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Exposure to nitrosatable drugs during pregnancy and childhood cancer: a matched case-control study in Denmark, 1996 – 2016

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Abstract

Exposure to nitrosatable drugs during pregnancy and childhood cancer: a matched case-control study in Denmark, 1996 – 2016

Background: Nitrosatable drugs can be synthesized to N-nitroso compounds in human stomach. In a pregnant woman, N-nitroso compounds can be translocated to the fetus through the placenta. Maternal exposure of nitrosatable compounds during pregnancy has been associated with childhood brain tumors and leukemia. However, few studies have investigated an association between nitrosatable drug exposure during pregnancy and childhood cancer. We examined if maternal prescriptions of nitrosatable drugs received during pregnancy are associated with childhood cancer.

Methods: A matched case-control study was conducted using Danish nationwide registry data from 1995 to 2016. Each childhood cancer case was matched with twenty-five controls. Maternal exposure of nitrosatable drugs during pregnancy was identified from the Danish National Prescription Register. A multivariable conditional logistic regression model was used to estimate adjusted odds ratios (adj.OR) with 95% confidence intervals (CI) for each childhood cancer type.

Results: Maternal prescriptions of nitrosatable drugs positively associate with central nervous system tumors (adj.OR = 1.25; 95% CI = 1.04–1.51) and neuroblastoma (adj.OR = 1.96; 95% CI = 1.34–2.85) in offspring. We also observed a positive association between perinatal exposure of nitrosatable drugs and acute lymphoblastic leukemia (adj.OR = 1.31; 95% CI = 1.07–1.59), however, it appeared to be due to confounding by indication, i.e., maternal infections.

Conclusion: Nitrosatable drug use during pregnancy potentially increased risk of central nervous system tumors and neuroblastoma. While a positive association between maternal prescriptions of nitrosatable drugs and acute

lymphoblastic leukemia should be interpreted cautiously because of confounding by indication.

Keywords: nitrosatable drug, N-nitroso compound, childhood cancer, pregnancy, Denmark

Background

N-nitroso compounds (NOC) refer to a class of organic agents that have a nitroso group as a part of their molecular structure. While they have been suspected of causing cancer,[1] epidemiologic studies have not yet firmly established a link between NOC exposure and risk of cancer in humans. Nevertheless, the latest evaluation conducted by the International Agency for Research on Cancer (IARC) concluded that ingested nitrates or nitrites under conditions that result in endogenous nitrosation are probably carcinogenic to humans (Group 2A).[2] Results reported previously might have lacked consistency due to the difficulties of measuring and identifying NOC exposures.

Humans are exposed to NOC from exogenous and endogenous sources. Exogenous sources of NOC exposure are foods (leafy vegetables and cured meats), tobacco smoking, and other environmental exposures. Endogenous sources are due to endogenous synthesis or in-vivo formation of NOC from ingested nitrate, nitrite, e.g., from food and drinking water, and nitrosatable compounds such as drugs containing amide and amines.[3–5] The majority of NOC exposure in human stems from endogenous synthesis.[5]

Endogenous synthesis of NOC requires nitrosatable amine precursors and nitrosating agents. Endogenous nitrosation can happen via several mechanisms and in multiple parts of the human body, the main site being the stomach through non-enzymatic formation, which requires an acidic environment. Ingested nitrosatable compounds can be synthesized to NOC in a pregnant woman and then be translocated to the fetus through the placenta. This process has been found to be responsible for causing neurogenic and lymphatic tumors in animal experiments.[6–12]

Previous epidemiological studies found nitrate and nitrite ingestion to be associated with many types of cancer in adults such as gastrointestinal tumors,

brain tumors, lymphoma, and urinary tract tumors.[13–18] With regards to childhood cancers, maternal nitrate and nitrite ingestion as well as nitrosatable drug exposure during pregnancy have been considered the major sources of NOC exposure. Maternal exposure of nitrosatable compounds during pregnancy has been associated with childhood brain tumors and leukemia, with most studies examining environmental exposures to nitrates from drinking water or dietary sources.[19–22] Fewer studies have investigated an association between nitrosatable drug exposure during pregnancy and childhood nervous system tumors, and results were inconclusive.[23–26] The effect sizes identified by previous studies ranged from 1.1 to 3.2 with wide confidence intervals due to a lack of power, especially to conduct subgroup analyses by type of drug; further, studies used different ways to classify nitrosatable drug exposure.[23–26] In addition, no prior dose-response analysis has been conducted. Thus, our study aims to add additional information about maternal prescriptions of nitrosatable drugs received during pregnancy and childhood cancer.

Methods

This matched case-control study relies on Danish nationwide registry data linking population data by use of a unique personal identification applied to all residents, from five sources including the Central Population Registry, the Danish Cancer Registry, the Danish National Patient Register, the Danish National Prescription Registry, and the Danish Medical Birth Registry. Details of data linkage and covariate information have been previously provided.[27]

Cases were ascertained from the Danish Cancer Registry using the International Classification of Childhood Cancer.[28,29] Twenty-five controls matched with each index case by birth date and child’s sex were randomly selected to form matched sets. Eligible controls were cancer free and alive at the date of

their index case's diagnosis. Study participants were all born in Denmark between 1995 to 2014 and cases were diagnosed with cancer between 1996 to 2016. As these are likely non-viable pregnancies, children born with birthweight less than 500 grams (n = 68) were excluded from analyses.

We identified information on redemption of prescription medications from the Danish National Prescription Register. This nationwide register, established in 1994, includes up to 97.5% of the Danish population.[30,31] Prescriptions for medications during pregnancy were identified from the estimated conception date until the date of birth, with gestational age at birth in days taken from the Medical Births Registry; when gestational duration was missing we used multiple imputation, as previously described.[32] The gestational age was identified from the first date of the last menstrual period in the Medical Births Registry, or based on ultrasonography. A list of nitrosatable drugs, i.e. drugs that have been found to form NOC, was generated from the literature.[24,33,34] We excluded one drug that was only available via parenteral administration. Prescriptions that occurred any time before the pregnancy period were not counted as pregnancy exposure. We also identified the Anatomical Therapeutic Chemical (ATC) codes for these drugs and matched them against the entries in the Danish National Prescription Registry. We categorized the nitrosatable drugs based on their functional groups (amides, secondary amines, tertiary amines) (see Supplementary Table S1). These functional group categories were not mutually exclusive. Because most of the nitrosatable drugs prescribed in this population were antibiotics, we distinguished those who were exposed to nitrosatable antibiotics as an additional exposure subgroup. The reference group was women without any prescriptions of nitrosatable drugs during pregnancy.

