UCLA

UCLA Electronic Theses and Dissertations

Title

Association Between Pharmacological and Infection Exposures in Maternal and Child and Risk of Childhood Cancers

Permalink

https://escholarship.org/uc/item/3nq5p5xf

Author

Sirirungreung, Anupong

Publication Date

2023

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

UNIVERSITY OF CALIFORNIA

Los Angeles

Association Between Pharmacological and Infection Exposures in Maternal and Child and Risk of Childhood Cancers

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Epidemiology

by

Anupong Sirirungreung

2023

© Copyright by

Anupong Sirirungreung

2023

ABSTRACT OF THE DISSERTATION

Association Between Pharmacological and Infection Exposures
in Maternal and Child and Risk of Childhood Cancers

by

Anupong Sirirungreung
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2023
Professor Beate R. Ritz, Chair

Childhood cancer is a complex group of diseases affecting children, causing significant physical, emotional, and financial burdens globally. Genetic predisposition, infections during pregnancy, and pharmaceutical exposures are potential risk factors for childhood cancer. Understanding childhood cancer is crucial for effective prevention and treatment strategies. This dissertation investigates the impact of maternal and child infections and pharmaceutical exposure during pregnancy on childhood cancer risk through population-based studies in Denmark and Taiwan.

The first study examined the effect of postnatal infection on childhood cancer risk using Danish nationwide registries from 1978 to 2016. The findings from this matched case-control study revealed a positive association between postnatal infections and various childhood cancers, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia, non-Hodgkin's lymphoma, and central nervous system tumors (CNS).

The second study explored infection and antibiotic exposure during pregnancy using Taiwan's Maternal and Child Health Database and national health and cancer registries from 2004 to 2015. This cohort study unveiled moderate associations between infections during pregnancy and the risk of hepatoblastoma, accompanied by a discernible elevation in the risk of ALL. Antibiotic prescriptions during pregnancy, especially tetracyclines, increased the risk of childhood ALL, and certain antibiotics raised hepatoblastoma risk.

The third investigation focused on nitrosatable drug exposure during pregnancy employing a meticulous matched case-control study and analyzing data sourced from Danish nationwide registries spanning the years 1995 to 2016. The study found that nitrosatable drug prescription during pregnancy was potentially associated with the risk of offspring’s CNS and neuroblastoma.

The final study assessed acetaminophen exposure during pregnancy using the Taiwan population-based cohort from 2004 to 2017. Prolonged acetaminophen use throughout all trimesters was potentially associated with elevating the risk of medulloblastoma, hepatoblastoma, and bone tumors.

In summary, this dissertation sheds light on the impact of maternal and child infections and pharmaceutical exposure during pregnancy on childhood cancer risk. Utilizing rigorous population-based case-control and cohort studies in Denmark and Taiwan, this research enhances our understanding of etiological factors of childhood cancer. The findings highlight the need to investigate potential risk factors such as infections, antibiotics, nitrosatable drugs, and acetaminophen use during pregnancy to advance prevention strategies for childhood cancers.

The dissertation of Anupong Sirirungreung is approved.

Julia E. Heck

Roch Arnaud Kibsa Nianogo

Catherine Ann Sugar

Beate R. Ritz, Committee Chair

University of California, Los Angeles

2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS AND ACRONYMS

ACE	Angiotensin-converting enzyme
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CNS	Central nervous system tumors
H2	Histamine type 2 receptor
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICCC-3	International Classification of Childhood Cancer - Third Edition
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases, Revision 10
ICD-8	International Classification of Diseases, Revision 8
ICD-9	International Classification of Diseases, Revision 9
ID	Incidence density rate
IPD	Inpatient department
IQR	interquartile range
NHL	Non-Hodgkin’s lymphoma
NIRD	National Insurance Research Database
NOC	N-nitroso compounds
Non-IPD	Non-inpatient department
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
RR	Risk ratio
SD	Standard deviation

SI	Simulation interval
SSRI	Selective serotonin reuptake inhibitors
STD	Sexually transmitted diseases
TMCHD	Taiwan Maternal and Child Health Database

ACKNOWLEDGEMENTS

I extend my heartfelt gratitude to my supervisor, Dr. Beate Ritz, whose invaluable guidance, support, and mentorship have been instrumental throughout my PhD studies. Her expertise, knowledge, and experience have been a priceless asset, and I am deeply thankful for her willingness to share her time and expertise with me. Her exceptional working and teaching style have inspired me to pursue a career as an epidemiologist and become a better mentor myself.

I would like to express sincere thanks to Dr. Julia Heck for providing me with the remarkable opportunity to collaborate on her projects related to maternal comorbidities, prescription drug use during pregnancy, and childhood cancer in Denmark, as well as connecting me with the Taiwan childhood cancer research team. Her expertise in childhood cancer epidemiology has not only enriched the development of my dissertation but has also shaped my future career path in this field within my home country. Her unwavering guidance and support have been invaluable to my growth as a researcher.

I am also grateful to the members of my PhD committee, Dr. Roch A. Nianogo and Dr. Catherine Sugar, for their constructive feedback and valuable suggestions. Special thanks go to subject matter experts, Dr. Johnni Hansen, Dr. Zeyan Liew, Dr. Pei-Chen Lee, and my colleagues, Dr. Di He, Dr. Xiwen Huang, and Ms. Ya-Hui Hu, for their unwavering support and dedication, which significantly contributed to the success of the reports we have published.

I am deeply appreciative of the financial support provided by the Royal Thai Government during my PhD studies. This support enabled me to fully focus on my research and academic pursuits.

Furthermore, I would like to acknowledge the support and encouragement I have received from my colleagues in the Fielding School of Public Health, particularly within the Department of Epidemiology. Their camaraderie and shared knowledge have enriched my PhD journey, making it more vibrant and enjoyable.

Finally, I extend my heartfelt thanks to my family and friends for their unwavering love and support. Their presence and encouragement throughout my PhD journey have been a source of strength and inspiration, for which I am truly grateful.

Chapter 1 is a version of Sirirungreung A, Hansen J, Ritz B, Heck JE. Association between medically diagnosed postnatal infection and childhood cancers: A matched case-control study in Denmark, 1978 to 2016. Int J Cancer. Published online May 27, 2023. doi:10.1002/ijc.34604 with kind permission from John Wiley and Sons.

Chapter 4 is a version of Sirirungreung A, Hansen J, He D, Huang X, Ritz B, Heck JE. Exposure to nitrosatable drugs during pregnancy and childhood cancer: a matched case-control study in Denmark, 1996 – 2016. Pharmacoepidemiol Drug Saf. Published online October 27, 2022. doi:10.1002/pds.5557 with kind permission from John Wiley and Sons.

VITA

Education:

2011 MD, Phramongkutklao College of Medicine, Bangkok, Thailand.

2016 MPH, Mahidol University, Bangkok, Thailand.

Publications:

Sririungreung A, Hansen J, Ritz B, Heck JE. Association between medically diagnosed postnatal infection and childhood cancers: A matched case-control study in Denmark, 1978 to 2016. Int J Cancer. Published online May 27, 2023. doi:10.1002/ijc.34604

Sririungreung A, Hansen J, He D, Huang X, Ritz B, Heck JE. Exposure to nitrosatable drugs during pregnancy and childhood cancer: a matched case-control study in Denmark, 1996 – 2016. Pharmacoepidemiol Drug Saf. Published online October 27, 2022. doi:10.1002/pds.5557

Su Mon T, Rattanathumsakul T, Puangmanee D, Kyawt Khine S, Phyo Than W, Binti Wahab A, Huy Tu N, Arjkumpa O, Thitichai P, **Sririungreung A**, Yeesoonsang S, Thammawijaya P, Thimasarn K. Field Evaluation of Malaria Surveillance System in Sai Yok District, Kanchanaburi Province, Thailand. OSIR. 2019 June; 12(2):38-45.

Kaewput W, Thongprayoon C, Varothai N, **Sririungreung A**, Rangsin R, Bathini T, Mao MA, Cheungpasitporn W. Prevalence and associated factors of hospitalization for dysglycemia among elderly type 2 diabetes patients: A nationwide study. World J Diabetes. 2019 Mar 15;10(3):212-223. doi: 10.4239/wjd.v10.i3.212. PubMed PMID: 30891156; PubMed Central PMCID: PMC6422861.

Sririungreung A, Buasom R, Jiraphongsa C, Sangrajrang S. Data Reliability and Coding Completeness of Cancer Registry Information Using Reabstracting Method in the National Cancer Institute: Thailand, 2012 to 2014. J Glob Oncol. 2018 Sep;4:1-9. doi: 10.1200/JGO.17.00147. PubMed PMID: 30241269; PubMed Central PMCID: PMC6223438.

Sirirungreung A, Thintip K, Yimchoho N, Saridaphirak N, Srethapranai V, Tipayamongknolgul M, Kittipichai W. Competencies in prevention, control and response to public health hazard of provincial field epidemiologists. Mahidol University; 2016.

Duangsin A, **Sirirungreung A**, Midtrapanon S. An outbreak Influenza A/H1N1 (2009) in a legion recruit training military camp, Roi Et province, Thailand, April – May 2014. WESR. 2015; 46(32):498-503.

Sirirungreung A, Yimchoho N, Monpungteim K, Pinthadis W, Jiraphongsa C. The 2009 pandemic Influenza A virus in an outbreak during 2014 in Samut Prakan. OSIR. 2015; 8(3):1-7.

Sirirungreung A, Chartpituck P, Eamratsameekool W, Laosiritaworn Y, Karnjanapiboonwong A, Jiraphongsa C. Abridged life table of Nonghi and Phanomphrai district, Roiet province, Thailand, 2011 – 2014. WESR. 2015; 46(24):369-376.

Sirirungreung A, Tithichai P, Saikumthorn P, Sopakul W, Waiyanate N. Injury investigation of a bus that plunged into ravine in Lampang province, Thailand, 25 – 27 October 2013. WESR. 2014; 45(29):449-456.

1. Background and Introduction

1.1. Childhood cancer

Childhood cancer is cancer that affects children between birth and 14 or 19 years of age,[1–3] and it has significant physical, emotional, and financial consequences for both the affected children and their families globally.[2] This group of diseases is diverse and complex, as it can emerge in any part of the body, such as the brain, lymphoid tissues, and hematologic system.

The classification of tumors in childhood cancer is primarily based on the morphology or cancer cell type. The International Classification of Childhood Cancer - Third Edition (ICCC-3)[4] categorizes childhood cancer into twelve main groups that can be further subdivided into forty-seven subgroups. This classification system emphasizes the intricacy of childhood cancer development, which varies depending on the type of cancer.

Childhood cancer is particularly distinct from adult cancers due to differences in the location of occurrence, histological appearance, and clinical behavior.[5,6] Several tumors display histological features similar to fetal tissues at different stages of development. Children with cancer often face a particularly challenging journey, characterized by short latent periods, rapid tumor growth, and high invasiveness. However, they are also generally more susceptible to chemotherapy than tumors that commonly appear in adults,[6,7] offering hope for effective treatment and recovery.

1.1.1. Epidemiology of childhood cancer

Globally, it is estimated that between 300,000 to 400,000 children aged 0 to 19 years are diagnosed with cancer each year.[8] The incidence of childhood cancer varies between 140.6 to 185.3 per million person-years, according to the most recent report on childhood cancer incidence worldwide.[9] Leukemia, central nervous system tumors (CNS), and lymphomas were the most commonly diagnosed cancers among children aged 0-14 years, while lymphomas and epithelial tumors/melanoma were the most commonly diagnosed among adolescents aged 15-

19 years.[9] However, the incidence of childhood cancer varies depending on several factors, including the region, cancer type, age group, gender, and ethnicity. In Denmark, the childhood cancer incidence rate stands at approximately 177 cases per million person-years, indicating one of the highest rates globally.[10,11] Conversely, in Taiwan, the incidence rate is around 130 cases per million person-years, which is similar to the rates observed in other Asian countries.[11,12]

Compared to the 1980s, the global incidence rate of cancer in children aged 0-14 years has increased from 124.0 to 140.6 per million person-years.[9] However, the incidence and mortality rates of childhood cancer are not uniformly distributed across high- and low-income countries.[13] The incidence rate is higher in more developed countries, but the mortality rate is lower compared to less developed countries.[14–18] This disparity may be attributed to differences in data quality and accessibility of treatment between countries.[13]

It is important to note that childhood cancer not only affects children but also places a financial and psychological burden on their families.[19–24] Therefore, identifying the causes of childhood cancer and implementing preventative measures is crucial, even with advancements in cancer treatment.

1.1.2. Etiology of childhood cancer

Numerous theories have been proposed over the years about the potential causes of childhood cancer, including genetic predisposition, prenatal and postnatal infections, radiation exposure, and environmental factors.[25] Although genetic factors are known to play a role in some cases,[26–29] the majority of childhood cancer cases are believed to develop due to non-genetic factors such as environmental exposures.[25,30] Childhood cancer differs from adult cancer in that its development appears to occur more rapidly following environmental exposures.[25] The International Agency for Research on Cancer (IARC) has suggested a framework to understand the timing of environmental exposures that can impact different stages

of child development and lead to the development of childhood cancer, ranging from germ cell mutations to fetal and early-life stages.[25]

For many years, researchers have studied the potential association between infection and childhood cancer, with most of these studies focusing on leukemia and lymphoma. Well-known theories related to this link were proposed by Greaves and Kinlen in 1988.[31,32] Greaves hypothesized that abnormal immune responses to common infections during pregnancy and after birth could lead to spontaneous mutations and cause leukemia.[31] Meanwhile, Kinlen suggested that a lack of herd immunity in a vulnerable population due to migration and population mixing could result in abnormal immune responses that cause childhood leukemia.[32] Several recent studies have suggested that there is a connection between infection and acute lymphoblastic leukemia (ALL) risk, not only during pregnancy but also in early childhood.[33,34] Various types of infections that happen during pregnancy, like varicella, rubella, and urinary tract infections, have been strongly associated with a higher risk of ALL.[34–36] However, there is still inconclusive evidence linking a specific type of infection to other less common childhood cancers, such as lymphoma, brain tumors, neuroblastoma, and hepatoblastoma.[37–42]

On the other hand, the health of the mother and the medications given to treat preexisting or emerging health problems while pregnant can impact fetal growth and development, and some drugs may elevate the chances of childhood cancer.[43–48] Antibiotics and painkillers are among the most frequently used pharmaceuticals by pregnant women, but data on their safety during pregnancy is frequently lacking.[49–54] Nitrosatable medications and acetaminophen are two notable drug categories that women take during pregnancy that may pose risks for childhood cancer.[55–57]

1.2. Infection

1.2.1. Maternal infection

Recent studies have discovered a link between maternal infection during pregnancy and leukemia, with strong evidence pointing to specific infections like varicella, rubella, and urinary tract infections as significantly increasing the risk of ALL and acute myeloid leukemia (AML).[34–36] In addition, cytomegalovirus infection during pregnancy has been associated with offspring ALL,[58,59] though the evidence for other less common childhood cancers remains inconclusive.

Greaves has provided an extensive explanation of how infection and ALL are linked.[60,61] According to him, ALL develops as a result of multiple factors in two stages. During the first stage, a pre-leukemic clone is formed during fetal development, caused by either fusion gene formation or hyperdiploidy. The second stage involves the development of overt leukemia due to the acquisition of secondary genetic changes after birth. The occurrence of this process is influenced by common infections and inherited genetics.[60,61] Recent epidemiological research also supports the delayed infection theory, highlighting specific risk factors. For instance, the study indicates that specific birth characteristics, including the interaction between cesarean section and birth order, elevate the risk of ALL to a degree surpassing what would be anticipated.[62]

Several studies have investigated the link between maternal infection during pregnancy and childhood brain and nervous system tumors, which are the second most prevalent form of pediatric cancer.[38,39,63,64] However, inconclusive results have been reported due to insufficient statistical power.[38,39,63,64] Some studies have suggested a positive association between viral infection during pregnancy and the risk of childhood nervous system tumors.[39,63] However, current theories regarding the causes of childhood brain tumors prioritize genetic and chemical exposure during pregnancy, rather than infection.[38,65]

There is limited evidence regarding the relationship between maternal infection during pregnancy and less common types of cancer. However, one case-control study suggested a positive correlation between maternal viral infection during pregnancy and the risk of Wilms' tumor.[66] Another cohort study found a potential increase in the risk of offspring cancer among mothers with hepatitis infection.[37]

1.2.2. Postnatal infection

In recent years, numerous studies have found a positive association between postnatal infection and ALL.[33] However, there is limited research on the specific types of infections and their relationship with sub-types of leukemia such as AML, as well as for other types of cancers.[42,67–70] Further research is needed to determine the link between postnatal infections and various types of childhood cancers.

The link between common childhood infections and lymphoma in children is not well-established, despite the fact that Epstein Barr virus is known to be causally related to lymphoma.[71–73] In adults, previous studies have reported conflicting associations between childhood infections and lymphoma.[74,75] While a Danish cohort study found a positive correlation between Hodgkin lymphoma in young adults and antimicrobial prescriptions,[74] a case-control study in Italy reported an inverse association between childhood infectious diseases and non-Hodgkin’s lymphoma (NHL) that presented in adulthood.[75]

There is limited research on the relationship between infection and less common cancers such as germ cell tumors and central nervous system tumors. One study in Sweden found a strong association between neonatal infections and childhood brain tumors, particularly low and high-grade astrocytoma and medulloblastoma.[64] However, previous studies on indirect evidence of early-life exposure to infections, such as antibiotic use, social contact, and childcare attendance, have had inconsistent results.[76–79] For germ cell tumors, a case-control study discovered a slightly inverse association between any infections within six months after birth

and cancer, while mumps had a moderately positive association and appendectomy had a highly positive association.[80]

1.3. Exposure to nitrosatable drugs during pregnancy

Nitrosatable drugs are a class of medications that can be metabolized in the body to produce N-nitroso compounds (NOCs), which are suspected carcinogens.[81] The drugs contain amine or amide groups that can be transformed into NOCs in acidic conditions of the stomach, primarily through non-enzymatic reactions.[82–84] Examples of these drugs are certain antibiotics, antihistamines, and diuretics, among others, although this list is not exhaustive.[55,56,85,86]

When a pregnant woman takes nitrosatable drugs, NOCs can be formed in her body and transferred to the fetus through the placenta. Animal experiments have demonstrated that this process can lead to the development of tumors in the nervous and lymphatic systems.[87–93] However, epidemiological studies have not yet established a clear link between NOC exposure and cancer risk in humans.[55,56,85,86] The inconsistent results of previous studies may be attributed to the difficulties of measuring and identifying NOC exposures. The IARC has evaluated that ingested nitrates or nitrites that lead to endogenous nitrosation are probably carcinogenic to humans (Group 2A).[94]

Previous epidemiological studies have suggested that the consumption of nitrate and nitrite may increase the risk of different types of cancer in adults such as tumors in the gastrointestinal tract, brain, lymphatic system, and urinary tract.[95–100] Moreover, maternal exposure to nitrosatable compounds during pregnancy has been linked to childhood brain tumors and leukemia, with many studies focusing on exposure to nitrates from sources such as food and drinking water.[101–104] However, research on the association between exposure to nitrosatable drugs during pregnancy and childhood nervous system tumors is limited, and the findings have been inconsistent. Some studies have investigated this relationship, but due to the difficulty in measuring and identifying NOC exposure, results have been inconsistent.[55,56,105,106]

1.4. Acetaminophen exposure during pregnancy and childhood cancer

Acetaminophen is a widely used medication during pregnancy for reducing fever and alleviating pain.[107–109] It is frequently taken by pregnant women in Western countries with a prevalence of around 50-60%,[110,111] and up to 70% in Taiwan.[112,113] Nonetheless, in recent years, there has been increasing concern regarding the safety of acetaminophen during pregnancy, as studies have indicated that it may have adverse effects on fetal neurodevelopment and contribute to respiratory illnesses.[112–117] However, there is currently only limited research on the relationship between acetaminophen use during pregnancy and childhood cancer.[57]

Acetaminophen can pass through the placenta and affect the fetus, as it is metabolized in the body.[118–121] Its impact on fetal development is a concern, as it can disrupt the endocrine and nervous systems, cause hepatotoxicity, and oxidative stress.[122–128] Research suggests that high doses of acetaminophen can lead to genetic damage and raise the risk of cancer,[129,130] but recent studies have found no such carcinogenic effects.[131–133]

Previous research has shown that the use of acetaminophen may be associated with an increased risk of hematologic cancers in adults,[134,135] but evidence on its link to other types of cancer is limited.[135] Additionally, research on the potential association between acetaminophen use during pregnancy and childhood cancer is scarce, with only one study investigating the potential relationship between acetaminophen use during pregnancy and early-onset leukemia in children, which suggested a possible protective effect against the development of cancer.[57] However, a case-control investigation conducted in Sweden hinted at a possible connection between the use of acetaminophen during pregnancy and the occurrence of childhood brain tumors.[136] Additionally, there have been isolated case reports indicating a potential link between acetaminophen exposure and childhood hepatoblastoma,[137–139] but recent epidemiological data did not provide substantial support for this claim.[140] It should be noted that most of these epidemiological studies categorized acetaminophen exposure in a simplistic manner (ever vs never) and lacked more detailed categories for chronic exposure.[57,136,140]

2. Postnatal infection and the risk of childhood cancer in Denmark

This chapter is based in part on the previously published article entitled “Association between medically diagnosed postnatal infection and childhood cancers: a matched case-control study in Denmark, 1978 to 2016” published in International Journal of Cancer.[141] I have permission from John Wiley and Sons to use the work in my dissertation (license number: 5557900919695).

2.1. Introduction

For many years, researchers have been studying infection as a potential risk factor for childhood cancer, particularly leukemia and lymphoma. This is because other types of childhood cancer are rare, making them difficult to study. Additionally, it's challenging to accurately measure infection and related exposures that occurred during the lifetimes of the children being studied.

Studies investigating the potential relationship between infection and leukemia have been conducted extensively since the proposal of Greaves's and Kinlen's hypotheses. In 1988, Greaves suggested that abnormal immune responses to common infections, both in utero and after birth, could lead to spontaneous mutations and the development of leukemia.[31] Kinlen, in the same year, proposed that population mixing and migration related to a lack of herd immunity could cause abnormal immune responses in a susceptible population and result in childhood leukemia.[32] Numerous studies have now suggested a positive correlation between postnatal infection and ALL.[33] However, there is currently limited detailed research on specific types of infections[42,69,70] or sub-types of leukemia such as AML.[42,68,142]

Although there is a widely acknowledged causal relationship between Epstein Barr virus and lymphoma,[71–73] the link between common childhood infections and lymphoma is limited. Previous research has found an inconsistent association between childhood infections and lymphoma in adults. For instance, a study in Denmark showed a positive association between antimicrobial prescriptions (which were used as a proxy for general infectious

diseases) and Hodgkin lymphoma among young adults.[74] On the other hand, a case-control study in Italy indicated an inverse association between childhood infectious diseases and NHL in adults.[143]

Limited information is available on the association between infection and less common cancers such as germ cell tumors and CNS.[144] A matched case-control study conducted in Sweden discovered a strong link between neonatal infections and childhood brain tumors.[145] Furthermore, they identified robust associations between early-life infections and specific types of childhood brain tumors such as astrocytoma and medulloblastoma.[145] However, previous studies on indirect evidence of early-life exposure to infections (e.g., antibiotic use, social contact, childcare attendance) were inconsistent.[76–79] For germ cell tumors, a case-control study discovered a slight negative association between any infections within six months after birth and cancer,[80] but the same study found a moderately positive association for mumps and a highly positive association for appendectomy.[80]

The Danish National Patient Register is a long-standing, nationwide, population-based registry that has gathered clinical information from all hospitals in Denmark.[146] It presents an opportunity to access infectious exposures that took place before the cancer diagnosis of the index child by employing a standard data linkage protocol.[147] Consequently, the aim of this study was to evaluate the correlation between medically diagnosed postnatal infection and childhood cancers in the Danish population.

2.2. Methods

A nationwide data base-linkage was used to conduct this matched case-control study on the Danish population. The study utilized the distinct personal identifier that is assigned to all Danish residents to connect information from five sources: the Central Population Registry, the Danish Cancer Registry, the Danish National Patient Register, and the Danish Medical Birth Registry. The data linkage process and covariate information have been previously described in detail.[147]

The Danish Cancer Registry was used to identify cases, which were then classified according to the ICCC-3.[4,148] To form matched sets, twenty-five controls were randomly chosen to match the index case by their birth date and sex. Eligible controls were alive and free of cancer at the time of their index case's diagnosis. The study population consisted of individuals born in Denmark between 1978 and 2013, with cancer diagnoses made between 1978 and 2016. Out of the initial number of eligible cases and controls, which was 4,219 and 105,475, respectively, we had to exclude some individuals. Those with missing information that was important for the study, such as diagnosis information and birth weight, were excluded, totaling 977 individuals, of which 34 were cases and 943 were controls. Children who were born with a birth weight less than 500 grams, as they were likely non-viable pregnancies, were also excluded from the analysis, which amounted to 1042 individuals, with 46 being cases and 996 being controls. Additionally, individuals with a diagnosis of Down's syndrome were also excluded from the study, as it is strongly associated with some types of cancer. This group included 67 individuals, of which 21 were cases and 46 were controls.[149] It's worth noting that the excluded cases and controls were not mutually exclusive.

The study obtained information on postnatal infections from the Danish National Patient Register, which records clinical diagnoses from inpatient, outpatient, and emergency department contacts.[146] The register does not include primary care visits. The diagnoses were classified according to the International Classification of Diseases, Revision 8 (ICD-8) from 1978 to 1994 and Revision 10 (ICD-10) from 1995 onwards. In 1995, outpatient and emergency department contacts begun to be included into the registry.[146] The exposure period for infections was from the date of birth until one year prior to the date of cancer diagnosis of the index case. This one-year lag-time was set in order to prevent protopathic bias.[150,151] Contaminations were categorized as viral or bacterial and according to the organ system affected by using a categorization adapted from Atladóttir et al[152] (Supplement Table ***2-S1***). The number of infection

episodes within the exposure period was counted, with the same diagnosis within a fourteen-day period considered as one episode.

The study also gathered demographic data and other relevant variables, such as parental age, family socioeconomic status, urbanicity of residence at birth, birth order, birth weight, number of children in the household, multiple birth (plural pregnancy), and maternal smoking at the first prenatal visit. These variables were obtained from either the Central Population Registry or the Danish Medical Birth Registry. The selection of variables for final analysis was based on modified disjunctive cause criteria and causal diagrams to control for potential confounding factors.[153]

We used a conditional logistic regression model to calculate crude and adjusted odds ratios along with their corresponding 95% confidence intervals for each type of childhood cancer. To control for confounding, we included potential risk factors such as maternal age (continuous), birth order (>1 vs 1), and multiple births (yes vs no).[147,154–157] Additionally, we included covariates such as residence at birth (urban, rural, small town) and the number of children in the household (1-only index child, 2, 3, >3), which are related to both infections and cancer according to the population mixing hypothesis.[32,158] These covariates were included in all final models assuming they are risk factors for most or all childhood cancers. We did not present results from models with less than five exposed cases.[159]

The study also took into account associations between certain infections and specific types of cancer that have been reported in previous studies. These included the association between enterovirus and leukemia (both ALL and AML),[42] as well as the association between germ cell tumors and appendicitis and mumps.[80]

Another analysis was conducted to investigate particular categories of infections and the frequency of infection episodes (1, 2-3, and ≥4 episodes, as well as continuous). The comparison group for these analyses consisted of children who had not been diagnosed with any type of infection in the Danish National Patient Register.

A sensitivity analysis was performed to investigate the effect of maternal smoking status on the results by adding this variable to adjusted models for the years when it was available (after 1995).[160] However, it should be noted that a previous analysis of Danish children with overlapping cases did not find an association between maternal smoking and most childhood cancers.[160] Another sensitivity analysis was conducted to compare estimates based on the ICD-8 and ICD-10 time periods by stratifying on birth year (<1995 vs. ≥1995). Additionally, the effect of infections diagnosed in different settings (inpatient vs. outpatient or emergency diagnosis) on the results was explored by stratification. All analyses were performed using R 4.2.0 software.

2.3. Results

The study included a total of 4,125 cases of childhood cancer and 103,526 matched controls. Table ***2-1*** presents the distribution of baseline characteristics of cases and controls, as well as their mothers. The data shows that cases were more likely to be firstborn children, with mothers who smoked and lived in urban areas at the time of birth.

Compared to controls, cases had a higher chance of having been diagnosed with postnatal infections (24.3% vs. 18.3%) and a higher likelihood of experiencing multiple episodes of infection (12.1% vs. 8.1%), as indicated in Table ***2-2***.

Table ***2-3*** presents the results of the analysis on the association between postnatal infection diagnosis and childhood cancer risk. The study found that children with ALL had higher odds of postnatal infection (adjusted OR [adj.OR] = 1.42; 95% confidence interval [CI] 1.23-1.63), as well as children with AML (adj.OR = 1.80; 95% CI 1.28-2.52), NHL (adj.OR = 1.53; 95% CI 1.19-1.97), CNS tumors (adj.OR = 1.57; 95% CI 1.39-1.77), astrocytoma (adj.OR = 1.29; 95% CI 1.03-1.62), medulloblastoma (adj.OR = 1.68; 95% CI 1.15-2.45), germ cell tumors (adj.OR = 1.45; 95% CI 1.12-1.88), and Wilms' tumor (adj.OR = 1.62; 95% CI 1.07-2.46) compared to controls.

The prevalence of enterovirus infection was too low among ALL (0.2%) and AML (0.4%) cases to detect any associations. However, we found that germ cell tumor cases were more likely to have a diagnosis of appendicitis (adj.OR = 2.14; 95% CI 1.14-4.02). No cases of germ cell tumors were exposed to mumps.

Adding maternal smoking status to the models did not significantly alter the adjusted odds ratios excepted for neuroblastoma (Supplement Table ***2-S2***). Stratified sensitivity analyses based on birth year and diagnostic setting did not reveal any significant differences in the results (Supplement Table ***2-S3***).

The odds ratios for different types of infections were estimated to determine their associations with childhood cancer (Table ***2-4***). Stronger positive associations were found for specific types of infections. For instance, viral infections were more strongly associated with AML (adj.OR = 2.45, 95% CI 1.48-4.03), CNS (adj.OR = 1.85, 95% CI 1.53-2.24), and medulloblastoma (adj.OR = 2.33, 95% CI 1.34-4.06), while enteric infections had doubled the odds of AML (adj.OR = 2.83, 95% CI 1.47-5.44), CNS (adj.OR = 2.08, 95% CI 1.65-2.63), and germ cell tumors (adj.OR = 2.41, 95% CI 1.53-3.80). Urinary tract infections showed the strongest positive association with ALL (adj.OR = 1.94, 95% CI 1.18-3.20), CNS (adj.OR = 2.04, 95% CI 1.40-2.96), and NHL (adj.OR = 2.44, 95% CI 1.04-5.76).

