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Atopic Dermatitis as a Precursor to Early Onset of Recurrent Wheeze, Bronchiolitis, and Childhood Asthma

Valentina Risteska-Nejashmikj*

University "Goce Delcev" - Faculty of Medical Sciences, Shtip, Republic of North Macedonia

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***Correspondence:** Valentina Risteska-Nejashmikj, University "Goce Delcev" Faculty of Medical Sciences-Shtip; Republic of North Macedonia.
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Abstract

INTRODUCTION: Childhood asthma frequently escapes timely diagnosis, a consequence of inadequate parental education, societal prejudices, and health-care professionals' limited knowledge. Bringing attention to atopic dermatitis (AD) as an early indicator of childhood asthma can enhance awareness about the elevated risk of recurrent wheezing, bronchiolitis, and asthma in children, thereby advancing their care and treatment.

AIM: The objective of this study is to investigate the correlation between AD and the occurrence of recurrent wheezing, bronchiolitis, as well as asthma, in children aged 0–3 years. The findings of this research aim to contribute to early detection practices and guide the implementation of suitable treatment strategies for this vulnerable age group.

MATERIALS AND METHODS: In this study, retrospective data were gathered from health records at the Pediatric Primary Health Care Practice - "Vitalino" in Veles, North Macedonia. The analysis encompassed 414 children aged 0–3 years, spanning the years 2019–2022. The primary focus of the investigation was on children exhibiting early-onset AD and its association with recurrent wheezing, as well as bronchiolitis and the development of early childhood asthma.

RESULTS: The conducted statistical analyses, including measures such as prevalence, odds ratio, and multiple regression, revealed a significant association between AD and the early occurrence of recurrent wheezing. In addition, the analyses demonstrated a noteworthy association not only between AD and early recurrent wheezing but also between AD and childhood asthma. Moreover, a significant connection was identified between bronchiolitis and childhood asthma. These findings contribute to a more comprehensive understanding of the complex interrelationships among AD, bronchiolitis, and the early onset of childhood asthma.

CONCLUSION: This study confirms that children under the age of 3 years who have early-onset AD are significantly more susceptible to recurrent wheezing and asthma. It is crucial to identify AD as a potential early indicator of childhood asthma. This knowledge can enhance awareness among health-care professionals and parents, leading to earlier detection of asthma symptoms in children. Ultimately, this can contribute to more effective management strategies for these young patients.

Introduction

Atopic dermatitis (AD) in children, often known as eczema, is a complex allergic condition marked by high levels of immunoglobulin E and peripheral eosinophilia [1], [2]. This condition, which is formed by an interaction of both genetic elements and environmental influences, usually presents itself in a form ranging from mild to moderate [3]. It is characterized by recurring episodes and often exhibits unique phenotypes, particularly among younger children [4]. Significantly, the presence of atopic disease in family history is closely linked to the occurrence of childhood AD. It is worth noting that this risk factor is evident in about 70% of individuals affected by the condition [5].

AD, which typically begins in childhood, impacts 10–20% of the pediatric population and primarily manifests within the initial years of life (90%) [6]. This condition has a significant clinical influence [7]. It frequently presents alongside other atopic diseases such as asthma, allergic rhinitis, and laryngitis. This allergic disorder follows a pattern known as the "atopic march," which starts with eczema and food allergies in infancy and progresses to allergic asthma and rhinitis during childhood [8].

AD presents as itchiness, colored skin patches, dryness, blisters, sensitivity, and pain. The rash's location varies with age - infants often have it on the face, scalp, and outer limbs, while in older children, it is usually on the head, neck, trunk, and limbs. The eczema area and severity index is used to assess severity [9]. Even mild childhood eczema can predispose children to early recurrent wheezing and asthma, emphasizing the need for accurate medical records [10]. Infancy complications can result in asthma and frequent viral infections, potentially causing underdiagnosis and unnecessary antibiotic use [11]. Diagnosing asthma in young children is challenging due to their age, atypical symptoms, and varying wheezing frequencies [12]. A criterion of three or more wheezing episodes since birth helps identify children at risk [13].

Childhood asthma and related conditions pose significant health and economic challenges, with a rising global prevalence of recurrent wheezing, particularly in less developed countries [14]. Factors such as genetics, environmental exposures, secondhand smoke, and air pollution add to the complexity of these conditions. The lack of early diagnostic criteria often results in under-recognition and inadequate treatment [15]. Asthma is the most common non-communicable disease in children, affecting 10–15% of the global population [16]. However, not all children with early recurrent wheezing develop asthma, indicating diverse clinical outcomes [11]. Identifying children at risk involves assessing major and minor criteria, including frequent wheezing and a history of asthma or eczema. A strict index involves frequent wheezing in the first 3 years, plus either one major risk factor (parental asthma or eczema) or two minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis) [17]. However, early asthma management is complex due to varied symptoms. Doctors use prediction models and guidelines for treating recurrent wheezing in children. Yet, the lack of universal early diagnostic criteria poses challenges. Future research could focus on personalized medicine, exploring phenotypes, biomarkers, and genetic and molecular studies [18]. A recent study showed a high prevalence of AD (18.8%by UK criteria, 14.9% by ISAAC) and asthma (20.1%) in 2-year-old, emphasizing the need to understand these conditions for effective strategies [19]. This highlights the need to understand these conditions' prevalence coexistence for effective prevention and treatment strategies.