Demographic information and other covariates including parental age, family socioeconomic status, urbanicity of residence at birth, birth order, birth

weight, and maternal smoking at the first prenatal visit were identified from the Central Population Registry or the Danish Medical Birth Registry. We selected covariates to be included in final models to control for confounding using disjunctive cause criteria and causal diagrams.[35]

A conditional logistic regression model was used to estimate crude and adjusted odds ratios and corresponding 95% confidence intervals for each type of childhood cancer. Because maternal age (continuous) and birth order (>1 vs 1) are suggested as potential risk factor for certain types of childhood cancer [27,36,37] and may confound associations with nitrosatable drug exposure, we included these covariates in all final models, assuming that they are risk factors for most or all childhood cancers. Result from models with less than five cases are not presented.[38]

Infections are an indication for antibiotic prescriptions and also potential risk factor for some childhood cancers.[39–42] Thus, results for antibiotics that are nitrosatable drugs face the problem of potential confounding by indication. Whenever statistical power allowed, we therefore conducted secondary analyses for four different groups of women including: those prescribed only non-nitrosatable antibacterial drugs, those prescribed only nitrosatable drugs that are not antibiotics, those prescribed only nitrosatable antibacterial drugs, and those prescribed combinations of these drugs. Antibacterial drugs were identified by ATC codes J01 (antibacterial for systemic use) and A07A (intestinal anti-infectives). The reference group for secondary analysis were women with no prescriptions for nitrosatable drugs and antibiotics during pregnancy.

Because maternal smoking status was only collected for a portion of the study period (≥1991), a sensitivity analysis was conducted where we included this variable into adjusted models. However, smoking was not associated with pediatric cancers in a previous analysis conducted with the same data, with the

exception of eye tumors.[43] We also conducted another sensitivity analysis adding infections during pregnancy as additional covariates. Maternal infections were identified from the Danish National Patient Register using inpatient and outpatient diagnosis based on the International Classification of Diseases, Revision 10 (see Supplementary Table S2), using a categorization adapted from Atladóttir et al.[44] All statistical analyses were conducted using R 4.0.2 software.[45]

Results

We included 1,749 childhood cancer cases and 43,841 matched controls in our analyses. The distribution of baseline characteristics of cases and controls and their parents is presented in Table 1. Cases were more likely to have been firstborn children.

Case mothers were more likely to have been prescribed nitrosatable drugs during pregnancy compared to controls (27.5% vs 22.7%) (Table 2). The most common nitrosatable drugs prescribed were antibacterials (19.1% among cases and 15.5% among controls). The majority of case and control mothers were prescribed only one nitrosatable drug throughout their pregnancy.

Mothers of neuroblastoma cases were twice as likely to have been prescribed nitrosatable drugs during pregnancy than controls (adjusted odds ratio [adj.OR] = 2.0; 95% confidence interval [CI] = 1.34–2.85). Higher odds of nitrosatable drug prescriptions during pregnancy were also observed among ALL cases (adj.OR = 1.3; 95% CI = 1.07–1.59) and CNS cases (adj.OR = 1.3; 95% CI = 1.04–1.51) (Table 3). In this study, adding maternal smoking or infection status into models did not change point estimations of adjusted odds ratios by more than ten percent among major cancers in Table 3.

Nitrosatable antibiotics were positively associated with neuroblastoma (adj.OR = 2.0; 95% CI = 1.31–3.13) and astrocytoma (adj.OR = 1.6; 95% CI =

1.11–2.34), especially diffuse astrocytoma (adj.OR = 2.3; 95% CI = 1.18–4.66). When considering the functional groups and nitrosatable antibiotics (Table 4), secondary amines appeared to have a stronger positive association with neuroblastoma (adj.OR = 2.9; 95% CI = 1.42–6.01), ALL (adj.OR = 1.9; 95% CI = 1.28–2.76) and AML (adj.OR = 2.6; 95% CI = 1.20–5.55) but not CNS tumors (adj.OR = 0.8; 95% CI = 0.50–1.37). Additionally, we found higher odds for prescriptions for tertiary amines among retinoblastoma cases (adj.OR = 2.2; 95% CI = 1.16–4.35).

When estimating odds ratios for different types of nitrosatable and antibacterial drugs (Table 5), we found similar possibly positive associations for ALL with non-nitrosatable antibiotics (adj.OR = 1.3; 95% CI = 0.99–1.72) and nitrosatable antibiotics (adj.OR = 1.3; 95% CI = 1.00–1.81). On the other hand, nitrosatable antibiotics appeared to have the strongest positive associations with CNS (adj.OR = 1.4; 95% CI = 1.09–1.84), astrocytoma (adj.OR = 1.8; 95% CI = 1.17–2.88), and neuroblastoma (adj.OR = 2.4; 95% CI = 1.39–4.09), while non-antibacterial nitrosatable drugs appeared to have the strongest positive associations with AML (adj.OR = 1.5; 95% CI = 0.78–3.04).

Discussion

Our results suggest that maternal exposure to nitrosatable drugs due to prescriptions during pregnancy increases the risks of certain childhood cancers. We found a strong positive association for neuroblastoma, and moderate size associations for CNS and ALL. However, for ALL there was also a tendency of an increase in risk for non-nitrosatable antibiotics suggesting that that the associations with ALL might be attributable to the underlying infections for which the antibiotics were prescribed and used rather than to nitrosatable antibiotics, though both situations may be possible. This tendency was weaker for AML, CNS,

astrocytoma and neuroblastoma where the strongest associations and highest point estimates were seen for nitrosatable drugs whether or not they were antibiotics, while non-nitrosable antibiotics did not increase risk notably.