We found that specific types of cancer had a higher possibility of being diagnosed after multiple infections, including ALL, AML, CNS, and NHL (Table ***2-5***).

2.4. Discussion

The study revealed that there is a link between postnatal infections and a higher risk of several types of childhood cancer. The associations were particularly strong when examining specific subtypes of infections, as well as the number of infection episodes in relation to certain types of cancer.

The clinical diagnoses in our study were limited to medical facilities that provided specialized, inpatient, or emergency care. Some childhood infections are not severe and can

resolve on their own within a short period, while others may only require treatment by a primary care physician. Therefore, the prevalence of infections in our study population was lower than what is reported in community surveys and by caregivers.[161–165] It is unclear from our data whether children with cancer experience more infections before diagnosis or if they have a higher likelihood of developing adverse reactions to infections, requiring specialized medical care. Some cancers, such as leukemia and lymphoma, are associated with dysregulated immune function,[61,166–168] which may make patients more vulnerable to severe infections that require medical attention. However, this association has not been extensively studied for other types of cancer. While a poor immune response to infections has been observed in children with immunodeficiency diseases who develop malignant lymphoma,[166–168] such conditions were rare in our study population.

Previous studies have tried to differentiate the risk of cancer from any infection versus medically diagnosed infections. In a meta-analysis, it was found that childhood infections were strongly linked to an increased risk of ALL when considering laboratory-confirmed infections only (odds ratio [OR] = 2.4). However, when self-reported infections were included, no associations were observed (OR = 1.1).[33] This supports the theory that an abnormal immune response to clinically diagnosed infections may be a factor in cancer development.[169,170]

In contrast to our findings, previous research indicated that day-care attendance, which is an indicator of early-life infection exposure, could decrease the risk of ALL.[171] Additionally, a study in Taiwan reported a negative association between enterovirus infections during childhood and ALL development, contrary to our results indicating a positive association between viral infections and ALL.[42] Therefore, our study cannot confirm or refute the hygiene-related hypothesis that delayed infections increase cancer risk, and further research is required to investigate the timing of these infections.

Our study showed that there is a significant positive association between urinary tract infections and ALL, which was not previously studied. However, two previous studies found

links between maternal lower genital tract infection during pregnancy and ALL in the offspring.[36,172] These types of infections can be passed from the mother to the child during delivery, but our study did not find any change in results when we excluded children born through cesarean section (Table ***2-S4***).

The associations between infection and CNS observed in our study were of moderate magnitude, and we found that viral and enteric infections showed a stronger positive association than overall infections. This finding supports the emerging model of the gut-brain axis and its potential role in the development of brain tumors.[173,174]

In our study, we found that individuals with germ cell tumors were more likely to have been diagnosed with infections, including appendicitis, compared to controls. It is important to note that mumps is rare in the Danish population due to high vaccination rates. Another study among men aged 18-45 years did not find any association between childhood infections and testicular cancer.[175] To our knowledge, there is no information about the exact biological mechanism linking infection and germ cell tumors.

We observed moderate size positive effects with infections for less common childhood cancers such as neuroblastoma, Wilms tumor, and retinoblastoma. However, the confidence intervals were wide, and as with previous studies, the results were not conclusive enough to draw any definitive conclusions. Nonetheless, some studies suggested that maternal vaginal infections and antibiotic use during pregnancy might be linked to neuroblastoma and Wilms' tumor.[176–178] Additionally, laboratory studies indicated that viruses could impact retinoblastoma gene products.[179–181]

Our study used a data-linkage method that relied on nationwide registries, which minimized the risk of selection bias. The use of registry data enabled us to obtain clinical diagnoses of infections prior to the child's cancer diagnosis, and without considering the outcomes, thus avoiding the possibility of recall bias. To avoid protopathic bias, which could

have overestimated the risk from infections, we applied a one-year lag time for exposure to infections.[150,151]

Despite being able to include cases of childhood cancer over many years, the present study has some limitations. Due to the rarity of some cancers, statistical power was limited, and we were unable to investigate them. Similarly, we did not have enough statistical power to examine associations between rare infections and cancer, such as the link between Epstein Barr virus and lymphoma, which have been proven to be causally related.[71–73] As such, results based on small sample sizes should be interpreted with caution.

Although clinical diagnoses of infections were recorded using a standard coding system, some infections may have been diagnosed based solely on clinical presentation without laboratory testing, potentially leading to misclassification of exposure. The transition from ICD-8 to ICD-10 coding in 1995 allowed for more detailed diagnoses in the latter study period, while earlier diagnoses may have been grouped into broader diagnostic categories, which may have increased misclassification if only one specific infectious agent was causative. However, this misclassification would likely have occurred independent of the outcome status and therefore would have resulted in bias towards the null.

Even though we tried to prevent protopathic bias by considering a one-year lag-time, some cancers may still have delayed diagnoses and varying symptom onset intervals.[151,182] Furthermore, some children who are underdiagnosed may receive more medical attention, which may slightly increase the chance of infection diagnoses and inflate the odds ratio estimations. However, we believe that the impact of these factors is minor, considering the one-year lag-time that we applied.

Finally, there is a possibility of uncontrolled confounding in our study because we lacked information on vaccination history and duration of breastfeeding, both of which are associated with reduced risk of leukemia.[183–186] However, breastfeeding is very common in Denmark and lasts for six to eight months on average.[187–189]

2.5. Conclusion

While it has been suggested that infection may be a risk factor for leukemia and lymphoma, limited evidence exists on the link between childhood infections and other types of childhood cancers. This case-control study utilized a large national registry data linkage to demonstrate a positive association between postnatal infections and many types of childhood cancers. The study confirms previous findings of increased medically diagnosed infections in children who later develop cancer, but also contradicts some earlier research on specific infections and cancers. Further research is needed to fully understand the potential pathways between childhood infection and cancer.

2.6. Tables

Table 2-1. Characteristics of childhood cancer cases and matched controls in Denmark, births 1978 to 2013

	Cases	Controls
Number	4125	103526
Year of birth, n (%)		
1978-1989	1647 (39.9)	41137 (39.7)
1990-1999	1425 (34.5)	36094 (34.9)
2000-2013	1053 (25.5)	26295 (25.4)
Age at cancer diagnosis (years), n (%)		
0-4	1867 (45.3)	-
5-9	932 (22.6)	-
10-14	592 (14.4)	-
15–19	734 (17.8)	-
Age at cancer diagnosis (years), mean (SD)	7.1 (5.9)	-
Sex, n (%)		
Female	1787 (43.3)	44922 (43.4)
Male	2338 (56.7)	58604 (56.6)
Mother's age (years), n (%)		
<29	2475 (60.0)	62448 (60.3)
30–39	1580 (38.3)	39383 (38.0)
40 and over	70 (1.7)	1695 (1.6)
Mother's age (years), mean (SD)	28.51 (4.96)	28.39 (4.96)
Mother smoking during pregnancy, n (%)[a]		
Yes	542 (24.4)	13387 (23.8)

Missing (%)	4.3	3.7
Birth order, n (%)		
1	1792 (43.4)	44428 (42.9)
2 or more	2333 (56.6)	59098 (57.1)
Residence at birth, n (%)		
Urban	1354 (32.8)	32818 (31.7)
Small town	1161 (28.1)	29440 (28.4)
Rural	1610 (39.0)	41268 (39.9)
Birth weight (grams), n (%)		
500-1499	8 (0.2)	150 (0.1)
1500-2499	188 (4.6)	5017 (4.8)
2500-3999	3124 (75.7)	80867 (78.1)
4000 and over	805 (19.5)	17492 (16.9)
Birth weight (grams), mean (SD)	3483 (602)	3448 (586)
Number of children in household, n (%)		
1: index child	340 (8.2)	8538 (8.2)
2: index child plus 1 sibling	1848 (44.8)	49599 (47.9)
3	1322 (32.0)	31513 (30.4)
>3	615 (14.9)	13876 (13.4)
Child is in multiple birth, n (%)	118 (2.9)	3089 (3.0)

[a] The record has been started since 1995 and completely implemented in 1996.

Table 2-2. Distribution of infection type and number of infection episodes among childhood cancer cases and matched controls in Denmark, births 1978 to 2013

	Cases (n=4125)	Controls (n=103526)
Infection type, n (%)		
All infection	1003 (24.3)	18988 (18.3)
Viral infection	309 (7.5)	5256 (5.1)
Bacterial infection	344 (8.3)	6273 (6.1)
Respiratory infection	570 (13.8)	10399 (10.0)
Enteric infection	178 (4.3)	2871 (2.8)
Urinary tract infection	62 (1.5)	968 (0.9)
Number of infection episodes, n (%)		
Never infected	3122 (75.7)	84538 (81.7)
1	500 (12.1)	10630 (10.3)
2-3	365 (8.8)	6190 (6.0)
4 and over	138 (3.3)	2168 (2.1)

Table 2-3. Conditional logistic regression odds ratios and 95% confidence intervals for childhood cancers and infection in Denmark, 1978 to 2013

Cancer type	Cases		Controls			
	Total	Exposed n (%)	Total	Exposed n (%)	OR (95% CI)	adj.OR[a] (95% CI)
Acute lymphoblastic leukemia	1165	279 (23.9)	29305	5521 (18.8)	1.39 (1.21-1.60)	1.42 (1.23-1.63)
Acute myeloid leukemia	237	54 (22.8)	6127	953 (15.6)	1.70 (1.21-2.38)	1.80 (1.28-2.52)
Central nervous system tumors	1513	406 (26.8)	37845	7391 (19.5)	1.58 (1.40-1.78)	1.57 (1.39-1.77)
Astrocytoma	477	111 (23.3)	11965	2317 (19.4)	1.30 (1.04-1.62)	1.29 (1.03-1.62)
Non-Hodgkin's lymphoma	306	101 (33.0)	7622	1890 (24.8)	1.52 (1.19-1.95)	1.53 (1.19-1.97)
Germ cell tumors	317	96 (30.3)	8150	1958 (24.0)	1.43 (1.10-1.84)	1.45 (1.12-1.88)
Neuroblastoma	258	26 (10.1)	6466	551 (8.5)	1.21 (0.78-1.89)	1.21 (0.77-1.88)
Wilms' tumor	194	32 (16.5)	4730	540 (11.4)	1.62 (1.07-2.45)	1.62 (1.07-2.46)
Medulloblastoma	161	43 (26.7)	4001	721 (18.0)	1.73 (1.19-2.51)	1.68 (1.15-2.45)
Retinoblastoma	136	9 (6.6)	3306	184 (5.6)	1.24 (0.60-2.58)	1.26 (0.60-2.64)

[a] Adjusted odds ratio for mother age (years), birth order (>1 vs 1), residence at birth (urban, rural, small town), number of children in household (1-only index child, 2, 3, >3) and multiple birth child (yes vs no)

Table 2-4. Conditional logistic regression odds ratios and 95% confidence intervals for childhood cancers and type of infection in Denmark, 1978 to 2013

Type of postnatal infection	Exposed cases n (%)	Exposed controls n (%)	OR (95% CI)	adj.OR[a] (95% CI)
Acute lymphoblastic leukemia				
(unexposed cases = 886; unexposed controls = 23784)				
Viral infection	84 (7.2)	1555 (5.3)	1.49 (1.18-1.89)	1.53 (1.21-1.93)
Bacterial infection	91 (7.8)	1695 (5.8)	1.48 (1.18-1.86)	1.52 (1.21-1.90)
Respiratory infection	164 (14.1)	3025 (10.3)	1.49 (1.25-1.77)	1.52 (1.27-1.81)
Enteric infection	37 (3.2)	821 (2.8)	1.24 (0.88-1.74)	1.26 (0.90-1.77)
Urinary tract infection	17 (1.5)	250 (0.9)	1.90 (1.15-3.13)	1.94 (1.18-3.20)
Acute myeloid leukemia				
(unexposed cases = 183; unexposed controls = 5174)				
Viral infection	20 (8.4)	253 (4.1)	2.40 (1.46-3.95)	2.45 (1.48-4.03)
Bacterial infection	17 (7.2)	316 (5.2)	1.60 (0.95-2.71)	1.73 (1.02-2.94)
Respiratory infection	36 (15.2)	529 (8.6)	2.03 (1.37-3.00)	2.14 (1.44-3.17)
Enteric infection	11 (4.6)	132 (2.2)	2.52 (1.32-4.80)	2.83 (1.47-5.44)
Central nervous system tumor				
(unexposed cases = 1107; unexposed controls = 30454)				
Viral infection	134 (8.9)	2082 (5.5)	1.86 (1.54-2.24)	1.85 (1.53-2.24)
Bacterial infection	145 (9.6)	2470 (6.5)	1.69 (1.41-2.03)	1.68 (1.40-2.01)
Respiratory infection	225 (14.9)	3984 (10.5)	1.62 (1.40-1.89)	1.61 (1.38-1.88)
Enteric infection	85 (5.6)	1161 (3.1)	2.10 (1.67-2.65)	2.08 (1.65-2.63)
Urinary tract infection	31 (2.0)	441 (1.2)	2.05 (1.41-2.97)	2.04 (1.40-2.96)
Astrocytoma				
(unexposed cases = 366; unexposed controls = 9648)				

Viral infection	33 (6.9)	636 (5.3)	1.41 (0.97-2.04)	1.41 (0.97-2.04)
Bacterial infection	41 (8.6)	741 (6.2)	1.50 (1.07-2.10)	1.49 (1.06-2.09)
Respiratory infection	59 (12.4)	1256 (10.5)	1.27 (0.96-1.70)	1.27 (0.95-1.69)
Enteric infection	24 (5.0)	366 (3.1)	1.76 (1.15-2.71)	1.77 (1.15-2.72)
Urinary tract infection	9 (1.9)	134 (1.1)	1.82 (0.91-3.61)	1.82 (0.91-3.62)
Non-Hodgkin's lymphoma				
(unexposed cases = 205; unexposed controls = 5732)				
Viral infection	30 (9.8)	503 (6.6)	1.72 (1.15-2.55)	1.71 (1.15-2.55)
Bacterial infection	41 (13.4)	625 (8.2)	1.87 (1.32-2.65)	1.87 (1.31-2.65)
Respiratory infection	60 (19.6)	1090 (14.3)	1.57 (1.17-2.12)	1.59 (1.18-2.15)
Enteric infection	15 (4.9)	269 (3.5)	1.59 (0.92-2.72)	1.58 (0.92-2.72)
Urinary tract infection	6 (2.0)	71 (0.9)	2.43 (1.03-5.71)	2.44 (1.04-5.74)
Germ cell tumors				
(unexposed cases = 221; unexposed controls = 6192)				
Viral infection	25 (7.9)	504 (6.2)	1.45 (0.94-2.24)	1.50 (0.97-2.32)
Bacterial infection	31 (9.8)	802 (9.8)	1.13 (0.76-1.67)	1.15 (0.78-1.71)
Respiratory infection	45 (14.2)	1087 (13.3)	1.21 (0.86-1.69)	1.23 (0.88-1.73)
Enteric infection	23 (7.3)	290 (3.6)	2.35 (1.49-3.70)	2.41 (1.53-3.80)
Appendicitis	11 (3.5)	147 (1.8)	2.10 (1.12-3.97)	2.14 (1.14-4.02)
Neuroblastoma				
(unexposed cases = 232; unexposed controls = 5915)				
Viral infection	5 (1.9)	148 (2.3)	0.86 (0.35-2.15)	0.85 (0.34-2.13)
Bacterial infection	6 (2.3)	152 (2.4)	1.01 (0.44-2.35)	1.00 (0.43-2.32)
Respiratory infection	17 (6.6)	300 (4.6)	1.46 (0.86-2.48)	1.44 (0.85-2.45)
Wilms' tumor				
(unexposed cases = 162; unexposed controls = 4190)				
Viral infection	10 (5.2)	159 (3.4)	1.73 (0.88-3.39)	1.72 (0.87-3.39)
Bacterial infection	8 (4.1)	156 (3.3)	1.40 (0.67-2.91)	1.42 (0.68-2.97)

Respiratory infection	19 (9.8)	290 (6.1)	1.80 (1.07-3.01)	1.76 (1.05-2.96)
Medulloblastoma				
(unexposed cases = 118; unexposed controls = 3280)				
Viral infection	16 (9.9)	197 (4.9)	2.37 (1.36-4.11)	2.33 (1.34-4.06)
Bacterial infection	13 (8.1)	215 (5.4)	1.75 (0.96-3.18)	1.71 (0.94-3.11)
Respiratory infection	22 (13.7)	401 (10.0)	1.58 (0.98-2.56)	1.55 (0.96-2.51)
Enteric infection	7 (4.3)	127 (3.2)	1.60 (0.72-3.53)	1.52 (0.68-3.39)
Retinoblastoma				
(unexposed cases = 127; unexposed controls = 3122)				
Bacterial infection	5 (3.7)	57 (1.7)	2.22 (0.85-5.77)	2.29 (0.88-5.99)

[a] Adjusted odds ratio for mother age (years), birth order (>1 vs 1), residence at birth (urban, rural, small town), number of children in household (1-only index child, 2, 3, >3) and multiple birth child (yes vs no)
Infections with less than five exposed cases were omitted from the table.

Table 2-5. Conditional logistic regression odds ratios and 95% confidence intervals for childhood cancers and number of infection episodes in Denmark, 1978 to 2013

Number of infection episodes	Cases	Controls	adj.OR [a]	95% CI	p–value
Acute lymphoblastic leukemia					
No infection	886	23784	1.00	[Reference]	
1 episode	148	3118	1.32	1.10-1.58	
2-3 episodes	99	1805	1.55	1.24-1.92	
4 episodes and over	32	598	1.53	1.06-2.21	
As continuous	-	-	1.09	1.04-1.14	<0.001
Acute myeloid leukemia					
No infection	183	5174	1.00	[Reference]	
1 episode	23	525	1.40	0.88-2.22	
2-3 episodes	21	326	2.02	1.25-3.28	
4 episodes and over	10	102	3.21	1.61-6.38	
As continuous	-	-	1.17	1.08-1.26	<0.001
Central nervous system tumors					
No infection	1107	30454	1.00	[Reference]	
1 episode	200	4162	1.37	1.17-1.61	
2-3 episodes	139	2385	1.67	1.38-2.01	
4 episodes and over	67	844	2.27	1.75-2.95	
As continuous	-	-	1.11	1.07-1.14	<0.001
Astrocytoma					
No infection	366	9648	1.00	[Reference]	
1 episode	58	1328	1.18	0.88-1.58	
2-3 episodes	37	756	1.32	0.93-1.87	

4 episodes and over	16	233	1.86	1.10-3.14	
As continuous	-	-	1.03	0.998-1.07	0.068
Non-Hodgkin's lymphoma					
No infection	205	5732	1.00	[Reference]	
1 episode	50	1018	1.41	1.02-1.94	
2-3 episodes	36	635	1.63	1.12-2.35	
4 episodes and over	15	237	1.83	1.06-3.15	
As continuous	-	-	1.11	1.05-1.17	<0.001
Germ cell tumors					
No infection	221	6192	1.00	[Reference]	
1 episode	49	1044	1.37	0.99-1.90	
2-3 episodes	38	641	1.77	1.23-2.54	
4 episodes and over	9	273	1.00	0.51-2.00	
As continuous	-	-	1.05	0.99-1.11	0.134
Neuroblastoma					
No infection	232	5915	1.00	[Reference]	
1 episode	12	343	0.90	0.49-1.66	
2-3 episodes	10	162	1.58	0.80-3.09	
4 episodes and over	4	46	-	-	
As continuous	-	-	1.05	0.99-1.12	0.096
Wilms' tumor					
No infection	162	4190	1.00	[Reference]	
1 episode	12	301	1.09	0.59-2.01	
2-3 episodes	19	179	2.96	1.74-5.01	
4 episodes and over	1	60	-	-	
As continuous	-	-	1.08	0.95-1.23	0.238
Medulloblastoma					
No infection	118	3280	1.00	[Reference]	

1 episode	25	391	1.81	1.14-2.85	
2-3 episodes	16	255	1.73	0.99-3.02	
4 episodes and over	2	75	-	-	
As continuous	-	-	1.04	0.91-1.19	0.537
Retinoblastoma					
No infection	127	3122	1.00	[Reference]	
1 episode	6	119	1.30	0.54-3.11	
2-3 episodes	3	57	1.36	0.41-4.54	
4 episodes and over	0	8	-	-	
As continuous	-	-	0.99	0.70-1.42	0.977

[a] Adjusted odds ratio for mother age (years), birth order (>1 vs 1), residence at birth (urban, rural, small town), number of children in household and multiple birth child.

2.7. Supplemental materials

Table 2-S1. International Classification of Diseases, Revision 8 (ICD-8) and Revision10 (ICD-10) diagnostic codes for infectious diseases categories

	ICD-8	ICD-10
All infection	000–136, 780.21, 788.89 + all below	A00–B99, G00–G09, R50.9, R56.0 + all below
Viral infection	008.8–008.9, 040–079, 381.00, 470–474, 480	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	000–005, 008.0–008.3, 010–039, 079.84, 090–104, 320–324, 381.01, 390–391, 464.03, 481–482, 501, 508.00–508.03, 510, 513, 540–542, 590, 595, 599.00, 599.06, 612–614, 616.0, 620, 622, 630, 635, 680–686, 710	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
Respiratory infection	032–034, 460–474, 480–486, 491.01, 501, 503, 506, 508.00–508.05, 510–511, 513	A36–A38, J00–J22, J32, J36–J37, J39.0–J39.1, J85–J86
Infectious enteritis	001–009	A01–A09
Skin infection	680–686	L00–L08
Urinary tract infection	590, 595, 599.00, 599.06, 635	N10–N12, N30, N34.0, N39.0, O23.0–O23.4

Genital infection incl. STD[a]	054.02, 079.84, 090–099, 131, 612–614, 616.0, 620, 622, 630	A50–A64, N70–N77, O23.5–O23.9
Appendicitis	540–542	K35–K37
Enterovirus infection	045, 046, 074	A870, A880, B971, A0839

[a] Sexually transmitted diseases (STD) include syphilis, Gonorrhea, Chlamydia, trichomoniasis, condyloma and genital herpes

Table adapted from Atladóttir et al.[152]

Table 2-S2. Sensitivity analysis by adding maternal smoking into conditional logistic regression for childhood cancers and postnatal infection

Cancer type	Model 1		Model 2		Model 3	
	adj.OR	95% CI	adj.OR	95% CI	adj.OR	95% CI
Acute lymphoblastic leukemia	1.42	1.23-1.63	1.50	1.25-1.80	1.13	1.13-1.70
Acute myeloid leukemia	1.80	1.28-2.52	1.84	1.14-2.97	1.21	1.21-3.24
Central nervous system tumors	1.57	1.39-1.77	1.64	1.39-1.94	1.24	1.24-1.83
Astrocytoma	1.29	1.03-1.62	1.35	0.98-1.87	0.82	0.82-1.81
Non-Hodgkin's lymphoma	1.53	1.19-1.97	1.54	1.09-2.17	1.21	1.21-2.68
Germ cell tumors	1.45	1.12-1.88	1.15	0.76-1.74	0.90	0.90-2.64
Neuroblastoma	1.21	0.77-1.88	0.84	0.45-1.55	0.37	0.37-1.47
Wilms' tumor	1.62	1.07-2.46	1.64	0.95-2.85	0.82	0.82-2.59
Medulloblastoma	1.68	1.15-2.45	1.62	0.97-2.71	0.65	0.65-2.32
Retinoblastoma	1.26	0.60-2.64	1.08	0.40-2.94	0.48	0.48-3.90

Model 1: adjusted odds ratio for mother age (years), birth order (>1 vs 1), residence at birth (urban, rural, small town), number of children in household (1-only index child, 2, 3, >3) and multiple birth child (yes vs no)

Model 2: added smoking status during pregnancy (yes vs no) to Model 1

Model 3: model 2 with restricted birth year ≥ 1995

Table 2-S3. Conditional logistic regression odds ratios and 95% confidence intervals for childhood cancers and type of infection in Denmark stratified by diagnostic setting and birth year, 1978 to 2013

Cancer type	IPD		Non-IPD		Birth year < 1995		Birth year ≥ 1995	
	adj.OR	95% CI	adj.OR	95% CI	adj.OR	95% CI	adj.OR	95% CI
Acute lymphoblastic leukemia	1.36	1.17-1.58	1.47	1.15-1.88	1.40	1.14-1.70	1.43	1.17-1.76
Acute myeloid leukemia	1.99	1.42-2.80	1.79	0.99-3.21	1.63	1.03-2.58	2.06	1.24-3.40
Central nervous system tumors	1.62	1.43-1.84	1.63	1.33-2.00	1.57	1.34-1.83	1.57	1.30-1.91
Astrocytoma	1.35	1.07-1.69	1.28	0.84-1.96	1.30	0.98-1.72	1.28	0.87-1.88
Non-Hodgkin's lymphoma	1.50	1.16-1.94	1.67	1.13-2.48	1.38	1.00-1.92	1.81	1.22-2.69
Germ cell tumors	1.48	1.14-1.93	1.11	0.70-1.74	1.44	1.07-1.93	1.51	0.88-2.59
Neuroblastoma	1.34	0.86-2.09	0.17	0.02-1.27	1.88	1.05-3.38	0.74	0.37-1.48
Wilms' tumor	1.73	1.14-2.64	0.91	0.36-2.33	1.74	0.95-3.19	1.68	0.93-3.02
Medulloblastoma	1.66	1.13-2.45	0.94	0.42-2.09	1.83	1.12-2.97	1.49	0.82-2.71
Retinoblastoma	0.86	0.36-2.05	1.93	0.56-6.71	1.06	0.36-3.13	1.59	0.57-4.44

IPD = inpatient department

Non-IPD = non-inpatient department including outpatient and emergency department

Table 2-S4. Conditional logistic regression odds ratios (OR) and 95% confidence intervals for childhood cancers and infection in Denmark, 1978 to 2013, excluded cesarian section children

Cancer type	Cases		Controls			
	Total	Exposed	Total	Exposed	OR (95% CI)	Adj.OR[a] (95% CI)
Acute lymphoblastic leukemia	1082	256	27385	5078	1.38 (1.19-1.60)	1.40 (1.20-1.62)
Acute myeloid leukemia	219	49	5743	887	1.67 (1.17-2.36)	1.75 (1.23-2.49)
Central nervous system tumors	1410	378	35786	6935	1.59 (1.40-1.80)	1.58 (1.39-1.79)
Astrocytoma	453	107	11448	2183	1.36 (1.08-1.71)	1.36 (1.08-1.71)
Non-Hodgkin's lymphoma	288	97	7262	1790	1.57 (1.22-2.02)	1.57 (1.22-2.03)
Germ cell tumors	298	93	7898	1910	1.41 (1.09-1.83)	1.44 (1.11-1.87)
Neuroblastoma	233	25	5969	500	1.31 (0.83-2.08)	1.32 (0.84-2.09)
Wilms' tumor	181	29	4375	482	1.57 (1.02-2.42)	1.58 (1.02-2.44)
Medulloblastoma	144	35	3777	664	1.52 (1.01-2.28)	1.48 (0.98-2.23)
Retinoblastoma	125	8	3020	168	1.21 (0.55-2.63)	1.22 (0.56-2.67)

[a] Adjusted odds ratio for mother age (years), birth order (>1 vs 1), residence at birth (urban, rural, small town), number of children in household (1-only index child, 2, 3, >3) and multiple birth child (yes vs no)

3. Maternal infection and antibiotic use during pregnancy and the risk of childhood cancer in Taiwan

This chapter is based in part on the previously published article entitled “Maternal medically diagnosed infection and antibiotic prescription during pregnancy and risk of childhood cancer: A population-based cohort study in Taiwan, 2004 to 2015” published in International Journal of Cancer.[190] I have permission from John Wiley and Sons to use the work in my dissertation (license ID: 1404535-1).

3.1. Introduction

The potential correlation between maternal infection during pregnancy and childhood cancers, particularly leukemia, has been the subject of extensive investigation for a significant period of time.[34–36,172] However, the available evidence regarding the association between maternal infection during pregnancy and less prevalent types of cancer, such as central nervous system tumors including medulloblastoma and hepatoblastoma, remains limited.[38,39,63,64] Additionally, there is a suggestion that antibiotic exposure during pregnancy may act as a potential risk factor for childhood cancers, either by mediating infection or independently causing cancer.[191–193]

Greaves has conducted thorough research on the association between infection and childhood ALL.[60] According to his theory, the development of ALL is a multifaceted process influenced by multiple factors occurring in two distinct stages: during fetal development and after birth.[60] This two-stage process is influenced by a combination of common infections and inherited genetic factors.[60] Although Greaves' recent theory highlights the significance of common infections in the development of ALL, placing emphasis on their potential role over specific infections, some studies have demonstrated that certain specific infections acquired during pregnancy, such as genitourinary tract infection, influenza, and varicella, were associated with an increased risk of childhood leukemia.[34–36,172]

Extensive research has also been conducted on maternal exposure to antibiotics during pregnancy in relation to the potential risk of childhood leukemia, similar to infections. However, the majority of findings have failed to provide sufficient evidence to establish a conclusive association,[194,195] with only a few studies demonstrating a moderate to strong link.[191,193] The presence of infections can complicate the interpretation of these results due to confounding by indication for antibiotics. Furthermore, there is a possibility that the antibiotics themselves may contribute to the development of cancer through alternative mechanisms. Some types of antibacterials, such as specific quinolones and metronidazole, have been suggested to act as carcinogens or genotoxins based on animal studies.[196,197] Moreover, many antibiotics are considered nitrosatable drugs, which have been associated with certain types of childhood cancer.[198]

On the other hand, several studies have attempted to explore the potential association between maternal infection during pregnancy and the risk of childhood brain and nervous system tumors, which represent the second most common type of childhood cancer. However, the findings have been inconclusive due to limited statistical power.[39,63] Some studies have identified a positive association between viral infection during pregnancy and the risk of childhood nervous system tumors.[39,63] For instance, a case-control study reported an increased risk of childhood brain tumors associated with influenza infection in pregnant women.[39] Additionally, research investigating the use of antibiotics by mothers during pregnancy has provided supporting evidence for the development of childhood brain tumors.[199]

The prevalence of hepatoblastoma is higher among children in Taiwan compared to other populations,[200] underscoring the importance of studying its potential relationship with maternal infection and antibiotic prescription during pregnancy within this specific context. Furthermore, a recent cohort study has suggested an association between parental hepatitis B infection and the risk of hepatoblastoma in children.[37]

Therefore, the objective of this study is to explore possible associations between maternal medically diagnosed infections and antibiotic prescriptions during pregnancy and the risk of childhood cancer in the Taiwanese population.

