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SHORT REPORT

Association Between Hemoglobin A1c and Pediatric Asthma Control

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Purpose: To examine the relationship between Hemoglobin A1c (HbA1c) and asthma outcomes in an urban cohort of children with asthma.

Methods: The AIRWEIGHS Study was a randomized controlled clinical trial of an air cleaner intervention testing the hypothesis that overweight/obese children would experience greater improvement in asthma control compared to normal weight children. The study enrolled 164 children with asthma from Baltimore, MD and assessed HbA1c levels and asthma outcomes during clinic visits at baseline and three months. HbA1c levels were analyzed as a continuous measure and categorized as either normal (<5.7%) or consistent with pre-diabetes (≥5.7%). Asthma outcomes included standardized questionnaires, spirometry, and fractional exhaled nitric oxide (FeNO). Generalized Estimating Equation (GEE) regression models were used to analyze the association between the HbA1c and asthma outcomes.

Results: Participants included 164 children with an average age of 11 (± 2) years, predominately African American (85%), male (59%), moderate or severe asthma by NAEPP criteria (59%), households with an income below $34,999 (60%), publicly insured (83%), and overweight/obese (61%). 52 participants were excluded from the analysis due to unsuccessful blood draws or participant refusal. Twenty of 112 distinct participants (18%) had HbA1c measurements ≥5.7%, consistent with prediabetes. Increased HbA1c levels were associated with worse asthma control as indicated by an increase in the Asthma Therapy Assessment Questionnaire (β-0.74 $p<0.05$). In the interaction analysis, BMI percentile had a significant interaction with HbA1c such that HbA1c had a stronger association with maximum symptoms days and exacerbation risk among children with lower versus higher BMI percentile values.

Conclusion: Higher HbA1c levels were associated with worse asthma control among children with asthma, adding to evidence that metabolic dysfunction may influence asthma morbidity. Additionally, HbA1c could have a stronger influence among non-obese children with underlying metabolic dysfunction, suggesting the need for future studies to investigate metabolic pathways in asthma.

Keywords: asthma, hemoglobin a1c, metabolic dysfunction, glycemic control

Introduction

Obesity and asthma are highly prevalent conditions that often coexist and disproportionately impact children from lower-income, marginalized populations. Obesity is a risk factor for childhood asthma incidence through several proposed mechanisms, including metabolic dysfunction, changes in lung physiology, inflammation, immune-mediated effects, and co-morbidities.[1] Insulin receptors have been identified in lung epithelial cells and may play a role in airway hyperresponsiveness, supporting the concept that obesity and asthma could be influenced by metabolic conditions such as diabetes and hyperglycemia.[2] Previous studies have also shown an association between HbA1c and worsening asthma outcomes, including hospitalizations and exacerbations in adults; however, studies in children are lacking.[3,4]

In our study, we aimed to address this gap in the literature by exploring the relationship between HbA1c and asthma morbidity in a pediatric population. We hypothesized that among a cohort of children with asthma, higher HbA1c levels,

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indicating worse glycemic control and underlying metabolic dysfunction, would be associated with higher asthma morbidity. The rationale for our hypothesis is grounded in the understanding that metabolic dysfunction may contribute to asthma pathogenesis and severity through dysregulated insulin signaling and inflammation pathways. By focusing on HbA1c as a marker, this study aims to investigate how metabolic dysfunction can influence asthma outcomes among children.

Materials and Methods

Study Population and Design

Our analysis included participants enrolled in the AIRWEIGHS study, a randomized controlled trial testing the hypothesis that overweight/obese children would experience greater improvement in asthma control compared to normal weight children. The clinical trial consisted of 164 children (8–17 years) with asthma from the Baltimore, MD area (NCT02763917). Children ages 8–17 years with symptomatic asthma and no current smoking were eligible for inclusion. Children with comorbid pulmonary and cardiac diseases were ineligible. No participants had a formal diagnosis of diabetes at study enrollment. Participants were recruited from multiple sources including previous asthma studies, local emergency departments, and community pediatric clinics. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine (IRB00074171). All participants and primary caregivers expressed written informed consent to study procedures.

