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Pre-school wheeze treatment patterns in the primary care setting in Italy

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Wheeze is one of the most common respiratory conditions in early childhood. Despite available guidelines, treatment management in pre-school children remains challenging. We aim to describe prescribing patterns for pre-schoolers with wheeze in primary care settings. This retrospective population-based birth cohort study analyzed data from the Italian Pedianet primary care database. Children born between 2010 and 2017 and followed from birth to at least 5 years were included. Wheeze episodes were identified through ICD-9-CM codes and validated free-text searches in outpatient records. Prescribing patterns across successive episodes were analyzed using State Sequence Analysis (SSA), overall and stratified by age at first episode, to describe treatment trajectories in primary care from 2010 to 2023. Among 66,981 eligible children, 24.28% experienced at least one wheeze episode. Treatment was provided in 64.96% of episodes, with a median of two treated episodes per child. Initial prescribing showed considerable variation: inhaled beta2-agonists, oral corticosteroids, and inhaled corticosteroids were most commonly used, either alone or combined. Prescribing patterns varied by age, with greater use of inhaled therapies in older children. SSA showed declining numbers of children receiving subsequent treatments and a progressive consolidation toward a limited number of therapeutic regimens over successive episodes. In this primary care cohort, prescribing for pre-school wheeze was heterogeneous and influenced by age at first diagnosis. These findings highlight gaps between real-world practice and current guidelines, emphasizing the need for clearer guidance and targeted implementation strategies for managing wheeze in early childhood.

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INTRODUCTION

Pre-school wheeze is a major clinical challenge and a leading cause of healthcare utilization, as approximately one-third of children aged 1–6 years experience symptoms and nearly 50% report at least one episode by the age of 6[1,2]. Pre-school wheeze was historically classified in episodic viral wheeze (EVW) characterised by symptoms exclusively triggered by viral respiratory tract infections, and multiple trigger wheeze (MTW) triggered also by other precipitants (e.g. allergens, exercise and tobacco smoke)[3], even though assessments of their utility for predicting response to treatment (phenotype-based management) has not been reported yet[4]. More recently, a European Respiratory Society (ERS) task force document reported that for clinical practice, it is more useful to describe pre-school wheeze illness using treatable traits reflecting underlying disease processes, rather than trying to classify patients into distinct phenotypes of uncertain aetiology[5].

Based on the currently available limited evidence, management strategies for wheeze largely depend on severity and underlying aetiology. Inhaled short-acting beta2-agonists (SABA) combination represents the first-line treatment in pre-school children over 1 year of age with wheeze[6,7]. Intermittent administration of inhaled corticosteroids (ICS) for 7–10 days in association with SABA in pre-schoolers with EVW is considered by the most recent Italian guidelines and recommendations[6]. In cases of uncontrolled respiratory symptoms and/or frequent or severe wheezing episodes, a 3-month trial of a daily low-dose ICS should be initiated according to the Global Initiative for Asthma (GINA) guidelines[7]. For children who respond inadequately to daily ICS, a leukotriene receptor antagonist (LTRA) such as montelukast may be considered[5]; however, evidence shows that LTRAs provide only modest benefit in persistent asthma and do not reduce exacerbations in viral-induced wheeze[8]. Moreover, daily ICS remains superior to LTRA monotherapy for symptom control and prevention of exacerbations, and clinicians should counsel caregivers regarding potential neuropsychiatric adverse effects of montelukast.

Given the uncertainties in the identification of children who remain symptomatic, clinical management is challenging, especially in a primary care setting, where resources are scarcer. This retrospective birth cohort study aims to evaluate the pattern of treatment prescribed to pre-schoolers with wheeze presenting to primary care paediatricians from 2010 to 2023.

DATA AND METHODS

Study population

In Italy, children are assigned to a family paediatrician (FP) who serves as the primary point of care within the National Health Service. Pedianet is a population-based paediatric primary care database that has been operating since 2004 and currently includes anonymized data from more than 500,000 children, covering approximately 4% of the national paediatric population each year. It provides a representative sample of Italian infants and children, both in terms of socio-demographic characteristics and clinical profiles[9,10]. Participating paediatricians across multiple Italian regions use a standardized clinical software system, allowing the collection of routinely recorded demographic, clinical, diagnostic, and prescription data, as described in detail

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elsewhere. All data are encrypted and anonymized prior to entry into the Pedianet database, and individual patients cannot be identified.

