this, the United Kingdom Childhood Cancer study reported a 3.6 times increased risk of all leukemias in children of mothers with severe hyperemesis gravidarum in pregnancy (n = 6 exposed cases) [13]. Another study reported a four times increase in risk of testicular cancer among male children of mothers with hyperemesis gravidarum, based on only eight exposed mothers [14]. In contrast, a large Scandinavian study concluded that hyperemesis gravidarum was not associated with an increased risk of leukemia or testicular cancer but found an association with lymphoma [15]. Instead of limiting to hyperemesis gravidarum, other papers have examined nausea or vomiting more broadly [16]. To address inconsistent results concerning possible associations between hyperemesis gravidarum and childhood cancer overall or among specific cancers, additional population-based studies are needed.

Previous studies that have examined the relationship between antinauseants and other drugs used for nausea and vomiting in pregnancy reported that maternal use of antinauseants was associated with no or only a weak increase in the risk of childhood cancers (OR range 0.9–1.4, across cancer types) [17–21]. Given the small number of studies, more research is needed.

This study aims to investigate associations between hyperemesis gravidarum and childhood cancer using data reported in national birth and cancer registers in Denmark. An earlier Scandinavian-registry-based study merged data from Norway, Sweden, and Denmark, and the study showed a marginal association between hyperemesis gravidarum and overall childhood cancer risk (all cancers combined; OR=1.19, 95% CI 0.97–1.48) [15]. We build upon this work by focusing only on Denmark with additional years of data and via linkage to the National Pharmaceutical Register to examine any putative role of antiemetic/antinauseant use (hereafter, antinauseants).

2. Methods

As previously described, in this matched case-control study, we used data obtained from linking multiple Danish registers using unique identification codes [22]. Cancer cases diagnosed between 1977 and 2013 were ascertained among children under 20 years of age from the Danish Cancer Registry. Using children under 20 years allowed the best statistical power for our sample for these rare cancers. Children with cancer were linked to their parents in the Central Population Registry using the 10-digit Central Person Number assigned to every person living in Denmark since 1968. Controls, free of cancer at the date of diagnoses of corresponding cases, were selected randomly from the Central Population Registry, and 25 controls were matched to cases by sex and birth date. Cancer types were categorized using the International Classification of Childhood Cancer (ICCC) [23].

We conducted analyses in two samples: the first relied on data from the National Patient Register (births 1977–2013), which allowed for the greatest statistical power due to the longer time period [24]. Then, to determine whether an increased risk might be due to medications used to treat hyperemesis gravidarum, we additionally utilized the National Prescription Register, which includes information on every prescription filled at a pharmacy in Denmark but is only available for the latter part of our study period (births 1995–2014)[25]. We estimated odds ratios and interpreted them as risk ratios as we were assessing rare outcomes.

2.1. Sample 1: 1977–2013 Sample

We obtained birth and demographic information from the Central Population and Medical Birth Registers and maternal diagnoses of hyperemesis gravidarum using a Danish modification of the International Classification of Diseases (ICD), ICD-8, and ICD-10 (638.0 and 638.9, 762.49, O21, O21.0, O21.1, O21.2, O21.8, O21.9) [26], from the National Patient Register and Medical Births Register [24,27]. The study sample included 6420 cancer cases and 160500 controls. A flow chart showing the selection of cases and control is shown in Fig. 1a.

