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Disentangling short-term and long-term asthma risk following early childhood lower respiratory tract infections

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Abstract

Early childhood lower respiratory tract infections (LRTIs) are consistently associated with subsequent asthma, but the extent to which this association reflects short-term diagnostic effects, reverse causation, or longer-term asthma susceptibility remains unclear. We analysed nationwide Hungarian health insurance claims data of 473,847 children with at least 7 years follow-up. LRTIs and asthma were identified from ICD-10 codes and dispensed medications. Associations were assessed using contingency-table odds ratios (ORs), Kaplan-Meier curves, and a time-varying Cox hazard model. Unlike in many previous studies, exposure (infection) and outcome (asthma onset) windows were explicitly separated to reduce reverse-time overlap between asthma and LRTI occurrence. LRTI before age 3 was associated with increased asthma risk at ages 3–7 (OR 1.84, 95% CI 1.77–1.92), with a stronger relative effect in girls. Asthma risk after first LRTI up to age 5 years showed a marked temporal pattern, peaking shortly after LRTI and declining over time while remaining elevated. Recurrent LRTIs showed a dose-response relationship (two episodes HR 1.19 (1.14–1.24); four or more episodes HR 1.38 (1.29–1.47)). Early-life LRTIs were associated with subsequent asthma through a pronounced temporal risk pattern characterised by a marked short-term increase and a persistent longer-term component. Although diagnostic and surveillance effects likely contribute to the observed association, the persistence of elevated risk after temporal separation of exposure and outcome supports an association not fully explained by short-term diagnostic effects.

Keywords: paediatric asthma, lower respiratory tract infection, epidemiology, retrospective cohort, population-wide analysis, electronic health claims data

Introduction

Lower respiratory tract infections (LRTIs) are common in early childhood and remain a major cause of global paediatric morbidity. As this period is also critical for lung growth and immune maturation, infections affecting the lower airways during early life may disrupt lung development and immune regulation, potentially increasing susceptibility to chronic respiratory diseases later in life [1]. Growing epidemiological evidence links early childhood respiratory infections with a higher risk of subsequent asthma. Observational studies have shown that LRTIs during the first years of life are associated with increased risk of asthma in later childhood [2], with some evidence of a dose-response relationship between infection frequency and asthma diagnoses [1]. A meta-analysis of multiple European birth cohorts reported that early-life LRTIs were associated both with reduced lung function and with increased odds of asthma at school age, with stronger associations observed for LRTIs compared to upper RTIs [3].

Beyond childhood respiratory morbidity, early-life LRTIs may also influence long-term respiratory health trajectories. Longitudinal analyses have indicated that severe respiratory infections in early childhood are associated with a higher risk of adverse respiratory outcomes throughout life [4]. Evidence from long-term population follow-up suggests that individuals who experienced LRTIs in early childhood may have a substantially increased risk of respiratory disease and related mortality in adulthood, highlighting the potential lifelong consequences of early respiratory insults [5].

Although numerous studies have reported an association between early childhood LRTIs and subsequent asthma, interpretation of this relationship remains challenging. The association is potentially bidirectional: asthma and asthma-related airway vulnerability may increase susceptibility to respiratory infections, while respiratory infections themselves may contribute to later asthma development. Consequently, studies that do not adequately separate infection exposure from asthma onset may overestimate the strength of the association due to reverse causation.

Administrative health claims data are primarily generated for reimbursement and healthcare administration. However, the use of standardised coding systems for diagnoses, procedures, and pharmacological treatments makes them valuable resources for secondary research, enabling reproducible analyses, consistent cohort definition, and large-scale population-based investigations [6, 7]. These robust, longitudinal datasets often cover nearly entire populations, providing real-world evidence that is highly representative of routine clinical practice.

The aim of the present study was to evaluate the association between early childhood LRTIs and subsequent asthma after temporally separating infection exposure from asthma onset in order to minimise reverse causation. Using population-wide health insurance claims data from a retrospective administrative cohort, we further characterised the temporal dynamics of post-LRTI asthma risk

and assessed how infection recurrence and clinical characteristics influenced this association.

