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Association between medically diagnosed postnatal infection and childhood cancers: A matched case-control study in Denmark, 1978 to 2016

Anupong Sirirungreung[1] | Johnni Hansen[2] | Beate Ritz[1] | Julia E. Heck[1,3]

[1]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, California, USA

[2]Danish Cancer Society Research Center, Copenhagen, Denmark

[3]College of Health and Public Service, University of North Texas, Denton, Texas, USA

Correspondence
Julia E. Heck, Department of Rehabilitation and Health Services, College of Health and Public Service, University of North Texas, Denton, Texas, USA.
Email: julia.heck@unt.edu

Abstract

Although the association between infection and childhood cancer has been long investigated, there is limited information on rarer cancers. This article aimed to explore the association between postnatal infection and childhood cancers in the Danish population. A matched case-control study was conducted using Danish nationwide registries from 1978 to 2016. Each childhood cancer case was matched 1:25 with controls by birth date within a week and sex. Postnatal infections were identified from the Danish National Patient Registry, which lists diagnoses seen in hospital, specialist or emergency care services. Multivariable conditional logistic regression was used to estimate adjusted odds ratios (adj.OR) and 95% confidence intervals (CI). Specific types of infections and the number of infection episodes were also considered. The study included 4125 childhood cancer cases and 103 526 matched controls with ages ranging from 0 to 19 years. Medically diagnosed postnatal infections were positively associated with many types of childhood cancer including acute lymphoblastic leukemia (adj.OR = 1.42; 95% CI: 1.23-1.63), acute myeloid leukemia (adj.OR = 1.80; 95% CI: 1.28-2.52), non-Hodgkin lymphoma (adj.OR = 1.53; 95% CI: 1.19-1.97) and central nervous system tumors (adj.OR = 1.57; 95% CI: 1.39-1.77). A higher number of infection episodes were also associated with an increased risk of these cancers. Specific infections such as viral, enteric and urinary tract infections were also strongly associated with specific types of cancer. In conclusion, children who later develop cancer appear to have adverse reactions to infections necessitating referral to specialized health care services, perhaps indicating dysregulated immune function.

KEYWORDS
childhood cancer, Denmark, postnatal infection

What's new?

Postnatal infection is suspected of being associated with childhood cancers, particularly leukemia. Associations between specific infection types and subtypes of childhood leukemia,

however, remain unknown. Here, associations between postnatal cancers were assessed using data from the Danish National Patient Register. Investigation revealed positive associations between postnatal infections and various types of childhood cancer, including acute lymphoblastic leukemia, acute myeloid leukemia, non-Hodgkin lymphoma and central nervous system tumors. Cancer risk increased with increasing number of infection episodes. Children who develop cancer may experience adverse reactions to infections that require specialized care, possibly indicating immune system dysregulation.

1 | INTRODUCTION

Infection has been investigated as a risk factor of childhood cancer for decades, with most studies focusing on leukemia and lymphoma. This is due to challenges including the rare incidence of other childhood cancer types and difficulties assessing infection and related exposures during the lifetime of the children studied.

Since Greaves' and Kinlen's hypotheses were proposed, studies on a relationship between infection and leukemia have been widely investigated. In 1988, Greaves speculated that leukemia arises from spontaneous mutations, in utero and after birth, because of abnormal immune response to common infections.[1] In the same year, Kinlen proposed that childhood leukemia was caused by an abnormal immune response in a susceptible population due to migration and population mixing related to a lack of herd immunity.[2] Currently, many studies have suggested a positive association between postnatal infection and acute lymphoblastic leukemia (ALL),[3-5] as some literature has proposed protective effects or no evidence for any connection between infection and ALL.[6,7] On the other hand, there is little detailed research on specific types of infections[8,9] and on subtypes of leukemia such as acute myeloid leukemia (AML).[9,10]

Although a causal relationship between Epstein Barr virus and lymphoma has been widely recognized,[11] the association between common childhood infections and lymphoma is limited, especially in children. Previous studies have found an inconsistent association between childhood infection and lymphoma in adults. A cohort study in Denmark suggested a positive association between antimicrobial prescriptions, as a proxy of general infectious diseases, and Hodgkin lymphoma among young adults.[12] In contrast, a case-control study in Italy suggested an inverse association between childhood infectious diseases and non-Hodgkin lymphoma (NHL) in adults.[13]

