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Assessment of adherence to asthma controllers in children and adolescents

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Abstract

Background: Low adherence to asthma controllers is known to increase the risk of uncontrolled disease and poor health outcomes. We aimed to study risk factors of long-term adherence to preventive medications in children and adolescents with asthma.

Methods: Adherence was assessed during a two-year period in 155 children with asthma followed in a tertiary pediatric asthma outpatient clinic using percentage of days covered (PDC) based on physician prescriptions and pharmacy claims data. The risk factor analysis included age, sex, ethnicity, BMI, atopic comorbidity, spirometry incentives, and fractional exhaled nitric oxide (FeNO).

Results: Ninety-five children, 50 (53%) males, mean age of 16.3 years (SD, 2.36), received at least one prescription for asthma controllers in the study period. Fifty-two (54%) children were classified as non-adherent with a PDC cutoff at 80%. Adherence was negatively associated with age: adherence ratio (AR) 0.84 (95% CI, 0.73-0.95), $P = .008$; forced expiratory volume in 1 second (FEV1): AR per L 0.6 (0.91-1.0), $P = .03$; unfilled inhaled beta-2-agonist prescription: AR 0.45 (0.23-0.89), $P = .02$; and FeNO level: AR per ppb 0.98 (0.97-0.99), $P = .03$, where age and FeNO retained significance in multivariate analysis. Type and number of asthma controllers were not associated with adherence.

Conclusions: This study shows low adherence to preventive medication among half of the children with asthma, which is associated with increasing age and FeNO level. Therefore, an extra effort should be directed toward teenagers transitioning from pediatric to adult medicine and toward inhaled corticosteroid-treated patients with elevated FeNO to increase their adherence to asthma controllers.

KEYWORDS

adherence, asthma, PDC, preventive medication, risk factors

Abbreviations: AR, adherence ratio; BMI, body mass index; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; NA, not available; OR, odds ratio; PDC, proportion of days covered; SABA, short-acting beta-2 agonist.

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1 | INTRODUCTION

Asthma is the most common chronic illness in children and a common cause of hospital admission.¹⁻³ Adherence to asthma controllers is low with rates from 30% to 70% often estimated using questionnaires and only a few studies using electronically monitored inhalers or pharmacy claims data on a short-term basis.⁴⁻⁹ Low adherence and poor asthma control increase morbidity, mortality, and healthcare costs^{4,7} and compromise the quality of life due to sleep disruption, missed school days, and limited recreational activities.^{4,10}

Multiple factors affect adherence including beliefs, health literacy, and relationships with health providers, caregivers, and peers.^{4,6,11} However, the lack of consensus on how to measure adherence to multiple medications has resulted in inconsistent approaches and difficulties comparing study findings.¹² Therefore, there is a need for more detailed studies of adherence to asthma controllers as a group to determine risk factors.¹³⁻¹⁵ Here, we assess long-term adherence and analyze risk factors of low adherence to multiple asthma controllers in a Danish pediatric asthma population using proportion of days covered (PDC) taking account of treatment cessations, dose adjustments, and polypharmacy using pharmacy claims data over a two-year period.

2 | METHODS

2.1 | Study design and population

We conducted a retrospective study of 155 children, who had performed an exercise challenge test at the tertiary pediatric asthma outpatient clinic at Herlev-Gentofte Hospital during 2015. The study period was the default two-year electronic window available for checking history of pharmacy claims, that is, 700 days from October 2017 to September 2019. The following inclusion criteria were used: (a) asthma diagnosed by a pediatrician at the clinic according to the GINA guidelines, and (b) at least one prescription of inhaled corticosteroids (ICS), ICS-long-acting beta-2-agonist (LABA) combination, and/or leukotriene receptor antagonist (LTRA) registered in the electronic medical records. Secondary investigations included pharmacy claims of inhaled short-acting beta-2-agonist (SABA) and nasal steroids, but not tablet antihistamines, which are sold over the counter in Denmark and therefore not available for our study. Neither of the children in the study received maintenance oral steroids.

All parents signed a consent form, and the study was approved by the local IRB, that is, the Knowledge Center of data reviews in the Capital Region of Denmark.

2.2 | Data for adherence assessment

The date of the first claim after the start of the study period post-prescription was set as commence date for the calculation of number

Key Message

Low adherence to asthma controllers is known to increase the risk of uncontrolled disease, but there is a lack of objective long-term assessments of adherence and its risk factors. Among children and adolescents with asthma, this two-year adherence assessment based on pharmacy claims data shows that half of the patients have low adherence, which is associated with increasing age and FeNO level. Therefore, extra clinical awareness should be raised to teenagers transitioning from pediatric to adult medicine, and to inhaled corticosteroid-treated patients with elevated FeNO all in order to improve their adherence to asthma controllers.

of days with supply and total number of days in the period. Number of packages and dose count were registered to calculate the total number of available doses. For SABA and nasal steroids, only data on the first redemption were collected as the use of these is often as-needed or seasonal.