Aim

We examined the connection between AD, recurrent wheezing, and bronchiolitis in the progression to early childhood asthma. This study could enhance our understanding of these conditions' natural progression, vital for designing targeted interventions and treatments.

Materials and Methods

This research involved a comprehensive retrospective analysis of extensive healthcare records from the Primary Health Care Polyclinic - Pediatric Primary Health Care Practice - "Vitalino" located in Veles, Republic of North Macedonia. The primary objective of this study was to investigate whether children with a history of AD and prior bronchiolitis faced an elevated risk of recurrent wheezing and subsequent development of childhood asthma. The analysis encompassed all children aged 0–3 years who were admitted from 2019 to 2022, inclusive of the year 2022. The study cohort comprised a total of 414 participants. The study was specifically designed to include children who had experienced two or three episodes of wheezing. Importantly, children who had only one episode of wheezing have not been included. In addition, the study did not include participants older than 3 years, and a child diagnosed with cystic fibrosis was also excluded. This careful selection of participants helped to ensure a focused and relevant study.

In terms of data collection and analysis, Microsoft Excel (Version 8) was employed for data collection, facilitating efficient organization and initial analysis of the gathered information. Subsequent data analysis, involving statistical computations and modeling, was conducted using Statistics for Windows (Version 10). The analytical procedures encompassed a range of statistical tests, including the calculation of prevalence, odds ratio, and multiple regression analysis. These tests were employed to comprehensively explore and interpret the relationships and patterns within the collected data.

In this investigation, informed consent was obtained from participants, mainly parents or guardians. Strict data security measures were in place, and confidentiality was prioritized using encrypted storage and coded identifiers. Participation was voluntary, with an option to withdraw anytime.

Potential limitations

The study on the link between AD, recurrent wheezing, bronchiolitis, and childhood asthma in children aged 0–3 years offers significant insights but has certain limitations. Its retrospective design and focus on a single center in Veles, North Macedonia, limit its generalizability. In addition, the lack of comprehensive family history data prevents the determination of potential genetic predispositions.

Results

In an effort to understand the prevalence of various health conditions within a specific age group, we conducted a comprehensive analysis of a cohort consisting of 414 children aged between 0 and 3 years, admitted in the period from 4 years (2019–2022). The data are organized (Table 1) that categorizes children based on specific characteristics, including the presence of AD, recurrent wheezing, childhood asthma, and a history of previous bronchiolitis. Each category specifies the number of children who fall into the respective group, accompanied by the corresponding prevalence expressed as a percentage of the total cohort. This breakdown serves as a valuable snapshot, shedding light on the prevalence rates of these

health conditions, essential for understanding their occurrence and potential correlations within the studied pediatric population. The analysis revealed that out of the 414 children, 102 had a history of AD, indicating a significant prevalence of this condition within the cohort. Furthermore, 108 children had experienced recurrent wheezing, and 46 had a previous episode of bronchiolitis during their early childhood. Notably, 33 children have shown early signs of childhood asthma.

Table 1: Prevalence of health conditions in a pediatric cohort (ages 0–3)

Health condition	Number of children	Prevalence (%)
Atopic dermatitis	102	24.64
Recurrent wheezing	108	26.09
Childhood asthma	33	7.97
Previous bronchiolitis	46	11.11
Total number of children	414	

The analysis underscores significant prevalence rates, notably 24.64% for AD and 26.09% for recurrent wheezing. In addition, 11.11% of children had experienced previous bronchiolitis, and 7.97% exhibited early signs of childhood asthma. These prevalence rates provide valuable insights into the health conditions common in this cohort of children. However, it is important to remember that these rates are specific to this particular cohort and may not reflect the prevalence in the general population. Further studies would be needed to confirm these findings.

Next, we conducted a detailed analysis of the data to explore the odds associated with having one medical condition in the presence of another – a point of particular interest in both medical and epidemiological investigations. The results are represented in Table 2.

