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CHAPTER 3

Insulin resistance and lung function in the general population: the NEO study


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Submitted
ABSTRACT

Background
It remains unclear whether insulin resistance and impaired lung function are causally related or merely common consequences of obesity.

Objective
Our objective was to examine the association between insulin resistance and lung function, while adjusting for confounding including confounding by body fat and systemic inflammation.

Design
This is a cross-sectional analysis of the baseline measurements of the Netherlands Epidemiology of Obesity (NEO) study, a population-based cohort of 6,671 participants aged 45 to 65 years. Baseline insulin and glucose concentrations were used to calculate the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were assessed by spirometry and expressed as percentage predicted (%). We performed linear regression analyses with FEV₁ and FVC, as dependent variables against \(10\log\text{HOMA-IR}\) adjusted for age, sex, waist circumference, total body fat, body mass index (BMI), smoking, obstructive lung diseases, ethnicity, education, use of bronchodilator and C-reactive protein.

Results
After exclusion of participants who used systemic corticosteroids (n=45), inhaled corticosteroids (n=444), or glucose lowering therapy (n=316), and those with missing data (n=619), in total 5,247 participants (44% men) were analysed, with a mean (SD) age of 56 (6) years, and BMI of 26.1 (4.2) kg/m². In the crude model, insulin resistance was associated with lung function (a 10-fold higher HOMA-IR corresponded to a decrease in FEV₁ (change of -7.5 % [95% CI: -9.6, -5.4] and a decrease in FVC % (change -11.6 % [-13.7, -9.5]).
After adjustment for confounding factors, a small non-clinically relevant association remained (FEV₁: -2.2 % [-5.1, 0.6]; FVC: -3.3 % [-5.9, -0.8]). In particular adjustment for measures of adiposity attenuated the associations.

Conclusion
In this population-based study, the observed association between insulin resistance and lung function was mainly explained by adiposity. Our results suggest that insulin resistance and impaired lung function are merely a common consequences of obesity.
INTRODUCTION

Obesity is a world-wide public health problem and well-established risk factor for major chronic diseases such as cardiovascular disease, certain cancers, insulin resistance and type 2 diabetes. In addition, several studies have reported associations between obesity and lung function.

Traditionally, a lower lung function in persons with obesity has been considered as a purely mechanical consequence. Possible explanations for this decrease in lung function are decreased pulmonary muscle strength, pressure of abdominal fat on the diaphragm and restricted expansion of the thorax cavity due to excessive adipose tissue. More recent hypotheses suggest the involvement of adipose tissue-mediated inflammation through release of inflammatory cytokines such as TNF-α and IL-6, and the activity of NF-kappa-B. C-reactive protein (CRP) is a marker of chronic inflammation produced by the liver in response to inflammatory mediators including those secreted by adipose tissue, and CRP levels have been associated with a decrease in lung function. In addition, the production of CRP has been linked to decreased insulin sensitivity.

Several studies indicate that both insulin resistance and type 2 diabetes are associated with a decreased lung function. It has been hypothesized that such a decrease is the result of loss in muscle strength resulting from insulin resistance. Insulin plays a role in glucose uptake, and is involved in muscle contraction and protein catabolism, necessary for liberating amino acids for muscle synthesis. A study performed in 1,429 young adults in the National Health and Nutrition Examination Survey observed a more pronounced inverse association between insulin resistance and lung function in individuals with overweight or obesity than in individuals with normal weight.

It remains unclear whether insulin resistance and impaired lung function are merely unrelated consequences of excess body fat, or whether they are causally related. Therefore, the aim of this study was to investigate the association between insulin resistance and lung function in a general population, and to what extent this association is explained by body fat and systemic inflammation.

MATERIALS AND METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study in 6,671 men and women aged 45 to 65 years, with an oversampling of persons with a body mass index (BMI) of 27 kg/m² or higher. Between September 2008 and September 2012 the study included individuals from the region of Leiden (in the West of The Netherlands) with a self-reported BMI of 27 kg/m² or higher. In addition, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited irrespective of their BMI, allowing for a reference distribution of BMI.

