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Weighing in on asthma: Insights on BMI, magnesium, and hospitalizations from the Ohio Pediatric Asthma Repository

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ABSTRACT

Objective: Little is known about weight status and its effects on clinical course during hospitalization for asthma exacerbation. We sought to evaluate associations between weight status, specifically body mass index (BMI), with inpatient clinical course and clinical history.

Methods: We retrospectively analyzed data from 2012 to 2013 on children hospitalized for asthma exacerbation in a state-wide longitudinal cohort, the Ohio Pediatric Asthma Repository. We examined BMI continuously (z scores) and categorically, comparing overweight and obese (Ov/Ob) to non-overweight and non-obese (nOv/nOb) children. We used linear mixed models controlling for site effects to determine if BMI was related to length of stay, as determined by physiologic readiness for discharge (PRD), defined as time to albuterol spaced every 4 h, need for nonstandard care or clinical history.

Results: Across six hospitals, 874 children were included in analyses. BMI was positively associated with PRD ($p=.008$) but this increase was unlikely to be clinically significant. Ov/Ob children were more likely than nOv/nOb to require nonstandard care with repeat magnesium dosing in intensive care after dosing in the emergency department (OR = 3.23, 95%CI 1.39–7.78). Hospitalization in the year prior to enrollment was positively associated with BMI percentile (73.3 vs. 66.0, $p=.028$). Sleep disordered breathing was also associated with higher BMI percentile (78.2 vs. 65.9; $p=.0013$).

Conclusions: Ov/Ob children had similar PRD to nOv/nOb children and were prone to repeat magnesium dosing. Previous hospitalization for exacerbation was positively associated with increasing BMI percentile. Additional research should investigate differential magnesium use by weight status, quantifying risks and benefits.

Abbreviations: BMI: body mass index; ED: emergency department; ICU: intensive care unit; Int/Mild: intermittent/mild; IV: intravenous; Mod/Sev: moderate/severe; nOv/nOb: non-overweight and non-obese; Ov/Ob: overweight and obese; OPAR: Ohio Pediatric Asthma Repository; OSA: obstructive sleep apnea; PRD: physiologic readiness for discharge; SDB: sleep disordered breathing

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Introduction

Obesity and asthma are substantial problems among US children, with approximately 20% of children being obese (1), and more than 6 million children suffering from asthma (2). Obesity and asthma commonly co-occur in children (3, 4). The underlying

mechanisms behind this association are not completely understood (5, 6). Heavier children tend to have more severe asthma (7), poorer asthma control, more frequent exacerbations (8, 9), including emergency departments (ED) visits (10, 11), greater likelihood of hospital admission (12), and poorer response

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to inhaled steroid therapy (13, 14). However, few studies have investigated differences in clinical course according to weight status in children during exacerbations requiring admission, and multiple factors associated with weight status could affect clinical course during admission for exacerbation. Increased perception of dyspnea (15) and symptom intensity (16) could lead to inaccurate assessments or nonstandard care, and comorbidities such as sleep disordered breathing (SDB) may prolong length of stay (17). Studies addressing asthma in hospitalized children in the context of weight have been done among small populations, as single-center studies, or via administrative databases (17–21). This is a notable gap in the literature, as differences in asthma phenotype by weight may persist during hospitalization, and optimal treatment strategies may differ for non-overweight versus overweight or obese children.

Given the rising cost of hospitalization for asthmatic children (>\$1.5 billion/year) (22), the overwhelming disease burden (2, 23) and persistent problems with obesity (1), it is necessary to explore the role of obesity in hospitalizations for asthmatic children. The objective of this study was to evaluate associations between body mass index (BMI) with inpatient clinical course during pediatric asthma hospitalization, and clinical history, using a novel state-wide, multi-center database, the Ohio Pediatric Asthma Repository (OPAR) (24). We hypothesized that overweight and obese (Ov/Ob) children would have longer time to physiologic readiness for discharge (PRD), and more often require nonstandard care (interventions used in severe exacerbations), compared to non-overweight, non-obese (nOv/nOb) children.

