Mikalsen, I. B., Dalen, I., Karlstad, Ø., Eide, G. E., Magnus, M., Nystad, W., & Øymar, K. (2019). Airway symptoms and atopy in young children prescribed asthma medications: A large-scale cohort study. *Pediatric Pulmonology*, *54*(10), 1557-1566. https://doi.org/10.1002/ppul.24437

Received: 4 January 2019 | Accepted: 15 June 2019

DOI: 10.1002/ppul.24437

ORIGINAL ARTICLE: ASTHMA

PEDIATRIC PULMONOLOGY WILEY

Airway symptoms and atopy in young children prescribed asthma medications: A large-scale cohort study

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Funding information
Norwegian Ministry of Health and Care Services; Norwegian Ministry of Education and Research; Norwegian Research Council, Grant/Award Number: 221097

Abstract

Diagnosing asthma and deciding treatment are difficult in young children. An inappropriate and too high prescription rate of inhaled corticosteroids (ICS) is suggested, but how airway symptoms are associated with prescriptions of asthma medication is less known. We studied how strongly wheeze, lower respiratory tract infections (LRTI), and atopic diseases are associated with dispensing of asthma medications during early childhood.

We used data from the Norwegian Mother and Child Cohort Study and the Norwegian Prescription Database at four age-intervals (0-6, 6-18, 18-36 months, and 3-7 years). Primary outcomes were dispensed asthma medications (no medication, short-acting β-2 agonist, or ICS). Relative risks (RRs) and average attributable fractions (AAFs) were estimated.

Both wheeze and LRTI were positively associated with both medication groups (0-6 months: no data on wheeze). The RRs and AAFs were higher for wheeze than LRTI. For ICS, the AAFs (95% CI) for wheeze vs LRTI were: 6 to 18 months: 69.2 (67.2, 71.2)% vs 10.4 (9.0, 11.8)%, 18 to 36 months: 33.0 (30.5, 35.5)% vs 10.0 (8.0, 12.0)%, and 3 to 7 years: 33.7 (31.0, 36.5)% vs 1.2 (0.5, 1.9)%. Except at 3 to 7 years of age, the AAFs were lower for atopic diseases than for LRTI and wheeze. Atopic diseases modified the associations between wheeze and ICS at 18 to 36 months and between LRTI or wheeze and ICS at 3 to 7 years.

In conclusion, both wheeze and LRTI were associated with prescriptions of asthma medications in young children, with the strongest associations seen for wheeze. Atopic diseases contributed to these associations only in the oldest age groups.

KEYWORDS

airway symptoms, allergy, asthma and early wheeze, asthma medication, atopy, children, pharmacology, prescription, the Norwegian Mother and Child Cohort Study (MoBa)

1 | INTRODUCTION

Episodes of lower respiratory tract infections (LRTI), wheeze, and cough are common in young children and are often diagnosed and treated as asthma.[1-3] These symptoms are also frequent in children without asthma, but will then often resolve by school age.[2,4] Recurrent LRTI and chronic cough may be misclassified as asthma and treated with inhaled corticosteroids (ICS).[1,5-7] Recently, a Lancet report underlined that characteristics of the airway disease such as markers of eosinophil inflammation are important when predicting response to ICS, and that the term asthma solely is a descriptive label for a collection of symptoms such as wheeze, breathlessness, and

cough.[8] Preschool children with transient wheeze, but without atopic comorbidities have often no airway eosinophilic inflammation and no response to ICS.[2,4,9] Overall, diagnosing and deciding treatment for asthma in young children are difficult due to variable phenotypes and lack of diagnostic tests.[2,4,10]

As consequence, the prescription of ICS for young children varies between countries.[11,12] A 20% prescription rate was found in Italian children 2 to 4 years of age, compared with 10% in Norway and 5% in UK and the Netherlands.[11,12] There are also substantial regional differences within countries, both in Norway[13] and other countries.[14,15] Many children fill only one prescription, indicating that ICS are given for single or transient episodes with asthma-like symptoms.[11,16] These findings may suggest a variable and inappropriate prescription of ICS for nonspecific asthma-like symptoms in children.[3,7]

Risk factors for asthma are thoroughly studied, but there is less knowledge about symptoms influencing prescribing of asthma medications to children. Using data from a large-scale prospective cohort study, the aim of this paper was therefore to study how strongly wheeze, LRTI, and atopic diseases are associated with prescriptions of asthma medications during childhood.