For this study, we included data from 194 FPs who contributed to the database from 1 January 2010 to 31 December 2023; the data were extracted in March 2024. The study population included all children born between January 1, 2010, and December 31, 2017, who were followed by family paediatricians (FPs) in the Pedianet network since birth up to a minimum of 5 years of age. Children with no valid information on sex and age were excluded, as well as those with the following conditions requiring corticosteroids therapy: autoimmune diseases, including chronic inflammatory demyelinating polyneuropathy (CIDP), rheumatic disorders, ulcerative colitis and Crohn's disease, granulomatosis with polyangiitis, adrenocortical insufficiency, cancer, thyroiditis, chronic hives, eczema, multiple sclerosis, nephrotic syndrome, sarcoidosis, lupus, myasthenia gravis, autoimmune hepatitis, giant-cell arteritis, Duchenne muscular dystrophy, uveitis, and organ transplant. Exemptions from medical co-payment and the International Classification of Diseases, Ninth edition, Clinical Modification (ICD-9-CM) diagnosis codes for the specific disease were used to select the children (Table S1).

Exposure ascertainment

A child with at least one wheeze episode was classified as a "child with wheeze". The wheeze episode was defined as any reported medical diagnosis of wheeze in the outpatient records for primary care visits identified with ICD-9-CM codes (519.11, 786.07), or free text in medical charts, retrieved by a string (containing terms "*wheez*" or "*broncosp*") and validated by a clinical data manager.

Treatment of interest

The treatment investigation included all prescriptions for inhaled beta2-agonists (ATC codes R03A*), inhaled glucocorticoids (R03BA*), oral glucocorticoids (H02A*), and cough and cold preparations (R05*). Prescriptions for the same treatment episode (i.e., the same day) were deduplicated by ATC. At each visit, any treatment or medical resource recorded within 7 days of a wheeze diagnosis was considered part of the same episode.

Statistical analysis

Baseline characteristics of the population, including participants' sex, presence of comorbidities (the list of comorbidities is provided in Table S2), and their area deprivation index (ADI), which served as a proxy for socioeconomic status, were summarized using frequencies and percentages for categorical variables, and medians and interquartile ranges for continuous variables.

Additionally, analysis was performed for children with only one treated episode. Age groups were defined according to completed years of life as follows: <1 year (<12 months), 1 year (12–<24 months), 2 years (24–<36 months), 3 years (36–<48 months), 4 years (48–<60 months) and 5 years (60–<72 months).

To further explore temporal changes in prescribing practices, we evaluated treatment patterns across calendar years stratified by age group.

State sequence analysis

State sequence analysis (SSA) is a valuable statistical methodology for describing a subject's prescription history as a sequence of categorical states. In this study, states are defined from the prescriptions of the considered treatments during each period. SSA allows comparing sequences across different subjects with respect to the succession of their component states and identifying common patterns. The study period was set from 1 January 2010 to 31 December 2023, and the analysis time unit, also called sequence granularity, was set to the number of treated events. This approach allows for analysing changes in prescribing patterns across successive episodes. To enhance the interpretability of results and ensure clearer visualization of trajectories, for the SSA we restricted the analysis to the first five treated states.

To visually represent the evolution of prescribing patterns across successive wheeze episodes, alluvial plots were generated using the *networkD3* package in R[11]. Each node in the plot corresponds to a distinct medication combination observed at a given treated episode, while the flows between nodes illustrate the transitions in prescribing patterns across the first five treated episodes. The width of each flow is proportional to the number of episodes following that specific transition path. This visualization approach complements SSA by providing a clear view of how children may transition between medication combinations and when treatment consistency or variation occurs.

The SSA was performed both on the overall cohort and stratified by age at the time of the first wheeze episode to explore potential differences in prescribing trajectories across developmental stages.

We adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidance for reporting on observational studies.

Ethics approval and consent to participate

This is an observational, retrospective, non-interventional study. According to a bylaw on the classification and implementation of observational drug-related research, as issued by the Italian National Drug Agency (an entity belonging to the Italian Ministry of Health), this study does not require approval by an ethics committee in Italy (Italian Drug Agency note on August 3, 2007). This study was conducted in accordance with the tenets of the Declaration of Helsinki and was compliant with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance's Guide on Methodological Standards in Pharmacoepidemiology. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

RESULTS

Among 322,910 children included in Pedianet from January 2010 to December 2023, 66,981 met the inclusion criteria for the study cohort. Of these, 16,266 (24.28%) experienced at least one wheeze episode, accounting for a total of 48,562 episodes, with a median of 1 episode per child [IQR: 1–3] (Fig. 1). Children with wheeze were more frequently male (57.87 vs 49.68%) and had a higher prevalence of at least one comorbidity compared with those without wheeze (17.61 vs 11.69%). The distribution across deprivation index categories was broadly similar between groups. Birth year was evenly distributed, although children with wheeze were slightly more represented in earlier birth cohorts (Supplementary Material Table S3). Among wheeze episodes, the majority occurred in males (58.93%) and in children without identified comorbidities (78.96%). The highest proportion of wheeze episodes was observed among children in the most deprived class (24.17%); however, cases were distributed across all categories. The median age at the first diagnosis was 1.33 years [IQR: 0.65–2.73]. The birth cohort distribution showed relatively balanced proportions of children born each year from 2010 to 2018, with only a slight decrease in 2018 (Supplementary Material Table S4).