Methods

Subject identification and eligibility

OPAR is a prospective study recruiting children hospitalized for asthma exacerbation at the six major Ohio children's hospitals (24). Children aged 2–17 years old hospitalized between December 2012 and September 2013 for asthma, wheezing, or reactive airway disease with a discharge diagnosis of asthma, and who had height and weight obtained during hospitalization were included in this analysis. We excluded patients with BMI z score >4 or <-4 , and children hospitalized less than 2 h, as this was inconsistent with typical exacerbations (Figure 1). Parental permission was obtained and we obtained assent in children 7 and older. A centralized Institutional Review Board at Cincinnati Children's Hospital Medical Center approved the study.

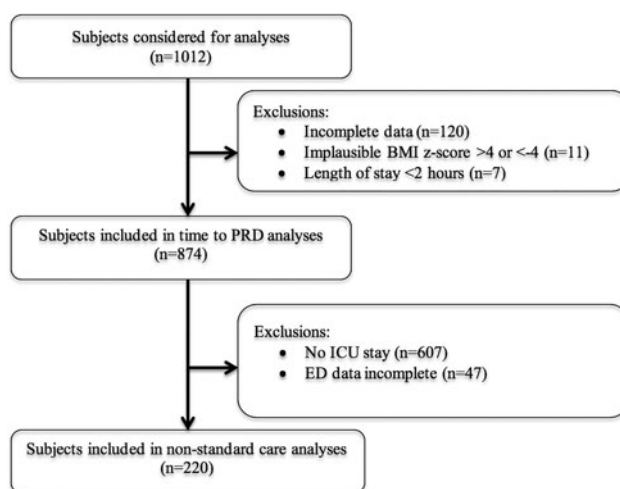


Figure 1. Derivation of study population.

Questionnaires and data collection

Parents completed written questionnaires regarding symptom history, chronic asthma severity, and triggers (24). Chronic asthma severity was evaluated by assessing impairment and risk of asthma hospitalizations, according to the Expert Panel Review 3 (25). We developed a four-category variable combining chronic asthma baseline severity based on parental-reported symptoms (intermittent/mild persistent or moderate/severe persistent) and risk of hospitalization based on parental report of hospitalization for asthma in last year as low (no hospital stay) or high (had ≥ 1 hospital stay) (24). We also examined parental report of prior year asthma hospitalization independently given reported links of hospitalization with weight status (12). Snoring frequency and physician diagnosis of obstructive sleep apnea (OSA) or SDB were also obtained through parental report. For this analysis, SDB was defined as snoring >2 nights per week, or parental report of physician diagnosis of OSA or SDB. Our definition of SDB was developed for the purpose of this study and has not been validated. Study staff collected medications administered, care practices and timing of admission and discharge, via chart review.

Weight status

We determined weight status according to BMI percentiles for age and z scores using the 2000 Centers for Disease Control growth charts. BMI% was classified into underweight (<5 th percentile), healthy weight (5th to <85 th percentile), overweight (85th to <95 th percentile), and obese (≥ 95 th percentile) (26). We examined weight status both dichotomously,

combining overweight and obese (Ov/Ob, ≥ 85 th percentile) and non-overweight and non-obese (nOv/nOb, < 85 th percentile), and continuously using z scores.

Clinical course

Each OPAR site provided care according to their institutional policies; asthma therapy was not standardized across hospitals. We defined physiologic readiness for discharge (PRD) as admission time to the inpatient unit to the time when albuterol treatments were spaced every 4 h (q4h). If a subject was discharged prior to q4h spacing, PRD was the time between admission to the inpatient unit and discharge. We defined nonstandard care by considering interventions often used in severe exacerbations among children admitted to the intensive care unit (ICU, $n = 220$, [Figure 1](#)). ICU admission alone was thought to be insufficient to determine if nonstandard care occurred given variability across sites in ICU admission practices. We defined nonstandard care as the receipt of any of the following: continuous albuterol, intravenous (IV) magnesium, respiratory support beyond nasal cannula (high flow nasal cannula, continuous positive airway pressure, and biphasic positive airway pressure), chest radiograph, ipratropium, and IV steroids. We excluded intubation given its deviation from typical asthma care and extremely low frequency in this subset. We anticipated we would not be able to draw valid conclusions about this subpopulation given the rarity of intubation.

Analysis

Given the skewed distribution, PRD was log transformed. BMI z scores were used for analyses and back-transformed to BMI percentiles. We compared the proportions of children that were nOv/nOb and Ov/Ob for each site using a chi-square test and examined bivariate associations between BMI and clinical history using mixed models with hospital as a random effect. Patients requiring nonstandard care were compared to those who did not using chi-square tests.