2 | MATERIALS AND METHODS

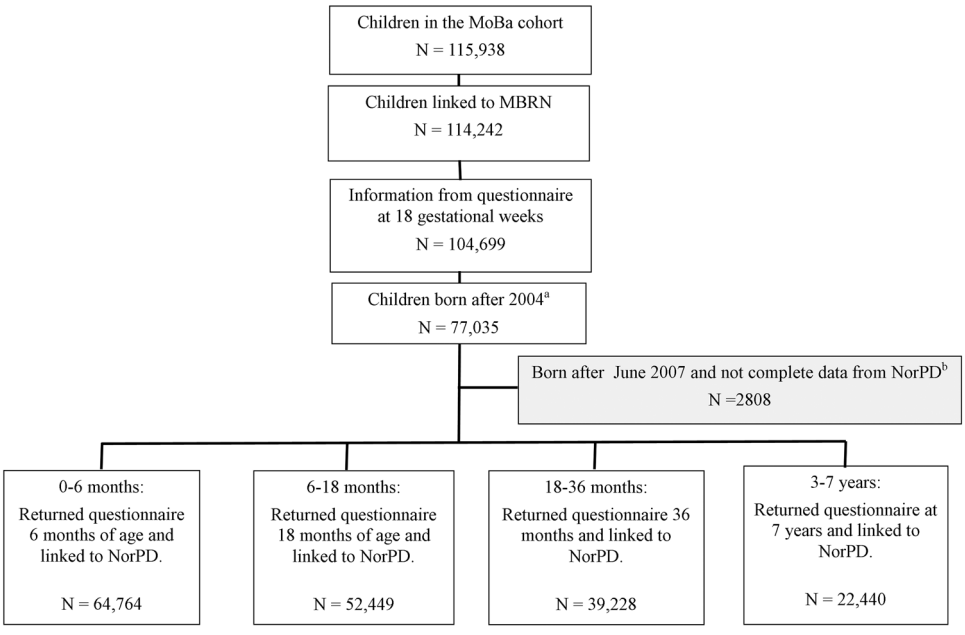
2.1 | Study subjects

This study included children from the Norwegian Mother and Child Cohort study (MoBa), a prospective population-based pregnancy cohort administered by the Norwegian Institute of Public Health.[17] Pregnant women were recruited during 1999 to 2008 at approximately 18 weeks of gestation, and 41% of the women provided a written consent to participate. Mothers could participate with more than one pregnancy; the cohort now includes approximately 114 500 children and 95 000 mothers. The present study is based on version nine of the quality-assured data files released for research in 2015. Data obtained through questionnaires in MoBa are linked to the Medical Birth Registry of Norway and the Norwegian Prescription Database (NorPD) using national 11-digit person identification numbers. All Norwegian pharmacies are obliged to send electronic data to NorPD on all dispensed drugs (irrespective of reimbursement status) to patients in ambulatory care since January 2004.[18]

Children with information from questionnaires at 18 gestational weeks, 6, 18, 36 months, and 7 years of age with data from the NorPD at four different age intervals (0-6, 6-18, 18-36 months, and 3-7 years) were included (Figure 1). The establishment and data collection in MoBa was previously based on a licence from the Norwegian Data Inspectorate and approval from The Regional Committee for Medical Research Ethics, and it is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committee for Medical Research Ethics (2011/2313) and the Norwegian Data Inspectorate (08/00854- 2/IUR).

2.2 | Outcome

Primary outcomes were dispensed asthma medications from pharmacy at the age intervals of follow-up (0-6, 6-18, 18-36 months, and 3-7 years), which correspond to the intervals for how information on airway symptoms and atopic diseases were gathered



Abbreviations: MoBa: Norwegian Mother and Child Cohort; MBRN: Medical Birth Registry of Norway; NorPD: Norwegian Prescription Database

a. As NorPD was established in 2004, only children born after January 2004 were included.

b. At 3-7 years, children were excluded if they had not reached 7 year by June 2015 as these children did not have complete data in NorPD at follow up.

FIGURE 1 Flow-chart for sample selection for the four different age groups included in the study

through the MoBa questionnaires. NorPD classifies medications according to the Anatomical Therapeutic Chemical (ATC) classification system. We included dispensed inhaled short-acting β-2 agonist (ATC code R03AC), ICS in any combination (single component inhaler [R03BA] or fixed combination inhalers with long-acting β-2 agonists [R03AK]). *A prescription* was defined as one dispensed prescription for ICS or short-acting β-2 agonist from pharmacy. We created three mutually exclusive outcome categories based on dispensed ICS and β-2 agonists: neither, short-acting β-2 only, and ICS with or without dispensing of short-acting β-2.

2.3 | Exposures

The exposures examined were LRTI, wheeze, and atopic diseases (atopic dermatitis, allergic rhinoconjunctivitis, and food allergy), all reported by the mothers at the end of each age interval of follow-up. No clinical or laboratory investigations were available for diagnosis.

Wheeze at 6 to 18 months of age was defined as at least one reported episode with wheezing, whistling, or chest tightness reported on the 18 months questionnaire. Wheeze at 18 to 36 months and 3 to 7 years of age was defined as at least one reported episode with wheezing and whistling or chest tightness before or after the age of 3 years reported on the 7-year questionnaire. The MoBa questionnaires at 6 and 36 months of age contain no questions regarding wheeze.

LRTI at 0 to 6 and 6 to 18 months of age was defined as positive answer to *does your child has/had bronchitis, respiratory syncytial virus, or pneumonia at 6 and 18 months of age.* LRTI at 18 to 36 months and 3 to 7 years of age was defined as positive answers to bronchitis or pneumonia reported at the 36 months and 7 year questionnaires respectively.

Atopic dermatitis ever was defined as a positive answer to *does your child has/had atopic dermatitis or childhood eczema at the actual, or previous age interval*. Allergic rhinoconjunctivitis at 18 to 36 months and 3 to 7 years was defined as allergy in nose, eyes, or hay fever between 18 and 36 months or ever respectively and reported at 36 months and 7 years of age. Allergy towards specific food allergens (egg, fish, peanuts, other nuts, and shellfish) and pets (cat and dog) were reported at 7 years of age. We defined allergies at 3 to 7 years of age as a positive answer to questions regarding allergic rhinoconjunctivitis, allergy to pets (cat and dog), or food allergens.

