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To cite this article: Cristina Longo, Gillian Bartlett, Tibor Schuster, Francine M. Ducharme, Brenda MacGibbon & Tracie A. Barnett (2019): Weight status and nonadherence to asthma maintenance therapy among children enrolled in a public drug insurance plan, Journal of Asthma, DOI: [10.1080/02770903.2019.1590593](https://doi.org/10.1080/02770903.2019.1590593)

To link to this article: <https://doi.org/10.1080/02770903.2019.1590593>

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 Published online: 26 Mar 2019.

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Weight status and nonadherence to asthma maintenance therapy among children enrolled in a public drug insurance plan

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ABSTRACT

Objective: The pediatric obese-asthma phenotype is associated with poor control, perhaps because of medication nonadherence. This study aimed to assess whether weight status is associated with nonadherence in children prescribed new asthma maintenance therapies.

Methods: A historical cohort was constructed from a clinical database linking individual patient and prescription data to Quebec's prescription claims registry. Children aged 2–18 years with specialist-diagnosed asthma who were newly prescribed one of the following maintenance controllers: leukotriene receptor antagonists (LTRA); low-dose inhaled corticosteroids (ICS); medium/high-dose ICS; or combination therapy (ICS with long-acting beta-2 agonists and/or LTRA), at the Asthma Center of the Montreal Children's Hospital from 2000–2007 were included. Primary nonadherence was defined as not claiming any prescriptions, whereas secondary nonadherence was measured with the proportion of prescribed days covered (PPDC $\leq$ 50%) among primary adherers over a 6-month follow-up period. A modified Poisson regression model served to estimate the effect of excess weight (BMI $>$ 85th percentile) on primary and secondary nonadherence.

Results: Approximately one third of patients were primary nonadherers and 60% took less than 50% of prescribed therapy. Excess weight was associated with a trend toward increased risk of primary nonadherence in children newly prescribed low-dose ICS (RR 1.53, 95%CI 0.94–2.49), and of secondary nonadherence in children initiating medium/high-dose ICS (RR 1.24; 95%CI 0.98–1.59).

Conclusions: Excess weight status is a possible determinant of primary nonadherence in children initiating low-dose ICS and secondary nonadherence to higher-dose ICS regimens. This hypothesis-generating study suggests that nonadherence may be a potential contributor to higher morbidity in children with obese-asthma.

ARTICLE HISTORY

Received 7 October 2018
Revised 19 February 2019
Accepted 28 February 2019

KEYWORDS

Compliance; controller therapy; inhaled corticosteroids; leukotriene receptor antagonists; long-acting beta-2 agonists; body mass index; obesity

Introduction

Asthma is one of the most prevalent pediatric diseases in the developed world, affecting 13% of Canadian children [1]. Despite the availability of safe treatments to manage asthma symptoms, an estimated 47% to 57% of patients remain poorly controlled [2,3]. Furthermore, asthma exacerbations are a major cause of hospitalization in children, costing billions in preventable health care costs [4].

One important modifiable risk factor for poor control and higher exacerbation rates in pediatric asthma is obesity [5]. Obesity is associated with increased systemic inflammation, bronchial hyperactivity, higher

symptom expression, health care utilization, rescue medication use, and lung impairment, as well as decreased quality of life in children with asthma [6]. Moreover, the pediatric obese-asthma phenotype appears to be characterized by poor response to inhaled corticosteroids (ICS) [7], possibly due to an underlying non-eosinophilic inflammatory process, impaired lung mechanics [8], or higher treatment nonadherence [9].

Nonadherence to treatment, estimated to be between 30% and 70%, is a major contributor to asthma morbidity [10]. In children, poor adherence has been associated with age, socioeconomic status (SES), ethnicity, exposure to smoke, misbeliefs

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 Supplemental data for this article can be accessed on the [publisher's website](#).

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regarding asthma, concerns about side effects, treatment complexity, and psychosocial factors such as depression and anxiety [11,12]. While childhood obesity has been associated with lower SES, weight-induced susceptibility to anxiety, feelings of stigmatization, and depression [13,14] also have the potential to impact medication-taking behaviors in this high-risk group. Furthermore, if response to therapy is indeed suboptimal, children with obese-asthma and their parents may be less likely to follow their prescribed regimens. However, to our knowledge, no studies have investigated the association between excess weight and treatment nonadherence in pediatric asthma.

Therefore, the primary objective of this study was to evaluate if weight status is associated with nonadherence in the 6 months following the initiation of maintenance controller therapies among children with asthma. We hypothesized that asthmatic children with excess weight would have higher medication nonadherence when compared to their normal weight counterparts.

Methods

Research design

A historical cohort was constructed from a clinical Pediatric Asthma Database linked to Quebec's prescription claims registry with 15,147 visit records for 4,621 children who consulted the Montreal Children's Hospital's Asthma Center between January 2000 and December 2007. The Pediatric Asthma Database included information on sociodemographics; height and weight; asthma severity, morbidity, and control indicators; phenotype; spirometry test results; respiratory comorbidities; asthma education center referrals; environmental exposures; and maintenance therapies prescribed by the consulting specialist for each Asthma Center visit. Clinical records were merged with the Québec prescription claims registry (RAMQ), which provided follow-up data on all dispensed medications for patients enrolled in the public drug insurance plan (42% of Quebec residents) [15]. This study received approval from the CHU Sainte-Justine Research Ethics Board, Montreal Children's Hospital, Commission d'accès à l'information, and RAMQ.