Physiologic readiness for discharge

To test the hypothesis that PRD would be associated with BMI z score, we used mixed models with PRD as the outcome, hospital as a random effect, and BMI z score as a predictor. Covariates included age, sex, insurance status, ICU stay, care practices (pulse

oximetry [continuous versus spot checks] and type of provider performing albuterol weaning assessments), and interventions (steroids, continuous albuterol, chest radiograph, ipratropium). Covariates not reaching marginal significance were removed. SDB was also considered as a covariate as SDB and obesity commonly co-occur in children with asthma ([27](#)), and SDB may prolong hospitalization ([17](#)). However, this was not significant and was not included in the final model. We included chronic asthma baseline severity and risk in the final model given clinical relevance.

Nonstandard care

Using linear mixed models, we evaluated the relationship between BMI z score and each nonstandard care intervention (continuous albuterol, ipratropium, magnesium, respiratory support, IV steroids, and chest radiograph) separately, accounting for age, sex, insurance status, and hospital. We determined whether an intervention was never received, received only in the ED, received only in the ICU, or received in both the ED and ICU. Interventions received in both locations, as compared to those received only in the ED, were considered evidence of nonstandard care when associated with BMI z score.

Care practices and interventions

We used linear mixed models with hospital as a random effect and with BMI z score as the outcome for bivariate screening between BMI and care practices (pulse oximetry, type of provider performing weaning assessments), ICU stay, and medical interventions (steroids, continuous albuterol, chest radiograph, ipratropium). An $\alpha = 0.05$ was considered significant for all analyses.

Results

Population characteristics

Eight hundred seventy-four patients ages 2–17 years with height and weight data available were included, after excluding 120 patients with missing data, 11 patients with implausible BMI z scores, and 7 patients with length of stay less than two hours ([Figure 1](#)). Most children excluded for missing data did not have information available on height and/or weight (112/120, 93%). Children with missing data were more likely to be younger in age than those included in analyses. Most patients were black, male and the median age was 6.0 years. Most patients had public insurance ([Table 1](#)).

Table 1. Sample characteristics.

	Physiologic readiness for discharge (PRD) sample						
	Total <i>n</i> = 874 <i>n</i> (%)	Non-overweight/ Non-obese <i>n</i> = 541 <i>n</i> (%)	Overweight/ Obese <i>n</i> = 333 <i>n</i> (%)	<i>p</i>	Odds ratio Overweight/ Obese	95% Upper confidence limit	95% Lower confidence limit
Age (years)				<.0001			
2–4	323 (37.0)	232 (42.9)	91 (27.3)		0.45	0.28	0.72
5–12	457 (52.3)	259 (47.9)	198 (59.5)		0.87	0.56	1.36
13–17	94 (10.8)	50 (9.2)	44 (13.2)		1		
Sex				.067			
Male	522 (59.7)	336 (62.1)	186 (55.9)		0.77	0.58	1.02
Female	352 (40.3)	205 (37.9)	147 (44.1)		1		
Race				.48			
Black	454 (51.9)	276 (51.0)	178 (53.5)		1.10	0.84	1.45
Not black	420 (48.1)	265 (49.0)	155 (46.5)		1		
Insurance				.12			
Private	217 (24.8)	144 (26.6)	73 (21.9)		0.77	0.56	1.07
Public	657 (75.2)	397 (73.4)	260 (78.1)		1		
Baseline asthma severity				.0021			
Intermit mild/high risk	143 (17.7)	100 (20.0)	43 (14.0)		0.83	0.54	1.28
Mod severe/high risk	206 (25.5)	107 (21.4)	99 (32.2)		1.79	1.24	2.59
Mod severe/low risk	170 (21.1)	103 (20.6)	67 (21.8)		1.26	0.85	1.87
Intermittent mild/low risk	288 (35.7)	190 (38.0)	98 (31.9)		1		
Sleep disordered breathing				.00025			
No	529 (70.8)	350 (75.6)	179 (63.0)		0.55	0.40	0.76
Yes	218 (29.2)	113 (24.4)	105 (37.0)		1		

Unadjusted associations of BMI, demographics, asthma severity, and SDB

More than one-third of children in our study sample were overweight (16.6%) or obese (21.5%). Most children in the sample were of healthy weight (56.1%) and few children were underweight (5.8%). The median BMI percentile for the entire sample was 71.7, the proportion of overweight and obese children was similar across institutions, and there were no significant differences in BMI *z* scores by site ($p = .73$, data not shown). Younger children and those without SDB had significantly lower odds of being Ov/Ob compared to their counterparts (Table 1). Children with more severe baseline asthma had significantly greater odds of being Ov/Ob (Table 1).

