



Elevated Childhood Insulin-related Asthma Is a Risk Factor for Reduced Lung Function

Tara F. Carr, Debra A. Stern, Wayne Morgan, Stefano Guerra, and Fernando D. Martinez

University of Arizona, Tucson, Arizona

ORCID ID: 0000-0001-7218-3246 (S.G.).

To the Editor:

Asthma and obesity remain two of the most common chronic conditions in children and adults. Although widely recognized to coexist in patients across the age spectrum, the causal and pathobiologic relationship between asthma and obesity remains incompletely understood. Forno and colleagues showed that being overweight or obese in a pediatric nonasthmatic cohort was related to dysanapsis (disproportionate growth between lung size and airway caliber) and therefore had a reduced FEV₁/FVC ratio characteristic of obstructive airway diseases (1). Those with asthma who showed evidence of dysanapsis had more severe disease. Connecting these findings with metabolic abnormalities often associated with obesity, an analysis of adolescents in the cross-sectional 2010 National Health and Nutrition Examination Survey (2) showed more airflow obstruction in those with asthma and metabolic syndrome than in

either characteristic alone. A recent analysis of data from the SARP-3 (Severe Asthma Research Program) (3) showed that adult patients with asthma with insulin resistance had lower FEV₁ and FVC not attributable to obesity, with reduced response to medications. Furthermore, patients with insulin resistance were more likely to have a decline in lung function over time. Taken together, these data suggest that obesity, metabolic syndrome, and insulin resistance may influence lung function in patients with asthma. The developmental origins of these associations have not been elucidated.

We recently showed that elevated insulin concentrations in early childhood predicted subsequent development of asthma in two longitudinal birth cohorts, the TCRS (Tucson Children's Respiratory Study) and the Avon Longitudinal Study of Adults and Children, irrespective of body mass index (BMI) (4). Here, we hypothesized that among individuals with asthma, elevated insulin in early childhood may be a risk factor for subsequent reduction in lung function.

TCRS is a longitudinal, nonselected birth cohort designed to study early life risk factors for chronic lung disease. This cohort enrolled 1,246 participants between 1980 and 1984 with continuous follow-up to the present time (5). Lung function was measured every 4–6 years by spirometry according to American Thoracic Society guidelines. Active asthma was recorded at each visit and defined as physician-diagnosed asthma with reports of asthma symptoms in the

Table 1. Relation of Age 6 Years Nonfasting Insulin (Highest Quartile vs. Lower Quartiles) Combined with Active Asthma at Ages 11, 16, 22, 26, 32, and 36 Years on Longitudinal Lung Function Measures Using Mixed Models, Adjusted for Survey Age and Height, Raw Body Mass Index at Age 6 Years, and Sex

Lung Function Measures Age 11–36 Yr	Low Insulin No Asthma	Nonfasting Insulin at Age 6 Yr and Active MD Diagnosed Asthma Age 11–36 Yr Groups					
		High Insulin No Asthma		Low Insulin Asthma		High Insulin Asthma	
		β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
FEV ₁ , ml	Reference	−58.7 (−149 to 32)	0.20	−104 (−167 to −41)	0.001	−79.8 (−184 to 24)	0.13
FVC, ml	Reference	1.1 (−103 to 106)	0.98	−90.8 (−167 to −14)	0.020	29.3 (−93 to 151)	0.64
FEV ₁ /FVC ratio	Reference	−0.01 (−0.03 to 0.002)	0.080	−0.004 (−0.01 to 0.005)	0.37	−0.03 (−0.04 to −0.01)	0.001
FEF _{25–75} , ml/s	Reference	−172 (−366 to 21.4)	0.081	−149 (−273 to −24)	0.019	−306 (−525 to −87)	0.006
FEF _{25–75} /FVC ratio	Reference	−0.04 (−0.09 to 0.01)	0.10	−0.02 (−0.05 to 0.01)	0.26	−0.09 (−0.15 to −0.04)	0.001

Definition of abbreviations: CI = confidence interval; FEF_{25–75} = forced expiratory flow, midexpiratory phase; MD = physician.

