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Maternal Infection in Pregnancy and Childhood Leukemia: A Systematic Review and Meta-analysis

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Abstract

Objective—To summarize the published evidence regarding the association between maternal infection during pregnancy and childhood leukemia.

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The other authors declare no conflicts of interest.

Study design—In this systematic review and meta-analysis (PROSPERO number, CRD42018087289), we searched PubMed and Embase to identify relevant studies. We included human studies that reported associations of at least one measure of maternal infection during pregnancy with acute lymphoblastic leukemia (ALL) or all childhood leukemias in the offspring. One reviewer extracted the data first using a standardized form, and the second reviewer independently checked the data for accuracy. Two reviewers used the Newcastle-Ottawa Scale to assess the quality of included studies. We conducted random effects meta-analyses to pool the ORs of specific type of infection on ALL and childhood leukemia.

Results—This review included 20 studies (ALL, n = 15; childhood leukemia, n = 14) reported in 32 articles. Most (>65%) included studies reported a positive association between infection variables and ALL or childhood leukemia. Among specific types of infection, we found that influenza during pregnancy was associated with higher risk of ALL (pooled OR, 3.64; 95% CI, 1.34–9.90) and childhood leukemia (pooled OR, 1.77; 95% CI, 1.01–3.11). Varicella (pooled OR, 10.19; 95% CI, 1.98–52.39) and rubella (pooled OR, 2.79; 95% CI, 1.16–6.71) infections were also associated with higher childhood leukemia risk.

Conclusions—Our findings suggest that maternal infection during pregnancy may be associated with a higher risk of childhood leukemia.

Leukemia, the most common cancer in children, accounts for about one-third of all childhood cancers worldwide.[1] Evidence has shown that acquired genetic mutations that initiate childhood leukemia occur in utero.[2] Factors affecting genetic stability and cell growth pathways in the fetus may be responsible for a significant proportion of childhood leukemia.

Maternal infection during pregnancy has long been a suspected risk factor for childhood leukemia.[3,4] Infectious agents with oncogenic potential may transfer from mother to fetus, leading to genomic instability.[5] Alternately, fetal infection may lead to immune tolerance because the adaptive immune response in the fetus is immature. This tolerance would allow the long-term persistence of the virus and proliferation of infected cells, resulting in a high viral load.[6,7] Maternal infection may also affect the development of the immune system in the fetus without transplacental transmission.[8] Levels of several cytokines at birth are different between children who develop acute lymphoblastic leukemia (ALL) and matched controls,[9,10] suggesting a role for dysregulated immune function at birth in the development of leukemia. There are, therefore, several plausible mechanisms that might explain the contribution of a specific type of maternal infection or infection in general to childhood leukemia.

The epidemiologic evidence for the association between maternal infection during pregnancy and childhood leukemia has accumulated steadily over the past 6 decades, but with inconsistent findings. Investigated types of infections range from specific pathogens (eg, cytomegalovirus [CMV]) to more general systemic infection (eg, urinary tract infection), based on data collected using laboratory tests, self-report, or medical records. A narrative review published in 2013 found that 11 of 16 articles reported that maternal infection was associated with an increased risk of childhood leukemia.[11] Other reviews of the association with infection at any point before childhood leukemia have only highlighted

a small number of studies on the contribution of maternal infection.[12–14] However, there has been no systematic review or meta-analysis of this association. Furthermore, evidence from studies using laboratory techniques (eg, examining viral DNA[15–17]) has not been summarized and reviewed. We, therefore, conducted a systematic review and meta-analysis to determine whether any maternal infection or specific types of infection during pregnancy was associated with childhood leukemia risk in the offspring.

Methods

The protocol of this systematic review and meta-analysis was registered in PROSPERO (CRD42018087289). We followed the PRISMA guidelines. Because ALL is the largest subgroup of childhood leukemia and relatively homogenous with regards to cell lineage, we used ALL as the primary outcome and all childhood leukemias (not categorized) as the secondary outcome.

We searched PubMed and Embase from inception through January 16, 2018, without language restriction. The search terms and strategy are shown in Table I (available at www.jpeds.com). We also screened the reference lists of included studies. All identified items were imported into Covidence (Veritas Health Innovation, Melbourne, Victoria, Australia), a systematic review software. An updated search was performed through July 17, 2018, with no additional eligible studies identified.

We included studies that were conducted in humans, reported associations between ≥1 measure of maternal infection during pregnancy, and used ALL or childhood leukemia as the outcome in the offspring up to the age of 19 years. Maternal infection during pregnancy can be measured using self-reported questionnaires, medical records, or biospecimens (eg, maternal blood during pregnancy, cord blood, or neonatal dried blood spot). It is possible that any infectious agent detected by dried blood spot was acquired after birth. However, because most causes of early onset neonatal sepsis (ie, clinical infection in the first week of life) are acquired from the mother either in utero or during the birth process, it was felt that infections detected on dried blood spot were most likely to be from maternal infection rather than postnatal exposures. We excluded studies that (1) were reviews, comments, case reports, or conference abstracts, (2) did not measure maternal infection at the individual level (eg, ecological study), (3) only reported results for maternal infection at times other than during pregnancy, (4) used indirect markers for maternal infections (eg, antimicrobial use, vaccination), (5) were restricted to children of specific subgroups (eg, children with trisomy 21), or (6) did not have a full-text article in English. Conference abstracts[18] were excluded from the final review and analysis, but were used to trace relevant full reports via additional searches or by contacting the authors. We also tracked full reports for research letters.[19]

The authors first screened titles and abstracts independently to identify potentially relevant papers, and then assessed the full text for eligibility. Any disagreement was resolved by discussion between the 2 reviewers and/or a third reviewer.

Data Extraction and Quality Assessment

One reviewer extracted the data first using a standardized form, and the second reviewer independently checked the data for accuracy. Disagreements were resolved by discussion between the 2 reviewers and/or a third reviewer. Extracted data items included authors, publication year; study design, study period, sources of participants, matching variables; sample size, country of origin, age at diagnosis of childhood leukemia; type, timing, and measurement method of maternal infection; type (ALL and/or childhood leukemia) and ascertainment method of leukemia; effect size (point estimate and 95% CI) and adjustment variables. When the effect estimate was not reported, we collected raw data of cell counts (details in the Appendix; available at www.jpeds.com). Duplicated publications were identified based on the description of study population, data source, study period, and authors. When multiple articles from a study were identified on the same exposure and outcome variables, only the report with the largest sample size was included; however, if the study samples were independent, they were treated as separate studies.[20,21] When multiple reports from the same study reported different exposures (infections), data were first extracted from each report separately and then linked across multiple reports. These multiple reports of a study were treated as a single study. Authors of 7 studies reported in 14 articles were contacted for additional information or clarification,[17,20,22–33] and 5 studies[17,22,25–33] responded, among which 2 provided clarification.[17,25–31]

Two reviewers used the Newcastle-Ottawa Scale (NOS) to assess the quality of included studies. Consisting of 9 items, the NOS assesses the following domains[34]: selection (4 items), comparability (2 items), and ascertainment of exposure/outcome (3 items). One star is awarded if the study meets 1 assessment item. We used birth date and maternal socioeconomic status for comparability assessment. High-quality studies were defined as those with a NOS score of ≥7, medium-quality as a score of 4–6, and low-quality as a score of ≤3.

Statistical Analyses

Based on the potential mechanisms we mentioned elsewhere in this article, it is possible that both infections in general and specific types of infection can contribute to childhood leukemia. We performed qualitative and quantitative syntheses depending on the infection variables examined to examine the possible broad effects (including immunologic response) of maternal infection; we used an aggregate variable referred to as a “proxy for any infection”. For those studies that reported effect estimates for more than one infection, we included only the infection variable with the highest prevalence in that study as a proxy for any infection. In studies where the association was reported only for a specific infection, we included this infection variable as proxy for any infection in the meta-analysis. Owing to substantial differences in the definition of proxy for any infection and high heterogeneity in effect estimates across studies, a formal meta-analysis was not appropriate; hence, we only qualitatively summarized results for this exposure variable. For each specific type of infection, we conducted quantitative synthesis (meta-analyses) if ≥2 studies presented effect estimates. When studies reported multiple types of immunoglobulins, we selected IgM as the measure of the specific infection given high level of IgM represents recent occurrence of infection (details in the Appendix). We used random effect models (DerSimonian-Laird

method[35]) to pool study-level effect measure of association between specific infections and childhood leukemia (ALL and childhood leukemia separately). We used the Cochran Q test and the I^2 statistic to assess the heterogeneity across studies. A *P* value of <.10 for the Cochran Q test was used to indicate heterogeneity. An I^2 value of ≥50% suggests substantial heterogeneity.[36]

We used the ORs to perform data syntheses (qualitative and quantitative syntheses) as it was the only effect measure reported in included studies. If the OR was not reported, we used data of cell counts, constructed 2 × 2 tables and calculated the crude OR. We added 0.5 to all cells before OR calculation when there was a null value in 1 of the 4 cells. Two studies, 1 for ALL[24] and 1 for childhood leukemia,[23] were excluded from the meta-analysis because the effect estimates and/or 95% CIs was not reported and could not be computed. An additional study was excluded from the data synthesis for childhood leukemia because of its low quality.[37] When ≥2 types of controls were reported, we only used results for the one that was closest to the concept of population-based controls (community controls rather than cancer controls[24]) or, alternatively, with the results with the best matching criteria.