Ov/Ob children have modest increase in PRD

Median PRD (defined as time to first q4h albuterol spacing) was 23.9 h, with a range of 2.1–226.1 h. Increased BMI *z* score was significantly associated with longer PRD ($p = .008$), with each increase in one unit of BMI *z* score having a 0.04 h increase in time to PRD. This equates to a 1.6 h increase in the estimated PRD for individuals at the 85th percentile compared to those at the 50th percentile for BMI. Likewise, there is a 2.6 h increase in estimated PRD in individuals at the 85th BMI percentile compared to those at the 25th BMI percentile. Based on our

regression models, if all Ov/Ob children ($n = 333$) were at the 50th percentile for BMI for age and sex, the cumulative reduction in PRD would be 36 days.

Overweight/obese children are more likely to receive nonstandard care, magnesium

Two hundred and twenty patients admitted to the ICU met criteria to be included in analyses for non-standard care (Figure 1). Patient characteristics were similar to the original sample. Compared to nOv/nOb children, Ov/Ob children were more likely to receive magnesium during their hospital stay (OR = 1.84, 95%CI 1.01–3.43) and had over three times the odds of receiving a second dose of magnesium in the ICU after receiving it in the ED (OR = 3.23, 95%CI 1.39–7.78). We present an additional depiction of the proportions of patients receiving magnesium in each respective location according to weight status in Figure 2. We also observed that children who required respiratory support in both the ED and ICU had higher BMI than those who received respiratory support in the ED only. However, children who required respiratory support in both the ED and the ICU had similar BMI to those who required no respiratory support, suggesting BMI was not associated with increased need for respiratory support. The remainder of variables we examined as part of non-standard care were not significantly associated with weight status.

Prior hospitalization combined with chronic asthma symptoms is associated with BMI

BMI was associated with increased chronic baseline severity and risk of hospitalization when evaluated in context of the four-category variable previously described in the Methods section ($p = .0011$, Figure 3A). When evaluated independently, patients with hospitalization in the year prior to enrollment had significantly increased BMI percentile (73.3 vs. 66.0, $p = .028$). When using the dichotomized BMI variable this difference was not significant ($p = .43$, data not shown) suggesting this was not a threshold effect.

Ov/Ob children are more likely to have SDB

Complete data pertaining to SDB were available for 85.5% of children (747/874) and 29.2% met our

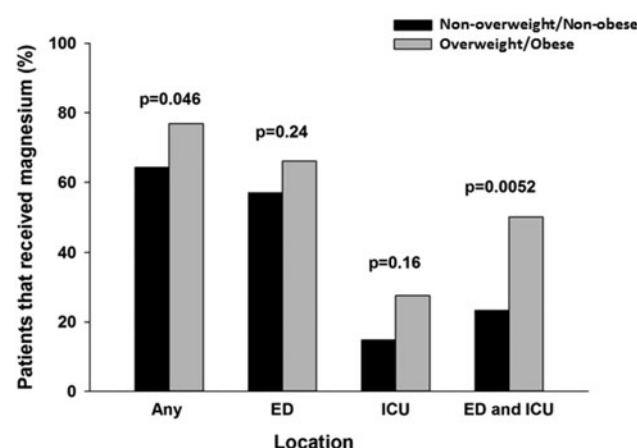


Figure 2. Intravenous magnesium administration by weight status and location of care. ED: dose received in emergency department; ICU: dose received in intensive care unit; ED and ICU: dose received in both locations.