Study population

The cohort included children aged 2 to 18 years with specialist-diagnosed asthma, newly prescribed one of the following asthma maintenance therapies at the

index visit: LTRA monotherapy (Step-2), low-dose ICS monotherapy (Step-2), medium/high-dose ICS monotherapy (Step-3), or ICS combination therapy, i.e. ICS/LABA, ICS/LTRA, or ICS/LABA with LTRA (Step-3/4). A diagnosis of asthma was confirmed based on spirometry testing in children aged >5 years and recurrent episodes of clinically documented wheezing or convincing parental reports of reversible airway obstruction in preschoolers as recommended by national guidelines [9,16]. Patients who were not enrolled in the public drug insurance plan at least 6 months prior to and following the index date or if they had a diagnosis of another chronic lung disease (i.e. bronchopulmonary dysplasia or cystic fibrosis) were excluded. Children were considered initiators of low-dose ICS and LTRA monotherapies if they had no claims for ICS and LTRA, respectively, in the 6 months preceding the visit date, i.e. the lookback period. The 6-month lookback period was considered sufficient to identify new users of prescribed therapy [17,18]. Initiators of medium/high-dose ICS or combination therapy were defined as children who had no claims of medium/high-dose ICS or ICS in combination with LTRA or LABA, respectively, during the lookback period. Children who had evidence of a switch in their maintenance therapy in the drug claims database within the 6 months following the index date were excluded. The index date was defined as the date at which all inclusion criteria were met. All eligible visits were included in the cohort; thus, one child may have contributed several index visits. The duration of the follow-up period was a fixed 6-month interval (182 days) following cohort entry—a period sufficiently long to accurately ascertain both primary and secondary adherence for all medications of interest, often dispensed with a 1-to 2-months' supply [19].

Outcome

Primary nonadherence was defined as a medication possession ratio (MPR) of '0', i.e. no medication dispensed for any asthma controller during the 6-month follow-up period [20]. The MPR was computed as the total number of days supplied during follow-up for each asthma controller prescribed at the index visit, divided by 182 days [19,21]. Secondary nonadherence, assessed only in children with an MPR > 0, was measured with the proportion of prescribed days covered (PPDC) both continuously and dichotomously (PPDC > 50%) [19]. The PPDC was calculated as the total number of follow-up days for which the prescribed maintenance medication(s) was dispensed

divided by the duration of the physician's prescription in days; the PPDC accounts for varying durations of physician prescriptions, which may not cover the entire follow-up period. The MPR and PDC were also considered as alternative measures of secondary non-adherence and both were examined continuously and dichotomously ($\text{MPR/PDC} \leq 50\%$). The PDC was computed as the total number of days 'covered' for which the patient was dispensed his/her prescribed therapy during follow-up, divided by 182 days [19]. Both the MPR and PPDC values were capped at 100% (see supplement for further details).

Exposures

Weight status

Using height and weight assessments documented at the index visit, the body mass index (BMI) Z-score was computed using age- and sex-adjusted WHO growth reference values [22]. BMI percentile was categorized into excess weight ($\text{BMI} > 85^{\text{th}}$ percentile), and normal weight ($\text{BMI} \leq 85^{\text{th}}$ percentile). Both dichotomous (excess weight vs. normal weight) and continuous (BMI percentile) measures were used in the analyses.

Treatment categories. From the accurate prescription and daily dose information recorded in the Pediatric Asthma Database at the index date, ICS formulations were converted into hydrofluoroalkane-propelled beclomethasone [HFA-BDP_{eq}] dose equivalents, using the Canadian Thoracic Society (CTS)'s recommended dose equivalencies by age group (for children aged <12 years: 1 mcg of HFA-BDP = 1 mcg HFA-fluticasone = 0.5 mcg Budesonide = 0.5 mcg CFC-BDP, and for children aged 12 years and older: 1 mcg of HFA-BDP = 1 mcg HFA fluticasone = 0.625 mcg BUD = 0.5 mcg CFC-BDP). These dose equivalencies were then categorized into low, medium, and high-dose ICS formulations based on the CTS age-specific cutoffs [9]. Children were then classified into four treatment categories: (1) LTRA monotherapy, (2) low-dose ICS monotherapy (i.e. ≤ 200 mcg/day [≤ 250 mcg/day if ≥ 12 years old] of HFA-BDP_{eq} measured ex-valve), (3) medium/high-dose ICS monotherapy (i.e. > 200 mcg/day [> 250 mcg/day if ≥ 12 years old] HFA-BDP_{eq} dose equivalents measured ex-valve), or (4) any combination therapy (i.e. ICS with LABA, ICS with LTRA or ICS/LABA with LTRA) [9].