2.3 | Proportion of days covered

Proportion of days covered was calculated as the total number of days with medical supply divided by the total number of days, that is, prescription days within the follow-up. Prescription days were carefully calculated with respect to therapy and dose adjustments, and the total number of days with medical supply was calculated with respect to discontinuations to diminish falsely estimated low adherence (see online Methods S1). Using this highly detailed approach, we taxonomically largely embraced and applied the conceptual definition as proposed by Vrijens et al, taking into account all three essential elements of medication adherence: (a) initiation; (b) implementation; and (c) persistence.^{16,17} The continuous PDC calculation was done for each controller and combined, and was used to defining adherent vs non-adherent using a cutoff value of 80%.¹⁸

2.4 | Risk factors

The following data were extracted from the electronic medical records: sex; Caucasian (y/n); BMI (kg/m²); rhinitis (y/n); eczema (y/n); food allergy (y/n); sensitization to house dust mites (y/n), cat/dog/horse (y/n), birch/grass/mugwort(y/n); any sensitization (y/n); FeNO (ppb); FEV1 (L); FEV1%-predicted; FEV1/FVC ratio (%); bronchodilator response (%-change in FEV1); age at end of the study period (years); filled prescription of SABA (y/n); and nasal steroids (y/n).

TABLE 1 Characteristics of children and adolescents with prescription of at least one preventive asthma medication during the study period

	Total no. of patients (n = 95)	No. missing
Demographics		
Age at end of study, y mean (SD)	16.33 (2.36)	
10-14 y, n (%)	30 (31.6)	
15-17 y, n (%)	41 (43.2)	
18-22 y, n (%)	24 (25.2)	
Males, n (%)	50 (52.6)	
Ethnicity		
Caucasian, n (%)	70 (73.7)	
Non-Caucasian, n (%)	25 (22.3)	
Comorbidities		
Sensitization ^a , n (%)	73 (76.8)	
Rhinitis, n (%)	70 (73.4)	
Eczema, n (%)	36 (37.9)	2
Predisposition ^b , n (%)	63 (66.3)	13
Prescriptions		
SABA	91 (95.8)	
ICS	41.5 (43.7)	
ICS-LABA	29.5 (31)	
Total with one inhaler ^c	71 (74.7)	
ICS + LTRA	4 (4.3)	
ICS-LABA + LTRA ^d	20 (21.0)	
Total with add-on LTRA	24 (25.3)	
NCS	75 (78.9)	
Lung function		
FeNO, ppb, median (IQR)	18 (22)	2
FEV1%-predicted, mean (SD)	88.27 (10.57)	
FEV1, L, mean (SD)	2.48 (0.65)	
FVC, L, mean (SD)	3.1 (0.81)	1
FEV1/FVC, mean (SD)	0.81 (0.07)	1
Reversibility, % ^e , mean (SD)	8.95 (8.35)	9

^aSensitized for at least one of the following: dust mites, pollen, furred animals, or foods.

^bPredisposed for at least one of the following: asthma, eczema, or allergy.

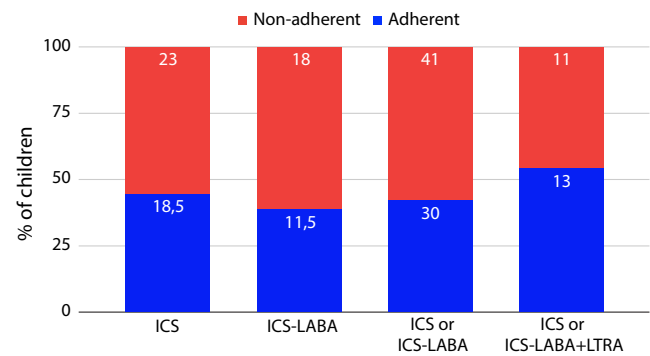
^cSeven patients changed between ICS and ICS-LABA during the study period and were equally distributed with 3 and 5 in each group of ICS and ICS-LABA, respectively.

^dOne patient received ICS, ICS-LABA, and LTRA during the study period and was categorized in this group.

^eChange in FEV1 from 10 min after exercise test (or most recent value) to post-SABA inhalation.

2.5 | Statistical analyses

Logistic regression was used for risk factor analysis of the binary PDC outcome (adherent/non-adherent). Due to negative

**FIGURE 1** Bar chart showing adherence as adherent vs non-adherent based on a PDC cutoff at 80% by type and number of asthma preventive medications. No significant differences in adherence were found between ICS, ICS-LABA, and ICS or ICS-LABA + LTRA add-on therapy or when comparing patients who received one device/medication vs those with add-on LTRA

skewness of the continuous PDC outcome (Figure S1), a quasibinomial distribution model was chosen to account for overdispersion in the risk factor analysis. This required transformation of the PDC variable to an adherence ratio (AR) calculated as days with medical supply divided by days without medical supply, resulting in a likelihood curvilinear variable. For example, a calculated PDC of 60% would equal 60 days with supply and 40 days without yielding an AR of $60/40 = 1.5$, interpreted as a higher likelihood of having days with medical supply, that is, a higher adherence. In multivariate analysis, all variables with number of missing data exceeding 10 were excluded to limit loss of power. All analyses were performed using R software version 3.6.1.