3.2. Methods

A population-based cohort study was conducted using the Taiwan Maternal and Child Health Database (TMCHD). This database encompasses information on mothers and children born between 2004 and 2015, comprising a total population of 2,385,071 maternal and child pairs. To enrich the dataset, it was linked with the Registry for Beneficiaries of the National Insurance Research Database (NIRD) (covering the period 2002-2017), Cancer registry (covering the period 1979-2017), and Taiwan birth registry (covering the period 2004-2015). These datasets were accessed through the Health and Welfare Data Science Center, which operates under the Ministry of Health and Welfare in Taiwan.

Certain criteria were employed to ensure data quality and appropriate sample selection for analysis. Children with incomplete parental information, International Classification of Diseases (ICD) codes, age, or sex at baseline were excluded from the analysis (n=17,174). Additionally, children with missing or duplicated registration records were excluded (n=73,718). Children with extremely low birth weights (<500 grams), who had a lower likelihood of surviving until the development of cancer, were also excluded from the analysis (n=1,071). Furthermore, children diagnosed with Down's syndrome, a condition strongly associated with specific cancer types,[149,201] were excluded from the analysis (n=1,006). Finally, children with missing information regarding their Anatomical Therapeutic Chemical (ATC) code (n=24,916) were excluded due to uncertainty regarding their exposure status.

The presence of maternal infection during pregnancy was determined by extracting information from the linkage of TMCHD with the NIRD. The TMCHD database was established in 2004 and contained the identifying information of both parents that we used to link to parents' medical claims data in the NIRD with records dating back to 1998.[202] Diagnoses recorded in the

database were categorized using the ICD-9 and ICD-10 coding systems. Maternal infection diagnoses were categorized based on their type (viral or bacterial) and the affected organ (such as respiratory, enteric, or urinary tract), using the categorization method developed by Atladóttir et al[152] (see Table ***3-S1*** for details).

Exposure to antibiotics during pregnancy was determined using the ATC code for antibacterials for systemic use (J01) and intestinal anti-infectives (A07A). Specific subcategories of antibiotics are described in Table **3-S2** of the Supplementary materials.

The exposure period was defined as the estimated date of conception until the date of birth. The estimated date of conception was calculated by subtracting the gestational age in days from the date of birth. Within this exposure period, episodes of infection were counted. If a pregnant woman received multiple diagnoses of the same disease within a span of two weeks, it would be considered as a single episode of the disease.

To identify children diagnosed with cancer between 2004 and 2017, a linkage was established between the database and the Taiwan Cancer Registry, a comprehensive and reliable population-based cancer registry.[203] The specific types of cancer of interest in this study were ALL, CNS (including medulloblastoma), and hepatoblastoma.

Cox proportional hazard models were employed to estimate the associations between medically diagnosed infections and antibiotic prescriptions during pregnancy and the risk of childhood cancer. Additional analyses were conducted to explore the number of infection episodes as both categorical variables (0, 1, 2-3, and 4 or more episodes) and continuous variables. The combined effects of infections and antibiotic exposure during pregnancy were examined in separate models, with the reference group consisting of those who had no exposure to infection and antibiotics during pregnancy.

All models were adjusted for birth year, sex, maternal age, family income, urbanization level, and parity based on a modified disjunctive cause criterion.[153] These factors

have been suggested as potential risk factors for certain types of childhood cancer, including child's age (represented by birth year) and sex,[204–206] maternal age,[147,201,207–210] and parity.[205,206] Family income and urbanization level were considered proxies for socioeconomic status, which has also been proposed as a potential risk factor for specific types of childhood cancer in Taiwan.[205,211] Moreover, some of these factors, such as birth year, parity, family income, and urbanization level, could potentially be associated with the exposure status of infection and antibiotic use during pregnancy in our study population. The proportional-hazards assumption was assessed through graphical evaluation. Models with fewer than five exposed cases were not presented due to the limited number of events. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3.3. Results

Table **3-1** presents the general characteristics of the maternal and child cohort. Initially, a total of 2,292,102 individuals were considered eligible for the study. Following the exclusion of participants with incomplete information regarding maternal exposure during pregnancy (n=24,916), the final analysis included 2,267,186 participants (Figure 3-S1). The median follow-up time was 7.96 years (interquartile range [IQR] = 6.2 years), and the median age at cancer diagnosis was 2.72 years (IQR = 4.06 years).

Regarding the association between maternal infection during pregnancy and childhood cancer, we observed a moderate increase in the risk of childhood hepatoblastoma among children whose mothers were diagnosed with infection during pregnancy, although the confidence interval was wide (adjusted hazard ratio [HR] = 1.34; 95% CI 0.90-1.98). Similarly, we found a slight increase in the risk of childhood ALL among children whose mothers had an infection during pregnancy (adjusted HR = 1.15; 95% CI 0.99-1.35). However, there was insufficient evidence to establish a conclusive association between infection during pregnancy and the risk of childhood CNS or medulloblastoma. Furthermore, we lacked sufficient evidence

to determine the association between specific types of infection and the four types of childhood cancers examined, as indicated in Table ***3-2***.

On the other hand, Table ***3-3*** presents an increased risk of childhood ALL among children whose mothers were prescribed antibiotics during pregnancy (adjusted HR = 1.30; 95% CI 1.04-1.63). The association was even stronger for children whose mothers were prescribed tetracyclines during pregnancy (adjusted HR = 2.15; 95% CI 1.34-3.45). The use of aminoglycosides during pregnancy was associated with an increased risk of hepatoblastoma in offspring (adjusted HR = 2.05; 95% CI 1.11-3.80), as were other antibacterials with different modes of action not classified in the preceding groups (adjusted HR = 5.26; 95% CI 2.29-12.12). However, there was insufficient evidence to definitively establish an association between antibiotic usage during pregnancy and the development of CNS in children, including medulloblastoma.

In Table ***3-4***, the relationship between medically diagnosed infections, antibiotic prescriptions during pregnancy, and the risk of childhood cancer was examined. Comparing those whose mothers had no exposure to both factors, it was found that children whose mothers were exposed only to an antibiotic prescription (without infection) had an increased risk of ALL (adjusted HR = 1.53; 95% CI 1.05-2.23). Similarly, children whose mothers were exposed to both a medically diagnosed infection and an antibiotic prescription during pregnancy had an increased risk of ALL (adjusted HR = 1.66; 95% CI 1.16-2.38). However, there was insufficient evidence to determine similar associations with other types of cancer (≤5 cases in reference group).

Insufficient evidence was found to indicate a clear association between the number of infection episodes during pregnancy and the risk of childhood cancer in offspring. However, it was observed that two to three episodes of infection during pregnancy were associated with an increased risk of ALL (adjusted HR = 1.24; 95% CI 1.03-1.50), while weak to null associations were found for four or more episodes (adjusted HR = 1.11; 95% CI 0.89-1.38) or one episode

(adjusted HR = 1.09; 95% CI 0.90-1.32) when compared to those who were never infected (Table ***3-S3***).

3.4. Discussion

Maternal infection during pregnancy was linked to a moderate increase in the risk of childhood hepatoblastoma and a slight increase in the risk of childhood ALL. Conversely, antibiotic prescriptions during pregnancy were associated with an elevated risk of childhood ALL, particularly when tetracyclines were used. Specific types of antibiotics were also associated with an increased risk of hepatoblastoma. Additionally, children whose mothers were exposed to antibiotic prescriptions (without infection) or both infection and antibiotic prescriptions during pregnancy had a higher risk of developing ALL. However, the number of infection episodes during pregnancy did not show a clear association with the risk of childhood cancer.

Notably, our findings indicate a more robust association between childhood ALL and mothers who received antibiotic prescriptions during pregnancy, even in the absence of an accompanying infection. This suggests a potential direct impact of antibiotic exposure on the risk of ALL in offspring. Interestingly, we observed that a relatively large proportion of participants (24.8%) had been prescribed antibiotics without a concomitant diagnosis for an infection, this may reflect at least some of these prescriptions having been given as prophylaxis in preparation for birth to prevent infections during the delivery process. This practice aligns with certain guidelines, including the prophylaxis strategy for preventing group B Streptococcus infection during pregnancy.[212–215] While it is possible that certain infections were diagnosed solely based on clinical symptoms without laboratory confirmation, it is unlikely that antibiotics would be prescribed without clear indications in Taiwan. This is because the national insurance system regulates prescription practices and maintains strict auditing standards within the healthcare system.[202] If these prescriptions were indeed given without a specific indication of

pregnancy-related infection, it may suggest an independent and direct effect of antibiotics on the risk of ALL in offspring. Further research is necessary to explore this possibility.

Our findings are consistent with prior research that indicates a positive correlation between common infections during pregnancy and the risk of childhood ALL.[34–36] In a previous cohort study conducted in Denmark, an elevated risk of childhood ALL was observed among children born to mothers who experienced infections during pregnancy (adjusted HR = 1.35; 95% CI 1.04-1.77).[35] However, in our study, specific infections such as urinary tract infection did not demonstrate evidence of an increased risk. Interestingly, previous studies conducted in European countries reported positive associations between genitourinary tract infections during pregnancy and childhood ALL, with HR and OR ranging from 1.34 to 1.92.[35,36,172] In contrast, a matched case-control study conducted in California suggested a slightly negative association, although wide confidence intervals were observed (OR = 0.70; 95% CI 0.42-1.17).[46] The variations in effect estimates for specific types of infections and their association with childhood ALL may be attributed to differences in the classification of exposure and the relatively small sample sizes of the respective studies.

Our exploratory findings suggest a potential link between maternal infection during pregnancy, specifically viral infections, and the likelihood of childhood hepatoblastoma. This observation is in line with a prior cohort study conducted in Taiwan, which also indicated a connection between maternal hepatitis B infection prior to childbirth and the risk of childhood hepatoblastoma, albeit with a wide confidence interval (adjusted HR = 1.40; 95% CI 0.56-3.52).[37] Conversely, a small matched case-control study carried out in North America did not identify a significant difference in the incidence of infections (hepatitis, measles, mumps, influenza, chickenpox, or infectious mononucleosis), nor in maternal antibiotic usage during pregnancy, between mothers of cases and control subjects.[216]

The underlying mechanism through which common infections during pregnancy may contribute to the risk of childhood ALL has been extensively elucidated by Greaves.[60,61]

However, in the context of hepatoblastoma, a potential mechanism might involve particular infections like hepatitis or viral infections, which can induce immune dysregulation in the mother. Viral hepatitis, in particular, has the capacity to infect fetal hepatocytes [217,218] and potentially induce mutations in liver cells, akin to the mechanisms implicated in hepatocellular carcinoma.[219,220]

Our findings suggest a potential link between the use of antibiotics during pregnancy, especially tetracyclines, and the risk of childhood ALL. This finding is consistent with previous studies conducted in Denmark, Sweden, and Canada, which also reported a similar association.[193,221] However, a study conducted in the United Kingdom found a slightly negative or inconclusive association between antibiotic use during pregnancy and childhood ALL (OR = 0.88; 95% CI 0.72-1.07).[191] These divergent results emphasize the need for further investigation to fully comprehend the relationship between antibiotic use during pregnancy and the risk of childhood leukemia. Notably, doxycycline, a commonly prescribed medication from the tetracycline group, has been linked to an increased occurrence of megakaryocytes and periportal leukocytic infiltration in liver cells, as well as DNA damage, as observed in a study on embryonic development in rats.[222] Furthermore, doxycycline is considered a nitrosatable drug, and maternal prescriptions of nitrosatable drugs have also been associated with childhood ALL.[223]

Our exploratory findings indicated a potential link between the use of beta-lactam antibacterials (excluding penicillins) during pregnancy and the risk of childhood hepatoblastoma. However, a cohort study conducted in Denmark and Sweden did not find a significant association between the use of other beta-lactam antibacterials and the risk of childhood cancers (HR = 0.88; 95% CI 0.50-1.57).[193] It is worth noting that penicillins, particularly pivampicillin, were found to increase the risk of hepatic tumors in children (HR = 8.31; 95% CI 2.88-23.99).[193] Cephalosporins, which are commonly prescribed within the beta-lactam antibacterials group, have been considered safe for pregnant women.[224–226] To our knowledge,

there is no specific evidence available regarding the potential teratogenic or carcinogenic effects of this group of medications.

By employing a data-linkage method that relies on comprehensive registries covering the entire population and national insurance data, we have minimized the potential for participation bias in our study. The integration of national insurance data allowed us to independently gather clinical diagnoses of infections and medical prescriptions before the detection of cancer in the offspring, reducing the likelihood of recall bias and establishing a clear temporal relationship between the exposure and the outcome.

However, despite the strengths of our study, there are certain limitations to consider. Although clinical diagnoses of infections were typically documented using a standardized coding system, it is possible that some infections were diagnosed based solely on clinical presentation without confirmation through laboratory testing. This scenario could introduce exposure misclassification. Nevertheless, we believe that such misclassification would have occurred regardless of the outcome status, resulting in non-differential misclassification, and biasing the results towards the null when comparing binary exposures.

Another potential limitation is the presence of uncontrolled confounding due to incomplete information on factors such as maternal vaccination and the use of over-the-counter supplements. These factors could be associated with both certain types of cancer and the exposure under investigation. However, given that there are only a limited number of established causes for childhood cancers, the potential for uncontrolled confounding is minimized in our study. It is important to highlight that the rates of vaccination among pregnant women in Taiwan appear to vary across different diseases, ranging from 20% to 70%.[227–230]

Studies that examine the impact of prenatal exposure on postnatal outcomes may encounter a bias known as live birth bias.[231] This bias arises because childhood cancers are only identified in children who were born alive,[231] while certain infections and antibiotic usage during pregnancy have been linked to congenital malformations that are also associated with

higher rates of fetal loss and stillbirth.[232–235] However, the extent of live birth bias in relation to childhood cancer is generally considered to be small.

Despite including a substantial number of mother and child pairs in our cohort, similar to studies focusing on rare diseases, our sample size was still limited for certain types of cancer and specific subcategories of exposure. Another limitation of our study was the issue of multiple comparisons. However, it is important to note that the majority of associations observed in our study are consistent with previous findings reported in the existing literature, which supports the validity of our results.

3.5. Conclusion

This large population-based cohort study has provided further evidence of potential associations between infection and antibiotic exposure during pregnancy and the risk of childhood ALL. Additionally, we explored the associations between specific types of antibiotic prescriptions and the risk of hepatoblastoma. Further investigations are needed to gain a better understanding of the underlying mechanisms linking these exposures to the development of childhood cancer.

3.6. Tables

Table 3-1. General characteristics of study population in Taiwan, 2004-2015

	Total	Infection during pregnancy[a]		Antibiotic prescription during pregnancy[a]	
		Yes	No	Yes	No
Number	2,292,102	1,552,387	714,799	1,942,047	325,139
Acute lymphoblastic leukemia	798	560	233	703	90
Central nervous system tumors	389	264	123	339	48
Hepatoblastoma	136	100	36	120	16
Medulloblastoma	86	56	30	79	7
Follow-up time (years), median (IQR)	7.96	7.79	8.19	8.06	7.27
	(6.20)	(6.18)	(6.25)	(6.29)	(5.60)
Age of cancer diagnosis, cases only (years), n (%)					
0-4	2,004	1,372	617	1,753	236
	(73.17)	(73.64)	(72.5)	(73.29)	(73.29)
5-9	587	401	180	508	73
	(21.43)	(21.52)	(21.15)	(21.24)	(22.67)
10-14	148	90	54	131	13
	(5.40)	(4.83)	(6.35)	(5.48)	(4.04)
Age of cancer diagnosis (years), median (IQR)	2.72	2.69	2.82	2.74	2.62
	(4.06)	(3.99)	(4.22)	(4.01)	(4.14)
Birth year, n (%)					
2004-2007	777,057	513,683	253,077	679,544	87,216
	(33.90)	(33.09)	(35.41)	(34.99)	(26.82)
2008-2011	708,476	482,785	218,181	589,139	111,827
	(30.91)	(31.10)	(30.52)	(30.34)	(34.39)
2012-2015	806,569	555,919	243,541	673,364	126,096
	(35.19)	(35.81)	(34.07)	(34.67)	(38.78)

Sex, n (%)					
Male	1,190,872	806,321	371,478	1,012,177	165,622
	(51.96)	(51.94)	(51.97)	(52.12)	(50.94)
Female	1,101,230	746,066	343,321	929,870	159,517
	(48.04)	(48.06)	(48.03)	(47.88)	(49.06)
Mother's age (years), n (%)					
<30	1,051,675	732,339	307,024	894,288	145,075
	(45.88)	(47.18)	(42.95)	(46.05)	(44.62)
30–<40	1,188,291	790,387	389,849	1,005,551	174,685
	(51.84)	(50.91)	(54.54)	(51.78)	(53.73)
40 and over	47,901	29,661	17,926	42,208	5,379
	(2.09)	(1.91)	(2.51)	(2.17)	(1.65)
Missing	4,235	-	-	-	-
	(0.18)				
Mother's age (years), mean (SD)	30.35	30.21	30.70	30.36	30.41
	(4.84)	(4.83)	(4.85)	(4.87)	(4.64)
Family income (TWD), n (%)					
<30,759	550,262	367,159	165,012	462,285	69,886
	(24.01)	(23.65)	(23.09)	(23.80)	(21.49)
30,759-48,200	547,531	391,347	152,727	475,623	68,451
	(23.89)	(25.21)	(21.37)	(24.49)	(21.05)
48,200-73,317	553,224	381,587	169,424	471,106	79,905
	(24.14)	(24.58)	(23.70)	(24.26)	(24.58)
≥73,317	550,296	351,074	198,421	454,377	95,118
	(24.01)	(22.62)	(27.76)	(23.40)	(29.25)
Missing	90,789	61,220	29,215	78,656	11,779
	(3.96)	(3.94)	(4.09)	(4.05)	(3.62)
Family income (TWD), mean (SD)	54584.00	53724.22	57644.25	54244.65	59205.91
	(36075.91)	(34738.74)	(38512.93)	(35557.11)	(38360.35)

Urbanization level of inhabited area, n (%)					
High	1,220,489	805,893	400,731	1,022,627	183,997
	(53.25)	(51.91)	(56.06)	(52.66)	(56.59)
Middle	861,047	595,854	256,386	732,517	119,723
	(37.57)	(38.38)	(35.87)	(37.72)	(36.82)
Low	209,813	150,089	57,485	186,289	21,285
	(9.15)	(9.67)	(8.04)	(9.59)	(6.55)
Missing	753	551	197	614	134
	(0.03)	(0.04)	(0.03)	(0.03)	(0.04)
Parity, n (%)					
1	922,928	610,804	296,657	793,062	114,399
	(40.27)	(39.35)	(41.50)	(40.84)	(35.18)
2	1,125,093	771,525	345,264	944,665	172,124
	(49.09)	(49.70)	(48.30)	(48.64)	(52.94)
3 or more	244,081	170,058	72,878	204,320	38,616
	(10.65)	(10.95)	(10.20)	(10.52)	(11.88)

[a] Missing information on medical diagnoses and/or drug prescription (n=24,916)

Table 3-2. Hazard ratios and 95% confidence intervals for the association between medically diagnosed infection during pregnancy and risk of childhood cancer in Taiwan, 2004-2015

	Number of events	Incidence density rate (per 100,000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia				
Non-infected cohort	233	4.07	ref	ref
Infected cohort, any type of infection	560	4.61	1.13 (0.97-1.31)	1.15 (0.99-1.35)
Viral infection	130	4.35	1.06 (0.85-1.31)	1.07 (0.86-1.34)
Bacterial infection	381	4.44	1.08 (0.92-1.27)	1.11 (0.94-1.32)
Respiratory infection	266	4.58	1.11 (0.93-1.33)	1.14 (0.95-1.36)
Enteric infection	23	6.09	1.49 (0.97-2.28)	1.60 (1.04-2.46)
Urinary tract infection	88	4.42	1.07 (0.84-1.36)	1.15 (0.89-1.47)
Central nervous system tumors				
Non-infected cohort	123	2.15	ref	ref
Infected cohort, any type of infection	264	2.17	1.01 (0.82-1.25)	0.98 (0.79-1.22)
Viral infection	76	2.54	1.18 (0.89-1.57)	1.13 (0.84-1.52)
Bacterial infection	194	2.26	1.05 (0.84-1.31)	1.01 (0.80-1.28)
Respiratory infection	123	2.12	0.98 (0.76-1.26)	0.94 (0.73-1.22)
Enteric infection	6	1.59	0.74 (0.33-1.67)	0.74 (0.33-1.69)
Urinary tract infection	46	2.31	1.07 (0.76-1.50)	1.02 (0.72-1.46)
Hepatoblastoma				
Non-infected cohort	36	0.63	ref	ref
Infected cohort, any type of infection	100	0.82	1.28 (0.88-1.88)	1.34 (0.90-1.98)
Viral infection	28	0.94	1.45 (0.89-2.38)	1.54 (0.92-2.56)
Bacterial infection	65	0.76	1.18 (0.79-1.77)	1.25 (0.82-1.90)
Respiratory infection	42	0.72	1.12 (0.72-1.75)	1.18 (0.74-1.86)
Urinary tract infection	11	0.55	0.84 (0.43-1.65)	0.84 (0.41-1.71)

Medulloblastoma				
Non-infected cohort	30	0.52	ref	ref
Infected cohort, any type of infection	56	0.46	0.88 (0.57-1.37)	0.83 (0.53-1.29)
Viral infection	16	0.54	1.02 (0.56-1.87)	0.99 (0.54-1.82)
Bacterial infection	45	0.52	1.00 (0.63-1.59)	0.93 (0.58-1.48)
Respiratory infection	31	0.53	1.01 (0.61-1.68)	0.99 (0.60-1.64)
Urinary tract infection	15	0.75	1.45 (0.78-2.69)	1.28 (0.68-2.43)

[a] Adjusted for birth year, sex, maternal age (years), family income (quartile), urbanization level (high, middle, low), and parity (1, 2, ≥3)

Number of hepatoblastoma and medulloblastoma cases exposed to enteric infections were ≤5.

Table 3-3. Hazard ratios and 95% confidence intervals for the association between antibiotic prescription during pregnancy and risk of childhood cancer in Taiwan, 2004-2015

	Number of events	Incidence density rate (per 100,000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia				
Not prescribed antibiotics	90	3.73	ref	ref
Any type of antibiotics	703	4.55	1.25 (1.01-1.56)	1.30 (1.04-1.63)
Tetracyclines	23	7.46	2.09 (1.32-3.30)	2.15 (1.34-3.45)
Amphenicols	13	4.99	1.43 (0.80-2.57)	1.28 (0.67-2.42)
Beta-lactam antibacterials – penicillin	287	3.97	1.09 (0.86-1.38)	1.15 (0.90-1.47)
Other beta-lactam antibacterials	561	4.62	1.27 (1.02-1.59)	1.31 (1.04-1.65)
Sulfonamides and trimethoprim	11	4.68	1.34 (0.72-2.51)	1.42 (0.75-2.69)
Macrolides, lincosamides and streptogramins	79	4.33	1.22 (0.90-1.65)	1.30 (0.95-1.78)
Aminoglycoside antibacterials	178	4.29	1.19 (0.92-1.54)	1.18 (0.91-1.55)
Quinolone antibacterials	15	3.78	1.05 (0.61-1.82)	1.04 (0.59-1.84)
Other antibacterials	16	4.06	1.12 (0.66-1.90)	1.08 (0.61-1.91)
Intestinal anti-infectives	13	4.08	1.15 (0.64-2.06)	1.22 (0.67-2.21)
Central nervous system tumors				
Not prescribed antibiotics	48	1.99	ref	ref
Any type of antibiotics	339	2.19	1.12 (0.82-1.51)	1.16 (0.84-1.59)
Tetracyclines	6	1.95	1.04 (0.45-2.43)	0.74 (0.26-2.09)
Amphenicols	6	2.30	1.24 (0.53-2.90)	1.32 (0.55-3.15)
Beta-lactam antibacterials – penicillin	172	2.38	1.22 (0.88-1.67)	1.29 (0.92-1.80)
Other beta-lactam antibacterials	273	2.25	1.14 (0.84-1.55)	1.17 (0.85-1.62)
Sulfonamides and trimethoprim	7	2.98	1.60 (0.72-3.54)	1.43 (0.60-3.43)

Macrolides, lincosamides and streptogramins	33	1.81	0.95 (0.61-1.48)	0.93 (0.58-1.48)
Aminoglycoside antibacterials	95	2.29	1.18 (0.83-1.67)	1.26 (0.87-1.81)
Quinolone antibacterials	11	2.77	1.44 (0.75-2.77)	1.55 (0.79-3.03)
Other antibacterials	8	2.03	1.05 (0.50-2.22)	1.16 (0.54-2.48)
Hepatoblastoma				
Not prescribed antibiotics	16	0.66	ref	ref
Any type of antibiotics	120	0.78	1.25 (0.74-2.10)	1.37 (0.79-2.40)
Beta-lactam antibacterials – penicillin	53	0.73	1.17 (0.67-2.05)	1.34 (0.74-2.43)
Other beta-lactam antibacterials	105	0.86	1.38 (0.82-2.34)	1.50 (0.86-2.64)
Macrolides, lincosamides and streptogramins	16	0.88	1.48 (0.74-2.95)	2.03 (0.98-4.20)
Aminoglycoside antibacterials	44	1.06	1.75 (0.99-3.11)	2.05 (1.11-3.80)
Other antibacterials	10	2.54	4.06 (1.84-8.95)	5.26 (2.29-12.12)
Medulloblastoma				
Not prescribed antibiotics	7	0.29	ref	ref
Any type of antibiotics	79	0.51	1.77 (0.82-3.84)	1.96 (0.85-4.51)
Beta-lactam antibacterials – penicillin	44	0.61	2.08 (0.94-4.62)	2.28 (0.96-5.38)
Other beta-lactam antibacterials	67	0.55	1.91 (0.88-4.16)	2.10 (0.91-4.85)
Macrolides, lincosamides and streptogramins	10	0.55	1.97 (0.75-5.18)	2.22 (0.80-6.18)
Aminoglycoside antibacterials	25	0.60	2.10 (0.91-4.85)	2.37 (0.96-5.83)

[a] Adjusted for birth year, sex, maternal age (years), family income (quartile), urbanization level (high, middle, low), and parity (1, 2, ≥3)

Antibiotic exposures that had a low occurrence of ≤5 cancer cases were excluded.