Confounders and covariates

Potential confounders and covariates included: socio-demographics (age, sex, ethnicity, and income

estimated from neighborhood census data), asthma phenotype (persistent vs. seasonal/episodic), other comorbidities (atopy, upper or lower respiratory conditions), self-reported smoking in the home, number of exacerbations in the previous year (emergency department visits, hospitalizations or oral corticosteroid bursts), physicians' global assessment of asthma severity (categorized as mild, moderate, or severe based on the intensity, frequency of symptoms, and/or the amount of daily medications required to achieve control as described elsewhere) [23,24], symptom triggers, mode of drug administration (e.g. type of inhaler device), and referral to the on-site Asthma Education Center. The latter was an important variable, as the standardized education addressed asthma pathophysiology, the role of asthma medications, assessment and correction of environmental exposures, and inhalation technique as well as tools for self-assessment and self-management, underlining the importance to medication adherence [25].

Statistical analysis

Multiple imputations were performed to address missing data for BMI percentile (1.6%), ethnicity (5.1%), global assessment of asthma severity (7.8%), asthma education center referral (14.3%), smoking (24.6%), and income (20.8%) at the index date. Two modified Poisson regression models, adjusted for all covariates with robust standard errors, were used to estimate whether weight status was associated with the risk of primary nonadherence ($\text{MPR} = 0$) and with secondary nonadherence (PPDC, MPR, $\text{PDC} \leq 50\%$) for different asthma maintenance therapy regimens [26]. An adjusted multiple linear regression model was fit for each continuous indicator of secondary nonadherence, separately, with weight status as the exposure (both continuous and dichotomized) using a generalized estimating equations (GEE) with an independence working correlation structure [27]. Weight status-treatment product terms were included in all models to estimate weight-specific effects by treatment group. Sensitivity analyses included: (1) flexible modeling techniques to verify the linearity of the BMI percentile-nonadherence relationship; (2) extending the look-back period used to define asthma maintenance therapy initiators to 1 year prior to the index visit, (3) age subgroup analyses (<12 years vs ≥ 12 years). The relative risks of primary nonadherence and secondary nonadherence for weight status were summarized in a forest plot. Clinical outcomes (medical consultations, emergency department visits, and hospitalizations for

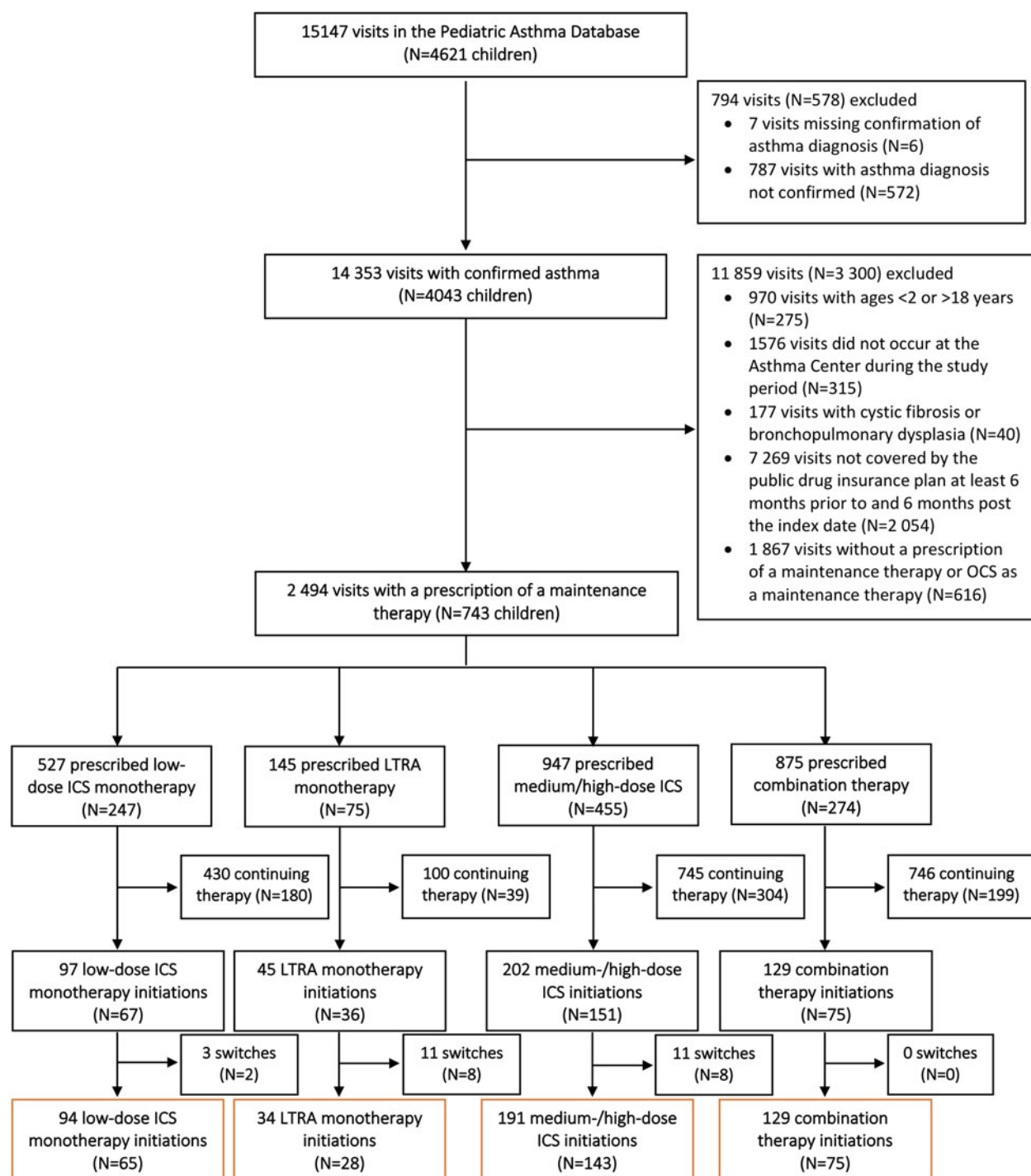


Figure 1. Study population flow chart.