There is little information on the association between infection and other childhood cancers such as central nervous system (CNS) tumors and germ cell tumors.[14] A matched case-control study in Sweden found a strong association between neonatal infections and childhood brain tumors.[15] They also reported strong associations between early-life infections and specific types of childhood brain tumors including low-grade astrocytoma, high-grade astrocytoma and medulloblastoma.[15] Previous studies on indirect evidence of early-life exposure to infections (eg, antibiotic use, social contact, childcare attendance) were inconsistent.[16-19] For germ cell tumors, a case-control study found a slight inverse association between any infection within 6 months after birth and cancer,[20] but the same study found a moderately positive association for mumps and a highly positive association for appendectomy.[20]

The Danish National Patient Register is one of the oldest nationwide population-based registries that has collected clinical data from all hospitals in Denmark.[21] With a standard data linkage protocol,[22] it provides an opportunity to access infectious exposures that occur before the cancer diagnosis of the index child. Therefore, the objective of our study was to assess the association between postnatal infection and childhood cancers in the Danish population.

2 | METHODS

This matched case-control study was conducted based on a nationwide data base-linkage for the Danish population. We used the unique personal identifier given to all Danish residents to link information from four sources: the Central Population Registry, the Danish Cancer Registry, the Danish National Patient Register and the Danish Medical Birth Registry. Details of data linkage and covariate information have previously been described.[22]

Cases were ascertained from the Danish Cancer Registry and classified according to the International Classification of Childhood Cancer.[23] Our study included cases with childhood cancer diagnoses including ALL, AML, CNS tumors, NHL, germ cell tumors, neuroblastoma, Wilms tumor, medulloblastoma and retinoblastoma. The vast majority of cases (98.2%) were diagnosed with their first primary cancer, while second primary cancers accounted for 1.7% and only 0.1% had a third primary cancer. Twenty-five controls matched with each index case by birth date within a week and child's sex were randomly selected to form matched sets. Eligible controls were cancer free and alive at the date of their index case's diagnosis. Study participants were all born in Denmark between 1978 and 2013 and cases were diagnosed with cancer between 1978 and 2016. Out of the total number of eligible cases and controls, which was 4219 and 105 475, respectively, we had to exclude some due to missing important information such as diagnosis details and birth weight (n = 977; cases n = 34; controls n = 943). As these are likely nonviable pregnancies, children born with birthweight <500 grams (n = 1042; cases n = 46; controls n = 996) were also excluded from analyses. Additionally, children with a diagnosis of Down syndrome (n = 67; cases n = 21; controls n = 46) were also excluded due to its strong relation with some types of cancer.[24] The number of excluded cases and controls were not mutually exclusive.

Information on postnatal infections was identified from the Danish National Patient Register (established 1978). In Denmark, with the exception of emergency care, patients first seek medical care from their primary care provider, who may then refer them to specialized care as necessary.[25] All hospital visits and diagnoses were systematically recorded and included in the registries. It is worth noting that the National Patient Register does not capture primary care visits, but does encompass inpatient, other outpatient and emergency department contacts.[21] Clinical diagnoses were classified by the International Classification of Diseases, Revision 8 (ICD-8) from 1978 to 1994 and using Revision 10 (ICD-10) starting in 1995, the same year that outpatient and emergency department contacts began to be included in the registry.[21] We identified postnatal infections by using a categorization adapted from Atladóttir et al[26] (Table S1). Specific groups of infections were categorized as viral or bacterial or affecting the respiratory, enteric or urinary tract. We considered the exposure period of infections as occurring between the date of birth until 1 year before the date of cancer diagnosis of the index case. This 1-year lag-time was set to avoid protopathic bias.[27] The number of infection episodes within the exposure period was counted. When the child had the same diagnosis more than once within a 14-day period, it was considered as one episode of the disease.

Demographic information and other covariates including parental age, 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 were identified from the Central Population Registry or the Danish Medical Birth Registry. We selected covariates to be included in final models to control for confounding using modified disjunctive cause criteria and causal diagrams.[28]

A conditional logistic regression model was used to estimate crude and adjusted odds ratios and their corresponding 95% confidence intervals (95% CI) for each type of childhood cancer. Maternal age (continuous), birth order (>1 vs 1) and multiple birth (yes vs no) have been suggested as potential risk factors for certain types of childhood cancer,[22,29-32] while residence at birth (urban, rural and small town) and the number of children in household (1—only index child, 2, 3 and >3) have been suggested to be related to both infections and cancer according to the population mixing hypothesis,[2,33] thus we included these covariates in all final models, assuming that they are risk factors for most or all childhood cancers. Results from models with less than five exposed cases are not presented.[34]

Additionally, associations between specific infections and cancer previously described in the literature were considered including associations between enterovirus and leukemia (ALL, AML)[9] and associations between germ cell tumors and appendicitis and mumps.[20]

In a separate analysis, we examined specific groups of infections and the number of infection episodes (1, 2-3 and ≥4 episodes; and as continuous). The reference group in these analyses was made up of children with no diagnosis of any infection in the National Patient Register.