At the baseline of the study, information on demography, lifestyle and medical history has been collected by questionnaires. Participants were asked to bring all their current medication that they used in the month preceding the study visit to the study centre, which was recorded by research nurses. Participants underwent an extensive physical examination, including anthropometry, blood sampling and spirometry. More detailed information about the study design and data collection has been described previously.
The present study is a cross-sectional analysis of the baseline measurements of the NEO study. From the 6,671 participants, we excluded all participants who were using systemic corticosteroids (n= 45), inhaled corticosteroids (n=145), a combination preparation of corticosteroids (n=299) or medication for diabetes (oral hypoglycemic agents or insulin) (n=316). We furthermore excluded participants if they had missing data on one or more of the following: lung function (n=182), blood insulin concentration (n=40), fasting glucose concentration (n=22), waist circumference (n=1), total body fat (n=27), number of packyears smoked (n=111), ethnicity (n=7), educational level (51), diabetes status (n=174), or self-reported asthma and COPD (n=4), leaving 5,247 participants for the analyses.

The study was approved by the medical ethics committee of the Leiden University Medical Center (LUMC) and all participants gave written informed consent.

**Data collection**

On the baseline questionnaire, participants reported ethnicity by self-identification in eight categories which we grouped into Caucasian and other. Tobacco smoking was reported and pack-years were calculated as the number of packs of cigarettes smoked per day multiplied by the number of years as a smoker. In addition, participants were subdivided into three categories: current smoker, former smoker and never smoker. Highest level of education was reported in 10 categories according to the Dutch education system and grouped into high versus low education. Participants reported their medical history of asthma, chronic obstructive pulmonary disease (COPD) and diabetes. At the study site, height and weight were measured without shoes and one kilogram was subtracted to correct for the weight of clothing. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Waist circumference was measured between the border of the lower costal margin and the iliac crest with the precision of 0.1 cm. Total body fat was estimated with a bioimpedance device (TBF-310, Tanita International Division, United Kingdom).

**Blood sampling**

After participants rested for 5 minutes, fasting blood samples were drawn from the antecubial vein. Fasting plasma glucose concentrations were determined by enzymatic and colorimetric methods (Roche Modular Analytics P800, Roche Diagnostics, Mannheim, Germany; CV < 5%) and serum insulin concentrations were determined by an immunoassay (Siemens Immulite 2500, Siemens Healthcare Diagnostics, Breda, The Netherlands; CV < 5%). All analyses were performed in the clinical chemistry laboratory of the LUMC. As a measure of insulin resistance we calculated the homeostasis model assessment of insulin resistance (HOMA-IR) as fasting glucose (mg/dl) * fasting insulin (µU/mL) / 22.5. Serum CRP concentrations at baseline were determined at the same laboratory using a commercial immunoturbidimetric assay with a detection limit of 3 mg/l. The between-assay coefficient of variation (CV) was 1.8%. The within-run CV was 1.8%, run-to-run CV 1.7% and day-to-day CV 2.8%.
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Lung function
All participants underwent spirometry to determine forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). Participants were required to perform at least three forced expiratory manoeuvres. The highest FEV₁ value with acceptable curves was used in the analyses. FEV₁ and FVC were expressed in litres and as a percentage of the predicted values (%pred) of individuals with similar characteristics (height, age, sex).³⁴ If no proper curve could be produced (i.e. because of a missing peak at exhalation, lack of extended exhalation or continuous inhalation during the test), lung function was defined as missing.

Statistical analyses
In the NEO study there is an oversampling of persons with a BMI of 27 kg/m² or higher. To correctly represent associations in the general population,³⁵ adjustments for the oversampling of individuals with a BMI ≥ 27 kg/m² were made. This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality,³⁶ whose BMI distribution was similar to the BMI distribution of the general Dutch population.³⁷ All results were based on weighted analyses. Consequently, the results apply to a population-based study without oversampling of participants with a BMI ≥ 27 kg/m².