The analysis by age at first wheeze episode showed that the number of subjects decreased with increasing age, from 4749 (35,95%) in the <1-year group to 580 (4,39%) in the 5-year group. The maximum number of wheeze episodes recorded per child

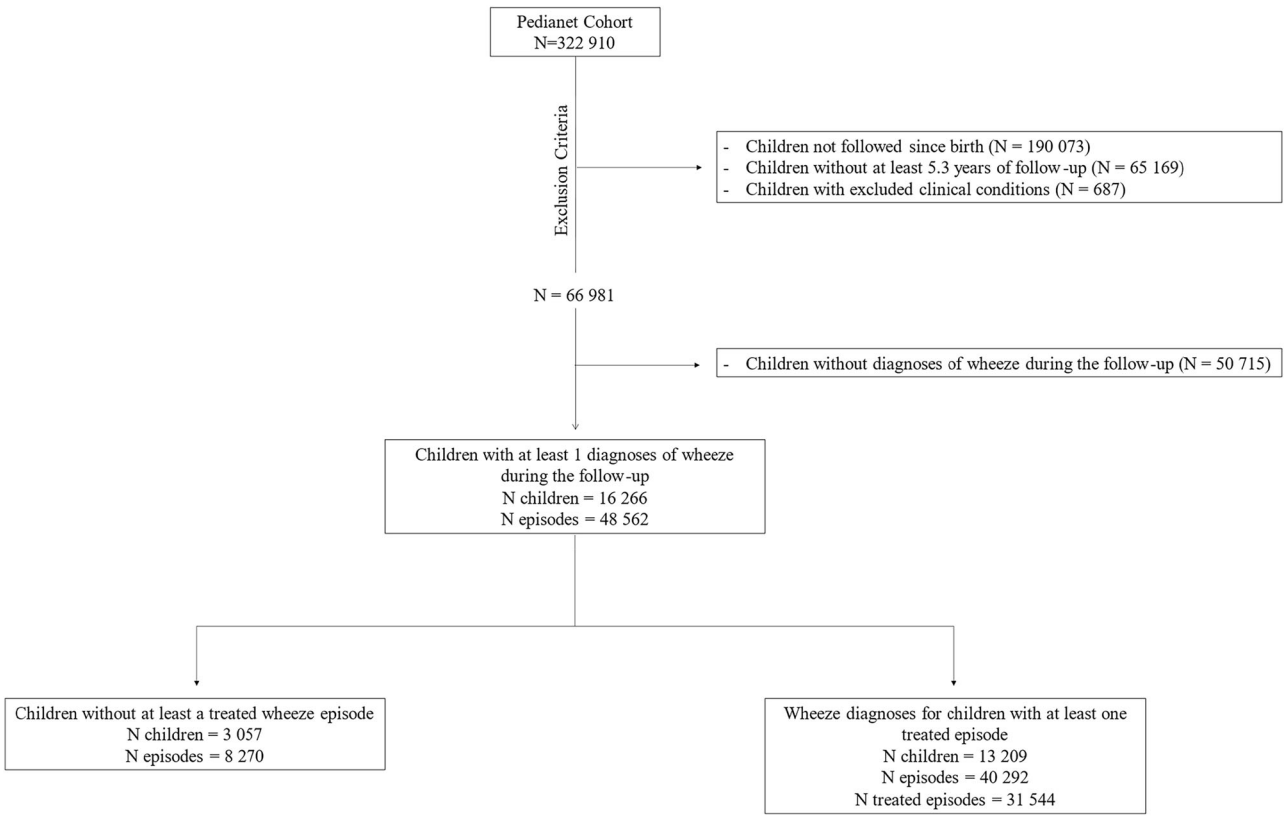


Fig. 1 Flow chart of the cohort. Pedianet, January 2010-March 2023.

Table 1. Heatmap showing frequencies and percentages of the most prevalent prescribing patterns by age group for children with one treated wheeze episode.

	Age Groups					
	<1 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)
Inhaled beta2-agonists	448 (24.75)	346 (24.33)	212 (22.29)	220 (23.33)	129 (20.51)	91 (20.97)
Oral corticosteroids	329 (18.18)	253 (17.79)	118 (12.41)	94 (9.97)	65 (10.33)	36 (8.29)
Inhaled beta2-agonists and inhaled glucocorticoids	315 (17.4)	319 (22.43)	258 (27.13)	275 (29.16)	194 (30.84)	136 (31.34)
Inhaled glucocorticoids	269 (14.86)	150 (10.55)	117 (12.3)	121 (12.83)	80 (12.72)	73 (16.82)
Oral corticosteroids and inhaled beta2-agonists	196 (10.83)	175 (12.31)	102 (10.73)	103 (10.92)	63 (10.02)	39 (8.99)
Oral corticosteroids and inhaled glucocorticoids	128 (7.07)	75 (5.27)	49 (5.15)	44 (4.67)	32 (5.09)	14 (3.23)
Oral corticosteroids and inhaled beta2-agonists and inhaled glucocorticoids	122 (6.74)	98 (6.89)	73 (7.68)	74 (7.85)	52 (8.27)	39 (8.99)