We estimated associations between hyperemesis gravidarum and childhood cancer risk using conditional logistic regression for the 1977–2013 birth sample. All analyses were done using SAS 9.3 software. Based on the literature, we adjusted for covariates that could be potential confounders [15,28]. These include maternal age, planned cesarean section, birth order (firstborn/later), hyperthyroidism before birth, hypothyroidism before birth, and anxiety before birth. A previous study noted that women with hyperemesis gravidarum are more likely to undergo a cesarean section [2], or have a planned cesarean section [7], and planned cesarean sections have been related to childhood cancer [29]. We determined details about planned cesarean sections in part from ICD codes (DO842, DO820), and in part from variables from the Medical Birth Register, in which the information collected changed over time. We adjusted for maternal anxiety (diagnosed before the index child's birth) because other studies have linked stress and anxiety in pregnancy with hyperemesis [30]. Likewise, hyperthyroidism presents with symptoms similar to anxiety. Both hypothyroidism and hyperthyroidism may present with hyperemesis gravidarum in pregnancy, and both have been linked to childhood cancer [3,31]. Other variables such as living in urban or rural areas, diabetes before birth, preeclampsia in the index pregnancy, and multiple births were considered for adjustment [32], but left out of the final model because they did not change the effect estimates by 10% or more [33]. Maternal smoking during pregnancy and body mass index (BMI) were only collected during the latter part of the study period. Thus, we were not able to adjust for BMI in models due to the small sample size from years when the variable was available. Adjusting for smoking did not change results so we present the model without adjustment for smoking. An earlier analysis of a Danish sample, with overlapping cases to the current study, found no relation between maternal smoking and most cancer types [34].

Sample 2: Pharmaceutical Registry Sample (births 1995–2014).

As per Danish national regulations, the National Prescription Register data are kept on the Statistics Denmark server [35]. Therefore, the analysis that included these medications was done separately with different but still randomly selected controls ascertained according to the same principles as listed above (matched by sex and birth date). Along with the National Prescription Register, this sample included all registers listed above. This analysis included 2521 cancer cases (diagnosed between 1996 and 2016) and 63,025 controls. Fig. 1b shows a flowchart of the selection of cases and controls. We ascertained any use of antinauseants (one or more prescriptions) from the National Pharmaceutical Register using Anatomical Therapeutic Chemical (ATC) Classification codes: R06AA02 (diphenhydramine), R06AE05 (meclizine), R06AD02 (promethazine), R06AA52 (dimenhydrinate/dramamine), R06AA09 (doxylamine/pyridoxine), N05AB04 (prochlorperazine), A03FA01(metoclopramide), A04AA01(ondansetron), A04AA02 (granisetron), A04AA04 (dolasetron) [35]. In a sensitivity analysis, we also examined the risk from 2 or more prescriptions, vs. none.

We estimated the effect of antinauseant medication use on childhood cancer risk using conditional logistic regression, with adjustment for the same covariates above as well as adjustment for hyperemesis gravidarum. Sensitivity analysis was performed to examine those who had only one prescription for antinauseants and those who had more than one prescription.

3. Results

3.1. 1977–2013 Sample

The demographics of sample participants are shown in Tables 1 and 2. The prevalence of hyperemesis gravidarum among controls was 0.8%. Mothers of cases were more likely to be overweight or obese compared