Baseline characteristics of the weighted study population were expressed as mean (SD), or as percentage, stratified by quartiles of HOMA-IR. Linear regressions were performed with FEV₁% and FVC% as dependent variables. Because of a skewed distribution HOMA-IR was log transformed and 10log HOMA-IR was used as a continuous independent variable. Regression coefficients and corresponding 95% confidence intervals (CI) can be interpreted as change in FEV₁% or FVC% for a tenfold increase in HOMA-IR.

First, the crude association between HOMA-IR and the measurements of lung function was examined. Second, this association was adjusted for age and sex. Third, the model was additionally adjusted for waist circumference and total body fat. Finally, the analyses were also adjusted for smoking (in packyears), asthma, COPD, use of bronchodilators, ethnicity, level of education, BMI and CRP.

To explore whether associations differ between persons with or without obesity, we tested the presence of an interaction between 10log HOMA-IR and BMI by including an interaction term between 10log HOMA-IR (continuous and in quartiles) and BMI (continuous and < or ≥ 30 kg/m²) in the models. Subsequently we stratified the analyses by BMI according to the WHO BMI cut-offs for being normal (<25), overweight (25-30), obese (30-35), or morbidly obese (≥35).³⁸ We repeated all analyses after exclusion of participants with obstructive airway disease and participants using glucose lowering therapy. Analyses were performed with STATA Statistical Software (Statacorp, College Station, Texas, USA), version 12.1.

RESULTS
Baseline characteristics
The present analysis included 5,247 participants (44% men) with a mean (SD) age of 56 (6) years, BMI of 26.1 (4.2) kg/m², FEV₁ of 108 (16) %pred, and FVC of 117 (16) %pred. Table 3.1 shows the characteristics of our study population by quartiles of HOMA-IR. There were more men in the higher quartiles of HOMA-IR. Mean BMI, waist circumference
and total body fat were higher in higher quartiles of HOMA-IR in both men and women. Both mean FEV\textsubscript{1} and FVC in percentage predicted were lower in higher quartiles of HOMA-IR, whereas mean FEV\textsubscript{1} and FVC in litres were equal among groups. Individuals in the higher quartiles of HOMA-IR more likely had smoked in the past. Current smokers were equally divided over HOMA-IR quartiles. In addition, the mean number of packyears smoked and prevalence of diabetes was higher in the higher HOMA-IR quartiles.

Table 3.1 Characteristics of participants of the Netherlands Epidemiology of Obesity study for the total population aged 45 to 65 years by quartiles of HOMA-IR.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt;1.58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>55 (50, 63)</td>
</tr>
<tr>
<td>Sex (% Men)</td>
<td>36</td>
</tr>
<tr>
<td>BMI</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>92 (92)</td>
</tr>
<tr>
<td>Women</td>
<td>81 (9)</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Women</td>
<td>34 (6)</td>
</tr>
<tr>
<td>Ethnicity (% White)</td>
<td>96</td>
</tr>
<tr>
<td>Serum insulin (µU/mL)</td>
<td>4.7 (1.5)</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>5.1 (.5)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.2 (0.9, 1.4)</td>
</tr>
<tr>
<td>Self reported asthma (%)</td>
<td>2</td>
</tr>
<tr>
<td>Self reported COPD (%)</td>
<td>2</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (% predicted)</td>
<td>111 (15)</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>120 (15)</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (in Litres)</td>
<td>3.3 (.8)</td>
</tr>
<tr>
<td>FVC (in Litres)</td>
<td>3.3 (1.0)</td>
</tr>
<tr>
<td>Smoking behavior</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>41</td>
</tr>
<tr>
<td>Former</td>
<td>41</td>
</tr>
<tr>
<td>Current</td>
<td>17</td>
</tr>
<tr>
<td>Smoking packyears</td>
<td>8 (12)</td>
</tr>
</tbody>
</table>