Pedianet, 2010–2023.

also decreases with age at diagnosis, from a peak of 59 in the youngest group to 4 in the oldest. The proportion of episodes in males was higher in <1 year-old children (62%) than 5-year-olds (49.66%). The proportion of patients with at least one comorbidity was relatively low and stable across age groups, ranging from about 16 to 20%. The most deprived group was slightly more represented in the youngest age group (Supplementary Material Table S5).

Among 48,562 episodes, about 31,544 (64.96%) were treated. Among treated children, the median number of treated episodes per child was 2 (IQR 1–6). Focusing on the first episode only, 11,633 (71.52%) out of the 16,266 children with wheeze received a treatment. Among 16,266 children with wheeze, 8278 (50.89%) experienced only one episode, and 6189 of these (38.05%) received a treatment. The prescription patterns for children with a single treated episode by age at diagnosis are shown in Table 1. The most frequently prescribed medications were inhaled beta2-agonist, either alone or combined with inhaled glucocorticoids, as well as oral corticosteroids. Inhaled beta2-agonists alone were most prescribed in younger children (<1 and 1 year old), whereas the combination of inhaled beta2-agonists and inhaled glucocorticoids became more frequent in older children, indicating an age-related shift in prescribing practices (Supplementary Material Table S6).

Treatment patterns across calendar years, stratified by age group, are reported in Supplementary Material Fig. S1. No abrupt changes in prescribing patterns were observed over the study period. Oral corticosteroids consistently represented the most