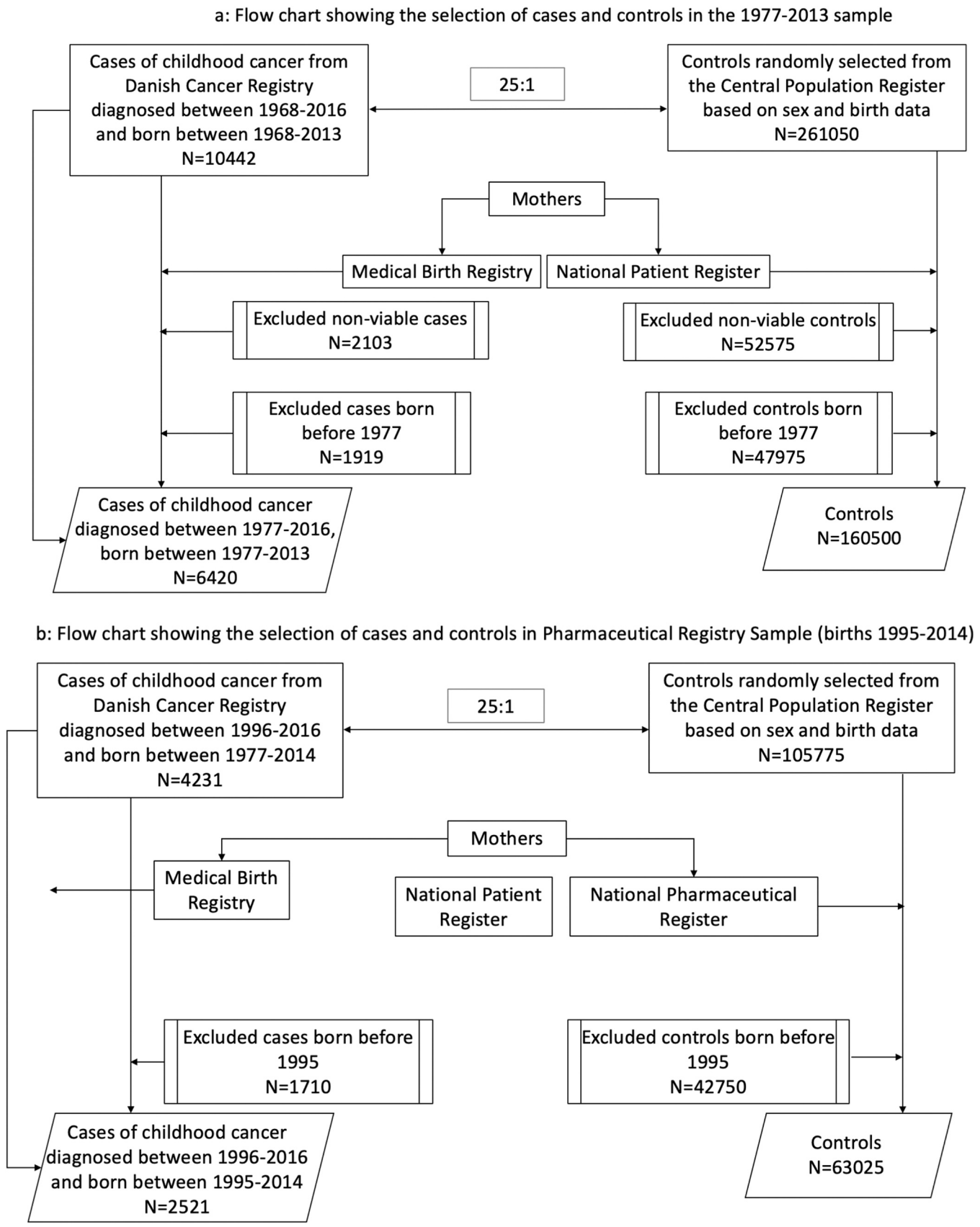

Fig. 1. a: Flow chart showing the selection of cases and controls in the 1977–2013 sample. b: Flow chart showing the selection of cases and controls in pharmaceutical Registry Sample (births 1995–2014).

Table 1
Demographic characteristics of cases and controls.

	1977–2013 sample (N = 166920)		Pharmaceutical registry sample for birth year > =1995 (N = 65546)	
Demographic or health factor	Controls (N = 160500) N (%)	Cases (N = 6420) N (%)	Controls (N = 63025) N (%)	Cases (N = 2521) N (%)
Maternal age group				
< 25	36926 (23.0)	1423 (22.2)	8388 (13.3)	321 (12.7)
25–29	60761 (37.9)	2472 (38.5)	21646 (34.3)	907 (36.0)
30–34	44553 (27.8)	1744 (27.2)	22240 (35.3)	851 (33.8)
35–39	15699 (9.8)	669 (10.4)	9176 (14.6)	384 (15.2)
40 +	2561 (1.6)	112 (1.7)	1574 (2.5)	58 (2.3)
Missing	0	0	1	0
Urbanicity of residence				
Urban	50986 (31.8)	2114 (32.9)	22054 (35.0)	896 (36.1)
Small town	46638 (29.1)	1808 (28.2)	17672 (28.0)	677 (27.3)
Rural	62876 (39.2)	2498 (38.9)	23299 (37.0)	910 (36.6)
Missing	0	0	0	38
Maternal smoking at first prenatal visit*	2075 4 (24.2)	818 (23.9)	12452 (20.6)	487 (20.1)
Pre-pregnancy BMI* *				
< 18.5	815 (4.1)	33 (4.1)	887 (4.2)	37 (4.2)
18.5–25	12778 (64.2)	496 (61.0)	13592 (63.6)	528 (60.6)
> 25	4041 (20.3)	181 (22.2)	4284 (20.1)	195 (22.4)
30+	2274 (11.4)	103 (12.7)	2592 (12.1)	112 (12.8)
Missing	140592	5607	41670	1649
Plural pregnancy	4620 (2.9)	190 (3.0)	2549 (4.0)	103 (4.1)
Hyperemesis gravidarum	1300 (0.8)	73 (1.1)	752 (1.2)	36 (1.4)
Firstborn child	68859 (42.9)	2827 (44.0)	25405 (40.3)	1074 (42.6)
Planned cesarean section	5248 (3.3)	246 (3.8)	4596 (7.3)	209 (8.3)
Preeclampsia	5548 (3.5)	237 (3.7)	1747 (2.8)	75 (3.0)
Diabetes* **	1862 (1.2)	86 (1.3)	1171 (1.9)	53 (2.1)
Hyperthyroidism* **	488 (0.3)	15 (0.2)	391 (0.6)	12 (0.5)
Hypothyroidism* **	342 (0.2)	12 (0.2)	330 (0.5)	7 (0.3)
Anxiety* **	163 (0.1)	9 (0.1)	90 (0.1)	7 (0.3)