Table 2: Distribution of children based on health conditions

Groups of children	Number of children (n)
Atopic dermatitis+/recurrent wheezing+	86
Atopic dermatitis+/recurrent wheezing −	16
Atopic dermatitis−/recurrent wheezing+	22
Atopic dermatitis−/recurrent wheezing −	290
Atopic dermatitis +/childhood asthma+	28
Atopic dermatitis +/childhood asthma −	74
Atopic dermatitis −/childhood asthma+	5
Atopic dermatitis −/childhood asthma −	307
Bronchiolitis +/childhood asthma +	12
Bronchiolitis +/childhood asthma −	34
Bronchiolitis −/childhood asthma +	20
Bronchiolitis −/childhood asthma −	348

The data suggests potential associations between exposure to health conditions such as AD and bronchiolitis, and higher rates of recurrent wheezing and childhood asthma. However, these correlations would need to be confirmed through further statistical analysis. To clarify these relationships, an odds ratio analysis was performed, complemented by Chi-square (X2) test calculations. This analysis provided insights into the associations between different health conditions. The results, including the odds ratios, 95% confidence intervals, Z statistics, and P-values for the analyzed condition pairs, are summarized in Table 3. This comprehensive analysis aids in understanding the potential correlations between these health conditions.

The analysis of the association between AD and recurrent wheezing involved four distinct groups within the studied population, as detailed in Table 2. These groups were defined based on the presence or absence of exposure to AD and the occurrence of recurrent wheezing. The odds ratio results for the “AD and Recurrent Wheezing” pair underscore a robust and clear link between AD and recurrent wheezing in children (Table 3). The odds ratio of 70.85 signifies that children with AD are approximately 71 times more likely to experience recurrent wheezing compared to those without it. The 95% confidence interval (35.63–140.90) lends strong support to this association, ruling out the possibility of no effect. In addition, the Z statistic, at 12.147, indicates a high improbability of this connection occurring by chance, and the p-value (<0.0001) provides compelling evidence against the null hypothesis of no association. In conclusion, these comprehensive results provide strong evidence of a significant and noteworthy association between AD and recurrent wheezing within the studied population.

Table 3: Associations between health conditions - odds ratios, confidence intervals, and statistical measures

Condition pair	Odds ratio	95% confidence interval	Z statistic	p-value
Atopic dermatitis and recurrent wheezing	70.8523	35.6273 to 140.9044	12.147	< 0.0001
Atopic dermatitis and childhood asthma	23.2324	8.6771 to 62.2033	6.260	< 0.0001
Bronchiolitis and childhood asthma	6.1412	2.7659 to 13.6353	4.460	< 0.0001

Subsequently, the investigation of the relationship between AD and childhood asthma revealed a significant association (Table 3). Children with AD are approximately 23 times more likely to develop asthma. This significant finding is supported by a 95% confidence interval of 8.68–62.20, a substantial Z statistic, and a $p < 0.0001$. These robust statistics highlight the strong and statistically significant association between AD and childhood asthma, underscoring the importance of this relationship in our understanding of these conditions.

Following our initial findings, we further investigated the relationship between bronchiolitis and childhood asthma. Our analysis categorized children based on their exposure to bronchiolitis and the presence or absence of childhood asthma (Table 2). The results revealed a significant association, with children who had bronchiolitis being about 6.1 times more likely to develop childhood asthma than those without this respiratory condition. This finding is supported by a 95% confidence interval of 2.77–13.64, a substantial Z statistic, and a $p < 0.0001$, all indicating a statistically significant link between bronchiolitis and childhood asthma (Table 3). However, it is important to note that while our results show a correlation, they do not establish causation, and further research is needed to understand the underlying causes of this association. Furthermore, these findings are specific to the population studied and may not be generalizable to other groups.

In the next stage, the study employed multiple linear regression to investigate the combined influence

of two independent variables, AD, and bronchiolitis, on the dependent variable, childhood asthma. The analysis revealed a moderate collective significant effect, as indicated by the F statistic (F [2, 400] = 44.23, p < 0.001), with R^2 and R^2adj both equaling 0.18. The subsequent table (Table 4) presents the t-values and p-values for each independent variable (AD and Bronchiolitis).

Table 4: Multiple linear regression analysis - predictors of childhood asthma

Moderate collective significant effect		
F	F (2, 400) = 44.23	p<0.001
R^2	0.18	
R^2 adj	0.18	
Variable analysis		
Variable	t-value	p-value
Atopic dermatitis	7.915	<0.001
Bronchiolitis	2.6	0.010

The t-values signify the strength and direction of the relationships, while the p-values determine their statistical significance. Both AD and bronchiolitis exhibit significant predictability for childhood asthma. Although the intercept is not explicitly mentioned, it is typically included in the linear regression equation. These results collectively suggest that the combination of AD and bronchiolitis has a moderate explanatory power for childhood asthma. The findings emphasize a moderate collective significant effect between AD and bronchiolitis, signifying their roles as predictors for the early onset of childhood asthma. It is essential to note that limited valid data on family history, a known predictor, was not available due to the retrospective nature of the study.

