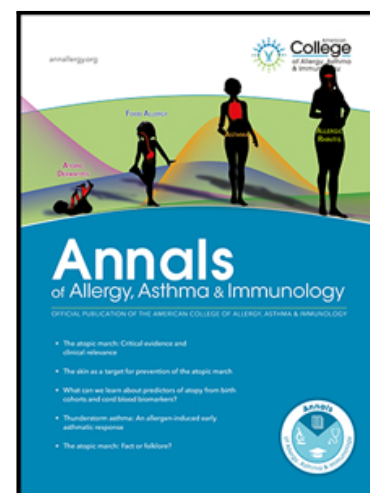


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Tricia Morphew MSc , Stanley P Galant MD

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Can asthma be well controlled with NAEPP guideline care in morbidly obese children? The Breathmobile.

Tricia Morpew MSc^{a,b}, Stanley P Galant MD^b

Affiliations: ^a Morpew Consulting, LLC, Bothell, WA; and ^b Children's Hospital of Orange County, Orange, CA

Address correspondence to: Tricia Morpew, Morpew Consulting LLC, 2208 242nd St SW, Bothell WA 98021

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Contributor's Statement:

Mrs. Morpew conceptualized and designed the study, conducted statistical analyses, interpreted results, drafted the initial manuscript, and approved the final manuscript as submitted.

Dr. Galant conceptualized and designed the study, interpreted results, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Abstract: Background

Obesity is thought to be associated with poor asthma control, increased health resource utilization, and reduced responsiveness to inhaled corticosteroids.

Objective: Based on previous experience our hypothesis was that by improved access to comprehensive guideline care that outcomes in normal weight would be comparable in obese asthmatic children.

Methods

This was a retrospective cohort study of predominately Hispanic children (3-18 years of age), in underserved areas of Orange County, CA, who enrolled in the Breathmobile Program from 2003 -2012. Outcomes were examined using Cox regression and generalized estimating equations analyses, adjusted for potential confounding factors.

Results

Clinical outcomes in over 1200 children followed for a mean of 6 visits (SD=2.2) across 403 days (SD=112) were improved, on average, regardless of BMI. MOB patients were able to achieve significant reductions of approximately 60% or more in report of ED visits, hospitalizations, school absenteeism, usual exercise limitations, and exacerbations to levels that were comparable to NW patients. The importance of close follow-up, particularly for the MOB patient, was evidenced by achieving 80% cumulative probability of well control asthma by visit 3, similar to patients in lower BMI risk groups with good adherence, when the visit interval did not exceed 90 days. These outcomes were achieved across all

BMI groups with similar mean step of therapy, adjusted for severity (p<.001).

Conclusion

Access to effective community-based care where trust, education, and continuity of care consistent with NAEPP guidelines is possible, as demonstrated by the Breathmobile Program, can provide an opportunity for asthmatic children in all BMI categories to achieve well controlled disease.

Key Words: Asthma, Obesity, Morbidly Obese, Pediatrics, Community Based Care

Abbreviations: NW=normal weight, OW=overweight, OB=obese, MOB=morbidly obese, BM=BreathmobileTM

Introduction

Obesity (OB) and asthma are currently the most common chronic conditions in children living in economically developed regions.¹⁻³ Nearly 8.6% of children in the United States have asthma.⁴ OB prevalence is at 17.2% and highest among Hispanic-American youth where approximately 1 in 5 children are obese.⁵ OB estimates are even higher in children with asthma at 28%.⁶ Common morbidity may complicate and perpetuate the interaction between asthma and OB such as gastroesophageal reflux and sleep disturbance.⁷ The indirect benefit of proper disease managed care in the asthmatic child is the potential to increase their ability to actively participate in physical activities supporting an aspect of healthier life choices related to decreased risk of OB.⁷

OB is now recognized as a major risk factor for developing asthma in children with several studies showing that increased adiposity, even in utero, often precedes the onset of asthma in children.⁸⁻¹⁰ In contrast, the effect of OB on asthmatic children remains conflictive. Several studies suggest that obesity is associated with increased asthma severity, poor asthma control, increased exacerbations, and healthcare utilization as well as decreased quality of life, air flow obstruction, and reduced inhaled corticosteroid responsiveness.¹¹⁻¹⁴ However, other studies do not confirm many of these associations,¹⁵⁻¹⁷, most recently in the pre-school OB asthmatic.¹⁸ These inconsistencies may be related to unconfirmed diagnosis of asthma, assessment of asthma control (self-report or clinical evaluation criteria), adjustment for baseline severity, adherence to controller medication, follow-up visit interval length, and differentials in composition of patient population (demographics, co-morbidities, and environmental exposures).^{19, 20} In addition, the perception of poor asthma control may be more related to OB than asthma itself.²¹ Furthermore, the definition of adiposity, the body mass index (BMI), currently recommended by the World Health Organization, may not effectively distinguish lean from fat mass which could be relevant in the growing child.²²

The relationship between OB and lung function in the asthmatic child has also not been definitively established. OB has been shown to correspond to reduced improvement in FEV1/FVC%

after initiation of controller therapy¹³, and to lower average baseline values.²³ Yet, other studies reported no significant differences in lung function between OB and normal weight (NW) asthmatic children.^{15, 24} Recently Forno et al found OB in asthmatic children to be associated with airway dysanapsis, which was related to increased morbidity.²⁵