asthma) were also described by nonadherence and weight groups. Data management and multiple imputations were performed with SAS version 9.4, while all analyses were conducted with R Studio version 1.0.44. We estimated that a sample size of 189 patients per treatment group would be required to detect a 10% difference in proportions of primary and secondary nonadherers between weight groups, setting power to 80% and a type I error of 0.05.

Results

The study cohort included 94 low-dose ICS, 34 LTRA, 191 medium/high-dose ICS, and 129 combination therapy (ICS-LABA or ICS-LTRA) prescription initiations (Figure 1). Children with excess weight appeared generally older, were more frequently non-Caucasians and of lower income, and reported exercise as a common symptom trigger. They were also more

Table 1. Baseline characteristics of study population.

Characteristic	Normal weight 244 Person-visits	Excess weight 204 Person-visits
Demographics		
Female (N, %)	94 (38.5)	76 (37.3)
Age in years ($\bar{x} \pm SD$)	8.4 $\pm$ 4.1	9.5 $\pm$ 3.8
Neighborhood income ($M \pm IQR$)	39300 $\pm$ 17346	37514 $\pm$ 17139
Ethnicity (N, %)		
Caucasian	158 (64.8)	104 (50.1)
African American	45 (18.4)	36 (17.6)
Asian	22 (9.0)	26 (12.7)
Other	19 (7.8)	38 (18.6)
Smoking in the home (N, %)	78 (32.0)	54 (26.5)
Prior morbidity		
Number of exacerbations for asthma in preceding year (N, %)		
Acute care visits		
0	37 (15.2)	38 (18.6)
1	54 (22.1)	49 (24.0)
2	40 (16.4)	39 (19.1)
3	113 (46.3)	78 (38.3)
Hospital admissions		
0	209 (85.7)	177 (86.8)
1	35 (14.3)	27 (13.2)
Oral corticosteroids		
0	161 (66.0)	142 (69.6)
1	43 (17.6)	39 (19.1)
2	40 (16.4)	23 (11.3)
Index visit		
Asthma phenotype (N, %)		
Episodic/seasonal	94 (38.5)	74 (36.3)
Persistent	150 (61.5)	130 (63.7)
Triggers (N, %) ^a		
Viral	183 (89.7)	148 (72.5)
Allergic	101 (41.4)	90 (44.1)
Exercise	106 (43.4)	119 (58.3)
Temperature	31 (12.7)	35 (17.2)
Global assessment of severity (N, %)		
Mild	178 (73.0)	141 (69.1)
Moderate-severe	66 (27.0)	63 (30.9)
Asthma-related comorbidities (N, %) ^a		
None	120 (49.2)	104 (51.0)
Atopy ^b	95 (38.9)	82 (40.2)
Chronic upper or lower respiratory conditions ^c	29 (11.9)	18 (8.8)
Asthma management		
Prescribed treatment step at index date (N, %)		
LTRA monotherapy	21 (8.6)	13 (6.4)
Low-Dose ICS monotherapy	57 (23.4)	37 (18.1)
Medium/High-dose ICS monotherapy	103 (42.2)	88 (43.1)
ICS combination therapy	63 (25.8)	66 (32.4)
Inhaler device (N, %)		
Metered dose inhaler (with or without aerochamber)	134 (54.9)	111 (54.4)
Diskus/Diskhaler	7 (2.9)	4 (2.0)
Turbohaler	52 (21.3)	66 (32.3)
Other	51 (20.9)	23 (11.3)
Referred to the asthma education center (N, %)	76 (31.1)	46 (22.5)

^aCategories are not mutually exclusive.^bAtopy includes eczema, allergic rhinitis, conjunctivitis, and food allergies.^cChronic upper or lower respiratory tract comorbidities comprises one of the following: history of recurrent otitis, sinusitis, pneumonia, gastroesophageal reflux disease, obstructive sleep apnea, bronchopulmonary aspergillosis, vocal cord dysfunction, or dysphagia.

frequently prescribed ICS combination therapy with fewer referred to the Education Center, with similar morbidity in the previous year (Table 1).

Overall, 126 (28%) and 196 (61%) children were considered to be primary and secondary nonadherers, respectively. The prevalence of primary and secondary nonadherence was 27% and 57%, respectively, among normal weight patients, increasing to 29% and 66% in those with excess weight. Combining all weight

categories, the overall proportion of primary nonadherers was highest in those prescribed low-dose ICS (48%) when compared to other therapies (21–26%), while secondary nonadherence was most prevalent in children initiating medium/high-dose ICS (65%) and/or combination therapies (74%) than in those initiating low-dose ICS or LTRA (29–48%) (Table 2).