Methods

Data source

The National Health Insurance Fund (NHIF), Hungary’s sole public health insurer, covers nearly the entire population (about 10 million people) across inpatient, outpatient, diagnostic, and reimbursed medication care. All stakeholders of the public healthcare delivery system submit the data to the NHIF required for reimbursement on a monthly basis. The robustness of the database enables complex, detailed analyses. We used depersonalised NHIF health insurance claims records from January 2010 to December 2021. Ethics approval was obtained from the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (ETT TUKEB, approval No. BM/5431-1/2026). The study used retrospectively collected, de-identified nationwide administrative health insurance claims data. As the study involved secondary analysis of de-identified, routinely collected administrative data and did not involve direct contact with participants, individual written informed consent was not required. All procedures were performed in accordance with the applicable Hungarian regulations and the GDPR framework.

We analysed health insurance claims records of active inpatient care, outpatient care and dispensed medication. Further technical description with exclusions included are detailed in the Supplementary Material.

Study population

Children born between 1st January 2010 and 1st January 2015 with at least 7 years of follow-up were included in the study.

Characteristics of the study population of 473,847 children are summarised in Table 1.

Table 1 Description of study population

Group	Males (%)	Females (%)	Total
Total population involved	243,718 (51.43%)	230,129 (48.57%)	473,847
Children with asthma between age 6–7	11,879 (63.23%)	6,908 (36.77%)	18,787
Children with LRTI between age 0–7	68,828 (56.73%)	52,489 (43.27%)	121,317
of which pneumonia accounted for	20,193 (55.18%)	16,405 (44.82%)	36,598

Data on ethnicity are not available in the NHIF database.

Definitions

In the NHIF health insurance claims records, we defined LRTI using inpatient type 1 or type 3 ICD-10 codes, or outpatient main ICD-10 codes, for bronchitis, bronchiolitis,

and pneumonia. Visits within 30 days were grouped into one LRTI episode, classified as pneumonia if any visit within the episode involved pneumonia. Asthma onset was defined from anti-asthmatic medication dispensing records at age 6–7 years, requiring at least two reimbursed dispensings for the same 7-digit ATC code with asthma ICD-10 coding on the prescription. We provide a complete technical description of ICD-10 codes used, the definition of LRTI case and asthma in the Supplementary Material.

Methods and statistical analysis

In this study, we calculated odds ratios and analysed their temporal changes, considering care category, pneumonia status, and number of visits during an LRTI case. We also plotted Kaplan-Meier curves to compare cumulative asthma risk after the first LRTI episode, censoring follow-up at the next episode to minimise confounding by recurrent infections. To complement this first-episode analysis, we fitted a time-varying Cox model in which asthma hazard was estimated from the evolving LRTI history, using the characteristics of the latest LRTI episode and the time elapsed since that episode. Contingency-table p-values were obtained from two-sided Fisher’s exact tests. The Cox model was fitted with Efron handling of ties and cluster-robust standard errors at the child level, and reported p-values were based on the robust model summary. Rolling-window OR analyses and Kaplan-Meier comparisons were interpreted descriptively; no multiple-testing correction was applied. Further details are provided in the Supplementary Material.

ChatGPT 5.2 was used to assist with language editing, readability checks, statistical code drafting, and figure-generation code drafting; all outputs were reviewed, verified, and edited by the authors, who take full responsibility for the content.

Results

Association of LRTI and asthma

Chronic lower respiratory conditions such as asthma are known to be associated with a higher risk of infections of the lower respiratory tract. In our analysis, the overall odds ratio (OR) of developing asthma before the age of 7 years in children with LRTI in the same period was 8.80 (95% CI 8.51–9.09), which is particularly high. However, the association is bidirectional, as asthma is a risk factor for LRTI, and LRTI is a risk factor for asthma.

In this paper, we focused on early childhood LRTI as a risk factor for the later development of asthma, and to avoid including children who had already had asthma prior to the occurrence of LRTI, we applied the following time windows: having LRTI prior to the age of 3 years, and developing asthma between 3–7 years of age (without overlap between the two periods).