Because maternal smoking status began to be collected in 1995,[35] a sensitivity analysis was conducted where we added this variable into adjusted models for the years available. It should be noted that maternal smoking was not associated with most childhood cancers in an analysis of Danish children, with overlapping cases as the current study.[35] In addition, a sensitivity analysis based on the subgroup of birth year (<1995 vs ≥1995) was conducted to compare estimates based on the ICD-8 and the ICD-10 time periods. Furthermore, we also stratified on infections diagnosed in different diagnostic settings (inpatient diagnosis vs outpatient or emergency diagnosis) to compare effects according to the likely severity of the infection. All statistical analyses were conducted using R 4.2.0 software.

3 | RESULTS

The study included 4125 childhood cancer cases and 103 526 matched controls. The distribution of baseline characteristics of cases and controls and their mothers is presented in Table 1. Cases were more likely to be a firstborn child and have a mother who smoked and resided at birth in an urban area.

Cases were more likely to have been diagnosed with postnatal infections compared to controls (24.3% vs 18.3%; Table 2). They also had a higher likelihood of having multiple infection episodes compared to controls (12.1% vs 8.1%).

Table 3 shows the association between postnatal infection diagnosis and risk of cancers. Higher odds of postnatal infection were observed among cases with ALL (adjusted odds ratio [adj.OR] = 1.42; 95% CI: 1.23-1.63), 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).

There was not sufficient statistical power to detect the associations between enterovirus infection and leukemia due to low prevalence of infected cases (0.2% among ALL and 0.4% among AML). We found that germ cell tumor cases were more likely to be diagnosed with appendicitis (adj.OR = 2.14; 95% CI: 1.14-4.02), while there were no cases diagnosed with mumps.

In sensitivity analyses, adding maternal smoking into models did not change point estimations of adjusted odds ratios by >10% (Table S3). Sensitivity analysis stratified by birth year and diagnostic setting showed similar results across groups (Table S4).

When estimating odds ratios for different types of infections (Table 4), we found stronger positive associations for specific types of infections. For example, viral infections appeared to have a stronger positive association 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 appeared to double 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 tumor (adj.OR = 2.41, 95% CI: 1.53-3.80). Urinary tract infections were most strongly positively associated with ALL (adj.OR = 1.94, 95% CI: 1.18-3.20), CNS

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

	Cases	Controls
Number	4125	103 526
Year of birth, n (%)		
1978-1989	1647 (39.9)	41 137 (39.7)
1990-1999	1425 (34.5)	36 094 (34.9)
2000-2013	1053 (25.5)	26 295 (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)	44 922 (43.4)
Male	2338 (56.7)	58 604 (56.6)
Mother's age (years), n (%)		
<29	2475 (60.0)	62 448 (60.3)
30-39	1580 (38.3)	39 383 (38.0)
40 and over	70 (1.7)	1695 (1.6)
Mother's age (years), mean (SD)	28.5 (5.0)	28.4 (5.0)
Mother smoking during pregnancy, n (%)[a]		
Yes	542 (24.4)	13 387 (23.8)
Missing (%)	4.3	3.7
Birth order, n (%)		
1	1792 (43.4)	44 428 (42.9)
2 or more	2333 (56.6)	59 098 (57.1)
Residence at birth, n (%)		
Urban	1354 (32.8)	32 818 (31.7)
Small town	1161 (28.1)	29 440 (28.4)
Rural	1610 (39.0)	41 268 (39.9)
Birth weight (g), n (%)		
500-1499	8 (0.2)	150 (0.1)
1500-2499	188 (4.6)	5017 (4.8)
2500-3999	3124 (75.7)	80 867 (78.1)
4000 and over	805 (19.5)	17 492 (16.9)
Birth weight (g), 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)	49 599 (47.9)
3	1322 (32.0)	31 513 (30.4)
>3	615 (14.9)	13 876 (13.4)
Child is in multiple birth, n (%)	118 (2.9)	3089 (3.0)

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

TABLE 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 = 103 526)
Infection type, n (%)		
All infection	1003 (24.3)	18 988 (18.3)
Viral infection	309 (7.5)	5256 (5.1)
Bacterial infection	344 (8.3)	6273 (6.1)
Respiratory infection	570 (13.8)	10 399 (10.0)
Enteric infection	178 (4.3)	2871 (2.8)
Urinary tract infection	62 (1.5)	968 (0.9)
Number of infection episodes, n (%)		
No postnatal infection diagnosis	3122 (75.7)	84 538 (81.7)
1	500 (12.1)	10 630 (10.3)
2-3	365 (8.8)	6190 (6.0)
4 and over	138 (3.3)	2168 (2.1)

(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 were more likely to have been diagnosed after multiple infections, including ALL, AML, CNS tumors and NHL (Table S2).