2.4 | Covariates

Factors that could influence both the exposures and outcomes were identified as potential confounders. Child characteristics included gender, gestational age, and day care attendance ever. Parental characteristics included parity, parental education, parental asthma, parental atopy, continued smoking after 18 weeks pregnancy, and household smoking ever after birth. Apart from parity (categorized into primiparous, 1, 2, and 3 or more) and education (categorized into less than secondary school, secondary school, up to 4 years of university, and 4 or more years of university), the parental characteristics were categorized as yes/no.

Data on parental pre-pregnancy factors were gathered from mothers through questionnaires at 18 weeks gestation, while information on paternal atopy and asthma was obtained from a questionnaire answered by the father.

We obtained information of gender, parity, and gestational age in weeks from the Medical Birth Registry.

Except for the first age interval, dispensing of ICS in previous age intervals was adjusted for and entered as a binary variable (yes/no).

2.5 | Statistics

The amount of missing information on individual values was low (< 5%). However, 34% had missing information on wheeze at 18 to 36 months of age, and at all age intervals 16% of children had missing information on paternal atopy or paternal asthma. Together, approximately 30% to 50% of observations had missing information on one or more variable in the multivariable analyses. The missing covariate information was imputed using multiple imputations by chained equations including all covariates and outcomes. We imputed 25 data sets.

We evaluated the associations between the exposures and outcomes within each age interval using Poisson regression with robust standard errors, to obtain relative risks (RRs) with 95% confidence intervals (CI).[19] Multiple regression models adjusted for potentially confounders were constructed. Clinically relevant interactions were included if the overall *P*-value for the interaction term in imputed data was < .01. We tested for interactions between wheeze/LRTI and allergic rhinoconjunctivitis (18-36 months) and between wheeze/LRTI and allergy (3-7 years) to study if atopic diseases contributed to the associations between airway symptoms and prescriptions of asthma medications. As no data regarding allergic rhinoconjunctivitis and allergy were available for the youngest age groups, we tested interactions between wheeze or LRTI and atopic dermatitis at 0 to 6 and 6 to 18 months of age. Except for 0 to 6 months of age, also interactions between LRTI and wheeze were tested.

To study the associations between exposures and the number of prescriptions with ICS, supplementary analyses were performed with zero inflated negative binomial (ZINB) models.[20] The ZINB model was preferred over standard negative binomial models based on the Akaike information criterion.[21] Effect estimates from the logistic model for structural zeros and for the conditional count model are presented as odds ratios (OR) and incidence rate ratios (IRR), respectively.

The proportions of prescriptions for any β-2 only and any ICS attributed to the exposures were estimated by average attributable fractions (AAFs)[22] with the R package `averisk`.[23] The AAFs were based on logistic regression models and adjusted for potentially confounders. Within-imputation variance as estimated by Monte Carlo simulation (B = 1000 simulations) was combined with between-imputation variance by Rubin's rule to obtain CIs. For models including interaction terms, the AAF for an exposure variable was derived as the average of all sequential AFs for the variable taken overall possible removal orders of the variables included in the model, and within-imputation variance was estimated using non-parametric bootstrap (B = 1000).

Analyses were carried out using SPSS version 24.0 (IBM Corp. Armonk, NY) and R version 3.4. Generally, *P*-values ≤ .05 were considered statistically significant.

3 | RESULTS

Table 1 presents the baseline characteristics for each age group. The proportion of children with wheeze was higher than for LRTI (no data available for wheeze 0-6 months).

3.1 | Unadjusted and adjusted associations for different age groups

Table 2-5 presents the proportions of children with symptoms receiving medications and unadjusted and adjusted RRs for each explanatory variable for imputed data. The corresponding results for the complete case analysis are given as supplementary tables (E-table 1-4). For both medication groups and at all ages, the highest adjusted RRs were found for wheeze (no data 0-6 months). Except 0 to 6 months and β-2 only at 3 to 7 years, there were significant interactions between LRTI and

TABLE 1 Characteristics of all included children with available information of dispensed asthma medication at four different age-intervals. Data from the Norwegian Mother and Child Cohort Study and the Norwegian Prescription Database