Children with LRTI prior to the age of 3 years were more likely to have asthma between 3–7 years of age, with an elevated OR of 1.84 (95% CI 1.77–1.92), as shown in Table 2. The association is attenuated in boys, with a decreased OR of 1.68 (1.60–1.77), while more pronounced in girls, whose OR is 1.99 (1.86–2.13), as shown in Table 2.

Table 2

Contingency table of developing asthma at age 3–7 and LRTI before age 3, with sex-stratified results

Asthma at age 3–7	LRTI before age 3		Total
	Yes	No	
Yes	3,312	8,653	11,965
No	78,368	376,692	455,060
Total	81,680	385,345	467,025
OR 1.84, 95% CI 1.77–1.92, $p < 10^{-16}$			

Asthma at age 3–7	Boys			Girls		
	LRTI before age 3		Total	LRTI before age 3		Total
	Yes	No		Yes	No	
Yes	2,103	5,234	7,337	1,209	3,419	4,628
No	44,731	187,108	231,839	33,637	189,584	223,221
Total	46,834	192,342	239,176	34,846	193,003	227,849
Boys: OR 1.68, 95% CI 1.60–1.77, $p < 10^{-16}$				Girls: OR 1.99, 95% CI 1.86–2.13, $p < 10^{-16}$		

Temporal dynamics of OR, subsequent effect of LRTI at 0–1 year of age

Unlike in many previous studies, exposure and outcome windows were explicitly separated in order to reduce reverse-time overlap between asthma and LRTI occurrence. To assess temporal changes in association, we recalculated ORs across non-overlapping 1-year rolling windows (details in the Supplementary Material). The OR of having asthma in a 1-year-wide window between ages 1–2 years, immediately after an LRTI at age 0–1 year is 5.75 (95% CI 5.29–6.26), but decreases steeply, as shown in Figure 1. By the end of the third year (so between ages 4–5), the OR is 1.07 (0.95–1.21), not significantly different from 1. Thus, affected children who had no asthma before the age of 4 years, had the same chance of having asthma later as those who had no LRTI at age 0–1 year, at least until the age of 7, the end of the observation period.

Age at the very first LRTI

To study the effect of age at first LRTI, we compared age-shifted exposure windows and subsequent non-overlapping asthma windows (full specification in Supplementary Material).

As shown in Figure 2, although the confidence band is widening, the OR of developing asthma increases significantly with age at the very first LRTI. In other words, the risk of developing asthma is higher in children who had their first LRTI at an older age, at least to the age of 5 years (the end of the observation period).

Visualisation of cumulative risk with Kaplan-Meier curves

We compared cumulative asthma risk across different groups using Kaplan-Meier (KM) curves with 95% confidence bands. Follow-up definition, censoring, and reference-group age alignment are detailed in the Supplementary Material.

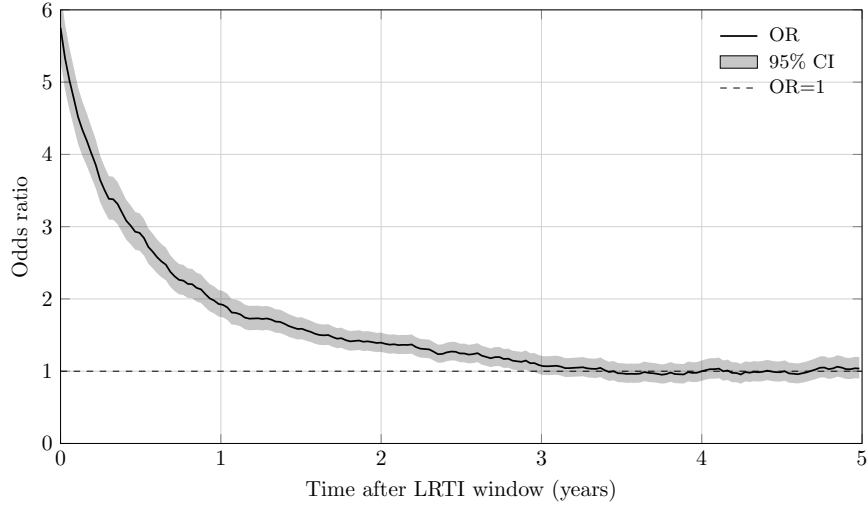


Fig. 1 Odds ratio of asthma in a 1-year-wide window by lag after an LRTI at ages 0–1 years.