* Smoking status at the first midwife consultation was collected from 1991 to 2013.
* * Pre-pregnancy BMI was collected from 2003 to 2013.
* ** Maternal diagnoses occurring at any time before the child's birth

Table 2
Maternal hyperemesis during pregnancy in relation to demographic factors.

	1977–2013 sample		Pharmaceutical registry sample for birth year > =1995	
Demographic or health factor	No Hyperemesis	Maternal Hyperemesis	No Hyperemesis	Maternal Hyperemesis
	N (%)	N (%)	N (%)	N (%)
Maternal age group				
< 25	37970 (23.0)	379 (27.6)	8559 (13.2)	150 (19.0)
25–29	62740 (37.9)	493 (35.9)	22287 (34.4)	266 (33.7)
30–34	45918 (27.7)	379 (27.6)	22824 (35.3)	267 (33.9)
35–39	16257 (9.8)	111 (8.1)	9472 (14.6)	88 (11.2)
40 +	2662 (1.6)	11 (0.8)	1615 (2.5)	17 (2.2)
Missing	0	0	1	0
Urbanicity of residence				
Urban	52642 (31.8)	458 (33.4)	22677 (35.0)	273 (34.7)
Small town	48054 (29.0)	392 (28.6)	18106 (28.0)	243 (30.8)
Rural	64851 (39.2)	523 (38.1)	23937 (37.0)	272 (34.5)
Missing	0	0	38	1
Maternal smoking at first prenatal visit*	21461(24.3)	111 (12.5)	12868 (20.7)	71 (9.4)
Pre-pregnancy BMI* *				
< 18.5	828 (4.1)	20 (6.7)	903 (4.1)	21 (6.3)
18.5–25	13108 (64.2)	166 (55.9)	13925 (63.6)	195 (58.2)
> 25–30	4150 (20.3)	72 (24.3)	4404 (20.1)	75 (22.4)
30 +	2338 (11.4)	39 (13.1)	2660 (12.2)	44 (13.1)
Missing	145123	1076	42866	453
Plural pregnancy	4723 (2.9)	87 (6.3)	2593 (4.0)	59 (7.5)
Firstborn child	71113 (43.0)	573 (41.7)	26180 (40.4)	299 (37.9)
Planned cesarean section	5406 (3.3)	88 (6.4)	4742 (7.3)	63 (8.0)
Preeclampsia	5716 (3.5)	69 (5.0)	1793 (2.8)	29 (3.7)
Diabetes* **	1930 (1.2)	18 (1.3)	1205 (1.9)	19 (2.4)
Hyperthyroidism* **	478 (0.3)	25 (1.8)	380 (0.6)	23 (2.9)
Hypothyroidism* **	351 (0.2)	<5	329 (0.5)	8 (1.0)
Anxiety* **	169 (0.1)	<5	94 (0.2)	<5

* Smoking status at the first midwife consultation was collected from 1991 to 2013.
* * Pre-pregnancy BMI was collected from 2003 to 2013.
* ** Maternal diagnoses occurring at any time before the child's birth

to controls. A higher proportion of mothers with hyperemesis gravidarum were less than 25 years of age at the time of the child's birth compared to mothers without hyperemesis gravidarum.