4 | DISCUSSION

Our results suggested that postnatal infections were associated with an increased risk of childhood cancer for ALL, AML, NHL, CNS tumors, astrocytoma, medulloblastoma, germ cell tumors and Wilms tumor. Different types of infections had varying associations with different types of cancer, with viral infections more strongly associated with AML, CNS tumors and medulloblastoma, enteric infections with AML, CNS tumors and germ cell tumors and urinary tract infections with ALL, CNS tumors and NHL. Additionally, there was a positive correlation between the number of infection episodes and certain types of cancer including ALL, AML, CNS tumors and NHL.

The clinical diagnoses in our study solely occurred in medical facilities with specialist, inpatient or emergency care. Some childhood infections are not severe and resolve in a short period of time without medical care; other infections are sufficiently mild to be treated solely by the primary care physician. This explains why we observed a low prevalence of infection in our population compared to community surveys and caregiver reports.[36-40] Our data cannot explain whether cancer cases experience a greater incidence of infections prediagnosis or alternatively if cases simply have adverse reactions to infections with greater frequency, necessitating referral to specialized health care services. Some cancers such as leukemia and lymphoma are related to dysregulated immune function[41,42] that causes cases to be more susceptible to severe infection requiring more medical attention,

TABLE 3 Conditional logistic regression odds ratios (OR) and 95% confidence intervals (95% CI) for childhood cancers and infection in Denmark, 1978 to 2013.

Cancer type	Cases		Controls		OR (95% CI)	Adj.OR[a] (95% CI)
	Total	Exposed, n (%)	Total	Exposed, n (%)		
Acute lymphoblastic leukemia	1165	279 (23.9)	29 305	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)	37 845	7391 (19.5)	1.58 (1.40-1.78)	1.57 (1.39-1.77)
Astrocytoma	477	111 (23.3)	11 965	2317 (19.4)	1.30 (1.04-1.62)	1.29 (1.03-1.62)
Non-Hodgkin 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).

however, this has not been explored at length for other cancer types. Although a poor immune response to infections has been seen in children with immunodeficiency diseases who develop malignant lymphoma,[41] these conditions were rare in our population.

Other studies attempted to distinguish between cancer risk from any infection vs from medically diagnosed infections only. A meta-analysis found that childhood infections were strongly associated with increased risk of ALL for laboratory confirmed infections only (odds ratio [OR] = 2.4) whereas null associations were observed when self-reported infections were included (OR = 1.1).[3] This seems to support the hypothesis of an abnormal immune response to clinically diagnosed infections.[43,44]

Previous studies found that day-care attendance, a surrogate for early life infection, reduced the risk of ALL.[45] Furthermore, contrary to our results suggesting a positive association between viral infection and ALL, a cohort study in Taiwan also reported a negative association between childhood enterovirus infections and ALL development.[9] Our findings cannot be used to confirm nor reject the hygiene-related hypothesis of delayed infections and future epidemiologic studies are needed to further examine the timing of these infections. It may be necessary to distinguish between exposure periods during early childhood (eg, first year of life) and later stages. Nonetheless, establishing precise cut-off points for each type of cancer is a challenging task.

We found a strong positive association between urinary tract infections and ALL which previous research has not addressed. However, several studies found associations between maternal genitourinary tract infection during pregnancy and offspring ALL.[46-48] These maternal infections can be transmitted to a child during delivery, however, the exclusion of children born by Cesarean section did not change the results (Table S5). While our findings may address the stronger association between urinary tract infections and ALL, if we examine the magnitude of the effect for other categories of infections in general, there appears to be a lack of specificity. This aligns with

the theory proposed by Greaves suggesting that common infections, rather than specific ones, may be responsible for causing ALL.[49]

Estimated effects between infection and CNS tumors in our study were moderate in size and our results suggested that viral and enteric infections showed a stronger positive association than overall infections. This finding coincides with the emerging model on the gut-brain axis and its contribution to brain tumors.[50,51]

Our results showed that germ cell tumor cases were more likely to have been diagnosed with infections than controls, particularly appendicitis.[20] Mumps is rare in the Denmark population due to high vaccination rates.[52] A study among men aged 18 to 45 years observed a null association between childhood infection and testicular cancer.[53] To our knowledge, the specific pathological pathways between infection and germ cell tumors are unknown.