Table 3-4. Hazard ratios and 95% confidence intervals for the association between infection and antibiotic prescription during pregnancy and risk of childhood cancer in Taiwan, 2004-2015

Infection	Prescribed antibiotics	Number of events	Incidence density rate (per 100,000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia					
No	No	36	3.16	ref	ref
No	Yes	197	4.29	1.41 (0.99-2.01)	1.53 (1.05-2.23)
Yes	No	54	4.25	1.34 (0.88-2.04)	1.47 (0.95-2.27)
Yes	Yes	506	4.65	1.51 (1.07-2.11)	1.66 (1.16-2.38)
Central nervous system tumors					
No	No	19	16.67	ref	ref
No	Yes	104	22.66	1.38 (0.85-2.25)	1.40 (0.85-2.31)
Yes	No	29	22.81	1.37 (0.77-2.44)	1.27 (0.70-2.32)
Yes	Yes	235	21.62	1.31 (0.82-2.09)	1.29 (0.80-2.09)

[a] Adjusted for birth year, sex, maternal age (years), family income (quartile), urbanization level (high, middle, low), and parity (1, 2, ≥3)

3.7. Supplemental materials

Table 3-S1. International Classification of Diseases, Revision 9 (ICD-9) and Revision 10 (ICD-10) diagnostic codes of infectious diseases categories

	ICD-9	ICD-10
Any infection	000–139, +all below	A00–B99, G00–G09, R50.9, R56.0 + all below
Microorganism-specific infection categories		
Viral infection	008.8, 042–079, 381.00, 321.2, 323.0, 466, 480, 487, 488, 711.5	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	000–005, 008.0–008.5, 010–041, 079.88, 090–104, 320, 320.9, 323.1, 324–326, 382, 390–391, 475, 481–482, 510, 513, 540–542, 590, 595, 599.0, 614–616, 670, 675, 680–686, 711.0, 711.4,	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 infection categories		
Respiratory infection	032–034, 460–466, 473, 475–476, 480–488, 490, 510–511, 513	A36–A38, J00–J22, J32, J36–J37, J39.0–J39.1, J85–J86

Infectious enteritis	001–009	A01–A09
Skin infection	680–686	L00–L08
Urinary tract infection	590, 595, 599.0, 647.9	N10–N12, N30, N34.0, N39.0, O23.0–O23.4
Genital infection incl. STD[a]	054.1, 090–099, 131.0, 614–616, 616.0, 646.6	A50–A64, N70–N77, O23.5–O23.9
Appendicitis	540–542	K35–K37

[a] Sexually transmitted diseases (STD) include syphilis, Gonorrhea, Chlamydia, trichomoniasis, condyloma and genital herpes

Table adapted from Atladóttir et al.[152]

Table 3-S2. Anatomical Therapeutic Chemical (ATC) codes classification of antibiotics

Classification	ATC code
Any type of antibiotics	All below
Tetracyclines	J01A
Amphenicols	J01B
Beta-lactam antibiotics – penicillin	J01C
Other beta-lactam antibiotics	J01D
Sulfonamides and trimethoprim	J01E
Macrolides, lincosamides and streptogramins	J01F
Aminoglycoside antibiotics	J01G
Quinolone antibiotics	J01M
Combinations of antibiotics	J01R
Other antibiotics	J01X
Intestinal anti-infectives	A07A

Table 3-S3. Hazard ratios and 95% confidence intervals for the association between number of infection episodes during pregnancy and risk of childhood cancer in Taiwan, 2004-2015

Number of infection episodes	Number of events	Incidence density rate (per 100,000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia				
Non-infected cohort (0 episode)	233	4.07	ref	ref
1 episode	190	4.32	1.06 (0.87-1.28)	1.09 (0.90-1.32)
2-3 episodes	236	4.99	1.22 (1.02-1.46)	1.24 (1.03-1.50)
4 episodes and over	134	4.44	1.08 (0.87-1.33)	1.11 (0.89-1.38)
Each additional episodes of infection (as continuous)	-	-	1.05 (0.98-1.12)	1.06 (0.99-1.13)
Central nervous system tumors				
Non-infected cohort (0 episode)	123	2.15	ref	ref
1 episode	92	2.09	0.97 (0.74-1.28)	0.96 (0.73-1.26)
2-3 episodes	110	2.33	1.08 (0.84-1.40)	1.05 (0.80-1.36)
4 episodes and over	62	2.05	0.95 (0.70-1.29)	0.91 (0.66-1.24)
Each additional episodes of infection (as continuous)	-	-	1.00 (0.91-1.10)	0.99 (0.90-1.08)
Hepatoblastoma				
Non-infected cohort (0 episode)	36	0.63	ref	ref
1 episode	36	0.82	1.29 (0.81-2.05)	1.30 (0.81-2.10)
2-3 episodes	39	0.83	1.29 (0.82-2.03)	1.40 (0.89-2.23)
4 episodes and over	25	0.83	1.27 (0.76-2.12)	1.29 (0.76-2.20)
Each additional episodes of infection (as continuous)	-	-	1.08 (0.93-1.26)	1.10 (0.94-1.29)
Medulloblastoma				
Non-infected cohort (0 episode)	30	0.52	ref	ref

1 episode	16	0.36	0.70 (0.38-1.28)	0.64 (0.35-1.20)
2-3 episodes	22	0.47	0.89 (0.51-1.54)	0.82 (0.47-1.44)
4 episodes and over	18	0.60	1.14 (0.63-2.04)	1.09 (0.61-1.96)
Each additional episodes of infection (as continuous)	-	-	1.04 (0.86-1.26)	1.02 (0.84-1.24)

[a] Adjusted for birth year, sex, maternal age (years), family income (quartile), urbanization level (high, middle, low), and parity (1, 2, ≥3)

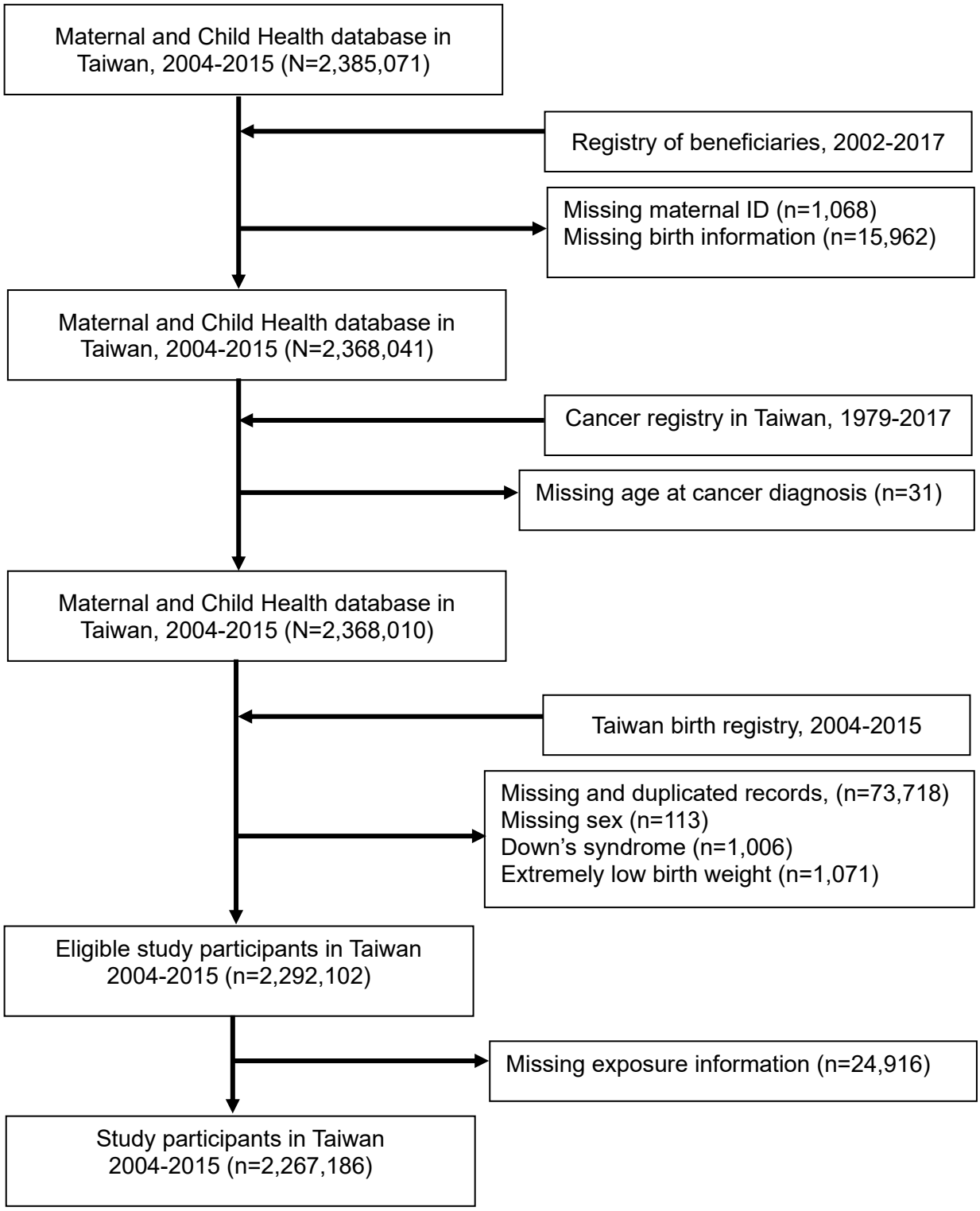

Figure 3-S1. Study participants flow chart in Taiwan 2004-2015

4. Maternal exposure to nitrosatable drugs during pregnancy and risk of childhood cancers in Denmark

This chapter is based in part on the previously published article entitled “Exposure to nitrosatable drugs during pregnancy and childhood cancer: A matched case–control study in Denmark, 1996-2016” published in Pharmacoepidemiology and Drug Safety.[198] I have permission from John Wiley and Sons to use the work in my dissertation (license number: 5557900547759).

4.1. Introduction

NOCs are a group of organic agents that contain a nitroso group in their molecular structure. There is suspicion that these compounds may cause cancer,[81] but studies have not yet definitively linked NOC exposure to cancer risk in humans. However, the IARC has concluded that ingesting nitrates or nitrites, which can lead to endogenous nitrosation, is likely to be carcinogenic to humans.[94] The difficulty of measuring and identifying NOC exposures has made it challenging to establish consistent results in previous studies.

Humans are exposed to NOC from both external and internal sources. Externally, NOC exposure can come from food, tobacco, and other environmental sources. Internally, NOC can be formed through endogenous synthesis from ingested nitrate, nitrite, or nitrosatable compounds like drugs containing amides and amines.[82–84] The majority of NOC exposure in humans comes from endogenous synthesis.[84]

Endogenous nitrosation can happen through several mechanisms, mainly in the stomach through non-enzymatic formation in an acidic environment. Pregnant women can pass NOC synthesized from ingested nitrosatable compounds to their fetus through the placenta, which has been found to cause neurogenic and lymphatic tumors in animal experiments.[87–93]

Previous studies have linked nitrate and nitrite ingestion to various types of cancer in adults such as gastrointestinal tumors, brain tumors, lymphoma, and urinary tract tumors.[95–100] Maternal exposure to nitrosatable compounds during pregnancy is a significant source of

childhood NOC exposure. Maternal exposure to 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.[101–104] Fewer studies on the effects of nitrosatable drugs during pregnancy on childhood nervous system tumors have yielded inconclusive results.[55,56,105,106] Additionally, there has been no dose-response analysis conducted, and the effect sizes identified by previous studies have been inconsistent. Therefore, this study aims to provide additional information about maternal prescriptions of nitrosatable drugs during pregnancy and childhood cancer.

4.2. Methods

This study is a matched case-control study that utilized Danish nationwide registry data to link information from various sources including the Central Population Registry, Danish Cancer Registry, Danish National Patient Register, Danish National Prescription Registry, and Danish Medical Birth Registry. Details of data linkage and covariate information have been previously provided.[147]

Cases were identified from the Danish Cancer Registry using a specific classification system for childhood cancer.[148,236] Individuals were alive and cancer-free at the time of the index case's diagnosis were eligible for controls. Controls were matched with cases based on their birth date and sex, and for each case, twenty-five controls were randomly chosen from the matched set. The study included participants who were born in Denmark between 1995 and 2014, and the cases were diagnosed between 1996 and 2016. Infants with birth weight less than 500 grams (n = 68) were excluded from the analysis since they are considered non-viable pregnancies.

We obtained data on the use of prescription drugs during pregnancy from the Danish National Prescription Register, which is a comprehensive nationwide registry that covers almost the entire population of Denmark (up to 97.5%).[237,238] We looked for prescriptions that were filled during the period from the estimated conception date until the date of birth, with gestational age

at birth in days obtained from the Medical Births Registry. In cases where gestational age was missing, we used multiple imputation, as previously described.[239] We identified nitrosatable drugs, which are drugs that have been found to form nitroso compounds, from a literature search and generated a list of these drugs,[55,85,86] excluding one that was only administered through injection. Prescriptions that were prescribed before pregnancy were not considered. We also identified the ATC codes for these drugs and matched them against entries in the Danish National Prescription Registry. We categorized the nitrosatable drugs based on their functional groups, which were amides, secondary amines, and tertiary amines, and created subgroups for those who were exposed to nitrosatable antibiotics (Supplement Table ***4-S1***). The reference group was made up of women who did not receive any prescriptions for nitrosatable drugs during pregnancy.

The study identified 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 from the Central Population Registry or the Danish Medical Birth Registry.

The study used a conditional logistic regression model to estimate crude and adjusted odds ratios and corresponding 95% confidence intervals for each type of childhood cancer, while controlling for confounding using disjunctive cause criteria and causal diagrams.[153] As maternal age (measured as a continuous variable) and birth order (whether the child was the first-born or not) have been proposed as risk factors for some types of childhood cancer and could potentially affect the association between nitrosatable drug exposure and cancer,[147,154,155] we controlled for these variables in all our final statistical models. We assumed that these factors are risk factors for most or all types of childhood cancer. We excluded results from models with less than five cases.[159]

Antibiotic prescriptions are often given to treat infections, which may also be a risk factor for certain types of childhood cancer.[240–243] As a result, there is a potential for confounding

by indication when studying the relationship between nitrosatable antibiotics and childhood cancer. To address this issue, we conducted secondary analyses for four different groups of women based on the type of antibiotic prescribed: 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. We identified antibacterial drugs using ATC codes J01 (antibacterial for systemic use) and A07A (intestinal anti-infectives). The reference group for these secondary analyses were women who did not receive prescriptions for nitrosatable drugs or antibiotics during pregnancy. We conducted these analyses whenever statistical power allowed.

A sensitivity analysis was performed to include maternal smoking status as a covariate in adjusted models because smoking status was only collected for part of the study period (≥1991). However, a previous analysis of the same data did not find an association between maternal smoking and pediatric cancers, except for eye tumors.[160] Additionally, a sensitivity analysis was conducted to add maternal infections during pregnancy as additional covariates. Information on maternal infections was obtained from the Danish National Patient Register using inpatient and outpatient diagnoses based on the ICD-10. The categorization used in the analysis was adapted from Atladóttir et al (Supplement Table ***4-S2***).[152] All statistical analyses were performed using R 4.0.2 software.

4.3. Results

In this study, we analyzed 1,749 cases of childhood cancer and 43,841 controls who were matched to the cases. Table ***4-1*** shows the characteristics of the cases, controls, and their parents. We found that cases were more likely to be firstborn children. We also observed that mothers of cases were more likely to have been given nitrosatable drugs during pregnancy compared to controls (27.5% vs 22.7%). The most commonly prescribed nitrosatable drugs were antibacterial, with 19.1% of cases and 15.5% of controls being prescribed them. The

majority of mothers, both cases and controls, were prescribed only one nitrosatable drug during their pregnancy. Table ***4-2*** provides more details on these findings.

Mothers of children with neuroblastoma had a twofold higher likelihood of being prescribed nitrosatable drugs during pregnancy compared to controls (adjusted OR = 2.0; 95% CI 1.34-2.85). Similarly, higher odds of nitrosatable drug prescriptions during pregnancy were observed among ALL cases (adjusted OR = 1.3; 95% CI 1.07-1.59) and CNS cases (adjusted OR = 1.3; 95% CI 1.04-1.51) (Table ***4-3***). The inclusion of maternal smoking or infection status in the models did not alter the adjusted odds ratios by more than ten percent among the major cancers presented in Table ***4-3*** (Supplement Table ***4-S3***).

The use of nitrosatable antibiotics was linked with a higher likelihood of developing neuroblastoma (adjusted OR = 2.0; 95% CI 1.31-3.13) and astrocytoma (adjusted OR = 1.6; 95% CI 1.11-2.34), particularly diffuse astrocytoma (adjusted OR = 2.3; 95% CI 1.18-4.66). When examining the functional groups and nitrosatable antibiotics (Table ***4-4***), secondary amines were found to have a stronger positive association with neuroblastoma (adjusted OR = 2.9; 95% CI 1.42-6.01), ALL (adjusted OR = 1.9; 95% CI 1.28-2.76) and AML (adjusted OR = 2.6; 95% CI 1.20-5.55), but not CNS (adjusted OR = 0.8; 95% CI 0.50-1.37). Moreover, the odds of prescriptions for tertiary amines were higher among retinoblastoma cases (adjusted OR = 2.2; 95% CI 1.16-4.35).

To estimate the odds ratios for different types of nitrosatable and antibacterial drugs (Table ***4-5***), we observed possibly positive associations for ALL with non-nitrosatable antibiotics (adjusted OR = 1.3; 95% CI 0.99-1.72) and nitrosatable antibiotics (adjusted OR = 1.3; 95% CI 1.00-1.81). However, we observed the strongest positive associations with CNS (adjusted OR = 1.4; 95% CI 1.09-1.84), astrocytoma (adjusted OR = 1.8; 95% CI 1.17-2.88), and neuroblastoma (adjusted OR = 2.4; 95% CI 1.39-4.09) for nitrosatable antibiotics, while non-antibacterial nitrosatable drugs had the strongest positive associations with AML (adjusted OR = 1.5; 95% CI 0.78-3.04).

4.4. Discussion

The findings of this study indicate that taking nitrosatable drugs during pregnancy may increase the risk of certain childhood cancers. We observed a strong positive link for neuroblastoma, and moderate connections for CNS and ALL. However, with ALL, there appeared to be a tendency towards a rise in risk with non-nitrosatable antibiotics, which suggests that the association with ALL could be because of the underlying infections that the antibiotics were prescribed and used for, rather than with nitrosatable antibiotics, although both situations could be possible. This tendency was not as strong for AML, CNS, astrocytoma, and neuroblastoma, where the most robust associations and highest point estimates were linked to nitrosatable drugs, regardless of whether they were antibiotics or not, and non-nitrosatable antibiotics did not significantly raise the risk.

The use of a different list of nitrosatable drugs in this study may explain why our results differ from those of previous studies. Previous studies focused on categorizing medications based on their intended uses rather than grouping them as nitrosatable drugs. For instance, some studies that investigated the link between maternal medication use and neuroblastoma found positive associations with specific types of medications, such as diuretic antihypertensives (adjusted OR = 3.2; 95% CI 1.0-9.7),[244] opioid agonists (adjusted OR = 3.4; 95% CI 1.4-8.4),[105] and analgesics (adjusted OR = 6.0; 95% CI 2.0-18.1).[245] While some drugs in these categories could potentially form NOC, the majority of them are not nitrosatable drugs. Although one study that reported an association between opioid agonists and neuroblastoma also had inconclusive results for other categories of medication that could potentially form nitroso compounds, such as diuretic antihistamines, analgesics, and antibiotics.[105] Previous cohort studies in Denmark showed that 15.3% of pregnant women were exposed to nitrosatable drugs during the first twenty-two weeks of pregnancy,[86,246] while this study found that 22.7% of the matched controls were exposed to such drugs during the entire pregnancy period.

Three case-control studies that investigated the link between maternal exposure to nitrosatable drugs and CNS observed relatively small associations ranging from 1.1 to 1.4.[55,56,244] Meanwhile, a cohort study indicated a stronger increase in risk for CNS (adjusted relative risk = 2.3; 95% CI 1.0-5.3).[247] Another matched case-control study discovered positive associations between maternal use of diuretics (OR = 2.0; p-value = 0.03) and antihistamines (OR = 3.4; p-value = 0.002) and CNS.[106]

Previous studies have linked ALL to maternal exposure to antibiotics. One case-control study found a positive association between self-reported maternal use of antibiotics from three months before conception until the end of pregnancy and ALL in the offspring (adjusted OR = 1.47; 95% CI 1.06-2.04).[248] Two cohort studies also reported small effect estimates for maternal antibiotics use during pregnancy and the risk of developing ALL, but with confidence intervals that included the null.[249,250] This study supports these findings, but also suggests that confounding by indication may explain the association.

Animal studies have suggested that NOC may have carcinogenic effects when passed from mother to offspring during pregnancy.[87–90] However, the exact mechanisms involved in this process are not yet well understood. The results presented in Table ***4-5*** may provide some insight into these mechanisms. For example, neuroblastoma, which is associated with abnormal cancer gene expression in immature cell types, has been found to have a stronger association with NOC exposure compared to other neurological cancers like CNS, glioblastoma, and medulloblastoma, which originate from more mature neural cells.[251,252] Animal studies have also shown that different cancer types may be activated through different pathways.[91,92] For instance, glioblastoma cells are induced by NOC through programmed death ligand 1 expression and regulated by Anti-c-Jun N-terminal kinase activation,[92] whereas leukemia tumor cells responded to NOC through ras and p53 genes expression in an animal model.[93]

When we looked at specific functional groups, we found that secondary amines were more strongly associated with most cancers except for CNS. However, a previous study on childhood brain tumors did not find any association between maternal use of nitrosatable amines or amides.[55] It is unclear why there would be a stronger association with secondary amines for most cancers, but one study suggested that some secondary amines are more effective at inhibiting histone deacetylases in cancer cells compared to tertiary amines.[253] Additionally, the molecular structure of secondary amines is more stable, and they can more easily pass through the blood-brain barrier.[85,253,254] However, we also found a stronger association between tertiary amines and retinoblastoma. To our knowledge, no studies have looked at the relationship between NOC and retinoblastoma, but NOC has been found to cause retinal neurotoxicity in rats.[255] Exposure to tertiary amines in the workplace has also been linked to ocular changes in adults.[256]

Some researchers have proposed that medications with a molecular weight exceeding 500 g/mol are less likely to be absorbed or permeate effectively. However, in this study, only 7 of the 164 drugs (4.3%) included in our list have a molecular weight exceeding 500 g/mol. As a result, we were unable to conduct sensitivity analyses based on this categorization.

This study has several strengths. Firstly, we used data derived solely from population-based nationwide registries, which minimizes selection bias. Secondly, we were able to collect prescription records during pregnancy, i.e., before a child's diagnosis, independently of the outcomes, thereby eliminating the risk of possible recall bias.

Despite its strengths, the study has several limitations. One of them is the lack of information on patient compliance since the data only records the redemption of prescription medication. Additionally, over-the-counter nitrosatable drugs are not captured in the prescription registry system unless the patient has a chronic disease (e.g., acetaminophen, analgesics, antihistamines). It was assumed that case and control mothers had similar compliance and a

similar likelihood of taking nitrosatable drugs over the counter, which could result in exposure misclassification that is non-differential and biased towards the null.

There was no available information on the dosage and method of administering the drugs. Although a drug that could only be administered parenterally was excluded, most of the drugs on the list have more than one administration route. Since endogenous NOC synthesis occurs primarily in the stomach, the drugs must be taken orally. The study classified exposed individuals as those who likely received only one prescription for nitrosatable drugs, which was most common in the third trimester. Animal studies have shown that even at low doses, NOC has a transplacental carcinogenic effect.[90] Thus, the impact of nitrosatable drug exposure may differ depending on the specific pregnancy time frame and dosage.

The absence of data on maternal dietary habits, water source, and supplement intake may lead to uncontrolled confounding. Maternal diet can be a source of exposure to nitrate and nitrite, while iron supplements and Vitamin C have been found to have a protective effect against some cancers associated with NOCs.[257–259] Therefore, the potential impact of these factors on the results cannot be ruled out.

When studying prenatal exposure and postnatal outcomes, live birth bias can occur because childhood cancers are only detected in live-born children. Nitrosatable drug use has also been linked to congenital malformations,[260–262] which can lead to poor fetal survival and stillbirth.[86] However, this type of live birth bias is typically small and tends to make estimates towards the null.[231]

Finally, it is important to note that most childhood cancers are very uncommon. Although we utilized national registry data that spanned several decades, the sample sizes for certain cancers were still limited. Therefore, the findings based on a small number of cases should be interpreted with care.

4.5. Conclusion

Maternal prescriptions of nitrosatable drugs during pregnancy can increase the risk of CNS and neuroblastoma in children. The association between maternal use of these drugs and ALL may be due to other factors such as maternal infections. The strength of the association depends on the type of nitrosatable drug and the type of cancer. Further research is required to confirm these findings and to explore the mechanisms linking NOC to specific types of childhood cancer. Meanwhile, it is important to exercise caution when using nitrosatable drugs during pregnancy and to avoid unnecessary use of these drugs.

4.6. Tables

Table 4-1. 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 4-2. 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 4-3. Conditional logistic regression odds ratios and 95% confidence intervals for childhood cancers and any type of maternal nitrosatable drug prescription received during pregnancy

Cancer type	Cases		Controls		Adjusted	95% CI
	Exposed	Unexposed	Exposed	Unexposed	OR[a]	
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 4-4. Conditional logistic regression odds ratios and 95% confidence intervals for childhood cancers and specific type of maternal nitrosatable drug prescription received during pregnancy

Group of nitrosatable prescription	Cases		Controls		Adjusted 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 4-5. Conditional logistic regression odds ratios and 95% confidence intervals cancers and specific type of maternal nitrosatable drug and antibacterial prescription received during pregnancy

Group of prescription	Cases	Controls	Adjusted OR[a]	95% CI
Acute lymphoblastic leukemia				
Not prescribed any in pregnancy	346	9496	1.0	[Reference]
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				
Not prescribed any in pregnancy	69	1890	1.0	[Reference]
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				
Not prescribed any in pregnancy	373	9985	1.0	[Reference]
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				
Not prescribed any in pregnancy	104	2783	1.0	[Reference]
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				
Not prescribed any in pregnancy	69	2300	1.0	[Reference]
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.

4.7. Supplemental materials

Table 4-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

NSAID = Non-steroidal anti-inflammatory drug, ACE = Angiotensin-converting enzyme, SSRI = Selective serotonin reuptake inhibitors, H2 = Histamine type 2 receptor

Table 4-S2. International Classification of Diseases, Revision 10 (ICD-10) diagnostic codes for infectious diseases categories

Infection category	ICD-10
Any infection	A00–B99, G00–G09, R50.9, R56.0 + all below
Microorganism-specific	
Viral infection	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	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	A36–A38, J00–J22, J32, J36–J37, J39.0–J39.1, J85–J86
Infectious enteritis	A01–A09
Skin infection	L00–L08
Urinary tract infection	N10–N12, N30, N34.0, N39.0, O23.0–O23.4
Genital infection included STDs*	A50–A64, N70–N77, O23.5–O23.9

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

(a) Table adapted from Atladóttir et al.[152]

Table 4-S3. Sensitivity analysis by adding medically diagnosed infection during pregnancy and maternal smoking into conditional logistic regression for childhood cancers and any type of maternal nitrosatable drug prescription received during pregnancy

Cancer type	Model 1		Model 2		Model 3	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Acute lymphoblastic leukemia	1.30	1.07 - 1.59	1.29	1.05 - 1.57	1.27	1.04 - 1.55
Acute myeloid leukemia	1.35	0.89 - 2.06	1.34	0.87 -2.07	1.39	0.90 -2.14
Central nervous system tumors	1.25	1.04 - 1.51	1.24	1.02 - 1.51	1.24	1.02 - 1.50
Gliomas	1.11	0.82 - 1.50	1.14	0.83 - 1.56	1.11	0.81 - 1.52
Astrocytoma	1.33	0.94 - 1.88	1.36	0.94 - 1.96	1.29	0.89 - 1.85
Non-Hodgkin's lymphoma	1.44	0.94 - 2.20	1.42	0.91 - 2.21	1.36	0.88 - 2.21
Germ cell tumors	1.21	0.75 - 1.98	1.11	0.66 - 1.88	1.19	0.72 - 1.97
Neuroblastoma	1.96	1.34 - 2.85	1.92	1.31 - 2.82	2.00	1.37 - 2.92
Wilms' tumor	0.82	0.48 - 1.39	0.80	0.47 - 1.37	0.79	0.46 - 1.36
Medulloblastoma	0.91	0.50 - 1.64	0.91	0.50 - 1.66	0.84	0.45 - 1.57
Retinoblastoma	1.53	0.89 - 2.63	1.47	0.85 - 2.57	1.58	0.92 - 2.73

Model 1: adjusted by mother age (years) and birth order (>1 vs 1)

Model 2: added medically diagnosed infection during pregnancy (yes vs no) to Model 1

(total no. of missing = 753; cases = 88; controls = 665)

Model 3: added smoking status during pregnancy (yes vs no) to Model 1

(total no. of missing = 1,590; cases = 67; controls = 1523)

5. Maternal acetaminophen exposure during pregnancy and the risk of childhood cancer in Taiwan

5.1. Introduction

Acetaminophen is a commonly used medication for pain relief and fever reduction during pregnancy.[107–109] Its widespread usage, including in Taiwan, has raised concerns about its safety for pregnant women.[110–113] There is a possibility that acetaminophen may have negative effects on fetal neurodevelopment, respiratory health, and the risk of attention-deficit/hyperactivity disorder and autism spectrum conditions in children.[112–117,263–265] Moreover, the chemical used in acetaminophen production, 4-nitrophenol, is considered a potential disruptor of the endocrine system.[266] Acetaminophen has also been identified as a major cause of liver failure in pregnant women, even when taken at recommended doses.[267,268] Surprisingly, there is limited research on the connection between acetaminophen exposure during pregnancy and childhood cancer.[57,136,140,269–271]

Acetaminophen can cross the placental barrier and affect the functioning of the placenta, potentially influencing fetal development. Its adverse effects on fetal development are attributed to disruptions in the endocrine and nervous systems, as well as hepatotoxicity and oxidative stress.[118–121,270] Experimental studies have shown that acetaminophen may impact germ cell development through prostaglandin E2-mediated effects, which could have implications for cancer risk.[272] The use of acetaminophen during pregnancy has also been associated with an increased risk of cryptorchidism (undescended testicles) and reduced anogenital distance in boys,[273–278] both of which are risk factors for testicular cancer.[279,280]

The existing evidence on the association between acetaminophen use during pregnancy and childhood cancer is limited. Initial studies suggested a potential link between analgesics and the risk of childhood cancer,[271,281] but more recent research has indicated a possible protective effect of acetaminophen against leukemia in children.[57,269] However, a case-control study in Sweden suggested a connection between acetaminophen use during pregnancy

and childhood brain tumors.[136] Some case reports have also suggested at a potential link between acetaminophen exposure and childhood hepatoblastoma,[137–139] but recent epidemiological data did not support this claim.[140]

Considering the limited evidence and mixed findings, our study aims to investigate the potential association between acetaminophen prescriptions during pregnancy and the risk of childhood cancer in Taiwan. Based on the hepatotoxic effects of acetaminophen and its association with adverse neurodevelopmental outcomes and cryptorchidism, we hypothesized that the increased risk of cancer would predominantly impact liver, brain, or germ cell tumors. In Taiwan, acetaminophen is exclusively accessible over the counter at pharmacies, excluding convenience stores or grocery outlets. Since physician-prescribed medications are provided at no cost, there is a push for women to depend on prescriptions, resulting in 67% of pregnant women obtaining acetaminophen through prescriptions, a percentage closely mirroring self-reported usage rates in the United States (65%).[112,282] This suggests that the majority of acetaminophen users in Taiwan acquire the medication through prescribed means.

5.2. Methods

We conducted a cohort study using the TMCHD, which contains information on mothers and children born between 2004 and 2015. The database includes a total of 2,385,071 pairs of maternal and child data. We linked this database with the National Health Insurance Research Database (NIRD; covering the period 2002-2017), Cancer registry (covering the period 1979-2017), and Taiwan birth registry (covering the period 2004-2015) through the Health and Welfare Data Science Center operated by the Ministry of Health and Welfare in Taiwan. We excluded children with incomplete parental and birth information (n=17,030), missing age at cancer diagnosis (n=31), missing or duplicated registration records (n=73,718), and missing information on their ATC code (n=24,908).

To identify maternal drug prescriptions during pregnancy, we accessed the TMCHD, which is connected to the NIRD. The NIRD contains medical claims data dating back to 1998

and provides a comprehensive healthcare system with a single-payer national insurance system. It maintains high-quality standards for pharmaceutical registry that are recognized internationally.[202] We specifically identified the use of acetaminophen during pregnancy by referring to the ATC code N02BE01. Combinations of acetaminophen (ATC code N02BE51) were excluded due to their low prescription prevalence during pregnancy (4.17%). The exposure period for acetaminophen was defined as the estimated date of conception until the date of birth, and we categorized trimester-specific exposures into three periods: 0-13 weeks, 13-28 weeks, and 28 weeks until birth.

To compare acetaminophen exposure during pregnancy, we focused on two main categories. The first category compared those who were prescribed acetaminophen at least once during pregnancy with those who were never prescribed it. The second category compared those with chronic exposure to acetaminophen (filled prescriptions in each trimester) with those who were never prescribed it. In addition, we explored the association between the number of acetaminophen prescriptions during pregnancy and the risk of cancer in offspring.

We established a linkage between the database and the Taiwan Cancer Registry to identify children diagnosed with cancer between 2004 and 2017.[203] The study focused on specific types of cancer, including acute ALL, AML, NHL, CNS, neuroblastoma, retinoblastoma, germ cell tumors, hepatoblastoma, Wilms tumors, bone tumors, astrocytoma, glioma, and medulloblastoma.

We used Cox proportional hazard models to estimate the associations between acetaminophen prescriptions and the risk of childhood cancer. The models were adjusted for various factors including mother’s age (years), father's age (years), family income (divided into quartiles), urbanization level (metropolitan cities, small cities and suburban areas, rural areas), and mother’s employment status during pregnancy (unemployed, employed). These variables were selected based on a comprehensive review of existing literature and expert opinions. Previous studies have indicated that both maternal and paternal age may contribute to the risk

of specific types of childhood cancer.[147,201,207–210] Therefore, we included them as covariates in our analysis, considering their potential impact. Additionally, we considered family income, urbanization level, and maternal employment status as proxies for socioeconomic status. Socioeconomic status has been suggested as a potential risk factor for certain types of childhood cancer in Taiwan.[205,211] Moreover, these factors could be associated with the exposure status of acetaminophen use during pregnancy in our study population, making them important variables to consider in our analysis.[112,113]

Given that sex plays a significant role in the development of bone tumors and germ cell tumors in children[283–285] and recognizing the potential association between prenatal acetaminophen exposure and child growth depending on sex,[286] we conducted a gender-based analysis. The aim was to explore whether child's sex could introduce a bias in the association between acetaminophen use during pregnancy and the occurrence of bone and germ cell tumors.

