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Reported associations between asthma and acute lymphoblastic leukemia: insights from a hybrid simulation study

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Abstract Numerous studies have reported a protective association between asthma and acute lymphoblastic leukemia (ALL), but the causal structure of this association remains unclear. We present a hybrid simulation to examine the compatibility of this association with uncontrolled confounding by infection or another unmeasured factor. We generated a synthetic cohort using inputs on the interrelations of asthma, ALL, infections, and other suggested risk factors from the literature and the Danish National Birth Cohort. We computed odds ratios (ORs) between asthma and ALL in the synthetic cohort with and without adjustment for infections and other (including unmeasured) confounders. Only if infection was an extremely strong risk factor for asthma (OR of 10) and an extremely strong protective factor against ALL (OR of 0.1) was the asthma-ALL association compatible with the literature (OR of 0.78). Similarly, strong uncontrolled confounding by an unmeasured factor could downwardly bias the asthma-ALL association, but not enough to replicate findings in the literature. This investigation illustrates that the reported protective association between asthma and ALL is unlikely to be entirely due to uncontrolled confounding by infections or an unmeasured confounder alone. Simulation can be used to advance our understanding of risk factors for rare outcomes as demonstrated by this study.

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Introduction

Leukemia is the most common childhood cancer, but ionizing radiation is the only known environmental cause of this disease. Many other reproductive and environmental exposures, including high birth weight, large size for gestational age, tobacco smoke exposure, magnetic fields, and socioeconomic status (SES) have been suspected as possible risk factors [1–16], but uncertainty remains.

The possible role of exposure to common infections in early life in the development of childhood leukemia, particularly acute lymphoblastic leukemia (ALL) is of interest. According to the "population mixing" hypothesis [17], childhood leukemia may develop as a rare response to a relatively common infection when new infections are introduced to a previously isolated population. However, the "delayed infection" hypothesis [18] proposes that a relative lack of early-life infections in modern societies disrupts normal immune development. This predisposes the immune system to an aberrant reaction when exposed to infection later in life, giving a growth advantage to existing pre-leukemic clones and causing progression to leukemia. Based on the delayed infection infection hypothesis, early exposure to infection is protective against the development of ALL.

Evidence for a protective effect of infection on ALL comes largely from epidemiologic studies of proxies for early-life infection and immune stimulation such as day care attendance, breast feeding, and birth order. Studies that directly assessed reports and diagnoses of childhood infections produced a range of results that tended to be imprecise and uninformative [19–32]. However, a meta-

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analysis found that day-care attendance, which is thought to be associated with earlier and more frequent common infections in childhood, appeared to reduce the risk of childhood leukemia [33]. Breastfeeding is known to protect against some infections, and the majority of research suggested it has a protective effect against childhood leukemia [23, 25, 34–36]. Similarly, most studies reported reduced risks of ALL with higher birth order and increased maternal parity, although some results were imprecise [1–5, 27, 37–46]. A recent pooled analysis of 11 case–control studies examined the risk of ALL in relation to breastfeeding, higher birth order, and day care attendance in the first year of life, and the study reported reduced ALL risk in relation to each of these exposures [47].

Asthma is a common condition in childhood, and it may also be the result of anomalous immune system development. Family history of asthma and atopy are strong predisposing factors, but they are not sufficient causes of the condition. Childhood asthma likely originates early in life when the developing immune and respiratory systems are especially vulnerable to assault by environmental risk factors in genetically predisposed individuals [48]. Male sex and low birth weight have been identified as risk factors [49, 50], and there is speculation that viral infections of the lower respiratory tract in early childhood may trigger the development of asthma, but the mechanism for this is unclear. It is uncertain whether viral infections cause asthma, or symptoms of viral infections are more apparent in asthma-susceptible children [48]. Conversely, some studies also suggest that upper respiratory tract infections in early life [49], day care attendance, breast feeding, and higher birth order may lower asthma risk [51–53].

As both asthma and leukemia may result from abnormal immune system development, a relationship between these conditions and possible common causes would be of interest. Several investigations have reported reduced risks of childhood ALL in relation to asthma (odds ratio (OR) of 0.5–0.8), although some results were imprecise [19, 23, 54–57]. Two meta-analyses reported summary odds ratios of 0.79 and 0.82 for the asthma-ALL association, but no association with acute myeloblastic leukemia was detected [58, 59]. This protective association could be the result of infection as a common underlying cause of both conditions. However, there are a multitude of infectious agents to which children are exposed and many ways to define and diagnose infection, making it difficult to pin-point a specific infection as a cause of both asthma and ALL. The severity and timing of infection may also be important considerations, but are assessed at best crudely in epidemiologic studies. Studies of both asthma and ALL have inconsistently (or not at all) accounted for infection. Another approach for examining infection as a common underlying cause of both asthma and ALL is with causal inference and simulation methods. We are not aware of any studies to date that have tried this approach.