We have provided comprehensive guideline based care for inner city, primarily Mexican-American children since 2003 utilizing a community based mobile asthma clinic, the Breathmobile™ (BM), a model of care originating in Los Angeles in 1995.²⁶ It had been observed that asthma related morbidity disproportionally affects African American and Hispanic children²⁷ and often associated with living in poverty with increased environmental triggers as well as poor access to quality medical care.²⁸ Our program has attempted to identify and reduce the barriers to care in this population by providing neighborhood access to care, cultural compatibility, elimination of economic concerns, and continuity of care by the same provider and staff at each visit which engenders trust and improved adherence.^{26, 29} In a recent BM multi-site study, including our site, nearly a third of asthmatic children in this large cohort had a co-morbid condition of OB.³⁰ Despite this prevalence of obesity, the BM approach resulted in significant improvement in asthma, including reduction in ED visits, hospitalization, and school absenteeism without modifications to asthma treatment approach based on OB status.^{26, 29-32} In addition, a previous BM study found asthma control was achievable in OB children comparable to NW children receiving the same level of controller medication.¹⁵ Still left unanswered is the effect of BM care on the morbidly obese (MOB) asthmatic in terms of asthma control, healthcare utilization, school absenteeism, exercise limitation, and lung function compared to the NW child.

Our hypothesis is that by improved access to comprehensive guideline-based care outcomes reflecting the goals of therapy in NW children are achievable in MOB asthmatics, a population whose asthma may be considered more difficult to control and less responsive to inhaled corticosteroids.

The purpose of this study therefore, was to examine efficacy of our program in MOB compared to normal weight asthmatic children.

METHODS

Study population and Design

This is a retrospective analyses of clinical and demographic data from 1204 children, ages 3 to 18 years, with physician diagnosis of asthma confirmed upon enrollment in Children's Hospital of Orange County (CHOC) Children's Breathmobile™ Program²¹ located in Orange County, California. Patients in the program predominately represent underserved children as majority of students at participating schools were eligible for free or reduced price meals. Study participants were children enrolled in the CHOC Children's Breathmobile™ program during the ten year period 2003-2012 who engaged in care for at least six months. The study observation period encompassed all visits from baseline through possible 1 ½ year follow-up.

Data were collected at each visit and entered into a standardized electronic medical record system, AsmaTrax (created by Loran Clement, MD, Los Angeles, CA).²¹ The baseline study data include age, gender, height, weight, ethnicity, allergen specific skin tests, spirometry, severity, prior year asthma-related school absenteeism, and lifetime asthma-related ED visits and hospitalizations converted to annual average based on duration of disease. Visit level data include medication prescribed, adherence (report of controller medication use as directed ≥ 5 d/wk), impairment/risk factors defining the patient's asthma control, and morbidity events in the visit interval (ED visits, hospitalizations, and school days missed) which were annualized based on cumulative sum relative to exposure time from baseline through last visit during study period. The provider utilized National Asthma Education and Prevention Program (NAEPP) criteria to define baseline disease severity and asthma control at follow-up visits.³³ Moderate-severe disease at baseline was classified when any of the following criteria were met: daily symptoms, night awakenings >1 /week, daily SABA use for symptom control (not prevention of exercise induced bronchospasm (EIB)), limitations with normal

activities (some or extreme), repeated exacerbations requiring oral corticosteroids (OCS), and/or lung function impairment ($FEV_1 \leq 80\%$ predicted or $FEV_1/FVC \leq 80\%$, depending on age and ability to perform test). Well controlled asthma at follow-up was defined by day symptoms (≤ 2 d/wk), night symptoms (≤ 1 x/month), no interference with normal activities, SABA use for symptom control not prevention of EIB (≤ 2 d/wk), OCS use ≤ 1 /yr, and age and performance dependent additional criteria of $FEV_1 > 80\%$ predicted and $FEV_1/FVC > 80\%$. Age- and gender- specific BMI percentiles abstracted from 2000 CDC growth charts were used to qualify a patient as normal weight (NW, $< 85^{\text{th}}$ percentile), overweight (OW, $85^{\text{th}}-94^{\text{th}}$ percentile), obese (OB, $95^{\text{th}}-98^{\text{th}}$ percentile), or morbidly obese (MOB, $99-100^{\text{th}}$ percentile). This study of retrospective data was approved by the Children's Hospital of Orange County Institutional Review Board.

Analysis

Patient characteristics in our study population were described in terms of valid percent with defined trait for categorical factors and mean (SD) for continuous factors. Distributional differences between BMI percentile groups were assessed for significance using the Chi-square test statistic and ANOVA, respectively. Analyses were then performed to examine BMI group differentials in relation to the following outcomes: 1) time to achieve well controlled asthma in patients who entered the program with persistent disease, 2) improvement in lung function from baseline to last visit, 3) morbidity reductions post vs. pre year, and 4) reduced probability of exercise limitations from baseline to last visit. Results presented were based on multivariate analyses with adjustment for the following factors: Age, gender, atopic (positive to one or more of nine allergens tested: cat, dog, feather, cockroach, mites, molds, weeds, trees, and grass), baseline severity (intermittent, mild, moderate-severe), and specific to each analyses: Time to control analyses included term for visit interval length (< 90 d or ≥ 90 days) and adherence with controller therapy in the visit interval (use as prescribed ≥ 5 d/wk); lung function analyses forced into each model interaction effects for time period by severity and time period by BMI group; morbidity and exercise limitation analyses