Age group total number	0-6 mo N = 64 764		6-18 mo N = 52 449		18-36 mo N = 39 228		3-7 y N = 22 440	
Variable, categories	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Boys	64 764	51.1	52 449	50.9	39 228	50.9	22 440	51.4
Gestational age weeks, mean (SD)	64 476	39.4 (1.9)	52 210	39.4 (1.9)	39 061	39.4 (1.9)	22 346	39.4 (1.9)
Wheeze			51 315	41.0	[a]25 840	15.6	21 922	19.6
LRTI	62 998	4.7	51 689	12.2	38 354	11.8	21 459	3.3
Atopic dermatitis ever	63 346	11.2	50 975	22.4	38 000	28.6	21 115	35.9
Allergic rhinoconjunctivitis					38 725	3.4	21 909	11.8
Allergy							21 964	12.1
Use ICS previous age interval			52 449	0.9	39 228	7.3	21 403	10.5
Day care	64 678	0.4	52 199	75.9	37 403	96.2		
Maternal parity	64 764		52 449		39 228		22 440	
Primiparous		47.5		48.7		49.8)		47.8
1		34.7		33.9		33.4		34.5
2		14.1		13.8		13.4		13.9
≥ 3		3.7		3.6		3.5		3.7
Maternal asthma	64 764	7.7	52 449	7.6	39 228	7.4	22 440	7.4
Paternal asthma[b]	54 144	9.0	44 147	9.0	33 297	9.0	19 162	8.9
Maternal atopy	63 132	29.7	51 614	29.6	38 817	29.7	22 219	29.4
Paternal atopy[b]	54 144	23.2	44 147	23.3	33 297	23.4	19 162	23.4
Maternal education	64 480		52 241		39 083		22 364	
< 12 y		6.3		5.5		4.8		4.8
12 y		28.8		27.8		26.6		26.7
13-16 y		40.5		41.4		42.2		43.6
≥ 17		24.4		25.3		26.5		24.8
Paternal education	64 242		52 050		38 970		22 312	
< 12 y		11.6		11.0		10.4		10.7
12 y		40.6		40.2		39.8		40.6
13-16 y		26.9		27.4		27.9		28.1
≥ 17 y		20.6		21.4		21.8		20.6
Continued maternal smoking after 18 wk pregnancy	58 154	8.1	47 759	7.2	36 049	6.5	20 628	6.6
Ever household smoking after birth	60 954	25.5	49 066	29.8	36 704	30.4	20 319	33.7

Abbreviations: ICS, inhaled corticosteroids; LRTI, lower respiratory tract infection; SD, standard deviation.
[a]Lower total number because the answers were gathered from the 7 y questionnaire.
[b]Lower total number for all ages because the answers were gathered from the questionnaire answered by the father.

TABLE 2 Distribution of children 0-6 months of age in different medication groups with respect to LRTI and atopic dermatitis and unadjusted/adjusted RRs as estimated by multiple Poisson regression[a] with robust standard errors, results from multiple imputation, N = 64 764

Models				Unadjusted model		Adjusted model	
Medication groups	All	B-2 only	Any ICS	B-2 only	Any ICS	B-2 only	Any ICS
Exposure	N	%	%	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI
LRTI							
No	60 975.7	0.3	0.6	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	3788.3	3.2	7.2	11.94 (7.77-18.37)	12.21 (8.23-18.13)	9.92 (6.60-14.92)	9.16 (6.59-12.74)
Atopic dermatitis ever							
No	57 484.1	0.4	0.9	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	7279.9	0.7	1.8	1.71 (1.26-2.32)	2.00 (1.64-2.43)	1.42 (1.03-1.95)	1.63 (1.34-1.98)

Abbreviations: B-2 only, inhaled short-acting β-2 agonist without ICS; CI, confidence interval; ICS, inhaled corticosteroids; LRTI, lower respiratory tract infection; RR, relative risk.

[a]All models included LRTI and atopic dermatitis and were adjusted for child characteristics (gestational age, gender, and day care) and parental characteristics (maternal asthma, paternal asthma, paternal atopy, maternal atopy, maternal education, paternal education, parity, continued maternal smoking after 18 wk pregnancy, and ever household smoking after birth).

Number of imputations = 25.

wheeze for both medication groups and all age groups (Table 2-5). Generally, the relative effect of wheeze was highest in children without LRTI; similarly, the relative effect of LRTI was highest in children without wheeze (E-table 5-7). For all age groups, prescriptions with ICS in the previous age interval was strongly associated with ICS (6-18 months: RR [95% CI]: 3.94 [3.64-4.27], 18 to 36 months: 4.88 [4.55-5.23], 3 to 7 years: 6.69 [6.07-7.38]; all results from multiple imputation), but not with β-2 only (data not shown). Except at 6 to 18 months of age (β-2 only) and 3 to 7 years of age (both medication groups), atopic dermatitis was positively associated with prescriptions of both medication groups (Table 2-5). In the ZINB models, both LRTI and wheeze were associated with the number of prescriptions of ICS for all age groups (E-table 9).

3.1.1 | 0 to 6 months of age

In this age group, 0.4% received at least one prescription of β-2 only, and 1.0% was prescribed ICS (Table 2). LRTI was strongly associated with prescriptions of both medication groups (Table 2). There were no interactions between atopic dermatitis and LRTI.

TABLE 3 Distribution of children 6 to 18 months of age in different medication groups with respect to wheeze, LRTI, and atopic dermatitis and unadjusted/adjusted RRs as estimated by multiple Poisson regression[a] with robust standard errors, results from multiple imputation, N = 52 449

Models				Unadjusted model		Adjusted model	
Medication groups	All	B-2 only	Any ICS	B-2 only	Any ICS	B-2 only	Any ICS
Exposure	N	%	%	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI
Wheeze							
No	30 964.3	0.7	1.2	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	21 484.7	4.6	16.9	6.45 (5.57-7.46)	13.97 (12.57-15.53)	5.91 (5.00-6.99)	10.74 (9.56-12.08)
LRTI							
No	45 723.3	1.8	5.5	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	6725.7	5.8	22.1	3.27 (2.86-3.73)	3.99 (3.70-4.32)	3.84 (2.66-5.54)	2.90 (2.13-3.93)
Atopic dermatitis ever							
No	40 720.0	2.2	6.6	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	11 729.0	2.8	11.4	1.29 (1.14-1.47)	1.75 (1.64-1.86)	1.07 (0.95-1.22)	1.36 (1.28-1.44)
Interaction term							
Wheeze × LRTI						0.46 (0.31-0.67)	0.65 (0.48-0.88)

Abbreviations: B-2 only, inhaled short-acting β-2 agonist without ICS; CI, confidence interval; ICS, inhaled corticosteroids; LRTI, lower respiratory tract infection; RR, relative risk.