Prespecified subgroup analyses were performed based on exposure measurement method (self-report, medical record, or laboratory test), study design (case-control, nested case-control, or cohort study), study region (Europe, North America, or others), and study quality (high or medium quality). Differences in effect estimates across subgroups were explored by random effects meta-regression. Prespecified sensitivity analysis was performed by excluding studies with less than ten subjects with exposure/outcome. We also repeated the meta-analysis by excluding studies that included cases >19 years of age or that combined the exposure periods 3 months before pregnancy and pregnancy. We used the Egger bias test[38] and a funnel plot to assess the publication bias. Subgroup analysis, sensitivity analysis, and publication bias analysis were performed for the most frequently reported type of infection (ie, influenza). We did not conduct subgroup, sensitivity or publication bias analyses for the other specific types of infection due to the small number of studies. All analyses were performed using STATA software (version 14.0, Stata Corp LP, College Station, Texas).

Results

Of 2072 records identified, 118 were eligible for full-text assessment. After further excluding 86 articles based on our exclusion criteria, the remaining 32 articles[3,4,15–17,20–33,37,39–50] consisted of 20 independent studies included in this review (Figure 1; available at www.jpeds.com). A selection of excluded studies and the reasons for exclusion are listed in Table II (available at www.jpeds.com).

Characteristics of Included Studies

The characteristics of 20 studies (32 individual publications) are shown in Table III. Of these, 13 were case-control, 4 nested case-control, and 3 cohort studies. Twelve studies used nonlaboratory data (self-report or medical records) for exposure assessment, 6 used laboratory data (DNA or immunoglobulin presence in maternal serum during pregnancy or neonatal blood spot at birth), and 2 used both nonlaboratory and laboratory data depending on the type of infection investigated. A total of 3559 ALL cases and 79 619 non-ALL

controls (from 15 studies), 7115 childhood leukemia cases and 88 611 non-childhood leukemia controls (from 14 studies) were included. Out of a maximum of 9, the NOS scores of the 32 articles published from the 20 studies, ranged from 3 to 8 (median, 7): 17 articles were high quality (score of ≥7), 14 medium quality (score of 4–6), and 1 low quality (score of ≤3) (Table IV; available at www.jpeds.com). For ALL, 15 studies investigated 37 different infection variables: 26 (70%) were viral or virus-related infection, 7 (19%) systemic symptoms (eg, urinary tract infection), 3 bacterial (including 1 chlamydia and 1 mycoplasma), and 1 fungal infection (Table V; available at www.jpeds.com). For childhood leukemia, 14 studies investigated 29 infections: 17 (59%) viral or virus-related infection, 8 (28%) systemic symptoms, 3 bacterial (including 1 chlamydia and 1 mycoplasma), and 1 fungal infection (Table VI; available at www.jpeds.com).

Qualitative Evaluation for a "Proxy for Any Infection"

Fourteen studies provided data on effect estimates for ALL and proxy for any infection, with study-level ORs ranging from 0.58 to 11.36 (Figure 2). Of these studies, 10 (71%) reported point estimate ORs of >1, of which 4 were statistically significant (ORs ranging from 2.02 to 11.36). For the 12 studies that had data on ORs for childhood leukemia, 8 (67%) showed proxy for any infection as a risk factor (OR > 1), of which 4 were statistically significant (ORs ranging from 1.55 to 9.09).

Meta-analysis of Specific Types of Infection

Seven types of infections were included in the meta-analyses for ALL. These included influenza (n = 4), urinary tract infection (n = 2), viral infection (n = 5), CMV (n = 3), Epstein-Barr virus (n = 3), human herpesvirus type 6 (n = 2), and species C adenovirus (n = 3). Among them, influenza during pregnancy was associated with a higher risk of ALL (pooled OR, 3.64; 95% CI, 1.34–9.90; I^2 = 54.7%). Both CMV (pooled OR, 3.00; 95% CI, 0.92–9.80; I^2 = 79.0%) and species C adenovirus (pooled OR, 3.69; 95% CI, 0.82–16.57; I^2 = 23.8%) showed an increased risk, but associations were not statistically significant and numbers of studies were low (Figure 3).

For childhood leukemia, 12 infections were included in meta-analyses, including genitourinary infection (n = 2), herpes simplex (n = 2), herpes zoster (n = 2), infectious hepatitis (n = 2), influenza (n = 6), mumps (n = 2), rubella (n = 3), urinary tract infection (n = 3), varicella (n = 2), viral infection (n = 6), CMV (n = 2), and Epstein-Barr virus (n = 2). Influenza (pooled OR, 1.77; 95% CI, 1.01–3.11; I^2 = 64.4%), rubella (pooled OR, 2.79; 95% CI, 1.16–6.71; I^2 = 0%), and varicella (pooled OR, 10.19; 95% CI, 1.98–52.39; I^2 = 0%) infections were significantly associated with a higher risk of childhood leukemia (Figure 4). There were no significant associations observed for other types of infections.

Subgroup analyses for influenza showed that pooled ORs among cohort studies seemed to be higher than those in case-control studies (eg, pooled OR, 7.91 [95% CI, 1.83–34.24][4,48] vs pooled OR, 2.10 [95% CI, 1.35–3.27][32,45] for ALL), but the *P* value for the interaction was >.1; both groups had lower heterogeneity compared with the overall analysis (Table VII; available at www.jpeds.com). The pooled ORs across different stratum of measurement method, study region, or study quality were similar. Sensitivity analyses excluding studies

with <10 subjects with exposure/outcome or excluding studies with cases >19 years of age had similar results to the overall analysis, although the CIs were wider (Table VIII; available at www.jpeds.com). When excluding studies that combined the exposure periods 3 months before pregnancy and pregnancy, the pooled ORs (eg, pooled OR, 6.87 [95% CI, 2.57–18.42] for ALL) seemed to be higher than those in overall analysis (pooled OR, 3.64 [95% CI, 1.34–9.90] for ALL).

Assessment of Publication Bias

Funnel plots appear symmetrical (Figure 5; available at www.jpeds.com), and the Egger test revealed that there was no evident publication bias or small-study effects (*P* values of >.4). The potential for publication bias for other infections could not be assessed owing to the small number of studies.

Results for Studies Not Included in Data Synthesis (Qualitative or Quantitative)

Among the infections not included in the meta-analysis because only 1 study reported the effect estimate, an increased risk of ALL and childhood leukemia was observed for lower genital tract infection (pooled OR, 1.63 [95% CI, 1.04–2.53] for ALL, 1.78 (pooled OR, 1.17–2.72) for childhood leukemia), sexually transmitted diseases (pooled OR, 6.65 [95% CI, 1.37–32.38] for ALL, 7.59 [95% CI, 1.58–36.56] for childhood leukemia), and mycoplasma pneumoniae (pooled OR, 1.6 [95% CI, 1.0–2.6] for ALL, 1.6 [95% CI, 1.0–2.5] for childhood leukemia) (Tables V and VI). Varicella infection was associated with higher risk of ALL (pooled OR, 17.2; 95% CI, 1.55–190.07) (Table V).

Discussion

In this systematic review and meta-analysis, we found that 3 types of infection (influenza, varicella, and rubella) were significantly associated with a higher risk of ALL and/or childhood leukemia, although numbers of studies were small. For the hypothesis of any infection, we were unable to perform a quantitative synthesis because of the high heterogeneity across studies; however, most of included studies reported a positive association of childhood leukemia when we used a variable of proxy for any infection.

Among the specific infections, the meta-analysis results for influenza seemed to be more robust, based on the number and quality of studies and sample size. However, the results should be interpreted with some degree of caution given there was substantial heterogeneity across studies reporting on influenza. This finding may be explained by study design (cohort vs case-control study) and different methods (self-reports, medical records, or 2 combined) used to collect influenza data across studies. We also found rubella and varicella infections during pregnancy were associated with increased risk of childhood leukemia, despite the small number of studies. It has been shown that these 2 infections may be transmitted from the mother to the fetus and cause congenital or neonatal infection[51,52]; thus, they are more likely to directly affect the fetus/child. However, further studies are needed to confirm the findings on these 2 infections.