included term for days in program thru last visit. In the adjusted models, two-way interaction effects (dependencies) between each adjustment factor and BMI group were assessed and retained in final model when significant at the .05 level. Assessment of time to achieve well controlled asthma utilized Cox regression analyses with specification of the TIES=EXACT approach. Generalized estimating equations analyses assessed improvement in average lung function parameters (normal distribution with identity link specified), reduction in probability of an ED visit, hospitalization, and exercise limitations (binomial distribution with logit link specified), and decrease in average number of school days missed (Poisson distribution with log link specified). Cox regression analyses were performed using SAS V9.2 while all remaining analyses were performed using SPSS V18.0.

RESULTS

Patient demographics

1204 predominately Hispanic children (90.3%) with a mean age of 7.7 years (SD=3.5) met study criteria (Table 1). More than half of children enrolling in the program during the 10 year period had BMI in excess of normal range: 22.1% OW, 22.4% OB, and 8.3% MOB. A significantly greater percentage of OB and MOB patients had moderate to severe disease compared to NW and OW patients (39.5% vs. 33.2%), $p=.036$. Nearly 80% of patients entering the program had persistent disease, yet the majority were not on controller therapy prior to their initial visit (68.3%). Average step of therapy prescribed at baseline was 2.7 (SD=1.2). Prescribing patterns were severity dependent ($p<.001$), but consistent across BMI risk groups at baseline and follow-up ($p\geq.05$). Adherence with therapy at last visit was high (87.3%), and also similar across BMI groups ($p\geq.05$). Specific to patients with persistent disease, adherence with controller therapy was 81%. In characterizing change in BMI we found minimal transition in classification with 73.5% remaining unchanged and 15.5% increasing BMI risk classification by their last visit. Patients had an average of 6 visits (SD=2.2), and the median visit interval length was 77 days (IQR=56-108 d).

Time to achieve well controlled asthma

Approximately 80% of patients with moderate-severe disease achieved well controlled asthma by their 3rd routine follow-up visit (visit interval ≤ 90 days) (Figure 1). These findings were consistent in NW, OW, OB, and MOB patients. Although extended visit interval length occurred infrequently (~20% of follow-up visits), this reduced the cumulative probability of achieving control by visit 3 to under 50% in MOB patients ($p=.010$), while differential effects were less significant in NW, OW, and OB patients ($p \geq .05$).

Lung function

On average, lung function improved significantly from baseline to last visit in patients across BMI risk groups ($p < .05$), with exception of FEV1/FVC% in MOB patients (Table 2). The decrease in average FEV1/FVC% of 3.2 percentage points in MOB patients significantly differed from the marginal improvement of 0.3 to 0.9 percentage points in lower BMI risk groups ($p=.047$). Although non-significant, a similar trend was observed with respect to FEF25-75% where a slight reduction of 1.3 percentage points was observed in MOB patients compared to improvement of 6.2 to 6.7 points in NW, OW, and OB patients ($p > .05$).

Asthma-related morbidity reductions

Reductions in asthma-related morbidities (Figure 2) and exercise limitations (Figure 3) were achieved in NW, OW, OB, and MOB patients ($p < .001$). Probability patient would require an ED visit was reduced post year by 50-60%. Probability patient would require hospitalization was reduced by more than 68% with some variation exhibited by BMI risk group (NW 81.2%, OW 70.5%, OB 68.7%, and MOB 72.0%). Average number of asthma-related school days missed was reduced from five days to one day per year in all BMI risk groups. Probability of exercise limitations hovered around 40-44% in our OB and MOB patients prior to enrollment in the BM

Program compared to 32-34% in NW and OW patients. The linear relationship of increased asthma severity and BMI risk with increased probability of exercise limitations observed at baseline ($p<.001$ and $p=.002$, respectively, data not shown) diminished with ongoing guideline³³ based care to less than 10% by last visit in all severity and BMI risk groups ($p<.001$). As expected, patients with intermittent and mild persistent disease had lower average morbidity and probability of exercise limitations than moderate-severe patients at baseline, but ongoing disease managed care resulted in significant reductions across all BMI and baseline severity groups. OCS fills is an important indicator of asthma risk and post year monitoring showed similarity across BMI risk groups where patients required less than 1.0 per year, on average. Pre year OCS fill data was not available for comparison.