3 | RESULTS

3.1 | Baseline characteristics

A total of 95 (61%) of the 155 participants were prescribed at least one asthma controller in the two-year follow-up period (Figure S2). Baseline characteristics of the participants are outlined in Table 1. The mean (SD) age was 16.3 years (2.4) years, and 50 (53%) were males. Seventy-one (75%) were prescribed one device/medication. Forty-two (44%) were prescribed ICS monotherapy, 29 (31%) ICS-LABA, 4 (4%) ICS + LTRA, and 20 (21%) ICS-LABA + LTRA. Almost all patients ($n = 91$) were prescribed as-needed SABA. Nasal steroids were prescribed in 75 (79%); 73 (77%) were sensitized; and 63 (66%) had atopic predisposition.

3.2 | Adherence to asthma controllers

The continuous PDC measurement during the two-year study period showed a median (IQR) of 76% (44-98) with 52 (54%) children classified as non-adherent using a PDC cutoff at 80%. Analyzing adherent vs non-adherent yielded no significant differences in the proportion

of adherent patients among those prescribed one device/medication vs those with add-on LTRA: 30 (42%) vs 13 (54%) (OR, 0.62; 95% CI, 0.24-1.57; $P = .44$) as well as no differences when comparing the proportion of adherent patients on different combinations of asthma preventive medication: ICS, 18.5 (45%) vs ICS-LABA, 11.5 (39%) vs ICS or ICS-LABA + LTRA, 13 (54%) ($P = .54$; Figure 1). Similar non-significant differences in adherence for type and number of asthma controllers were observed when analyzing the continuous PDC measurement using non-parametric tests (Kruskal-Wallis rank-sum test, $P = .76$) or as AR ($P = .19$; Figure S3).

3.3 | Nasal steroids, SABA, and adherence

A total of 44 (59%) of the 75 patients who were prescribed nasal steroids were non-adherent to their asthma controllers compared to 8 (40%) of the 20 patients who were not prescribed nasal steroids. Subgrouped by filled vs unfilled nasal steroid prescriptions, 36 (58%) of those who did fill their nasal steroid prescription were non-adherent to their asthma controllers compared to 8 (62%) of those who did not fill their prescription. The proportion of non-adherent patients showed no significant differences across prescription and fill status for nasal steroids ($P = .32$) (Table 2).

A total of 70 (77%) of the 91 patients who were prescribed a SABA filled in the prescription of whom 40 (57%) were non-adherent to their asthma controllers compared to 14 (67%) of the patients who did not fill in their SABA prescription. Patients who did not fill their SABA prescription showed lower adherence to asthma controllers compared to patients who did fill their SABA prescription: AR, 0.45 (95% CI, 0.23-0.89); $P = .02$ (Figure 2).

3.4 | Risk factor analysis of adherence

Adherence to asthma controllers was negatively associated with age, that is, AR was 16% lower per 1-year increase in age: AR, 0.84 (0.73-0.95); $P = .01$. This was also observed by logistic regression analysis yielding significantly higher odds of non-adherence with increasing age: OR, 1.20 (1.00-1.45); $P = .05$. Baseline FeNO and FEV1 values were negatively associated with AR: FeNO per ppb increase, 0.98 (0.97-0.99); $P = .01$, and FEV1 per L increase, 0.6 (0.38-0.94); $P = .03$, respectively. However, these findings were not significant in the binary outcome analysis although both showed increased OR for non-

All risk factors were subsequently analyzed adherence with increasing values: FeNO, 1.02 (0.99-1.04); $P = .11$, and FEV1, 1.53 (0.82-2.99); $P = .19$ (Figure 3). The remaining risk factors showed no significant associations with adherence (Table 2). In multivariate models. Backward selection with a p-value cutoff at 0.1 yielded two significant variables, which were age and FeNO level. Age was the only significant risk factor left in the binary multivariate model: OR per year, 1.20 (1.00-1.45); $P = .05$. In the continuous PDC model, both age and FeNO level were significantly associated with adherence: AR for age, 0.88 (0.77-0.99); $P = .05$; and AR for FeNO, 0.98 (0.97-0.99); $P = .03$.

4 | DISCUSSION

4.1 | Primary findings

This study shows low adherence to asthma controllers as approximately half of the children were non-adherent based on filled prescriptions over a 2-year period. Lower adherence was associated