Model sample size $n = 321$, observations = 1,284; respective insulin/asthma group sample sizes at each age: age 11 years (170, 56, 30, and 19); age 16 years (142, 40, 31, and 19); age 22 years (138, 36, 22, and 21); age 26 years (96, 25, 25, and 12); age 32 years (117, 36, 28, and 18); and age 36 years (125, 40, 23, and 15). Bold value denotes significant to $P < 0.05$.

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previous year. Nonfasting blood was collected around age 6 years, and insulin was measured on a subset of individuals with available serum samples, as previously described; 29% were undetectable (4).

Consistent with our previous study, individuals in the highest quartile of insulin concentrations were defined as high insulin; the lower three quartiles were combined into the low insulin group. BMI at age 6 years was calculated using the height and weight of each participant measured by the study nurse or, if not available, by questionnaire reports. Participants were included in this analysis if they had nonfasting insulin measurements and BMI at age 6 years, any subsequent determination of lung function (11, 16, 22, 26, 32, or 36 yr), and asthma diagnosis information available at age 6 years and

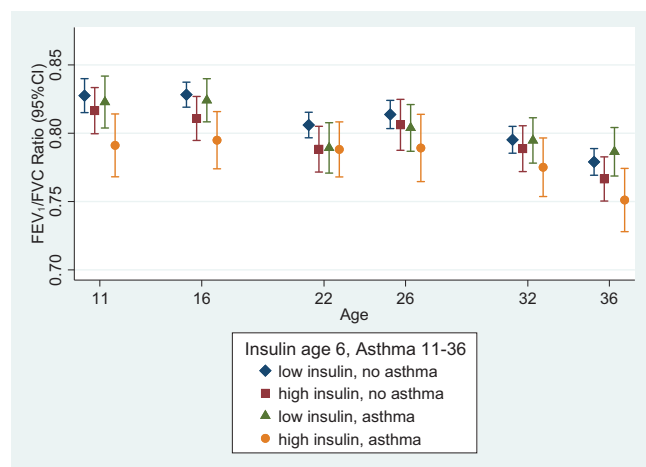


Figure 1. Predictive values from the longitudinal mixed model of the FEV₁/FVC ratio and the insulin–asthma groups estimated at each survey age using the mean values of the covariates, including an interaction term between survey age and the insulin–asthma groups. Mixed model predictive values, overall $P=0.011$. CI = confidence interval.

at least one time point subsequently; 321 were identified. At each of these six surveys, participants were categorized into one of four groups on the basis of their insulin at age 6 years (low vs. high) and their active asthma status at that survey (no vs. yes asthma). These participants are 48% male, 62% non-Hispanic White, and 25% Hispanic White. Additional demographic information by insulin status is as previously published; parental characteristics, early life exposures, skin test positivity, and total IgE were similar between high and low insulin groups (4).