In this investigation, we present a data- and literature-driven hybrid simulation of the association between childhood asthma and ALL, considering the impact of infection and other potential confounders on this association. We incorporate information on the observed associations between exposures and outcomes in the Danish National Birth Cohort (DNBC) in combination with findings in the existing literature to account for "all" possible confounders and biasing paths. The aims of the study are: (1) to simulate a synthetic cohort integrating published information and data from an existing cohort on the relations among asthma, ALL, and their reported or suggested risk factors such as infections, and (2) to use the synthesized data to conduct simulated experiments examining whether reported associations between asthma and ALL could be compatible with uncontrolled confounding by infections or some other unmeasured confounding variables.

Methods

We designed and conducted a hybrid simulation study that generated cohort data using inputs on the interrelations of asthma, ALL, and infections from an existing cohort study—the Danish National Birth Cohort (DNBC)—and from the literature. We then analyzed the simulated cohort data to investigate whether or not adjusting for the role of infections with and without further uncontrolled confounding could explain the magnitude and direction of the supposed association between asthma and ALL.

First, we reviewed the literature, paying particular attention to systematic reviews of interrelations of asthma, ALL, and infections in the presence of other covariates. A summary of findings on the association between asthma and ALL in prior studies is shown in Table 1. We then constructed directed acyclic graphs (DAGs) to represent the reported, assumed, or plausible relations between asthma, ALL, infections, and other covariates, putting a query on the assumption that asthma causes ALL directly or indirectly. Competing DAGs were included for further discussion and justification whenever conflicting literature suggested as such. Whenever possible, we also extracted published information on the magnitude and direction of the associations between the variables.

Second, we analyzed DNBC data to extract information on the prevalences or incidences of the variables represented in the DAGs from the previous step and on the magnitude and direction of the associations between the variables to the extent possible in the DNBC. The DNBC is a birth cohort that enrolled 91,661 pregnant women in

Table 1 Findings of prior studies investigating the relationship between asthma and ALL

Study	Design	Sample	Relative risk estimate (95 % CI)		Confounding adjustments
Chang et al. [67]	Case–control (record-based)	846 cases	Asthma before 1 year of age:	0.88 (0.55, 1.42)	Income-related insurance amount[a], urbanization[a]
		3374 controls	Asthma < 1 year before ALL diagnosis:	1.43 (1.10, 1.85)	(matched on age, sex, time of diagnosis)
			Asthma > 1 year before ALL diagnosis:	1.24 (0.99, 1.55)	
Rudant et al. [23]	Case–control	634 cases	History of asthma:	0.7 (0.4, 1.0)	Age, sex, parental professional category, degree of urbanization
		1494 controls	History of asthma and asthma treatment:	0.6 (0.3, 1.4)	
Linabery et al. [58]	Meta-analysis	7 studies	Combined OR:	0.79 (0.61, 1.02)	
Dahl [59]	Meta-analysis	6 studies	Combined OR:	0.82 (0.63, 1.10)	
Wen et al. [54][d,e]	Case–control	1842 cases	Overall:	0.8 (0.6, 1.0)	Months of breastfeeding, maternal education, race, family income
		1986 controls	ALL diagnosis at age 0–1 year:	0.6 (0.2, 1.7)	
			ALL diagnosis at age 2–5 years:	0.7 (0.5, 1.1)	(matched on age, race, telephone area code and exchange)
			ALL diagnosis at age 6–10 years:	0.9 (0.5, 1.4)	
			ALL diagnosis at age 11+ years:	0.7 (0.3, 1.3)	
Schüz et al. [55][d,e]	Case–control	1294 cases	Asthma:	0.61 (0.26, 1.40)	SES, urbanization
		2957 controls			(matched on age, sex, and year of birth)
Jourdan-Da Silva et al. [19][d,e]	Case–control	408 cases	Asthma:	0.5 (0.3, 0.9)	Age, sex, region
		567 controls	Asthma or bronchodilators:	1.0 (0.6, 1.8)	(matched on age, sex, and region)
			Asthma and bronchodilators:	0.3 (0.1, 0.7)	
Spector et al. [68][d,e]	Case–control (record-based)	180 cases	Asthma diagnosis ≥ 1 year before ALL diagnosis:	1.56 (0.85, 2.87)	Breast feeding, maternal age, birth weight, sib-ship, and race[b]
		718 controls	Asthma diagnosis < 1 year before ALL diagnosis:	3.10 (1.39, 6.95)	(matched on HMO, gender, date of birth)
Rosenbaum et al. [56][d,e]	Case–control	255 cases	Asthma history before ALL diagnosis:	0.59 (0.25, 1.37)	maternal education, birth year, maternal smoking, and breast feeding
		760 controls	Asthma history after ALL diagnosis:	0.84 (0.40, 1.76)	(matched on birth year, sex, and race)
Söderberg et al. [57][c,d]	Case–control (record-based)	875 cases	Asthma:	0.5 (0.2, 1.1)	age, sex, SES
		14,865 controls			(matched on 5-year age-group, sex, year of diagnosis)
Hughes et al. [69][d,e]	Case–control (record-based)	720 cases	Probable asthma:	0.97 (0.71, 1.33)	age, sex, region, and deprivation index
		1337 controls	Definite asthma:	0.95 (0.69, 1.31)	(matched on age, sex, and study region)