Our findings may differ from other studies due to the list of nitrosatable drugs we employed. Previous studies of prescription drug use in pregnancy mainly classified medications according to their indications and did not group them as nitrosatable drugs. For example, previous studies on maternal medication use and neuroblastoma reported positive associations for particular types of medications including diuretic antihypertensives (adj.OR = 3.2; 95% CI = 1.0–9.7),[46] opioid agonists (adj.OR = 3.4; 95% CI = 1.4–8.4),[23] and analgesics (adj.OR = 6.0; 95% CI = 2.0–18.1).[47] Although some drugs in these classes of medication potentially form NOC, the majority of them are not nitrosatable drugs. However, the same study that reported an association for opioid agonists and neuroblastoma also reported inconclusive results for other classes of medication that potentially form NOC such as diuretic antihistamines, analgesics, and antibiotics.[23] The prevalence of nitrosatable drug exposure during the first 22 weeks of pregnancy reported in previous cohort studies in Denmark was 15.3% [34,48] while our study found that 22.7% of the matched controls were exposed during the entire pregnancy period.

Three case control studies on maternal exposure to nitrosatable drugs and CNS mostly observed modest size associations ranging from 1.1 to 1.4,[24,26,46] while a cohort study suggested a stronger increase in risk of CNS tumors (adjusted relative risk = 2.3; 95% CI = 1.0–5.3).[49] In addition, a matched case-control study found positive associations for maternal use of diuretics (OR = 2.0; p-value = 0.03) and antihistamines (OR = 3.4; p-value = 0.002) and CNS tumors.[25]

ALL has previously been associated with maternal exposure to antibiotics. A case-control study reported a positive association between self-reported maternal antibiotics use from 3 months before conception through the end of pregnancy and ALL in the offspring (adj.OR = 1.47; 95% CI = 1.06–2.04).[50] Two additional cohort studies also reported modest size effect estimates for maternal antibiotics during pregnancy and the risk of developing ALL but the 95% confidence interval included the null.[51,52] Our results corroborate these reports, but also suggest that confounding by indication may be considered as an explanation.

Experimental animal studies suggested a potential transplacental carcinogenic effects for NOC,[6–9] however, the mechanisms involved in carcinogenesis are not yet well understood. The results we present in Table 5 may give some clue about the mechanism involved. For example, neuroblastoma is related to abnormalities of cancer gene expression in younger and immature rather than mature cell types [53,54] and animal studies found that adult and young neural cell types respond differently to NOC.[10,11] This might explain the difference we see in terms of the estimated effect of NOC on neuroblastoma risk versus other neurological cancers including CNS, glioblastoma, and medulloblastoma which are found to originate from more mature neural cells. In addition, the activation of carcinogenesis pathways may be different by cancer type. Glioblastoma cells are induced by NOC through the expression of a programmed death ligand 1 and regulated by Anti-c-Jun N-terminal kinase activation.[11] In contrast, leukemia tumor cells responded to NOC, as N-nitroso-N-butylurea, through *ras* and *p53* genes expression in an animal model.[12]

When we restricted the analyses to specific functional groups, secondary amines showed stronger associations for most cancers except CNS tumors. However, a previous case-control study on childhood brain tumors found no

association for maternal use of any type of nitrosatable amines or amides.[24] Why there would be a stronger association with secondary amines for most cancers is not yet known but a mechanistic study suggested that some secondary amines exhibit a superior potency in inhibiting histone deacetylases in cancer cells compared with tertiary amines.[55] The molecular structure of secondary amines was also found to be more stable, and they have a greater ability to penetrate the blood-brain barrier.[33,55,56] It should be noted, however, that we also found a stronger association between tertiary amines and retinoblastoma. To our knowledge, no previous studies have examined the relationship between NOC and retinoblastoma, but NOC was found to induce retinal neurotoxicity in rats.[57] Occupational exposure to tertiary amines was also found to be associated with ocular changes in adults.[58]

It has been suggested that the medicines that have a molecular weight greater than 500 g/mol are more likely to have poor absorption or permutation.[59] However, only 7 out of 164 drugs (4.3%) on our list have a molecular weight greater than 500 g/mol. Thus, we were not able to conduct sensitivity analyses based on this categorization.

The strengths of our study include using solely linkage derived data from population-based nationwide registries which prevents selection bias. Registry data also allowed us to collect prescription records during pregnancy, i.e., prior to a child's diagnosis and independently of the outcomes eliminating any risk of possible recall bias.

The present study is nevertheless subject to several limitations. Although the information on redemption of prescription medication was historically recorded with good coverage,[30,31] we have no information on patient compliance. Some nitrosatable drugs are sold over the counter and are not captured by the prescription registry system unless the patient has a chronic disease (e.g.,

acetaminophen, analgesics, antihistamines). We assumed that case and control mothers were likely to have a same compliance as well as a similar chance of taking nitrosatable drugs over the counter which would likely result in nondifferential exposure misclassification with a bias toward the null.

Information on dosage and route of drug administration were unavailable. We excluded a drug that was only available for parenteral administration, but most of the medications on our list also have more than one route of administration. The endogenous synthesis of NOC mostly happens in the stomach; therefore, the drugs would need to be ingested by mouth. In this study, those classified as exposed were likely to have received only a one-time prescription for nitrosatable drugs which found to be most prevalent in the third trimester. An animal study found a transplacental carcinogenic effect of NOC at a relatively low dose of exposure.[9] Thus, it should be noted that the impact of nitrosatable drug exposure may vary across the specific time window of pregnancy and dosage.