The strengths of our review include its adherence to a registered protocol, methodologic advantages, no obvious evidence publication bias, and consistent results in sensitivity

analyses, suggesting the robustness and validity of our findings. Several limitations, however, should be noted. First, few studies reported results for a variable of any infection; thus, it was difficult to test our hypothesis that any infection might be linked with childhood leukemia via general immunologic response. To address this issue, we used a specific type of infection as a proxy to represent any infection for studies that did not report a variable of any infection. However, the high heterogeneity across studies precluded a meta-analysis for this proxy variable. Second, for the meta-analysis of specific infections, and relatively strong associations were observed for varicella and rubella and childhood leukemia, the number of studies were too small to draw confident conclusions. Third, we were unable to perform subgroup analyses by exposure timing, age at diagnosis, and race/ethnicity because very few studies reported results stratified on these variables. Fourth, most of the included studies failed to adjust for socioeconomic status or other maternal characteristics such as age and obesity, which are potential confounders.[53–55] Therefore, the associations observed in the original individual studies as well as in our meta-analyses might be confounded by ≥1 factors.

The findings from this systematic review highlight the lack of consistent epidemiologic evidence to support an association for specific infections and childhood leukemias. However, plausible biological mechanisms have been reported in studies examining in utero exposures to maternal infections and childhood cancer. Besides the genetic and immunologic mechanisms that we outlined elsewhere in this article, fetal infection may initiate immune dysregulation, through initial B-cell sensitization during programming of central tolerance, thereby altering adaptive immune response independent of viral load and cryptically contributing to leukemia. Another possibility is that maternal infections (especially those leading to severe illnesses) might result in adverse and other pregnancy outcomes, for example, cesarean delivery[56,57] and shorter gestational length[58] that, in turn, increase the risk of childhood leukemia.[54,59] In addition, it is possible that the use of antibiotics or other medications to treat infection and related symptoms, rather than the infection itself, could be related to the risk of leukemia. Whether the medication use acts as a mediator or directly on the causal pathway requires further investigation.

Although this review does not include postnatal infections, it is important to distinguish timing of infection and leukemia risk. A popular theory known as the delayed infection or hygiene hypothesis posits that a paucity of infections early in life may increase the risk of childhood leukemia.[2,60] Our analysis focused on the pregnancy window and suggests that maternal infections during pregnancy are associated with childhood leukemia. As mentioned, maternal infection might alter the fetal immune system development, and one might hypothesize that this alteration may become overt in childhood if there is no correction by the early (postnatal) exposure to infection. However, we were not able to investigate this possibility with the evidence currently available. Further research is needed to understand critical windows of infection, and interaction by timing of infections to further elucidate temporally varying risk and the underlying mechanism of leukemogenesis.

Our findings suggest directions for future epidemiologic research on this topic. The observation that the association of influenza was stronger in cohort studies than case-control studies suggests that there should be more emphasis on this study design in the future. Not

only would this approach reduce the possibility of recall bias, it would provide a greater opportunity for obtaining predisease biospecimens. However, adequately powered prospective studies in this field are scarce owing to the rarity of childhood leukemia. In addition, given that limited information was available on exposure timing, age at diagnosis and race/ethnicity among the studies included in our review, future studies should also explore whether the relationship between maternal infection and childhood leukemia varies across different strata of these factors.

Our findings suggest that, although based on a small number of studies, specific infections during pregnancy are associated with childhood leukemia. These findings justify the need for further research; however, they should not be used as a basis for supporting specific preventive measures. Further studies are needed to confirm our findings, ideally with larger sample sizes, including a greater collection of prospective evidence, and more accurate methods for detecting and measuring infection. ■

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

ALL	Acute lymphoblastic leukemia
CMV	Cytomegalovirus
NOS	Newcastle-Ottawa Scale

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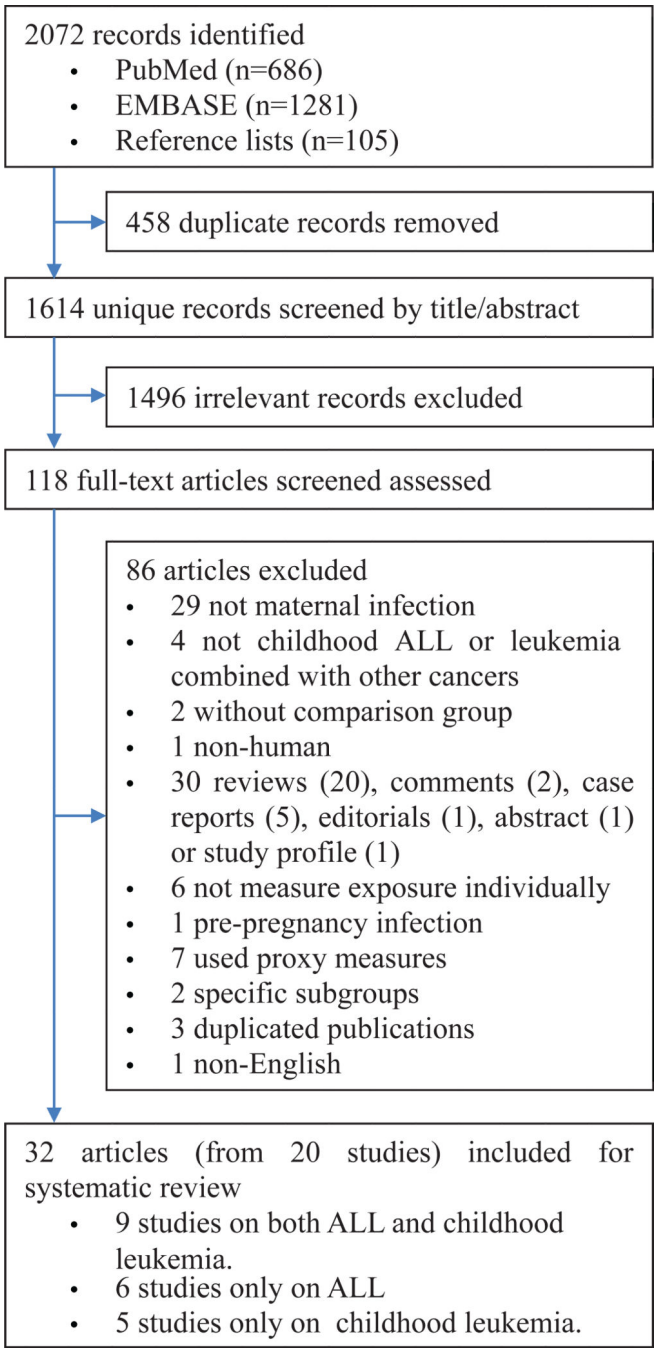

Figure 1.
Study selection flow chart.