ALL acute lymphoblastic leukemia, *CI* confidence interval, *HMO* health maintenance organization, *OR* odds ratio, *SES* socioeconomic status

[a] Adjusted estimates were not reported because they were almost identical to unadjusted estimates

[b] Covariates were dropped from model if they did not change the point estimates meaningfully

[c] Information pulled from Linabery et al. [58]. Study publication reports results on all ages (including adults) combined and does not report separate results for ALL

[d] Included in meta-analysis by Linabery et al. [58]

[e] Included in meta-analysis by Dahl et al. [59]

Denmark between 1996 and 2002, with about 10 % enrolled more than once during this time period [60]. In total, 96,841 children were born from these pregnancies (92,675 singletons). The DNBC has been following the mothers and children since the prenatal period and has collected information on their various lifestyle and environmental exposures and health characteristics. Data from the DNBC participants is also linked to the Danish Hospital Discharge Register, which includes all diagnoses made during inpatient stays in Danish hospitals or visits to specialty outpatient clinics. It does not include diagnoses made during visits to primary care physicians.

Although convincing evidence of a causal relationship between a common underlying cause and both asthma and childhood leukemia is lacking, we identified risk factors which are reportedly associated with both childhood leukemia and asthma. For asthma, we estimated ORs from the DNBC, where asthma was defined as being diagnosed with asthma in the hospital register between the ages of 3 and 7 years or being diagnosed with asthma by the age of 7 years according to the mother's report. Given the rarity of childhood leukemia, we obtained ORs from the literature, using meta-analyses, when available. Table 2 lists the variables and the information extracted for this study from singleton-born children from the DNBC, as well as estimates based on the literature of risk factors for asthma and ALL.

Third, we used the information on the aforementioned parameters (that is, on the levels and distributions of the variables and their interrelations) to simulate data compatible with two working DAGs, DAG 1 (Fig. 1) exhibiting the main assumed causal structure of the asthma-ALL association and DAG 2 (Fig. 2) exhibiting additional uncontrolled confounding. We simulated a cohort of 100,000 children using equations with the defined parameter values, listed in Table 2. All variables were binary, drawn from Bernoulli trials, B[1, p], where p was the probability of observing the variable in the cohort.

In particular, the probability of asthma used in the simulations was specified as:

$$
\begin{aligned}
&1/(1+\exp(-(\log-\text{odds}(\text{asthma}_{\text{background}}=1)\\
&\quad+\log(\text{OR}_{\text{infection}-\text{asthma}})+\log(\text{OR}_{\text{eczema/hives}-\text{asthma}})\\
&\quad+\log(\text{OR}_{\text{mediumSES}-\text{asthma}})+\log(\text{OR}_{\text{highSES}-\text{asthma}})\\
&\quad+\log(\text{OR}_{\text{normal birthweight}-\text{asthma}})\\
&\quad+\log(\text{OR}_{\text{high birthweight}-\text{asthma}})+\log(\text{OR}_{\text{2nd}-\text{born}-\text{asthma}})\\
&\quad+\log(\text{OR}_{\text{3rd/later}-\text{born}-\text{asthma}})\\
&\quad+\log(\text{OR}_{\text{sex}-\text{asthma}})+\log(\text{OR}_{\text{daycare}-\text{asthma}})\\
&\quad+\log(\text{OR}_{\text{prenatal smoking}-\text{asthma}})\\
&\quad+\log(\text{OR}_{\text{childhood smoke exposure}-\text{asthma}})\\
&\quad+\log(\text{OR}_{\text{breastfeeding}-\text{asthma}})+\log(\text{OR}_{\text{U}-\text{asthma}}))).
\end{aligned}
$$