DISCUSSION

In this “real world” model of asthma care, the BM, a community-based healthcare delivery system for underserved children, has been shown to successfully improve asthma control and decrease morbidity, despite the fact that many children presented with the co-morbid condition of OB.^{26, 29-32} In the current analyses of 1204 children, we found 22.4% of asthmatic children were OB and 8.3% MOB. Nonetheless, MOB patients were able to achieve significant reductions of approximately 60% or more in ED visits, hospitalizations, school absenteeism, probability of exercise limitations, and exacerbations to levels that were comparable to NW patients. The importance of close follow-up, particularly for the MOB patient, was evidenced by achieving 80% cumulative probability of well control asthma by visit 3, similar to patients in lower BMI risk groups with good adherence, when the visit interval did not exceed 90 days. Average spirometric values were in the normal range at baseline and improved by the last visit with the exception of FEV1/FVC% in MOB children which slightly decreased, but still remained in normal range. What makes these outcomes so striking is that they occurred despite the fact that the mean step of therapy did not significantly differ across BMI categories after adjustment for severity, nor was there significant loss of weight since

most children had either no change in weight category or actually gained weight over the BM implementation period. It should also be noted that nearly 70% of those with persistent asthma were not on controller medication at baseline indicating inadequate therapy at the time of referral. In that situation we did see that a significantly greater percentage of OB and MOB had moderate to severe asthma compared to overweight (OW) and NW children. That being said, OB and MOB patients were not less responsive, on average, after initiation of ICS therapy. These data suggest that MOB asthmatic children can experience the same benefit from comprehensive BM type care as NW children as long as they achieve good continuity of care (< 90 day visit interval), and adherence to therapy, which can be challenging for underserved populations.

In a similar BM population Kwong et al found in children with persistent asthma that there were no significant differences between OB and NW children in time to reach control, or maintenance of control over a 12-month observation period.¹⁵ In addition, there were no significant differences in baseline FEV1%, FVC% or FEF25-75% predicted or number of controller medications required between these two cohorts. In a more recent study, Scott and colleagues, utilizing multi-site BM data of over 8,000 patients, including our site, found in mild to moderate persistent children that factors contributing to maintaining well controlled asthma included medication adherence, visit interval (<90 vs ≥ 90 days), age, race, health insurance, and BMI.³⁰ In our study we extended the classification of BMI and found routine follow-up care was of critical importance in achieving well controlled disease, particularly in MOB asthmatic children. In both studies approximately 80% of patients achieved well controlled asthma by visit three with good adherence and routine follow-up care.

In contrast to outcomes achieved by the BM program, several studies suggest a more profound impact of OB on asthma compared to NW children. These include a high risk of excessive beta 2 adrenergic drugs, poor asthma control, increased exacerbations, and air flow obstruction.¹¹⁻¹⁴ For example, Quinto and associates utilizing a large cohort of children, in a managed care model,

ages 5 to 17 years reported that OW and OB children had worse asthma control and more exacerbations than normal weight children.¹¹ Possible explanations for the differences from our study could include visit interval, which was not given, but could be significant, particularly for the MOB. In addition, control was defined by the number of short acting beta agonists (greater than 6 units) and oral corticosteroids usage, rather than the multi-dimensional guidelines applied to the current and prior BM studies. In a recent meta-analysis of 14 studies evaluating the relationship of OB to poor asthma control and exacerbations in children, Ahmadizar and colleagues found a small, but significant increase in exacerbations, defined by oral corticosteroid use.³⁴ However, there were no significant differences in asthma control nor ED visits or hospitalizations in the OB compared to NW children. They point out that factors which may have influenced outcomes include tools defining asthma control, since they found the Asthma Control Test and Asthma Control Questionnaire can give opposite results, and whether the child received specialty or primary care, since there were no significant differences related to BMI in the former. In contrast to these studies, Peters et al reported in a 12-month perspective study in children that there was no relationship between BMI, severity of asthma, spirometry, quality of life or healthcare utilization.⁶ In addition, Lang et al reported no difference in exacerbation rate or step-up therapy, but OB asthmatic children appeared to have more severe asthma and demonstrated a reduced FEV1/FVC ratio compared to NW children.¹⁷ In a more recent study, Lang reported that although OB preschool asthmatic children had more severe asthma before starting on therapy, after initiating therapy they had similar symptomatology and exacerbations rate while receiving the same dose of ICS as NW children, suggesting no evidence of ICS non-responsiveness in the OB preschool age child.¹⁸ In our study reductions in ED visits, hospitalizations, school days missed, following one year of the intervention were achieved in all BMI risk groups even after adjustment for potential factors in patients receiving essentially the same step-up therapy per guideline criteria for all BMI categories.

The response to inhaled corticosteroids is a very important phenotype in childhood asthma. Until recently there had been only one study comparing inhaled corticosteroids (ICS) responsiveness

in OW/OB school aged children compared to NW children.¹⁹ Forno et al in a randomized double blind placebo controlled post hoc analysis found a significant relationship between BMI and budesonide effect on pre-bronchodilator FEV1/FVC ratio, and bronchodilator response, as well as a reduction in healthcare utilization, suggesting a decreased response to ICS in those overweight/obese.¹³ In contrast to these findings we found differences in the response to controller therapy for the FEV1/FVC ratio only in the MOB compared to the normal weight BMI risk group. Several key characteristics may offer a potential explanation for the different outcome in our study where we found similar reduction in morbidity across BMI categories including the MOB. Differences between the Breathmobile and Forno studies include ethnicity, predominately inner-city Hispanic children vs. Caucasian children; asthma severity, mild to moderate asthma in 70% (20% intermittent, 10% severe) vs. 100% mild to moderate; visit intervals of less than 90 days for most children vs. 4 months; and average step up therapy was approximately step 3 and included the use of combination therapy vs. a fixed low dose budesonide. More recently Longo et al reported in an observational study that OB asthmatic children had a reduced response to ICS compared to NW children as measured by time to first exacerbation, and exacerbation free periods after initiating step 3 therapy, particularly with medium dose ICS.¹⁹ However, ICS combination therapy with either a LABA or LTRA appeared to be equally effective across BMI categories. In our study approximately 75% of those on step 3 therapy received ICS monotherapy, 25% combination ICS therapy across all BMI categories, with no notable differences in responsiveness.