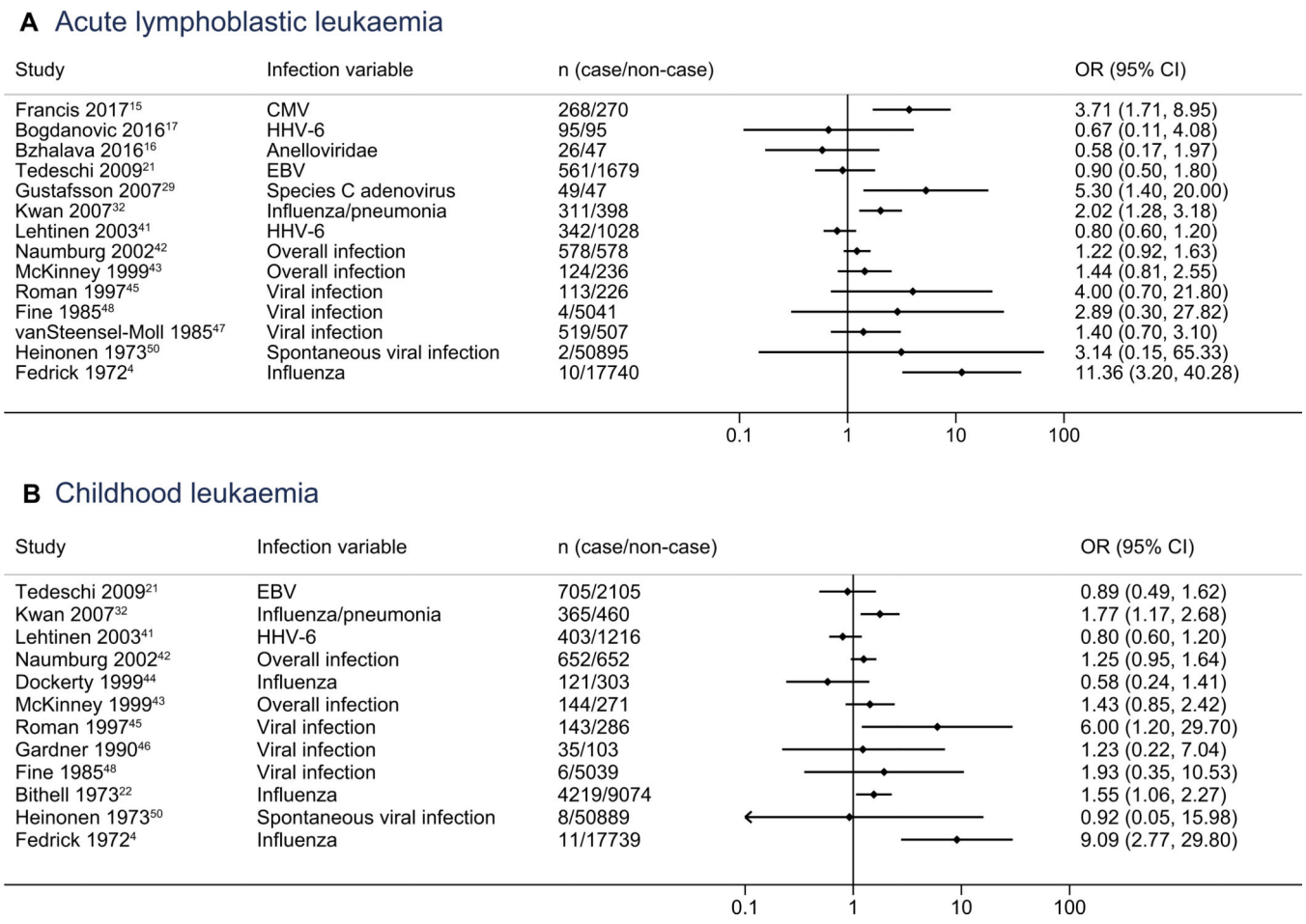

Figure 2.

Qualitative summary of a proxy of any infection for **A**, ALL and **B**, all childhood leukemias. *EBV*, Epstein-Barr virus; *HHV-6*, human herpesvirus type 6.

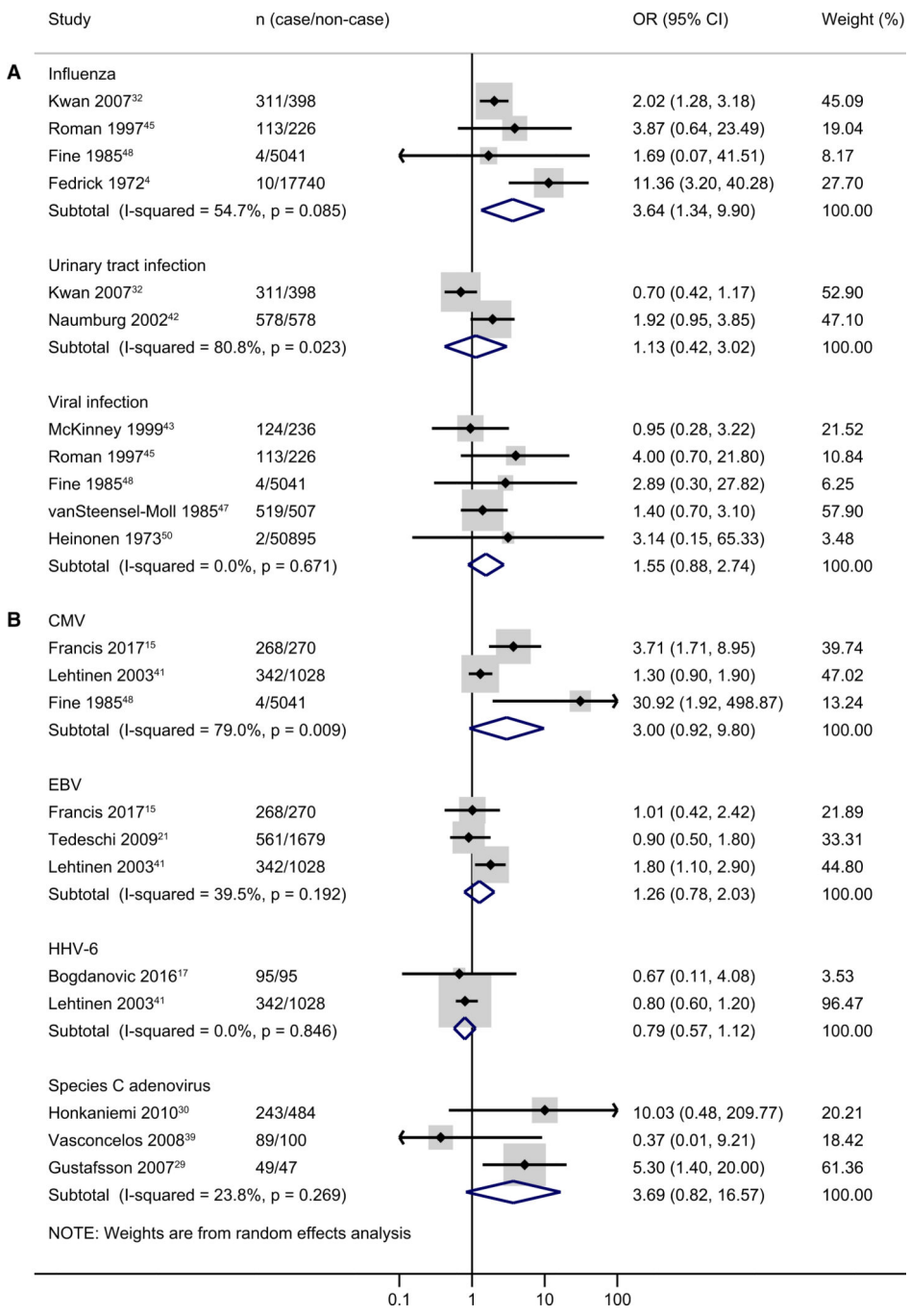

Figure 3.

Meta-analysis of specific type of infection for ALL (**A**, nonlaboratory data; **B**, laboratory data). The study of Fine et al 1985 used both self-report or medical record data for CMV.

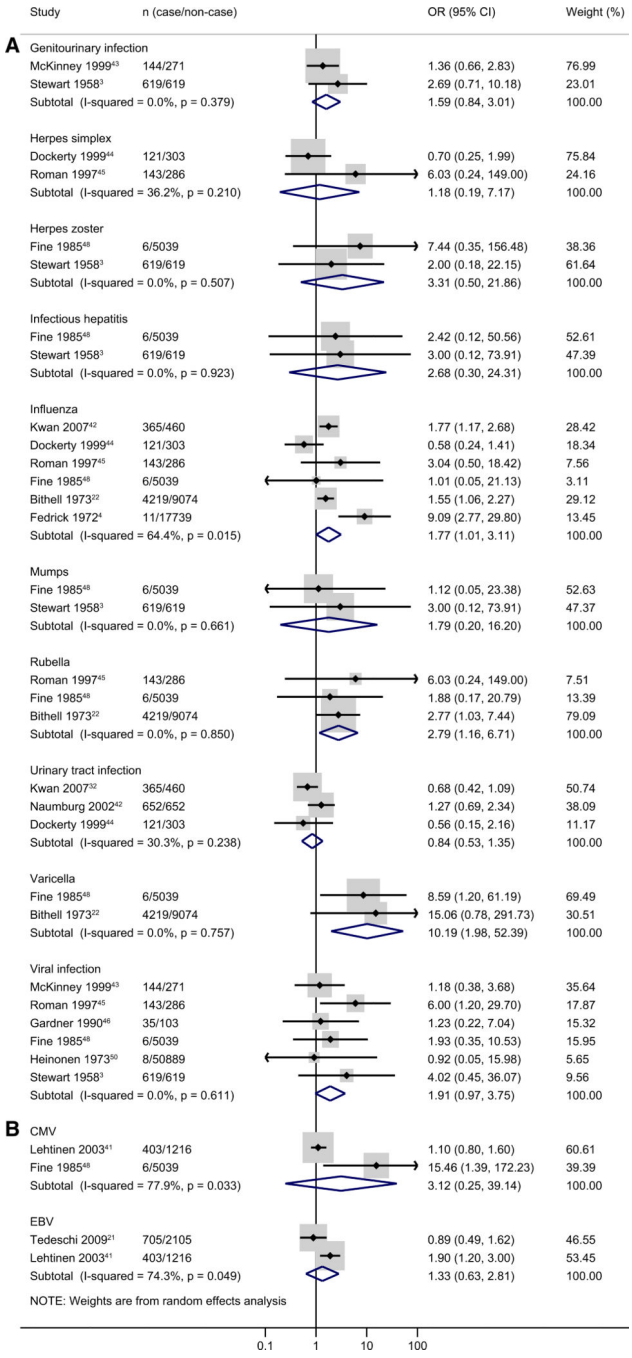

Figure 4.