In general, children were more likely to be primary nonadherent to low-dose ICS (RR 3.01),

Table 2. Relative risks of primary and secondary nonadherence for different maintenance therapies by weight status.

Type of nonadherence/ maintenance therapy	All weight categories		Normal weight		Excess weight	
	No. of nonadherers/ person-visits (%)	RR ^a (95% CI)	No. of nonadherers/ person-visits (%)	RR ^a (95% CI)	No. of nonadherers/ person-visits (%)	RR ^a (95% CI)
Primary nonadherence (MPR = 0)						
Combination therapy	33/129 (26)	2.23 (0.97-5.10)	18/63 (29)	2.54 (0.88-7.39)	15/66 (23)	1.84 (0.56-6.05)
Medium/high-dose ICS monotherapy	41/191 (21)	1.49 (0.66-3.37)	22/103 (21)	1.57 (0.94-4.81)	19/88 (22)	1.39 (0.46-4.22)
Low-dose ICS monotherapy	45/94 (48)	3.01 (1.37-6.62)	23/57 (40)	2.61 (0.86-7.92)	22/37 (59)	3.74 (1.25-11.10)
LTRA monotherapy ^b	7/34 (21)	1.00 (ref)	4/21 (19)	1.00 (ref)	3/13 (23)	1.00 (ref)
Secondary nonadherence (PPDC ≤ 50%)						
Combination therapy	71/96 (74)	1.62 (1.04-2.52)	32/45 (71)	1.36 (0.86-2.13)	39/51 (76)	2.42 (1.04-5.64)
Medium/high-dose ICS monotherapy	98/150 (65)	1.38 (0.90-2.11)	49/82 (60)	1.07 (0.67-1.69)	49/68 (72)	2.20 (0.97-5.00)
Low-dose ICS monotherapy	14/49 (29)	0.65 (0.37-1.16)	11/34 (32)	0.62 (0.34-1.15)	3/15 (20)	0.64 (0.19-2.23)
LTRA monotherapy ^b	13/27 (48)	1.00 (ref)	9/17 (53)	1.00 (ref)	4/10 (40)	1.00 (ref)

^aModels adjusted for age, sex, ethnicity, average neighborhood income, asthma phenotype, comorbidities, smoking in the home, number of emergency department visits, hospitalizations or oral corticosteroids bursts in the preceding year, physicians' global assessment of asthma severity, environmental exposures, mode of administration (type of device), and referral to the asthma education center. Medication possession ratio (MPR); Proportion of prescribed days covered (PPDC).

^bReference category.

medium/high-dose ICS (RR 1.49), and combination therapy (RR 2.23) than those receiving a new prescription of LTRA monotherapy at the index visit (Table 2). A trend toward a higher risk of primary nonadherence for children with excess weight was observed when prescribed low-dose ICS (RR 1.53, 95%CI 0.94-2.49), but not LTRA (RR 1.04, 95%CI 0.24-4.48), medium/high-dose ICS (RR 0.92, 95%CI 0.50-1.70), or combination therapies (RR 0.73, 95%CI 0.37-1.45) (Figure 2).

Among those filling at least one prescription, children who initiated low-dose ICS were at an overall lower risk of secondary nonadherence than those using LTRA monotherapy, irrespective of weight; however, a higher risk was observed for medium/high-dose ICS and combination therapy initiators (Table 2). Estimates remained consistent with alternative measures of secondary nonadherence such as the MPR or PDC (Supplemental Table E-1). Excess weight showed a trend toward an increased average risk of secondary nonadherence (RR 1.09; 95%CI 0.92-1.30) for all treatments and, more specifically, to medium/high-dose ICS (RR 1.24; 95%CI 0.98-1.59) and combination therapy (RR 1.07; 0.84-1.37), although both did not reach statistical significance. Secondary nonadherence to low-dose ICS and LTRA were on average lower in children with excess weight (ICS RR 0.63, 95%CI 0.39-1.82; LTRA RR 0.60, 95%CI 0.25-1.46; Figure 2). Similar associations were observed with the alternative measures of secondary nonadherence in children with excess weight

(Supplemental Table E-1). Clinical outcomes did not appear to differ by weight status, but a higher proportion of children with a PPDC ≤ 50% had more emergency department or hospital visits for asthma than those with a PPDC > 50% over the 6-month follow-up period (Supplemental Tables E-2a and E-2b).

Whether analyzed continuously or dichotomously, excess weight was consistently associated with a trend toward an increased risk of secondary nonadherence in medium/high-dose ICS monotherapy and combination therapy initiators, and with an average lower risk of nonadherence in those initiating low-dose ICS and LTRA monotherapies (Supplemental Table E-3). Estimates were similar when using alternative measures of secondary nonadherence. Conclusions were consistent when applying a 1-year lookback period for both primary (data not shown) and secondary nonadherence (Supplemental Table E-4). Flexible modeling suggested a possible non-linear relationship between continuous BMI percentile and secondary nonadherence in those initiating low-dose ICS, medium/high-dose ICS, and combination therapy (data not shown). The age subgroup analysis suggested that the increased risk for primary nonadherence to low-dose ICS among children with excess weight compared to those with normal weight is driven by the <12 years age group, although no firm conclusions can be drawn for either primary or secondary nonadherence outcomes due to wide confidence intervals (Supplemental Tables E-5 and E-6).