[a]All models included wheeze, LRTI, atopic dermatitis and clinically relevant interactions if $P < .01$ for the interaction term and were adjusted for child characteristics (gestational age, gender, day care, previous use of inhaled corticosteroids) and parental characteristics (maternal asthma, paternal asthma, paternal atopy, maternal atopy, maternal education, paternal education, parity, continued maternal smoking after 18 wk pregnancy, and ever household smoking after birth).

Number of imputations = 25.

TABLE 4 Distribution of children 18 to 36 months of age in different medication groups with respect to wheeze, LRTI, atopic dermatitis and ARC and unadjusted/adjusted RRs as estimated by multiple Poisson regression[a] with robust standard errors, results from multiple imputation, N = 39 228

Models				Unadjusted model		Adjusted model	
Medication groups Exposure	All N	B-2 only %	Any ICS %	B-2 only RR 95% CI	Any ICS RR 95% CI	B-2 only RR 95% CI	Any ICS RR 95% CI
Wheeze							
No	33 032.6	1.6	5.3	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	6195.4	6.1	40.9	3.75 (3.20-4.41)	7.67 (7.16-8.21)	4.17 (3.41-5.10)	4.33 (3.90-4.80)
LRTI							
No	34 315.3	1.9	8.7	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	4912.7	5.3	26.7	2.74 (2.27-3.30)	3.06 (2.79-3.36)	2.93 (2.31-3.73)	2.43 (2.11-2.80)
Atopic dermatitis ever							
No	28 036.5	2.1	9.3	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	11 191.5	3.0	15.2	1.44 (1.26-1.65)	1.64 (1.54-1.74)	1.24 (1.08-1.42)	1.14 (1.08-1.20)
ARC							
No	37 874.4	2.3	10.3	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	1353.6	4.6	30.4	2.03 (1.57-2.62)	2.96 (2.72-3.23)	1.23 (0.94-1.61)	2.00 (1.66-2.41)
Interaction term							
Wheeze × LRTI						0.47 (0.34-0.64)	0.55 (0.48-0.64)
Wheeze × ARC							0.58 (0.47, 0.62)

Abbreviations: ARC, allergic rhinoconjunctivitis; B-2 only, inhaled short-acting β-2 agonist without ICS; CI, confidence interval; ICS, inhaled corticosteroids; LRTI, lower respiratory tract infection; RR, relative risk.

[a]All models included wheeze, LRTI, atopic dermatitis, ARC, and clinically relevant interactions if $P < .01$ for the interaction term and were adjusted for child characteristics (gestational age, gender, day care, previous use of inhaled corticosteroids) and parental characteristics (maternal asthma, paternal asthma, paternal atopy, maternal atopy, maternal education, paternal education, parity, continued maternal smoking after 18 wk pregnancy, and ever household smoking after birth).

Number of imputations = 25.

For β-2 only the AAFs (95% CI) were 36.7 (29.0, 44.5)% for LRTI and 4.2 (− 0.1, 8.5)% for atopic dermatitis, whereas for ICS the AAFs were 36.4 (31.6, 41.3)% for LRTI and 6.3 (3.3, 9.3)% for atopic dermatitis (E-table 8).

3.1.2 | 6 to 18 months of age

In this age group, 2.3% received at least one prescription of β-2 only, and 7.7% were prescribed ICS (Table 3). Wheeze was reported in 76% of children with LRTI.

Wheeze and LRTI were associated with prescriptions of β-2 only and ICS, and there were significant interactions between LRTI and wheeze in both medication groups (β-2 only: $P < .001$ and ICS: $P = .005$) (Table 3). The RRs for the various combinations correspond to the RRs of the main variable multiplied by the interaction term; that is, for ICS imputed data, the RR of wheeze in children with LRTI equals 10.74 × 0.65 = 6.98 (Table 3). The stratified RRs for different combinations are shown in E-table 5. There were no interactions between atopic dermatitis and LRTI or between atopic dermatitis and wheeze.

For β-2 only the AAFs (95% CI) were 59.2 (54.7, 63.6)% for wheeze, 12.6 (9.3, 15.9)% for LRTI and 1.1 (− 0.9, 3.3)% for atopic dermatitis, whereas for ICS the AAFs were 69.2 (67.2, 71.2)% for wheeze, 10.4 (9.0, 11.8)% for LRTI, and 5.0 (4.0, 6.1)% for atopic dermatitis (E-table 8).

3.1.3 | 18 to 36 months of age

In this age group, 2.3% received at least one prescription of β-2 only, and 11.0% were prescribed ICS (Table 4).

Wheeze and LRTI, but not allergic rhinoconjunctivitis, were positively associated with prescription of β-2 only, and there was a significant interaction between LRTI and wheeze ($P < .001$) (Table 4).