Prior research has suggested that infections during pregnancy might increase the risk of certain childhood cancers.[34–36,39,63] Additionally, pregnant women with infections are more likely to use acetaminophen to reduce fever.[107–109] Consequently, fever and infection have the potential to act as variables that could distort the association between acetaminophen exposure during pregnancy and childhood cancer. To account for the influence of these potential confounding factors, to the extent that the sample size permitted, we carried out an analysis stratified by the presence or absence of a medical diagnosis of fever and/or infections.

We also investigated the association between maternal acetaminophen prescription in two distinct time frames: the pre-pregnancy period (one year before conception) and the post-pregnancy period (one year after birth). This methodology was employed as a negative control period, allowing us to explore the crucial exposure window and potential relationships between acetaminophen use during these specific time periods.[287,288] The acetaminophen prescription

status during pregnancy was also included in the final model for this negative control exposure analysis.

To address potential biases and ensure the reliability of our findings, we conducted a probabilistic bias analysis.[289–291] This approach accounts for various sources of bias and assesses the robustness of the results. Previous studies in Europe have indicated that acetaminophen prescriptions may not accurately reflect the actual drug intake during pregnancy since it is often prescribed on an as-needed basis. These studies reported low sensitivity and high specificity in determining the exposure status of acetaminophen among pregnant women.[292,293] Therefore, we considered the possibility of non-differential misclassification of exposure as a potential source of bias in our study. Another potential source of bias was a live-birth bias, which can occur when investigating the impact of prenatal exposures on health outcomes that are observable only after the child's birth in the pregnancy cohort.[231] We also investigated the potential for unmeasured confounding, particularly confounding by indications such as pregnancy-related infections and inflammation. These factors are closely associated with the use of acetaminophen and have been reported to have links with certain cancers in children.[34,35,37,172,242] For details on the parameters used in the probabilistic bias analysis, please refer to supplementary Table ***5-5S1***. We performed Monte Carlo simulations with 100,000 replications to generate bias-adjusted estimates of the associations, including the 2.5th and 97.5th simulation limits.

We visually assessed the proportional-hazards assumption and excluded models that had fewer than five exposed cases due to limited occurrences of the events being studied. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). The probabilistic bias analysis was performed using the 'episensr' package (version 1.2.0) in R 4.3.

5.3. Results

Table ***5-1*** provides the general characteristics of the participants in our cohort study. Initially, a total of 2,294,292 individuals were eligible for the study. After excluding participants

with incomplete maternal exposure information during pregnancy (n=24,908), the final analysis included 2,269,384 participants (Figure 5-S1). The median follow-up time for children whose mothers were exposed to acetaminophen during pregnancy was 7.88 years (interquartile range [IQR] = 6.21 years), while for those unexposed, it was 8.12 years (IQR = 6.16 years). The prevalence of acetaminophen exposure during pregnancy was 78.4%. Children whose mothers were prescribed acetaminophen during pregnancy had a higher likelihood of receiving acetaminophen prescriptions one year before pregnancy (72.17% vs. 53.73%) and one year after delivery (77.71% vs. 61.83%) compared to those without acetaminophen prescription during pregnancy.

Although we did not establish conclusive evidence supporting an association between ever prescribed acetaminophen during pregnancy and most childhood cancers (Table ***5-2***), our analysis revealed a notable increase in the risk of childhood hepatoblastoma (adjusted HR = 1.30; 95% CI 0.83-2.05), bone tumors (adjusted HR = 1.40; 95% CI 0.80-2.43), and medulloblastoma (adjusted HR = 1.89; 95% CI 0.97-3.66) among children whose mothers were prescribed acetaminophen during pregnancy. However, it is important to note that the confidence intervals for these associations were relatively wide. Furthermore, in Table ***5-3***, we observed stronger associations between acetaminophen prescription in all three trimesters and the risk of medulloblastoma (adjusted HR = 2.43; 95% CI 1.10-5.39), hepatoblastoma (adjusted HR = 1.73; 95% CI 0.97-3.10), and bone tumors (adjusted HR = 1.85; 95% CI 0.92-3.72). These findings were comparable with the analysis regarding the number of prescriptions during pregnancy (Table ***5-S2***).

We did not found associations between mothers being prescribed acetaminophen one year prior to pregnancy and the risk of childhood cancers, with the exception of a slightly elevated risk that was observed for germ cell tumors (adjusted HR = 1.25; 95% CI 0.94-1.67) (Table 5-S3). Likewise, there were no substantial associations between maternal acetaminophen prescriptions in the year following childbirth, except for astrocytoma (adjusted

HR = 1.41; 95% CI 0.95-2.09) and bone tumors (adjusted HR = 1.53; 95% CI 0.88-2.63). It is important to note that the confidence intervals were wide and included null.

The sex-stratified analysis revealed distinct outcomes concerning acetaminophen exposure during pregnancy and the risk of bone tumors. Among girls, a stronger effect was observed (adjusted HR = 1.97, 95% CI 0.83-4.62), while in boys, the effect did include the null (adjusted HR = 1.02, 95% CI 0.49-2.13). However, when it came to germ cell tumors, the sex-stratified analysis indicated no substantial effect of acetaminophen exposure during pregnancy, whether for girls (adjusted HR = 0.80, 95% CI 0.53-1.21) or boys (adjusted HR = 1.09, 95% CI 0.71-1.66). For additional details on the results, please refer to supplementary Table 5-S5.

Furthermore, in stratified analysis distinguishing between mothers with or without a medical diagnosis of fever and/or infections, the hazard ratios for the use of acetaminophen stayed consistent with the ones we initially reported for all mothers. (Table 5-S5).

In the probabilistic bias analysis (Table 5-S6), which considered various biases including non-differential exposure misclassification, live-birth bias, and confounding by indication, we observed a consistent trend of increased effect estimates for the associations between acetaminophen prescription during all three trimesters and the risk of medulloblastoma (bias-adjusted risk ratio [RR]=3.51; 95% simulation interval [SI] 1.66-7.94) and bone tumors (bias-adjusted RR=2.65; 95% SI 1.21-5.61) compared to the adjusted HR estimates from Table ***5-3***. However, we noticed a slight decrease in the effect moving towards the null for hepatoblastoma (bias-adjusted RR=1.50; 95% SI 0.90-2.61). The primary factor contributing to the observed variability in the effects was the presence of non-differential misclassification bias, as indicated by the assumed sensitivity and specificity of the exposure parameters.

5.4. Discussion

In this nationwide linkage study, we did not discover a substantial association between acetaminophen prescription during pregnancy and childhood cancer risk.

Nevertheless, a possible connection between acetaminophen prescriptions throughout all pregnancy trimesters and childhood hepatoblastoma, bone tumors, and medulloblastoma emerged in our data. Our sensitivity analyses and probabilistic bias analysis provide evidence for robustness of these findings, particularly when considering the potential for exposure misclassification bias.

The results of our study align with previous research that emphasizes the association between chronic and heavy use of acetaminophen during pregnancy, rather than occasional or minimal consumption, and adverse outcomes in children.[113,116,265,275,278] Therefore, it is crucial to differentiate between sporadic and regular usage of acetaminophen to gain a comprehensive understanding of its potential hazards and effects on the child development.

Previous studies examining the link between prenatal acetaminophen exposure and the risk of childhood cancers lacked the necessary statistical power to establish conclusive connections. These studies differed significantly from ours, primarily focusing on ever/never usage rather than regular use. In accordance with a previous study,[269] we did not identify a correlation between acetaminophen use during pregnancy (either ever or throughout all trimesters) and the risk of childhood ALL. This contradicts the results of a smaller case-control study, which suggested a robust protective effect for acetaminophen use during the first and second trimesters (OR = 0.39; 95% CI 0.17-0.93 and OR = 0.37; 95% CI 0.16-0.88, respectively).[57] However, it is worth noting that the data on acetaminophen use in this case-control study relied on maternal recall after the diagnosis of offspring cancer, with reported acetaminophen prevalence being relatively low compared to another analgesic drug (Dipyrone).[57] Our findings also did not support a connection between acetaminophen prescription during pregnancy and the risk of all central nervous system (CNS) tumors combined, contrary to a prior case-control study that suggested such an association (OR = 1.7; 95% CI 0.6-5.4); presumably the earlier study lacked sufficient statistical power to examine specific CNS subtypes.[136] Conversely, despite a recent epidemiological study finding no

evidence supporting a link based on ever use (OR = 1.0; 95% CI 0.7-1.5),[140] our results align with multiple case reports suggesting a possible association between acetaminophen exposure during pregnancy and childhood hepatoblastoma.[137–139]

The suspected mechanism underlying the association between acetaminophen exposure and the risk of childhood hepatoblastoma may be explained by its hepatotoxicity and oxidative stress properties, as suggested by previous research.[122–125] Additionally, acetaminophen has been implicated in negative effects on the endocrine system and fetal neurodevelopment,[126–128] which could potentially contribute to the development of bone tumors and medulloblastoma. Further research is needed to unravel the specific pathways involved in the development of bone tumors and medulloblastoma. Additionally, associations with other types of cancers, particularly those related to endocrine and neural development, such as CNS and germ cell tumors, could not be established in our study. It is worth noting that acetaminophen is classified as a nitrosatable drug,[85] and some studies have suggested a potential association between nitrosatable drugs and the risk of certain childhood cancers.[45,198,294]

Our study design minimized participation bias by integrating comprehensive registries and national insurance data through a data-linkage approach. This allowed us to collect information on acetaminophen prescriptions before the detection of cancer in the offspring, reducing potential recall bias and establishing a clear temporal relationship between exposure and outcome.

However, despite the strengths of our study design, we must acknowledge several limitations. In Taiwan, citizens could either get reimbursed at clinics or purchase acetaminophen over the counter, and it's possible that individuals who were prescribed the medication might not have actually taken it, as it's usually prescribed on an as-needed basis for symptom relief. This introduces the potential for misclassification of exposure. Nevertheless, we believe that any

such misclassification is likely to be random, which would tend to bias the results toward no effect, as we demonstrated in our probabilistic bias analysis. Additionally, we did not have access to precise information about the dosage of acetaminophen administered. To our knowledge, there is no prospective self-reported medication use data available for a study of this size on childhood cancer incidence, and such a design is unlikely to be feasible. Although our data suggest a link between exposure to acetaminophen prescription during all three trimesters of pregnancy and an elevated risk of certain childhood cancers, further research is needed to explore the dosage and duration of acetaminophen use during pregnancy in order to thoroughly investigate the true extent of regular exposure to the medication.

Although we accounted for the majority of potential confounding factors associated with acetaminophen prescription during pregnancy and the risk of childhood cancers, as well as through our bias analysis, it is crucial to recognize that there might still be unmeasured confounders that influence the associations we observed. For example, the use of multiple medications, specifically nitrosatable drugs in combination with acetaminophen, could potentially be linked to the risk of childhood cancer and introduce additional confounding factors that were not taken into account in our study. Previous research has indicated the potential association between polypharmacy and childhood cancer risk, highlighting the need to consider these factors in future investigations.[45,198,294,295]

Studies that investigate prenatal exposure and subsequent postnatal outcomes are vulnerable to live birth bias, which means that childhood cancers are only detected in children who were born alive.[231] There is also a potential association between acetaminophen exposure and the occurrence of congenital malformations, which are linked to increased rates of fetal loss and stillbirth, although the available evidence is inconclusive.[296–299] Although our bias analysis and a previous study suggested that the impact of live birth bias was minimal, it is important to acknowledge and consider its potential influence, particularly when dealing with more complex bias structures.[231]

The absence of associations between acetaminophen use before and after pregnancy implies that variables without significant fluctuations over a one-year span re not responsible for the observed association with acetaminophen exposure during pregnancy, particularly in the cases of medulloblastoma and hepatoblastoma. Nevertheless, we found some positive associations in the year following delivery, specifically in relation to astrocytoma and bone tumors. This may be attributed to uncontrolled confounding variables following a similar bias pathway for these types of cancers, or it could be linked to the correlation between acetaminophen exposure during and after pregnancy.[300]

Furthermore, it is necessary to address the limitations of our probabilistic bias analysis. While this analysis helped us address some uncertainties related to biases in our study, it relied on assumptions about bias structures and parameter distributions.[301] These assumptions may not fully capture the full range of biases and parameter values that could exist in situations beyond what we considered. Additionally, we did not incorporate the bias factors from our final models into the analysis, assuming that they would have minimal impact on the estimations. Therefore, caution should be exercised when interpreting the results adjusted for bias.[301]

Finally, despite including a substantial number of mother and child pairs in our cohort, similar to studies on rare cancers, our sample size remains limited for certain types of cancer. Given the scarcity of studies focusing on this specific issue, further investigation in other populations is necessary to validate and confirm our findings.

5.5. Conclusion

The current study did not provide sufficient evidence to establish a definite link between acetaminophen prescription during pregnancy and the risk of childhood cancers. However, there were notable indications that consistent use of acetaminophen throughout all three trimesters of pregnancy could potentially increase the likelihood of hepatoblastoma, bone tumors, and medulloblastoma in children. The absence of an association during negative control

periods indicates that uncontrolled variables which effects remain relatively consistent over a one-year period did not explain the observed associations with acetaminophen exposure during pregnancy, specifically in the case of medulloblastoma and hepatoblastoma. Our robust probabilistic bias analysis confirmed the validity of these findings, indicating that the true associations might have been underestimated. Previous studies have also reported conflicting results regarding the association between acetaminophen exposure during pregnancy and childhood cancers. Further research is necessary to gain a better understanding of the mechanisms and potential risks associated with the use of acetaminophen during pregnancy and its impact on the development of childhood cancer.

5.6. Tables

Table 5-1. General characteristics of mother and child pairs in the study cohort, 2004 to 2015

	Acetaminophen prescription during pregnancy	No acetaminophen prescription during pregnancy
Number of children	1,778,746	490,638
Acute lymphoblastic leukemia, n (per 100,000)	619 (34.80)	178 (36.28)
Acute myeloid leukemia, n (per 100,000)	155 (8.71)	40 (8.15)
Non-Hodgkin lymphoma, n (per 100,000)	508 (28.56)	148 (30.16)
Central nervous system tumors, n (per 100,000)	308 (17.32)	79 (16.10)
Astrocytoma, n (per 100,000)	141 (7.93)	34 (6.93)
Medulloblastoma, n (per 100,000)	74 (4.16)	12 (2.45)
Glioma, n (per 100,000)	182 (10.23)	45 (9.17)
Neuroblastoma, n (per 100,000)	204 (11.47)	53 (10.8)
Retinoblastoma, n (per 100,000)	114 (6.41)	31 (6.32)
Wilms tumor, n (per 100,000)	62 (3.49)	20 (4.08)
Hepatoblastoma, n (per 100,000)	110 (6.18)	27 (5.50)
Bone tumors, n (per 100,000)	82 (4.61)	15 (3.06)
Germ cell tumors, n (per 100,000)	208 (11.69)	61 (12.43)
Follow-up time (years), median (IQR)	7.88 (6.21)	8.12 (6.16)
Child's sex, n (%)		
Boy	923689 (51.93)	255196 (52.02)
Girl	854965 (48.07)	235421 (47.98)
Missing	92	21
Birth weight (grams), n (%)		
<2499	153550 (8.63)	40030 (8.16)

2500-3999	1593973 (89.61)	441790 (90.04)
≥4000	31223 (1.76)	8818 (1.80)
Parity, n (%)		
1	702138 (39.47)	206200 (42.03)
2 or more	1076608 (60.53)	284438 (57.97)
Mother's age at birth (years), n (%)		
<20	35807 (2.01)	8626 (1.76)
20-29	801539 (45.06)	194215 (39.58)
30-34	657117 (36.94)	193233 (39.38)
35-39	249757 (14.04)	81370 (16.58)
≥40	34526 (1.94)	13194 (2.69)
Mean (SD)	30.23 (4.83)	30.87 (4.84)
Father's age at birth (years), n (%)		
<20	5960 (0.35)	1335 (0.29)
20-29	467285 (27.56)	102442 (22.20)
30-34	659330 (38.88)	179846 (38.97)
35-39	403181 (23.78)	122202 (26.48)
≥40	159841 (9.43)	55709 (12.07)
Mean (SD)	33.09 (5.35)	33.91 (5.44)
Missing	83149	29104
Family income (NTD), n (%)		
<30759	417634 (24.42)	115111 (24.57)
30759-48200	441115 (25.79)	103433 (22.08)
48200-73317	436399 (25.52)	115105 (24.57)
≥73317	415103 (24.27)	134877 (28.79)
Missing	68495	22112
Urbanization level of inhabited area, n (%)		
Metropolitan cities	923066 (51.91)	284759 (58.06)

Small cities and suburban areas	687287 (38.65)	165723 (33.79)
Rural areas	167792 (9.44)	40009 (8.16)
Missing	601	147
Mother's employment status during pregnancy, n (%)		
Unemployed	390,405 (22.02)	113,081 (23.13)
Employed	1,382,372 (77.98)	375,851 (76.87)
Missing	5,969	1,706
Maternal acetaminophen prescription within 1 year before pregnancy, n (%)		
No	474945 (27.01)	209806 (44.32)
Yes	1283760 (72.99)	263600 (55.68)
Missing	20041	17232
Maternal acetaminophen prescription 1 year after delivery, n (%)		
No	396437 (22.29)	187186 (38.16)
Yes	1382217 (77.71)	303350 (61.84)
Missing	92	102

Table 5-2. Hazard ratios and 95% confidence intervals for the association between acetaminophen prescription (any vs none) during pregnancy and risk of childhood cancer in Taiwan, 2004 to 2015

	Exposed n (ID)[b]	Unexposed n (ID)[b]	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia	619 (4.43)	178 (4.56)	0.97 (0.82-1.14)	0.98 (0.83-1.17)
Acute myeloid leukemia	155 (1.11)	40 (1.02)	1.08 (0.76-1.53)	1.06 (0.74-1.52)
Non-Hodgkin lymphoma	508 (3.63)	148 (3.79)	0.96 (0.80-1.15)	1.00 (0.83-1.21)
Central nervous system tumors	308 (2.20)	79 (2.02)	1.09 (0.85-1.39)	1.06 (0.82-1.36)
Astrocytoma	141 (1.01)	34 (0.87)	1.16 (0.80-1.69)	1.11 (0.75-1.64)
Medulloblastoma	74 (0.53)	12 (0.31)	1.72 (0.94-3.17)	1.89 (0.97-3.66)
Glioma	182 (1.30)	45 (1.15)	1.13 (0.82-1.57)	1.08 (0.77-1.51)
Neuroblastoma	204 (1.46)	53 (1.36)	1.07 (0.79-1.44)	1.06 (0.78-1.44)
Retinoblastoma	114 (0.82)	31 (0.79)	1.02 (0.68-1.51)	1.02 (0.68-1.53)
Wilms tumors	62 (0.44)	20 (0.51)	0.86 (0.52-1.42)	0.79 (0.47-1.32)
Hepatoblastoma	110 (0.79)	27 (0.69)	1.13 (0.74-1.72)	1.30 (0.83-2.05)
Bone tumors	82 (0.59)	15 (0.38)	1.53 (0.88-2.65)	1.40 (0.80-2.43)
Germ cell tumors	208 (1.49)	61 (1.56)	0.95 (0.71-1.26)	0.94 (0.70-1.26)

[a] Model adjusted for mother's age (years), father's age (years), family income (in quartile), urbanization level (metropolitan cities, small cities and suburban areas, rural areas), and employment status (unemployed, employed)
[b] Number of events (incidence density rate per 100,000 person-years)

Table 5-3. Hazard ratios and 95% confidence intervals for the association between acetaminophen prescription during pregnancy in trimester and risk of childhood cancer in Taiwan, 2004 to 2015

	Number of events	Incidence density rate (per 100,000 person-years)	HR (95% CI)	Adjusted HR (95% CI)a
Acute lymphoblastic leukemia				
Not prescribed in pregnancy	178	4.56	1 (ref)	1 (ref)
Only one trimester	316	4.75	1.04 (0.87-1.25)	1.05 (0.87-1.27)
Two trimesters	206	4.10	0.90 (0.73-1.09)	0.90 (0.73-1.10)
All three trimesters	97	4.22	0.92 (0.72-1.18)	0.97 (0.75-1.24)
Acute myeloid leukemia				
Not prescribed in pregnancy	40	1.02	1 (ref)	1 (ref)
Only one trimester	80	1.20	1.17 (0.80-1.71)	1.15 (0.78-1.71)
Two trimesters	48	0.96	0.93 (0.61-1.41)	0.90 (0.58-1.40)
All 3 trimesters	27	1.17	1.14 (0.70-1.86)	1.14 (0.68-1.90)
Non-Hodgkin lymphoma				
Not prescribed in pregnancy	148	3.79	1 (ref)	1 (ref)
Only one trimester	260	3.91	1.03 (0.84-1.26)	1.07 (0.87-1.32)
Two trimesters	171	3.41	0.90 (0.72-1.12)	0.93 (0.74-1.17)
All 3 trimesters	77	3.35	0.88 (0.67-1.16)	0.96 (0.72-1.27)
Central nervous system tumors				
Not prescribed in pregnancy	79	2.02	1 (ref)	1 (ref)
Only one trimester	144	2.16	1.07 (0.81-1.41)	1.04 (0.78-1.38)
Two trimesters	110	2.19	1.08 (0.81-1.44)	1.05 (0.78-1.42)
All 3 trimesters	54	2.35	1.16 (0.82-1.64)	1.10 (0.77-1.58)

Astrocytoma				
Not prescribed in pregnancy	34	0.87	1 (ref)	1 (ref)
Only one trimester	67	1.01	1.16 (0.77-1.75)	1.14 (0.75-1.75)
Two trimesters	51	1.02	1.17 (0.76-1.80)	1.08 (0.69-1.70)
All 3 trimesters	23	1.00	1.15 (0.68-1.95)	1.08 (0.63-1.87)
Medulloblastoma				
Not prescribed in pregnancy	12	0.31	1 (ref)	1 (ref)
Only one trimester	35	0.53	1.71 (0.89-3.30)	1.90 (0.94-3.85)
Two trimesters	22	0.44	1.43 (0.71-2.88)	1.61 (0.76-3.41)
All 3 trimesters	17	0.74	2.41 (1.15-5.04)	2.43 (1.10-5.39)
Glioma				
Not prescribed in pregnancy	45	1.15	1 (ref)	1 (ref)
Only one trimester	87	1.31	1.13 (0.79-1.63)	1.11 (0.77-1.60)
Two trimesters	67	1.34	1.16 (0.79-1.69)	1.08 (0.73-1.60)
All 3 trimesters	28	1.22	1.06 (0.66-1.69)	1.01 (0.62-1.64)
Neuroblastoma				
Not prescribed in pregnancy	53	1.36	1 (ref)	1 (ref)
Only one trimester	108	1.62	1.19 (0.86-1.65)	1.18 (0.84-1.64)
Two trimesters	65	1.30	0.94 (0.65-1.35)	0.93 (0.64-1.35)
All 3 trimesters	31	1.35	0.98 (0.63-1.53)	0.99 (0.63-1.55)
Retinoblastoma				
Not prescribed in pregnancy	31	0.79	1 (ref)	1 (ref)
Only one trimester	58	0.87	1.09 (0.71-1.69)	1.05 (0.67-1.64)
Two trimesters	37	0.74	0.91 (0.57-1.47)	0.95 (0.59-1.54)
All 3 trimesters	19	0.83	1.03 (0.58-1.81)	1.08 (0.61-1.93)
Wilms tumors				
Not prescribed in pregnancy	20	0.51	1 (ref)	1 (ref)
Only one trimester	34	0.51	0.99 (0.57-1.73)	0.87 (0.49-1.53)
Two trimesters	14	0.28	0.54 (0.27-1.06)	0.53 (0.27-1.05)
All 3 trimesters	14	0.61	1.18 (0.59-2.33)	1.14 (0.57-2.26)
Hepatoblastoma				
Not prescribed in pregnancy	27	0.69	1 (ref)	1 (ref)
Only one trimester	51	0.77	1.10 (0.69-1.76)	1.28 (0.79-2.10)
Two trimesters	36	0.72	1.02 (0.62-1.68)	1.14 (0.67-1.94)

All 3 trimesters	23	1	1.43 (0.82-2.49)	1.73 (0.97-3.10)
Bone tumors				
Not prescribed in pregnancy	15	0.38	1 (ref)	1 (ref)
Only one trimester	39	0.59	1.53 (0.84-2.77)	1.44 (0.79-2.63)
Two trimesters	25	0.50	1.30 (0.69-2.47)	1.12 (0.58-2.17)
All 3 trimesters	18	0.78	2.04 (1.03-4.05)	1.85 (0.92-3.72)
Germ cell tumors				
Not prescribed in pregnancy	61	1.56	1 (ref)	1 (ref)
Only one trimester	89	1.34	0.85 (0.62-1.18)	0.88 (0.63-1.24)
Two trimesters	82	1.63	1.04 (0.75-1.45)	1.01 (0.72-1.43)
All 3 trimesters	37	1.61	1.03 (0.68-1.54)	0.92 (0.60-1.42)

[a] Model adjusted for mother's age (years), father's age (years), family income (in quartile), urbanization level (metropolitan cities, small cities and suburban areas, rural areas), and employment status (unemployed, employed)

5.7. Supplemental materials

Table 5-5S1. Parameters for probabilistic bias analysis for the association between acetaminophen prescription during pregnancy and risk of childhood cancer in Taiwan, 2004 to 2015

Parameter	Value	Distribution	Bias	References
Sensitivity of exposure classification	c(0.61, 0.74, 0.67)	Triangular (min, max, median)	Non-differential misclassification of exposure	van Gelder, M. M. H. J., et al, (2018) and additional assumption
Specificity of exposure classification	c(0.88, 0.98, 0.93)	Triangular (min, max, median)	Non-differential misclassification of exposure	Cohen, J. M., et al, (2018) and additional assumption
Selection probability among case exposed	c(0.4, 0.6)	Uniform (min, max)	Selection bias (live-birth bias)	Presume
Selection probability among case un-exposed	c(0.5, 0.7)	Uniform (min, max)	Selection bias (live-birth bias)	Presume
Selection probability among non-case exposed	c(0.6, 0.8)	Uniform (min, max)	Selection bias (live-birth bias)	Presume
Selection probability among non-case un-exposed	c(0.7, 0.9)	Uniform (min, max)	Selection bias (live-birth bias)	Presume
Confounder-disease relative risk or the confounder-exposure odds ratio	1.68	Log normal (mean)	Unmeasured confounder	Presume
Lower 95% CI of confounder-disease odds ratio	1.51	Log normal (SD)	Unmeasured confounder	Presume

Upper 95% CI of confounder-disease odds ratio	1.85	Log normal (SD)	Unmeasured confounder	Presume
Prevalence of uncontrolled confounder among exposed	c(0.75, 0.95, 0.85)	Triangular (min, max, median)	Unmeasured confounder	Presume
Prevalence of uncontrolled confounder among un-exposed	c(0.65, 0.55, 0.75)	Triangular (min, max, median)	Unmeasured confounder	Presume

Table 5-S2. Hazard ratios and 95% confidence intervals for the association between number of acetaminophen prescriptions during pregnancy and risk of childhood cancer in Taiwan, 2004 to 2015

	Number of events	Incidence density rate (per 100,000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia				
Not prescribed in pregnancy	178	4.56	1 (ref)	1 (ref)
1 prescription	195	4.78	1.05(0.86-1.29)	1.05(0.86-1.30)
2-3 prescriptions	245	4.27	0.93(0.77-1.13)	0.95(0.78-1.16)
over 3 prescriptions	179	4.31	0.94(0.76-1.15)	0.96(0.77-1.18)
Acute myeloid leukemia				
Not prescribed in pregnancy	40	1.02	1 (ref)	1 (ref)
1 prescription	51	1.25	1.23(0.81-1.86)	1.20(0.78-1.84)
2-3 prescriptions	56	0.98	0.95(0.63-1.42)	0.93(0.61-1.42)
over 3 prescriptions	48	1.16	1.11(0.73-1.70)	1.10(0.71-1.72)
Non-Hodgkin lymphoma				
Not prescribed in pregnancy	148	3.79	1 (ref)	1 (ref)
1 prescription	162	3.97	1.05(0.84-1.31)	1.08(0.86-1.36)
2-3 prescriptions	204	3.55	0.94(0.76-1.16)	0.97(0.78-1.21)
over 3 prescriptions	142	3.42	0.90(0.72-1.13)	0.96(0.76-1.22)
Central nervous system tumors				
Not prescribed in pregnancy	79	2.02	1 (ref)	1 (ref)
1 prescription	83	2.03	1.01(0.74-1.37)	1.01(0.73-1.38)
2-3 prescriptions	135	2.35	1.16(0.88-1.53)	1.13(0.85-1.51)
over 3 prescriptions	90	2.17	1.07(0.79-1.44)	1.00(0.73-1.37)

Astrocytoma				
Not prescribed in pregnancy	34	0.87	1 (ref)	1 (ref)
1 prescription	43	1.05	1.21(0.77-1.90)	1.20(0.76-1.91)
2-3 prescriptions	58	1.01	1.16(0.76-1.77)	1.12(0.72-1.73)
over 3 prescriptions	40	0.96	1.11(0.70-1.75)	1.01(0.63-1.63)
Medulloblastoma				
Not prescribed in pregnancy	12	0.31	1 (ref)	1 (ref)
1 prescription	17	0.42	1.36(0.65-2.84)	1.51(0.69-3.34)
2-3 prescriptions	33	0.57	1.87(0.97-3.62)	2.09(1.03-4.26)
over 3 prescriptions	24	0.58	1.88(0.94-3.76)	1.97(0.93-4.15)
Glioma				
Not prescribed in pregnancy	45	1.15	1 (ref)	1 (ref)
1 prescription	54	1.32	1.15(0.77-1.71)	1.14(0.76-1.70)
2-3 prescriptions	80	1.39	1.21(0.84-1.74)	1.16(0.80-1.69)
over 3 prescriptions	48	1.16	1.00(0.67-1.51)	0.92(0.60-1.40)
Neuroblastoma				
Not prescribed in pregnancy	53	1.36	1 (ref)	1 (ref)
1 prescription	71	1.74	1.29(0.91-1.85)	1.24(0.86-1.79)
2-3 prescriptions	69	1.20	0.87(0.61-1.25)	0.91(0.63-1.30)
over 3 prescriptions	64	1.54	1.11(0.77-1.60)	1.09(0.75-1.58)
Retinoblastoma				
Not prescribed in pregnancy	31	0.79	1 (ref)	1 (ref)
1 prescription	39	0.96	1.22(0.76-1.95)	1.16(0.72-1.89)
2-3 prescriptions	47	0.82	1.01(0.64-1.60)	1.03(0.65-1.63)
over 3 prescriptions	28	0.67	0.83(0.50-1.38)	0.87(0.52-1.45)
Wilms tumors				
Not prescribed in pregnancy	20	0.51	1 (ref)	1 (ref)
1 prescription	22	0.54	1.06(0.58-1.94)	0.96(0.52-1.78)