Uncontrolled confounding may remain an issue due to a lack of information on maternal dietary, water supply and supplement intake. Maternal diet may be a source of nitrate and nitrite exposure, while iron supplements and Vitamin C has been found to be protective against some cancers attributed to NOCs.[60–62]

Live birth bias can occur in studies of prenatal exposure that target postnatal outcomes because childhood cancers are being ascertained only in live-born children and nitrosatable drug use has be associated with congenital malformations [63–65] that are also associated with poor fetal survival and stillbirth.[34] However, the magnitude of this type of live birth bias appears to be small and generally biases estimates towards the null.[66]

Finally, most childhood cancers are extremely rare. Although we used national registry data that was collected over several decades, sample sizes for some cancers are still small. Thus, these results based on small number still need to be interpreted cautiously.

Conclusion

Maternal prescriptions of nitrosatable drugs during pregnancy increased the risk of CNS tumors and neuroblastoma in offspring. Associations between maternal prescriptions of nitrosatable drugs and ALL may be due to confounding by indication, i.e., maternal infections. Additionally, the patterns of association were found to differ across types of cancers and depended on the specific type of nitrosatable drug. Future studies are needed to corroborate our observations and to address potential biological pathways between NOC and specific types of childhood cancer. Meanwhile, caution regarding the use of nitrosatable drug in pregnancy is necessary and any unnecessary use of these drugs should be avoided.

Key Points

- Nitrate and nitrite ingestion have been found associated with many types of cancer in adults.
- Maternal nitrosatable drug use could be one of the major sources of N-nitroso compounds exposure during pregnancy.
- This matched case-control study investigated the association between maternal prescriptions of nitrosatable drugs received during pregnancy and childhood cancer using Danish nationwide registry data.
- We found that nitrosatable drug exposure during pregnancy potentially increased the risk of central nervous system tumors and neuroblastoma in offspring.

- Future studies are needed to corroborate our observations and to address potential biological pathways between N-nitroso compound exposure and specific types of childhood cancer.

Plain Language Summary

Nitrosatable drugs are a type of medicine that can be transformed to N-nitroso compounds which have been found to be associated with many types of cancer in adults. This transformation process mainly occurs in the human stomach. Maternal nitrosatable drug ingestion could be one of the major sources of N-nitroso compound exposures during pregnancy which can be translocated to the fetus through the placenta and could be a potential cause of childhood cancer. However, few studies have investigated an association between nitrosatable drug exposure during pregnancy and childhood cancer. Using Danish nationwide registry data, this matched case-control study investigated the association between maternal prescriptions of nitrosatable drugs received during pregnancy and childhood cancer. We found that nitrosatable drug exposure during pregnancy potentially increased the risk of central nervous system tumors and neuroblastoma in offspring. Therefore, future studies are needed to corroborate our observations and to address potential biological pathways between N-nitroso compound exposure and specific types of childhood cancer.

Data availability

The data used for this study are subject to General Data Protection Regulation (GDPR) regulations, with permissions required prior to data access.

Conflict of interest

The authors have declared no conflicts of interest and no financial relationships relevant to this article to disclose.

Ethics statement

This study is based on deidentified information from Danish national registers. This study was approved by Office of the Human Research Protection Program, University of California, Los Angeles (IRB#13-001904), the University of North Texas (IRB-20-255), and the Danish Data Protection Agency.

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Author contribution:

Data: Johnni Hansen and Julia E Heck had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Julia E Heck. *Acquisition, analysis, or interpretation of data:* All authors. *Drafting of manuscript:* Anupong Sirirungreung. *Critical revision of the manuscript for important intellectual content:* Julia E Heck and Beate Ritz. *Statistical analysis:* Anupong Sirirungreung. *Code review:* Di He and Xiwen Huang.

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Table 1. Characteristics of childhood cancer cases and matched controls in Denmark, births 1995 – 2014

	Cases	Controls
Number	1749	43841
Year of birth, n (%)		
1995 – 1999	642 (36.7)	16103 (36.7)
2000 – 2009	923 (52.8)	23139 (52.8)
2010 – 2014	184 (10.5)	4599 (10.5)
Age at cancer diagnosis (years), n (%)		
0-4	1023 (58.5)	-
5-9	401 (22.9)	-
10-14	190 (10.9)	-
15-19	135 (7.7)	-
Age at cancer diagnosis (years), mean (SD)	5.2 (4.8)	-
Sex, n (%)		
Female	796 (45.5)	20014 (45.7)
Male	953 (54.5)	23827 (54.3)
Mother's age (years), n (%)		
<29	841 (48.1)	20616 (47.0)
30-39	865 (49.5)	22129 (50.5)
40 and over	43 (2.5)	1096 (2.5)
Mother's age (years), mean (SD)	29.9 (4.8)	29.9 (4.8)
Father's age (years), n (%)		
<29	557 (32.1)	13506 (31.0)
30-39	988 (57.0)	25244 (58.0)
40 and over	189 (10.9)	4796 (11.0)
Missing (%)	15 (0.9)	295 (0.7)
Father's age (years), mean (SD)	32.4 (5.8)	32.6 (5.8)
Mother smoking at the first prenatal visit, n (%)[a]		
Yes	342 (20.3)	8570 (20.3)
Missing (%)	67 (3.8)	1523 (3.5)
Birth order, n (%)		
1	752 (43.0)	17654 (40.3)
1 or more	997 (57.0)	26187 (59.7)
Residence at birth, n (%)		
Greater Copenhagen	429 (24.9)	10959 (25.0)
Rural Zealand	163 (9.5)	4690 (10.7)
Aarhus	113(6.6)	2766 (6.3)
Odense	75 (4.4)	1682 (3.8)
Other	940 (54.7)	23744 (54.2)
Missing (%)	29 (1.7)	0 (0.0)
Birth weight (grams), n (%)		
570 – 1499	15 (0.9)	301 (0.7)
1500 – 2499	72 (4.1)	1910 (4.4)
2500 – 3999	1282 (73.3)	33122 (75.5)
4000 and over	380 (21.7)	8508 (19.4)
Birth weight (grams), mean (SD)	3520 (617)	3501 (601)

[a] Data collection started in 1995 was completely implemented in 1996.