Wheeze, LRTI and allergic rhinoconjunctivitis were positively associated with prescription of ICS. For ICS, there were significant interactions between LRTI and wheeze and between wheeze and allergic rhinoconjunctivitis (both $P < .001$) (Table 4). The RRs for all combinations are shown in E-table 6. The highest RRs were found when the main exposures were not combined with other exposures, that is, the RR for wheeze was higher in children without LRTI and allergic rhinoconjunctivitis than in children with LRTI and allergic rhinoconjunctivitis. Similarly, the highest RR for LRTI was found in children without wheeze, and the highest RR for allergic rhinoconjunctivitis was found in children without wheeze.

For β-2 only the AAFs (95% CI) were 27.8 (22.9, 32.7)% for wheeze, 13.6 (9.5, 17.7)% for LRTI and 0.9 (− 0.3, 2.2)% for allergic

TABLE 5 Distribution of children 3 to 7 years of age in different medication groups with respect to wheeze, LRTI, atopic dermatitis and allergy and unadjusted/adjusted RRs as estimated by multiple Poisson regression[a] with robust standard errors, results from multiple imputation, N = 22 440

Models				Unadjusted model		Adjusted model	
Medication groups	All	B-2 only	Any ICS	B-2 only	Any ICS	B-2 only	Any ICS
Exposure	N	%	%	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI
Wheeze							
No	18 038.0	1.5	4.9	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	4402.0	6.9	38.8	4.53 (3.86-5.33)	7.93 (7.35-8.54)	4.42 (3.68-5.31)	3.34 (2.98-3.70)
LRTI							
No	21 701.9	2.4	10.9	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	738.1	6.3	31.2	2.59 (1.92-3.49)	2.87 (2.51-3.28)	1.48 (1.10-2.00)	2.05 (1.59-2.65)
Atopic dermatitis ever							
No	14 402.7	2.2	9.0	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	8037.3	3.1	16.2	1.39 (1.17-1.65)	1.80 (1.67-1.94)	1.05 (0.88-1.25)	0.99 (0.93-1.05)
Allergy							
No	19 716.1	2.2	9.5	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Yes	2723.9	5.4	26.6	2.47 (2.06-2.97)	2.80 (2.60-3.03)	1.71 (1.40-2.08)	1.98 (1.71-2.29)
Interaction term							
Wheeze × LRTI							0.62 (0.47-0.81)
Wheeze × allergy							0.74 (0.63-0.87)
LRTI × allergy							0.69 (0.56-0.83)

Abbreviations: B-2 only, inhaled short-acting β-2 agonist without ICS; CI, confidence interval; ICS, inhaled corticosteroids; LRTI, lower respiratory tract infection; RR, relative risk.

[a]All models included wheeze, LRTI, atopic dermatitis, allergy and clinically relevant interactions if $P < .01$ for the interaction term and were adjusted for child characteristic (gestational age, gender, day care, previous use of inhaled corticosteroids) and parental characteristics (maternal asthma, paternal asthma, paternal atopy, maternal atopy, maternal education, paternal education, parity, continued maternal smoking after 18 wk pregnancy, and ever household smoking after birth).

Number of imputations = 25.

rhinoconjunctivitis, whereas for ICS the AAFs were 33.0 (30.5, 35.5)% for wheeze, 10.0 (8.0, 12.0)% for LRTI and 2.3 (1.6, 3.0)% for allergic rhinoconjunctivitis (E-table 8).

3.1.4 | 3 to 7 years of age

In this age group, 2.6% received at least one prescription of β-2 only, and 11.5% were prescribed ICS (Table 5). Wheeze was reported in 51% of children with LRTI. Ever physician diagnosed asthma at 7 years was reported in 10.7% of children, and 91.9% of these had at least one previous prescription of ICS ever.

Wheeze, LRTI, and allergy were positively associated with both medication groups (Table 5). For ICS, there were significant interactions between wheeze and LRTI ($P = .001$), between wheeze and allergy and between LRTI and allergy (both $P < .001$). The RRs for different combinations are shown in E-table 7. As for the other age groups, the highest RRs were found when the main exposure was not combined with other exposures.

For β-2 only the AAFs (95% CI) were 37.2 (31.4, 43.0)% for wheeze, 1.7 (0.1, 3.3)% for LRTI, and 7.7 (4.4, 11.0)% for allergy, whereas for ICS the AAFs were 33.7 (31.0, 36.5)% for wheeze, 1.2 (0.5, 1.9)% for LRTI, and 8.3 (6.8, 9.8)% for allergy (E-table 8).

4 | DISCUSSION

Our main finding was that both wheeze and LRTI were independently and positively associated with any prescription of β-2 and ICS, and with the number of prescriptions of ICS at all ages. For both medication groups and all ages, the highest RRs were found for wheeze, and the AAFs were substantially higher for wheeze than for LRTI, suggesting that more prescriptions are attributable to wheeze than to LRTI. The AAFs estimate the proportion of prescriptions that could be avoided if exposure were eliminated. Except at 6 to 18 months of age, the sum of the estimated AAFs were < 50%, meaning that other factors than the explanatory variables included in the present study, such as previous prescription of ICS, are also associated with prescriptions. At 18 to 36 months of age, allergic rhinoconjunctivitis modified the association between wheeze and ICS, and at 3 to 7 years of age, allergy modified the associations between LRTI or wheeze and ICS. The RRs of the interaction terms were all < 1, therefore the relative effects were higher when the main exposure was not combined with other exposures. Symptomatic children have often already received at least one prescription, and adding a symptom has less effect than the main symptom alone. However, data regarding

prescribers' characteristics were not available and the study was not designed to study causal relationships and the exact reasons for the prescriptions.