	Adherence		PDC < 80% (non-adherent)	
	Likelihood of days with medicine (95% CI)	P	OR (95% CI)	P
Age, years	0.84 (0.73-0.95)	.008	1.20 (1.003-1.45)	.05
BMI, kg/m ²	1.0 (0.9-1.12)	.9	0.98 (0.84-1.13)	.7
Sex, female	0.82 (0.45-1.48)	.5	0.9 (0.4-2.02)	.8
Caucasian	0.61 (0.32-1.2)	.15	1.68 (0.67-4.45)	.3
FeNO, ppb	0.98 (0.97-0.99)	.007	1.02 (0.99-1.04)	.1
FEV1, L	0.6 (0.38-0.94)	.03	1.53 (0.82-2.99)	.2
FEV1, %-predicted	1.01 (0.98-1.04)	.6	0.99 (0.95-1.03)	.6
FEV1/FVC	0.96 (0.91-1.00)	.07	1.03 (0.97-1.1)	.4
Reversibility, %	1.00 (0.96-1.03)	.8	1.00 (0.95-1.06)	.9
SABA redeemed ^a	0.45 (0.23-0.89)	.02	2.17 (0.78-6.18)	.15
No. of drugs, two ^b	1.62 (0.81-3.4)	.19	0.62 (0.24-1.57)	.3
Sensitization	1.71 (0.83-3.74)	.16	0.62 (0.23-1.6)	.3
Rhinitis	1.26 (0.64-2.56)	.5	0.86 (0.34-2.17)	.75
Eczema	0.66 (0.35-1.24)	.2	1.65 (0.46-3.87)	.24

TABLE 2 Result from univariate risk factor analysis of adherence to asthma controllers using quasibinomial modeling and logistic regression

^aSABA redeemed was defined as filling at least one prescription during the study period.

^bICS and ICS-LABA categorized as 1 device prescription, and LTRA added to either of the two categorized as a two-drug prescription.

with increasing age and higher FeNO, whereas there were no differences in adherence between type and number of controllers, status of nasal steroids, atopic comorbidity, or predisposition.

4.2 | Strengths and limitations

The primary strength is the unique access to pharmacy claims data on all asthma controllers prescribed for a well-characterized patient group enabling assessment of multiple medication adherence as opposed to previous studies investigating monotherapeutic regimens.¹² PDC calculated from pharmacy claims and prescriptions from electronic medical records is unbiased compared to questionnaire-based adherence estimations reported being too inaccurate.¹⁸⁻²¹ We obtained information on *all* prescriptions filled from *any* pharmacy in Denmark, that is, not restricting the participants to use one specific pharmacy, which is

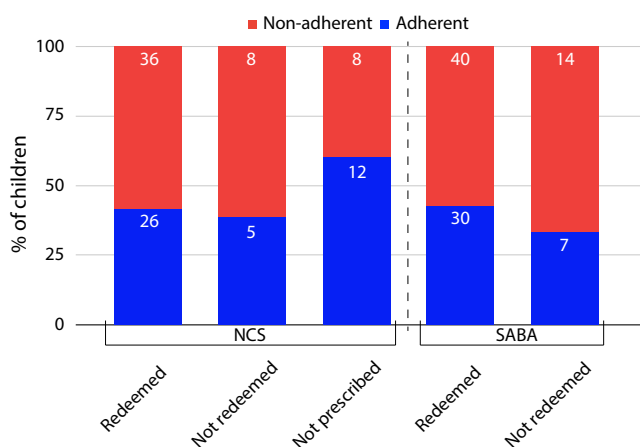


FIGURE 2 Bar chart showing adherence as adherent vs. non-adherent based on a PDC cutoff at 80% by prescription and redeem status of NCS and SABA. There were no significant differences in distribution of adherent vs non-adherent children for either NCS or SABA status

a limitation in other studies.¹⁸ Further, the 2-year observation period and analyses of PDC as numeric, binary, and curvilinear overcame the non-consistent way of assessing adherence.^{4,12}

All patients were from a tertiary pediatric asthma clinic, which limits diagnostic heterogeneity and presumably increases adherence due to objective confirmation of the asthma diagnosis.²² In Denmark, milder asthma cases are typically treated in general practice using either low-dose ICS plus as-needed SABA or as-needed ICS-formoterol as per the new GINA guidelines.²³ This is of importance because as-needed use of ICS-formoterol may lead to underestimation of adherence due to lower possession ratios. Further, due to the public Danish healthcare system, the population is unaffected by differences in medical access associated with health insurance inequality, which may affect adherence.^{13,24,25} However, filling prescriptions might still have a socially unequal distribution due to medication costs and pharmacy travel distances.

We used date of the first claim after the start of the study period as commence date to level out potential differences in ICS stock in homes and cross-use of devices in families with more than one suffering from asthma, even though no home visits were conducted. However, this could still have resulted in underestimation of the PDC calculated. A limitation of using pharmacy claims for assessing adherence is that we cannot determine whether the patient takes the medication as some individuals might create stocks of unused medication. However, this is diminished by the long follow-up, which increases the probability that the medication is taken when it is collected multiple times.

