Published in final edited form as:

J Allergy Clin Immunol Pract. 2019 ; 7(6): 1868–1873.e5. doi:10.1016/j.jaip.2019.02.029.

Association Between Pre-Diabetes/Diabetes and Asthma Exacerbations in a Claims-Based Obese Asthma Cohort

Tianshi David Wu, MD MHS¹, Emily P. Brigham, MD MHS¹, Corinne A. Keet, MD PhD², Todd T. Brown, MD PhD³, Nadia N. Hansel, MD MPH¹, and Meredith C. McCormack, MD MHS¹

¹Division of Pulmonary and Critical Care, Johns Hopkins University, Baltimore, Maryland, United States

²Division of Pediatric Allergy and Immunology, Johns Hopkins University, Baltimore, Maryland, United States

³Division of Endocrinology, Diabetes, and Metabolism – School of Medicine, Johns Hopkins University, Baltimore, Maryland, United States

Abstract

Background: Metabolic dysfunction may contribute to worsened asthma in obesity. The relationship between pre-diabetes and diabetes, metabolic conditions more common in obesity, with asthma outcomes is not well-characterized.

Objective: We sought to determine the association between pre-diabetes/diabetes and asthma exacerbations in an obese asthma cohort.

Methods: A retrospective cohort of US adults with obese asthma, age 18–64, was created from a claims-based health services database spanning 2010–2015. Individuals with a hemoglobin A1c (HbA1c) measurement were identified, categorized as within normal (<5.6%), pre-diabetes (5.7–6.4%), and diabetes (≥6.5%) ranges. Exacerbations, defined as asthma-related hospitalization, emergency department visit, or corticosteroid prescription ±14 days of an asthma-related outpatient visit, were ascertained. Associations were fit with zero-inflated negative binomial models, adjusted for age, sex, region, smoking, medication use, and comorbidities.

Results: 5,722 individuals were identified. Higher HgbA1c was associated with higher asthma exacerbation rates. In the fully-adjusted model, compared to individuals with normal HbA1c, those

Corresponding Author: Meredith C. McCormack, MD MHS, Division of Pulmonary and Critical Care Medicine, 1830 E. Monument St, 5th Floor, Baltimore, MD 21205, mmccor16@jhmi.edu.

Author Contributions

Conception and design of work: TDW, CAK, MCM

Analysis of data: TDW

Interpretation of data: All authors

Drafting, critical revision, and final approval of manuscript: All authors

Conflicts of Interest

TDW: No conflicts of interest.

EPB: No conflicts of interest.

CAK: Personal fees from Up-To-Date, American Board of Allergy and Immunology.

TTB: No conflicts of interest.

NNH: Grants and personal fees from AstraZeneca, GlaxoSmithKline; grants from Boehringer Ingelheim, COPD Foundation.

MCM: Personal fees from Up-To-Date.

in the pre-diabetes range had a 27% higher rate (95% CI, 5%–52%), and those in the diabetes range had a 33% higher rate (95% CI, 2%–73%).

Conclusion: Pre-diabetes and diabetes were associated with higher rates of asthma exacerbation among obese adults with asthma. Results support evidence that insulin resistance and metabolic syndrome, metabolic features common in pre-diabetes/diabetes, can influence asthma morbidity.

Keywords

Asthma; exacerbation; metabolic dysfunction; diabetes; pre-diabetes; hemoglobin A1c; administrative; claims

Introduction

Obese asthma has been described as a distinct phenotype that is more difficult-to-treat and associated with worsened outcomes(1). Metabolic dysfunction has been proposed as a possible explanation (2). Insulin resistance and metabolic syndrome, conditions more common in obesity, have been associated with increased asthma prevalence and morbidity(3–6). These studies support the emerging paradigm that asthma can be altered by metabolic conditions external to the lung, a compelling hypothesis that may open additional therapeutic options in obese asthma. However, the evidence to date has been restricted to cross-sectional studies, which substantially limits the ability to infer causal connections.