For other less common childhood cancers including neuroblastoma, Wilms tumor and retinoblastoma we also estimated moderate size positive effects with infections; however, the confidence intervals were wide and—similar to previous studies—the results were not sufficiently definitive to reach conclusions. Nevertheless, some studies suggested that maternal vaginal infections and antibiotic use during pregnancy might be associated with neuroblastoma and Wilms tumor.[54,55] Also, laboratory studies suggested that viruses affect retinoblastoma gene products.[56,57]

Because we used a data-linkage approach based on nationwide population-based registries, the risk of selection bias is limited. Registry data also allowed us to collect clinical diagnoses of infections before the index child's cancer diagnosis and independently of the outcomes eliminating any risk of possible recall bias. We applied an 1-year lag time for exposure to infections to prevent protopathic bias which would have been expected to overestimate the risk from infections in our study.[27]

The present study is nevertheless subject to several limitations. Although we were able to include cancer cases across decades, we still lacked statistical power to investigate some extremely rare

TABLE 4 Conditional logistic regression odds ratios (OR) and 95% confidence intervals (95% CI) 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 = 23 784*)				
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 = 30 454*)				
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 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)

(Continues)

TABLE 4 (Continued)

Type of postnatal infection	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Adj.OR[a] (95% CI)
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)

Note: Infections with less than five exposed cases were omitted from the table.
[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).

cancers. We also did not have enough statistical power to assess associations between rare infections and cancers such as Epstein-Barr virus and lymphoma, for which a causal relationship has been demonstrated.[11] Results based on small sample sizes require cautious interpretation of results.

Even though clinical diagnoses of infections were historically recorded with a standard coding system, some infections may have been diagnosed solely by clinical presentation without having been confirmed by laboratory testing, leading to a potential misclassification of the 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 were more likely to be grouped into broader diagnostic categories, potentially increasing misclassification if only one specific infectious agent is causative. However, we assume that such misclassification would have occurred independent of outcome status and thus would have been nondifferential, resulting in bias toward the null.

Despite considering a 1-year lag-time to prevent protopathic bias, some cancers may still present with delayed diagnoses and varying symptom onset intervals.[58] Additionally, some underdiagnosed children may receive more medical attention, increasing the chance of infection diagnoses, which may slightly inflate the odds ratio estimations. However, we believe that the impact is minor after taking into account the 1-year lag-time.

Finally, uncontrolled confounding may remain due to a lack of information on vaccination experience and duration of breast feeding, factors which may relate to postnatal infections that have been found to be protective against leukemia.[59,60] Yet, breastfeeding in Denmark is near universal and lasts 6 to 8 months on average.[61,62]

5 | CONCLUSION

Although infection has long been proposed as a potential risk factor for leukemia and lymphoma, the evidence on associations between childhood infection and other less common types of cancer in children remains limited. With a large national registry data linkage, this case-control study showed a positive association between postnatal infection with many types of childhood cancers and affirmed prior studies' reports of increases in medically diagnosed infections in children who later develop cancer. Our findings both confirmed and contradicted the previous studies of particular infections and cancers. Additional investigations are needed to address the potential pathways between childhood infection and cancer.

AUTHOR CONTRIBUTIONS

Anupong Sirirungreung: Performed statistical analysis and drafted an article; Responsible for data acquisition, analysis and interpretation as well as critically revising the article for important intellectual content. **Johnni Hansen:** Responsible for the integrity of the data and the accuracy of the data analysis; responsible for data acquisition, analysis and interpretation as well as critically revising the article for important intellectual content. **Beate Ritz:** Responsible for data acquisition, analysis and interpretation as well as critically revising the article for important intellectual content. **Julia E. Heck:** Designed the study; responsible for the integrity of the data and the accuracy of the data analysis; responsible for data acquisition, analysis and interpretation as well as critically revising the article for important intellectual content. The work reported in the article has been performed by the authors, unless clearly specified in the text.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Our study is based on deidentified information from Danish national registers and permission is required prior to data access. Further details are available from the corresponding author upon request.

ETHICS STATEMENT

Our study was approved by Office of the Human Research Protection Program, University of California, Los Angeles (IRB#13-001904), the University of North Texas (IRB-20-255) and the Danish Data Protection Agency.

ORCID

Anupong Sirirungreung https://orcid.org/0000-0003-2571-2680

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