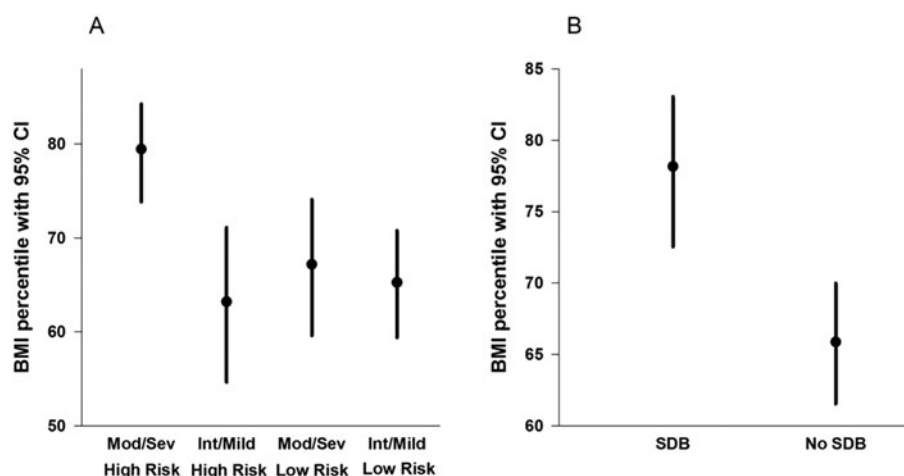


Figure 3. Body mass index (BMI) percentile with confidence intervals for chronic severity and risk of hospitalization in prior year for asthma (Frame A, $p = .0011$) and sleep disordered breathing (SDB) (Frame B, $p = .0013$). Mod/Sev: moderate to severe persistent asthma; Int/Mild: intermittent to mild persistent asthma. High risk: ≥ 1 hospital stay in prior year, low risk: no hospital stay in past year.

definition of SDB (Table 1). Children with SDB had significantly higher BMI than those that did not have SDB (78.2 vs. 65.9, $p = .0013$, Figure 3B). When BMI was dichotomized, nOv/nOb children were less likely to have SDB than Ov/Ob children (OR = 0.55, 95%CI 0.40–0.76, Table 1). More obese children had SDB (43.5%) than overweight children (27.2%, data not shown). Among patients that met criteria for SDB ($n = 218$), few ($n = 27$) reported a physician diagnosis of OSA or SDB (12.4%). Among children with a diagnosis of SDB-OSA, more than one-third (11 out of 27) reported being untreated. There were no significant differences in SDB according to age or sex.

Care practices and interventions remain consistent across weight ranges

We examined care practices according to weight status in order to determine if Ov/Ob children are cared for differently than nOv/nOb children. Analyses showed no significant differences by weight status (BMI z score) for common care practices during hospitalization, including provider performing the last assessment before weaning to q4h treatments, or type of oxygen saturation monitoring. There were no significant differences by weight for ICU admission, chest radiograph, continuous albuterol, ipratropium, or steroids (data not shown).

Discussion

In a state-wide, multi-center, prospective cohort of asthma hospitalizations, we detected a modest increase in PRD associated with increase in BMI, unlikely to

be noticeable for individual patients, but likely of importance when considered cumulatively. Ov/Ob children were prone to receive magnesium during hospitalization, and specifically to receive repeat dosing in the ICU after dosing in the ED. Children with increasing BMI percentile more often had history of hospitalization in the year prior to admission. Similarly, a higher BMI percentile was more often identified in those with a combination of increased baseline asthma severity (moderate to severe) and those at high risk for hospitalization (hospitalization in the year prior to study). Collectively, these results highlight that weight status is likely associated with differential use of IV magnesium during intensive care stays for exacerbations, that BMI percentile for age is relevant to hospitalization history, and despite differences in magnesium usage by weight status, Ov/Ob children have similar PRD compared to nOv/nOb children.

The observed marginal increase in PRD for Ov/Ob versus nOv/nOb children is consistent with two recent studies that found length of stay did not differ markedly by weight (19, 20), though at least one study reported a clinically significant increased length of stay (21). Our results are especially informative as we examined time to PRD in the context of care practices. Other studies have linked obesity with increased length of stay, though these studies were limited to single centers (21), use of administrative data (17), focused solely on ICU patients, and did not use BMI in determining weight status (18). Ultimately, the differences we identified in PRD according to BMI are unlikely to be noticeable, even at extreme BMIs. However, the cumulative effects of mildly prolonged hospital stays in heavier children are likely costly, and should be considered further as a contributing factor to the increasing cost of care for hospitalized asthmatics.