2-3 prescriptions	23	0.40	0.77(0.42-1.41)	0.70(0.38-1.28)
over 3 prescriptions	17	0.41	0.78(0.41-1.50)	0.76(0.40-1.45)
Hepatoblastoma				
Not prescribed in pregnancy	27	0.69	1 (ref)	1 (ref)
1 prescription	29	0.71	1.04(0.62-1.75)	1.21(0.70-2.10)
2-3 prescriptions	41	0.71	1.02(0.63-1.65)	1.19(0.72-1.99)
over 3 prescriptions	40	0.96	1.36(0.83-2.22)	1.56(0.93-2.63)
Bone tumors				
Not prescribed in pregnancy	15	0.38	1 (ref)	1 (ref)
1 prescription	17	0.42	1.08(0.54-2.16)	1.02(0.50-2.06)
2-3 prescriptions	37	0.64	1.68(0.92-3.07)	1.62(0.89-2.97)
over 3 prescriptions	28	0.67	1.76(0.94-3.30)	1.46(0.76-2.80)
Germ cell tumors				
Not prescribed in pregnancy	61	1.56	1 (ref)	1 (ref)
1 prescription	59	1.45	0.93(0.65-1.33)	0.97(0.67-1.40)
2-3 prescriptions	76	1.32	0.84(0.60-1.18)	0.82(0.58-1.16)
over 3 prescriptions	73	1.76	1.12(0.80-1.57)	1.07(0.75-1.52)

[a] Model adjusted for mother’s age (years), father's age (years), family income (in quartile), urbanization level (metropolitan cities, small cities and suburban areas, rural areas), and employment status (unemployed, employed)

Table 5-S3. Hazard ratios and 95% confidence intervals for the association between acetaminophen prescription one-year before pregnancy and one-year after delivery and risk of childhood cancer in Taiwan, 2004 to 2015

	Number of events	Incidence density rate (per 100,000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia				
One-year before pregnancy				
Unexposed	227	4.20	1 (ref)	1 (ref)
Exposed	554	4.55	1.10 (0.94-1.28)	1.07 (0.91-1.26)
One-year after delivery				
Unexposed	216	4.67	1 (ref)	1 (ref)
Exposed	582	4.36	0.93 (0.79-1.09)	0.92 (0.78-1.08)
Acute myeloid leukemia				
One-year before pregnancy				
Unexposed	65	1.2	1 (ref)	1 (ref)
Exposed	128	1.05	0.86 (0.63-1.16)	0.88 (0.64-1.22)
One-year after delivery				
Unexposed	47	1.02	1 (ref)	1 (ref)
Exposed	149	1.12	1.11 (0.79-1.55)	1.07 (0.75-1.51)
Non-Hodgkin lymphoma				
One-year before pregnancy				
Unexposed	192	3.56	1 (ref)	1 (ref)
Exposed	455	3.74	1.06 (0.90-1.26)	1.05 (0.88-1.25)
One-year after delivery				
Unexposed	177	3.82	1 (ref)	1 (ref)

Exposed	481	3.61	0.94 (0.79-1.12)	0.95 (0.80-1.14)
Central nervous system tumors				
One-year before pregnancy				
Unexposed	110	2.04	1 (ref)	1 (ref)
Exposed	269	2.21	1.09 (0.87-1.36)	1.13 (0.89-1.42)
One-year after delivery				
Unexposed	88	1.90	1 (ref)	1 (ref)
Exposed	300	2.25	1.18 (0.93-1.50)	1.26 (0.98-1.63)
Astrocytoma				
One-year before pregnancy				
Unexposed	50	0.93	1 (ref)	1 (ref)
Exposed	122	1	1.07 (0.77-1.49)	1.13 (0.80-1.60)
One-year after delivery				
Unexposed	36	0.78	1 (ref)	1 (ref)
Exposed	140	1.05	1.36 (0.93-1.97)	1.41 (0.95-2.09)
Medulloblastoma				
One-year before pregnancy				
Unexposed	24	0.44	1 (ref)	1 (ref)
Exposed	59	0.49	1.03 (0.64-1.67)	0.96 (0.59-1.58)
One-year after delivery				
Unexposed	24	0.52	1 (ref)	1 (ref)
Exposed	62	0.46	0.83 (0.52-1.34)	0.87 (0.53-1.44)
Glioma				
One-year before pregnancy				
Unexposed	65	1.2	1 (ref)	1 (ref)
Exposed	157	1.29	1.06 (0.79-1.42)	1.12 (0.82-1.52)
One-year after delivery				
Unexposed	51	1.10	1 (ref)	1 (ref)

Exposed	177	1.33	1.20 (0.88-1.65)	1.25 (0.90-1.74)
Neuroblastoma				
One-year before pregnancy				
Unexposed	82	1.52	1 (ref)	1 (ref)
Exposed	170	1.4	0.91 (0.69-1.18)	0.96 (0.73-1.26)
One-year after delivery				
Unexposed	76	1.64	1 (ref)	1 (ref)
Exposed	182	1.36	0.83 (0.63-1.09)	0.80 (0.61-1.06)
Retinoblastoma				
One-year before pregnancy				
Unexposed	48	0.89	1 (ref)	1 (ref)
Exposed	93	0.76	0.85 (0.60-1.21)	0.83 (0.58-1.19)
One-year after delivery				
Unexposed	35	0.76	1 (ref)	1 (ref)
Exposed	111	0.83	1.13 (0.77-1.66)	1.18 (0.79-1.76)
Wilms tumors				
One-year before pregnancy				
Unexposed	27	0.5	1 (ref)	1 (ref)
Exposed	54	0.44	0.91 (0.57-1.45)	1.00 (0.61-1.63)
One-year after delivery				
Unexposed	21	0.45	1 (ref)	1 (ref)
Exposed	61	0.46	1.02 (0.62-1.69)	1.10 (0.65-1.85)
Hepatoblastoma				
One-year before pregnancy				
Unexposed	49	0.91	1 (ref)	1 (ref)
Exposed	88	0.72	0.78 (0.55-1.11)	0.75 (0.52-1.08)
One-year after delivery				
Unexposed	36	0.78	1 (ref)	1 (ref)

Exposed	101	0.76	0.95 (0.65-1.40)	0.92 (0.62-1.36)
Bone tumors				
One-year before pregnancy				
Unexposed	28	0.52	1 (ref)	1 (ref)
Exposed	68	0.56	1.02 (0.66-1.60)	0.99 (0.63-1.57)
One-year after delivery				
Unexposed	17	0.37	1 (ref)	1 (ref)
Exposed	80	0.60	1.55 (0.91-2.62)	1.53 (0.88-2.63)
Germ cell tumors				
One-year before pregnancy				
Unexposed	72	1.33	1 (ref)	1 (ref)
Exposed	194	1.6	1.21 (0.92-1.59)	1.25 (0.94-1.67)
One-year after delivery				
Unexposed	68	1.47	1 (ref)	1 (ref)
Exposed	206	1.54	1.12 (0.84-1.48)	1.10 (0.82-1.47)

[a] Model adjusted for mother's age (years), father's age (years), family income (in quartile), urbanization level (metropolitan cities, small cities and suburban areas, rural areas), employment status (unemployed, employed), and acetaminophen prescribed during pregnancy (yes vs no)

Table 5-S4. Hazard ratios and 95% confidence intervals for the association between acetaminophen prescription (any vs none) during pregnancy and risk of germ cell tumors and bone tumors in offspring stratified by sex in Taiwan, 2004 to 2015

	Exposed n (ID)[b]	Unexposed n (ID)[b]	HR (95% CI)	Adjusted HR (95% CI)[a]
Bone tumors				
Boys	36 (0.50)	9 (0.44)	1.12 (0.54-2.33)	1.02 (0.49-2.13)
Girls	46 (0.69)	6 (0.32)	2.14 (0.92-5.02)	1.97 (0.83-4.64)
Germ cell tumors				
Boys	113 (1.55)	30 (1.47)	1.05 (0.70-1.57)	1.09 (0.71-1.66)
Girls	95 (1.42)	31 (1.66)	0.85 (0.57-1.28)	0.80 (0.53-1.21)

[a] Model adjusted for mother's age (years), father's age (years), family income (in quartile), urbanization level (metropolitan cities, small cities and suburban areas, rural areas), and employment status (unemployed, employed)
[b] Number of events (incidence density rate per 100,000 person-years)

Table 5-S5. Hazard ratios and 95% confidence intervals for the association between acetaminophen prescription (any vs none) during pregnancy and risk of childhood cancer restricted among those without infection nor inflammation during pregnancy Taiwan, 2004 to 2015

	Exposed ID[b]	Unexposed ID[b]	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia	4.00	4.28	1.07 (0.73-1.57)	1.09 (0.73-1.62)
Acute myeloid leukemia	1.08	1.71	1.59 (0.81-3.10)	1.38 (0.68-2.83)
Central nervous system tumors	1.46	2.26	1.55 (0.87-2.76)	1.36 (0.75-2.46)
Germ cell tumors	1.38	1.01	0.73 (0.36-1.49)	0.77 (0.36-1.65)

[a] Model adjusted for mother's age (years), father's age (years), family income (in quartile), urbanization level (metropolitan cities, small cities and suburban areas, rural areas), and employment status (unemployed, employed)
[b] Number of events (incidence density rate per 100,000 person-years)

Table 5-S6. Probabilistic bias analysis estimations and 95% simulation interval for the association between acetaminophen prescription during pregnancy and risk of childhood cancer in Taiwan, 2004-2015

Estimation	Misclassification bias adjusted RR (95% SI)	Selection bias adjusted OR (95% SI)	Confounding adjusted RR (95% SI)	Multiple Bias adjusted RR (95% SI)
ALL, during pregnancy	NA[a]	1.01 (0.68-1.50)	0.88 (0.74-1.04)	NA[a]
ALL, all 3 trimesters	0.88 (0.86-0.89)	0.96 (0.62-1.49)	0.83 (0.65-1.07)	0.80 (0.62-1.02)
CNS tumors, during pregnancy	NA[a]	1.13 (0.73-1.76)	0.98 (0.76-1.26)	NA[a]
CNS tumors, all 3 trimesters	1.21 (1.18-1.24)	1.20 (0.73-1.99)	1.04 (0.74-1.48)	1.10 (0.78-1.53)
Medulloblastoma, during pregnancy	NA[a]	1.79 (0.88-3.65)	1.56 (0.85-2.87)	NA[a]
Medulloblastoma, all 3 trimesters	3.90 (3.16-5.91)	2.49 (1.09-5.69)	2.16 (1.04-4.54)	3.51 (1.66-7.94)
Hepatoblastoma, during pregnancy	NA[a]	1.18 (0.68-2.07)	1.03 (0.67-1.57)	NA[a]
Hepatoblastoma, all 3 trimesters	1.66 (1.57-1.81)	1.49 (0.77-2.91)	1.30 (0.75-2.27)	1.50 (0.90-2.61)
Bone tumors, during pregnancy	NA[a]	1.59 (0.82-3.07)	1.38 (0.79-2.40)	NA[a]
Bone tumors, all 3 trimesters	2.88 (2.49-3.68)	2.11 (0.97-4.58)	1.84 (0.92-3.64)	2.65 (1.21-5.61)

[a] Not available due to negative case counts for the exposed or unexposed groups

RR = relative risk; OR = odds ratio; 95% SI = 95% simulation interval; ALL = acute lymphoblastic leukemia; CNS = central nervous system

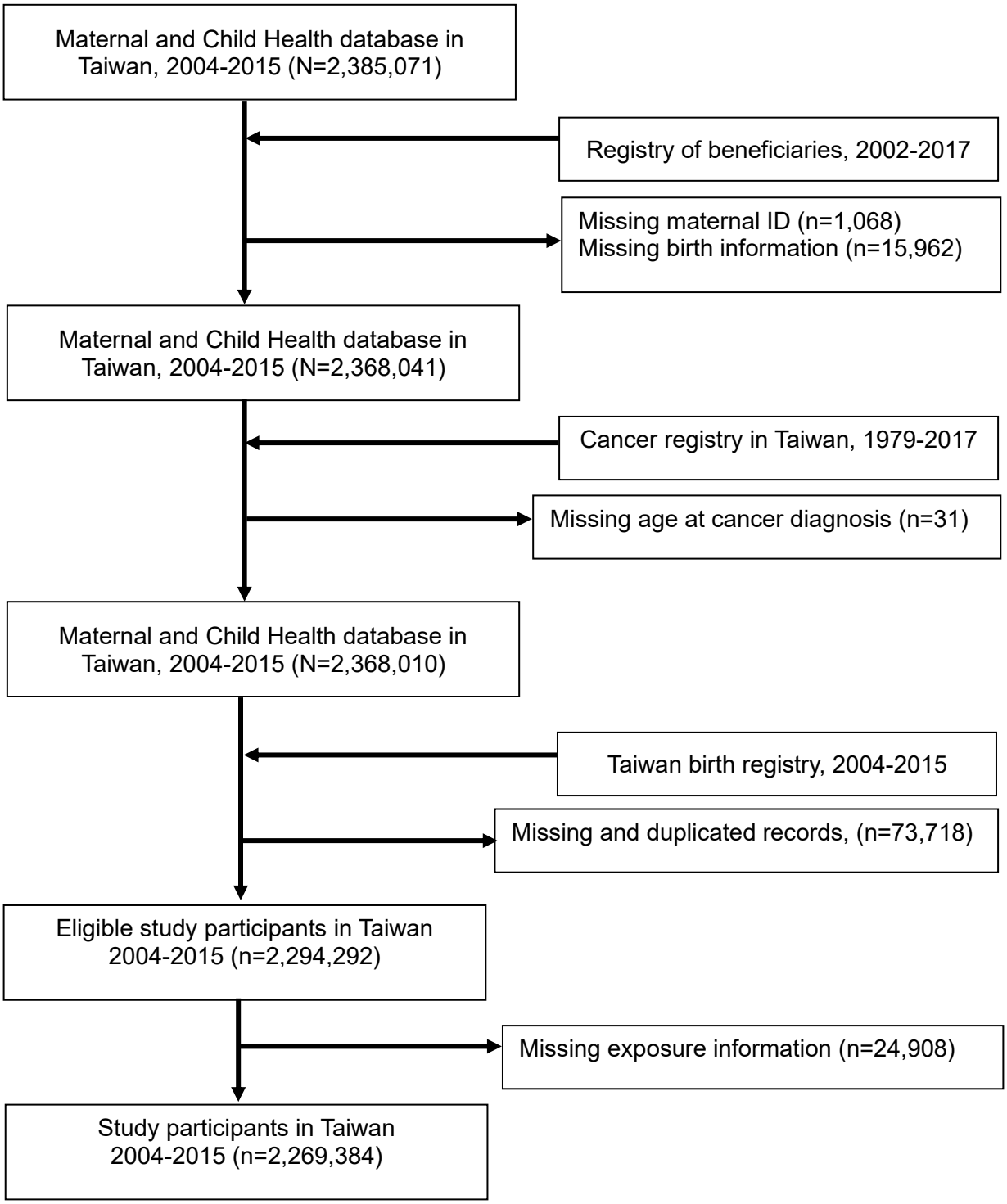

Figure 5-S1. Study participants flow chart in Taiwan 2004 to 2015

6. Public Health Relevance and Expected Contributions

This dissertation aimed to investigate how maternal and child infections and pharmaceutical exposure during pregnancy impact the risk of childhood cancers. Through population-based case-control studies in Denmark and cohort studies in Taiwan, utilizing comprehensive linkage of childhood cancer registries and healthcare information, this research has not only confirmed but also expanded our understanding of the association between childhood cancer and infections occurring during pregnancy and after birth. Additionally, the study sheds light on the importance of examining drug use during pregnancy, especially concerning nitrosatable drugs, antibiotics, and acetaminophen, as they may potentially be linked to specific types of cancer.

In Denmark, the investigation into postnatal infections and childhood cancer risk revealed a correlation between infections occurring after birth and several types of cancer, such as leukemia, lymphoma, nervous system tumors, germ cell tumors, and Wilms' tumor. On the other hand, the research in Taiwan on maternal infections during pregnancy found suggestive associations between infections during pregnancy and specific childhood cancers, including ALL and hepatoblastoma.

The findings from both studies support Greaves' theory of ALL development as a result of multiple factors during two stages: pregnancy and after birth. Furthermore, they highlight the significance of common infections, rather than specific types, in contributing to the development of ALL. The analysis of the association between maternal exposure to antibiotics during pregnancy and childhood leukemia risk underscores the importance of considering other factors that influence the immune response of both the mother and child and their role in cancer development.

Regarding drug exposure, the study in Denmark suggests a potential link between nitrosatable drug exposure during pregnancy and the risk of childhood CNS and neuroblastoma. Similarly, the research in Taiwan indicates a potential association between chronic exposure to

acetaminophen throughout all three trimesters of pregnancy and the risk of hepatoblastoma, bone tumors, and medulloblastoma.

Based on the research findings, several policy recommendations can be proposed. Implementing preventive measures for infections among pregnant women and children is crucial to reduce maternal and child mortality. Moreover, the study emphasizes the need for infection prevention during pregnancy to not only prevent early-life losses but also to reduce the incidence of childhood cancer.

The research also underscores the importance of cautious drug use, particularly with antibiotics and nitrosatable drugs. While some of these drugs may have benefits for pregnant women, specific recommendations can be made to mitigate potential risks of childhood cancer. Regarding acetaminophen, occasional use during pregnancy (defined as 1 prescription only) appeared safe in our study for most cancer types, but further study is required to confirm its safety, not only in preventing childhood cancer but also in avoiding other potential diseases. The study results can serve as valuable information for pharmacovigilance and risk-benefit considerations when prescribing drugs during pregnancy.

While this research significantly contributes to our understanding of infection and drug exposure in childhood cancer risk, several areas for future research should be explored. More epidemiological and pathological studies are needed to explore specific pathological linkages between childhood cancer and infections, such as Epstein Barr virus and lymphoma.

Understanding the specific period of infection exposure is another crucial aspect to explore. This knowledge can lead to more targeted recommendations for infection prevention and control and provide deeper insights into childhood cancer development.

Identifying the dosage of medication is critical in confirming the dose relationship of particular drugs and childhood cancer risk. However, limitations in available pharmacological registry data may present challenges in determining accurate dosages and comparing different

drug classes. Investigating various dosages and exposure periods, particularly in the case of acetaminophen and childhood cancer risk, could be highly beneficial.

Validation studies for exposure are necessary to address potential misclassification biases in medical record data used to identify infection and drug exposure. Some infections may have mild symptoms, leading patients not to seek formal healthcare, and certain infections may only be diagnosed symptomatically. Moreover, over-the-counter drug use during pregnancy may introduce potential misclassification of drug exposure. Validation studies can help identify biases and adjust effect estimations accordingly.

Although this study utilized large population-based registry data, some rare cancer types encountered limitations in statistical power. Nevertheless, the findings from this research can serve as valuable information for future meta-analyses on this subject.

In conclusion, this research significantly adds to our knowledge of the association between childhood cancer and infections and drug exposures during pregnancy. It emphasizes the importance of infection prevention and control among pregnant women and children, as well as the judicious use of antibiotics and nitrosatable drugs. Moreover, the study provides insights into potential risks associated with acetaminophen use during pregnancy. Overall, these findings have significant public health implications, guiding policymakers in implementing preventive measures and making informed decisions about drug use during pregnancy. As we move forward, there remain important areas for further research to deepen our understanding of childhood cancer and its relationship with infections and pharmaceutical exposures.

7. References

1. Abu-Ghosh AM, Toretsky JA. Childhood Cancer. *Encyclopedia of Cancer*. Published online 2008:639-644. doi:10.1007/978-3-540-47648-1_1089
2. World Health Organization. Childhood cancer. Fact sheets. Published 2021. Accessed March 10, 2023. https://www.who.int/news-room/fact-sheets/detail/cancer-in-children
3. National Cancer Institute. NCI Dictionary of Cancer Terms. Definition of childhood cancer. Published 2023. Accessed March 10, 2023. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/childhood-cancer
4. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. *Cancer*. 2005;103(7):1457-1467. doi:10.1002/cncr.20910
5. Marsden HB. The classification of childhood tumours. *IARC Sci Publ*. 1988;(87):9-16.
6. Jemal A, Center MM, Ward E, Thun MJ. Cancer occurrence. *Methods in Molecular Biology*. 2009;471:3-29. doi:10.1007/978-1-59745-416-2_1/FIGURES/8_1
7. Manton KG, Akushevich I, Kravchenko J. U.S. Cancer Morbidity: Modeling Age-Patterns of Cancer Histotypes. Published online 2009:247-311. doi:10.1007/978-0-387-78193-8_7
8. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the total incidence of global childhood cancer: a simulation-based analysis. *Lancet Oncol*. 2019;20(4):483-493. doi:10.1016/S1470-2045(18)30909-4
9. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol*. 2017;18(6):719-731. doi:10.1016/S1470-2045(17)30186-9
10. Grabas MR, Kjaer SK, Frederiksen MH, et al. Incidence and time trends of childhood cancer in Denmark, 1943–2014. *Acta Oncol (Madr)*. 2020;59(5):588-595. doi:10.1080/0284186X.2020.1725239

11. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660

12. Hung GY, Horng JL, Lee YS, Yen HJ, Chen CC, Lee CY. Cancer incidence patterns among children and adolescents in Taiwan from 1995 to 2009: A population-based study. *Cancer*. 2014;120(22):3545-3553. doi:10.1002/cncr.28903

13. Pineros M, Mery L, Soerjomataram I, Bray F, Steliarova-Foucher E. Scaling up the surveillance of childhood cancer: A global roadmap. *J Natl Cancer Inst*. 2021;113(1):9. doi:10.1093/JNCI/DJAA069

14. Surveillance Epidemiology and End Results Program. SEER Cancer Stat Facts. Childhood Cancer. Published 2022. Accessed March 2, 2023. https://seer.cancer.gov/statfacts/

15. Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990-2001: incidence and survival. *Int J Cancer*. 2008;122(11):2607-2611. doi:10.1002/IJC.23428

16. Boschmonar MG, Alvarez YG, García AM, Soto TN, Roger MC, Garrote LF. Childhood cancer survival in Cuba. *Eur J Epidemiol*. 2000;16(8):763-767. doi:10.1023/A:1026793615987

17. Wiangnon S, Jetsrisuparb A, Komvilaisak P, Suwanrungruang K. Childhood cancer incidence and survival 1985-2009, Khon Kaen, Thailand. *Asian Pacific Journal of Cancer Prevention*. 2014;15(18):7989-7993. doi:10.7314/APJCP.2014.15.18.7989

18. Bao P ping, Zheng Y, Wu C xiao, et al. Population-based survival for childhood cancer patients diagnosed during 2002-2005 in Shanghai, China. *Pediatr Blood Cancer*. 2012;59(4):657-661. doi:10.1002/PBC.24043

19. Russell KB, Patton M, Tromburg C, et al. Psychosocial risk, symptom burden, and concerns in families affected by childhood cancer. *Supportive Care in Cancer*. 2022;30(3):2283-2292. doi:10.1007/s00520-021-06646-3

20. Bekui BAA, Ohene LA, Badzi C, Ampomah MO, Aziato L. Physical and socioeconomic burden of caregiving on family caregivers of children with cancer at a tertiary Hospital in Ghana. *Nurs Open*. 2023;10(2):915-925. doi:10.1002/nop2.1359

21. Rod NH, Bengtsson J, Elsenburg LK, et al. Cancer burden among adolescents and young adults in relation to childhood adversity: a nationwide life-course cohort study of 1.2 million individuals. *The Lancet regional health Europe*. 2023;27:100588. doi:10.1016/j.lanepe.2023.100588

22. Wang J, Coyte PC, Shao D, et al. The Relationship between the Unmet Needs of Chinese Family Caregivers and the Quality of Life of Childhood Cancer Patients Undergoing Inpatient Treatment: A Mediation Model through Caregiver Depression. *Int J Environ Res Public Health*. 2022;19(16). doi:10.3390/ijerph191610193

23. Borrescio-Higa F, Valdés N. The Psychosocial Burden of Families with Childhood Blood Cancer. *Int J Environ Res Public Health*. 2022;19(1). doi:10.3390/ijerph19010599

24. Rahman S, Variyath S, Al-Yateem N, al Marzouqi A, Subu M. Economic and Social Burden of Childhood Cancer in Bangladesh. *Asian Pacific Journal of Cancer Prevention*. 2023;24(1):69-74. doi:10.31557/apjcp.2023.24.1.69

25. International Agency for Research on Cancer. *Epidemiology of Childhood Cancer*. (Little J, ed.). International Agency for Research on Cancer; 1999. https://publications.iarc.fr/_publications/media/download/3588/e1502995a3a0e71e8427f4f2f51a445bf60ddf9d.pdf

26. Draper GJ, Sanders BM, Brownbill PA, Hawkins MM, Draper GJ. Patterns of risk of hereditary retinoblastoma and applications to genetic counselling. *Br J Cancer*. 1992;66(1):211-219. doi:10.1038/BJC.1992.244

27. Madanat-Harjuoja LM, Pitkäniemi J, Hirvonen E, Malila N, Diller LR. Linking population-based registries to identify familial cancer risk in childhood cancer. *Cancer*. 2020;126(13):3076-3083. doi:10.1002/CNCR.32882

28. Ritenour LE, Randall MP, Bosse KR, Diskin SJ. Genetic susceptibility to neuroblastoma: current knowledge and future directions. *Cell Tissue Res*. 2018;372(2):287-307. doi:10.1007/S00441-018-2820-3

29. Nakano Y, Rabinowicz R, Malkin D. Genetic predisposition to cancers in children and adolescents. *Curr Opin Pediatr*. 2023;35(1):55-62. doi:10.1097/MOP.0000000000001197

30. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. *Pediatr Clin North Am*. 2015;62(1):11-25. doi:10.1016/J.PCL.2014.09.013

31. Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukemia. *Leukemia*. 1988;2(2):120-125. http://www.ncbi.nlm.nih.gov/pubmed/3278171

32. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet*. 1988;2(8624):1323-1327. doi:10.1016/s0140-6736(88)90867-7

33. Hwee J, Tait C, Sung L, Kwong JC, Sutradhar R, Pole JD. A systematic review and meta-analysis of the association between childhood infections and the risk of childhood acute lymphoblastic leukaemia. *Nature Publishing Group*. 2017;118. doi:10.1038/bjc.2017.360

34. He JR, Ramakrishnan R, Hirst JE, et al. Maternal Infection in Pregnancy and Childhood Leukemia: A Systematic Review and Meta-analysis. *J Pediatr*. 2020;217(8):98-109.e8. doi:10.1016/j.jpeds.2019.10.046

35. He JR, Yu Y, Fang F, et al. Evaluation of Maternal Infection During Pregnancy and Childhood Leukemia Among Offspring in Denmark. *JAMA Netw Open*. 2023;6(2):e230133-e230133. doi:10.1001/JAMANETWORKOPEN.2023.0133

36. He JR, Hirst JE, Tikellis G, et al. Common maternal infections during pregnancy and childhood leukaemia in the offspring: findings from six international birth cohorts. *Int J Epidemiol*. 2022;51(3):769-777. doi:10.1093/ije/dyab199

37. Heck JE, Wu CK, Huang X, et al. Cohort study of familial viral hepatitis and risks of paediatric cancers. *Int J Epidemiol*. 2022;51(2):448. doi:10.1093/IJE/DYAB262

38. Birch JM, Hartley AL, Teare MD, et al. The inter-regional epidemiological study of childhood cancer (IRESCC): case-control study of children with central nervous system tumours. *Br J Neurosurg*. 1990;4(1):17-25. doi:10.3109/02688699009000677

39. Linos A, Kardara M, Kosmidis H, et al. Reported influenza in pregnancy and childhood tumour. *Eur J Epidemiol*. 1998;14(5):471-475. doi:10.1023/A:1007437200858

40. Nyari TA, Dickinson HO, Parker L. Childhood cancer in relation to infections in the community during pregnancy and around the time of birth. *Int J Cancer*. 2003;104(6):772-777. doi:10.1002/IJC.11030

41. Menegaux F, Olshan AF, Neglia JP, Pollock BH, Bondy ML. Day care, childhood infections, and risk of neuroblastoma. *Am J Epidemiol*. 2004;159(9):843-851. doi:10.1093/AJE/KWH111

42. Lin JN, Lin CL, Lin MC, et al. Risk of leukaemia in children infected with enterovirus: A nationwide, retrospective, population-based, Taiwanese-registry, cohort study. *Lancet Oncol*. 2015;16(13):1335-1343. doi:10.1016/S1470-2045(15)00060-1

43. Bonaventure A, Simpson J, Ansell P, Roman E, Lightfoot T. Prescription drug use during pregnancy and risk of childhood cancer - is there an association? *Cancer Epidemiol*. 2015;39(1):73-78. doi:10.1016/J.CANEP.2014.10.008

44. Kaatsch P, Scheidemann-Wesp U, Schüz J. Maternal use of antibiotics and cancer in the offspring: results of a case-control study in Germany. *Cancer Causes Control*. 2010;21(8):1335-1345. doi:10.1007/S10552-010-9561-2

45. Schüz J, Weihkopf T, Kaatsch P. Medication use during pregnancy and the risk of childhood cancer in the offspring. *Eur J Pediatr*. 2007;166(5):433-441. doi:10.1007/S00431-006-0401-Z

46. Kwan ML, Metayer C, Crouse V, Buffler PA. Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring. *Am J Epidemiol*. 2007;165(1):27-35. doi:10.1093/AJE/KWJ336

47. Momen NC, Olsen J, Gissler M, Kieler H, Haglund B, Li J. Exposure to systemic antibacterial medications during pregnancy and risk of childhood cancer. *Pharmacoepidemiol Drug Saf*. 2015;24(8):821-829. doi:10.1002/PDS.3806

48. Momen NC, Munk-Olsen T, Li J, et al. Antidepressant use during pregnancy and childhood cancer in the offspring. *Pharmacoepidemiol Drug Saf*. 2018;27(1):114-118. doi:10.1002/PDS.4352

49. Hoeke H, Roeder S, Bertsche T, Borte M, von Bergen M, Wissenbach DK. Assessment of maternal drug intake by urinary bio monitoring during pregnancy and postpartally until the third perinatal year. *Pharmacoepidemiol Drug Saf*. 2016;25(4):431-437. doi:10.1002/PDS.3943