Table 2. Distribution of maternal nitrosatable drug prescription received during pregnancy among childhood cancer cases and matched controls, births 1995 – 2014

	Cases (n=1749)	**Controls (n=**43841)
Maternal nitrosatable drug prescriptions during pregnancy, n (%)[a]		
Any nitrosatable drugs	481 (27.5)	9973 (22.7)
Amides	398 (22.8)	8153 (18.6)
Secondary amines	74 (4.2)	1443 (3.3)
Tertiary amines	174 (9.9)	3844 (8.8)
Nitrosatable antibacterial drugs	334 (19.1)	6784 (15.5)
Number of nitrosatable drug prescriptions during pregnancy, n (%)		
0 (never been prescribed)	1268 (72.5)	33868 (77.3)
1	370 (21.2)	7836 (17.9)
2	89 (5.1)	1690 (3.9)
3 or more	22 (1.3)	447 (1.0)
Maternal antibiotic and nitrosatable antibiotic prescription during pregnancy, n (%)		
Never been prescribed any	1086 (62.1)	29802 (68.0)
Other antibacterial drugs	182 (10.4)	4066 (9.3)
Other nitrosatable drugs	113 (6.5)	2496 (5.7)
Nitrosatable antibacterial drugs	193 (11.0)	3832 (8.7)
Other combinations	175 (10.0)	3645 (8.3)

[a] Not mutually exclusive

Table 3. Conditional logistic regression odds ratios (OR) and 95% confidence intervals for childhood cancers and any type of maternal nitrosatable drug prescription received during pregnancy

Cancer type	Cases		Controls		adj.OR[a]	95% CI
	Exposed	Unexposed	Exposed	Unexposed		
Acute lymphoblastic leukemia	147	408	3062	10816	1.3	1.07 – 1.59
Acute myeloid leukemia	33	79	676	2158	1.4	0.89 – 2.06
Central nervous system tumors	162	429	3444	11338	1.3	1.04 – 1.51
Gliomas	60	175	1395	4478	1.1	0.82 – 1.50
Astrocytoma	47	117	948	3141	1.3	0.94 – 1.88
Diffuse astrocytoma	14	29	261	804	1.5	0.79 – 3.02
Pilocytic astrocytoma	29	80	624	2077	1.2	0.78 – 1.87
Non-Hodgkin's lymphoma	33	75	634	2048	1.4	0.94 – 2.20
Germ cell tumors	24	65	515	1741	1.2	0.75 – 1.98
Neuroblastoma	44	86	728	2611	2.0	1.34 – 2.85
Wilms' tumor	18	78	538	1844	0.8	0.48 – 1.39
Medulloblastoma	15	52	411	1274	0.9	0.50 – 1.64
Retinoblastoma	20	48	376	1312	1.5	0.89 – 2.63
Unilateral retinoblastoma	11	34	240	877	1.3	0.64 – 2.61
Bilateral retinoblastoma	8	14	130	416	1.8	0.73 – 4.45

[a] Adjusted by mother age (years) and birth order (>1 vs 1)

Table 4. Conditional logistic regression odds ratios (OR) and 95% confidence intervals for childhood cancers and specific type of maternal nitrosatable drug prescription received during pregnancy

Group of nitrosatable prescription	Cases		Controls		adj.OR[a]	95% CI
	Exposed	Unexposed	Exposed	Unexposed		
Acute lymphoblastic leukemia						
Amides	119	408	2488	10816	1.3	1.05 – 1.61
Secondary amines	30	408	435	10816	1.9	1.28 – 2.76
Tertiary amines	55	408	1189	10816	1.2	0.94 – 1.67
Nitrosatable antibiotics	97	408	2059	10816	1.3	1.03 – 1.62
Acute myeloid leukemia						
Amides	27	79	562	2158	1.3	0.85 – 2.09
Secondary amines	8	79	87	2158	2.6	1.20 – 5.55
Tertiary amines	12	79	268	2158	1.2	0.66 – 2.28
Nitrosatable antibiotics	21	79	462	2158	1.3	0.77 – 2.08
Central nervous system tumor						
Amides	135	429	2815	11338	1.3	1.05 – 1.56
Secondary amines	16	429	518	11338	0.8	0.50 – 1.37
Tertiary amines	62	429	1302	11338	1.3	0.96 – 1.66
Nitrosatable antibiotics	116	429	2366	11338	1.3	1.06 – 1.62
Gliomas						
Amides	52	175	1130	4478	1.2	0.87 – 1.65
Tertiary amines	18	175	532	4478	0.9	0.53 – 1.42
Nitrosatable antibiotics	51	175	966	4478	1.4	1.00 – 1.91
Astrocytoma						
Amides	41	117	768	3141	1.4	0.99 – 2.06
Tertiary amines	15	117	361	3141	1.1	0.64 – 1.94
Nitrosatable antibiotics	40	117	665	3141	1.6	1.11 – 2.34
Diffuse astrocytoma						
Amides	13	29	216	804	1.8	0.88 – 3.50
Nitrosatable antibiotics	14	29	181	804	2.3	1.18 – 4.66
Pilocytic astrocytoma						
Amides	24	80	502	2077	1.2	0.77 – 1.97