Using longitudinal mixed models, we compared lung function from age 11 years to 36 years (after adjustment for height, raw BMI at age 6 years, sex, and age) across the four insulin–asthma groups (Table 1). Overall, the FEV₁/FVC ratio differed significantly between groups ($P=0.011$, three degrees of freedom). Compared with the low insulin/no asthma group, the FEV₁/FVC ratio was significantly reduced in the group with high insulin and asthma (coefficient, -0.03 [95% confidence interval (CI), -0.04 to -0.01]; $P=0.001$). Predictive values from mixed models for the FEV₁/FVC ratio are shown in Figure 1, adjusted for the same covariates. Similar results were found for forced expiratory flow, midexpiratory phase (FEF_{25–75}) (coeff, -306 ml [95% CI -525 to -87]; $P=0.006$) and FEF_{25–75}/FVC ratio (coefficient, -0.09 [95% CI -0.15 to -0.04]; $P=0.001$). The low insulin/asthma group showed an expected pattern of reduced FEV₁ and midflows, with a proportional reduction in FVC (Table 1). There was a significant difference in FEV₁/FVC ratio and the FEF_{25–75}/FVC ratio between the low insulin/asthma and high insulin/asthma groups ($P=0.013$ and $P=0.012$, respectively). Postbronchodilator values showed a similar pattern. Compared with the low insulin/no asthma group, the postbronchodilator FEV₁/FVC ratio was significantly reduced in the group with high insulin and asthma (coefficient, -0.02 [95% CI -0.03 to -0.005]; $P=0.009$). Again, among those with asthma, the high insulin group had a lower postbronchodilator FEV₁/FVC ratio and FEF_{25–75}/FVC ratio than the low insulin group ($P=0.035$ and $P=0.016$, respectively). Adjustment for BMI, measured at the same time as asthma, did not affect the relationship between the insulin–asthma groups and lung function.

Sensitivity analyses, including time-dependent smoking and pack-years, atopy at age 6 years on the basis of skin test responses and total IgE, and allergic rhinitis at age 6 years, did not change the results in Table 1. An additional analysis classifying participants on the basis of incident asthma did not change the results.

The TCRS data show that individuals with high insulin in early life and active asthma have lung function characterized by low FEV₁/FVC ratio, reduced FEF_{25–75}, and low FEF_{25–75}/FVC ratio with relatively preserved FEV₁ and FVC, compatible with airway dysanapsis. This relationship was not explained by atopic comorbidities nor the presence of active asthma symptoms. These results suggest that the observed association between airway dysanapsis and obesity may be at least in part attributable to increased insulin concentrations in early life. Murine models have identified multiple potential synergistic mechanisms through which insulin may contribute to a low lung function state. Insulin induces the deposition of collagen in the airway, leading to remodeling (6). Insulin may directly contribute to airway hyperreactivity through suppression of muscarinic M2 receptor function (7) and also potentiate M3 muscarinic receptor agonist-induced airway smooth muscle contraction via increasing intracellular calcium responses independent of obesity (8). Whether insulin can also affect lung parenchymal growth has not been elucidated.

One potential weakness is that the use of a nonfasting insulin sample without corresponding glucose limited our ability to identify insulin resistance (e.g., using a homeostatic model assessment of insulin resistance) as a predictor of outcomes. However, fasting and nonfasting insulin measurements have a moderate correlation (9). We previously also showed that the relationship between high insulin and asthma in a separate cohort, for which fasting insulin was available, was similar to the effect of nonfasting insulin (4).

In summary, in those with active asthma, a high fasting insulin concentration at age 6 years is associated with subsequent evidence of dysanaptic airway growth. These data underscore the importance of elucidating the insulin-related mechanisms through which abnormal lung growth and airflow limitation develop over the lifetime. ■

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Correspondence and requests for reprints should be addressed to Tara Carr, M.D., University of Arizona, Tucson, Arizona. Email: taracarr@arizona.edu.

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6 Moving the Dial on Airway Inflammation in Response to Trikafta in Adolescents with Cystic Fibrosis

Agathe Lepissier¹, Anne Sophie Bonnel^{2,3}, Nathalie Wizla⁴, Laurence Weiss⁵, Marie Mittaine⁶, Katia Bessaci⁷, Eitan Kerem⁸, Véronique Houdouin^{9,10}, Philippe Reix^{11,12}, Christophe Marguet^{13,14*}, Isabelle Sermet-Gaudelus^{1,2,10,15*} and the MODUL-CF Pediatric French Network for Cystic Fibrosis