50. Choi EY, Jeong HE, Noh Y, et al. Neonatal and maternal adverse outcomes and exposure to nonsteroidal anti-inflammatory drugs during early pregnancy in South Korea: A nationwide cohort study. Thorley J, ed. *PLoS Med*. 2023;20(2):e1004183. doi:10.1371/JOURNAL.PMED.1004183

51. Allegaert K, van den Anker JN. Perinatal and neonatal use of paracetamol for pain relief. *Semin Fetal Neonatal Med*. 2017;22(5):308-313. doi:10.1016/J.SINY.2017.07.006

52. Black E, Khor KE, Kennedy D, et al. Medication Use and Pain Management in Pregnancy: A Critical Review. *Pain Pract*. 2019;19(8):875-899. doi:10.1111/PAPR.12814

53. Lupattelli A, Picinardi M, Cantarutti A, Nordeng H. Use and Intentional Avoidance of Prescribed Medications in Pregnancy: A Cross-Sectional, Web-Based Study among 926 Women in Italy. *Int J Environ Res Public Health*. 2020;17(11). doi:10.3390/IJERPH17113830

54. Cantarutti A, Rea F, Franchi M, Beccalli B, Locatelli A, Corrao G. Use of Antibiotic Treatment in Pregnancy and the Risk of Several Neonatal Outcomes: A Population-Based Study. *Int J Environ Res Public Health*. 2021;18(23). doi:10.3390/IJERPH182312621

55. McKean-Cowdin R, Pogoda JM, Lijinsky W, Holly EA, Mueller BA, Preston-Martin S. Maternal prenatal exposure to nitrosatable drugs and childhood brain tumours. *Int J Epidemiol*. 2003;32(2):211-217. doi:10.1093/ije/dyg050

56. Carozza SE, Olshan AF, Faustman EM, et al. Maternal exposure to N-nitrosatable drugs as a risk factor for childhood brain tumours. *Int J Epidemiol*. 1995;24(2):308-312. doi:10.1093/ije/24.2.308

57. Couto AC, Ferreira JD, Pombo-De-Oliveira MS, Koifman S. Pregnancy, maternal exposure to analgesic medicines, and leukemia in Brazilian children below 2 years of age. *Eur J Cancer Prev*. 2015;24(3):245-252. doi:10.1097/CEJ.0000000000000070

58. Wiemels JL, Talbäck M, Francis S, Feychting M. Early Infection with Cytomegalovirus and Risk of Childhood Hematologic Malignancies. *Cancer Epidemiol Biomarkers Prev*. 2019;28(6):1024-1027. doi:10.1158/1055-9965.EPI-19-0044

59. Gallant RE, Arroyo K, Metayer C, Kang AY, de Smith AJ, Wiemels JL. Associations between early-life and in utero infections and cytomegalovirus-positive acute lymphoblastic leukemia in children. *Int J Cancer*. 2023;152(5):845-853. doi:10.1002/IJC.34292

60. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat Rev Cancer*. 2018;18(8):471-484. doi:10.1038/S41568-018-0015-6

61. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer*. 2006;6(3):193-203. doi:10.1038/nrc1816

62. Pombo-de-Oliveira MS, EMiLI Study Group, Petridou ET, et al. The Interplay of Cesarean-Section Delivery and First-Birth Order as Risk Factors in Acute Lymphoblastic Leukemia. *Cancer Epidemiol Biomarkers Prev*. 2023;32(3):371-379. doi:10.1158/1055-9965.EPI-22-0664

63. Fear NT, Roman E, Ansell P, Bull D. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). *Cancer Causes Control*. 2001;12(5):443-449. doi:10.1023/A:1011201524589

64. Linet MS, Gridley G, Cnattingius S, et al. Maternal and perinatal risk factors for childhood brain tumors (Sweden). *Cancer Causes Control*. 1996;7(4):437-448. doi:10.1007/BF00052670

65. Bunin G. What Causes Childhood Brain Tumors? Limited Knowledge, Many Clues. *Pediatr Neurosurg*. 2000;32(6):321-326. doi:10.1159/000028961

66. Bunin GR, Kramer S, Marrero O, Meadows AT. Gestational risk factors for Wilms' tumor: results of a case-control study. *Cancer Res*. 1987;47(11):2972-2977. http://www.ncbi.nlm.nih.gov/pubmed/3032418

67. Chang JS, Tsai CR, Tsai YW, Wiemels JL. Medically diagnosed infections and risk of childhood leukaemia: A population-based case-control study. *Int J Epidemiol*. 2012;41(4):1050-1059. doi:10.1093/ije/dys113

68. Silva JD, Perel Y, Mé Chinaud F, et al. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. *Br J Cancer*. 2004;90:139-145. doi:10.1038/sj.bjc.6601384

69. McKinney PA, Cartwright RA, Saiu JM, et al. The inter-regional epidemiological study of childhood cancer (IRESCC): a case control study of aetiological factors in leukaemia and lymphoma. *Arch Dis Child*. 1987;62(3):279-287. doi:10.1136/adc.62.3.279

70. Shu XO, Linet MS, Gao RN, et al. Chloramphenicol Use and Childhood Leukaemia in Shanghai. *The Lancet*. 1987;330(8565):934-937. doi:10.1016/S0140-6736(87)91420-6

71. National Toxicology Program. Report on Carcinogens Monograph on Epstein-Barr Virus: RoC Monograph 07 [Internet]. *Report on Carcinogens Monograph on Epstein-Barr Virus*. Published online April 20, 2016. doi:10.22427/ROC-MGRAPH-07

72. de-Thé G. Epstein-Barr virus and Burkitt's lymphoma worldwide: the causal relationship revisited. *IARC Sci Publ*. 1985;(60):165-176. http://www.ncbi.nlm.nih.gov/pubmed/2998987

73. Purtilo DT, Manolov G, Manolova Y, Harada S, Lipscomb H, Tatsumi E. Role of Epstein-Barr virus in the etiology of Burkitt's lymphoma. *IARC Sci Publ*. 1985;(60):231-247.

74. Hjalgrim H, Søegaard SH, Hjalgrim LL, Rostgaard K. Childhood use of antimicrobials and risk of Hodgkin lymphoma: A Danish register-based cohort study. *Blood Adv*. 2019;3(9):1489-1492. doi:10.1182/bloodadvances.2018029355

75. Parodi S, Seniori Costantini A, Crosignani P, et al. Childhood infectious diseases and risk of non-Hodgkin's lymphoma according to the WHO classification: A reanalysis of the Italian multicenter case–control study. *Int J Cancer*. 2020;146(4):977-986. doi:10.1002/ijc.32393

76. Shaw AK, Li P, Infante-Rivard C. Early infection and risk of childhood brain tumors (Canada). *Cancer Causes Control*. 2006;17(10):1267-1274. doi:10.1007/s10552-006-0066-y

77. Harding NJ, Birch JM, Hepworth SJ, McKinney PA. Infectious exposure in the first year of life and risk of central nervous system tumors in children: analysis of day care, social contact, and overcrowding. *Cancer Causes Control*. 2009;20(2):129-136. doi:10.1007/s10552-008-9224-8

78. Schmidt LS, Kamper-Jørgensen M, Schmiegelow K, et al. Infectious exposure in the first years of life and risk of central nervous system tumours in children: analysis of birth order, childcare attendance and seasonality of birth. *Br J Cancer*. 2010;102:1670-1675. doi:10.1038/sj.bjc.6605679

79. Lupatsch JE, Bailey HD, Lacour B, et al. Childhood brain tumours, early infections and immune stimulation: A pooled analysis of the ESCALE and ESTELLE case-control

studies (SFCE, France). *Cancer Epidemiol*. 2018;52:1-9. doi:10.1016/j.canep.2017.10.015

80. Shu XO, Nesbit ME, Buckley JD, Krailo MD, Robinson LL. An exploratory analysis of risk factors for childhood malignant germ-cell tumors: report from the Childrens Cancer Group (Canada, United States). *Cancer Causes Control*. 1995;6(3):187-198. doi:10.1007/BF00051790

81. International Agency for Research on Cancer. Relevance of N-nitroso compounds to human cancer: exposures and mechanisms. Proceedings of the IXth International Symposium on N-Nitroso Compounds. Baden, Austria, 1-5 September 1986. *IARC Sci Publ*. 1987;(84):1-663.

82. Bartsch H. N-nitroso compounds and human cancer: where do we stand? *IARC Sci Publ*. 1991;(105):1-10.

83. Jakszyn P, Bingham S, Pera G, et al. Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study. *Carcinogenesis*. 2006;27(7):1497-1501. doi:10.1093/carcin/bgl019

84. Tricker AR. N-nitroso compounds and man: sources of exposure, endogenous formation and occurrence in body fluids. *Eur J Cancer Prev*. 1997;6(3):226-268.

85. Brambilla G, Martelli A. Genotoxic and carcinogenic risk to humans of drug-nitrite interaction products. *Mutat Res Rev Mutat Res*. 2007;635(1):17-52. doi:10.1016/j.mrrev.2006.09.003

86. Thomsen AML, Liew Z, Riis AH, et al. Nitrosatable drug exposure during pregnancy and risk of stillbirth. *Pharmacoepidemiol Drug Saf*. 2019;28(9):1204-1210. doi:10.1002/pds.4867

87. Maekawa A, Ishiwata H, Odashima S. Transplacental carcinogenesis and chemical determination of 1-butyl-1-nitrosourea in stomach content after simultaneous oral administration of 1-butylurea and sodium nitrite to ACI/N rats. *Gan*. 1977;68(1):81-87.

88. Börzsönyi M, Pintér A, Surján A, Farkas I. Transplacental induction of lymphomas in Swiss mice by carbendazim and sodium nitrite. *Int J Cancer*. 1976;17(6):742-747. doi:10.1002/ijc.2910170609

89. Fox RR, Meier H, Bedigian HG, Crary DD. Genetics of transplacentally induced teratogenic and carcinogenic effects in rabbits treated with N-nitroso-N-ethylurea. *J Natl Cancer Inst*. 1982;69(6):1411-1417.

90. Anderson LM, Hagiwara A, Kovatch RM, Rehm S, Rice JM. Transplacental initiation of liver, lung, neurogenic, and connective tissue tumors by N-nitroso compounds in mice. *Fundam Appl Toxicol*. 1989;12(3):604-620. doi:10.1016/0272-0590(89)90033-x

91. Capilla-Gonzalez V, Gil-Perotin S, Garcia-Verdugo JM. Postnatal exposure to N-ethyl-N-nitrosurea disrupts the subventricular zone in adult rodents. *European Journal of Neuroscience*. 2010;32(11):1789-1799. doi:10.1111/j.1460-9568.2010.07450.x

92. Kiriyama Y, Tani A, Kadoya M, Okamoto R, Nochi H. Induction of PD-L1 by Nitric Oxide via JNK Activation in A172 Glioblastoma Cells. *Biol Pharm Bull*. 2020;43(6):1020-1022. doi:10.1248/BPB.B20-00087

93. Osaka M, Tsuruyama T, Koami K, Matsuo S, Sugiyama T. ras and p53 genes are infrequently involved in N-nitroso-N-butylurea (NBU)-induced rat leukemia. *Cancer Lett*. 1998;124(2):199-204. doi:10.1016/S0304-3835(97)00491-6

94. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC monographs on the evaluation of carcinogenic risks to humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. *IARC Monogr Eval Carcinog Risks Hum*. 2010;94:v-vii, 1-412.

95. Essien EE, Said Abasse K, Côté A, et al. Drinking-water nitrate and cancer risk: A systematic review and meta-analysis. *Arch Environ Occup Health*. Published online November 3, 2020:1-17. doi:10.1080/19338244.2020.1842313

96. Barry KH, Jones RR, Cantor KP, et al. Ingested Nitrate and Nitrite and Bladder Cancer in Northern New England. *Epidemiology*. 2020;31(1):136-144. doi:10.1097/EDE.0000000000001112

97. Giles GG, McNeil JJ, Donnan G, et al. Dietary factors and the risk of glioma in adults: results of a case-control study in Melbourne, Australia. *Int J Cancer*. 1994;59(3):357-362. doi:10.1002/ijc.2910590311

98. van Loon AJ, Botterweck AA, Goldbohm RA, Brants HA, van Klaveren JD, van den Brandt PA. Intake of nitrate and nitrite and the risk of gastric cancer: a prospective cohort study. *Br J Cancer*. 1998;78(1):129-135. doi:10.1038/bjc.1998.454

99. Weyer PJ, Cerhan JR, Kross BC, et al. Municipal drinking water nitrate level and cancer risk in older women: the Iowa Women's Health Study. *Epidemiology*. 2001;12(3):327-338. doi:10.1097/00001648-200105000-00013

100. Knekt P, Järvinen R, Dich J, Hakulinen T. Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. *Int J Cancer*. 1999;80(6):852-856. doi:10.1002/(sici)1097-0215(19990315)80:6<852::aid-ijc9>3.0.co;2-s

101. Stayner LT, Schullehner J, Semark BD, et al. Exposure to nitrate from drinking water and the risk of childhood cancer in Denmark. *Environ Int*. 2021;155:106613. doi:10.1016/j.envint.2021.106613

102. Mueller BA, Searles Nielsen S, Preston-Martin S, et al. Household water source and the risk of childhood brain tumours: results of the SEARCH International Brain Tumor Study. *Int J Epidemiol*. 2004;33(6):1209-1216. doi:10.1093/ije/dyh215

103. Kaplan S, Novikov I, Modan B. Nutritional factors in the etiology of brain tumors: potential role of nitrosamines, fat, and cholesterol. *Am J Epidemiol*. 1997;146(10):832-841. doi:10.1093/oxfordjournals.aje.a009201

104. Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology*. 23(1-2):78-84. doi:10.1159/000073979

105. Cook MN, Olshan AF, Guess HA, et al. Maternal medication use and neuroblastoma in offspring. *Am J Epidemiol*. 2004;159(8):721-731. doi:10.1093/aje/kwh108

106. Preston-Martin S, Yu MC, Benton B, Henderson BE. N-Nitroso compounds and childhood brain tumors: a case-control study. *Cancer Res*. 1982;42(12):5240-5245. http://www.ncbi.nlm.nih.gov/pubmed/7139628

107. Food and Drug Administration. FDA has reviewed possible risks of pain medicine use during pregnancy. FDA Drug Safety Communication. Published 2015. Accessed March 4, 2023. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-has-reviewed-possible-risks-pain-medicine-use-during-pregnancy

108. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The american headache society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20. doi:10.1111/head.12499

109. Lau CI, Wang YF, Treatment Guideline Subcommittee of the Taiwan Headache Society. 2022 Taiwan Guidelines for Acute Treatment of Migraine. *Acta Neurol Taiwan*. 2022;31(2):89-113.

110. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open*. 2014;4(2):4365. doi:10.1136/BMJOPEN-2013-004365

111. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol*. 2005;193(3):771-777. doi:10.1016/J.AJOG.2005.02.100

112. Chen MH, Pan TL, Wang PW, et al. Prenatal Exposure to Acetaminophen and the Risk of Attention-Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan. *J Clin Psychiatry*. 2019;80(5):15264. doi:10.4088/JCP.18M12612

113. Li CY, Dai YX, Chang YT, et al. Prenatal exposure to acetaminophen increases the risk of atopic dermatitis in children: A nationwide nested case-control study in Taiwan. *Pediatric Allergy and Immunology*. 2021;32(5):1080-1088. doi:10.1111/PAI.13465

114. McCrae JC, Morrison EE, MacIntyre IM, Dear JW, Webb DJ. Long-term adverse effects of paracetamol – a review. *Br J Clin Pharmacol*. 2018;84(10):2218. doi:10.1111/BCP.13656

115. Stanley AY, Durham CO, Sterrett JJ, Wallace JB. Safety of Over-the-Counter Medications in Pregnancy. *MCN The American Journal of Maternal/Child Nursing*. 2019;44(4):196-205. doi:10.1097/NMC.0000000000000537

116. Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. *Brain Sciences 2018, Vol 8, Page 127*. 2018;8(7):127. doi:10.3390/BRAINSCI8070127

117. Petersen TG, Liew Z, Andersen AMN, et al. Use of paracetamol, ibuprofen or aspirin in pregnancy and risk of cerebral palsy in the child. *Int J Epidemiol*. 2018;47(1):121-130. doi:10.1093/ije/dyx235

118. Nitsche JF, Patil AS, Langman LJ, et al. Transplacental Passage of Acetaminophen in Term Pregnancy. *Am J Perinatol*. 2017;34(6):541-543. doi:10.1055/S-0036-1593845

119. Chen JH, Lin IH, Sun CK, et al. Transplacental transfer of acetaminophen in pregnant rats. *Biomed Pharmacother*. 2022;154. doi:10.1016/J.BIOPHA.2022.113613

120. Conings S, Tseke F, van den Broeck A, et al. Transplacental transport of paracetamol and its phase II metabolites using the ex vivo placenta perfusion model. *Toxicol Appl Pharmacol*. 2019;370:14-23. doi:10.1016/J.TAAP.2019.03.004

121. Mian P, Allegaert K, Conings S, et al. Integration of Placental Transfer in a Fetal-Maternal Physiologically Based Pharmacokinetic Model to Characterize Acetaminophen Exposure and Metabolic Clearance in the Fetus. *Clin Pharmacokinet*. 2020;59(7):911-925. doi:10.1007/S40262-020-00861-7

122. Rollins DE, Von Bahr C, Glaumann H, Moldéus P, Rane A. Acetaminophen: potentially toxic metabolite formed by human fetal and adult liver microsomes and isolated fetal liver cells. *Science*. 1979;205(4413):1414-1416. doi:10.1126/SCIENCE.38505

123. Du K, Ramachandran A, Jaeschke H. Oxidative stress during acetaminophen hepatotoxicity: Sources, pathophysiological role and therapeutic potential. *Redox Biol*. 2016;10:148-156. doi:10.1016/J.REDOX.2016.10.001

124. Ghanizadeh A. Acetaminophen may mediate oxidative stress and neurotoxicity in autism. *Med Hypotheses*. 2012;78(2):351. doi:10.1016/J.MEHY.2011.11.009

125. Parker W, Hornik CD, Bilbo S, et al. The role of oxidative stress, inflammation and acetaminophen exposure from birth to early childhood in the induction of autism. *Journal of International Medical Research*. 2017;45(2):407-438. doi:10.1177/0300060517693423/ASSET/IMAGES/LARGE/10.1177_0300060517693423-FIG2.JPEG

126. Albert O, Desdoits-Lethimonier C, Lesné L, et al. Paracetamol, aspirin and indomethacin display endocrine disrupting properties in the adult human testis in vitro. *Human Reproduction*. 2013;28(7):1890-1898. doi:10.1093/HUMREP/DET112

127. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH. Prenatal paracetamol exposure and child neurodevelopment: A review. *Horm Behav*. 2018;101:125-147. doi:10.1016/J.YHBEH.2018.01.003

128. Kristensen DM, Mazaud-Guittot S, Gaudriault P, et al. Analgesic use — prevalence, biomonitoring and endocrine and reproductive effects. *Nature Reviews Endocrinology 2016 12:7*. 2016;12(7):381-393. doi:10.1038/nrendo.2016.55

129. Rannug U, Holme JA, Hongslo JK, Srám R. International Commission for Protection against Environmental Mutagens and Carcinogens. An evaluation of the genetic toxicity of paracetamol. *Mutat Res*. 1995;327(1-2):179-200. doi:10.1016/0027-5107(94)00184-7

130. Bender RP, Lindsey RH, Burden DA, Osheroff N. N-acetyl-p-benzoquinone imine, the toxic metabolite of acetaminophen, is a topoisomerase II poison. *Biochemistry*. 2004;43(12):3731-3739. doi:10.1021/BI036107R

131. Murray FJ, Monnot AD, Jacobson-Kram D, et al. A critical review of the acetaminophen preclinical carcinogenicity and tumor promotion data and their implications for its carcinogenic hazard potential. *Regulatory Toxicology and Pharmacology*. 2020;118:104801. doi:10.1016/J.YRTPH.2020.104801

132. Sirois JE. Comprehensive investigation evaluating the carcinogenic hazard potential of acetaminophen. *Regulatory Toxicology and Pharmacology*. 2021;123:104944. doi:10.1016/J.YRTPH.2021.104944

133. Weinstein R, Parikh-Das AM, Salonga R, et al. A systematic assessment of the epidemiologic literature regarding an association between acetaminophen exposure and cancer. *Regulatory Toxicology and Pharmacology*. 2021;127:105043. doi:10.1016/J.YRTPH.2021.105043

134. Prego-Domínguez J, Takkouche B. Paracetamol Intake and Hematologic Malignancies: A Meta-Analysis of Observational Studies. *J Clin Med*. 2021;10(11). doi:10.3390/JCM10112429

135. Weiss NS. Use of acetaminophen in relation to the occurrence of cancer: a review of epidemiologic studies. *Cancer Causes and Control*. 2016;27(12):1411-1418. doi:10.1007/S10552-016-0818-2/METRICS

136. Stålberg K, Haglund B, Strömberg B, Kieler H. Prenatal exposure to medicines and the risk of childhood brain tumor. *Cancer Epidemiol*. 2010;34(4):400-404. doi:10.1016/J.CANEP.2010.04.018

137. Robinson HB, Bolande RP. Case 3 Fetal Hepatoblastoma with Placental Metastases. *http://dx.doi.org/103109/15513818509025915*. 2009;4(1-2):163-167. doi:10.3109/15513818509025915

138. Hartley AL, Birch JM, Kelsey AM, Jones PHM, Harris M, Blair V. Epidemiological and familial aspects of hepatoblastoma. *Med Pediatr Oncol*. 1990;18(2):103-109. doi:10.1002/MPO.2950180204

139. Satgé D, Sasco AJ, Little J. Antenatal therapeutic drug exposure and fetal/neonatal tumours: review of 89 cases. *Paediatr Perinat Epidemiol*. 1998;12(1):84-117. doi:10.1111/J.1365-3016.1998.00080.X

140. Musselman JRB, Georgieff MK, Ross JA, et al. Maternal pregnancy events and exposures and risk of hepatoblastoma: A Children's Oncology Group (COG) study. *Cancer Epidemiol*. 2013;37(3):318-320. doi:10.1016/J.CANEP.2012.12.005

141. Sirirungreung A, Hansen J, Ritz B, Heck JE. Association between medically diagnosed postnatal infection and childhood cancers: A matched case-control study in Denmark, 1978 to 2016. *Int J Cancer*. Published online May 27, 2023. doi:10.1002/ijc.34604

142. Chang JS, Tsai CR, Tsai YW, Wiemels JL. Medically diagnosed infections and risk of childhood leukaemia: A population-based case-control study. *Int J Epidemiol*. 2012;41(4):1050-1059. doi:10.1093/ije/dys113

143. Parodi S, Seniori Costantini A, Crosignani P, et al. Childhood infectious diseases and risk of non-Hodgkin's lymphoma according to the WHO classification: A reanalysis of the Italian multicenter case–control study. *Int J Cancer*. 2020;146(4):977-986. doi:10.1002/ijc.32393

144. Heck JE, Wu CK, Huang X, et al. Cohort study of familial viral hepatitis and risks of paediatric cancers. *Int J Epidemiol*. 2022;51(2):448-457. doi:10.1093/IJE/DYAB262

145. Linet MS, Gridley G, Cnattingius S, et al. *Maternal and Perinatal Risk Factors for Childhood Brain Tumors (Sweden)*. Vol 7.; 1996.

146. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National patient registry: A review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

147. Contreras ZA, Hansen J, Ritz B, Olsen J, Yu F, Heck JE. Parental age and childhood cancer risk: A Danish population-based registry study. *Cancer Epidemiol*. 2017;49(5):202-215. doi:10.1016/j.canep.2017.06.010

148. Birch JM, Marsden HB. A classification scheme for childhood cancer. *Int J Cancer*. 1987;40(5):620-624. doi:10.1002/ijc.2910400508

149. Mezei G, Sudan M, Izraeli S, Kheifets L. Epidemiology of childhood leukemia in the presence and absence of Down syndrome. *Cancer Epidemiol*. 2014;38(5):479-489. doi:10.1016/j.canep.2014.07.006

150. Tamim H, Monfared AAT, LeLorier J. Application of lag-time into exposure definitions to control for protopathic bias. *Pharmacoepidemiol Drug Saf*. 2007;16(3):250-258. http://www.ncbi.nlm.nih.gov/pubmed/17245804

151. Saha V, Love S, Eden T, Micallef-Eynaud P, MacKinlay G. Determinants of symptom interval in childhood cancer. *Arch Dis Child*. 1993;68(6):771-774. doi:10.1136/adc.68.6.771

152. Atladóttir HO, Thorsen P, Østergaard L, et al. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *J Autism Dev Disord*. 2010;40(12):1423-1430. doi:10.1007/s10803-010-1006-y

153. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol*. 2019;34(3):211-219. doi:10.1007/s10654-019-00494-6

154. Von Behren J, Spector LG, Mueller BA, et al. Birth order and risk of childhood cancer: A pooled analysis from five US States. *Int J Cancer*. 2011;128(11):2709-2716. doi:10.1002/ijc.25593

155. Schüz J, Luta G, Erdmann F, et al. Birth order and risk of childhood cancer in the Danish birth cohort of 1973–2010. *Cancer Causes and Control*. 2015;26(11):1575-1582. doi:10.1007/s10552-015-0651-z

156. Lupatsch JE, Kreis C, Konstantinoudis G, Ansari M, Kuehni CE, Spycher BD. Birth characteristics and childhood leukemia in Switzerland: a register-based case-control study. *Cancer Causes Control*. 2021;32(7):713-723. doi:10.1007/s10552-021-01423-3

157. Puumala SE, Carozza SE, Chow EJ, et al. Childhood Cancer among Twins and Higher Order Multiples. *Cancer Epidemiol Biomarkers Prev*. 2009;18(1):162-170. doi:10.1158/1055-9965.EPI-08-0660

158. Kinlen LJ. An examination, with a meta-analysis, of studies of childhood leukaemia in relation to population mixing. *Br J Cancer*. 2012;107:1163-1168. doi:10.1038/bjc.2012.402

159. Greenland S, Schwartzbaum JA, Finkle WD. Problems due to small samples and sparse data in conditional logistic regression analysis. *Am J Epidemiol*. 2000;151(5):531-539. doi:10.1093/oxfordjournals.aje.a010240

160. Momen NC, Olsen J, Gissler M, Li J. Exposure to maternal smoking during pregnancy and risk of childhood cancer: a study using the Danish national registers. *Cancer Causes and Control*. 2016;27(3):341-349. doi:10.1007/s10552-015-0707-0

161. Vissing NH, Chawes BL, Rasmussen MA, Bisgaard H. Epidemiology and risk factors of infection in early childhood. *Pediatrics*. 2018;141(6). doi:10.1542/PEDS.2017-0933/37677

162. Christensen N, Bruun S, Søndergaard J, et al. Breastfeeding and Infections in Early Childhood: A Cohort Study. *Pediatrics*. 2020;146(5). doi:10.1542/PEDS.2019-1892/75328

163. Atladóttir HÓ, Henriksen TB, Schendel DE, Parner ET. Using Maternally Reported Data to Investigate the Association between Early Childhood Infection and Autism Spectrum Disorder: the Importance of Data Source. *Paediatr Perinat Epidemiol*. 2012;26(4):373-385. doi:10.1111/J.1365-3016.2012.01296.X

164. Sabourin KR, Reynolds A, Schendel D, et al. Infections in Children with Autism Spectrum Disorder: Study to Explore Early Development (SEED). *Autism Res*. 2019;12(1):136. doi:10.1002/AUR.2012

165. Dalsager L, Christensen N, Husby S, et al. Association between prenatal exposure to perfluorinated compounds and symptoms of infections at age 1–4 years among 359 children in the Odense Child Cohort. *Environ Int*. 2016;96:58-64. doi:10.1016/J.ENVINT.2016.08.026

166. Hollingsworth HC, Stetler-Stevenson M, Gagneten D, Kingma DW, Raffeld M, Jaffe ES. Immunodeficiency-associated malignant lymphoma. Three cases showing genotypic evidence of both T- and B-cell lineages. *Am J Surg Pathol*. 1994;18(11):1092-1101.