We were particularly interested in the effectiveness of our program to reduce exercise limitation which was problematic in approximately 40% of our asthmatics at baseline. Our data showed that exercise limitation at baseline was related to both severity and BMI risk group, which is consistent with reports showing that both OB³⁵ and asthma³⁶ can limit exercise and increase exercise induced bronchospasm severity.³⁷ Most children in our study population had no change in their BMI classification, so the dramatic decrease in exercise limitation (>80%) was most likely due to their improved asthma status. This improvement could potentially contribute to reduced OB risk in

asthmatic children with encouragement and education regarding healthy life choices. Pediatric studies of weight loss interventions for the obese asthmatics are scarce.³⁸ A few studies have reported improvement in pulmonary function, inflammatory biomarkers, and exercise induced bronchial spasm.³⁹⁻⁴¹ However, these studies often had the limitation of small sample size and lack of a randomized clinical trial design.^{20, 38} It should be noted that potential community educational programs for our inner-city OW/OB children, while available, may be difficult to implement due to potential for low adherence to the multi session design these programs often require.

The major limitation of this study design is the retrospective nature of the analysis which could introduce selection bias compared to a randomized clinical trial design. Although there was no control group to examine efficacy of the BM program, our goal was to compare MOB with NW asthmatic patients, and adjustment was made for potential confounding factors. Another potential limitation was annualization of pre-year morbidity where lifetime morbidity was divided by the duration of asthma which could be subject to recall and measurement bias. However, there was no significant differences in average duration of asthma among the BMI categories. In addition, we recently reported similar morbidity reduction results in this population utilizing Medical claims data, but did not compare BMI risk groups.³¹ Another important consideration was provider determined adherence was based on the self-reported use of controller medication, which may be an overestimation of the actual use.⁴² Finally, our population was primarily low SES Hispanic children, which may not be generalizable to other populations.

In this “real word” healthcare setting we found that well controlled asthma associated with reduction in morbidity, and decreased exercise limitation in inner city, primarily Hispanic, asthmatics is achievable in children with the co-morbid condition of MOB. Access to effective community-based care where trust, education, and continuity of care consistent with NAEPP guidelines is possible, as demonstrated by the BM Program, can provide an opportunity for asthmatic children in all BMI categories to achieve well controlled disease.

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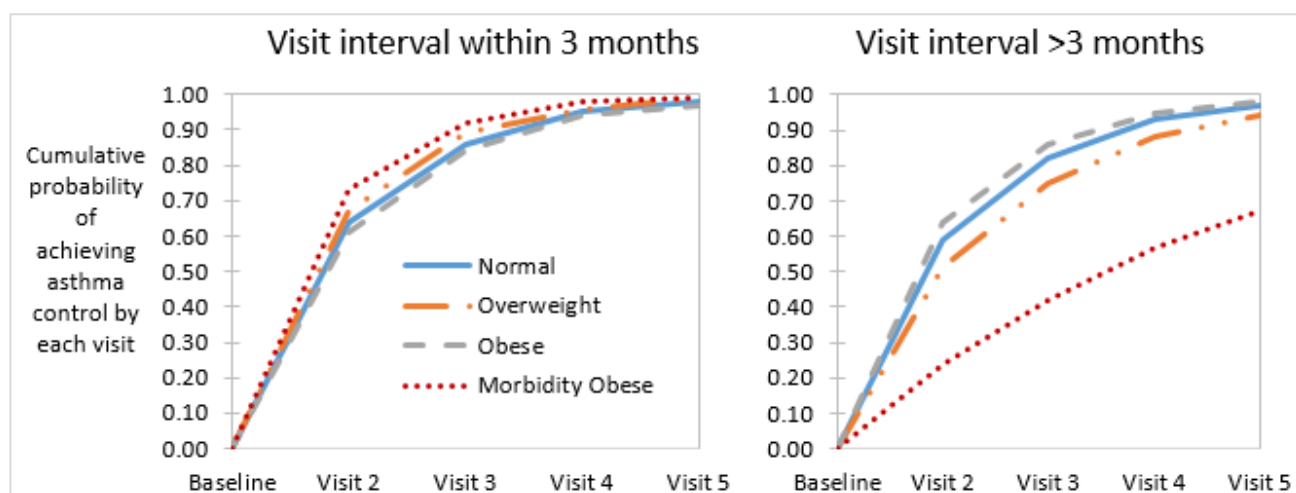


Figure 1. Time to achieve asthma control. Extended visit interval length (>3 months) significantly decreased the cumulative probability of achieving asthma control by each subsequent visit in morbidly obese patients ($p=.010$).

Cumulative probability estimates adjust for the following covariates: BMI risk group (normal, overweight, obese, morbidly obese), baseline severity (mild, moderate-severe), adherent with therapy prescribed at prior visit (Y vs. N), atopic (Y vs. N), visit interval (≤ 90 d vs. >90 d), gender, age (continuous), and significant interaction effect between visit interval and BMI risk group.