Pre-diabetes and diabetes are metabolic conditions characterized by worsening degrees of chronic hyperglycemia. They may be diagnosed by measurement of serum hemoglobin A1c (HbA1c), which reflects glucose homeostasis in the prior 2–3 months (7). Among obese adults, the hallmark of pre-diabetes and diabetes is underlying insulin resistance and hyperinsulinemia, and a substantial proportion can be expected to fulfill criteria for metabolic syndrome(8).

Some studies have reported positive associations between diabetes and asthma exacerbations(9, 10). However, these have generally included participants with treated diabetes, introducing confounding from medication effects, and none have used laboratory testing to diagnose diabetes nor to quantify the degree of dysglycemia. Further, the role of pre-diabetes, a common precursor condition associated with increased risk of incident diabetes, has not been examined. The implication of pre-diabetes and diabetes as risk factors for exacerbation in obese asthma would have important value in identifying patients who may be a greater risk for worsened disease. Additionally, it would provide supportive longitudinal evidence that metabolic dysfunction can impact asthma morbidity.

Our objective was to determine the association between pre-diabetes and diabetes with risk of asthma exacerbation in a longitudinal setting. Such a question is challenging to answer within clinical asthma cohorts, which must balance sample size with confounding from the impact of diabetes treatment, obesity status, and inaccuracies in HbA1c that can arise from medical comorbidities, such as hematologic conditions. Instead, the availability of a nationwide linked administrative claims and laboratory database presented a unique

opportunity to address this objective, providing sufficient power to allow creation of an obese asthma cohort without these complicating factors.

We constructed a retrospective observational cohort of obese individuals with asthma and HbA1c measurements from a US-based health services research database. We hypothesized that those with HbA1c in the pre-diabetes and diabetes ranges, compared to the normal range, would have higher rates of asthma exacerbation.

Methods

Data Source

The Truven Health MarketScan Research Databases are a collection of health services research databases maintained by Truven Health Analytics (Ann Arbor, Michigan)(11). This study utilized a linked dataset between the MarketScan Commercial Claims and Encounters Database, which is comprised of aggregated inpatient, outpatient, and prescription claims information from major employer-sponsored insurance plans spanning all fifty of the United States, and the MarketScan Laboratory Database, which contains laboratory data for these participants. The study was drawn from January 1, 2010 to December 31, 2015.

Cohort Definition

A cohort was assembled of persons with asthma, based on the presence of at least one inpatient or two outpatient encounters with a compatible International Classification of Diseases Clinical Modification (ICD) code (ICD-9 493.x or ICD-10 J45.x, J46.x) within the study period. Additional inclusion criteria were age 18–64 years, enrollment for at least one calendar year, participation in a health plan that submitted full prescription information to the database, and an obesity diagnosis. We excluded participants with a diagnosis of another comorbid pulmonary condition, a rheumatologic condition that may require systemic corticosteroids for symptoms unrelated to asthma, or any conditions that may decrease accuracy of HbA1c measurements (hemoglobinopathies, nutritional and iron deficiency anemias, malignancies, and advanced chronic kidney disease or dialysis status). All utilized ICD codes are included in the supplement (Table S1). Restriction of our cohort to those with a diagnosis of obesity, either as a condition or supporting code, has been validated as approximately 95% specific for true prevalent obesity(12, 13) (Table S1). This was chosen to reduce confounding by body mass, to establish more uniform indications for HbA1c testing, and to select participants likely to have similar pathophysiologic processes giving rise to hyperglycemia(14).

Exposure Definition

Participants with a HbA1c measurement, obtained following at least one year of enrollment and after fulfillment of asthma inclusion criteria, were identified (Figure S1 in the supplement). We excluded individuals who filled a prescription for any hypoglycemic medication within the previous year to prevent confounding by medication effects (Table S2 in the supplement). To limit potential for reverse causation, where individuals with more severe asthma may have higher HbA1c by virtue of repeated corticosteroid use, we excluded those who filled a prescription for a systemic corticosteroid in the 3 months prior. Finally,

HbA1c measurements below 3% or above 18% were excluded due to biological implausibility(15).