Table 2 Input values (odds ratios) for the relationship between covariates and ALL, Asthma, and infection used to develop the synthetic cohort

Covariate	ALL (OR)	Asthma (OR)	Proportion in DNBC ($0 <$ probability < 1)
Infection	0.40[b]	3.00[a]	0.05
High SES (compared to low)	1.50[b]	0.70[a]	0.67
Medium SES (compared to low)	1.25[b]	0.90[a]	0.29
Eczema/hives	0.70[b]	2.23[a]	0.19
High birth weight (compared to low)	1.30[b]	0.50[b]	0.23
Normal birth weight (compared to low)	1.15[b]	0.75[b]	0.74
3rd- or later-born (compared to 1st-born)	0.85[b]	0.92[a]	0.16
2nd-born (compared to first-born)	0.90[b]	0.98[a]	0.74
Male sex	1.27[b]	1.81[a]	0.51
Day care	0.80[b]	0.78[a]	0.89
Prenatal smoking	1.03[b]	1.28[a]	0.34
Childhood smoke exposure	1.16[b]	1.27[a]	0.50
Breast feeding	0.84[b]	0.82[a]	0.74
Unmeasured factor (U)	3.00	3.00	0.05
	1.50	1.50	
	0.67	0.67	
	0.33	0.33	

ALL acute lymphoblastic leukemia, *DNBC* Danish national birth cohort, *OR* odds ratio, *SES* socioeconomic status

[a] Odds ratio value observed in DNBC

[b] Estimated odds ratio values based on other studies

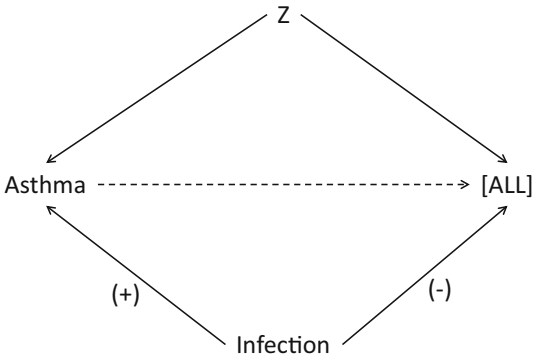

Fig. 1 DAG of a main causal structure where infection is a risk factor for asthma and a protective factor against ALL, and Z is the set of other measured factors associated with both asthma and ALL. Z includes SES, eczema/hives, birth weight, birth order, sex, day care attendance, maternal prenatal smoking, child's postnatal smoke exposure, and breast feeding. *ALL* acute lymphoblastic leukemia, *DAG* directed acyclic graph, *SES* socioeconomic status

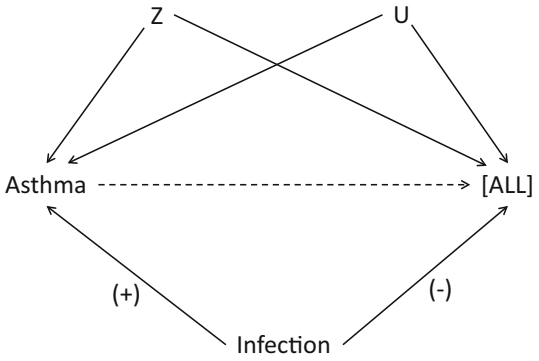

Fig. 2 DAG of main causal structure with the presence of an unmeasured risk factor (U) of both asthma and ALL. *ALL* acute lymphoblastic leukemia, *DAG* directed acyclic graph