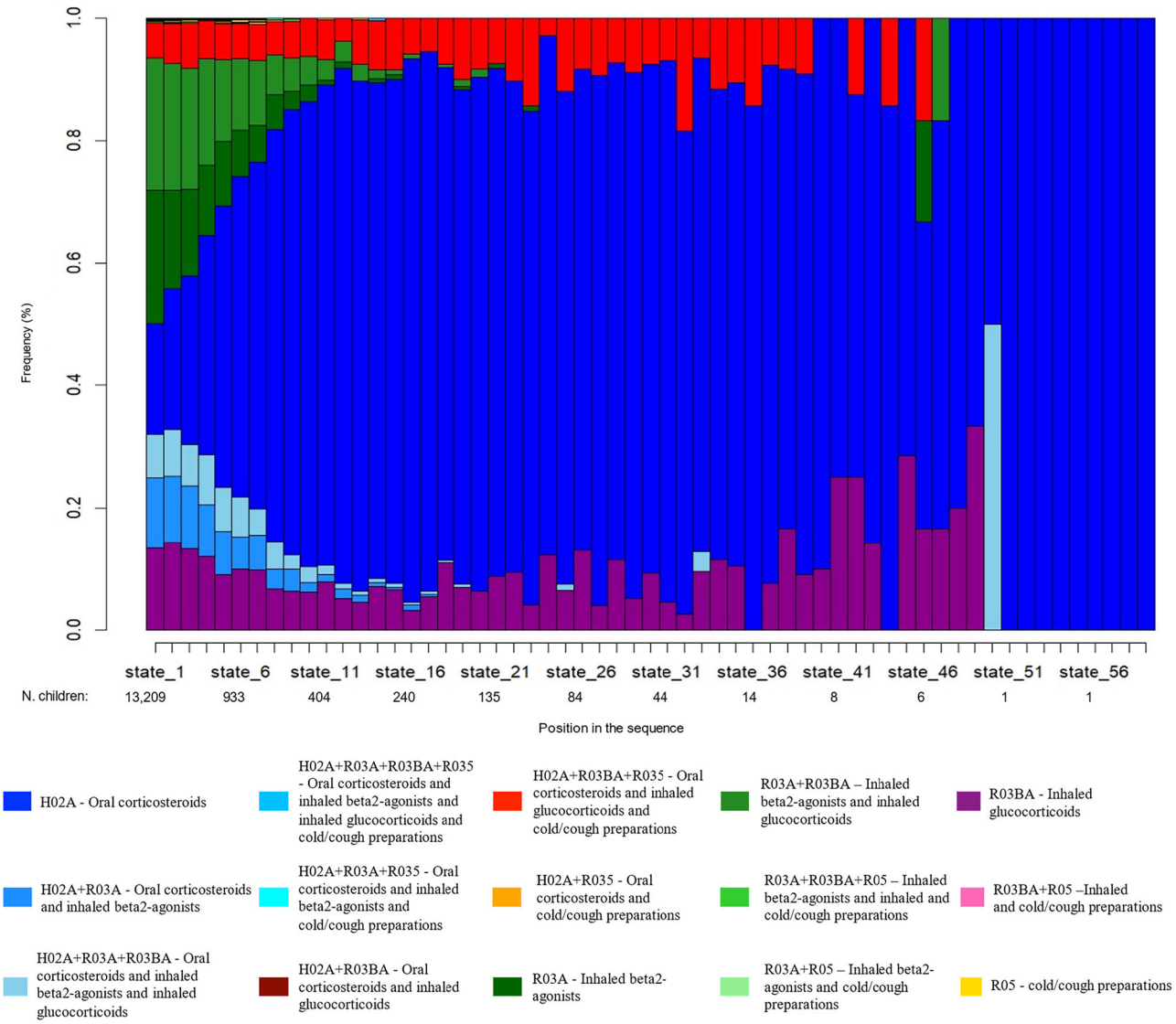


Fig. 2 Frequency distribution of states for 31,544 episodes in 13209 children. Pedianet, 2010–2023. The x-axis represents the *state*, defined as the number of treated episodes per child, with a maximum of 59 episodes. The y-axis shows the proportion of each treatment or treatment combination at every state.

frequently prescribed treatment across all age groups throughout. In children aged <1 year, their use remained stable at approximately 35–40% from 2010 to 2019, while in older children (5 years), prescriptions increased in more recent years, peaking above 40% between 2021 and 2023. Inhaled therapies showed relatively stable or slightly increasing trends over time. In children aged 2–5 years, combination therapy with inhaled beta2-agonists and glucocorticoids was consistently more frequent than inhaled glucocorticoids alone, accounting for approximately 15–25% of prescriptions. For children <2 years of age, there was an inflection in beta2-agonist prescriptions after 2014. Overall, these findings suggest a persistence of established prescribing patterns over time, with modest shifts in older age groups in more recent years.

State sequence analysis

The evolution of treatment prescribed across 31,544 sequential treated wheeze episodes in 13,209 children is illustrated in Fig. 2. The figure highlights a distinct shift in prescribing patterns across 59 successive episodes, with the number of children decreasing markedly from 13,209 at state 1 to only one child by state 56. In the early episodes, a diverse range of treatment combinations was observed, particularly involving oral corticosteroids, inhaled beta2-agonists, inhaled glucocorticoids, and their combinations. As the number of episodes increased, prescribing became more uniform, with oral corticosteroid monotherapy gradually emerging as the predominant approach. In later episodes, there was a moderate resurgence in the use of combination therapies (Supplementary Material Table S7).

Considering only the first five treated episodes, among the 13,209 children with at least one treated episode, 5402 (40.90%) progressed to a second treated episode, 2859 (21.64%) to a third, 1754 (13.28%) to a fourth, and 1224 (9.27%) reached a fifth treated episode.

The treatment trajectories across the first five treated episodes are displayed using an alluvial plot (Fig. 3). At the first treated state, prescriptions are highly heterogeneous, with several distinct treatments and combinations represented. The most common initial treatments are inhaled beta2-agonists, oral corticosteroids, and inhaled glucocorticoids, either alone or in combination. A strong decline in the number of children continuing treatment is observed. Correspondingly, the diversity of prescription pathways