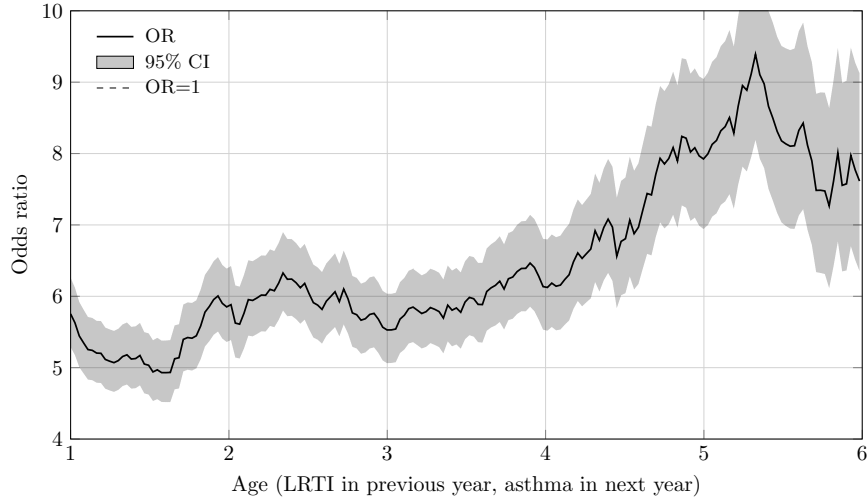


Fig. 2 Age-specific odds ratio of onset of asthma in the following year after LRTI in the previous year.

In the aligned reference group (children without LRTI), the cumulative risk of asthma by the end of follow-up is 0.0181 (95% CI 0.0150–0.0212), that is 1.81% of these children developed asthma during the observation period. Increased asthma risk in children with LRTI across different groups was observed, with a rapid increase immediately after LRTI; however, after 3 years, the slope of the increase is similar to that of the reference group, as we already showed in Figure 1.

Cumulative risk by age at first LRTI

LRTI episodes at an early age are considered severe. However, as we have seen in Figure 2, the OR of developing asthma in the subsequent year is higher for those who had their first LRTI at an older age. To further investigate this, in Figure 3, we compare the cumulative risk of asthma between children at different ages at the first LRTI, creating groups in one-year bins. The cumulative risk of asthma is the highest for those who had their first LRTI at age 3–7 years, and the lowest for those who had their first LRTI at age 0–1 year, with the OR of the groups in between showing a monotonous decreasing pattern. These first-episode KM comparisons were designed to isolate the age pattern of the initial LRTI without interference from the accumulating burden of subsequent episodes. We then examined a complementary question in the Cox model presented below, in which asthma hazard was estimated from the evolving LRTI history with time measured from the latest LRTI episode.