Study Procedures

Participants were seen at baseline and 3 months. At baseline, HbA1c levels, asthma characterization, body anthropometric measurements, and lung function outcomes were assessed. The HbA1c blood test, commonly used to diagnose prediabetes (5.7–6.4%) and diabetes (>6.5%), represents average glucose levels over the prior three months. Participants and caretakers completed validated questionnaires, including maximum symptom days (MSD), Asthma Symptom Utility Index (ASUI), Asthma Control Test (ACT), and Asthma Therapy Assessment Questionnaire (ATAQ) to characterize asthma symptoms, control, and severity. Anthropometric measurements included height, weight, waist, and hip circumference. BMI percentile, used in children and teens, was calculated according to the Center for Disease Control calculator.

Lung function was assessed using spirometry and fractional exhaled nitric oxide (FeNO). Spirometry was performed using the New Diagnostic Design Easy on-PC spirometer following American Thoracic Society guidelines. Pre-bronchodilator FEV1% predicted values were determined using Global Lung Function Initiative (GLI) race-neutral reference equations. Fractional exhaled nitric oxide (FeNO) levels were measured using the NIOX VERO device. Average exhaled nitric oxide grading inflammation levels were characterized as 1–20 parts per billion (ppb) =low, 20–50 ppb=moderate, and >50 ppb=high.

Statistical Analysis

Summary statistics were generated for baseline demographic characteristics including age, race, BMI category, and National Asthma Education and Prevention Program (NAEPP) severity. Generalized Estimating Equation (GEE) regression models were used to analyze the association between HbA1c and asthma outcomes, accounting for repeated measures over time. HbA1c levels were analyzed as a continuous measure and dichotomized as either normal (<5.7%) or consistent with pre-diabetes (≥5.7%). HbA1c was specified as the predictor and each asthma symptom as the outcome in separate regression analysis, using covariates of age, gender, race, caregiver education, treatment group, and BMI percentile. Statistical models were adjusted for randomization group, age, gender, race, and education and effect modification by BMI percentile was tested using an interaction term.

Data Sharing Statement

The authors confirm that individual deidentified participant data from this study will be made available. The following specific data will be shared: asthma outcomes, clinical characteristics, and metabolic characteristics. Study-related

documents such as the study protocol, statistical analysis plan, and informed consent form will be made available upon reasonable request. Data will be accessible upon request by contacting the corresponding author, Requests will be reviewed to ensure ethical and appropriate data use. Data will be available starting from publication for three years.

Results

Participants included 164 children with an average age of 11 (± 2) years, predominately African American (85%), male (59%), moderate or severe by NAEPP criteria (59%), households with an income below $34,999 (60%), publicly insured (83%), and overweight/obese (61%). Of these, 112 participants had available HbA1c measurements and 52 were excluded due to unsuccessful blood draws or participant refusals. Participants were stratified by HbA1c levels, with 92 participants having HbA1c <5.7% and 20 participants having HbA1c >5.7%. (Figure S1). Overall, 112 participants had HbA1c results, ranging from 4.2% to 6.1%, with a mean (SD) of 5.3 (0.40) % (Figure S2 and Table S1). Of these, 20 of 112 participants (18%) had HbA1c measurements at or above 5.7% consistent with prediabetes.

The correlational relationships between HbA1c and BMI percentile (r=0.023, p=0.74), waist-to-hip ratio (r=0.036, p=0.61), and waist circumference (r=0.08, p=0.26), demonstrated a weak linear relationship between HbA1c and body mass (Figure S3). For instance, 66% of the cohort had a BMI percentile over 80% but with a broad distribution of HbA1c values.