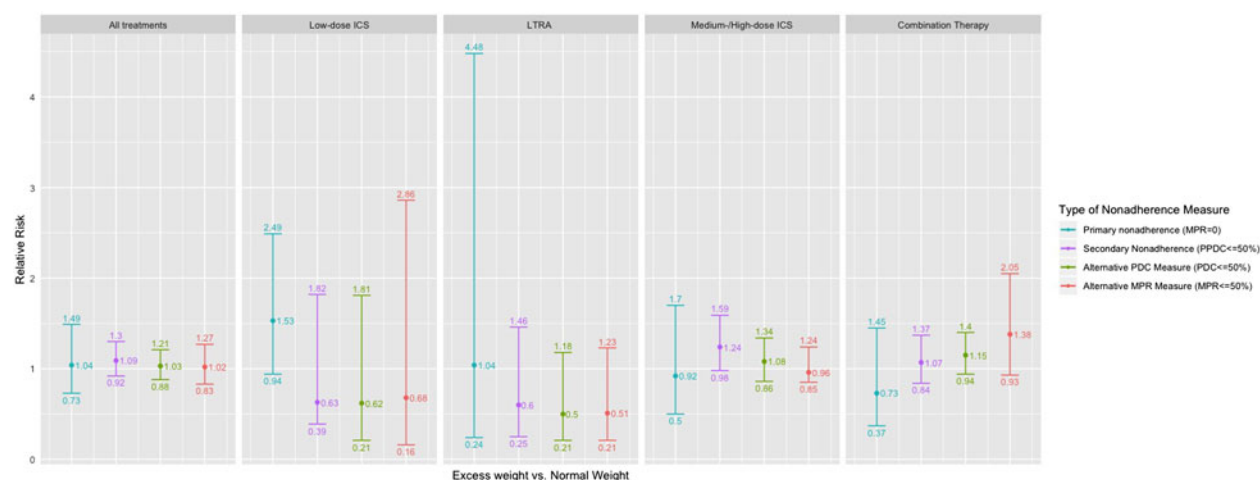


Figure 2. Relative risks of nonadherence for excess weight vs. normal weight by prescribed asthma maintenance therapy. Primary nonadherence was defined as an MPR of 0. Secondary nonadherence (PDC $\leq$ 50%, MPR $\leq$ 50%, or PPDC $\leq$ 50%) was evaluated among children who filled at least one prescription during follow-up.

Discussion

In this cohort of children initiated on a new daily maintenance therapy, nonadherence was quite common; a third of patients did not fill their initial prescriptions, while 60% took less than 50% of prescribed therapy. Overall, primary nonadherers were most often children initiated on low-dose ICS, whereas secondary nonadherence was elevated (reaching up to 72%) for those prescribed higher-dose ICS and combination therapy compared to monotherapy maintenance regimens. A trend toward a higher risk of primary nonadherence was observed in children with excess weight prescribed a new low-dose ICS monotherapy. Excess weight was also associated with secondary nonadherence; specifically, children with higher BMI percentiles were more often nonadherent to medium/high-dose ICS or combination therapy regimens.

To our knowledge, our study is the first to report the prevalence of primary nonadherence (28%) in children, which was slightly higher than previously reported in adults [21,28]. The concern about growth suppression as a possible ICS side effect [29], which can be highly prevalent in children, may have influenced parents' hesitation to fill a first ICS prescription leading to a higher proportion of primary nonadherers in our pediatric cohort [30]. Our overall proportion of secondary nonadherers (60%) was consistent with other pediatric clinical studies, with average nonadherence rates to ICS ranging between 50% and 86% [31–33], with the highest prevalence observed in children experiencing frequent and severe exacerbations [31].

Three studies, two in adults and one in children, explored primary adherence to different asthma

therapies, although none evaluated BMI status [21,28]. In a study of 69,652 adults with asthma, primary nonadherence to ICS monotherapy (all doses) was less (14%) than to LTRA (20%) or ICS/LABA combination therapy (18%) [21]. Williams and colleagues found primary nonadherence to ICS monotherapies in adults with asthma was approximately 8% [28]. In the pediatric study, Ducharme and colleagues reported that 14% and 22% of the 530 children prescribed low-dose ICS and LTRA monotherapies, respectively, never filled their prescription during follow-up [34]. In our cohort, children prescribed ICS-based therapies were at the highest risk of not filling their initial prescription compared to those initiated on LTRA monotherapy. Possible reasons for the divergence of our overall primary nonadherence estimates from other studies relates to our specific pediatric population and the different lookback and follow-up periods used to define treatment groups and primary nonadherence. Importantly, excess weight was associated with a trend toward a higher risk of not filling a first low-dose ICS prescription when compared to normal weight, while this was not observed for other regimens. One reason for this finding may be the concern about ICS-associated weight gain [35]; a worry perhaps relieved in more severe patients who were stepped up to a higher-dose of ICS or combination therapy because this side effect had not previously occurred while on low-dose ICS.