Few large population studies have evaluated how airway symptoms and atopic diseases are associated with prescriptions of asthma medications. An Italian study including children 1 to 5 years of age found that frequent wheeze, emergency department visits, allergic disease, and prescriptions by doctors with a high prescribing volume were associated with prescriptions of anti-inflammatory therapy, underlining that the patient characteristics alone cannot explain how doctors decide to prescribe.[24] A Dutch study reported a low grade of continuation of asthma medications through childhood, particularly if the treatment started early, and children prescribed asthma medications often had other conditions than asthma.[3] Similarly, an Australian study found a high rate of co-dispensing of ICS and antibiotics, suggesting that ICS often are prescribed for LRTI.[7] In the present study, wheeze and LRTI were also associated with number of prescriptions in the ZINB model. Due to various effect estimates, the results from the Poisson regression analyses (RR) and the ZINB models (IRR) are not directly comparable. However, most Norwegian children receive only one or few prescriptions and with low persistence, suggesting that ICS are frequently given for intermittent asthma-like symptoms.[11,13]

In the present study, the prevalence of children receiving at least one prescription of ICS was high compared with findings from UK and the Netherlands,[12] and the present study may suggest factors associated with this high prescription rate. For 0 to 6 months of age, the RRs of LRTI were substantially higher than for older children, but as wheeze was not registered, LRTI may have been strongly associated with wheezing episodes in this age group. For the three oldest age groups, the RRs for LRTI were moderate varying from 2 to 3. Although LRTI may trigger asthma symptoms, prescribing ICS for children with recurrent LRTI without wheeze is not in line with guidelines for asthma.[4,25]

Wheeze is the major symptom of asthma, and the strong association between wheeze and prescriptions may therefore partially reflect an appropriate treatment for children in the present study.[4] However, recurrent episodes with wheeze are also common in preschool children without asthma.[4] Guidelines underline that wheezing episodes should initially be treated with β-2 agonist, and ICS should only be prescribed to preschool children with frequent or severe wheezing episodes or wheeze combined with other asthma characteristics such as atopic comorbidities.[4] Although, the present study does not include data regarding wheezing phenotypes, in general focusing on phenotypes and the possible underlying mechanism and not only on the diagnostic term may enhance a more appropriate prescribing of asthma medications for preschool children.[8]

4.1 | Other atopic diseases

Except at 3 to 7 years of age, atopic dermatitis was positively associated with prescriptions of ICS, but low RRs suggest that atopic dermatitis had little impact, as also reported by others.[26,27] Lower prevalence of atopy than LRTI and wheeze (18-36 months), can partly explain the low AAFs particularly for allergic rhinoconjunctivitis (18-36 months), although there were moderately associations. Allergic rhinoconjunctivitis (18-36 months) and allergy (3-7 years) modified the association between wheeze and ICS as shown by others,[24] but had overall a small additional effect. These findings were surprising, as guidelines underlines that atopic comorbidity is important to consider when predicting response to ICS.[4] Atopy was reported by parents and not based on objective tests, which may influence our results.

4.2 | B-2 vs ICS

Prescription of ICS was our main focus as ICS is the cornerstone in treatment of asthma, but also of major concern due to potential side effects as impaired growth and adrenal suppression in young children.[4] Moreover, the low proportion of children receiving β-2 only shows that when Norwegian doctors prescribe asthma medications, this includes ICS for most children. This is in contrast to UK, but in line with findings from Italy and the Netherlands.[12]

4.3 | Previous prescription of ICS

Previous prescription of ICS was strongly associated with prescription of ICS in the next age interval, but not with β-2 only. A response to ICS may support the diagnosis of asthma,[4] but we could not examine whether continuous prescriptions were due to response to treatment or to the prescriber's practice and barriers to discontinue the therapy.[28] Doctors should continuously evaluate the asthma diagnosis due to the various and transient wheezing phenotypes during childhood.[4,10]

4.4 | Strengths and limitations

The main strengths of this study are the use of a large population-based sample linked to an independent source for outcome data (NorPD), the prospective data collection and the adjustment for a large number of covariates.[29]

The main limitation is the lack of information regarding wheeze at 6 and 36 months of age. Data regarding wheeze from 18 to 36 months of age was gathered retrospectively from the 7-year questionnaire with a risk of recall bias. In addition, the childhood respiratory symptoms were collected through questionnaires, which may cause misclassification. Further, a selection bias at inclusion may have occurred, as women participating in MoBa are older, less likely to be single, smoke and to have more than two deliveries than other pregnant women registered in the Medical Birth Registry of Norway during the same period.[30]

5 | CONCLUSION

Both wheeze and LRTI were associated with prescriptions of asthma medications in young children, with the strongest associations seen for wheeze. Atopic diseases contributed to these associations in the oldest age groups, but had overall little impact on the prescriptions.

