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RESEARCH ARTICLE

The relationship between childhood leukaemia and childhood asthma: A pharmacoepidemiological study from the Netherlands

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Abstract

Background: It has been suggested that childhood asthma lowers the risk of childhood leukaemia. Studies have found an inverse association between these conditions. However, most studies on this relationship are based on questionnaires and telephone interviews, introducing recall bias. Therefore, we conducted a matched case–control study based on drug prescription data to assess the relationship between both conditions.

Methods: In a large database, covering more than one million individuals, we identified cases of children who had been prescribed 6-mercaptopurine (6-MP). This drug is used in the outpatient maintenance therapy of childhood leukaemia. We matched every child with leukaemia on sex and age (±6 months) to children without leukaemia (controls). The variable of having had asthma was defined as receiving at least two prescriptions for an inhaled corticosteroid within 12 months.

Results: We identified 59 children aged 2–18 who had been prescribed 6-MP (cases), and they were matched to 21,918 controls. Of the children with childhood leukaemia, three (5%) had childhood asthma, whereas in the control group 4889 (22%) had childhood asthma (odds ratio [OR] 0.19; 95% confidence interval 0.06–0.60).

Conclusion: In this study on the relationship between childhood asthma and childhood leukaemia, we found a strong inverse association.

KEYWORDS
asthma, atopy, childhood leukaemia, pharmacoepidemiology

1 | INTRODUCTION

It has been suggested that atopic diseases such as childhood asthma (CA) lower the chance of developing acute leukaemia (AL) in childhood. However, scientific support for this assertion is weak. Most studies on the relationship between the occurrence of atopic diseases and AL in children are based on data collected by questionnaires and telephone interviews, introducing recall bias.[1–3] Therefore, we conducted a case–control study to assess the possible association between CA and AL by using drug prescription data, which limits the risk of recall bias.

Abbreviations: 6-MP, 6-mercaptopurine; AL, acute leukaemia; ATC code, Anatomical and Therapeutical
Classification code: CA, childhood asthma; CI, confidence interval; IADB.nl, interaction database of the Netherlands; OR, odds ratio.

2 | METHODS

2.1 | Data source

The drug prescription data were obtained from the population-based prescription database interaction database of the Netherlands (IADB.nl) of the University of Groningen, the Netherlands. The IADB database is a continuously growing database that contains prescription data from 1996 onwards, from community pharmacies in the northern and eastern parts of the Netherlands. Prescription data include information about dispensed medication (date of dispensing, amount dispensed, daily dose, prescriber, total amount of defined daily doses [DDD] and Anatomical and Therapeutical Classification code [ATC code]) and limited information about the individual the medication was dispensed to (sex and birthdate). Registration of prescriptions in the database occurs irrespective of healthcare insurance and prescriber. However, prescriptions during hospital stays and over-the-counter drugs are not included. In the database, each individual has a unique, anonymous identifying number. The database covers a population of approximately 1.1 million people. The population in the IADB.nl is largely representative of the entire Dutch population.[4]

2.2 | Definition of cases, controls and exposure

Cases of children aged 2–18 were identified based on the use of 6-mercaptopurine (6-MP) (ATC code L01BB02), which is a drug specifically prescribed to treat AL. This drug has been part of outpatient maintenance therapy for AL in Dutch protocols for over 30 years and is not approved to be prescribed for other indications. The date of the first 6-MP prescription is the index date. No medication 420 days before the index date was included in the study database to ensure that medication used for the AL treatment was excluded.

Controls not using 6-MP were matched to the cases regarding age (maximal deviation: 6 months) and sex.

The exposure of diagnoses of CA is defined as having been prescribed inhaled corticosteroids (ATC code R01AD) at least twice within 12 months, more than 420 days prior to the index date. We calculated prevalence, odds ratio (OR) and 95% confidence interval (CI).

3 | RESULTS

We found 59 cases of AL and 21,918 matched controls (371 controls per case). Within our study population, 44% was male and 56% was female. The mean age of both cases and controls was 10.3 years, with a median age of 11 years (range 2–18 years). Of the children with AL, three (5%) had asthma, whereas in the control group 4889 (22%) had asthma (OR [95% CI] = 0.19 [0.06–0.60]).

4 | DISCUSSION

We found a strong inverse association between CA and AL. Our results are based on prescription data from the widely researched prescription database IADB.nl with proven accuracy of prescription rates; hence, potential information bias was minimal.[4] Furthermore, recall bias, a limitation of other studies, was absent.