The few adult studies that explored excess weight as a possible predictor of secondary nonadherence reported conflicting findings [36–38]. In a large population survey involving 1.7 million Californian adults, overweight patients reported that they were less adherent to their daily controller therapies than their

normal weight counterparts (OR 0.75, 95%CI 0.57–0.98) [36]. Conversely, in a population-based cohort including 1186 Danish adult asthma patients, self-reported use and adherence to any asthma medication did not significantly differ between weight categories [37]. Another cross-sectional chart review of 182 adults with difficult-to-control asthma showed that mean BMI did not significantly differ between patients prescribed inhaled combination therapy who displayed good versus poor adherence (prescription fill rate >50%) [38]. Several design differences may explain the apparent divergence between our findings and prior literature. First, we focused on children, instead of exclusively or predominantly adults, who were newly initiated on different asthma maintenance therapies. Second, in addition to estimating whether weight status was associated with overall nonadherence, we also assessed the weight status-nonadherence relationship by treatment step. Lastly, we used objective rather than self-reported measures of nonadherence, which were characteristics of the former two studies. Our study appears to be the first to demonstrate that weight status may be associated with both primary and secondary nonadherence to different treatment in children with specialist-diagnosed asthma. It is also the first to report associations by treatment step within and across weight categories. Specifically, we observed a positive trend between excess weight and secondary nonadherence in those initiating higher-dose ICS and combination therapies, and an inverse trend with nonadherence to low-dose ICS or LTRA monotherapies.

While nonadherence is an important cause of poor control, morbidity, and suboptimal treatment response (as shown by the higher proportion of moderate-to-severe asthma exacerbations in children taking $\leq 50\%$ of their prescribed medications compared to those taking >50%), our findings suggest an even higher prevalence of secondary nonadherence in overweight children with more severe asthma initiating intensive therapy (higher-dose ICS or combination therapy). These results may be explained by weight-related differences in: perceived symptom severity [39]; treatment inefficacy [7,40]; beliefs about weight gain as a possible treatment side-effect [41]; and confusion about the cause of symptoms, predominantly dyspnea (obesity vs. asthma) [10]. In addition, perhaps a higher level of anxiety related to weight stigmatization and exercise performance at school [42] may negatively influence adherence to intense or complex therapy regimens in these children [33,43].

The strengths of this cohort study include availability of data on several clinical variables that may have influenced treatment adherence (such as severity), confirmation of asthma diagnosis by a pediatric asthma specialist (rather than self-report), as well as access to diligent documentation in the medical chart of the prescribed drug, strength, posology of asthma therapy and importantly whether it was prescribed for daily vs intermittent use. However, we also acknowledge the following study limitations. First, prescribing and asthma management practices may have evolved since data collection for this cohort (2000–2007); however, we do not expect these changes to have impacted the underlying hypothesized mechanism of the excess weight-treatment nonadherence relationship in children. In fact, the prevalence of childhood obesity has increased significantly since then, making our findings potentially more relevant to today's clinical context. Second, surrogate measures of medication use (PPDC, PDC, MPR) may underestimate secondary nonadherence as patients may fill their prescriptions without consuming the medication as prescribed and, in the absence of daily electronic monitoring, we could not rule out the possibility of intermittent use, although these patients would still be considered nonadherent to their prescribed daily medication therapies [44]. Outcome misclassification for secondary nonadherence may have been magnified using indices calculated over 6 months for low-dose ICS, i.e. when the expected duration of the initial drug claim (2–3 month supply) covers a larger proportion of the follow-up period than LTRA (1 month supply). This may underestimate the true prevalence of nonadherence for low-dose ICS. We expect, however, any outcome misclassification to be nondifferential across weight status, possibly leading to a bias toward the null. Third, in some patients, step-up therapy was prescribed to children without evidence of a first trial of monotherapy, which may have been due to the severity and poor control at the index visit or the lack of awareness of poor adherence from prior prescribed monotherapy not divulged by patients. The 6-month lookback period used to define treatment initiators may have led to the inclusion of patients who were not 'true' initiators, but rather poorly adherent or intermittent users, which may have influenced their decision to fill their initial prescriptions. However, the sensitivity analyses extending the lookback period to 1 year supported the appropriateness of our definition. Fourth, we attempted to reduce outcome misclassification by excluding patients who had clear evidence of a step-up in therapy during follow-up. Moreover, the

possibility of a step-down in therapy was likely minimized by our relatively short follow-up period as guidelines recommend reevaluating the asthma management strategy at 3–6 months following the initiation of a new maintenance therapy [45]. Fifth, the Pediatric Asthma Database did not contain accurate data on reversible airway obstruction at the index visit as physicians did not routinely document the specific criteria used to confirm asthma diagnoses. Asthma misdiagnosis, although rates have been shown to be nondifferential across weight status in children and unlikely to occur in tertiary care settings where physicians have unlimited access to required testing [46], may have biased findings toward the null. Lastly, because we aimed to explore the association between excess weight and nonadherence for different asthma maintenance therapies prescribed at the index date, further stratification of the sample by treatment led to imprecise estimates reflected by the relatively wide confidence intervals. As such, we were not able to draw firm conclusions from the age subgroup analyses or explore whether medication nonadherence led to poor clinical outcomes in those with higher weight status. We emphasize that the present study should be considered as hypothesis-generating and suggest that these results be reproduced and pursued in larger prospective studies.