5.1 | Possible implications

These results must be interpreted with caution due to the weaknesses of this observational study. However, together with the known high prescription rate of asthma medications in Norway, our results may suggest that emphasis particularly should be on correct evaluation of which children with recurrent wheeze that may benefit from treatment with ICS, also including the predictive role of atopic comorbidity.[4] Although a large group of children with LRTI also report wheeze, guidelines should underline that ICS should not be prescribed to children with recurrent episodes of LRTI without wheeze. This will be in line with an increasing focus on the pathophysiology of childhood airway disease and not considering asthma as a homogenous label in young children.[8]

ACKNOWLEDGMENTS

The Norwegian Mother, Father and Child Cohort Study are supported by the Norwegian Ministry of Health and Care Services and the Norwegian Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study. The Norwegian Research Council (grant number 221097 to Wenche Nystad) also supported this study.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics*. 2007;120:855-864.
2. Papadopoulos NG, Arakawa H, Carlsen KH, et al. International consensus on (ICON) pediatric asthma. *Allergy*. 2012;67:976-997.
3. Schokker S, Groenhof F, van derVeen WJ, van derMolen T. Prescribing of asthma medication in primary care for children aged under 10. *Prim Care Respir J*. 2010;19:28-34.
4. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2018. https://ginasthma.org/
5. Zuidgeest MG, vanDijk L, Smit HA, et al. Prescription of respiratory medication without an asthma diagnosis in children: a population based study. *BMC Health Serv Res*. 2008;8:16.
6. Klok T, Kaptein AA, Duiverman E, Oldenhof FS, Brand PL. General practitioners' prescribing behaviour as a determinant of poor persistence with inhaled corticosteroids in children with respiratory symptoms: mixed methods study. *BMJ Open*. 2013;3:3.
7. Poulos LM, Ampon RD, Marks GB, Reddel HK. Inappropriate prescribing of inhaled corticosteroids: are they being prescribed for respiratory tract infections? A retrospective cohort study. *Prim Care Respir J*. 2013;22:201-208.
8. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet*. 2018;391:350-400.
9. Bush A, Pavord ID. We can't diagnose asthma until <insert arbitrary age>. *Arch Dis Child*. 2018;103:729-731.
10. Brand PL, Caudri D, Eber E, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J*. 2014;43:1172-1177.
11. Oymar K, Mikalsen IB, Furu K, Nystad W, Karlstad O. Prescription patterns of inhaled corticosteroids for preschool children-a Norwegian register study. *Pediatr Allergy Immunol*. 2015;26:655-661.
12. Sen EF, Verhamme KM, Neubert A, et al. Assessment of pediatric asthma drug use in three European countries; a TEDDY study. *Eur J Pediatr*. 2011;170:81-92.
13. Mikalsen IB, Karlstad O, Furu K, Oymar K. Prescribing of asthma drugs for children 2004-2015. *Tidsskr Nor Laegeforen*. 2018;138(4):1-10.
14. Dombkowski KJ, Cabana MD, Cohn LM, Gebremariam A, Clark SJ. Geographic variation of asthma quality measures within and between health plans. *Am J Manag Care*. 2005;11:765-772.
15. Goedken AM, Brooks JM, Milavetz G, Rudzianski NJ, Chrischilles EA. Geographic variation in inhaled corticosteroid use for children with persistent asthma in Medicaid. *J Asthma*. 2017;55:1-8.
16. Koster ES, Wijga AH, Zuidgeest MG, et al. Patterns of asthma medication use: early asthma therapy initiation and asthma outcomes at age 8. *Pharmacoepidemiol Drug Saf*. 2010;19:991-999.
17. Magnus P, Birke C, Vejrup K, et al. Cohort profile update: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2016;45:382-388.
18. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol*. 2010;106:86-94.
19. Greenland S. Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. *Am J Epidemiol*. 2004;160:301-305.
20. Greene WH. Accounting for excess zeros and sample selection in poisson and negative binomial regression models. NYU Working Paper 1994;EC-94-10.
21. Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Control*. 1974;19:716-723.
22. Eide GE, Gefeller O. Sequential and average attributable fractions as aids in the selection of preventive strategies. *J Clin Epidemiol*. 1995;48:645-655.
23. Ferguson J, Alvarez-Iglesias A, Newell J, Hinde J, O'Donnell M. Estimating average attributable fractions with confidence intervals for cohort and case-control studies. *Stat Methods Med Res*. 2016;27(4):1141-1152.
24. Montella S, Baraldi E, Bruzzese D, Mirra V, Di Giorgio A, Santamaria F. group of Primary Care P. What drives prescribing of asthma medication to preschool wheezing children? A primary care study. *Pediatr Pulmonol*. 2013;48:1160-1170.
25. Bush A, Fleming L. Is asthma overdiagnosed? *Arch Dis Child*. 2016;101:688-689.

26. Dharma C, Lefebvre DL, Tran MM, et al. Patterns of allergic sensitization and atopic dermatitis from 1 to 3 years: effects on allergic diseases. *Clin Exp Allergy*. 2017;48:48-59.
27. Belgrave DC, Granell R, Simpson A, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. *PLoS Med*. 2014;11:e1001748.
28. Gionfriddo MR, Hagan JB, Rank MA. Why and how to step down chronic asthma drugs. *BMJ*. 2017;359:j4438.
29. Furu K, Karlstad O, Skurtveit S, et al. High validity of mother-reported use of antiasthmatics among children: a comparison with a population-based prescription database. *J Clin Epidemiol*. 2011;64:878-884.
30. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. 2009;23:597-608.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Mikalsen IB, Dalen I, Karlstad Ø, et al. Airway symptoms and atopy in young children prescribed asthma medications: a large-scale cohort study. *Pediatric Pulmonology*. 2019;54:1557-1566. https://doi.org/10.1002/ppul.24437