Results were based on analyses weighted towards the BMI distribution of the general population. Total population n=5247; 2308 men and 2938 women. Results are shown as mean (SD), percentage or median (25th, 75th percentile). HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; BMI: Body mass index; FEV\textsubscript{1}: forced expiratory volume in one second; FVC: forced vital capacity.
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Association between HOMA-IR and lung function measurements

First, the association between insulin resistance and lung function was examined (Figure 3.1). The crude association between $10\log$ HOMA-IR and $FEV_1$ was -7.5 %pred (95% CI: -9.6, -5.4), meaning that per 10-fold higher HOMA-IR the $FEV_1$ decreased with 7.5 %pred. This association was -7.2 %pred (95% CI: -9.4, -5.1) after adjustment for age and sex, but attenuated after adjustment for waist circumference and total body fat (-2.0 %pred, 95% CI: -4.6, 0.5). After additional adjustment for BMI, smoking, obstructive lung diseases, ethnicity, education, use of bronchodilator and CRP, the association was -2.2 %pred (95% CI: -5.1, 0.6). The crude association between $10\log$ HOMA-IR and FVC (-11.6 %pred; 95% CI: -13.7, -9.5) attenuated after adjustment for age and sex (-9.4 %pred; -11.5, -7.4) and further attenuated after adjustment for waist circumference and total body fat (-3.4 %pred; -5.7, -1.1). This association did not further change after adjustment for BMI, smoking, obstructive lung diseases, ethnicity, education, use of bronchodilator and CRP (-3.3 %pred; -5.9, -0.8). Thus a tenfold higher HOMA-IR was associated with a 3.3 %pred lower lung function.

Figure 3.1: The association between $10\log$ HOMA-IR and $FEV_1$ (3.1.a) and FVC (3.1.b) in Netherlands Epidemiology of Obesity study for the total population aged 45 to 65

Results were based on analyses weighted towards the BMI distribution of the general population. Total population n=5247; 2308 men and 2938 women. HOMA-IR: Homeostatis Model Assessment of Insulin Resistance; BMI: Body mass index; $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity
Association between HOMA-IR and lung function stratified by BMI

When considering the interaction between obesity and insulin resistance in the models, the interaction term between BMI and HOMA-IR was significant in all models (P=0.000). Subsequent analyses were stratified by four BMI groups according to the WHO classification: BMI below 25 kg/m² (43.5% of participants), BMI between 25 and 30 kg/m² (42.1%), BMI between 30 and 35 kg/m² (10.5%), and BMI of 35 kg/m² or higher (3.9% of participants) (Table 3.2 and 3.3).

### Table 3.2 The association between $10\log$ HOMA-IR and FEV\textsubscript{1} in Netherlands Epidemiology of Obesity study for the total population aged 45 to 65 in four BMI categories

<table>
<thead>
<tr>
<th>Model</th>
<th>$\Delta$% in FEV\textsubscript{1} % pred</th>
<th>95% confidence interval</th>
<th>$\Delta$% in FEV\textsubscript{1} % pred</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>-3.4</td>
<td>7.4 - 11.7</td>
<td>-6.5</td>
<td>-9.6 - -3.3</td>
</tr>
<tr>
<td>Adjusted *</td>
<td>-3.6</td>
<td>6.8 - 10.4</td>
<td>-6.1</td>
<td>-9.2 - -2.9</td>
</tr>
<tr>
<td>Adjusted **</td>
<td>-1.5</td>
<td>2.9 - 6.3</td>
<td>-2.3</td>
<td>-5.6 - 0.9</td>
</tr>
<tr>
<td>Adjusted ***</td>
<td>-2.3</td>
<td>2.4 - 6.1</td>
<td>-1.7</td>
<td>-4.9 - 1.5</td>
</tr>
</tbody>
</table>