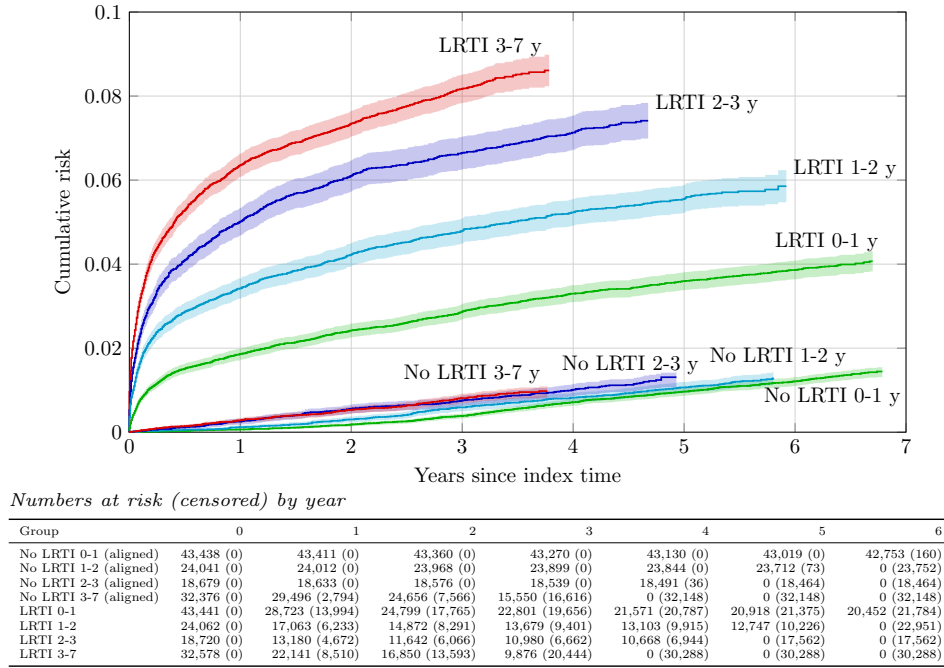
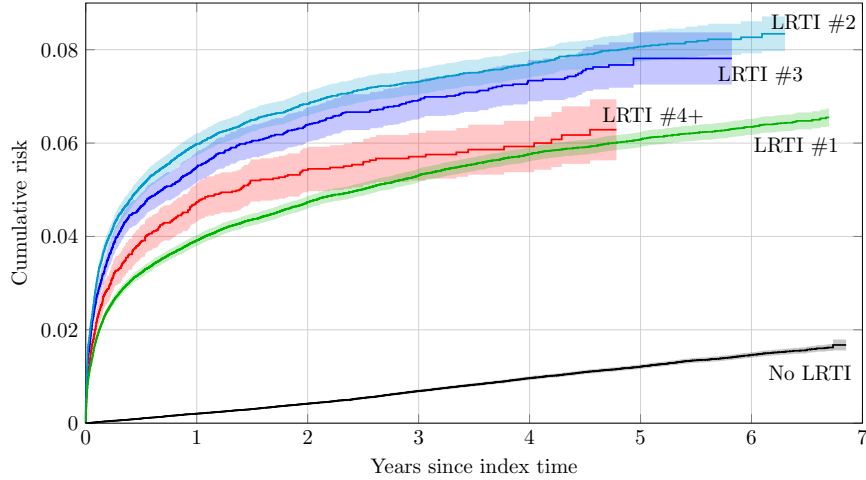


Fig. 3 Cumulative asthma risk by age at first LRTI with age-specific no-LRTI references.

Cumulative risk by number of LRTI episodes

To compare children by LRTI burden, we grouped them by the order of the indexed LRTI episode (#1, #2, #3, #4+) and plotted the corresponding KM curves together in Figure 4. A slightly elevated asthma risk was observed after the second LRTI episode, but in the unadjusted Kaplan–Meier comparison, the risk in the 4+ episode group was close to that observed after the first LRTI episode.



Numbers at risk (censored) by year

Group	0	1	2	3	4	5	6
No LRTI (aligned)	298,894 (0)	281,596 (16,706)	256,573 (41,153)	219,219 (77,861)	169,665 (126,990)	117,962 (178,216)	62,277 (233,669)
LRTI #1	118,797 (0)	81,107 (33,409)	68,163 (45,715)	57,336 (56,163)	45,342 (67,934)	33,665 (79,451)	20,452 (92,585)
LRTI #2	47,212 (0)	25,609 (19,077)	19,814 (24,664)	15,197 (29,190)	10,765 (33,583)	6,620 (37,678)	2,499 (41,790)
LRTI #3	23,509 (0)	10,880 (11,508)	7,908 (14,388)	5,689 (16,569)	3,704 (18,539)	1,983 (20,244)	407 (21,819)
LRTI #4+	13,390 (0)	5,408 (7,453)	3,662 (9,167)	2,462 (10,358)	1,440 (11,378)	652 (12,159)	60 (12,751)

Fig. 4 Cumulative asthma risk by LRTI episode count with aligned no-LRTI reference.