Outcome Definition

The primary outcome was asthma exacerbation, defined as a hospitalization with asthma as the principal diagnosis, an emergency department visitation with asthma as a diagnosis, or an oral corticosteroid prescription within ± 14 days of an ambulatory visit where asthma was a diagnosis(16, 17). All events within 14 days of the first qualifying event were considered as part of one exacerbation. Composite outcomes of this design have been used in other claims-based asthma studies(17, 18), which allow eligible corticosteroid prescriptions to precede clinic visits to reflect circumstances in which treatment was called-in treatment and the patients was later seen as an outpatient Outcomes were assessed for one year after a participant's HbA1c measurement, a time frame chosen to limit misclassification due to subsequent changes in glucose or health status. Follow-up was censored if an individual was no longer covered by their insurance plan or if a hypoglycemic medication was started (Figure S1 in the supplement).

Covariate Definitions

Age was modeled as disjoint categories of 18–29/30–39/40–49/50–65 years old. Geographic region in the United States was categorized as Northeast, North Central, South, and West. Two individuals with an unknown geographic region were imputed as Northeast (the most common region). Comorbidity burden was assessed by the Charlson Comorbidity Index (CCI)(19, 20). Obstructive sleep apnea and gastroesophageal reflux disease, conditions which may be mistaken for worsened asthma in obesity(21), and smoking(22) were also recorded. Asthma controller use was categorized as an inhaled corticosteroid (ICS), ICS with an adjunct controller (inhaled long-acting beta agonist, inhaled long-acting muscarinic antagonist, leukotriene modifier, or theophylline), an adjunct controller without an ICS, or none. Covariates were determined over the year prior to a participant's HbA1c measurement.

Statistical Approach

Associations between HbA1c and rates of asthma exacerbation were estimated with zero-inflated negative binomial models(23). This model addresses an excess number of zero events by consideration of the study population as including a distinct group of individuals with zero likelihood of recording an exacerbation (the “never exacerbators”). A count model, which estimates the rate of exacerbation, is simultaneously fit with an inflation model, which estimates the probability of being a never exacerbator. Covariates in the count model are selected conventionally, intended to associate with rate of exacerbation, while covariates in the inflation model are intended to predict membership in the never exacerbator group. These latter covariates were selected based on the conceptualization of the never exacerbator as a younger individual with intermittent asthma.

In the primary analysis, HbA1c was parameterized as clinically-defined categories of normal ($<5.7\%$), in the pre-diabetic range ($5.7\%–6.4\%$), and in the diabetic range ($\geq 6.5\%$)(7). Crude, age- and sex-adjusted, and fully-adjusted estimates were produced. The fully-adjusted count model controlled for age, sex, region, asthma controller use, CCI, smoking,

obstructive sleep apnea, and gastroesophageal reflux disease. The inflation model included age, sex, and asthma controller use. All analyses included offset terms to account for unequal follow-up time. A test for trend was performed by parameterizing HbA1c category as a continuous variable. Interactions by sex, by inhaled corticosteroid use, and by those older and younger than age 40 were examined.

We performed a number of sensitivity analyses: We (1) excluded all individuals with an ICD code for type 1 diabetes, under the premise that the code may reflect suspicion for the specific disease rather than screening for diabetes in general, and understanding that type 1 diabetes reflects a distinct pathophysiology; (2) excluded those who were censored due to initiation of hypoglycemic medications, to explore potential bias introduced by these individuals, who may represent those with better medical access; (3) replaced the CCI with individual indicator variables for congestive heart failure, myocardial infarction, peripheral vascular disease, and cardiovascular disease, to directly explore confounding by these conditions; (4) used a more restrictive definition of ambulatory exacerbation, reducing the eligible range of corticosteroid from ± 14 days to ± 5 days of an asthma-related office visit, to increase confidence that the filled corticosteroid was related to asthma; and (5) required the asthma diagnosis to occur in the primary position of an emergency department visit to qualify as an exacerbation, to increase confidence that the emergency department visit was related to asthma. Finally, we (6) fit equivalent negative binomial models (without zero inflation) to test for model sensitivity to inflation parameters.

Next, because there were some individuals with outlying HbA1c measurements at the right tail, we tested for non-linearity by fitting a continuous model with HbA1c as a linear and quadratic term. Predicted rates of asthma exacerbation by HbA1c were subsequently generated from this model. A cubic model did not demonstrate superior fit beyond the quadratic model as assessed by the Akaike Information Criterion.