Meta-analysis of specific type of infection for all childhood leukemias (**A**, nonlaboratory data; **B**, laboratory data). The study of Fine et al 1985 used both self-report or medical record data for CMV.

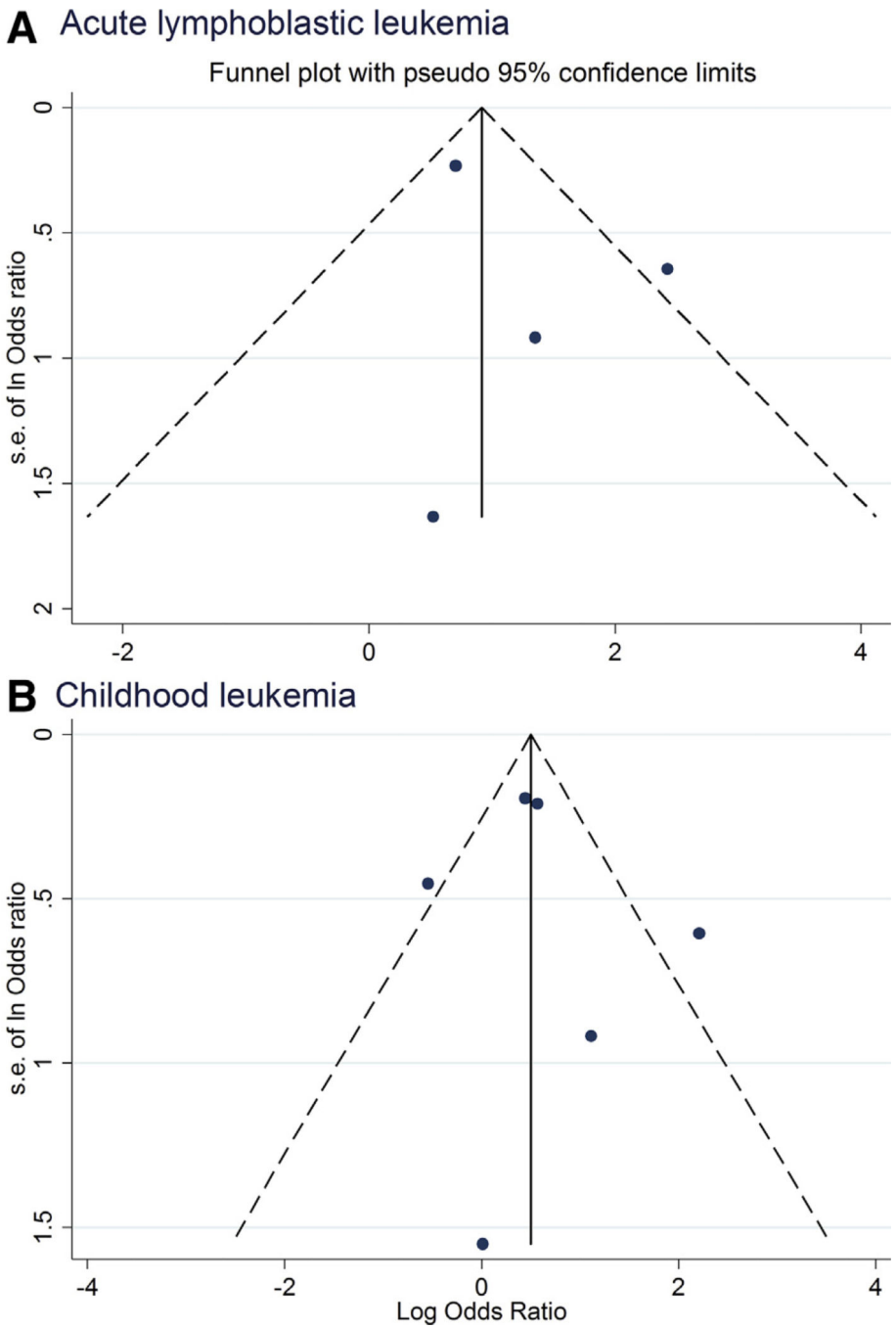

Figure 5.
Funnel plots of influenza for **A**, ALL and **B**, all childhood leukemias.

Table I.

Search term in PubMed and EMBASE

Nos.	Search terms
PubMed (searched on 16 January 2018)	
#1	"Bacterial Infections and Mycoses"[Mesh] OR "Virus Diseases"[Mesh] OR "Parasitic Diseases"[Mesh] OR Infect*[TIAB] OR bacteri*[TIAB] OR virus[TIAB] OR viral[TIAB] OR fungus[TIAB] OR fungi[TIAB] OR fungal[TIAB] OR parasite*[TIAB]
#2	"Maternal Exposure"[Mesh] OR maternal[TIAB]
#3	intrauterine[TIAB] OR "in utero"[TIAB] OR prenatal[TIAB] OR antenatal[TIAB]
#4	"Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR "Pregnancy Trimesters"[Mesh] OR pregnan* [TIAB] OR gestation*[TIAB] OR conception*[TIAB] OR trimester*[TIAB]
#5	"Fetus"[Mesh] OR fetus*[TIAB] OR foetus*[TIAB] OR foetal*[TIAB] OR fetal*[TIAB]
#6	"Fetal Blood"[Mesh] OR "Dried Blood Spot Testing"[Mesh] OR cord blood*[TIAB] OR Guthrie card*[TIAB] OR blood spot*[TIAB]
#7	#2 OR #3 OR #4 OR #5 OR #6
#8	#1 AND #7
#9	"Leukemia"[Mesh] OR leukemia[TIAB] OR leukemia[TIAB]
#10	"Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh] OR newborn*[TIAB] OR neonat*[TIAB] OR infan*[TIAB] OR toddler*[TIAB] OR child*[TIAB] OR adolescen*[TIAB] OR juvenile[TIAB] OR teen*[TIAB] OR girl*[TIAB] OR boy*[TIAB] OR youth*[TIAB] OR paediatric*[TIAB] OR pediatric*[TIAB]
#11	#9 AND #10
#12	#8 AND #11
EMBASE via Ovid (1974 to 15 January 2018)	
#1	exp infection/ or (infect* or bacteri* or virus or viral or fungus or fungi or fungal or parasite*).tw.
#2	maternal exposure/ or maternal.tw.
#3	prenatal exposure/ or prenatal period/ or (intrauterine or in utero or prenatal or antenatal).tw.
#4	exp pregnancy/ or exp conception/ or pregnant woman/ or (pregnan* or gestation* or conception* or trimester*).tw.
#5	fetus/ or (fetus* or foetus* or foetal* or fetal*).tw.
#6	fetus blood/ or umbilical cord blood/ or dried blood spot testing/ or (cord blood* or Guthrie card* or blood spot*).tw.
#7	2 or 3 or 4 or 5 or 6
#8	1 and 7
#9	exp leukemia/ or (leukemia or leukemia).tw.
#10	exp juvenile/ or (newborn* or neonat* or infan* or toddler* or child* or adolescen* or juvenile or teen* or girl* OR boy* or youth* or paediatric* or pediatric*).tw.
#11	9 and 10

Nos.	Search terms
#12	8 and 11

Table II.