¹INSERM U1151, Institut Necker Enfants Malades, Paris, France; ²Hôpital Necker Enfants Malades, Assistance Publique Hôpitaux de Paris, Paris, France; ³Hôpital André Mignot, Le Chesnay, France; ⁴Hôpital Jeanne de Flandre, Lille, France; ⁵Hôpital de Haute-pierre, Strasbourg, France; ⁶Hôpital des Enfants-CHU de Toulouse, Toulouse, France; ⁷American Memorial Hospital, Reims, France; ⁸Hadassah Hebrew University Medical Center, Jerusalem, Israel; ⁹Hôpital Robert Debré, Paris, France; ¹⁰Université Paris Cité, Paris, France; ¹¹Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron, France; ¹²UMR 5558 CNRS Equipe EMET Université Claude Bernard Lyon 1, Lyon, France; ¹³CHU de Rouen, Rouen, France; ¹⁴UMR 1311, Université de Normandie, Rouen, France; ¹⁵European Respiratory Network-Lung, Frankfurt, Germany

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*Co-last authors.

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To the Editor:

Cystic fibrosis (CF) lung disease is characterized by excessive and sustained airway inflammation (1). The CFTR (cystic fibrosis transmembrane conductance regulator) highly effective modulator therapy (HEMT) elxacaftor, tezacaftor, and ivacaftor (ETI) demonstrated remarkable pulmonary improvement in patients with CF (2). Although the respiratory benefit reflects a better airway surface hydration and improved mucociliary clearance, data are missing regarding the effect of ETI on inflammation, specifically in patients with relatively mild lung disease. The aim of the current study is to assess the short-term effect of ETI on lung inflammation in adolescents with CF.

Methods

Study design. Patients with CF were enrolled in a multicenter real-life longitudinal study (NCT04301856). Data were collected at initiation (M0) and 1 month (M1). This included antibiotic treatment, pulmonary function tests, sweat tests, inflammatory markers in blood sampling (C-reactive protein [CRP], leukocytes, and polymorphonuclear neutrophil [PMN] counts), sputum cultures, and inflammatory biomarkers. The study was approved by the Centre Institutional Review Board. All parents gave informed consent.

Sputum sample preparation. Sputum was collected by sputum induction. Sputum samples were immediately placed on ice and frozen at -80°C . After thawing, 200 μl of sputum was processed as per laboratory protocol, and supernatant was frozen at -80°C until analysis (3, 4).

Sputum inflammatory biomarkers. Neutrophil elastase (NE) activity was measured using a fluorometric assay (Sigma-Aldrich). IL-1 β , IL-4, IL-6, IL-8, IFN- γ , and TNF- α (tumor necrosis factor α) concentrations were measured using V-PLEX Viral Panel 2 Human Kit, and V-PLEX Human IL-8 Kit (Meso Scale Discovery, Inc.). All tests were performed in triplicate.

Statistical analyses. Data were expressed as median (interquartile range). Comparisons were analyzed using the Fisher test, paired Student's *t* test, ANOVA, or simple regression analysis. FEV₁ change at M1 was quantified by its relative change from baseline.

Results

Patient population. Seventy-six European White adolescents (33 girls, median [interquartile range] age, 15 [3] yr), were enrolled from seven centers across France. Forty-six patients were p.Phe508del homozygous and had received Orkambi (lumacaftor/ivacaftor) before enrollment; the 30 remaining patients were compound heterozygous for F508del and a minimal function mutation and had not been previously treated with CFTR modulators.

Most of the patients presented with mild lung disease, as assessed by a median predicted FEV₁ (ppFEV₁) of 76% (Table 1). Patients colonized with *Pseudomonas aeruginosa* ($n = 18$), *Stenotrophomonas maltophilia*, or *Achromobacter xylosoxidans* ($n = 17$) had a significantly decreased ppFEV₁ (71% [18%] vs. 80% [20%]; $P = 0.04$). Thirty-one patients received oral or intravenous (IV) antibiotic therapy at initiation of ETI because of bronchial exacerbation.

Lung function and clinical parameters. Patients presented a significant improvement after 1 month of ETI treatment relative to baseline in both weight (+1.1 [2.9] kg) and FEV₁ (+24% [31%]),