Similarly, the probability of ALL given asthman and other covariates was specified as:

$$
\begin{aligned}
&1/(1+\exp(-(\log-\text{odds}(\text{ALL}_{\text{background}}=1)\\
&\quad+\log(\text{OR}_{\text{asthma}-\text{ALL}})+\log(\text{OR}_{\text{infection}-\text{ALL}})\\
&\quad+\log(\text{OR}_{\text{eczema/hives}-\text{ALL}})+\log(\text{OR}_{\text{mediumSES}-\text{ALL}})\\
&\quad+\log(\text{OR}_{\text{highSES}-\text{ALL}})+\log(\text{OR}_{\text{normal birthweight}-\text{ALL}})\\
&\quad+\log(\text{OR}_{\text{high birthweight}-\text{ALL}})+\log(\text{OR}_{\text{2nd}-\text{born}-\text{ALL}})\\
&\quad+\log(\text{OR}_{\text{3rd/later}-\text{born}-\text{ALL}})+\log(\text{OR}_{\text{sex}-\text{ALL}})\\
&\quad+\log(\text{OR}_{\text{daycare}-\text{ALL}})+\log(\text{OR}_{\text{prenatal smoking}-\text{ALL}})\\
&\quad+\log(\text{OR}_{\text{childhood smoke exposure}-\text{ALL}})\\
&\quad+\log(\text{OR}_{\text{breastfeeding}-\text{ALL}})+\log(\text{OR}_{\text{U}-\text{ALL}}))).
\end{aligned}
$$

The background prevalences for most variables of interest were based on their prevalences in the DNBC. However, the background prevalence for asthma was set to 0.1 based on estimates in the literature [61]. The background cumulative incidence for ALL over 10 years was set to 0.001, which is higher than the actual known value. However, some models failed to converge when the background cumulative incidence was set to 0.0005, and therefore we increased it as it had no effect on the results of interest in this study. The background prevalence for U was set to 0.05. In order to determine if confounding by infection or other unmeasured confounders could have produced the asthma-ALL association reported in the literature, we assumed a true null effect of asthma on ALL and set $\text{OR}_{\text{asthma}-\text{ALL}}=1$.

Using these equations, we drew 1000 Monte Carlo samples of size 10^6 each. This was repeated for different scenarios in which the magnitude and direction of the infection-ALL association and the infection-asthma association were varied around the values found in the literature, from 0.1 to 0.9 and from 2 to 10, respectively. For DAG 1, we analyzed each of the 1000 samples by fitting one unadjusted and three adjusted logistic regression models of ALL given asthma. The adjusted models were as follows: (1) "minimally-adjusted" that adjusted for only SES and sex because these covariates were commonly included in previous studies; (2) "fully-adjusted" that included infection and other causes of ALL as covariates; and (3) "fully-adjusted, minus infection" that adjusted for other causes of ALL but omitted infection. For each of the 1000 samples, we saved the odds ratios for the asthma-ALL association from the models in each scenario. The resulting 1000 ORs from each model were then summarized to yield the median as the point estimate and their 2.5th and 97.5th percentiles as the 95 % simulation (uncertainty) interval in each scenario.

The simulation and modeling steps were repeated for DAG 2, except that the infection-ALL and infection-asthma associations were held constant at 0.40 and 3.00, respectively, while the associations between an uncontrolled confounder (U) and ALL and between U and asthma were each varied (OR from 0.33 to 3.00) in the different scenarios. For DAG 2, we fitted four adjusted logistic regression models of ALL given asthma: (1) "minimally-adjusted" that adjusted for only SES and sex; (2) "fully-adjusted" that included infection, U, and other causes of ALL; (3) "fully-adjusted, minus U" that adjusted for infection and other causes of ALL but omitted U; and (4) "fully-adjusted, minus U and infection" that adjusted for other causes of ALL but omitted U and infection.

Results

The simulated impact of infection on the association between asthma and ALL is presented in Table 3. Minimal adjustment for only SES and sex resulted in a slight shift of the asthma-ALL relationship toward a more negative association. Full adjustment including infection removed the association completely. Omitting adjustment for infection reduced but did not completely remove the asthma-ALL association. Thus, the negative association between asthma and ALL reported in other studies could only partly be the result of confounding by infection. The pattern remained the same regardless of the infection-ALL or the infection-asthma associations. However, the magnitude of the asthma–ALL association observed in previous studies (OR of 0.79–0.82 in meta-analyses) was only observed in our simulation when infection was an extremely strong risk factor for asthma (OR of 10) and an extremely strong protective factor against ALL (OR of 0.1).