Our population had a mean age of approximately 16 years, no participants were less than 10 years, and 25% of the patients were more than 18 years at end of the follow-up. Therefore, most patients were transitioning from pediatrics to adult medicine during follow-up, which limits generalizability to preschoolers, where parents carry the medication responsibility.²⁶

Finally, we only analyzed adherence to asthma controllers based on the type of active ingredient and did not differentiate between

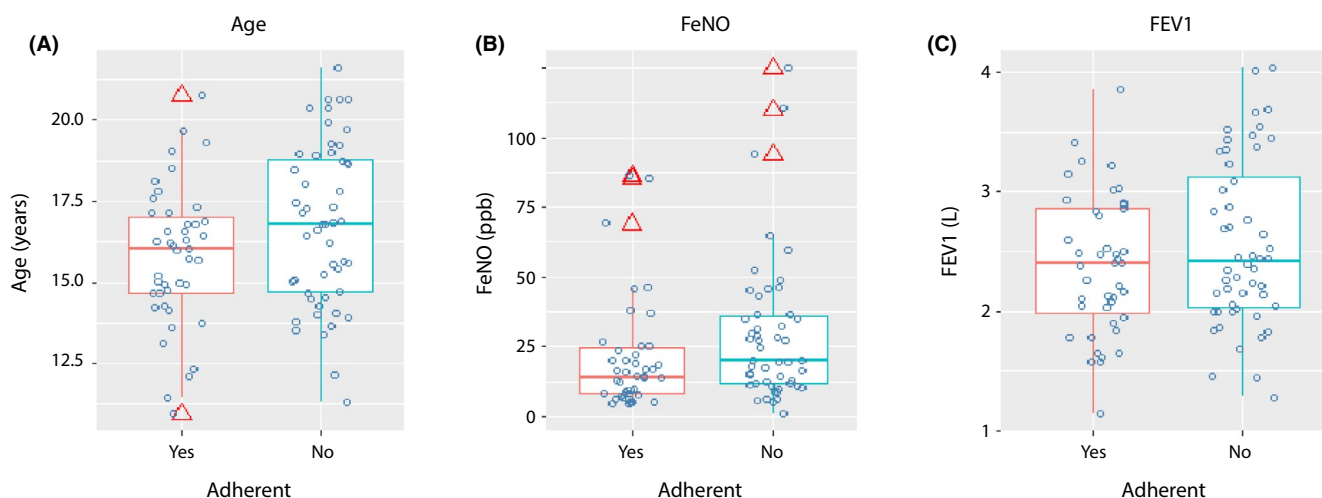


FIGURE 3 Boxplots showing age (Panel A), FeNO level (Panel B), and FEV1 (Panel C) stratified by adherence status as adherent vs non-adherent based on a PDC cutoff at 80%

different types of inhalers,²⁷ which would have required more participants.

4.3 | Interpretation

Using different detailed methods of assessing PDC, we observed low adherence to asthma controllers with 54% of the patients classified as non-adherent and a median PDC of 76%. Increasing age and FeNO were negatively associated with adherence, suggesting these may pinpoint patients at risk of low adherence.

Our findings support earlier studies of adherence among children, adolescents, and young adults with asthma although reported adherence rates vary.^{5,18,21} One study showed median adherence rates ranging from 33% to 85.5%, whereas another reported an electronically measured mean of 48%, and a third comparing adherence rates by electronic monitoring vs patient diaries showed medians of 58% vs 95%. Finally, a study that also used electronic monitoring, over a 3-month period, found a median adherence of 74% and concluded this method as a useful tool for identifying children with true severe therapy-resistant asthma in need of step-up treatment. Our collected data solely provided baseline information on asthma control status making us unable to compare with the latter.²⁸ These varying results reflect methodological differences as qualitative approaches (parent reporting, questionnaires) are more inaccurate than objective methods (electronic monitoring, pharmacy claims).^{18,20,29}

McQuaid et al showed that adherence was negatively associated with age, but also with minority status, ethnicity, and asthma morbidity using one-month electronic monitoring and information on prescriptions based on the families' reports.^{5,13} We did not observe association with ethnicity, which could be power-related as only 25 (22%) were non-Caucasian. Another study with a short follow-up of 2 weeks also found higher age was associated with low adherence in minority adolescents.²⁵ We used a uniquely long two-year observation period and included variables in the risk factor analyses representing different domains, for example, family-level (ethnicity) and individual-level (age, lung function), accommodating a recent review calling for this.⁶

Our results advocate for consideration of why increasing age is a negative predictor for adherence. Possible explanations include the diminishing role of caregivers' in asthma medication management as the child gets older. Previous studies showed that 7-year-old children had assumed approx. 20% of daily medication responsibility, which was 50% at age 11, 75% at age 15, and 100% at age 19 years.²⁶ Adolescents often lead a busy lifestyle including risk behaviors such as tobacco, alcohol, and drug use, which challenge the routines of taking medication on a daily basis, that is, enhancing risk of low adherence, loss of disease control, exacerbations, and hospital admissions.^{4,18,30} Further, adolescents differ from younger children going through a developmental transition in cognition, knowledge, autonomy, identity, and peer relations, which is known to impact asthma self-management.²⁵ This also includes that the impact of children's health beliefs on adherence increases as they reach adolescence,

exert greater independence, and are less affected by parental medication beliefs and guidance.³¹

Unfortunately, we did not have any variables of socioeconomic status of relevance in a pediatric context, that is, parents' income, their employment status, and level of education.³² However, adherence can be categorized as *intentional* (lack of trust in medicine, concern of side effects, economy) or *unintentional* (forgetfulness, unawareness, faulty inhaler technique), where low adherence is mostly unintentional, which is less affected by socioeconomic factors.^{4,14} Blais et al¹¹ distinguished between primary adherence (first prescription fill) and secondary adherence (PDC) reporting that if only secondary adherence is considered, then adherence might be overestimated. We did not differentiate between primary and secondary adherence but used a highly detailed PDC calculation including a potential risk of overestimation rather than underestimation.