Hyperemesis gravidarum was related to an overall increased risk of childhood cancers, with the highest point estimates for non-Hodgkin's leukemia (NHL) and neuroblastoma (Table 3). We also observed an association between hyperemesis gravidarum and the risk of acute lymphoblastic leukemia (ALL; OR = 1.63, 95% CI 0.98, 2.72), and NHL (OR = 2.41, 95% CI 0.95, 6.08).

We observed a higher birthweight in offspring with ALL (mean=2.19 kg) or neuroblastoma (mean=2.40 kg) whose mothers had hyperemesis compared to offspring with ALL (mean=2.14 kg) or neuroblastoma (mean=2.15 kg) whose mothers did not have hyperemesis.

3.2. Pharmaceutical Registry Sample (1995–2014)

The demographic distribution of Pharmaceutical Registry Sample subjects is described in Table 1 and Table 2. The prevalence of hyperemesis gravidarum among controls was 1.2%. There were more planned cesarean sections among mothers of cases in the pharmaceutical sample data. Of the women receiving antinauseants for whom an indication was given for their prescription, 24.7% received antinauseant medication due to vomiting in pregnancy, including both mild and severe vomiting. The second most common indication was "normal pregnancy," at 18.0%. Among the cases in the Pharmaceutical Registry sample (n = 2521), the phi coefficient for the correlation between a hyperemesis diagnosis and any antinauseant medication was 0.2456, which indicated a weak positive association between hyperemesis diagnosis and antinauseant prescriptions.

After adjustment for hyperemesis gravidarum and all other covariates, there was no compelling association between antinauseant use and the risk of childhood cancer (Table 4), although some point estimates were elevated with wide confidence intervals. Sensitivity analysis showed no difference in childhood cancer risk between offspring of mothers who had one prescription of antinauseants compared to those who had more than one prescription. Among those who had two or more prescriptions, the sample size was limited but we did not observe increases for any type of cancer (OR=0.85, 95% CI 0.59–1.24) or for ALL (OR=0.80, 95% CI 0.37–1.73).

Table 3
Maternal hyperemesis during pregnancy in relation to childhood cancer risk (1977–2013 sample).

Cancer type	Total	N (%)	Crude OR	Adjusted OR (95% CI) *
Controls	160500	1300 (0.8)	Ref	Ref
All cancers	6420	73 (1.1)	1.41 (1.11, 1.79)	1.43 (1.12, 1.81)
ALL	1222	16 (1.3)	1.59 (0.95, 2.64)	1.63 (0.98, 2.72)
Lymphoma	757	9 (1.2)	1.70 (0.86, 3.36)	1.78 (0.90, 1.04)
NHL	322	5 (1.6)	2.34 (0.93, 5.90)	2.41 (0.95, 6.08)
CNS tumors	1583	17 (1.1)	1.25 (0.76, 2.04)	1.24 (0.76, 2.02)
Intracranial and intraspinal embryonal tumors	674	8 (1.2)	1.75 (0.85, 3.61)	1.83 (0.89, 3.77)
Glioma	778	9 (1.2)	1.50 (0.76, 2.95)	1.49 (0.75, 2.93)
Neuroblastoma	275	5 (1.8)	2.51 (1.00, 6.33)	2.52 (1.00, 6.36)
Astrocytoma	502	6 (1.2)	1.38 (0.60, 3.17)	1.38 (0.60, 3.16)

* Conditional logistic regression. Adjusted for maternal age, planned cesarean section, and hyperthyroidism before birth, firstborn, anxiety before birth, and hypothyroidism before birth.

Table 4
Maternal antinausea medications use during pregnancy in relation to childhood cancer risk (Pharmaceutical registry sample for birth year 1995–2014).