In the presence of an unknown confounder, U, where the U-asthma and U-ALL associations were opposite in direction, the asthma-ALL association was downwardly biased (Table 4). Minimal adjustment for only SES and sex induced an even more downwardly biased association. Adjustment for all confounders except U and infection had

Table 3 Impact of infection on the association between asthma and ALL

Set	Varied inputs		OR and 95 % uncertainty interval for Asthma → ALL			
	Infect → ALL (odds ratio)	Infect → Asthma (odds ratio)	Unadjusted	Minimally adjusted[a]	Fully-adjusted[b]	Fully-adjusted[c] (minus infection)
1	0.9	2.0	0.99 (0.81, 1.20)	0.97 (0.79, 1.18)	1.00 (0.82, 1.22)	1.00 (0.82, 1.22)
2	0.9	3.0	0.98 (0.81, 1.19)	0.96 (0.79, 1.17)	1.00 (0.82, 1.22)	0.99 (0.82, 1.21)
3	0.9	5.0	0.98 (0.81, 1.18)	0.96 (0.79, 1.16)	1.00 (0.82, 1.22)	0.99 (0.82, 1.20)
4	0.9	7.0	0.98 (0.81, 1.18)	0.96 (0.79, 1.15)	1.00 (0.83, 1.22)	0.98 (0.82, 1.19)
5	0.7	2.0	0.98 (0.80, 1.19)	0.96 (0.78, 1.17)	1.00 (0.82, 1.22)	0.99 (0.81, 1.21)
6	0.7	3.0	0.97 (0.79, 1.18)	0.95 (0.78, 1.15)	1.00 (0.82, 1.22)	0.98 (0.80, 1.19)
7	0.7	5.0	0.95 (0.78, 1.15)	0.93 (0.77, 1.13)	1.00 (0.82, 1.22)	0.96 (0.79, 1.17)
8	0.7	7.0	0.94 (0.78, 1.14)	0.92 (0.76, 1.12)	1.00 (0.82, 1.22)	0.95 (0.78, 1.15)
9	0.5	2.0	0.97 (0.79, 1.18)	0.95 (0.77, 1.16)	1.00 (0.82, 1.23)	0.98 (0.80, 1.20)
10	0.5	3.0	0.95 (0.78, 1.16)	0.93 (0.76, 1.14)	1.00 (0.82, 1.22)	0.96 (0.78, 1.17)
11	0.5	5.0	0.92 (0.76, 1.12)	0.91 (0.74, 1.10)	1.00 (0.82, 1.22)	0.93 (0.76, 1.14)
12	0.5	7.0	0.91 (0.75, 1.10)	0.89 (0.73, 1.08)	1.00 (0.82, 1.22)	0.91 (0.75, 1.11)
13	0.4	2.0	0.96 (0.79, 1.18)	0.94 (0.77, 1.15)	1.00 (0.82, 1.23)	0.97 (0.79, 1.19)
14	0.4	3.0	0.94 (0.77, 1.15)	0.92 (0.75, 1.13)	1.00 (0.82, 1.23)	0.95 (0.78, 1.16)
15	0.4	5.0	0.91 (0.75, 1.11)	0.89 (0.73, 1.09)	1.00 (0.82, 1.22)	0.92 (0.75, 1.12)
16	0.4	7.0	0.89 (0.73, 1.08)	0.87 (0.72, 1.06)	1.00 (0.82, 1.22)	0.90 (0.73, 1.09)
17	0.2	2.0	0.95 (0.78, 1.17)	0.93 (0.76, 1.15)	1.00 (0.82, 1.23)	0.96 (0.78, 1.18)
18	0.2	3.0	0.92 (0.75, 1.13)	0.91 (0.74, 1.11)	1.00 (0.82, 1.23)	0.93 (0.76, 1.15)
19	0.2	5.0	0.88 (0.72, 1.08)	0.86 (0.71, 1.06)	1.00 (0.82, 1.23)	0.89 (0.73, 1.09)
20	0.2	7.0	0.85 (0.70, 1.04)	0.84 (0.68, 1.02)	1.00 (0.82, 1.23)	0.86 (0.70, 1.05)
21	0.1	10.0	0.80 (0.65, 0.98)	0.78 (0.64, 0.96)	1.00 (0.82, 1.23)	0.80 (0.65, 0.99)

ALL acute lymphoblastic leukemia, *Infect* infection, *OR* odds ratio

[a] Adjusted for ses and sex

[b] Adjusted for eczema/hives, ses, birthweight, birth order, sex, day-care, prenatal smoking, child's smoke exposure, breast feeding, and infection

[c] Adjusted for eczema/hives, ses, birthweight, birth order, sex, day-care, prenatal smoking, child's smoke exposure, and breast feeding

a minimal impact on removing the bias due to confounding. Adding infection to the adjustment removed bias considerably, while only full adjustment brought the asthma–ALL association back to the null.