The direction of association between FeNO and adherence is presumably that lower adherence to ICS-containing medication leads to higher FeNO, that is, type 2 inflammation as a result of poor disease control and inadequate anti-inflammatory treatment. Few studies have examined the use of FeNO in adherence monitoring, but the findings are consistent with ours showing that FeNO and adherence are inversely associated³³ and that elevated FeNO correlated with non-adherence in children with acute asthma symptoms.³⁴ We found no association between adherence and atopic comorbidity and no significant influence of nasal steroid prescription or fill status on adherence to asthma controllers. This may be a result of inadequate power as FeNO is often increased under these conditions, why results of significance would be expected.³⁵

Asthma severity was indirectly examined by assessment of type and number of preventive medications, which express the internationally recognized stepwise treatment algorithms, and showed no association with adherence. This finding differs from an older study showing that LTRA outperformed ICS in adherence.³⁶ However, the study participants had a mean age of 8.6 years vs 16.3 years in our study, which hampers comparability and may indicate that per oral treatment is easier to administrate to younger children than inhaler devices. Airway obstruction was assessed by FEV1, FEV1/FVC ratio, and bronchodilator response of which none were significant in the multivariate models. Increasing FEV1 in L was significantly associated with decreasing adherence, and FEV1/FVC ratio showed a trend of association, which is opposite to our expectation and presumably driven by the association with age, that is, height, as they were not significant adjusted for age.

Our results highlight that healthcare providers need a continuous awareness of low adherence when treating asthma in children and adolescents. Particularly, consideration should be given to uncontrolled asthma in ICS-treated patients with continuously elevated FeNO, and the adolescent group, since adherence seems to decrease with age. The latter underscores the need for transition consultations for adolescents with participation of both their pediatrician and their future adult respiratory physician with sufficient

time to discuss health beliefs and other parameters affecting adherence. These should be organized as split consultations with an initial talk only with the adolescent and thereafter a talk with the adolescent together with the parents to facilitate that the adolescent takes responsibility of his/her asthma. Still, further investigations on this subject are needed as adherence behavior during childhood and adolescence has a dynamic pattern influenced by stages of development, especially including adolescents as they undergo transitions of physiology and cognition with changes of understanding, parent relations, and health beliefs.^{5,18,31}

5 | CONCLUSION

This study shows that adherence to asthma controllers in a pediatric population followed at a tertiary outpatient clinic is poor. Useful clinical predictors of low adherence are higher age and FeNO, which should be considered by the clinician as key variables for developing a tailored adherence intervention and hereby improve adherence, asthma control, and health outcomes.

CONFLICT OF INTERESTS

All authors declare no potential, perceived, or real conflict of interest regarding the content of this manuscript. The funding agencies did not have any role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript. No pharmaceutical company was involved in the study.

AUTHOR CONTRIBUTIONS

Mads Marckmann: Data curation (lead); Formal analysis (lead); Writing-original draft (lead). **Mette N. Hermansen:** Conceptualization (equal); Writing-review & editing (equal). **Kirsten S. Hansen:** Conceptualization (equal); Writing-review & editing (equal). **Bo L. Chawes:** Conceptualization (lead); Methodology (lead); Project administration (lead); Supervision (lead); Writing-review & editing (lead).