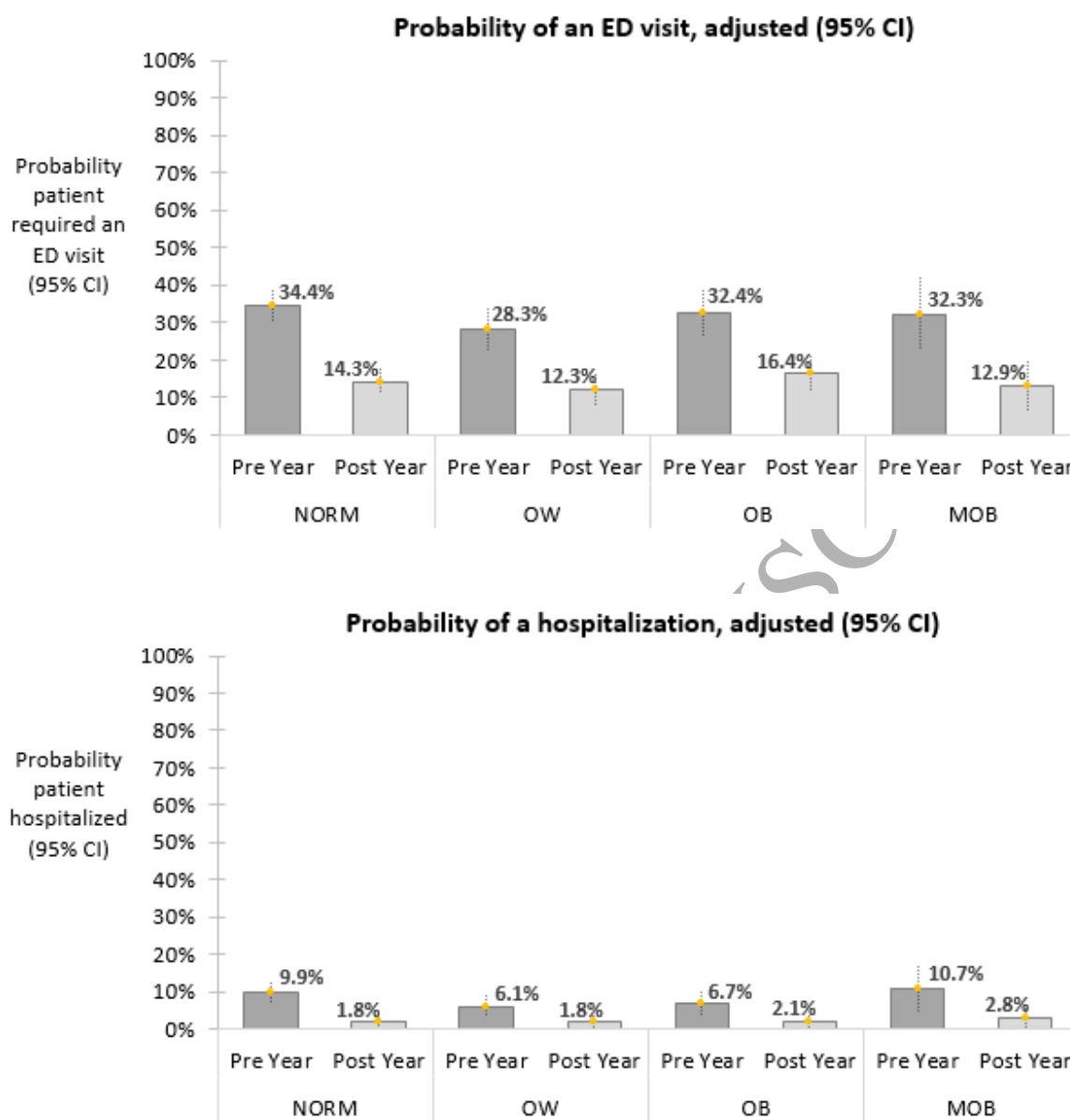


Figure 2. Morbidity reductions (probability of an asthma-related ED visit and hospitalization) post vs. pre year significant across baseline BMI categories ($p < .001$).

Probability (95% CIs) were estimated using generalized estimating equations with binomial distribution specified at average covariate values (or distribution of categorical factors) in patient population. Adjustment was made for age at entry, gender, atopy, days in BM program thru last visit, baseline severity (intermittent, mild persistent, moderate-severe persistent), baseline BMI risk group (normal, overweight, obese, morbidly obese), time period (pre or post year), and interaction effects between baseline severity*time period and BMI risk group*time period. Probability patient hospitalized further adjusted for significant interaction effect between gender and BMI risk group.