Statistical significance was accepted at a two-tailed p-value of <0.05 . Cohort extraction was performed in SAS 9.3 (Cary, North Carolina) and statistical analysis was performed in Stata 15 (College Station, Texas). Because this analysis was performed in a commercially available and de-identified dataset, it was not subject to institutional review.

Results

From the initial database of eligible people, 158,446 individuals with asthma and obesity were identified. Among these, 11,230 individuals had HbA1c values within the linked laboratory database. 5,508 of these individuals were excluded, most often due to pre-measurement use of diabetes medications or corticosteroids, resulting in a final cohort size of 5,722 individuals. Compared to the population without an HbA1c measurement, those in the final cohort were older, had a higher comorbidity burden, and were marginally less likely to be on an asthma controller (Table S3 in the supplement). A flow diagram of cohort derivation is included as Figure S2 in the supplement.

The mean age was 49 and over two-thirds were female (Table 1). Approximately half were using asthma controllers. Less than 20% of individuals had diagnosed obstructive sleep

apnea or gastroesophageal reflux disease. The mean Charlson Index was 0.38, reflecting low comorbidity burden.

Over 3,868 person-years of follow-up, there were 866 exacerbations, corresponding to an incidence rate of 2.2 events per 10 person-years. The number of exacerbations ranged from 0–8, with very few (45, 1%) having more than two during follow-up. In crude, age- and sex-adjusted, and fully-adjusted models, participants with an HbA1c in the pre-diabetes and diabetes ranges had higher rates of asthma exacerbation (p-value for trend <0.05 for all comparisons). In the fully-adjusted model, compared to individuals with HbA1c in the normal range, those in the pre-diabetes and diabetes ranges had a 27% and 33% higher asthma exacerbation rate, respectively (p-value for trend = 0.01).

There was no evidence of effect modification by those older and younger than 40 (p-interaction = 0.48), by sex (p-interaction = 0.33), or by inhaled corticosteroid use (p-interaction = 0.29). Repeat analyses excluding individuals who had an ICD code for type 1 diabetes, excluding those who initiated hypoglycemic medications during follow-up, introducing cardiovascular covariates, utilizing a more restrictive definition of ambulatory exacerbation, and utilizing a more restrictive definition of emergency department exacerbation produced consistent results. Finally, conventional negative binomial models were fit; there were no associations between HbA1c and asthma exacerbation in the crude model, but results were maintained in the age- and sex-adjusted and fully-adjusted models (not shown).

In the continuous model, the association between HbA1c and rate of asthma exacerbation was linear for the majority of measurements but decreased at higher values (Figure 1). In exploratory analysis, we determined that this finding was driven by individuals with measurements above 9%, who had few exacerbations recorded (Figure S3). These individuals represented less than two percent of the study population. In the linear portion of the curve, a half percentage increase in HbA1c was associated with a 14% increase in rate of asthma exacerbation (95% confidence interval, 4% to 25%).

Discussion

In a large claims-based cohort of obese individuals with asthma who were not taking hypoglycemic medications, individuals with HbA1c in the pre-diabetes and diabetes ranges, compared to the normal range, had higher rates of asthma exacerbation. These results identify pre-diabetes and diabetes as risk factors for exacerbation in obese asthma.

Obese asthma defines a distinct phenotype is more severe and refractory to treatment. Because the majority of individuals with severe asthma are obese, but not all obese individuals with asthma will develop severe disease, investigation of risk factors that confer increased likelihood of exacerbation and poor control are critical toward improving our understanding of this condition(24). Pre-diabetes and diabetes are diagnosed through routine testing that is widely available and globally standardized. Because these conditions are prevalent in obesity and have well-established causal associations with cardiovascular

outcomes, there is existing justification for diabetes screening, which our results suggest has potential application in the management of obese asthma.

Our results are consistent with other reports of a positive association between diabetes and asthma exacerbation. In the Severe Asthma Research Program-3 cohort, the prevalence of diabetes was higher in those with exacerbations in the prior year(9). In a study combining two UK-based health services research databases, diabetes was associated with an 11% higher odds of having two or more exacerbations in the subsequent year(18). Our study extends these results into a population of individuals without potential confounding by diabetes medications, examines participants with pre-diabetes, and utilizes objective laboratory results to characterize the degree of dysglycemia, allowing estimation of exacerbation risk with high granularity.