Tertiary amines	12	80	241	2077	1.3	0.70 – 2.43
Nitrosatable antibiotics	22	80	439	2077	1.3	0.80 – 2.09
Non-Hodgkin's lymphoma						
Amides	27	75	509	2048	1.5	0.94 – 2.34
Tertiary amines	11	75	247	2048	1.2	0.64 – 2.34
Nitrosatable antibiotics	23	75	436	2048	1.5	0.91 – 2.42
Germ cell tumors						
Amides	22	65	427	1741	1.4	0.82 – 2.24
Tertiary amines	11	65	208	1741	0.5	0.18 – 1.41
Nitrosatable antibiotics	20	65	360	1741	1.5	0.86 – 2.48
Neuroblastoma						
Amides	38	86	601	2611	2.0	1.37 – 3.03
Secondary amines	9	86	100	2611	2.9	1.42 – 6.01
Tertiary amines	14	86	284	2611	1.5	0.87 – 2.77
Nitrosatable antibiotics	30	86	486	2611	2.0	1.31 – 3.13
Wilms' tumor						
Amides	15	78	454	1844	0.8	0.46 – 1.44
Nitrosatable antibiotics	13	78	375	1844	0.9	0.48 – 1.60
Medulloblastoma						
Amides	11	52	349	1274	0.8	0.40 – 1.52
Tertiary amines	5	52	153	1274	0.8	0.31 – 2.02
Nitrosatable antibiotics	13	52	283	1274	1.2	0.61 – 2.17
Retinoblastoma						
Amides	15	48	297	1312	1.5	0.80 – 2.65
Tertiary amines	12	48	152	1312	2.2	1.16 – 4.35
Nitrosatable antibiotics	14	48	240	1312	1.7	0.91 – 3.13
Unilateral retinoblastoma						
Amides	9	34	185	877	1.4	0.65 – 2.93
Tertiary amines	7	34	100	877	1.9	0.81 – 4.38
Nitrosatable antibiotics	9	34	150	877	1.8	0.82 – 3.81
Bilateral retinoblastoma						
Amides	5	14	108	416	1.4	0.48 – 3.94
Tertiary amines	5	14	50	416	2.9	0.98 –

	8.71

Note: reference groups were those who were not prescribed nitrosatable medication during pregnancy.
[a] Matched by child's birth date and sex; and adjusted by mother age (years) and birth order (>1 vs 1).

Table 5. Conditional logistic regression odds ratios (OR) and 95% confidence intervals cancers and specific type of maternal nitrosatable drug and antibacterial prescription received during pregnancy

Group of prescription	Cases	Controls	adj.OR[a]	95% CI
Acute lymphoblastic leukemia				
Never been prescribed any	346	9496	1.0	Referent
Other antibacterial drugs	62	1320	1.3	0.99 – 1.72
Other nitrosatable drugs	33	795	1.1	0.80 – 1.65
Nitrosatable antibacterial drugs	54	1139	1.3	1.00 – 1.81
Other combinations[b]	60	1128	1.5	1.14 – 2.00
Acute myeloid leukemia				
Never been prescribed any	69	1890	1.0	Referent
Other antibacterial drugs	10	268	1.0	0.52 – 2.04
Other nitrosatable drugs	10	178	1.5	0.78 – 3.04
Nitrosatable antibacterial drugs	10	259	1.1	0.54 – 2.12
Other combinations[b]	13	239	1.5	0.83 – 2.82
Central nervous system tumors				
Never been prescribed any	373	9985	1.0	Referent
Other antibacterial drugs	56	1353	1.1	0.82 – 1.46
Other nitrosatable drugs	40	838	1.3	0.92 – 1.79
Nitrosatable antibacterial drugs	71	1353	1.4	1.09 – 1.84
Other combinations[b]	51	1253	1.1	0.81 – 1.48
Astrocytoma				
Never been prescribed any	104	2783	1.0	Referent
Other antibacterial drugs	13	358	1.0	0.53 – 1.74
Other nitrosatable drugs	7	229	0.8	0.37 – 1.77
Nitrosatable antibacterial drugs	26	379	1.8	1.17 – 2.88
Other combinations[b]	14	340	1.1	0.62 – 1.93
Neuroblastoma				
Never been prescribed any	69	2300	1.0	Referent
Other antibacterial drugs	17	311	1.7	1.01 – 3.02
Other nitrosatable drugs	12	187	2.2	1.18 – 4.19
Nitrosatable antibacterial drugs	18	276	2.4	1.39 – 4.09
Other combinations[b]	14	265	1.8	1.00 – 3.29

Note: reference groups were those who were not prescribed nitrosatable medication during pregnancy.
[a] Matched by child's birth date and sex; and adjusted by mother age (years) and birth order (>1 vs 1).
[b] Other combinations of antibacterial drugs and nitrosatable drugs.

Supplementary Tables

Table S1 List of nitrosatable drugs to be identified with Anatomical Therapeutic Chemical (ATC) codes

No.	Name of drug	ATC code	Compound	Class/indication
1	Acebutolol	C07AB04	2, amide	Cardiovascular, Beta blocker
2	Albuterol (salbutamol)	R03AC02	2	Asthma, Beta adrenergic
3	Ambroxol	R05CB06	2, amide	Cough, Mucolytic
4	Amitriptyline	N06AA09	3	Antidepressant, Tricyclic
5	Amoxicillin	J01CA04	amide	Anti-infective, Beta lactam
6	Ampicillin	J01CA01	amide	Anti-infective, Beta lactam
7	Amytal (as amobarbital)	N05CA02	amide	Barbiturate
8	Antipyrine (as muzolimine)	C03CD01	3	Analgesic
9	Atenolol	C07AB03	2, amide	Cardiovascular, Beta blocker
10	Atropine	A03BA01	3	Anticholinergic
11	Azatadine	R06AX09	3	Antihistamine
12	Brompheniramine	R06AB01	3	Antihistamine
13	Butabarbital (combinations of barbiturates)	N05CB01	2	Barbiturate
14	Caffeine	N06BC01	3, amide	Stimulant
15	Carbamazepine	N03AF01	3, amide	Antiepileptic
16	Carbinoxamine	R06AA08	3	Cough suppressant
17	Cefaclor	J01DC04	amide	Anti-infective, Beta lactam
18	Cefadroxil	J01DB05	2, amide	Anti-infective, Beta lactam
19	Cefalexin	J01DB01	amide	Anti-infective, Beta lactam
20	Cephradine	J01DB09	amide	Anti-infective, Beta lactam
21	Chlordiazepoxide	N05BA02	2, 3	Benzodiazepine
22	Chloroquine	P01BA01	2, 3	Anti-infective
23	Chlorothiazide	C03AA04	2, 3, amide	Cardiovascular, Thiazide diuretic
24	Chlorpheniramine	R06AB02	3	Antihistamine
25	Chlorpromazine	N05AA01	3	Antiemetic, Phenothiazine
26	Chlorzoxazone	M03BB03	amide	Muscle relaxant
27	Cimetidine	A02BA01	2, 3	Gastrointestinal, H2 blocker
28	Clemastine	R06AA04	3	Antihistamine
29	Clindamycin	J01FF01	3, amide	Anti-infective, Macrolide
30	Clomiphene	G03GB02	3, amide	Fertility
31	Clomipramine	N06AA04	3	Antidepressant, Tricyclic
32	Clonidine	N02CX02	2, 3	Cardiovascular, Antihypertensive
33	Cloxacillin	J01CF02	amide	Anti-infective, Beta lactam
34	Codeine	R05DA04	3	Analgesic, Opioid
35	Desipramine	N06AA01	2, 3	Antidepressant, Tricyclic
36	Dextromethorphan	R05DA09	3, amide	Cough suppressant
37	Diazepam	N05BA01	3, amide	Benzodiazepine
38	Dichloralphenazone	N05CC04	3, amide	Migraine