* Adjusted for age and sex
** Adjusted for age, sex, waist circumference and total body fat
*** Adjusted for age, sex, waist circumference, total body fat, BMI, smoking, obstructive lung diseases, ethnicity, education, use of bronchodilator and CRP

Results were based on analyses weighted towards the BMI distribution of the general population. Total population $n=5247$; 2308 men and 2938 women. Results are shown as delta in FEV\textsubscript{1} % predicted. HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; BMI: Body mass index; FEV\textsubscript{1}: forced expiratory volume in one second; CRP: C-reactive protein

### Table 3.3 The association between $10\log$ HOMA-IR and FVC in four BMI categories

<table>
<thead>
<tr>
<th>Model</th>
<th>$\Delta$% in FVC % pred</th>
<th>95% confidence interval</th>
<th>$\Delta$% in FVC % pred</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>-8.6</td>
<td>-11.5 - -5.7</td>
<td>-13.6</td>
<td>-18.3 - -8.9</td>
</tr>
<tr>
<td>Adjusted *</td>
<td>-7.5</td>
<td>-10.4 - -4.5</td>
<td>-11.9</td>
<td>-16.8 - -7.0</td>
</tr>
<tr>
<td>Adjusted **</td>
<td>-4.0</td>
<td>-7.0 - -1.0</td>
<td>-9.2</td>
<td>-14.2 - -4.2</td>
</tr>
<tr>
<td>Adjusted ***</td>
<td>-2.9</td>
<td>-5.8 - -1.1</td>
<td>-7.4</td>
<td>-12.4 - -2.4</td>
</tr>
</tbody>
</table>

* Adjusted for age and sex
** Adjusted for age, sex, waist circumference and total body fat
*** Adjusted for age, sex, waist circumference, total body fat, BMI, smoking, obstructive lung diseases, ethnicity, education, use of bronchodilator and CRP

Results were based on analyses weighted towards the BMI distribution of the general population. Total population $n=5247$; 2308 men and 2938 women. Results are shown as delta in FVC % predicted. HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; BMI: Body mass index; FVC: forced vital capacity; CRP: C-reactive protein
Mean BMI of these four BMI categories was respectively 22.6 (SD: 1.6), 27.1 (1.4), 31.9 (1.3), and 38.8 (3.7) kg/m². Mean HOMA-IR was respectively 1.6 (1.1), 2.5 (1.6), 3.5 (2.3) and 5.3 (5.4). Lung function was lower in higher BMI groups: FEV₁ was respectively 110.5 (15.1), 108.2 (15.8), 105.3 (15.5) and 100.7 (16.1) %pred, while FVC was respectively 120.8 (15.4), 108.2 (15.8), 105.3 (15.5) and 100.7 (16.1) %pred. After adjustment for all known confounding factors, the association between HOMA-IR and FEV₁ and FVC was weakest in participants with a BMI below 25 (FEV₁: -2.3% predicted, 95% CI: -7.0, 2.4; FVC: -3.0% predicted, 95% CI: -7.0, 1.1 per 10-fold higher HOMA-IR) and was stronger in individuals with a BMI between 30 and 35 (FEV₁: -2.9% predicted, 95% CI: -5.8, -0.1; FVC: -5.9% predicted, 95% CI: -8.6, -3.1 per 10-fold higher HOMA-IR) and in individuals with a BMI above 35 (FEV₁: -7.4% predicted, 95% CI: -12.4, -2.4; FVC: -8.6% predicted, 95% CI: -13.1, -4.1 per 10-fold higher HOMA-IR) (Table 3.2 and 3.3). The association between a tenfold higher HOMA-IR and FEV₁ and FVC in persons with a BMI between 25 and 30 were for FEV₁: -1.7% predicted (95% CI: -4.9, 1.5), and for FVC: -3.0% predicted (95% CI: -6.1, 0.1) after adjustment for all confounding factors.