Cancer type	Total	N (%)	Crude OR	Adjusted OR (95% CI) *
Controls	63025	2133 (3.4)	Ref	Ref
All cancers	2521	91 (3.6)	1.07 (0.86, 1.32)	1.05 (0.84, 1.30)
ALL	558	18 (3.2)	0.91 (0.56, 1.47)	0.90 (0.55, 1.48)
AML	114	6 (5.3)	1.45 (0.62, 3.39)	1.65 (0.69, 3.88)
Lymphomas	283	11 (3.9)	1.19 (0.64, 2.21)	1.13 (0.60, 2.16)
NHL	108	5 (4.6)	1.39 (0.55, 3.48)	1.52 (0.59, 3.80)
CNS tumors	596	16 (2.7)	0.86 (0.52, 1.42)	0.84 (0.50, 1.42)
Intracranial tumors	221	9 (4.1)	1.33 (0.67, 2.64)	1.28 (0.62, 2.59)
Neuroblastoma	135	8 (5.9)	1.66 (0.79, 3.47)	1.45 (0.66, 3.08)

* Conditional logistic regression. Adjusted for hyperemesis during the index pregnancy, maternal
age, planned cesarean section, hyperthyroidism before birth, firstborn, anxiety before birth,
hypothyroidism before birth.

4. Discussion

This population-based study in Denmark examined the relationship between hyperemesis gravidarum and childhood cancer risk. The prevalence of hyperemesis in control mothers in our study sample was 0.8% which is comparable to the prevalence reported in other Danish studies, and falls within the 0.3%– 3.6% prevalence estimated globally [36,37]. There was an overall increase in the odds of childhood cancer risk in the offspring of mothers with hyperemesis gravidarum, and also for some cancer subtypes particularly for NHL, ALL, and neuroblastoma, supporting results seen elsewhere [13]. Importantly, after adjustment for hyperemesis our study observed no cancer risk from the prescription of antinauseants. As this is in line with most other studies on antinauseants, if it continues to be replicated it is encouraging for pregnant women. Our point estimate of the association between hyperemesis gravidarum and lymphoma was similar to that reported by Vandraas et al. (RR=1.68) [15], supporting their results. Some findings differed from Vandraas et al., perhaps due to slight variation in hyperemesis ICD coding used, as well as their use of ICD-10 instead of ICCC to identify cases. We also examined subtypes of lymphoma.

There are a limited number of studies that have previously investigated the relationship between hyperemesis gravidarum and childhood cancers. To the best of our knowledge, no prior study has reported an increased risk of neuroblastoma with hyperemesis gravidarum as found in our study. However, some studies have shown weak associations (OR= 1.20, 95% CI 0.70, 1.90 [38]; OR = 1.10, 95% CI = 0.90, 1.50 [16]) between either the use of antinauseants, or self-reported "morning sickness," in relation to neuroblastoma, respectively. Vomiting is estimated to impact 52% of pregnant women, with varying severity, and another 28% experience nausea without vomiting [39], thus childhood cancer studies likely found differing results due to the widely varying

definitions of the exposure.

Nausea and vomiting are common in pregnancy and typically decrease or stop as the pregnancy progresses. However, the duration and severity of the symptoms vary from one pregnancy to another. There is no consensus on the definition of hyperemesis gravidarum, and our data source did not detail the severity or frequency of nausea and vomiting. Thus, we could not examine dose-response effects nor determine the threshold at which risk may be increasing. While we could not ascertain information on non-pharmacologic treatments, steps such as diet regulation (such as eating "little and often" or eating at certain times of the day) are typically attempted by the mother prior to presentation and diagnosis.

The lack of a rigorous definition for hyperemesis gravidarum could have been a limitation, and misclassification could have occurred in both directions (towards or away from the null). Previous studies have defined hyperemesis gravidarum with different criteria, and some defined it as severe nausea and vomiting preventing food and fluid intake with or without abnormal laboratory results [40]. Fairweather et al. included hospital admission in their definition [1,41]. It is challenging to determine the severity of nausea and vomiting in defining the threshold for when hyperemesis gravidarum is diagnosed.