Discussion

In this investigation, we used a hybrid approach that incorporated information about the potential risk factors for asthma and ALL from the published literature and from associations in the existing DNBC data to generate a large synthetic cohort of children. By performing simulation experiments using our synthesized data, we examined whether the reported associations between asthma and ALL could be compatible with uncontrolled confounding by infections or some other unmeasured confounders.

In our simulations, we were only able to replicate the asthma-ALL association observed in previous studies (OR of 0.79 to 0.82 in meta-analyses) when we imposed a very strong positive association between infection and asthma (OR of 10). Such a strong association between infection and asthma is not compatible with the OR observed in the DNBC (OR = 3.0). While a few studies have reported extremely strong associations (OR > 10) between early-life hospitalization for infection with specific wheeze-associated viral species (particularly rhinovirus and respiratory syncytial virus) and later asthma development [62, 63], it is uncertain whether infection was a cause of asthma in such cases or if asthma-susceptible children were more likely to show severe symptoms in response to specific infections that required hospitalization [64]. The strongest protective asthma-ALL association we were able to produce (OR = 0.78) was observed only when $OR_{infection\text{-}ALL} = 0.1$ and $OR_{infection\text{-}asthma} = 10$, which is an extreme scenario that is probably not compatible with reality. In the more realistic scenarios, where $OR_{infection\text{-}ALL}$ ranged from 0.4 to 0.7 and $OR_{infection\text{-}asthma}$ ranged from 2 to 3, only a slight, if any, protective asthma-ALL association was observed (OR > 0.9).

Table 4 Impact of unmeasured confounding on the association between asthma and ALL

Set	Varied inputs		OR and 95 % uncertainty interval for Asthma → ALL				
	U → ALL (OR)	U → Asthma (OR)	Unadjusted	Minimally adjusted[a]	Fully-adjusted[b]	Fully-adjusted[c] (minus U)	Fully-adjusted[d] (minus U and infection)
1	0.67	3.00	0.92 (0.76, 1.12)	0.90 (0.74, 1.10)	1.00 (0.82, 1.22)	0.98 (0.80, 1.19)	0.93 (0.76, 1.13)
2	0.33	3.00	0.90 (0.73, 1.10)	0.88 (0.72, 1.07)	1.00 (0.82, 1.23)	0.95 (0.77, 1.16)	0.90 (0.74, 1.11)
3	0.67	1.50	0.94 (0.77, 1.14)	0.92 (0.75, 1.12)	1.00 (0.82, 1.23)	0.99 (0.81, 1.22)	0.94 (0.77, 1.16)
4	0.33	1.50	0.93 (0.76, 1.14)	0.91 (0.74, 1.11)	1.00 (0.81, 1.23)	0.98 (0.80, 1.21)	0.94 (0.76, 1.15)
5	3.00	0.67	0.91 (0.75, 1.11)	0.89 (0.74, 1.09)	1.00 (0.82, 1.22)	0.97 (0.80, 1.18)	0.92 (0.76, 1.12)
6	1.50	0.67	0.93 (0.76, 1.14)	0.91 (0.75, 1.12)	1.00 (0.82, 1.22)	0.99 (0.81, 1.21)	0.94 (0.77, 1.15)
7	3.00	0.33	0.88 (0.72, 1.08)	0.86 (0.71, 1.05)	1.00 (0.82, 1.22)	0.94 (0.77, 1.15)	0.89 (0.73, 1.09)
8	1.50	0.33	0.93 (0.76, 1.13)	0.91 (0.74, 1.11)	1.00 (0.81, 1.23)	0.98 (0.80, 1.21)	0.93 (0.76, 1.15)

OR for infection-ALL held constant at 0.40, and OR for infection-asthma held constant at 3.00

ALL acute lymphoblastic leukemia, *OR* odds ratio

[a] Adjusted for ses and sex

[b] Adjusted for eczema/hives, ses, birthweight, birth order, sex, day-care, prenatal smoking, child's smoke exposure, breast feeding, infection, and U

[c] Adjusted for eczema/hives, ses, birthweight, birth order, sex, day-care, prenatal smoking, child's smoke exposure, breast feeding, and infection