A selection of excluded studies and the corresponding exclusion reasons

Nos.	Citation	Exclusion reasons
1	Influenza during pregnancy in relation to subsequent childhood leukemia and lymphoma. Am J Epidemiol 1974;100:399–409.	Not measure at the individual level
2	Maternal health conditions during pregnancy and acute leukemia in children with Down syndrome: A Children's Oncology Group study. Pediatr Blood Cancer 2009;52:602–8.	Restricted to children of specific subgroups
3	Childhood cancer in relation to infections in the community during pregnancy and around the time of birth. Int J Cancer 2003;104:772–7.	Not measure at the individual level
4	Markers of infection, breast-feeding and childhood acute lymphoblastic leukemia. Br J Cancer 2000;83:1559–64.	Used indirect markers for maternal infections
5	Association between influenza during pregnancy and childhood leukemia. Br Med J 1973;4:265–7.	Not measure at the individual level
6	Antibiotic use from conception to diagnosis of child leukemia as compared to the background population: a nested case-control study. Pediatr Blood Cancer 2015;62:1155–61.	Used indirect markers for maternal infections
7	Letter: sequelae of virus infection in pregnancy. Br Med J 1974;2:502.	Duplicated publication
8	Childhood leukemia and maternal infectious diseases during pregnancy. J Natl Cancer Inst 1974;53:943–7.	Not measure at the individual level
9	Childhood and maternal infections and risk of acute leukemia in children with Down syndrome: a report from the Children's Oncology Group. Br J Cancer 2004;91:1866-72.	Restricted to children of specific subgroups
10	Prescription drug use during pregnancy and risk of childhood cancer - is there an association?. Cancer Epidemiol 2015;39:8–73.	Used indirect markers for maternal infections
11	Foetal infection, childhood leukemia and cancer. Br J Cancer 1983;48:849–52.	Used indirect markers for maternal infections
12	Childhood leukemia and mother-foetus infection. Br J Cancer 1980;42:158–61.	Maternal infection that did not occur during pregnancy
13	Maternal use of antibiotics and cancer in the offspring: results of a case-control study in Germany. Cancer Causes Control 2010;21:1335–45.	Used indirect markers for maternal infections
14	Excess leukemia in cohorts of children born following influenza epidemics. Am J Epidemiol 1975;101:77–83.	Not measure at the individual level
15	Incidence of neoplasms in children born after influenza epidemics. Br Med J 1972;4:631–4.	Not measure at the individual level
16	Malignant disease in children whose mothers had chickenpox, mumps, or rubella in pregnancy. Br Med J 1972;4:629–31.	Duplicated publication
17	Sequelae of virus infection in pregnancy. Child Health 1976;31:72–83.	Duplicated publication
18	Childhood cancers and their association with pregnancy drugs and illnesses. Paediatr Perinat Epidemiol 1989;3:66–94.	Combined with other childhood cancers

Table III.

Characteristics of included studies

Study nos.	Publication	Year	Country	Study design	Study period*	Subject source	Matching/adjusting variables	Sample size	Investigated exposure (agents)	Measurement method and exposure timing
#1	Francis et al[15]	2015	USA	Nested case-control†	1982–2006 (birth year)	Population based	Birth date, race and sex/race, age, and sex	268 ALL and 270 controls	CMV,‡ EBV (DNA)	Digital droplet PCR in neonatal blood spot
#2	Bogdanovic et al[17]	2016	Sweden	Case-control	1992–2006	Population based	Age or birthdate and birthplace	95 ALL and 95 controls	HHV-6,‡ parvovirus B19, HERV (DNA)	Next-generation sequencing in pooled samples and real-time PCR in individual samples of neonatal blood spots
	Gustafsson et al[31]	2012						50 ALL and 100 controls	KIPyV, WUPyV, MCPyV (DNA)	Nested PCR in neonatal blood spots
	Honkaniemi et al[30]	2010						243 ALL and 484 controls	Species C adenovirus (DNA)	
#3	Bzhalava et al[16]	2016	Sweden	Nested case-control	1977–2005	Population based	None	26 ALL cases and 47 controls	Anelloviridae,‡ viruses from environmental samples, papillomaviridae, “unclassified” viruses (DNA)	Next generation sequencing in first trimester maternal sera
#4	Kumar et al[37]	2014	India	Case-control	2008–2012	Hospital based	Age, sex and residency	132 leukemia and 132 controls	Infection‡	Self-report interview on exposure during pregnancy
#5	Tedeschi et al[21]	2009	Finland and Iceland	Nested case-control	1983–2006	Population based	Mother’s country, age at serum sampling, date of specimen collection and children’s birth date and sex/birth order and sibship size	705 leukemia (561 ALL) and 2105 controls	EBV (VCA IgM,‡ EA and ZEBRA IgG)	ELISA in first trimester maternal sera
#6	Vasconcelos et al[39]	2008	USA	Case-control	1995–2002	Population based	Birth date, sex, ethnicity, maternal	89 ALL and 100 controls	Species C adenoviruses (DNA)	Seminested PCR in neonatal blood spots
	Kwan et al[32]	2007					county of residence at birth, or plus maternal race/household income, maternal education, and maternal age at the birth of the child	365 leukemia (311 ALL) and 460 controls	Influenza/pneumonia,‡ urinary tract infection, sexually transmitted diseases	Self-report interview on exposure from 3 months before pregnancy through the end of pregnancy

Study nos.	Publication	Year	Country	Study design	Study period*	Subject source	Matching/adjusting variables	Sample size	Investigated exposure (agents)	Measurement method and exposure timing
#7	Gustafsson et al[29]	2007	Sweden	Case-control	1980–2001	Hospital based	Birthdate or age and birthplace	49 ALL and 47 controls	Species C adenoviruses DNA≠	Nested PCR in neonatal blood spots
	Gustafsson et al[28]	2006						48 ALL and 46 controls	CMV (DNA)	
	Bogdanovic et al[27]	2004						54 ALL and 47 controls	HHV-6, EBV (DNA)	
	Isa et al[26]	2004						54 ALL and 50 controls	Parvovirus B19 (DNA)	
	Priftakis et al[25]	2003						54 ALL and 37 controls	BKV, JCV (DNA)	
#8	Leppik et al[33]	2007	Finland and Iceland	Nested case-control	1975–1997	Population based	Mothers' country, age at serum sampling, date of specimen collection and children's birth date and sex	30 leukemia and 30 controls	TT virus (DNA)	PCR in first trimester maternal sera
	Tedeschi et al[20]	2007						343 leukemia (304 ALL) and 973 controls	EBV (VCA IgM, EA IgG and IgM, ZEBRA IgG and IgM)	ELISA in first trimester maternal sera
	Lehtinen et al[40]	2005						402 leukemia (341 ALL) and 1212 controls	Mycoplasma pneumoniae, chlamydia trachomatis, helicobacter pylori (IgM and IgG)	
	Lehtinen et al[41]	2003						403 leukemia (342 ALL) and 1216 controls	HHV-6 (IgM,≠ IgG); CMV, EBV VCA (IgM, IgG)	
#9	Naumburg et al[42]	2002	Sweden	Case-control	1973–1989	Population based	Sex and birth in the same year and month/ adjustments for potential confounders only marginally influenced the risk estimates, such as mothers age, parity, mode of delivery (vaginal or caesarian), maternal smoking, elapsed time from rupture of the membranes to delivery, gestational age at birth, birth weight, birth weight	652 leukemia (578 ALL) and 652 controls	Infection,≠ lower genital tract infection, urinary tract infection, other infection	Data extracted from medical record on exposure during pregnancy

Study nos.	Publication	Year	Country	Study design	Study period*	Subject source	Matching/adjusting variables	Sample size	Investigated exposure (agents)	Measurement method and exposure timing
							for gestational age, and type of birth (single or multiple).			
#10	Dockerty et al[44]	1999	New Zealand	Case-control	1990–1993	Population based	None	121 leukemia and 303 controls	Influenza,≠ cystitis or kidney infection, cold sores/oral herpes, any other infection	Self-reported questionnaire on exposure during pregnancy or in the 3 months before the pregnancy
#11	McKinney et al[43]	1999	UK	Case-control	1991–1994	Population based	Age, sex and health board area of residence	144 leukemia (124 ALL) and 271 controls	Any infection,≠ respiratory tract infection, viral infection, genitourinary infection, fungal infection	Data abstracted from medical record on exposure during pregnancy
#12	Roman et al[45]	1997	UK	Case-control	1962–1992	Hospital based	Hospital catchment area of birth, sex and year and month of birth	143 leukemia (113 ALL) and 286 controls	Viral infection,≠ influenza, vulvar warts, herpes simplex, rubella	Data abstracted from medical record on exposure during pregnancy
#13	Buckley et al[24,§]	1994	USA and Canada	Case-control	1982–1991	Hospital based	Birth year, race, income, geographical region and family size	404 ALL and 440 community controls	Infection	Self-administered questionnaire on exposure during pregnancy
#14	Gardner et al[46]	1990	UK	Case-control	1950–1985	Population based	Sex, birth date and residence	35 leukemia and 103 local controls	Viral infection≠	Self-reported questionnaire on exposure during pregnancy
#15	McKinney et al[23,§]	1987	UK	Case-control	1980–1983	Population based	Sex and age	171 leukemia and 342 controls	Influenza, urinary tract infection	Self-reported interview on exposure during pregnancy
#16	Fine et al[48]	1985	UK	Prospective and retrospective cohorts	1946–1972	Population based	Sex and date and area of birth	6 leukemia (4 ALL) and 5039 nonleukemia	Viral infection,≠ influenza, varicella, herpes zoster, mumps, rubella, measles, infectious hepatitis, CMV, miscellaneous viruses	Self-reported interview or medical records from general practice, local authority, hospital and virus laboratory sources
#17	Van Steensel-Moll et al[47]	1985	Netherlands	Case-control	1973–1980	Population based	Birth date, sex and municipality/age and sex	519 ALL and 507 controls	Viral infections≠	Self-administered questionnaires on exposure during pregnancy
#18	Madden et al[49]	1983	USA	Nested case-control	1959–1966	Hospital based	Maternal age, race, date of delivery, hospital,	7 leukemia deaths and 7 controls	BKV IgM	ELISA in maternal sera series