Our results regarding receipt of magnesium in Ov/Ob children with asthma support limited prior evidence that specifically relates to weight status and asthma exacerbation in children. One other study of ICU patients identified increased use of magnesium in heavier children, though this was also a single-institution study with limited sample size (18). Though our study was not designed to elucidate factors driving increased use of magnesium, there are multiple factors that could be relevant to the observed pattern. It is certainly possible that severity of exacerbation plays a role in the differential use of magnesium in Ov/Ob children. However, it is important to consider other reasons for differential magnesium use in Ov/Ob children as well. One possibility is that providers interpret

symptoms as more severe in heavier children, possibly due to more difficult assessments in children with large body habitus. Standard dosing may also be insufficient for Ov/Ob children, as pharmacokinetics suggest that body weight increases both volume of distribution and clearance of magnesium, factors that could lead to subtherapeutic magnesium levels (28). Additionally, heavier children may have interpreted symptoms differently than nOv/nOb children leading to repeat magnesium dosing. Heavier children more often report dyspnea (15, 29), and rate symptoms as more severe than as measured through lung function (16). Consistent with our data, differences in subjective interpretation of symptoms could theoretically prompt magnesium use, but ultimately not lead to airway support if evidence of impaired ventilation is absent. Given the small sample size for the nonstandard care sample, and that our analyses for nonstandard care did not account for severity of asthma exacerbation, our findings should be replicated in larger studies. However, our results support evidence that heavier children hospitalized with asthma remain a distinct group in the setting of severe exacerbations (18, 21, 30), and may preferentially receive, or respond differently to, typical therapies.

Previous literature inconsistently demonstrates associations between increased weight and hospitalizations for asthma exacerbations (8, 12, 19, 20, 30, 31). Our results support weight status as a risk factor for history of hospitalization. Overweight and obesity should be identified when present as a potentially complicating factor for asthma, however evidence suggests that this co-morbidity is commonly overlooked among children admitted for asthma (32). Hospitalizations are important opportunities to engage with parents regarding the potential for weight to complicate asthma, at a time when parents may be acutely aware of the need for improved control. Adjusting controller medication regimens during hospitalization for exacerbation, and early referral to specialty care after discharge may also be beneficial in the global care of these patients, especially as Ov/Ob children are at risk for inadequate response to typical controller therapy (13, 14, 33).

This study has multiple limitations. First, severity of exacerbation prompting hospitalization was not explicitly captured and therefore could not be accounted for in analyses. Our PRD analysis did, however, account for severity-associated factors (IV steroids, continuous albuterol), and another recent study addressed severity of exacerbation using similar factors (21). Second, evaluation and management of patients admitted for exacerbations were not

standardized across institutions, and magnesium dosing and criteria for ICU admittance were not standardized. Another potential limitation of this study is our sampling method, which included patient recruitment from major referral centers across Ohio. Using this method to recruit our sample may limit the generalizability of results to children living in primarily urban areas where referral hospitals exist. We also did not include patients in October and November as this data was not yet available, which could also have influenced our sample and outcomes. Therefore, we cannot comment on the effect of infectious triggers on hospital course for asthma exacerbations during the fall season. Additionally, given the correlation between several of the predictor variables, multiple testing correction was not performed, thus results should be interpreted with caution.

Conclusions

Ov/Ob children admitted with asthma have similar PRD to nOv/nOb children, are at increased risk for receiving magnesium, and with increasing BMI comes a worrisome pattern of prior asthma hospitalization. Efforts to address pediatric obesity in the asthmatic population should continue with a specific focus on achieving improved baseline control in this high-risk population and better understanding of triggers particularly relevant to the Ov/Ob population. Additional studies are needed to elucidate factors driving magnesium use in Ov/Ob children, including patient, provider, and system-level factors, and to more closely examine the risk profiles of repeated magnesium doses, while quantifying benefits.

Declaration of interest

Dr. Simmons reports grants from PCORI, outside the submitted work. Dr. Khurana Hershey reports grants from NIH outside the submitted work. Dr. Kercksmar reports personal fees from GSK, outside the submitted work. Dr. Martin reports grants from NIH, outside the submitted work. All other authors have no conflict of interest. The study sponsor (ODJFS) had no role in study design, data collection, analysis, or interpretation, writing of the manuscript, or the decision to submit for publication.

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