[d] Adjusted for eczema/hives, ses, birthweight, birth order, sex, day-care, prenatal smoking, child's smoke exposure, and breast feeding

The presence of one unmeasured, and therefore uncontrolled, confounder is unlikely to explain the protective association of asthma on ALL. Even in the case where we imposed strong negative confounding, where $OR_{U\text{-}ALL} = 3.00$ and $OR_{U\text{-}asthma} = 0.33$, we observed an $OR_{asthma\text{-}ALL}$ of 0.86, which is still weaker than the estimates reported in the literature. The existence of unmeasured negative confounding stronger than what we examined here appears unlikely albeit not impossible. We note that multiple unmeasured confounding variables will likely introduce more bias at comparable or even lower bias parameters than illustrated in this study, provided all the unmeasured confounders introduce confounding in the same direction (i.e. all positive or negative but not opposing confounding). As an illustrative exercise, this study paves the way for studying how more complicated multiple unmeasured confounding variables can explain part or all of the reported asthma–ALL associations. Nonetheless, it should be noted that increasing the number of unmeasured confounding variables presents some challenges. For example, assuming uncontrolled confounding due to two or more unmeasured confounding variables makes it challenging to reason about the nature (and identity) of those variables while making it easier to explain away a large portion of the reported asthma–ALL associations.

The associations between risk factors and asthma and ALL that were used to develop our models are based on estimates from the DNBC and various studies in the literature that often contradicted one another. In some cases, we used our judgement to select estimates that we felt best represented most findings in the literature or were most likely to be compatible with reality. For example, while the association between birth weight and asthma was first extracted directly from available data in the DNBC, the result did not follow a dose–response pattern of increased risk with lower birth weight, as would be expected [50]. Therefore, we used an estimate for the association that we felt was more consistent the existing literature than with the DNBC. Similarly, while SES has been examined as a potential risk factor for ALL in numerous studies, the findings have been inconsistent overall [15]. We also considered performing the simulation in two different ways, one with a negative SES-ALL association, and another with a positive SES-ALL association. However, as SES was not the main focus of this investigation, we decided to use only the positive association in the final analysis. This choice does not affect our results and the interpretation of our findings given adjustment for SES in the models studied here.

As childhood leukemia is a rare, but devastating disease, and the incidence of asthma has increased in recent years, a causal relationship between the two conditions would be remarkable. Such a finding would be groundbreaking for understanding the development of childhood leukemia and its underlying risk factors. Therefore, the protective asthma–ALL association reported in the literature needs to be examined further. One alternative explanation for the association may be the presence of multifactorial uncontrolled confounding with or without competing risk biases. For example, asthma will never be detected in children who die from childhood leukemia before asthma develops. This could lead to a survivor bias, which may have affected

previous studies. The previous studies that reported an asthma–ALL association all used a case–control design, which is a major limitation of nearly all epidemiologic studies of childhood leukemia. Case–control studies are prone to selection bias, which could have affected the results, and this should be examined. For example, a negative association between asthma and ALL could be induced if controls with asthma were more likely to participate than healthy controls. Further, it would be informative to use simulation techniques or other methods to examine whether the rapid increase in childhood asthma is compatible with the slight increase in childhood leukemia in recent years after accounting for other potential confounding factors.

Another environmental agent that has been suspected for several decades as a risk factor for childhood leukemia is exposure to magnetic fields. While the biological mechanism for an effect of magnetic fields on the development of childhood leukemia is unclear and unlikely based on basic biophysics, numerous case–control studies, including three meta-analyses have consistently reported associations between residential magnetic field exposure and childhood leukemia [16, 65, 66]. Once again, it is uncertain whether these reported associations reflect a true effect or are the result of selection bias or other sources of bias.

We were able to simulate a very large cohort sample that was based on numerous parameters extracted from both the literature and an existing large and well-documented cohort. The rarity of childhood leukemia makes it difficult to study its risk factors, and most attempts have been limited to the case–control study design. There is an urgent need for new methods to explore the risk factors for childhood leukemia. While new methods for collecting data are necessary, bias analysis and simulation methods offer important approaches for integrating and exploring relations between childhood leukemia and potential risk factors. This study offers readers just one example of how simulation methods can be used to advance our understanding and interpretation of childhood leukemia risk factors, as we demonstrated that the reported associations between asthma and ALL are unlikely to be due to uncontrolled confounding by infections or other unmeasured confounders.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no conflicts of interest.

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