DISCUSSION

We hypothesized that insulin resistance might lead to lung function impairment. We therefore investigated the association between insulin resistance and lung function in a general population aged 45 to 65 years, and explored to what extent this association could be explained by obesity. We observed a weak association between insulin resistance and lung function, but this was mainly explained by adiposity. Insulin resistance seemed to interact with BMI, with somewhat stronger associations in higher BMI groups. However, even in the group with a BMI of 35 or higher the association was not clinically relevant (7.4 percent predicted lower lung function per 10-fold higher HOMA-IR). We therefore conclude that our study does not provide evidence for a clinically relevant association between insulin resistance and lung function.

Various explanations have been proposed for the potential association between insulin resistance and lung function. First of all, insulin resistance has been associated with poor muscle strength, as defined by handgrip strength. Insulin plays a role in glucose uptake and promotes intracellular glucose metabolism, both required for adequate muscle contraction. As skeletal muscles are actively used in the manoeuvres used in obtaining a FEV₁ and FVC, a decline in muscle strength negatively influences lung function. Insulin also prevents breakdown of proteins, decreasing free amino acids availability which is essential for protein synthesis in muscle tissue.

Multiple studies have associated insulin resistance with a small decrease in lung function while in our study there was no clinically relevant association. An explanation for this difference could be the differences in study group, different lung function outcome measurements and different ways of adjusting for adiposity. The fact that the observed association between insulin resistance and lung function in our study was mainly explained by adiposity suggests that insulin resistance and impaired lung function are merely separate consequences of obesity.
Strengths of our study are the population size and extensive phenotyping of the population, allowing adjustment for the most important confounding factors. The present study also has a few limitations that should be considered. Firstly, insulin resistance was assessed using the HOMA index of insulin resistance instead of the hyperinsulinemic euglycemic clamp. The HOMA index is strongly correlated with the hyperinsulinemic euglycemic glucose clamp in large cohorts and is more practical to assess in large epidemiologic studies, but it should be noted that this is a surrogate measure of insulin resistance and may therefore not account for the total effect of insulin resistance. Although we studied insulin resistance in relation to lung function and multiple cross-sectional studies have used insulin resistance as determinant and lung function as outcome, some follow-up studies showed that lower baseline lung function is a risk factor for both insulin resistance and type 2 diabetes.

We cannot exclude that after stratification and adjustment for BMI, BMI could still have influenced our results. The small non-clinically relevant negative association between insulin resistance and lung function follows the same pattern as the negative association between BMI and lung function, which is also more pronounced at higher BMI. In fact, two studies even showed that BMI is negatively associated with lung function in overweight and obese individuals, but positively associated in lean individuals. The authors speculated that a higher BMI in lean individuals indicates more muscle mass instead of adipose tissue, while in overweight and obese individuals the excessive fat tissue, especially abdominal fat, obstructs normal breathing. Also, overweight results in loss of muscle strength required for optimal FEV1 and FVC curves. In addition to the mechanical factors of adiposity, adipose tissue also secretes various cytokines and hormones, such as IL-6, TNF-α, leptin, and adiponectin that may affect lung function. Moreover, CRP and TNF-α have also been negatively associated with insulin resistance. After adjustment of our models for CRP (measured using a high-sensitivity CRP test), the weak associations remained. Nevertheless, our results suggest that insulin resistance and impaired lung function are merely separate consequences of obesity.

In conclusion, in this study we observed a small but non-clinically relevant association between insulin resistance and lung function that was mainly explained by adiposity. The influence of overweight could be the result of mechanical and endocrine factors affecting lung function. Future prospective studies are needed to explore the association between insulin resistance and lung function. In addition, it should be noted that the presently observed lung functions were within the normal range as expected in a general population. It will therefore be relevant to investigate these relationships also in patients with obstructive lung disease, to determine whether these relationships are possibly more pronounced, and to begin to understand how high BMI contributes to the development of obstructive lung disease.
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ACKNOWLEDGEMENTS
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