Increased HbA1c levels were associated with worse asthma control and management as indicated by the significant increase in ATAQ score (Table 1); for example, each percentage point increase in HbA1c levels was associated with a 0.74 increase in ATAQ score (95% CI: 0.07–1.41, P=0.030), indicating worse asthma control (Figure 1). There were no significant associations between HbA1c (both continuous and dichotomous) and all other asthma questionnaires, lung function outcomes, and exacerbations. There was evidence that BMI modified the association between HBA1c and outcomes, such that the association with maximum symptoms days and asthma exacerbations were strongest among the children with a lower BMI compared to higher BMI (Figure 1 and Table 1).

Compared to those with normal HbA1c <5.7%, individuals with HbA1c ≥ 5.7% had significantly higher ATAQ scores (2.2 ± 1.9 vs 3.3 ± 1.7, P=0.020). In contrast, there were no significant differences in questionnaire results (maximum symptom days, ASUI, ACT) or lung function outcomes (FEV1% predicted, best FEV1, FeNO, and exacerbations) between participants with normal HbA1c levels <5.7% and higher HbA1c levels >5.7% consistent with prediabetes (Table S1). Results were similar in models that adjusted for waist circumference or waist-to-hip ratio instead of BMI.

Table 1 Associations Between Continuous Hemoglobin A1c and Asthma and Lung Function Outcomes by BMI Percentile

	Overall		Effect Modification by Body Mass				
			Low BMI (5th percentile)		High BMI (95th percentile)		Interaction p-value
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	
Maximum Symptom Days (higher =worse asthma)	0.32 (−1.24, 1.88)	0.69	3.06 (−0.31, 6.42)	0.08	−0.83 (−2.82, 1.15)	0.41	0.07
ATAQ (higher =worse control)	0.74 (0.07, 1.41)	0.03	1.61 (−0.15, 3.38)	0.07	0.37 (−0.49, 1.23)	0.40	0.27
ACT (lower =worse control)	−0.14 (−1.61, 1.34)	0.86	−1.90 (−5.49, 1.69)	0.30	0.63 (−1.34, 2.60)	0.53	0.28
FEV_1% predicted (GLI)	−0.99 (−7.78, 5.79)	0.77	3.22 (−7.80, 14.23)	0.57	−2.89 (−13.00, 7.23)	0.58	0.48
Average eNO, ppb	2.57 (−6.79, 11.94)	0.59	−0.80 (−19.05, 17.45)	0.93	4.10 (−7.20, 15.41)	0.48	0.66
ER/Hospital exacerbation (IRR)*	0.83 (0.31, 2.20)	0.71	5.08 (0.81, 31.95)	0.08	0.48 (0.16, 1.46)	0.19	0.05
Any exacerbation (IRR)**	0.70 (0.33, 1.48)	0.35	2.45 (0.59, 10.28)	0.22	0.47 (0.20, 1.10)	0.08	0.07

Notes: Models adjusted for treatment group, age, gender, race, education, BMI percentile. *asthma exacerbation requiring ER/hospitalization. **asthma exacerbation requiring either ER/hospitalization or unscheduled physician visit.