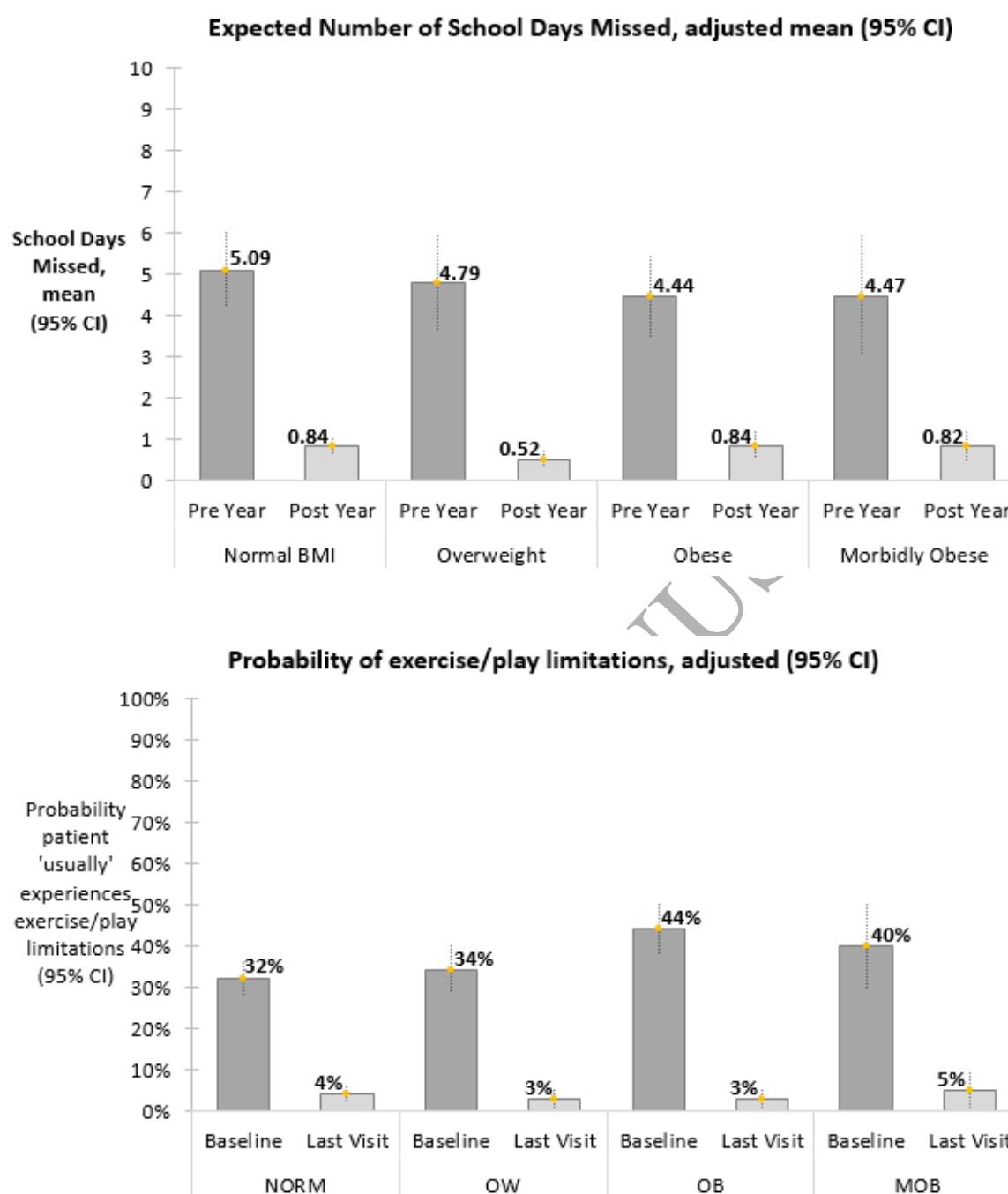


Figure 3. Reduction in average number of school days missed post vs. pre year and reduction in probability of exercise limitations at last visit compared to initial visit were significant across BMI categories ($p < .001$). Mean number of asthma-related school days missed (95% CIs) for each BMI risk group were estimated using generalized estimating equations with Poisson distribution specified at average covariate values (or distribution of categorical factors) in patient population. Adjustment was made for age at entry, gender, atopy, days in BM program thru last visit, baseline severity (intermittent, mild persistent, moderate-severe persistent), baseline BMI risk group (normal, overweight, obese, morbidly obese), time period (pre or post year), and interaction effects between baseline severity*time period and BMI risk group*time period. Expected number of school days missed further adjusted for significant interaction effect between age and BMI risk group. Estimated probability of activity limitations were produced using adjusted generalized estimating equations analyses with binomial distribution specified at covariate values representing distribution of categorical factors and average age of 7.7 years in patient population.

Table 1. Demographic and clinical profile of patients who entered BM program and engaged in care for at least six months, described by BMI percentile classification at baseline.