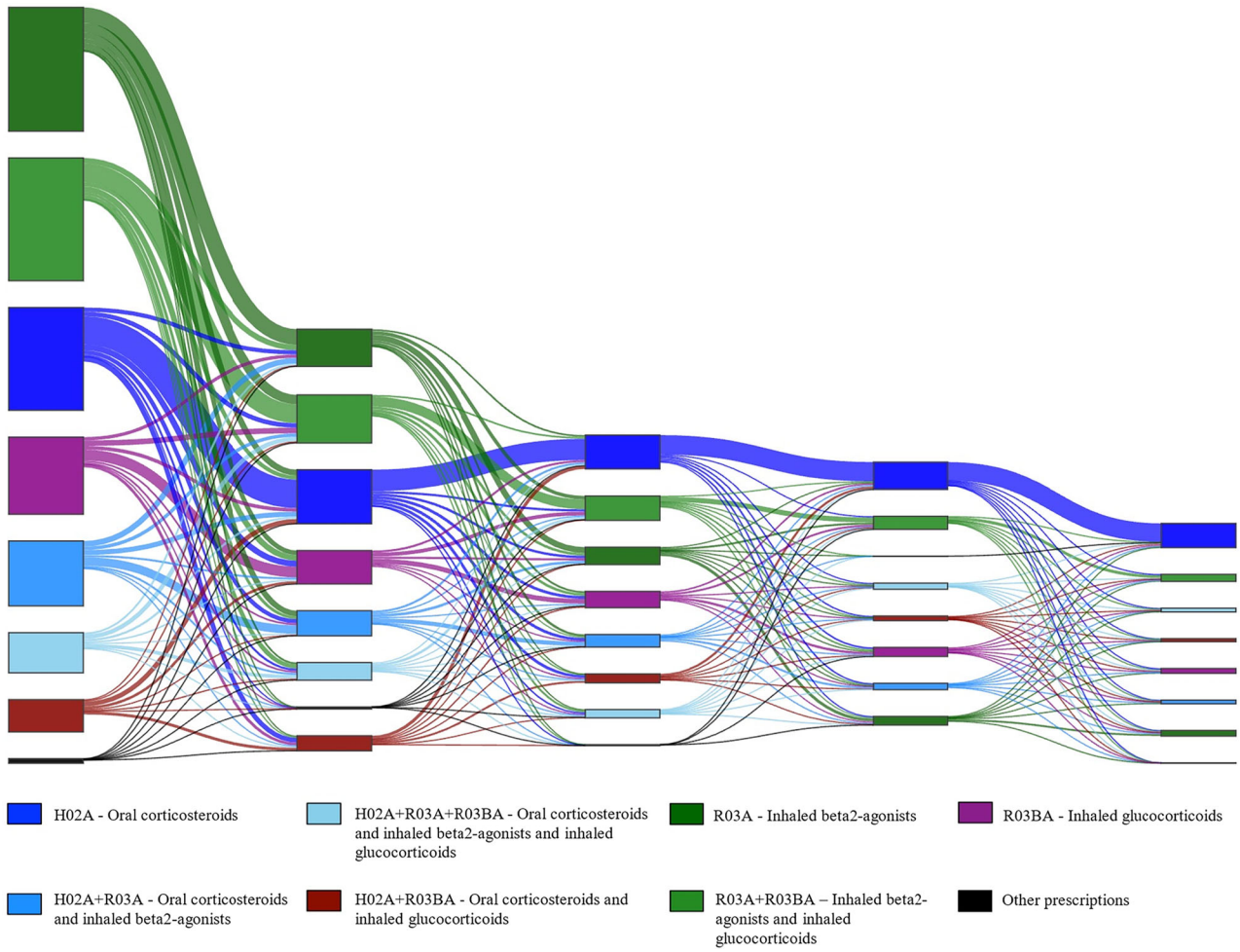


Fig. 3 Alluvial plot of prescribing patterns across 5 states. Pedianet, 2010–2023.

narrows while many children with different treatment options appear in the first episode, subsequent states show consolidation into a smaller set of dominant flows. By the fourth and fifth treated episodes, only a small subset of children remain in treatment, and most trajectories converge toward persistent use of a limited number of regimens (notably oral corticosteroids alone, and a combination of inhaled beta2-agonist and inhaled glucocorticoids). Overall, two main patterns emerge: (i) a sharp drop in the proportion of children continuing to later treated episodes, and (ii) a reduction in heterogeneity of prescriptions over time, suggesting that ongoing treatment is sustained only in a minority of children and tends to stabilize into a few recurrent therapeutic patterns.

Analysis by age at the first wheeze episode

The distribution of treated wheeze episodes by age at first diagnosis showed a clear pattern. The highest number of children with a treated first episode was observed among children <1 year of age. Across all age groups, the number of children declined steadily with each additional treated episode, indicating that progressively fewer children experienced further treated wheeze episodes after their initial one (Supplementary Material Table S8).

Treatment strategies also evolve with age at first wheeze diagnosis. In infants, oral corticosteroids dominated the treatment sequence, reflecting a standardized approach. Starting from the 1 year age group, sequences became more varied, with an increasing use of inhaled beta2-agonists and inhaled corticosteroids, and their combinations. From age 2 onward, treatment patterns were more heterogeneous, with inhaled beta2-agonists and inhaled corticosteroids playing a leading role, and oral corticosteroids were less frequently prescribed. In older age groups (3–5 years), the shift toward inhaled therapies became more pronounced; however, the declining number of patients in these age groups may influence the perceived weight of the patterns. Overall, a consistent transition from systemic to inhaled therapies was observed with increasing age at first diagnosis (Supplementary Material Fig. S2). The alluvial plots of treatment prescriptions stratified by age at first wheeze diagnosis are shown in Fig. 4. In the younger age groups (<1 year and 1 year of age), a consistent pattern of oral corticosteroid use beyond the first episode was observed, whereas inhaled treatments were discontinued in most cases. As age at first diagnosis increased, particularly in the 4- and 5-year groups, a shift toward combined inhaled beta2-agonists and corticosteroids at the first event emerged.