Although a mechanism for the relationship between hyperemesis gravidarum and childhood cancer is not well understood, adverse exposure in-utero coupled with environmental exposures may increase the susceptibility to diseases in later life. Hyperemesis gravidarum in mothers has been most often associated with hormone-sensitive cancers in offspring and is also more common in conditions such as a first pregnancy and maternal higher body mass index [4], all related to high pregnancy estrogen levels. Pregnancy estrogens may also be related to offspring cancer risk [42]. At the same time, another study suggested that having lower estrogen levels in later pregnancies could be associated with reduced risk of neuroblastoma in children [43]. Elevated estradiol levels have been reported in patients with hyperemesis gravidarum [3,4], but not in all studies [41]. Changes in hormonal levels may affect different regulatory pathways and may alter organogenesis [44].

Another plausible explanation for the association between hyperemesis gravidarum and childhood cancer could be due to possible extreme weight loss (>15% of pre-pregnancy weight), nutritional and electrolyte deficiencies, which could lead to vitamin B1 and vitamin K deficiency [45]. These factors, including maternal stress during pregnancy, are related to risks of adverse birth outcomes, including cardiac, renal, and neuromuscular complications, including fetal intracranial hemorrhage and hydrocephalus [46]. In addition, infants of mothers with hyperemesis gravidarum have a higher risk of preterm delivery and very low birth weight, likely due to nutrient deficiency in-utero [2,47]. These risks have separately been associated with different childhood cancers in previous studies [12]. However, we did not observe a lower birthweight among ALL or neuroblastoma cases whose mothers had hyperemesis.

Hyperemesis gravidarum has been associated with preeclampsia and lower insulin sensitivity in offspring [48]; although the mechanism is unclear, preeclampsia and low insulin sensitivity have been associated with cancers such as ALL and neuroblastoma [32,49]. However, adjustment for preeclampsia and diabetes in our data did not change our results. It is possible that other factors are associated with hyperemesis gravidarum, such as chronic hypertension, liver disease, and chronic renal disease [50] could each contribute to childhood cancer risk, however, there was a low prevalence of such disorders in our sample [32] and maternal renal and liver diseases have not previously been linked to childhood cancer, with the exception of viral hepatitis [51], a cause of pregnancy liver disease. Viral hepatitis was rare in our study.

Hyperemesis gravidarum is linked to increased levels of human chorionic gonadotropin (HCG) hormone, with levels proportional to the degree of nausea. HCG has been linked to molar pregnancies and has been used as a marker for trophoblastic tumors, germ cell tumors, and gastrointestinal cancers [52]. However, its role in childhood cancers has not been investigated. There is, however, an association between hyperemesis gravidarum and placental dysfunction [8,53], and placenta dysfunction has been linked to childhood cancer in our previous study [54].

The strength of our study is its population-based design with a relatively large sample size for this topic. Also, the cases of maternal hyperemesis gravidarum were obtained from clinical records, preventing recall bias. However, on the other side, not all cases of hyperemesis gravidarum may have been included in our study based on information from hospital records. Our findings were based on a small number of exposed cases due to rarity of the disease, and we were not able to adjust for maternal BMI because it was only collected during a part of the study period. Maternal BMI may be a risk factor for some childhood cancers [55].

In conclusion, we found a suggestive increased risk of childhood cancer in offspring of mothers with hyperemesis gravidarum compared to unexposed mothers. Importantly, we did not find evidence that treatment with antinauseants confers an increased risk.

Ethics approval

Human subjects approvals were obtained from the Danish Data Protection Agency, the University of California, Los Angeles, and the University of North Texas.

Consent to participate

This was a no-contact study, with a waiver of informed consent granted.

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CRediT authorship contribution statement

Helen Orimoloye: Writing – original draft, Methodology, Writing – review & editing, Formal analysis. **Chuanjie Deng**: Formal analysis, Writing – review & editing. **Julia Heck**: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision. **Johnni Hansen**: Resources, Writing – review & editing. **Jorn Olsen**: Writing – review & editing. **Chai Saechao**: Methodology, Writing – review & editing. **Beate Ritz**: Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets analyzed in the current study are subject to the General Data Protection Regulation, with restrictions on data sharing in place.

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