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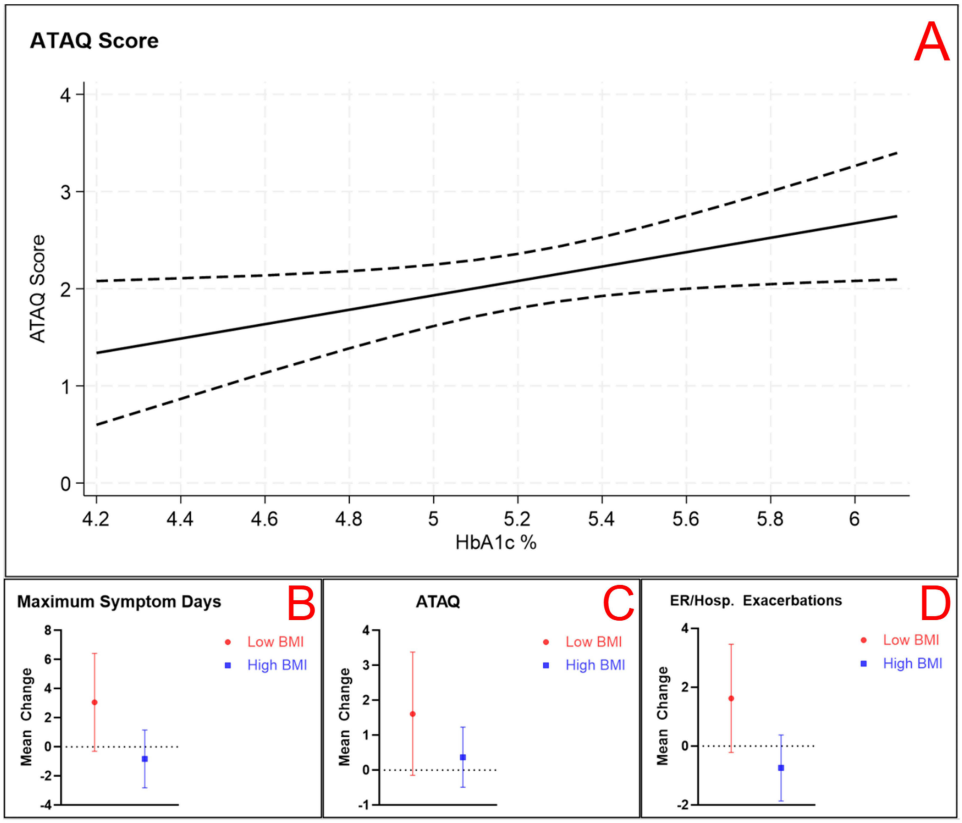

Figure 1 The association between HbA1c and asthma outcomes. (**A**) (top figure) shows the point estimate and its 95% confidence interval for the mean ATAQ level across HbA1c levels, based on running regression of ATAQ on HbA1c, adjusted by covariates (β=0.74, 95% CI: 0.07–1.41, P=0.030). The three figures in the bottom panel show the point estimate and 95% confidence interval for the mean change in maximum symptom days (**B**), the mean change in ATAQ (**C**), and mean change in the log incidence rate of exacerbations requiring ER/Hospitalization (**D**) for every 1 percentage unit increase in HbA1c for "low" BMI percentile (5th percentile level) and "high" BMI percentile (95th percentile level).

Abbreviations: ATAQ, Asthma Therapy Assessment Questionnaire; HbA1c, hemoglobin A1c.

Discussion

In a cohort study of children ages 8–17 with asthma, we examined the association between HbA1c and asthma-related outcomes including asthma control, lung function, and exacerbations. We report that higher HbA1c was associated with worse asthma control in children indicated by higher ATAQ scores. We also found that the association between HbA1c and asthma morbidity seemed to be more prominent among children with lower BMI. For instance, the association between HbA1c and maximum symptoms days and exacerbation risk was shown to be greater among children with low BMI percentile when compared to the high BMI percentile. These findings in a pediatric population add to the emerging evidence of metabolic dysfunction as a driver of asthma morbidity.

Prior studies have demonstrated associations between HbA1c and risk of asthma exacerbations. In a large claims-based cohort of 5722 obese adults with asthma in the US, individuals with elevated HbA1c levels in the prediabetes and diabetes range had a 27 and 33% higher rate of asthma exacerbations compared to those with normal HbA1c levels.[3] In a large cross-sectional study of 47,606 adults with asthma in the United Kingdom, individuals with higher HbA1c in the pre-diabetic and diabetic range had 1.68 times significantly higher odds of having an asthma hospitalization compared to those with normal HbA1c levels.[4] In the present study, In the present study, HbA1c was not associated with asthma exacerbations although there was a trend in this direction among children with a lower BMI. The difference in findings could be due to our smaller sample size, relatively short duration of follow-up, a lack of participants with HbA1c meeting the definition of diabetes, or a true lack of association in children.

Previous studies have also reported associations between indicators of poor glycemic control and decreased lung function. Yang et al found an inverse but weak association between continuous and dichotomous HbA1c levels and FEV1

z-score (β=−0.013, $p<0.01$ and β=−0.102, $p<0.05$ respectively).[4] Another study found that children with asthma with either metabolic syndrome or insulin resistance were associated with significantly worse lung function (lower FEV1/FVC; lower FEV1 and FVC respectively).[5] Our results did not demonstrate a consistent relationship between HbA1c and lung function.