Discussion

AD, a widespread chronic inflammatory skin disorder characterized by recurring eczematous lesions and severe itching, affects approximately 20% of children globally in Europe [20]. A comprehensive study investigating the prevalence of AD in Central, Eastern, and Western Europe revealed notable disparities among children under 5 years across various European countries. Estonia and the Russian Federation have the highest prevalence rates in both genders, in stark contrast to Romania and Latvia, which exhibit the lowest rates [21]. This research offers crucial insights into the diverse prevalence of AD in early childhood across different European regions. In the group of children we examined, the prevalence of AD was found to be 24.64%. Indeed, the significant prevalence of AD in children aged 0–3 years highlights its substantial impact. This prevalence underscores the intricate interplay of genetic and environmental factors that contribute to these health outcomes. It is a vivid reminder of the complexity of this condition and the multifaceted approach required for its management and treatment.

Our research highlights the substantial prevalence of AD and recurrent wheezing in children, both posing significant health concerns. AD, affecting a significant 3% of the population, is a key risk factor for the onset of other allergic diseases, leading to the traditional atopic march [22]. Concurrently, the rising incidence of recurrent wheezing presents a major respiratory issue. The global prevalence of wheezing varies, with rates from 29% in Northern Europe to 48% in Southern Europe, and an overall prevalence of 27% in the US [23].

Furthermore, our study reveals a significant correlation between AD and recurrent wheezing, as well as a substantial association between AD and childhood asthma. The disruption of the skin barrier due to AD contributes to sensitization, extending immune reactivity to the respiratory system, leading to recurrent wheezing, and initiating the atopic march towards asthma [24]. Recognizing this linkage is crucial for a comprehensive management approach, encouraging early identification of AD and proactive measures against recurrent wheezing. This understanding underscores the importance of early intervention and holistic management strategies in mitigating the progression of these conditions.

Asthma, the most prevalent non-communicable disease in children, has affected 10–15% of the global population in the past year. Interestingly, not all children with early-life recurrent wheezing develop asthma symptoms, indicating the varied clinical outcomes of these conditions. Factors such as environmental triggers, viral infections, and genetic predisposition play crucial roles in these scenarios [16]. A study investigating the connection between early-onset AD and asthma in children revealed that 21.6% of 1549 children with AD developed asthma by age 8. Risk factors include male sex, lower birth order, maternal asthma history, pre-pregnancy maternal obesity, and early exposure to tobacco smoke. Early-life food allergies, respiratory infections, and prolonged AD symptoms also influenced asthma development [25]. These insights could inform personalized asthma prevention.

The Tucson Children's Respiratory Study developed two indices to predict asthma in children. The stringent index includes frequent wheezing during the first 3 years of life and either one major risk factor (parental history of asthma or eczema) or two minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis). Children with a positive loose index were 2.6–5.5 times more likely to have asthma between ages 6 and 13 years, increasing to 4.3–9.8 times with a stringent index. Over 95% of children with a negative stringent index never had active asthma. The study concludes that asthma development can be reasonably predicted using these parameters [26].

Comparing our findings with international data allows us to understand shared or unique risk factors and the diverse management strategies employed

worldwide. The prevalence of early childhood asthma aligns with global trends, reflecting the intricate interplay of factors like air quality, allergen exposure, and genetic predisposition [27].

In a study by Jartti *et al*., Rhinovirus bronchiolitis was identified as a significant risk factor for school-age asthma. The study highlighted the role of genetic factors and airway inflammation in increasing susceptibility to these infections. It also suggested that recurrent infections could lead to the onset of atopic asthma [28]. Our research, albeit on a smaller cohort, underscores the considerable prevalence of bronchiolitis, pointing to a significant burden of respiratory viral infections. Factors such as regional variations in viral circulation, healthcare accessibility, and prevention strategies can influence these rates [29]. A comparative analysis with global data enhances our understanding of the prevalence and impact of bronchiolitis across different populations.

These insights significantly enhance our understanding of regional differences and potential risk factors associated with childhood asthma globally. Our research offers valuable insights into the prevalence and risk factors of AD, recurrent wheezing, bronchiolitis, and asthma in early childhood. These findings emphasize the need for continued research and the development of effective management strategies to address these conditions. The goal is to improve the quality of life for these children and potentially prevent the progression of these conditions.

Conclusion

Our study highlights the complex relationship between AD and various respiratory conditions in early childhood, emphasizing the significant prevalence of AD and its influences on pediatric health. We found a critical correlation between AD and recurrent wheezing, driven by AD's impact on the skin barrier and the subsequent atopic march. The association between AD and childhood asthma underscores the importance of early diagnosis and interventions. Our findings also reveal a noteworthy connection between bronchiolitis and childhood asthma, emphasizing the need for comprehensive respiratory care. Overall, our study contributes to the understanding of early childhood respiratory health and emphasizes the importance of preventive measures and holistic health management.

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