PEER REVIEW

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REFERENCES

- Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis*. 2014;18(11):1269-1278.
- Kocevar VS, Bisgaard H, Jönsson L, et al. Variations in pediatric asthma hospitalization rates and costs between and within Nordic Countries. *Chest*. 2004;125(5):1680-1684.
- Sevelsted A, Phipps CB, Bisgaard H. Stable admission rate for acute asthma in Danish children since 1977. *Eur J Epidemiol*. 2016;31(3):325-329.
- Ahmad A, Sorensen K. Enabling and hindering factors influencing adherence to asthma treatment among adolescents: A systematic literature review. *J Asthma*. 2016;53(8):862-878.
- McQuaid EL, Kopel SJ, Klein RB, Fritz GK. Medication adherence in pediatric asthma: reasoning, responsibility, and behavior. *J Pediatr Psychol*. 2003;28(5):323-333.
- Gray WN, Netz M, McConville A, Fedele D, Wagoner ST, Schaefer MR. Medication adherence in pediatric asthma: a systematic review of the literature. *Pediatr Pulmonol*. 2018;53(5):668-684.
- McQuaid EL, Everhart RS, Seifer R, et al. Medication adherence among latino and non-latino white children with asthma. *Pediatrics*. 2012;129(6):e1404-e1410.
- McNally KA, Rohan J, Schluchter M, et al. Adherence to combined montelukast and fluticasone treatment in economically disadvantaged african american youth with asthma. *J Asthma*. 2009;46(9):921-927.
- Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. *Respirology*. 2008;13(4):559-563.
- Poowuttikul P, Hart B, Thomas R, Poor SE. Adherence with medication refill and medical supplies maintenance as risk factors for inpatient asthma admission in children. *Glob Pediatr Health*. 2017;4:2333794X1771058.
- Bauman LJ, Wright E, Leickly FE, et al. Relationship of adherence to pediatric asthma morbidity among inner-city children. *Pediatrics*. 2002;110(1):e6.
- Pednekar PP, Ågh T, Malmenäs M, et al. Methods for measuring multiple medication adherence: a systematic review-report of the ISPOR Medication Adherence and Persistence Special Interest Group. *Value Health*. 2019;22(2):139-156.
- McQuaid EL. Barriers to medication adherence in asthma. *Ann Allergy Asthma Immunol*. 2018;121(1):37-42.
- Lee JXW, Wojtczak HA, Wachter AM, et al. Understanding asthma medical nonadherence in an adult and pediatric population. *J Allergy Clin Immunol Pract*. 2015;3(3):436-437.
- Blais L, Kettani F-Z, Forget A, Beauchesne M-F, Lemièrre C, Ducharme FM. Assessing adherence to inhaled corticosteroids in asthma patients using an integrated measure based on primary and secondary adherence. *Eur J Clin Pharmacol*. 2017;73(1):91-97.
- Vrijens B, Geest SD, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705.
- Vrijens B, Dima AL, Van Ganse E, et al. What we mean when we talk about adherence in respiratory medicine. *J Allergy Clin Immunol Pract*. 2016;4(5):802-812.
- Lasmar L, Camargos P, Champs NS, et al. Adherence rate to inhaled corticosteroids and their impact on asthma control. *Allergy*. 2009;64(5):784-789.
- Garcia-Marcos PW, Brand PLP, Kaptein AA, Klok T. Is the MARS questionnaire a reliable measure of medication adherence in childhood asthma? *J Asthma*. 2016;53(10):1085-1089.
- Bender B, Wamboldt FS, O'Connor SL, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Ann Allergy Asthma Immunol*. 2000;85(5):416-421.
- Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol*. 1996;98(6 Pt 1):1051-1057.
- Backer V, Stensen L, Sverrild A, Wedge E, Porsbjerg C. Objective confirmation of asthma diagnosis improves medication adherence. *J Asthma*. 2018;55(11):1262-1268.
- Global Initiative for Asthma. Global strategy for asthma management and prevention, 2020.
- Vaswani R, Garg A, Parikh L, Vaswani S. Non-adherence to subcutaneous allergen immunotherapy: inadequate health

- insurance coverage is the leading cause. *Ann Allergy Asthma Immunol*. 2015;115(3):241-243.
25. Mosnaim G, Li H, Martin M, et al. Factors associated with levels of adherence to inhaled corticosteroids in minority adolescents with asthma. *Ann Allergy Asthma Immunol*. 2014;112(2):116-120.
 26. Orrell-Valente JK, Jarlsberg LG, Hill LG, Cabana MD. At what age do children start taking daily asthma medicines on their own? *Pediatrics*. 2008;122(6):e1186-e1192.
 27. Sicras A, Ferrer V, Collar JM, Navarro R, Sáez M. Persistence to treatment by type of inhaler device in patients with asthma and chronic obstructive pulmonary disease. *Semergen*. 2017;43(5):375-386.
 28. Jochmann A, Artusio L, Jamalzadeh A, et al. Electronic monitoring of adherence to inhaled corticosteroids: an essential tool in identifying severe asthma in children. *Eur Respir J*. 2017;50(6):1700910.
 29. Pearce CJ, Fleming L. Adherence to medication in children and adolescents with asthma: methods for monitoring and intervention. *Expert Rev Clin Immunol*. 2018;14(12):1055-1063.
 30. Bender BG. Risk taking, depression, adherence, and symptom control in adolescents and young adults with asthma. *Am J Respir Crit Care Med*. 2006;173(9):953-957.
 31. Drotar D, Bonner MS. Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. *J Dev Behav Pediatr*. 2009;30(6):574-582.
 32. Vukojević M, Zovko A, Talić I, et al. Parental socioeconomic status as a predictor of physical and mental health outcomes in children – literature review. *Acta Clin Croat*. 2017;56(4):742-748.
 33. Wang Z, Pianosi P, Keogh K, et al. The clinical utility of fractional exhaled nitric oxide (feno) in asthma management [Internet]. Rockville, MD: Agency for Healthcare Research and Quality; 2017 [cited 2019 Dec 7]. (AHRQ Comparative Effectiveness Reviews). Available from: <http://www.ncbi.nlm.nih.gov/books/NBK487497/>
 34. Tsai Y-G, Sun H-L, Chien J-W, Chen C-Y, Lin C-H, Lin C-Y. High exhaled nitric oxide levels correlate with nonadherence in acute asthmatic children. *Ann Allergy Asthma Immunol*. 2017;118(4):521-523.e2.
 35. Hallberg J, Ballardini N, Almqvist C, et al. Impact of IgE sensitization and rhinitis on inflammatory biomarkers and lung function in adolescents with and without asthma. *Pediatr Allergy Immunol*. 2019;30(1):74-80.
 36. Ducharme FM, Noya FJD, Allen-Ramey FC, Maiese EM, Gingras J, Blais L. Clinical effectiveness of inhaled corticosteroids versus montelukast in children with asthma: prescription patterns and patient adherence as key factors. *Curr Med Res Opin*. 2012;28(1):111-119.