There are several pathways by which metabolic dysfunction may influence airway biology and physiology, influencing the clinical course of asthma.[1,2] These pathways include systemic and airway inflammation, as well as immune-mediated mechanisms.[1,2] Insulin receptors in lung epithelial cells could also further explain this relationship through the development of a dysregulated insulin signaling pathway directly contributing to airway hyperresponsiveness. Metabolic dysfunction is often associated with obesity, which can independently impact asthma control.

In our main analysis, we report that there were no significant associations between HbA1c and asthma-related questionnaires (MSD and ACT), lung function outcomes, and exacerbations. However, in the interaction analysis, BMI percentile and HbA1 were shown to have a significant interaction such that HbA1c's association with maximum symptoms days and exacerbation risk were greater among those with low BMI 5th percentile when compared to the high BMI 95th percentile (Table 1). This finding suggests that HbA1c could have a stronger influence among non-obese children with poor glycemic control and underlying metabolic dysfunction, highlighting the complexity of the HbA1c and BMI relationship and its effect on asthma morbidity.

It is also possible that HbA1c has reduced diagnostic accuracy as BMI increases, particularly among obese individuals, as has been suggested in prior literature, potentially due to differences in glucose metabolism.[2,6] Further studies are needed to investigate this relationship and its effect on susceptible subgroups, such as children with poor glycemic control who have lower body mass, to provide a better understanding of underlying mechanisms and inform future therapeutic trials.

Our study presented several strengths. We leveraged a pediatric asthma trial with detailed characterization, including standard questionnaires, lung function, anthropometric data and biomarkers. There are also limitations to this study. The study excluded 36/164 participants from the analysis due to missing HbA1c measurements either from unsuccessful blood draws or participant refusal. Our pediatric cohort predominantly consisted of African American children with asthma in low-income and urban communities, and therefore may not be generalizable to other populations. Lastly, none of our participants had HbA1c levels >6.5%, limiting our ability to investigate the relationship between diabetes and asthma control. Furthermore, we were unable to perform subgroup analyses due to small sample size. Future studies with larger sample sizes and longer duration of follow-up that also include comprehensive metabolic and anthropometric assessment are needed to address these limitations.

In adults, the repurposing of diabetes medications that improve insulin sensitivity for patients with asthma is being investigated, driven by observational evidence of potential benefits for metformin, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors.[7–9] Our findings support a need for further investigation in pediatric populations to determine whether similar trials may benefit children and careful consideration of BMI and metabolic dysfunction in the scope of asthma care.

Conclusion

In conclusion, we found that higher levels of HbA1c in children with asthma were associated with worse asthma control indicated by higher scores on the Asthma Therapy Assessment Questionnaire. In the BMI interaction analysis, we also found that HbA1c was associated with worse asthma symptoms and increased exacerbation risk among children with low BMI (5th percentile) compared to children with high BMI (95th percentile). Our findings add to the existing literature by demonstrating how poor glycemic control and underlying metabolic dysfunction can increase asthma morbidity in a population of children with asthma.

Abbreviations

HbA1c, hemoglobin A1c; ATAQ, Asthma Therapy Assessment Questionnaire; GEE, Generalized Estimating Equation; BMI, body mass index.

IRB Approval

Granted prior to conducting the study.

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Disclosure

Dr Emily Brigham reports an unrestricted award from AstraZeneca. This award is unrelated to the work presented. Dr Nadia Hansel reports grants from NIH, COPD Foundation, Astra Zeneca, GSK; advisory board of Astra Zeneca, GSK, Regeneron, and Sanofi, outside the submitted work. Dr Meredith McCormack reports personal fees from UptoDate, Boehringer Ingelheim, GlaxoSmithKline, Aridis, MGC Diagnostics, and ndd Medical Technologies, outside the submitted work. The authors report no other conflicts of interest in this work.

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