39	Diclofenac	M01AB05	2	Analgesic, NSAID
40	Dicyclomine	A03AA07	3	Anticholinergic
41	Diltiazem	C08DB01	3, amide	Cardiovascular, Calcium channel blocker
42	Dimenhydrinate (cinnarizine)	N07CA52	3, amide	Antiemetic, Antihistamine
43	Diphenhydramine	R06AA02	3	Antihistamine
44	Diphenoxylate	A07DA01	3	Antidiarrheal, Opioid
45	Dipyrone	N02BB02	3	Analgesic
46	Doxycycline	J01AA02	3, amide	Anti-infective, Tetracycline
47	Doxylamine	R06AA09	3	Antihistamine
48	Enalapril	C09AA02	2, amide	Cardiovascular, ACE Inhibitor
49	Ephedrine (oral)	R03CA02	2	Decongestant
50	Epinephrine (for local oral treatment)	A01AD01	2	Asthma
51	Erythromycin	J01FA01	3	Anti-infective, Macrolide
52	Ethambutol	J04AK02	2	Anti-infective, Antimycobacterial
53	Fenfluramine	A08AA02	2	Anorexigenic
54	Fluoxetine	N06AB03	2	Antidepressant, SSRI
55	Furosemide	C03CA01	2, amide	Cardiovascular, Diuretic
56	Hydralazine	C02DB02	2, 3	Cardiovascular, Antihypertensive
57	Hydrochlorothiazide	C03EA01	2, amide	Cardiovascular, Thiazide
58	Hydroxyzine	N05BB01	3	Antihistamine
59	Hyoscamine	A03BA03	3	Anticholinergic
60	Imipramine	N06AA02	3	Antidepressant, Tricyclic
61	Indomethacin	M01AB01	amide	Analgesic, NSAID
62	Isometheptane	A03AX10	2	Migraine
63	Isoniazid	J04AC01	3, amide	Anti-infective
64	Lidocaine (oral topical)	R02AD02	2, 3	Anesthetic, Topical mucous membranes
65	Lorazepam	N05BA06	amide	Benzodiazepine
66	Meclizine	R06AE05	3	Antihistamine
67	Meperidine	N02AB02	3	Analgesic, Opioid
68	Metformin	A10BA02	2, 3	Antidiabetic, Biguanide
69	Methadone	N07BC02	3	Analgesic, Opioid
70	Methamphetamine	N06BA03	2	Stimulant
71	Metoclopramide	A03FA01	3, amide	Antiemetic, Prokinetic
72	Metoprolol	C07AB02	2	Cardiovascular, Beta blocker
73	Metronidazole	J01XD01	3	Anti-infective
74	Minocycline	A01AB23	3, amide	Anti-infective, Tetracycline
75	Minocycline	J01AA08	3, amide	Anti-infective, Tetracycline
76	Morphine	N02AA01	3	Analgesic, Opioid
77	Nadolol	C07AA12	2	Cardiovascular, Beta blocker
78	Naratriptan	N02CC02	3	Migraine
79	Nicardipine	C08CA04	2, 3	Cardiovascular, Calcium channel blocker

80	Nicotine	N07BA01	3	Nicotine replacement
81	Nifedipine	C08CA05	2	Cardiovascular, Calcium channel blocker
82	Nimodipine	C08CA06	3	Cardiovascular, Calcium channel blocker
83	Nortriptyline	N06AA10	3	Antidepressant, Tricyclic
84	Oxacillin	J01CF04	amide	Anti-infective, Beta lactam
85	Oxprenolol	C07AA02	2	Cardiovascular, Beta blocker
86	Oxycodone	N02AA05	3	Analgesic, Opioid
87	Oxytetracycline	J01AA06	3, amide	Anti-infective, Tetracycline
88	Paregoric (as for morphine)	N02AG01	3	Antidiarrheal, Opioid
89	Paroxetine	N06AB05	2	Antidepressant, SSRI
90	Phenoxymethylpenicillin	J01CE02	amide	Anti-infective, Beta lactam
91	Perphenazine	N05AB03	3	Antipsychotic
92	Phenobarbital	N03AA02	amide	Antiepileptic, Barbiturate
93	Phenytoin	N03AB02	amide	Antiepileptic
94	Pindolol	C07AA03	2	Cardiovascular, Beta blocker
95	Primidone	N03AA03	amide	Antiepileptic
96	Probenecid	M04AB01	3, amide	Uricosuric
97	Prochlorperazine	N05AB04	3	Antiemetic, Phenothiazine
98	Promethazine	R06AD02	3	Antiemetic, Phenothiazine
99	Dextropropoxyphene	N02AC04	3	Analgesic, Opioid
100	Propranolol	C07AA05	2	Cardiovascular, Beta blocker
101	Pseudoephedrine	R01BA03	2	Decongestant
102	Ranitidine	A02BA02	3	Gastrointestinal, H2 blocker
103	Ritodrine	G02CA01	2	Tocolytic
104	Scopolamine	A04AD01	3	Anticholinergic
105	Sotalol	C07AA07	2, amide	Cardiovascular, Beta blocker
106	Sulfamethoxazole	J01EE01	amide	Anti-infective, Sulfonamide
107	Sulfisoxazole	J01EB05	amide	Anti-infective, Sulfonamide
108	Terbutaline	R03CC03	2	Asthma, Beta adrenergic
109	Terfenadine	R06AX12	3	Antihistamine
110	Tetracycline	J01AA07	3, amide	Anti-infective, Tetracycline
111	Timolol	C07AA06	2, 3	Cardiovascular, Beta blocker
112	Tizanidine	M03BX02	2	Muscle relaxant
113	Trichlormethiazide	C03AA06	2, amide	Cardiovascular, Thiazide diuretic
114	Triprolidine	R06AX07	3	Antihistamine
115	Vancomycin	A07AA09	2, amide	Anti-infective
116	Verapamil	C08DA01	2	Cardiovascular, Calcium channel blocker
117	Acetaminophen	N02BE01	amide	Analgesic, Other
118	Acetohexamide	A10BB31	amide	Antidiabetic, Sulfonylureas
119	Ajmaline	C01BA05	3	Cardiovascular,