Within obese individuals, elevations in HbA1c may be explained by insulin resistance and metabolic syndrome(8). These conditions have been associated in cross-sectional studies with more severe or uncontrolled asthma(3–6), and they form the evidence base for an emerging paradigm that proposes a mechanistic connection between metabolic dysfunction and asthma(2). This relationship has been described as an “outside in” process, whereby systemic comorbidities can modulate pulmonary diseases. Our results represent novel data in support of this hypothesis. Importantly, and in contrast to previous studies within this field, our findings are presented within a longitudinal cohort, allowing for investigation of directionality and temporality. This represents an important innovation toward the overall goal of establishing evidence for a causal relationship between metabolic diseases and respiratory sequelae.

Potential mechanisms may involve effects of hyperinsulinemia, alterations in adipokines such as leptin and adiponectin, and augmentation of systemic inflammation and oxidative stress (25, 26). *In vitro* and animal models, exposure to insulin has been associated with pathologic airway changes similar to those seen in asthma, and inhaled insulin has been associated with transient decreases in pulmonary function in human studies(27–30). Obesity-associated decreases in adiponectin and increases in leptin have been associated with worsened systemic inflammation and airway hyper-reactivity(31). Increased systemic inflammation, manifested by elevated serum IL-6, has been cross-sectionally associated with higher prevalence of severe asthma, which was notably also associated with metabolic dysfunction(4).

Hyperglycemia itself may additionally contribute to these findings. Chronic hyperglycemia has been associated with increased systemic oxidative stress, decreased immune system function, and diminished pulmonary reserve(32–34). We note, however, that point estimates for pre-diabetes and diabetes were similar, which would not be expected if results were driven by hyperglycemia alone.

Our findings raise a possibility that therapeutic intervention on insulin resistance and metabolic syndrome may be beneficial in selected individuals with asthma. Reported experience with diabetes medications that affect these processes have had mixed results. A pharmacoepidemiologic study of individuals with asthma and diabetes reported decreased

odds of exacerbation after initiation of metformin(35). In contrast, a twelve-week pilot study of thiazolidinediones in obese individuals with asthma did not show improvements in airway hyperresponsiveness or disease control(36). In this latter study, the baseline degree of metabolic dysfunction was not reported.

There was evidence of non-linearity in the association between HbA1c and rate of asthma exacerbation, driven by individuals with outlying measurements. There are a number of possible methodological explanations. Because our primary outcome is partially conditioned on the use of corticosteroids, these findings may reflect clinical reluctance to prescribe steroids to those with more severe diabetes. These participants may also be less likely to have asthma outcomes recorded due to competing risks from other comorbidities or lack of engagement with the medical system. Finally, as a possible physiologic explanation, these individuals may predominantly have hyperglycemia from primary beta cell loss and insulin deficiency in absence of insulin resistance, which represents a distinct pathophysiology that may not affect asthma. Overall, confidence in the finding of non-linearity is limited because of the rarity of observations in this high range.

Finally, it should be noted that our cohort had a relatively low rate of asthma exacerbation. This is partially due to an intentional consequence of methodology, as recent corticosteroid use was excluded, creating a group of individuals with relatively well-controlled disease at baseline, and could also be a result of inaccuracies in detecting asthma in claims databases. Additionally, the true asthma exacerbation rate is also likely underestimated, as our outcome only represented exacerbations which led to urgent health care contact or need for systemic corticosteroids, which does not capture the full spectrum of asthma morbidity. Using an identical case definition, our asthma exacerbation rates were similar to those measured from two other administrative databases in the United States and United Kingdom(17).

Our study has a number of strengths. By leveraging a large and nationally-drawn administrative database, we were able to assemble a sizable cohort of individuals. Outcomes were followed longitudinally, establishing temporality to the association. The study's exclusion criteria were carefully designed to overcome some important comorbidities that add variability or bias to HbA1c. By excluding those who used corticosteroids prior to HbA1c measurement, we protected against reverse causation by excluding those with poor control; and by only considering those who were not using hypoglycemic medications, we ensured that the degree of HbA1c elevation reflected the degree of underlying physiologic impairment in glucose metabolism.