Study nos.	Publication	Year	Country	Study design	Study period*	Subject source	Matching/adjusting variables	Sample size	Investigated exposure (agents)	Measurement method and exposure timing
							socioeconomic relationships			
	Heinonen et al[50]	1973		Prospective cohort			None	8 leukemia (including 2 ALL¶) deaths and 50 889 controls	Spontaneous viral infections‡	Self-reported interview and review of hospital and other records on exposure during pregnancy
#19	Bithell et al[22]	1973	UK	Case-control	1953–1967	Population based	None	4219 leukemia deaths and 9074 controls	Influenza,‡ rubella, varicella, other virus infections	Self-reported interviews and review of antenatal records (whenever possible) on exposure during pregnancy
	Stewart et al[3]	1958					Age (birth in the same month or half year), sex, locality	619 leukemia deaths and 619 controls	Genitourinary tract, virus infection, rubella, mumps, herpes zoster, infective hepatitis	
#20	Fedrick and Alberman[4]	1972	UK	Prospective cohort	1958	Population based	Birth date	11 leukemia (10 ALL**) and 17 739 nonleukemia	Influenza‡	Self-reported questionnaires on exposure during pregnancy

BKV, BK virus; *EBV*, Epstein-Barr virus; *EA*, early antigen; *ELISA*, enzyme-linked immunosorbent assay; *HHV-6*, human herpesvirus type 6; *HERV*, human endogenous retroviruses; *JCV*, JC virus; *KIPyV*, Karolinska Institutet polyomavirus; *MCPyV*, Merkel cell polyomavirus; *PCR*, polymerase chain reaction; *TT* virus, Torque teno viruses; *VCA*, viral capsid antigen; *WUPyV*, Washington University polyomavirus.

*Diagnosis year of cases for case-control study or recruitment year of mothers or babies for cohort study.

†This study was categorized as nested case-control study because the cases and controls were drawn from the same source population at birth (Childhood Cancer Record Linkage Program).

‡Variables that were selected as the "proxy of any infection" variable in qualitative summary in Figure 2.

§The studies of Buckley et al[24] in 1994[24] and McKinney et al[23] in 1987[23] were not included in any meta-analysis because the effect estimate or 95% CI was not reported and could not be computed.

¶Two cases of "leukemia, lymphoblastic" or "leukemia, lymphocytic" in the nonexposed group were treated as ALL.

**One case of lymphoblastic leukemia in the non-exposed group was treated as ALL.

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Table IV.

Quality assessment of included studies using the NOS*

Study nos.	Publication	Year	Selection (4 items)	Comparability† (2 items)	Exposure/outcome assessment (3 items)	Total score
#1	Francis et al15	2017	★★★★	★	★★★	8
#2	Bogdanovic et al17	2016	★★★★		★★★	7
	Gustafsson et al31	2012	★★★	★	★★★	7
	Honkaniemi et al30	2010	★★★★	★	★★★	8
#3	Bzhalava et al16	2016	★★★★		★★★	7
#4	Kumar et al37	2014	★		★★	3
#5	Tedeschi et al21	2009	★★★★	★	★★★	8
#6	Vasconcelos et al39	2008	★★★	★	★★★	7
	Kwan et al32	2007	★★★★	★★	★★	8
#7	Gustafsson et al29	2007	★★★	★	★★★	7
	Gustafsson et al28	2006	★★★		★★★	6
	Bogdanovic et al27	2004	★★★		★★★	6
	Isa et al26	2004	★★★		★★★	6
	Priftakis et al25	2003	★★★	★	★★★	7
#8	Leppik et al33	2007	★★★	★	★★★	7
	Tedeschi et al20	2007	★★★★	★	★★★	8
	Lehtinen et al40	2005	★★★★	★	★★★	8
	Lehtinen et al41	2003	★★★★	★	★★★	8
#9	Naumburg et al42	2002	★★★★	★	★★	7
#10	Dockerty et al44	1999	★★★	★	★★	6
#11	McKinney et al43	1999	★★★		★★	5
#12	Roman et al45	1997	★★	★	★★	5
#13	Buckley et al24	1994	★★★	★	★	5
#14	Gardner et al46	1990	★★★★	★	★	6
#15	McKinney et al23	1987	★★★		★★	5
#16	Fine et al48	1985	★★★	★	★★	6
#17	Van Steensel-Moll et al47	1985	★★★	★	★★	6
#18	Madden et al49	1983	★★★	★★	★★★	8

Study nos.	Publication	Year	Selection (4 items)	Comparability† (2 items)	Exposure/outcome assessment (3 items)	Total score
	Heinonen et al50	1973	★★★★		★★	6
#19	Bithell et al22	1973	★★★★		★★	6
	Stewart et al3	1958	★★★★		★	5
#20	Fedrick and Alberman4	1972	★★★★	★	★★★	8

*One star is awarded if the study meets 1 assessment item.

†The 2 items used for comparability assessment were birth date and maternal socioeconomic status (eg, educational level, income).

Table V.

Results of studies on ALL that were not included into any data synthesis (qualitative or quantitative) and reasons for exclusion

Infection variables	No. of study Investigating	No. of study included in data synthesis	Studies not included in any data synthesis			
			Study ID	Year	Results	Reason for exclusion
Proxy of any infection	15*	14*	Buckley et al24	1994	OR, 1.0, $P \geq .1$	Did not provide exact CI for OR
Viral infection	5†	5†	None	–		
Influenza	4‡	4‡	None	–		
CMV	4	3	Gustafsson et al28	2006	Not found in both case and control group	OR cannot be calculated
EBV	4	3	Bogdanovic et al27	2004	Not found in both case and control group	OR cannot be calculated
HHV-6	3	2	Bogdanovic et al27	2004	Not found in both case and control group	OR cannot be calculated
Species C adenovirus	3	3	None	–		
Rubella	2	0	Roman et al45	1997	None of case or control had exposure	Only 1 study had a valid OR and 95% CI for rubella
			Fine et al48	1985	OR, 1.25; 95% CI, 0.05–30.79	
Urinary tract infection	2	2	None	–		
Parvovirus B19	2	0	Isa et al[26]	2004	Not found in both case and control group	Only 1 study had valid OR and 95% CI for Parvovirus B19
			Bogdanovic et al[17]	2016	OR, 3.06; 95% CI, 0.12–76.20	
Varicella	1		Fine et al[48]	1985	OR, 17.2; 95% CI, 1.55–190.07	Only 1 study reporting
Genitourinary infection	1		McKinney et al[43]	1999	OR, 1.18; 95% CI, 0.5–2.79	Only 1 study reporting
Herpes zoster	1		Fine et al[48]	1985	OR, 12.4; 95% CI, 0.50–307.32	Only 1 study reporting
Infectious hepatitis	1		Fine et al[48]	1985	OR, 4.03; 95% CI, 0.16–99.33	Only 1 study reporting
Mumps	1		Fine et al[48]	1985	OR, 1.87; 95% CI, 0.08–45.94	Only 1 study reporting
BKV	1		Priftakis et al[25]	2003	Not found in both case and control group	OR cannot be calculated
Chlamydia trachomatis	1		Lehtinen et al[40]	2005	OR, 0.7; 95% CI, 0.2–2.3	Only 1 study reporting
Fungal infection	1		McKinney et al[43]	1999	OR, 0.34; 95% CI, 0.07–1.54	Only 1 study reporting
Helicobacter pylori	1		Lehtinen et al[40]	2005	OR, 0.8; 95% CI, 0.3–1.9	Only 1 study reporting
Herpes simplex	1		Roman et al[45]	1997	None of cases or controls had exposure	OR cannot be calculated