167. Piquer Gibert M, Alsina L, Giner Muñoz MT, et al. Non-Hodgkin lymphoma in pediatric patients with common variable immunodeficiency. *Eur J Pediatr*. 2015;174(8):1069-1076. doi:10.1007/S00431-015-2508-6

168. Shad A, Magrath I. Non-Hodgkin's lymphoma. *Pediatr Clin North Am*. 1997;44(4):863-890. doi:10.1016/s0031-3955(05)70534-4

169. Wiemels J. Perspectives on the causes of childhood leukemia. *Chem Biol Interact*. 2012;196(3):59-67. doi:10.1016/j.cbi.2012.01.007

170. Whitehead TP, Metayer C, Wiemels JL, Singer AW, Miller MD. Childhood Leukemia and Primary Prevention. *Curr Probl Pediatr Adolesc Health Care*. 2016;46(10):317-352. doi:10.1016/j.cppeds.2016.08.004

171. Urayama KY, Buffler PA, Gallagher ER, Ayoob JM, Ma X. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. *Int J Epidemiol*. 2010;39(3):718. doi:10.1093/IJE/DYP378

172. Naumburg E, Bellocco R, Cnattingius S, Jonzon A, Ekbom A. Perinatal exposure to infection and risk of childhood leukemia. *Med Pediatr Oncol*. 2002;38(6):391-397. doi:10.1002/mpo.10084

173. Mehrian-Shai R, Reichardt JKV, Harris CC, Toren A. The Gut–Brain Axis, Paving the Way to Brain Cancer. *Trends Cancer*. 2019;5(4):200-207. doi:10.1016/j.trecan.2019.02.008

174. Li Y, Jiang H, Wang X, et al. Crosstalk Between the Gut and Brain: Importance of the Fecal Microbiota in Patient With Brain Tumors. *Front Cell Infect Microbiol*. 2022;12. doi:10.3389/fcimb.2022.881071

175. Trabert B, Graubard BI, Erickson RL, Mcglynn KA. Childhood infections, orchitis and testicular germ cell tumours: a report from the STEED study and a meta-analysis of existing data. *Br J Cancer*. 2012;106:1331-1334. doi:10.1038/bjc.2012.45

176. Daniels JL, Pan IJ, Olshan AF, Breslow NE, Bunin GR, Ross JA. Obstetric history and birth characteristics and Wilms tumor: A report from the Children's Oncology Group. *Cancer Causes and Control*. 2008;19(10):1103-1110. doi:10.1007/s10552-008-9174-1

177. Olshan AF, Breslow NE, Falletta JM, et al. Risk factors for Wilms tumor. Report from the National Wilms Tumor Study. *Cancer*. 1993;72(3):938-944. doi:10.1002/1097-0142(19930801)72:3<938::aid-cncr2820720345>3.0.co;2-c

178. Michalek AM, Buck GM, Nasca PC, Freedman AN, Baptiste MS, Mahoney MC. Gravid health status, medication use, and risk of neuroblastoma. *Am J Epidemiol*. 1996;143(10):996-1001. doi:10.1093/oxfordjournals.aje.a008682

179. Whyte P, Buchkovich KJ, Horowitz JM, et al. Association between an oncogene and an anti-oncogene: the adenovirus E1A proteins bind to the retinoblastoma gene product. *Nature*. 1988;334(6178):124-129. doi:10.1038/334124a0

180. DeCaprio JA, Ludlow JW, Figge J, et al. SV40 large tumor antigen forms a specific complex with the product of the retinoblastoma susceptibility gene. *Cell*. 1988;54(2):275-283. doi:10.1016/0092-8674(88)90559-4

181. Dyson N, Howley PM, Münger K, Harlow E. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science*. 1989;243(4893):934-937. doi:10.1126/science.2537532

182. Dang-Tan T, Franco EL. Diagnosis delays in childhood cancer. *Cancer*. 2007;110(4):703-713. doi:10.1002/CNCR.22849

183. Su Q, Sun X, Zhu L, et al. Breastfeeding and the risk of childhood cancer: a systematic review and dose-response meta-analysis. *BMC Med*. 2021;19(1):90. doi:10.1186/s12916-021-01950-5

184. Amitay EL, Keinan-Boker L. Breastfeeding and Childhood Leukemia Incidence: A Meta-analysis and Systematic Review. *JAMA Pediatr*. 2015;169(6):e151025. doi:10.1001/jamapediatrics.2015.1025

185. Marron M, Brackmann LK, Kuhse P, et al. Vaccination and the Risk of Childhood Cancer-A Systematic Review and Meta-Analysis. *Front Oncol*. 2020;10:610843. doi:10.3389/fonc.2020.610843

186. Morra ME, Kien ND, Elmaraezy A, et al. Early vaccination protects against childhood leukemia: A systematic review and meta-analysis. *Sci Rep*. 2017;7(1):15986. doi:10.1038/s41598-017-16067-0

187. Bruun S, Buhl S, Husby S, et al. Breastfeeding, Infant Formula, and Introduction to Complementary Foods-Comparing Data Obtained by Questionnaires and Health Visitors' Reports to Weekly Short Message Service Text Messages. *Breastfeed Med*. 2017;12(9):554-560. doi:10.1089/BFM.2017.0054

188. Vestermark V, Høgdall CK, Plenov G, Birch M, Toftager-Larsen K. The duration of breast-feeding: A longitudinal prospective study in Denmark. *Scand J Public Health*. 1991;19(2):105-109. doi:10.1177/140349489101900205

189. Weile B, Rubin DH, Krasilnikoff PA, Kuo HS, Jekel JF. Infant feeding patterns during the first year of life in Denmark: Factors associated with the discontinuation of breast-feeding. *J Clin Epidemiol*. 1990;43(12):1305-1311. doi:10.1016/0895-4356(90)90096-8

190. Sirirungreung A, Lee PC, Hu YH, Liew Z, Beate Ritz |, Heck JE. Maternal medically diagnosed infection and antibiotic prescription during pregnancy and risk of childhood cancer: A population-based cohort study in Taiwan, 2004 to 2015. *Int J Cancer*. Published online October 4, 2023. doi:10.1002/IJC.34744

191. Bonaventure A, Simpson J, Ansell P, Roman E, Lightfoot T. Prescription drug use during pregnancy and risk of childhood cancer – Is there an association? *Cancer Epidemiol*. 2015;39(1):73-78. doi:10.1016/J.CANEP.2014.10.008

192. Kaatsch P, Scheidemann-Wesp U, Schüz J. Maternal use of antibiotics and cancer in the offspring: results of a case-control study in Germany. *Cancer Causes Control*. 2010;21(8):1335-1345. doi:10.1007/S10552-010-9561-2

193. Momen NC, Olsen J, Gissler M, Kieler H, Haglund B, Li J. Exposure to systemic antibacterial medications during pregnancy and risk of childhood cancer. *Pharmacoepidemiol Drug Saf*. 2015;24(8):821-829. doi:10.1002/PDS.3806

194. Ye X, Monchka BA, Righolt CH, Mahmud SM. Maternal use of antibiotics and cancer incidence risk in offspring: A population-based cohort study in Manitoba, Canada. *Cancer Med*. 2019;8(11):5367-5372. doi:10.1002/CAM4.2412

195. Hjorth S, Pottegård A, Broe A, et al. Prenatal exposure to nitrofurantoin and risk of childhood leukaemia: a registry-based cohort study in four Nordic countries. *Int J Epidemiol*. 2022;51(3):778-788. doi:10.1093/IJE/DYAB219

196. Garry VF, Nelson RL. Host-mediated transformation: metronidazole. *Mutation Research Letters*. 1987;190(4):289-295. doi:10.1016/0165-7992(87)90011-X

197. Itoh T, Moto M, Takahashi M, Sakai H, Mitsumori K. Liver initiation activity of norfloxacin but not nalidixic acid, pipemidic acid, and ciprofloxacin on in vivo short-term liver initiation assay in rats. *Toxicology*. 2006;222(3):240-246. doi:10.1016/J.TOX.2006.02.019

198. Sirirungreung A, Hansen J, He D, Huang X, Ritz B, Heck JE. Exposure to nitrosatable drugs during pregnancy and childhood cancer: a matched case-control study in Denmark, 1996 – 2016. *Pharmacoepidemiol Drug Saf*. Published online October 27, 2022. doi:10.1002/pds.5557

199. Shaw AK, Li P, Infante-Rivard C. Early infection and risk of childhood brain tumors (Canada). *Cancer Causes and Control*. 2006;17(10):1267-1274. doi:10.1007/S10552-006-0066-Y/TABLES/3

200. Liu YL, Lo WC, Chiang CJ, et al. Incidence of cancer in children aged 0–14 years in Taiwan, 1996–2010. *Cancer Epidemiol*. 2015;39(1):21-28. doi:10.1016/J.CANEP.2014.11.010

201. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol*. 2001;30(6):1428-1437. doi:10.1093/IJE/30.6.1428

202. Li CY, Chen LH, Chiou MJ, Liang FW, Lu TH. Set-up and future applications of the Taiwan Maternal and Child Health Database (TMCHD). *Taiwan Journal of Public Health*. 2016;35(2):209-220. doi:10.6288/TJPH201635104053

203. Chiang CJ, Chen YC, Chen CJ, You SL, Lai MS. Cancer Trends in Taiwan. *Jpn J Clin Oncol*. 2010;40(10):897-904. doi:10.1093/JJCO/HYQ057

204. Orimoloye HT, Qureshi N, Lee PC, et al. Maternal anemia and the risk of childhood cancer: A population-based cohort study in Taiwan. *Pediatr Blood Cancer*. 2023;70(3):e30188. doi:10.1002/PBC.30188

205. Heck JE, Lee PC, Wu CK, et al. Gestational risk factors and childhood cancers: A cohort study in Taiwan. *Int J Cancer*. 2020;147(5):1343-1353. doi:10.1002/IJC.32905

206. Huang X, Hansen J, Lee PC, et al. Maternal diabetes and childhood cancer risks in offspring: two population-based studies. *Br J Cancer*. 2022;127(10):1837. doi:10.1038/S41416-022-01961-W

207. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *Int J Epidemiol*. 2006;35(6):1495-1503. doi:10.1093/IJE/DYL177

208. Johnson KJ, Carozza SE, Chow EJ, et al. Parental age and risk of childhood cancer: A pooled analysis. *Epidemiology*. 2009;20(4):475. doi:10.1097/EDE.0B013E3181A5A332

209. Domingues A, Moore KJ, Sample J, Kharoud H, Marcotte EL, Spector LG. Parental Age and Childhood Lymphoma and Solid Tumor Risk: A Literature Review and Meta-Analysis. *JNCI Cancer Spectr*. 2022;6(3):pkac040. doi:10.1093/jncics/pkac040

210. Sergentanis TN, Thomopoulos TP, Gialamas SP, et al. Risk for childhood leukemia associated with maternal and paternal age. *Eur J Epidemiol*. 2015;30(12):1229-1261. doi:10.1007/S10654-015-0089-3/FIGURES/3

211. Li CY, Lin RS, Lin CH. Urbanization and childhood leukaemia in Taiwan. *Int J Epidemiol*. 1998;27(4):587-591. doi:10.1093/IJE/27.4.587

212. Tsai HJ. Antibiotic prophylaxis for cesarean delivery: before skin incision or after umbilical cord clamping? *Taiwan J Obstet Gynecol*. 2011;50(1):129-130. doi:10.1016/J.TJOG.2010.06.004

213. Lee CC, Hsu JF, Prasad Janapatla R, et al. Clinical and Microbiological Characteristics of Group B Streptococcus from Pregnant Women and Diseased Infants in Intrapartum Antibiotic Prophylaxis Era in Taiwan. *Sci Rep*. 2019;9(1). doi:10.1038/S41598-019-49977-2

214. Wang CH, Kung WJ, Lee CH, et al. High rates of colonization and antimicrobial resistance of group B streptococcus highlight the need for vaccination even after implementation of guidelines for intrapartum antibiotic prophylaxis. *Vaccine*. 2022;40(2):282-287. doi:10.1016/J.VACCINE.2021.11.069

215. Li QY, Wang DY, Li HT, Liu JM. Screening-based and Risk-based Strategy for the Prevention of Early-onset Group B Streptococcus/Non-group B Streptococcus Sepsis in the Neonate: A Systematic Review and Meta-analysis. *Pediatr Infect Dis J*. 2020;39(8):740-748. doi:10.1097/INF.0000000000002674

216. Buckley JD, Sather H, Ruccione K, et al. A case-control study of risk factors for hepatoblastoma. A report from the Childrens Cancer Study Group. *Cancer*. 1989;64(5):1169-1176. doi:10.1002/1097-0142(19890901)64:5<1169::aid-cncr2820640534>3.0.co;2-i

217. Lin M, Chen Q, Yang LY, et al. Hepatitis B virus infection and replication in primarily cultured human fetal hepatocytes. *World J Gastroenterol*. 2007;13(7):1027-1031. doi:10.3748/wjg.v13.i7.1027

218. Lázaro CA, Chang M, Tang W, et al. Hepatitis C virus replication in transfected and serum-infected cultured human fetal hepatocytes. *Am J Pathol*. 2007;170(2):478-489. doi:10.2353/ajpath.2007.060789

219. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatol*. 2016;64(1 Suppl):S84-S101. doi:10.1016/j.jhep.2016.02.021

220. Bousali M, Papatheodoridis G, Paraskevis D, Karamitros T. Hepatitis B Virus DNA Integration, Chronic Infections and Hepatocellular Carcinoma. *Microorganisms*. 2021;9(8):1787. doi:10.3390/microorganisms9081787

221. Shaw AK, Infante-Rivard C, Morrison HI. Use of medication during pregnancy and risk of childhood leukemia (Canada). *Cancer Causes Control*. 2004;15(9):931-937. doi:10.1007/S10552-004-2230-6

222. Abd-Allah ER, Abd El-Rahman HA. Influence of doxycycline administration on rat embryonic development during organogenesis. *J Biochem Mol Toxicol*. 2021;35(1). doi:10.1002/JBT.22613

223. Sirirungreung A, Hansen J, He D, Huang X, Ritz B, Heck JE. Exposure to nitrosatable drugs during pregnancy and childhood cancer: A matched case-control study in Denmark, 1996-2016. *Pharmacoepidemiol Drug Saf*. 2023;32(4). doi:10.1002/PDS.5557

224. Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA, Hu DJ. Antibacterial Medication Use During Pregnancy and Risk of Birth Defects: National Birth Defects Prevention Study. *Arch Pediatr Adolesc Med*. 2009;163(11):978-985. doi:10.1001/ARCHPEDIATRICS.2009.188

225. Czeizel AE, Rockenbauer M, Sørensen HT, Olsen J. Use of cephalosporins during pregnancy and in the presence of congenital abnormalities: a population-based, case-control study. *Am J Obstet Gynecol*. 2001;184(6):1289-1296. doi:10.1067/MOB.2001.113905

226. Song Q, Yan J, Bu N, Qian Y. Efficacy and safety of broad spectrum penicillin with or without beta-lactamase inhibitors vs first and second generation cephalosporins as prophylactic antibiotics during cesarean section: a systematic review and meta-analysis. *https://doi.org/101080/0144361520232195946*. 2023;43(1):2195946. doi:10.1080/01443615.2023.2195946

227. Chang YW, Chou FH. Acceptance of Pertussis Vaccination among Pregnant Women in Taiwan. *J Community Health Nurs*. 2021;38(2):85-102. doi:10.1080/07370016.2021.1887565

228. Chao A, Huang YC, Chang YL, et al. Seroprevalence of influenza A H1N1 and seroconversion of mothers and infants induced by a single dose of monovalent vaccine. *Taiwan J Obstet Gynecol*. 2013;52(3):356-359. doi:10.1016/J.TJOG.2013.06.002

229. Cheng PJ, Huang SY, Su SY, Peng HH, Chang CL. Increasing postpartum rate of vaccination with tetanus, diphtheria, and acellular pertussis vaccine by incorporating pertussis cocooning information into prenatal education for group B streptococcus prevention. *Vaccine*. 2015;33(51):7225-7231. doi:10.1016/J.VACCINE.2015.10.121

230. Wu CH, Hsu TY, Kung FT, ChangChien CC, Tsai CC, Lu SN. Changes in the Prevalence of HBsAg and HBeAg: a Study of 8696 Parturients in a Well Vaccinated Area. *Sci Rep*. 2017;7(1). doi:10.1038/S41598-017-01234-0

231. Liew Z, Olsen J, Cui X, Ritz B, Arah OA. Bias from conditioning on live birth in pregnancy cohorts: An illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. *Int J Epidemiol*. 2015;44(1):345-354. doi:10.1093/ije/dyu249

232. Chen LJ, Chiou JY, Huang JY, Su PH, Chen JY. Birth defects in Taiwan: A 10-year nationwide population-based, cohort study. *J Formos Med Assoc*. 2020;119(1 Pt 3):553-559. doi:10.1016/J.JFMA.2019.08.006

233. Keskin-Arslan E, Erol H, Uysal N, Karadas B, Temiz T, Kaplan YC. Pregnancy outcomes following maternal macrolide use: A systematic review and meta-analysis. *Reprod Toxicol*. 2023;115:124-146. doi:10.1016/J.REPROTOX.2022.12.003

234. Goldberg O, Moretti M, Levy A, Koren G. Exposure to nitrofurantoin during early pregnancy and congenital malformations: a systematic review and meta-analysis. *J Obstet Gynaecol Can*. 2015;37(2):150-156. doi:10.1016/S1701-2163(15)30337-6

235. Sheehy O, Santos F, Ferreira E, Bérard A. The use of metronidazole during pregnancy: a review of evidence. *Curr Drug Saf*. 2015;10(2):170-179. doi:10.2174/1574886310021505151245 48

236. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. *Cancer*. 2005;103(7):1457-1467. doi:10.1002/cncr.20910

237. Wallach Kildemoes H, Toft Sørensen H, Hallas J. The Danish national prescription registry. *Scand J Public Health*. 2011;39(7):38-41. doi:10.1177/1403494810394717

238. Sørensen HT, Hansen I, Ejlersen E, Sabroe S, Hamburger H. Identification of patients treated with strong analgesics: an assessment of two Danish information systems with respect to epidemiological research. *J Med Syst*. 1996;20(1):57-65. doi:10.1007/BF02260874

239. Hall C, Hansen J, von Ehrenstein OS, et al. Occupational livestock or animal dust exposure and offspring cancer risk in Denmark, 1968-2016. *Int Arch Occup Environ Health*. 2020;93(5):659-668. doi:10.1007/s00420-020-01524-7

240. He JR, Ramakrishnan R, Hirst JE, et al. Maternal Infection in Pregnancy and Childhood Leukemia: A Systematic Review and Meta-analysis. *Journal of Pediatrics*. 2020;217:98-109.e8. doi:10.1016/j.jpeds.2019.10.046

241. Dickinson HO, Nyari TA, Parker L. Childhood solid tumours in relation to infections in the community in Cumbria during pregnancy and around the time of birth. *Br J Cancer*. 2002;87(7):746-750. doi:10.1038/sj.bjc.6600530

242. Fear NT, Roman E, Ansell P, Bull D. Malignant neoplasms of the brain during childhood: The role of prenatal and neonatal factors (United Kingdom). *Cancer Causes and Control*. 2001;12(5):443-449. doi:10.1023/A:1011201524589

243. Michalek AM, Buck GM, Nasca PC, Freedman AN, Baptiste MS, Mahoney MC. Gravid health status, medication use, and risk of neuroblastoma. *Am J Epidemiol*. 1996;143(10):996-1001. doi:10.1093/oxfordjournals.aje.a008682

244. Schüz J, Weihkopf T, Kaatsch P. Medication use during pregnancy and the risk of childhood cancer in the offspring. *Eur J Pediatr*. 2007;166(5):433-441. doi:10.1007/s00431-006-0401-z

245. Kramer S, Ward E, Meadows AT, Malone KE. Medical and drug risk factors associated with neuroblastoma: a case-control study. *J Natl Cancer Inst*. 1987;78(5):797-804.

246. Thomsen AML, Ramlau-Hansen CH, Schullehner J, et al. Prenatal nitrosatable prescription drug intake, drinking water nitrate, and the risk of stillbirth: a register- and

population-based cohort of Danish pregnancies, 1997–2017. *Environ Health*. 2021;20(1). doi:10.1186/s12940-021-00805-z

247. Olshan AF, Faustman EM. Nitrosatable drug exposure during pregnancy and adverse pregnancy outcome. *Int J Epidemiol*. 1989;18(4):891-899. doi:10.1093/ije/18.4.891

248. Kaatsch P, Scheidemann-Wesp U, Schüz J. Maternal use of antibiotics and cancer in the offspring: results of a case–control study in Germany. *Cancer Causes & Control*. 2010;21(8):1335-1345. doi:10.1007/s10552-010-9561-2

249. Momen NC, Olsen J, Gissler M, Kieler H, Haglund B, Li J. Exposure to systemic antibacterial medications during pregnancy and risk of childhood cancer. *Pharmacoepidemiol Drug Saf*. 2015;24(8):821-829. doi:10.1002/pds.3806

250. Ye X, Monchka BA, Righolt CH, Mahmud SM. Maternal use of antibiotics and cancer incidence risk in offspring: A population-based cohort study in Manitoba, Canada. *Cancer Med*. 2019;8(11):5367-5372. doi:10.1002/cam4.2412

251. Brodeur GM. Neuroblastoma: Biological insights into a clinical enigma. *Nat Rev Cancer*. 2003;3(3):203-216. doi:10.1038/nrc1014

252. Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. *Lancet*. 2007;369(9579):2106-2120. doi:10.1016/S0140-6736(07)60983-0

253. Abdelkarim H, Neelarapu R, Madriaga A, et al. Design, Synthesis, Molecular Modeling, and Biological Evaluation of Novel Amine-based Histone Deacetylase Inhibitors. *ChemMedChem*. 2017;12(24):2030-2043. doi:10.1002/cmdc.201700449

254. Silverman RB, Lawton GR, Ralay Ranaivo H, Chico LK, Seo J, Watterson DM. Effect of potential amine prodrugs of selective neuronal nitric oxide synthase inhibitors on blood-brain barrier penetration. *Bioorg Med Chem*. 2009;17(21):7593-7605. doi:10.1016/j.bmc.2009.08.065

255. Takahata K, Katsuki H, Kume T, et al. Retinal neuronal death induced by intraocular administration of a nitric oxide donor and its rescue by neurotrophic factors in rats. *Invest Ophthalmol Vis Sci*. 2003;44(4):1760-1766. doi:10.1167/iovs.02-0471

256. Page EH, Cook CK, Hater MA, Mueller CA, Grote AA, Mortimer VD. Visual and ocular changes associated with exposure to two tertiary amines. *Occup Environ Med*. 2003;60(1):69-75. doi:10.1136/oem.60.1.69

257. Mirvish SS. Experimental evidence for inhibition of N-nitroso compound formation as a factor in the negative correlation between vitamin C consumption and the incidence of certain cancers. *Cancer Res*. 1994;54(7 SUPPL.).

258. Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Cogliano V. Carcinogenicity of nitrate, nitrite, and cyanobacterial peptide toxins. *Lancet Oncol*. 2006;7(8):628-629. doi:10.1016/S1470-2045(06)70789-6

259. Kwan ML, Metayer C, Crouse V, Buffler PA. Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring. *Am J Epidemiol*. 2007;165(1):27-35. doi:10.1093/aje/kwj336

260. Brender JD, Werler MM, Shinde MU, et al. Nitrosatable drug exposure during the first trimester of pregnancy and selected congenital malformations. *Birth Defects Res A Clin Mol Teratol*. 2012;94(9):701-713. doi:10.1002/bdra.23060

261. Vuong AM, Shinde MU, Brender JD, et al. Nitrosatable drug exposure during pregnancy and preterm and small-for-gestational-age births. *Paediatr Perinat Epidemiol*. 2015;29(1):60-71. doi:10.1111/ppe.12169

262. Brender JD, Werler MM, Kelley KE, et al. Nitrosatable drug exposure during early pregnancy and neural tube defects in offspring: National Birth Defects Prevention Study. *Am J Epidemiol*. 2011;174(11):1286-1295. doi:10.1093/aje/kwr254

263. Alemany S, Avella-García C, Liew Z, et al. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity

symptoms in childhood: Meta-analysis in six European population-based cohorts. *Eur J Epidemiol*. 2021;36(10):993-1004. doi:10.1007/S10654-021-00754-4

264. Ricci C, Albanese CM, Pablo LA, et al. In utero acetaminophen exposure and child neurodevelopmental outcomes: Systematic review and meta-analysis. *Paediatr Perinat Epidemiol*. Published online 2023. doi:10.1111/PPE.12963
265. Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. *Am J Epidemiol*. 2018;187(8):1817-1827. doi:10.1093/AJE/KWY086
266. Hass U, Christiansen S, Axelstad M, et al. *Evaluation of 22 SIN List 2.0 Substances According to the Danish Proposal on Criteria for Endocrine Disrupters*.; 2012. Accessed April 12, 2023. https://mst.dk/media/mst/67169/SIN%20report%20and%20Annex.pdf
267. Kamath P, Kamath A, Ullal SD. Liver injury associated with drug intake during pregnancy. *World J Hepatol*. 2021;13(7):747. doi:10.4254/WJH.V13.I7.747
268. Casey LC, Fontana RJ, Aday A, et al. Acute Liver Failure (ALF) in Pregnancy: How Much Is Pregnancy-Related? *Hepatology*. 2020;72(4):1366. doi:10.1002/HEP.31144
269. Ognjanovic S, Blair C, Spector LG, Robison LL, Roesler M, Ross JA. Analgesic use during pregnancy and risk of infant leukaemia: A Children's Oncology Group study. *Br J Cancer*. 2011;104(3):532. doi:10.1038/SJ.BJC.6606046
270. Thiele K, Solano ME, Huber S, et al. Prenatal acetaminophen affects maternal immune and endocrine adaptation to pregnancy, induces placental damage, and impairs fetal development in mice. *Am J Pathol*. 2015;185(10):2805-2818. doi:10.1016/J.AJPATH.2015.06.019
271. Gilman EA, Margaret L, Wilson K, Kneale GW, Waterhouse JAH. Childhood cancers and their association with pregnancy drugs and illnesses. *Paediatr Perinat Epidemiol*. 1989;3(1):66-94. doi:10.1111/j.1365-3016.1989.tb00371.x

272. Hurtado-Gonzalez P, Anderson RA, Macdonald J, et al. Effects of Exposure to Acetaminophen and Ibuprofen on Fetal Germ Cell Development in Both Sexes in Rodent and Human Using Multiple Experimental Systems. doi:10.1289/EHP2307

273. Zafeiri A, Raja EA, Mitchell RT, Hay DC, Bhattacharya S, Fowler PA. Original research: Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: cohort study of 151 141 singleton pregnancies. *BMJ Open*. 2022;12(5):48092. doi:10.1136/BMJOPEN-2020-048092

274. Jensen MS, Henriksen TB, Rebordosa C, et al. Analgesics during pregnancy and cryptorchidism: Additional analyses. *Epidemiology*. 2011;22(4):610-612. doi:10.1097/EDE.0B013E31821ECA69

275. Jensen MS, Rebordosa C, Thulstrup AM, et al. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. *Epidemiology*. 2010;21(6):779-785. doi:10.1097/EDE.0B013E3181F20BED

276. Gurney J, Richiardi L, McGlynn KA, Signal V, Sarfati D. Analgesia use during pregnancy and risk of cryptorchidism: a systematic review and meta-analysis. *Hum Reprod*. 2017;32(5):1118. doi:10.1093/HUMREP/DEX047

277. Lind DV, Main KM, Kyhl HB, et al. Maternal use of mild analgesics during pregnancy associated with reduced anogenital distance in sons: a cohort study of 1027 mother–child pairs. *Human Reproduction*. 2017;32(1):223-231. doi:10.1093/HUMREP/DEW285

278. Fisher BG, Thankamony A, Hughes IA, Ong KK, Dunger DB, Acerini CL. Prenatal paracetamol exposure is associated with shorter anogenital distance in male infants. *Hum Reprod*. 2016;31(11):2642-2650. doi:10.1093/HUMREP/DEW196

279. Lip SZL, Murchison LED, Cullis PS, Govan L, Carachi R. A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. *Arch Dis Child*. 2013;98(1):20-26. doi:10.1136/ARCHDISCHILD-2012-302051

280. Moreno-Mendoza D, Casamonti E, Riera-Escamilla A, et al. Short anogenital distance is associated with testicular germ cell tumour development. *Andrology*. 2020;8(6):1770-1778. doi:10.1111/ANDR.12863

281. Schwartzbaum JA. Influence of the mother's prenatal drug consumption on risk of neuroblastoma in the child. *Am J Epidemiol*. 1992;135(12):1358-1367. doi:10.1093/oxfordjournals.aje.a116247

282. Li CY, Dai YX, Chang YT, et al. Prenatal exposure to acetaminophen increases the risk of atopic dermatitis in children: A nationwide nested case-control study in Taiwan. *Pediatr Allergy Immunol*. 2021;32(5):1080-1088. doi:10.1111/PAI.13465

283. Schraw JM, Sok P, Desrosiers TA, et al. Associations between birth defects and childhood and adolescent germ cell tumors according to sex, histologic subtype, and site. *Cancer*. Published online 2023. doi:10.1002/CNCR.34906

284. Silva IDS, Swerdlow AJ. Sex differences in the risks of hormone-dependent cancers. *Am J Epidemiol*. 1993;138(1):10-28. doi:10.1093/OXFORDJOURNALS.AJE.A116773

285. Sala A, Barr RD. Osteopenia and Cancer in Children and Adolescents The Fragility of Success. *Cancer*. 2007;109:1420-1451. doi:10.1002/cncr.22546

286. Liew Z, Nohr EA, Morgen CS, et al. Prenatal Exposure to Acetaminophen and Overweight in Childhood. *Obesity*. 2019;27(8):1314-1322. doi:10.1002/OBY.22526

287. Liew Z, Ernst A. Intrauterine Exposure to Acetaminophen and Adverse Developmental Outcomes: Epidemiological Findings and Methodological Issues. *Curr Environ Health Rep*. 2021;8(1):23-33. doi:10.1007/S40572-020-00301-5/METRICS

288. Liew Z, Kioumourtzoglou MA, Roberts AL, O'reilly ÉJ, Ascherio A, Weisskopf MG. Practice of Epidemiology Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II. *Am J Epidemiol*. 2019;188(4):768-775. doi:10.1093/aje/kwy288

289. Arah OA, Chiba Y, Greenland S. Bias Formulas for External Adjustment and Sensitivity Analysis of Unmeasured Confounders. *Ann Epidemiol*. 2008;18(8):637-646. doi:10.1016/j.annepidem.2008.04.003

290. Vanderweele TJ, Arah OA. Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. *Epidemiology*. 2011;22(1):42-52. doi:10.1097/EDE.0b013e3181f74493

291. Lash TL, Fox MP, Maclehose RF, Maldonado G, Mccandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969-1985. doi:10.1093/ije/dyu149

292. Van Gelder MMHJ, Vorstenbosch S, Te Winkel B, Van Puijenbroek EP, Roeleveld N. Practice of Epidemiology Using Web-Based Questionnaires to Assess Medication Use During Pregnancy: A Validation Study in 2 Prospectively Enrolled Cohorts. *Am J Epidemiol*. 2018;187(2):326-336. doi:10.1093/aje/kwx239

293. Cohen JM, Wood ME, Hernandez-Diaz S, Nordeng H. Agreement between paternal self-reported medication use and records from a national prescription database. *Pharmacoepidemiol Drug Saf*. 2018;27(4):413-421. doi:10.1002/PDS.4411

294. McKean-Cowdin R, Pogoda JM, Lijinsky W, Holly EA, Mueller BA, Preston-Martin S. Maternal prenatal exposure to nitrosatable drugs and childhood brain tumours. *Int J Epidemiol*. 2003;32(2):211-217. doi:10.1093/IJE/DYG050

295. Wood ME, Burch RC, Hernandez-Diaz S. Polypharmacy and comorbidities during pregnancy in a cohort of women with migraine. *Cephalalgia*. 2021;41(3):392-403. doi:10.1177/0333102420975394

296. Thulstrup AM, Sørensen HT, Nielsen GL, et al. Fetal growth and adverse birth outcomes in women receiving prescriptions for acetaminophen during pregnancy. EuroMap Study Group. *Am J Perinatol*. 1999;16(7):321-326. doi:10.1055/s-2007-993879

297. Rebordosa C, Kogevinas M, Bech BH, Sørensen HT, Olsen J. Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes. *Int J Epidemiol*. 2009;38(3):706-714. doi:10.1093/ije/dyp151

298. Rebordosa C, Kogevinas M, Horváth-Puhó E, et al. Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. *Am J Obstet Gynecol*. 2008;198(2):178.e1-7. doi:10.1016/j.ajog.2007.08.040

299. Feldkamp ML, Meyer RE, Krikov S, Botto LD. Acetaminophen use in pregnancy and risk of birth defects: findings from the National Birth Defects Prevention Study. *Obstetrics and gynecology*. 2010;115(1):109-115. doi:10.1097/AOG.0b013e3181c52616

300. Bitzén PO, Gustafsson B, Jostell KG, Melander A, Wåhlin-Boll E. Excretion of paracetamol in human breast milk. *Eur J Clin Pharmacol*. 1981;20(2):123-125. doi:10.1007/BF00607148

301. Lash TL, Fox MP, Fink AK. Applying Quantitative Bias Analysis to Epidemiologic Data. Published online 2009. doi:10.1007/978-0-387-87959-8