Conclusions

Our findings have important implications for clinical practice. Both primary and secondary nonadherence to daily maintenance therapies is notably prevalent in children with asthma and is even more pronounced in those with excess weight. Specifically, when compared to their normal weight counterparts, children with excess weight and their parents may be less likely to initiate a low-dose ICS maintenance therapy, the cornerstone of asthma management, even when prescribed by a pediatric asthma specialist. Among those filling their initial prescription, children with excess weight may be more likely to be nonadherent to medium/high-dose ICS and combination therapies than normal weight children. Whether this increase in risk for primary and secondary nonadherence to ICS-based maintenance therapies may be the result of treatment non-response or other reasons in children with the obese-asthma phenotype remains to be further investigated. Specifically, the results support the importance of objectively evaluating adherence to asthma medications in the event of poor treatment response as well as addressing barriers of, and

facilitators to, adherence to prescribed ICS therapy regimens with all children and parents. Further larger research studies are warranted to confirm our findings in different age groups and to explore the behavioral- and treatment-associated factors that may differentially lead to poorer asthma medication adherence, and ultimately worse clinical outcomes, in children with excess weight compared to their normal weight counterparts.

Acknowledgements

The authors would like to thank the Fonds de la Recherche du Québec en Santé (FRQ-S) for the infrastructure support provided to the Research CentreCenter of the CHU Sainte-Justine, the doctoral scholarship awarded to Cristina Longo, and the senior career award to Tracie A. Barnett. They would also like to acknowledge the curators of the Montreal Pediatric Asthma Database, led by Dr. Francine Ducharme, for allowing access to this comprehensive database, McGill's Family Medicine Graduate Programs, and the Research Institute of CHU Sainte-Justine for their support.

Disclosure statement

Francine M. Ducharme has received research funds from Merck Canada, unrestricted funds from Boehringer Ingelheim, Takeda, Novartis, and Glaxosmithkline, and was an consultant to Merck and Boehringer Ingelheim. All other authors have no potential conflicts of interest to disclose.

Funding

This study was funded by the Fonds de la Recherche du Québec en Santé (FRQ-S).

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ONLINE SUPPLEMENT

S1. Measures Used to Define Treatment Nonadherence

The medication possession ratio (MPR) and MPR-related measures, such as the Proportion of Days Covered (PDC), are the most commonly used descriptive statistics for overall medication use and (non)adherence, respectively, in the current literature (1). A relatively new measure of patient (non)adherence, the proportion of prescribed days covered (PPDC), was developed by Blais and colleagues to account for different physician prescribing patterns, which is particularly common in asthma (2). The differences between these measures are described in more detail below.

The MPR was computed as the total number of days for which each prescribed asthma therapy at the index visit was dispensed to the patient divided by the fixed 182-day follow-up period (1,3). If the prescribed maintenance therapy required the dispensation of more than one medication (e.g. combination therapy), the numerator of the MPR was calculated as the sum of the total number of days supplied for each medication dispensed, divided by the number of distinct medications prescribed at the index visit. In the case of multiple medications, the MPR does not distinguish when the medications are dispensed and if the claims overlap. For example, let us suppose a patient was prescribed ICS/LTRA combination therapy at the index visit and he/she claims the 30-day ICS prescription but not the 30-day LTRA prescription at the community pharmacy on that same day. Let us further suppose that the patient claims the LTRA prescription 10 days following the dispensation of the ICS and the follow-up period was fixed at 30-days. In this scenario, although the patient was not adherent to the combination therapy regimen for the first 10 days following the index visit, the MPR would have been 100% for that patient, thus underestimating nonadherence, while accurately measuring overall use of the maintenance therapy.

The PDC was calculated using the total number of days 'covered' with all prescribed medications at the index date during follow-up, divided by 182 days (3). A covered day would be a day during follow-up in which all the drugs prescribed at the index date are held simultaneously by the patient (4). In the previous example, the patient only held both ICS and LTRA prescriptions simultaneously for 20 out of the 30-day follow-up period; thus, the PDC for this patient would have been 67% (4). For this reason, the PDC reflects the overall adherence to the prescribed asthma maintenance therapy.

The PPDC was computed as the total number of days for which the asthma maintenance therapy was covered, i.e. the same numerator as the PDC, divided by the number of days for which the drug was prescribed by the physician (2,5,6). This measure is useful when the duration and number of refills commonly vary between physician prescriptions (5). For instance, in the previous example, if we extended the follow-up period to 60 days, but the patient's prescription did not allow for any refills for the 30-day ICS and LTRA prescriptions, the patient must wait to consult with a physician in order to receive another prescription. Therefore, the lack of ICS and/or LTRA dispensations during this waiting period would be wrongfully classified as nonadherent days throughout follow-up for the MPR and PDC summary measures. The PPDC addresses this issue by substituting the fixed follow-up period (182 days) with the expected physician-prescribed duration in the denominator.⁵ Going back to the example, even if the follow-up period was 60-days and the patient covered 50% of the follow-up period, the PPDC for this patient would have been 100% since the patient adhered to the prescription provided to him/her by the physician at the index visit.

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