Infection variables	No. of study Investigating	No. of study included in data synthesis	Studies not included in any data synthesis			
			Study ID	Year	Results	Reason for exclusion
Lower genital tract infection	1		Naumburg et al[42]	2002	OR, 1.63; 95% CI, 1.04–2.53	Only 1 study reporting
Sexually transmitted diseases	1		Kwan et al[32]	2007	OR, 6.65; 95% CI, 1.37–32.38	Only 1 study reporting
Vulvar warts	1		Roman et al[45]	1997	OR, 7.64; 95% CI, 0.31–188.95	Only 1 study reporting
Measles	1		Fine et al[48]	1985	OR, 20.88; 95% CI, 0.84–520.58	Only 1 study reporting
Miscellaneous viruses	1		Fine et al[48]	1985	OR, 3.85; 95% CI, 0.16–94.69	Only 1 study reporting
Mycoplasma pneumoniae	1		Lehtinen et al[40]	2005	OR, 1.6; 95% CI, 1.0–2.6	Only 1 study reporting
Respiratory tract infection	1		McKinney et al[43]	1999	OR, 1.64; 95% CI, 0.60–4.46	Only 1 study reporting
Anelloviridae	1		Bzhalava et al[16]	2016	OR, 0.58; 95% CI, 0.17–1.97	Only 1 study reporting
HERV	1		Bogdanovic et al[17]	2016	The same HERV composition was found in both case and control groups	OR cannot be calculated
JCV	1		Priftakis et al[25]	2003	Not found in both case and control group	OR cannot be calculated
KIPyV	1		Gustafsson et al[31]	2012	Not found in both case and control group	OR cannot be calculated
MCPyV	1		Gustafsson et al[31]	2012	Not found in both case and control group	OR cannot be calculated
Papillomaviridae	1		Bzhalava et al[16]	2016	OR, 0.58; 95% CI, 0.02–14.88	Only 1 study reporting
Viruses from environmental samples	1		Bzhalava et al[16]	2016	OR, 0.51; 95% CI, 0.16–1.61	Only 1 study reporting
WUPyV	1		Gustafsson et al[31]	2012	Not found in both case and control group	
“Unclassified” viruses	1		Bzhalava et al[16]	2016	OR, 1.56; 95% CI, 0.50–4.82	Only 1 study reporting
Other infection	1		Naumburg et al[42]	2002	OR, 1.13; 95% CI, 0.81–1.60	Only 1 study reporting

BKV, BK virus; *EBV*, Epstein-Barr virus; *HHV-6*, human herpesvirus type 6; *HERV*, human endogenous retroviruses; *JCV*, JC virus; *KIPyV*, Karolinska Institutet polyomavirus; *MCPyV*, Merkel cell polyomavirus; *OR*, odds ratio; *WUPyV*, Washington University polyomavirus.

*Three studies (Naumburg et al[42] in 2002, McKinney et al[43] in 1999, Buckley et al[24] in 1994) used a variable of total infection; for other studies, we selected specific type of infection that had the highest prevalence as any infection.

†One study used a variable of spontaneous viral infection.

‡One study used a variable of influenza/pneumonia.

Table VI.

Results of studies on all childhood leukemias that were not included into any data synthesis (qualitative or quantitative) and reasons for exclusion

Infection variables	No. of study Investigating	No. of study included in data synthesis	Studies not included in any data synthesis			
			Study ID	Year	Results	Reason for exclusion
Proxy of any infection	14*	12*	McKinney et al[23]	1987	None of relative risks for influenza and urinary tract infection was >2 or reached significance at the 5% level	Did not provide exact OR and CI
			Kumar et al[37]	2014	OR, 0.86; 95% CI, 0.40–1.84	Low quality assessed by the NOS
Influenza	7†	6†	McKinney et al[23]	1987	None of the relative risks was greater than 2 or reached significance at the 5% level	Did not provide exact OR and CI
Viral infection	6‡	6‡	None	–		
Urinary tract infection	4§	3§	McKinney et al[23]	1987	None of the relative risks was greater than 2 or reached significance at the 5% level	Did not provide exact OR and CI
Rubella	3	3	None	–		
CMV	2	2	None	–		
Varicella	2	2	None	–		
EBV	2	2	None	–		
Genitourinary infection	2	2	None	–		
Herpes simplex	2¶	2¶	None	–		
Herpes zoster	2	2	None	–		
Infectious hepatitis	2	2	None	–		
Mumps	2	2	None	–		
BKV	1		Madden et al[49]	1983	OR, 0.29; 95% CI, 0.01–8.39	Only 1 study reporting
Chlamydia trachomatis	1		Lehtinen et al[40]	2005	OR, 0.7; 95% CI, 0.2–2	Only 1 study reporting
Fungal infection	1		McKinney et al[43]	1999	OR, 0.28; 95% CI, 0.06–1.26	Only 1 study reporting
Helicobacter pylori	1		Lehtinen et al[40]	2005	OR, 1.1; 95% CI, 0.5–2.4	Only 1 study reporting
HHV-6	1		Lehtinen et al[41]	2003	OR, 0.8; 95% CI, 0.6–1.2	Only 1 study reporting
Lower genital tract infection	1		Naumburg et al[42]	2002	OR, 1.78; 95% CI, 1.17–2.72	Only 1 study reporting
Sexually transmitted diseases	1		Kwan et al[32]	2007	OR, 7.59; 95% CI, 1.58–36.56	Only 1 study reporting
vulvar warts	1		Roman et al[45]	1997	OR, 6.03; 95% CI, 0.24–149.00	Only 1 study reporting

Infection variables	No. of study Investigating	No. of study included in data synthesis	Studies not included in any data synthesis			
			Study ID	Year	Results	Reason for exclusion
Measles	1		Fine et al[48]	1985	OR, 12.5; 95% CI, 0.59–265.15	Only 1 study reporting
Miscellaneous viruses	1		Fine et al[48]	1985	OR, 2.31; 95% CI, 0.11–48.20	Only 1 study reporting
Mycoplasma pneumoniae	1		Lehtinen et al[40]	2005	OR, 1.6; 95% CI, 1.0–2.5	Only 1 study reporting
Respiratory tract infection	1		McKinney et al[43]	1999	OR, 1.46; 95% CI, 0.58–3.67	Only 1 study reporting
TT virus	1		Leppik et al[33]	2007	No obvious differences between cases and controls	OR cannot be calculated
Any other infection	1		Dockerty et al[44]	1999	OR, 1.45; 95% CI, 0.55–3.82	Only 1 study reporting
Other infection	1		Naumburg et al[42]	2002	OR, 1.13; 95% CI, 0.83–1.55	Only 1 study reporting
Other virus infection	1		Bithell et al[22]	1973	OR, 0.69; 95% CI, 0.34–1.41	Only 1 study reporting

TT virus, Torque teno viruses.

*Three studies (Kumar et al[37] in 2014, Naumburg et al[42] in 2002, McKinney et al[43] in 1999) used a variable of total infection; for other studies, we selected a specific type of infection that had the highest prevalence as any infection.

†One study used a variable of influenza/pneumonia.

‡One study used a variable of spontaneous viral infection.

§One study used a variable of cystitis or kidney infection.

¶One study used a variable of cold sores/oral herpes.

Table VII.

Meta-analysis of influenza by subgroups

Subgroups	ALL				All childhood leukemias			
	No.	I^2	OR (95% CI)	P_i*	No.	I^2	OR (95% CI)	P_i*
Measurement method								
Self-report	2	84.2%	4.31 (0.80–23.12)	Ref	3	85.0%	1.96 (0.59–6.48)	Ref
Medical record†	2	0%	3.17 (0.66–15.26)	.81	3	0%	1.59 (1.10–2.30)	.92
Study design								
Case-control study	2	0%	2.10 (1.35–3.27)	Ref	4	46.9%	1.43 (0.93–2.20)	Ref
Cohort study	2	15%	7.91 (1.83–34.24)	.16	2	42.5%	4.82 (0.69–33.85)	.12
Study region								
Europe	3	0%	6.87 (2.57–18.42)	Ref	4	63.2%	2.82 (0.97–8.19)	Ref
North America	1	–	2.02 (1.28–3.18)	.17	1	–	1.77 (1.17–2.68)	.66
Others	–	–	–	–	1	–	0.58 (0.24–1.41)	.22
Study quality								
High quality	2	84.2%	4.31 (0.80–23.12)	Ref	2	84.6%	3.63 (0.74–17.84)	Ref
Medium quality	2	0%	3.17 (0.66–15.26)	.82	4	37.8%	1.22 (0.63–2.35)	.26

*P for interaction.

†The studies of Fine et al[48] in 1985 and Bithell et al[22] in 1973 were categorized as “medical record,” although this study used both self-report and medical record data.

Table VIII.

Sensitivity analysis for influenza

Sensitivity analysis	ALL			All childhood leukemias		
	No.	I^2	OR (95% CI)	No.	I^2	OR (95% CI)
After excluding studies with <10 subjects with exposure/outcome	2	84.2%	4.31 (0.80–23.12)	4	77.8%	1.74 (0.92–3.32)
After excluding studies that included cases >19 years of age	3	68.7%	3.69 (0.96–14.28)	5	70.5%	1.70 (0.93–3.12)
After excluding studies that combined the exposure periods 3 months before pregnancy and pregnancy	3	0%	6.87 (2.57–18.42)	4	63.2%	2.82 (0.97–8.19)