Note that the curves of the groups with more than one LRTI episode are still drawn from zero; however, the children in these groups spend some time in the previous groups, and therefore the individual risk of a certain child should be summed up from the curves of the groups of the previous LRTI episodes. To overcome this issue, a different approach should be taken.

As episode-indexed KM curves restart follow-up at each indexed LRTI and do not fully capture the cumulative effect of recurrent infections within the same child, we complemented them with a time-varying Cox model. Unlike the KM analyses above, which focus on the first LRTI to avoid confounding by later episodes, the Cox model uses the full evolving infection history and measures time from the latest LRTI episode.

Cumulative risk by localisation

Children were categorised by the first LRTI episode as pneumonia or other LRTI. The KM curves of these categories and the aligned reference group without LRTI are shown in Figure 5: the pneumonia and the other LRTI curves are slightly but clearly distinct, with significant difference. LRTI other than pneumonia (i.e. bronchitis, bronchiolitis) resulted in a higher cumulative risk of asthma than pneumonia did.

Multivariable Cox model of asthma hazard after LRTI

The time-varying Cox model (Table 3) helped reconcile the descriptive analyses by estimating asthma hazard from the evolving LRTI history under joint adjustment. Asthma hazard was the highest immediately after LRTI and declined steeply over time, with hazard ratios (HRs) of 71.59 (95% CI 66.44–77.13) during days 0–30,

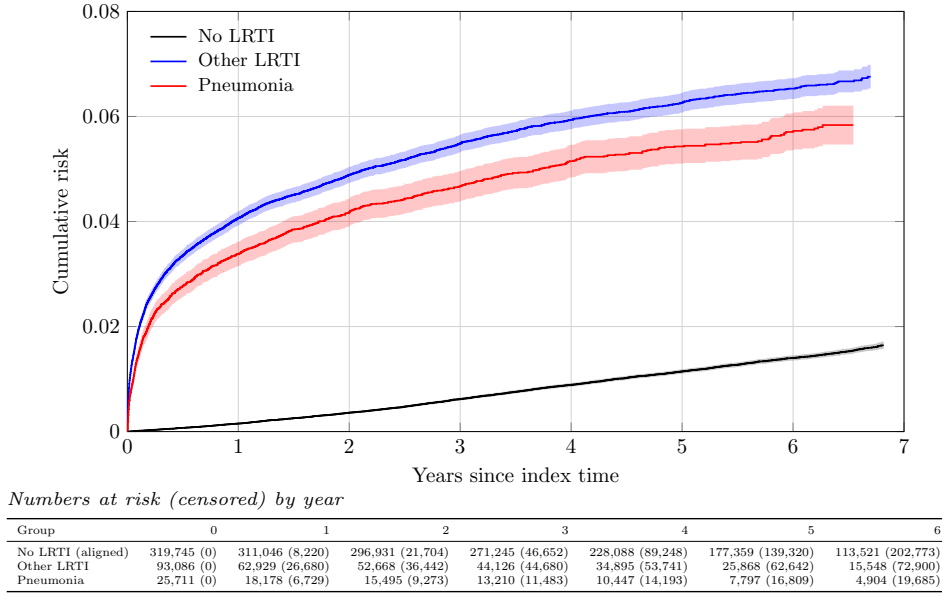


Fig. 5 Cumulative asthma risk by first LRTI pneumonia status (censoring at second LRTI).

24.60 (22.60–26.77) during days 30–60, 11.92 (10.95–12.99) during days 60–120, 4.39 (4.06–4.74) during days 120–365, and 1.84 (1.69–2.00) during days 365–730. This pattern suggests that the excess hazard is concentrated in an early post-infectious or diagnostically intensified period, and then attenuates over time. The HR below 1 and beyond two years (0.88 (0.82–0.95) during days 730–2,190) should not be interpreted as protective, but may reflect an earlier diagnosis among susceptible children or a depletion of susceptibles.

Recurrent LRTIs remained independently associated with higher hazard. A clear dose–response pattern was observed, with asthma hazard increasing progressively with the number of previous LRTI episodes. Compared to the first episode, two episodes were associated with HR 1.19 (95% CI 1.14–1.24), three episodes with HR 1.10 (1.04–1.16), and four or more episodes with HR 1.38 (1.29–1.47).