Valid % or mean (SD)	Overall	Normal BMI	Overweight	Obese	Morbidly Obese
	N=1204	N=568, 47.2%	N=266, 22.1%	N=270, 22.4%	N=100, 8.3%
Demographics:					
Age, mean (SD) [†]	7.7 (3.5)	7.5 (3.5)	7.4 (3.4)	8.4 (3.4)	7.1 (3.4)
Male, %	62.2%	63.4%	57.1%	64.4%	63.0%
Hispanic, % [†]	90.3%	88.0%	90.5%	92.8%	95.9%
Clinical Status at Baseline:					
Asthma Severity					
Intermittent	20.1%	18.3%	22.2%	20.4%	24.0%
Mild Persistent	44.8%	47.9%	45.9%	41.1%	34.0%
Moderate	25.2	23.1%	24.1%	29.6%	29.0%
Severe	9.9	10.7%	7.9%	8.9%	13.0%
Atopic	73.3%	75.9%	68.5%	74.6%	67.3%
Controller Naïve	72.4%	70.2%	77.0%	73.8%	68.7%
Asthma-related Morbidity (prior year)					
ED visits (any), %	34.6%	37.1%	30.8%	33.0%	35.0%
ED visits (>=2), %	13.6%	14.1%	12.4%	12.6%	17.0%
Hospitalizations (any), % [†]	12.0%	14.4%	9.0%	8.5%	15.0%
School missed (>=5 d), %	32.9%	32.0%	28.2%	38.1%	36.0%
Lung Function at Baseline: ^a					
FVC % predicted	(N=720) 98.2 (17.7)	(N=322) 97.6 (18.0)	(N=157) 99.2 (18.6)	(N=187) 99.0 (17.1)	(N=54) 96.8 (15.2)
FEV1% predicted	95.7 (17.4)	94.8 (17.4)	97.4 (18.2)	95.8 (17.7)	94.9 (13.4)
FEV1/FVC%	86.6 (9.3)	86.6 (9.6)	87.6 (8.8)	85.5 (9.4)	87.0 (9.1)
FEF25-75% predicted	89.2 (29.4)	87.6 (28.9)	90.9 (29.4)	89.9 (28.9)	91.8 (33.9)
Treatment and Adherence:					
Step of therapy ^b across visits, adjusted for baseline severity	2.7 (1.1)	2.7 (1.1)	2.6 (0.9)	2.7 (0.9)	2.7 (0.9)
Adherent with therapy reported at last visit	87.3%	86.9%	89.8%	86.6%	85.0%
Change in BMI by Last Visit: ^c					
Improved	12.0%	-----	26.3%	18.1%	25.0%
Unchanged	73.5%	83.5%	49.6%	75.6%	75.0%
Worsened	14.5%	16.5%	24.1%	6.3%	-----

^a Lung function measured in subset of patients able to perform test (assessed in majority of patients >=7 years old).^b STEP1 (SABA only), STEP2 (monotherapy w/low-dose ICS), STEP 3 (monotherapy w/medium dose ICS or combination therapy w/low dose ICS), STEP 4 (combination therapy w/medium dose-ICS), STEP 5 (combination therapy w/high-dose ICS).^c Change in BMI category (e.g. *improved* from overweight to normal, *unchanged* from overweight, or *worsened* from overweight to obese or morbidly obese) ~ not tested for between group differences due to dependency of definition on initial category.[†] p<.05 based on chi-square test statistic for categorical factors and ANOVA for continuous factors.

Table 2. Estimated one year change in lung function across BMI risk groups, adjusted for potential confounders and effect modifiers ^a.

mean (95% CI) ^a	Normal BMI	Overweight	Obese	Morbidly Obese
FEV1% predicted				
Baseline	94.3 (92.4, 96.3)	96.1 (93.1, 99.1)	95.6 (93.2, 98.0)	96.2 (92.8, 99.6)
Last Visit	99.3 (97.8, 100.8)	101.3 (99.0, 103.6)	101.3 (99.5, 103.1)	101.4 (97.7, 105.0)
[p<.001,p=.338,p=.974] [‡]	+5.0	+5.2	+5.7	+5.2
FVC% predicted ^b				
Baseline	97.5 (95.5, 99.5)	97.7 (94.4, 101.0)	97.8 (95.3, 100.3)	97.1 (93.1, 101.1)
Last Visit	101.3 (99.9, 102.8)	103.8 (101.6, 106.1)	103.6 (101.8, 105.4)	105.8 (102.3, 109.4)
[p<.001,p=.063,p=.232] [‡]	+3.8	+6.1	+5.8	+8.7
FEV1/FVC%				
Baseline	86.1 (84.9, 87.3)	86.6 (84.9, 88.3)	85.8 (84.5, 87.1)	88.0 (85.7, 90.4)
Last Visit	87.0 (86.3, 87.8)	86.9 (85.7, 88.1)	86.6 (85.6, 87.5)	84.8 (82.5, 87.0)
[p=.443,p=.887,p=.047] [‡]	+0.9	+0.3	+0.8	-3.2
FEF 25-75% predicted				
Baseline	86.9 (90.4, 95.7)	89.8 (85.4, 94.2)	89.7 (85.6, 93.7)	95.3 (86.8, 103.7)
Last Visit	93.1 (90.4, 95.7)	96.2 (92.0, 100.4)	96.4 (93.0, 99.9)	94.0 (86.7, 101.4)
[p=.004,p=.287,p=.291] [‡]	+6.2	+6.4	+6.7	-1.3

^a Means (95% CI) were estimated using generalized estimating equations with normal distribution specified and evaluated at average covariate values (or distribution of categorical factors) in patient population included in each respective model. Adjustment was made for age at entry, gender, atopy, days in BM program thru last visit, baseline severity (intermittent, mild persistent, moderate-severe persistent), baseline BMI risk group (normal, overweight, obese, morbidly obese), time_period (baseline or last visit), and forced interaction effects between baseline severity*time_period and BMI risk group*time_period.

^b Average FVC% further adjusted for significant interaction effect between age and BMI risk group (significant difference detected after age 9).

[‡] [P-values associated with the following effects: time_period, BMI Risk Group, BMI Risk Group*time_period]