DISCUSSION

In this cohort, 16,266 children experienced at least one wheeze episode between 2010 and 2023, totalling 48,562 episodes. Pharmacological treatment was administered in 64.96% of these episodes, with prescribing patterns varying by age. Overall, sequential analysis showed that initial episodes were managed with a wide range of therapies, mainly including oral corticosteroids, inhaled beta2-agonists, inhaled glucocorticoids, or combinations of these. Stratification by age at first diagnosis revealed a

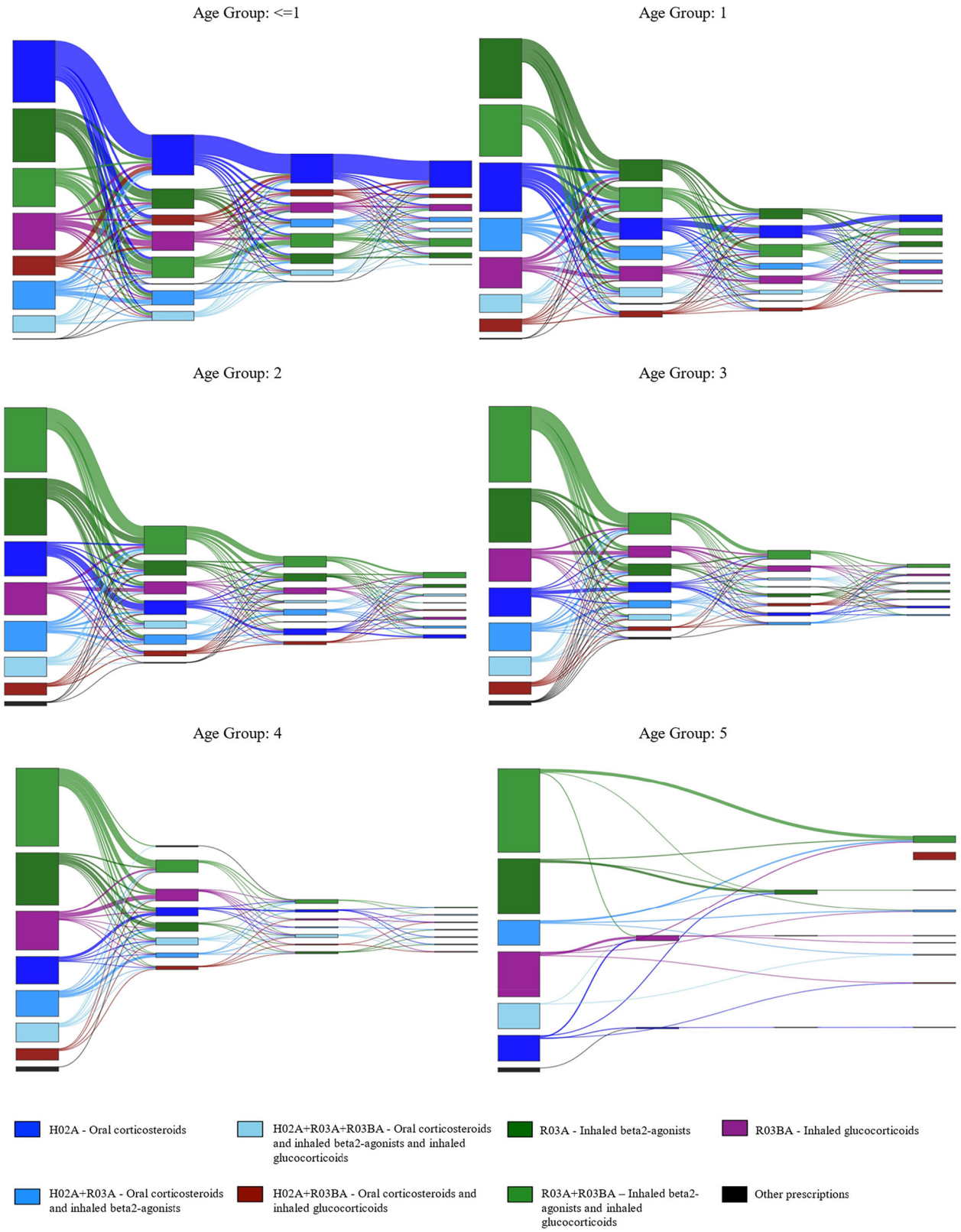


Fig. 4 Alluvial plots of prescribing patterns across states by age at first diagnosis.

developmental change in prescribing habits: oral corticosteroids was the dominant therapy for infants under one year of age, while the use of inhaled beta2-agonists and inhaled glucocorticoids, and combinations of inhaled therapies increased progressively in children whose first diagnosis occurred after two years of age.

Our study shows that among children with wheeze episodes, the majority were male, and 24.17% of these episodes occurred in children from the most deprived socioeconomic class, in line with previous studies[12,13]. Regarding socioeconomic status, a retrospective cohort study by Lo et al. analysed pre-school children in

England and found that those in the most deprived socio-economic quintile had significantly higher rates of acute wheeze presentations and hospitalizations than those from less deprived groups[14].