Pneumonia was associated with a slightly lower hazard than other LRTIs (HR 0.83, (0.79–0.87)), and boys had a higher baseline hazard than girls (HR 1.44, (1.40–1.48)).

Discussion

The principal finding of this nationwide cohort study is that the association between childhood lower respiratory tract infections (LRTIs) and subsequent asthma is strongly time-dependent. Asthma hazard peaked immediately after infection, declined rapidly during the following months, yet remained elevated beyond the acute period and increased with recurrent infections. Previous studies have consistently linked early-life LRTIs with subsequent asthma development [1, 2, 4], impaired later respiratory function [3], and adverse respiratory outcomes extending into adulthood [5]. Our

Table 3 Exponentiated coefficients (HR) from the time-varying Cox model based on the evolving LRTI history, with covariates defined from the latest LRTI episode and the time elapsed since that.

Covariate	HR	95% CI	p-value
Sex: male (vs. female)	1.44	1.40–1.48	$< 10^{-16}$
<i>Post-LRTI terms (active only if any LRTI occurred)</i>			
Age at last LRTI: 1–2 (vs. 0–1)	1.13	1.05–1.21	8.1×10^{-4}
Age at last LRTI: 2–3 (vs. 0–1)	1.14	1.06–1.23	5.8×10^{-4}
Age at last LRTI: 3–4 (vs. 0–1)	0.93	0.85–1.01	0.08
Age at last LRTI: 4–5 (vs. 0–1)	0.98	0.89–1.07	0.60
Age at last LRTI: 5–6 (vs. 0–1)	1.02	0.92–1.14	0.66
Age at last LRTI: 6–7 (vs. 0–1)	1.20	1.06–1.37	0.005
Pneumonia (vs. not)	0.83	0.79–0.87	2.1×10^{-14}
LRTI number before: 2 (vs. 1)	1.19	1.14–1.24	5.0×10^{-15}
LRTI number before: 3 (vs. 1)	1.10	1.04–1.16	0.002
LRTI number before: 4+ (vs. 1)	1.38	1.29–1.47	1.7×10^{-21}
Time since last LRTI: 0–30 days	71.59	66.44–77.13	$< 10^{-16}$
Time since last LRTI: 30–60 days	24.60	22.60–26.77	$< 10^{-16}$
Time since last LRTI: 60–120 days	11.92	10.95–12.99	$< 10^{-16}$
Time since last LRTI: 120–365 days	4.39	4.06–4.74	$< 10^{-16}$
Time since last LRTI: 365–730 days	1.84	1.69–2.00	1.1×10^{-45}
Time since last LRTI: 730–2,190 days	0.88	0.82–0.95	0.001

findings extend this evidence by demonstrating that the observed association is not temporally uniform but comprises distinct short-term and long-term risk components, while also showing an increased risk of asthma among children with recurrent infections.

Unlike most previous studies, we analysed the LRTI–asthma association using explicit temporal separation of exposure and outcome to minimise reverse causation, and found that a substantial association persists, with distinct short-term and long-term risk components and a dose–response relationship with recurrent infections.

By separating exposure (LRTI before age 3) and outcome (asthma between ages 3–7), we aimed to reduce reverse causation, a central methodological challenge in this field.

Beyond the temporal structure of risk, our analyses also revealed substantial heterogeneity in the association according to infection recurrence, age at infection, sex, and anatomical localisation. These findings support the concept that the relationship between childhood LRTIs and asthma is influenced by multiple factors, consistent with the recognised heterogeneity of childhood asthma [8].

The magnitude and timing of the association provide further insight. The markedly elevated hazard immediately after LRTI, followed by a rapid decline, suggests that part of the observed association is attributable to increased diagnostic activity (diagnostic trigger) and overlap between post-infectious wheeze and early asthma phenotypes. Although temporarily, the elevated risk beyond the acute period, together with the dose-response relationship observed for recurrent infections, support a contribution beyond diagnostic effects. This pattern is consistent with longitudinal studies indicating that repeated early-life respiratory insults may influence long-term respiratory trajectories [4, 5]. Previous findings suggest that recurrent lower airway

inflammation during early life may contribute to persistent airway dysfunction or immune alterations that promote asthma development [1].