SUPPORTING INFORMATION

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

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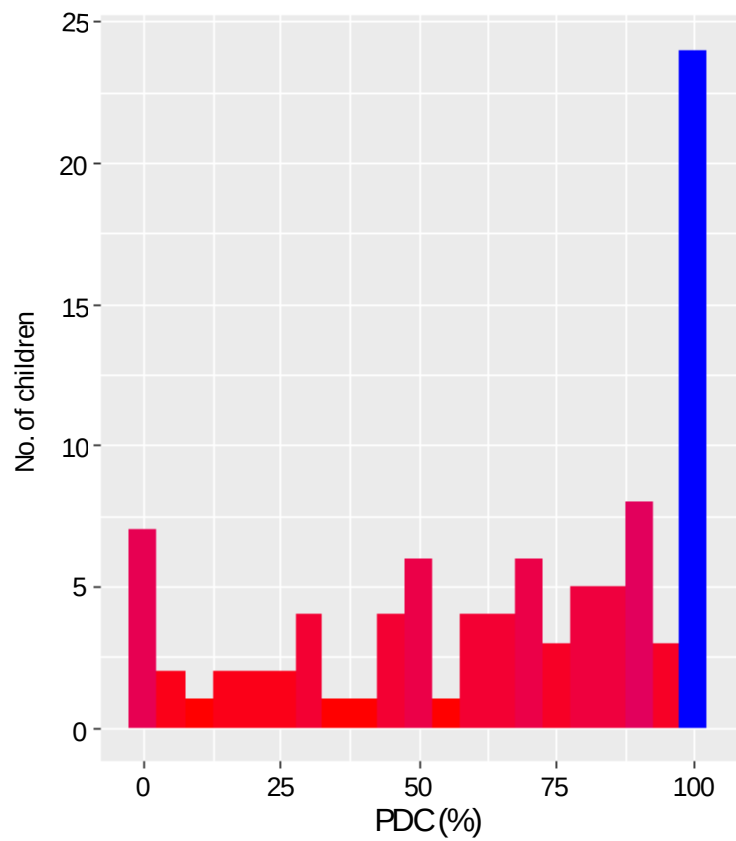
Online Supplement

eMethods

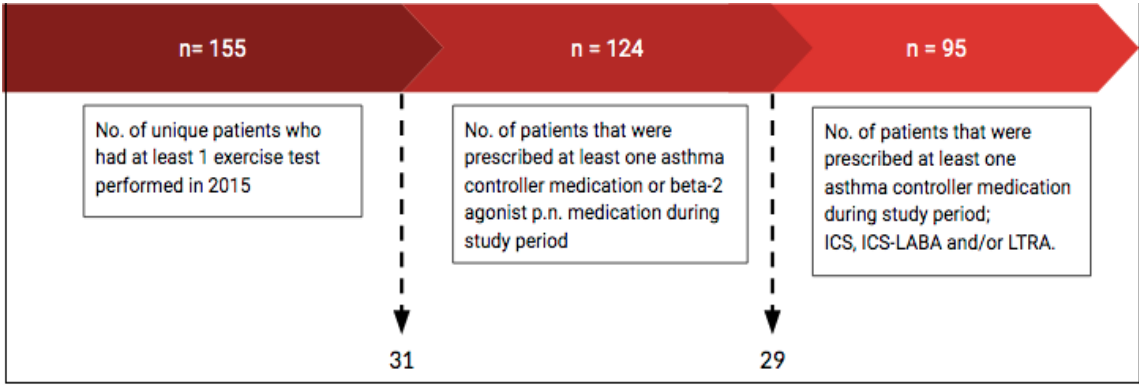
Exemplifying an advanced calculation of a single drug PDC: a physician prescribes 30 days of 2 inhalations followed by 30 days of 4 inhalations giving the patient a need of $(30 \times 2 + (30 \times 4)) = 180$ doses. The patient only filled one prescription of 120 doses covering the first dose regime of 30 days with 60 doses leaving only $(60 \text{ doses} / 4 \text{ doses per day}) = 15$ days of the second regime covered eventually resulting in a PDC of $(45 \text{ days with medical supply} / 60 \text{ days in period}) \times 100\% = 75\%$.

eFigures

eFigure 1: Histogram showing a skewed distribution of the continuous PDC outcome. Median 76% (IQR, 44-98%).



eFigure 2: Study group flow-chart.



eFigure 3: Boxplots showing the continuous PDC measurements by combinations of preventive asthma medications. A non-parametric test showed no significant differences between the groups (Kruskal-Wallis rank sum test, $p=0.8$). Seven patients were switched from ICS to ICS-LABA and one patient was prescribed both ICS, ICS-LABA and LTRA during study period were excluded leaving 87 children in the analysis.