Compared with the literature, our study has the strongest inverse association, with an OR of 0.19. Zierhut et al. employed structured telephone questionnaires in a case–control study. The data of 1018 patients and 1076 controls were included in the study. A family history of food and drug allergies revealed a slightly reduced risk (OR [95% CI] = 0.83 [0.65–0.96]).[1] Wen et al. studied the association between allergic diseases and AL and used data collected via a telephone survey of 1842 patients with AL and 1986 matched controls. The researchers found that a combined history of one or more allergic disorders was associated with a reduced risk of 0.7 (95% CI: 0.6–0.8).[2] In a German study of 1130 AL cases and 2957 controls, data collection consisted of a self-administered questionnaire, followed by a telephone interview. The study found an OR of 0.52 (95% CI: 0.40–0.67) for the association between AL and having any atopic disease, including hay fever, asthma and dermatitis.[3]

Hughes et al. used data from primary care records for a case–control study. Their study included 720 AL cases and 1337 controls. Asthma was defined as having had a prescription of a drug typically used for asthma. The study found an OR of 0.99 (95% CI: 0.74–1.34).[5]

A possible explanation for the difference between their study and our study is that our definition of asthma only includes children who had received at least two prescriptions for inhaled corticosteroids. Many young children (e.g., with viral wheeze) receive prescriptions for betamimetics. Those children do not have asthma. We speculate that by using our more stringent criterion, we only included children with CA. Moreover, recall bias is impossible because we used prescription data. Therefore, we believe our figures are more reliable than in previous studies.

It could be that allergic diseases such as CA protects against AL. Possible mechanisms, including genetical and immunological factors, have been mentioned.[1,2,3,5] However, it could be that CA is a proxy for unmeasured exposures. The incidence of both CA and AL is influenced by several factors such as breastfeeding and early childhood infections.[6-10]

Before accepting the results, the limitations of this study should be discussed. The employed database does not contain a formal diagnosis and lacks information about confounding factors such as breastfeeding and parental smoking. In addition, the number of AL cases is relatively limited. We used 6-MP as a proxy for AL, as this drug is not approved for indications other than leukaemia, which limits the risk of including children diagnosed with other diseases like inflammatory bowel disease. As being present in the database for at least 2 years before the start of 6-MP treatment was a prerequisite for inclusion in our study population, we have no information about children who started this treatment at a younger age (<2 years). However, this group of children is relatively

small, and we do not believe this factor influences the outcome. The database does not give information about the disease phenotype. Furthermore, children who did not reach the outpatient treatment stage because they died before are lacking from this study. This situation occurs rarely, and we do not think this factor significantly influenced the outcome.

5 | CONCLUSION

Despite these limitations, we believe our data strongly support the inverse association between CA and childhood AL in children.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Zierhut H, Linet MS, Robison LL, Severson RK, Spector L. Family history of cancer and non-malignant diseases and risk of childhood acute lymphoblastic leukaemia: a Children's Oncology Group study. *Cancer Epidemiol*. 2012;36(1):45-51. doi:10.1016/j.canep.2011.06.004
2. Wen W, Shu XO, Linet MS, et al. *Cancer Causes Control*. 2000;11(4):303–307. doi:10.1023/a:1008958724739
3. Schüz J, Morgan G, Böhler E, Kaatsch P, Michaelis J. Atopic disease and childhood acute lymphoblastic leukemia. *Int J Cancer*. 2003;105(2):255–260. Portico. doi:10.1002/ijc.11054
4. Visser ST, Schuiling-Veninga CC, Bos JH, de Jong-van den Berg LT, Postma MJ. The population-based prescription database IADB.nl: its development, usefulness in outcomes research and challenges. *Expert Rev Pharm Out Rese*. 2013;13(3):285–292. doi:10.1586/erp.13.20
5. Hughes AM, Lightfoot T, Simpson J, et al. Allergy and risk of childhood leukaemia: Results from the UKCCS. *Int J Cancer*. 2007;121(4):819–824. doi:10.1002/ijc.22702
6. Hossenbaccus L, Linton S, Ramchandani R, Gallant MJ, Ellis AK. Insights into allergic risk factors from birth cohort studies. *Ann Allergy Asthma Immunol*. 2021;127(3):312–317. doi:10.1016/j.anai.2021.04.025
7. Güngör D, Nadaud P, Dreibelbis C, et al. Shorter Versus Longer Durations of Any Human Milk Feeding and Food Allergies, Allergic Rhinitis, Atopic Dermatitis, and Asthma: a Systematic Review. USDA Nutrition Evidence Systematic Review; 2019.
8. Gong Q-Q, Quan D-D, Guo C, Zhang C, Zhang Z-J. Association between maternal breastfeeding and risk of systemic neoplasms of offspring. *Ital J Pediatr*. 2022;48(1). doi:10.1186/s13052-022-01292-9
9. Rudant J, Orsi L, Menegaux F, et al. Childhood Acute Leukemia, Early Common Infections, and Allergy: The ESCALE Study. *Am J Epidemiol*. 2010;172(9):1015–1027. doi:10.1093/aje/kwq233
10. Beigelman A, Bacharier LB. Early-life respiratory infections and asthma development. *Curr Opin Allergy Clin Immunol*. 2016;16(2):172–178. doi:10.1097/aci.0000000000000244

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