				Antiarrhythmics
120	Alprenolol	C07AA01	2	Cardiovascular, Beta blocker
121	Antipyrine (as Phenazone)	N02BB01	3	Analgesic, Other
122	Bamethan	C04AA31	2	Cardiovascular, Vasodilator
123	Bephenium hydroxynaphthoate	P02CX02	NA	Anthelmintic
124	Betanidine	C02CC01	NA	Cardiovascular, Antiadrenegic agents
125	Bromazepam	N05BA08	2, amide	Benzodiazepine
126	Bromhexine	R05CB02	NA	Cough, Mucolytic
127	Carbidopa (as Levodopa)	N04BA02	NA	Aopaminergic agents
128	Chlorprothixene	N05AF03	3	Antipsychotic
129	Cinnarizine	N07CA02	3	Antivertigo preparations
130	Cyclizine	R06AE03	3	Antihistamine
131	Dilazep	C01DX10	3	Cardiovascular, Other vasodilators
132	Dimetofrine	C01CA12	2	Cardiovascular, Adrenergic and dopaminergic agents
133	Dipyridamole	B01AC07	3, amide	Antithrombotic agents
134	Disulfiram	N07BB01	NA	Drugs used in alcohol dependence
135	Etilefrine	C01CA01	NA	Cardiovascular, Adrenergic and dopaminergic agents
136	Flupentixol	N05AF01	3	Antipsychotic
137	Gallopamil	C08DA02	3	Cardiovascular, Calcium channel blocker
138	Guanethidine	C02CC02	3	Cardiovascular, Antihypertensive
139	Isoxsuprine	C04AA01	2	Cardiovascular, Vasodilator
140	Maprotiline	N06AA21	NA	Antidepressants
141	Mebendazole	P02CA01	amide	Anthelmintic
142	Meprobamate	N05BC01	NA	Anxiolytics
143	Methapyrilene	R06AC05	3	Antihistamine
144	Methyldopa	C02AB01	amide	Cardiovascular, Antiadrenergic agents
145	Morsydomine (as Molsidomine)	C01DX12	NA	Cardiovascular, Vasodilator
146	Nitrendipine	C08CA08	2	Cardiovascular, Calcium channel blocker
147	Opipramol	N06AA05	3	Antidepressants
148	Phenacetin	N02BE03	NA	Analgesic
149	Phenelzine	N06AF03	NA	Antidepressants
150	Pipamperone	N05AD05	3, amide	Antipsychotic
151	Piperazine	P02CB01	2	Anthelmintic
152	Piromidic acid	J01MB03	3	Anti-infective, Quinoline derivatives
153	Prenylamine	C01DX02	2	Cardiovascular, calcium channel blockers
154	Procainamide	C01BA02	NA	Cardiovascular, Antiarrhythmics

155	Pyrantel pamoate	P02CC01	3	Anthelmintic
156	Quinacrine (as Mepacrine)	P01AX05	2	Antiprotozoal
157	Sulfadimidine	J01EB03	NA	Anti-infective, Sulfonamide
158	Thiothixene (as Tiotixene)	N05AF04	3	Antipsychotic
159	Tolazamide	A10BB05	NA	Antidiabetic, Sulfonylureas
160	Tolazoline	C04AB02	2	Cardiovascular, Vasodilator
161	Tolbutamide	A10BB03	NA	Antidiabetic, Sulfonylureas
162	Trapidil	C01DX11	3	Cardiovascular, Vasodilator
163	Trimetazidine	C01EB15	2, 3	Cardiovascular, Other
164	Tripelennamine	R06AC04	3	Antihistamine

Compound type: 2 = secondary amine; 3 = tertiary amine; NA = not available

Table S2 International Classification of Diseases, Revision 10 (ICD-10) diagnostic codes for infectious diseases categories

Infection category	ICD-10
Any infection (INF)	A00–B99, G00–G09, R50.9, R56.0 + all below
Microorganism-specific	
Virus infection (VI)	A08, A80–A99, B00–B34, B97, G02.0, G05.1, H67.1, J10–J12, J17.1, J20.3–J20.7, J21.0, M01.4–M01.5
Bacterial infection (BI)	A00–A05, A15–A59, A65–A79, B95–B96, G00, G01, G04.2, G05.0, G06–G09, H66, H67.0, I00–I01, J13–J15, J17.0, J20.0–J20.2, J36, J39.0–J39.1, J85–J86, K35–K37, L00–L08, M00, M01.0–M01.3, N10–N12, N30, N34.0, N39.0, N70–N77, O23
Organ specific	
Respiratory infection (RI)	A36–A38, J00–J22, J32, J36–J37, J39.0–J39.1, J85–J86
Infectious enteritis (EI)	A01–A09
Skin infection (SI)	L00–L08
Urinary tract infection (UI)	N10–N12, N30, N34.0, N39.0, O23.0–O23.4
Genital infection included STDs* (GI)	A50–A64, N70–N77, O23.5–O23.9

* Sexually transmitted diseases (STDs) include syphilis, gonorrhea, chlamydia, trichomoniasis, condyloma and genital herpes

[(a)] Table adapted from Atladóttir et al. [45]