However, there are some limitations. Due to the administrative nature of our data, we do not have access to a number of plausible confounders, especially ethnicity, socioeconomic indices, and behavioral parameters. For example, some individuals with HbA1c in the diabetes range may be chronically untreated, which can be associated with other factors related to chronic illness that can worsen asthma. Although we restricted our cohort to those with obesity, we lacked specific measures of body mass index. We were dependent on diagnostic codes to detect asthma and collect covariates, which are vulnerable to misclassification. This is most relevant for smoking status, which has acknowledged limitations in sensitivity, despite a validation study that has supported its utility for

identifying smoking in claims data(22). Underestimation of exacerbation rates is possible, as earlier noted. Finally, because the MarketScan database is comprised of adults covered under employer-sponsored health plans, our population does not include individuals over the age of 65, and individuals were lost to follow-up on employment change, which in some cases may be influenced by asthma severity. These sources of confounding and misclassification may variously bias our results away or toward the null. Confirmation of findings in other these other populations is warranted.

In a large claims-based obese asthma cohort, individuals with HbA1c within the pre-diabetes and diabetes ranges had higher rate of asthma exacerbation. Our findings implicate pre-diabetes and diabetes as risk factors for exacerbation in obese asthma and represent novel longitudinal evidence that metabolic dysfunction may impact asthma morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Statement

Investigator effort is supported by grants from the National Institute of Environmental Health Sciences (F32ES028578 to TDW, R01ES026170 to CAK, P50ES018176 to NNH and MCM), the National Institute of Allergy and Infectious Diseases (K24AI120834 to TTB), the National Center for Advancing Translational Sciences (KL2TR001077 to EPB), and the United States Environmental Protection Agency (83615201 to NNH and MCM). The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health or the United States Environmental Protection Agency.

Abbreviations

CCI	Charlson Comorbidity Index
FEV1	Forced expiratory volume in first second
HbA1c	Hemoglobin A1c
ICD	International Classification of Diseases
ICS	Inhaled corticosteroid

References

1. Forno E, Han Y-Y, Muzumdar RH, Celedón JC. Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma. *Journal of Allergy and Clinical Immunology* 2015;136(2):304–11. e8. [PubMed: 25748066]
2. Peters MC, Fahy JV. Metabolic consequences of obesity as an “outside in” mechanism of disease severity in asthma. *Eur Respiratory Soc*; 2016.
3. Suratt BT, Ubags ND, Rastogi D, Tantisira KG, Marsland BJ, Petrache I, et al. An Official American Thoracic Society Workshop Report: Obesity and Metabolism. An Emerging Frontier in Lung Health and Disease. *Annals of the American Thoracic Society* 2017;14(6):1050–9. [PubMed: 28570148]
4. Kuschnir FC, Felix MMR, Kuschnir MCC, Bloch KV, Jordão EAdOC, Solé D, et al. Severe asthma is associated with metabolic syndrome in Brazilian adolescents. *Journal of Allergy and Clinical Immunology* 2018.

5. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *The Lancet Respiratory Medicine* 2016;4(7):574–84. [PubMed: 27283230]
6. Cardet JC, Ash S, Kusa T, Camargo CA, Israel E. Insulin resistance modifies the association between obesity and current asthma in adults. *European Respiratory Journal* 2016;ERJ-00246-2016.
7. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes care* 2010;33(Suppl 1):S62. [PubMed: 20042775]
8. Lorenzo C, Wagenknecht LE, Hanley AJ, Rewers MJ, Karter AJ, Haffner SM. A1C between 5.7 and 6.4% as a marker for identifying pre-diabetes, insulin sensitivity and secretion, and cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study (IRAS). *Diabetes care* 2010;33(9):2104–9. [PubMed: 20573754]
9. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *American journal of respiratory and critical care medicine* 2017;195(3):302–13. [PubMed: 27556234]
10. Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *Journal of asthma and allergy* 2016;9:1. [PubMed: 26793004]
11. Danielson E Health research data for the real world: the MarketScan databases Ann Arbor, MI: Truven Health Analytics 2014.
12. Caplan EO, Kamble PS, Harvey RA, Smolarz BG, Renda A, Bouchard JR, et al. Positive predictive value between medical-chart body-mass-index category and obesity versus codes in a claims-data warehouse. *Current medical research and opinion* 2018;34(1):117–21. [PubMed: 28795870]
13. Lloyd JT, Blackwell SA, Wei II, Howell BL, Shrank WH. Validity of a claims-based diagnosis of obesity among medicare beneficiaries. *Evaluation & the health professions* 2015;38(4):508–17. [PubMed: 25380698]
14. Association AD. Professional Practice Committee: Standards of Medical Care in Diabetes—2018. *Am Diabetes Assoc*; 2018.
15. Leong A, Dasgupta K, Bernatsky S, Lacaille D, Avina-Zubieta A, Rahme E. Systematic review and meta-analysis of validation studies on a diabetes case definition from health administrative records. *PLoS One* 2013;8(10):e75256. [PubMed: 24130696]
16. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA, Gern J, et al. Asthma outcomes: exacerbations. *Journal of Allergy and Clinical Immunology* 2012;129(3):S34–S48. [PubMed: 22386508]
17. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC pulmonary medicine* 2017;17(1):74. [PubMed: 28449686]
18. Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Gossage D, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *The Journal of Allergy and Clinical Immunology: In Practice* 2014;2(6):741–50. e4. [PubMed: 25439366]
19. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical care* 2005;1130–9. [PubMed: 16224307]
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases* 1987;40(5):373–83. [PubMed: 3558716]
21. Kasasbeh A, Kasasbeh E, Krishnaswamy G. Potential mechanisms connecting asthma, esophageal reflux, and obesity/sleep apnea complex—a hypothetical review. *Sleep medicine reviews* 2007;11(1):47–58. [PubMed: 17198758]
22. Wiley LK, Shah A, Xu H, Bush WS. ICD-9 tobacco use codes are effective identifiers of smoking status. *Journal of the American Medical Informatics Association* 2013;20(4):652–8. [PubMed: 23396545]
23. Greene WH. Accounting for excess zeros and sample selection in Poisson and negative binomial regression models 1994.

24. Dixon AE, Poynter ME. Mechanisms of asthma in obesity. Pleiotropic aspects of obesity produce distinct asthma phenotypes. *American journal of respiratory cell and molecular biology* 2016;54(5):601–8. [PubMed: 26886277]
25. Peters U, Dixon AE, Forno E. Obesity and asthma. *Journal of Allergy and Clinical Immunology* 2018;141(4):1169–79. [PubMed: 29627041]
26. Baffi CW, Wood L, Winnica D, Strollo PJ, Gladwin MT, Que LG, et al. Metabolic syndrome and the lung. *Chest* 2016;149(6):1525–34. [PubMed: 26836925]
27. Lessmann E, Grochowy G, Weingarten L, Gieseemann T, Aktories K, Leitges M, et al. Insulin and insulin-like growth factor-1 promote mast cell survival via activation of the phosphatidylinositol-3-kinase pathway. *Experimental hematology* 2006;34(11):1532–41. [PubMed: 17046573]
28. Dekkers BG, Schaafsma D, Tran T, Zaagsma J, Meurs H. Insulin-induced laminin expression promotes a hypercontractile airway smooth muscle phenotype. *American journal of respiratory cell and molecular biology* 2009;41(4):494–504. [PubMed: 19213874]
29. Nie Z, Jacoby DB, Fryer AD. Hyperinsulinemia potentiates airway responsiveness to parasympathetic nerve stimulation in obese rats. *American journal of respiratory cell and molecular biology* 2014;51(2):251–61. [PubMed: 24605871]
30. Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. *Annals of internal medicine* 2006;145(9):665–75. [PubMed: 17088580]
31. Sood A, Shore SA. Adiponectin, leptin, and resistin in asthma: basic mechanisms through population studies. *Journal of allergy* 2013;2013.
32. Nogueira-Machado JA, Chaves MM. From hyperglycemia to AGE-RAGE interaction on the cell surface: a dangerous metabolic route for diabetic patients. *Expert opinion on therapeutic targets* 2008;12(7):871–82. [PubMed: 18554155]
33. Zuo L, Otenbaker NP, Rose BA, Salisbury KS. Molecular mechanisms of reactive oxygen species-related pulmonary inflammation and asthma. *Molecular immunology* 2013;56(1–2):57–63. [PubMed: 23665383]
34. Baker EH, Archer JR, Srivastava SA. Hyperglycemia, Lung Infection, and Inflammation. *Clinical Pulmonary Medicine* 2009;16(5):258–64.
35. Li CY, Erickson SR, Wu CH. Metformin use and asthma outcomes among patients with concurrent asthma and diabetes. *Respirology* 2016;21(7):1210–8. [PubMed: 27245632]
36. Dixon AE, Subramanian M, DeSarno M, Black K, Lane L, Holguin F. A pilot randomized controlled trial of pioglitazone for the treatment of poorly controlled asthma in obesity. *Respiratory research* 2015;16(1):143. [PubMed: 26610598]