Regarding age at first LRTI, our findings suggest that asthma risk increasing with age at infection is largely driven by rising baseline susceptibility rather than a fundamentally different effect of infection timing. This interpretation is consistent with the notion that additional risk factors for asthma, such as atopy or environmental exposures, accumulate over time and interact with infectious insults.

The observed sex differences are notable. While boys had a higher baseline hazard of asthma, consistent with known epidemiological patterns in early childhood [9], the relative increase in risk associated with LRTI was more pronounced in girls. This finding is particularly interesting given that LRTIs are generally more common and more severe in boys [10]. Evidence indicates that boys exhibit relative immaturity of the immune system early in life [11, 12], whereas females generally mount stronger immune response to infection than men [13]. These differences may influence not only susceptibility to infection but also the downstream consequences of airway inflammation, infection-induced epithelial injury and subsequent airway remodelling, leading to asthma development [14]. Our findings suggest sex-related differences in these consequences.

An unexpected observation was that non-pneumonia LRTIs (i.e. bronchitis and bronchiolitis) were associated with a slightly higher subsequent asthma risk than pneumonia. This may reflect differences in pathophysiology, as bronchitis and bronchiolitis primarily affect the conducting airways, where inflammation, epithelial injury, and mucus obstruction are central processes in asthma development. In contrast, pneumonia predominantly involves the alveolar compartment.

Overall, our findings support a model in which early-life LRTIs are linked to subsequent asthma risk through multiple pathways.

Strengths and limitations

This study has several notable strengths. It is based on a nationwide, population-wide dataset with long follow-up, reducing selection bias and enabling robust estimation of associations. The longitudinal structure of the data further enabled the assessment of time-varying associations. The large sample size allowed detailed subgroup and time-resolved analyses, including recurrence, subgroup heterogeneity, and temporal patterns of risk. The scale of the database also made it possible to detect patterns and associations that may not be apparent in smaller, clinically collected datasets. The temporal separation of exposure and outcome represents an important methodological strength by reducing the risk of reverse causation.

This study is subject to limitations inherent in the administrative data. In our cohort, the observed asthma prevalence was lower than that reported in European populations, ranging between 4–14% [15]. This difference likely reflects the use of administrative data capturing clinically diagnosed and treated cases, rather than questionnaire-based or symptom-based definitions applied in many epidemiological studies. Case definitions relied on coding and treatment records without clinical data available, allowing misclassification, particularly wheezing in early childhood. Despite temporal separation of exposure and outcome windows, reverse causation

cannot be fully excluded because undiagnosed asthma or asthma susceptibility may have been present before the recorded LRTI episode. Key confounders (e.g. environmental exposures, socioeconomic status, family history) were not available, leading to potential residual confounding.

Conclusion

Asthma risk following childhood LRTIs showed a pronounced temporal structure, characterised by a marked short-term increase followed by a persistent long-term component and a dose-response relationship with recurrent infections. Although diagnostic and surveillance effects likely contribute to the observed association, the persistence of elevated risk after temporal separation of exposure and outcome suggests that the relationship extends beyond short-term diagnostic artefacts.

Data availability

The data were obtained from the National Health Insurance Fund of Hungary, and contain sensitive health information about individuals. The disclosure of such health records, even in an anonymized form is not allowed by legal regulation, i.e. the European Union General Data Protection Regulation (GDPR), in particular provisions on special-category data (health data) and lawful processing; relevant national legislation on personal data protection.

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Author contributions

Conceiving the study and study design: JL, ACS; accessing and verifying data: ZR, ACS, BF, KÁ, JL; developing methodology: ZR; conducting data analysis: ZR, ACS; data collection: KÁ; preparing the first draft of the manuscript: ZR, JL; writing the manuscript: ZR, JL, BF. All authors critically reviewed and revised the manuscript and approved the final version for submission. All authors agree to be responsible for all aspects of the work and have final responsibility for the decision to submit for publication.

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