A large proportion of wheeze in young children is virally induced and may not be associated with underlying asthma or other chronic conditions. Therefore, deciding when wheeze is truly an isolated event or represents a clinical presentation of childhood asthma may be difficult[15,16]. In our study, we considered all the episodes of wheeze, without taking into consideration if these events were associated to viral infections or if these wheeze events could hide a diagnosis of asthma. Indeed, we found that prescribing patterns changed with age at the first wheeze diagnosis: in infants oral corticosteroids dominated the treatment sequence, while children with the first diagnosis at 2 years or more were most often treated with salbutamol and/or inhaled corticosteroids. This prescribing pattern aligns with what is recommended by most recent Italian guidelines, including an inhaled SABA as first-line treatment in pre-school children over 1 year of age with wheeze not associated with bronchiolitis[6,7] or intermittent administration of high doses ICS for 7–10 days in association with SABA at the onset of respiratory symptoms in young children with EVW[6]. The calendar time analysis highlighted how, for children <2 years of age, there was a reduction in beta2-agonist prescriptions after 2014, possibly indicating an initial impact of the AIFA (Agenzia Italiana del Farmaco) note on the 17 November 2014, regarding important safety information restricting the branded nebulized beta2-agonist salbutamol explicitly to children >2 years old due to reported overdoses from dosing errors[17]. Further, the treatments pattern aligns with the GINA guidelines, which recommend a stepwise approach for children ≤5 years with asthma, with daily low-dose inhaled corticosteroids as the preferred controller therapy and as-needed inhaled SABA for symptom relief[18]. Unfortunately, from prescription data it was not possible to gather information on treatment duration.

In our study, oral corticosteroids were the preferred treatment for children <1 year of age presenting with wheeze, with a progressive decline in their prescription among older age groups at first diagnosis. According to the GINA 2025 recommendations, systemic corticosteroids are indicated primarily for children with severe presentations requiring emergency department care or hospitalization. In contrast, the prescribing patterns observed in our cohort—particularly the frequent use of oral corticosteroids in infants <1 year—suggest that these medications may have been used even in the absence of clear guideline-supported indications. This discrepancy highlights the need to align clinical practice more closely with current evidence-based recommendations. Similarly, a study by Jones et al. reported that oral corticosteroids are frequently prescribed in pre-school-aged children (2–5 years), largely because clinicians tend to extrapolate asthma treatment guidelines developed for older children.

The slight decline in systemic corticosteroid prescription with the increase in the age at the first wheeze diagnosis could reflect a more selected and evidence-based approach to treatment, as clinicians gain a clearer understanding of each child's wheeze pattern and are better able to avoid unnecessary exposure to systemic steroids and their potential adverse effects, aligning with asthma treatment recommendations[19].

Our study presents notable strengths but also some limitations that may influence the interpretation of results. A key strength of this study is its focus on an area where both evidence and prescribing guidelines are still limited. Unlike asthma, which has well-established management protocols (GINA), the treatment of wheeze episodes in children under five years lacks clear guidance and consistent prescribing data. The study also benefits from a large sample size and generalizability, providing a representative picture of paediatric care. Whereas most previous research on wheeze-related prescriptions has focused on hospital or tertiary care settings, this study examines the primary care outpatient setting, offering a broader view of how wheeze in young children is managed in everyday clinical settings.

A limitation of this study lies in the absence of data on medicine dispensation, which prevents assessment of actual medication use and limits the ability to account for potential non-adherence. Second, the lack of detailed clinical information, such as the severity of wheeze episodes or the presence of atopy, restricts the interpretation of our results. Third, because we used prescription data and medications in Italy are sold in boxes with pre-specified units, we were not able to assess treatment duration. Fourth, we have included episodes of explicitly recorded diagnosis of wheeze, treating wheeze as a clinical diagnosis rather than a symptom. In a post-hoc analysis, we observed that only a small proportion of first wheeze episodes occurring within the first two years of life (approximately 2%) had a concomitant diagnosis of bronchiolitis within a ±7-day window. This suggests that, in routine clinical practice, bronchiolitis and wheeze are generally coded as distinct diagnostic entities. When bronchiolitis is diagnosed, treatment decisions are likely driven primarily by that diagnosis, even if wheezing is present as part of the clinical presentation, rather than being recorded and managed as a wheeze episode per se.

CONCLUSIONS

This study provides valuable insights into the real-world management of wheeze episodes among children in primary care in Italy, showing frequent use of pharmacological treatments and marked age-related differences in prescribing patterns. Oral corticosteroids were commonly prescribed alone in infants, despite limited support from current recommendations, while older children were more often treated with inhaled therapies, mostly in combination, in line with guidelines. These findings highlight a gap between recommendations and clinical practice and underscore the need for clearer, harmonized guidance and improved implementation in the management of pre-school wheeze.

DATA AVAILABILITY

Data may be obtained from a third party and is not publicly available. The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request from the corresponding author.

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COMPETING INTERESTS

The authors declare no competing interests.

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