Highlights

1. What is already known about this topic?

Metabolic dysfunction has been hypothesized to modulate asthma control and severity, especially in the context of obesity. Few studies have reported positive associations between diabetes and asthma exacerbation, but the relationship has not been well-characterized.

2. What does this article add to our knowledge?

Pre-diabetes and diabetes, ascertained by measurement of hemoglobin A1c, were identified as risk factors for asthma exacerbation within a longitudinal obese asthma cohort, suggesting that metabolic derangements underlying these conditions may affect asthma exacerbations.

3. How does this study impact current management guidelines?

The hemoglobin A1c, a nationally-standardized and commonly available blood test, may have value in identifying obese patients at risk for asthma exacerbation.

Figure 1.

Predicted incidence rate of asthma exacerbation with 95% confidence intervals. Hemoglobin A1c is parameterized as a linear and quadratic term. Vertical lines denote thresholds for pre-diabetes (5.7%–6.4%) and diabetes (≥6.5%). Display is truncated at an A1c of 9%, which excludes approximately 2% of outlying observations.

Table 1

Participant characteristics and HbA1c measurements, n=5,722

Characteristic	Number (%)
Age	
Age in years, mean±SD	49±11
18–29	414 (7)
30–39	881 (15)
40–49	1404 (25)
50–59	1990 (35)
60–65	1033 (18)
Female sex	4116 (72)
Asthma controller use	
None recorded	3162 (55)
Inhaled corticosteroid (ICS) only	489 (9)
ICS + other controller *	1552 (27)
Other controller only *	519 (9)
Smoking	245 (4)
Comorbidities	
Obstructive sleep apnea	633 (11)
Gastroesophageal reflux	948 (17)
Charlson Index, mean±SD	0.38±0.81
Geographic region	
Northeast	1757 (31)
North Central	642 (11)
South	1666 (29)
West	1657 (29)
Hemoglobin A1c (%)	
Measurement, median (IQR)	5.8 (5.5–6.2)
Normal (<5.7)	2072 (36)
Pre-diabetes (5.7–6.4)	2716 (48)
Diabetes (≥ 6.5)	934 (16)

* Other controller defined as an inhaled muscarinic antagonist, long-acting beta agonist, leukotriene modifier, or theophylline

Table 2
Associations between hemoglobin A1c category and incidence rates of asthma exacerbation^{*}

HbA1c Category	Crude Model		Age and Sex Adjusted		Full Model [§]	
	IRR (95% CI)	P-value	IRR (95% CI)	P-value	IRR (95% CI)	P-value
Normal (<5.7%)	Referent	<0.01	Referent	<0.01	Referent	0.01
Pre-diabetes (5.7%–6.4%)	1.27 (1.06–1.52)		1.29 (1.07–1.55)		1.27 (1.05–1.52)	
Diabetes (≥ 6.5%)	1.34 (1.04–1.73)		1.37 (1.06–1.76)		1.33 (1.02–1.73)	

^{*} Estimated by zero-inflated negative binomial models, with age, sex, and controller use in the inflation model; p-value represents a test for linear trend across HbA1c category

[§] Adjusted for age, sex, geographic region, controller use, smoking, sleep apnea, acid reflux, and the Charlson Comorbidity Index

IRR = Incidence rate ratio