Title: Covariation in Change in Lung Function and Change in BMI: The NHLBI Pooled Cohorts Study

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Introduction

Chronic lower respiratory diseases (CLRD)—which include COPD, emphysema, chronic bronchitis, and asthma—are the fourth leading cause of death and a major source of health care costs.1-4 Obesity, which is increasingly prevalent in the general population,5-7 has been previously associated with asthma, sleep apnea, airflow limitation, and restrictive physiology on spirometry,8-10 and significant weight loss has been associated with improvements in lung function in the general population.11-13 Hence, obesity may represent a potentially modifiable risk factor for low lung function and CLRD.

Yet, the dynamics of the relationship between obesity and lung function are complex and reciprocal. From a mechanistic standpoint, obesity may directly restrict ventilatory capacity. Additionally, low lung function may promote sedentary/obesogenic behavior, and shared risk factors—such as aging, immune response, diet, and microbiome14—may contribute to, and reinforce, both obesity and low lung function.

In epidemiologic studies, weight/body mass index (BMI, ratio of weight to height-squared; kg/m²) and lung function have been shown to interact in different ways depending on the weight
status and lung function of the individual. For example, obesity has been associated with worsened lung function and lung disease in the general population, but heavier weight and weight gain are associated with decreased mortality in patients with COPD.\textsuperscript{15-19} One study found that people classified as experiencing weight gain have greater decrements in FVC, but only if classified overweight to begin with, whereas weight gain was predictive of decrements in FEV1 across all baseline weight classifications.\textsuperscript{20} Another study found that lighter participants (BMI < 21.3 kg/m\textsuperscript{2}) tended to experience an increase in FEV1 and FVC but an initial decrease in FEV1/FVC through age 38, whereas those with BMI \geq 26.4 kg/m\textsuperscript{2} experienced decrements in FEV1 and FVC but increasing FEV1/FVC.\textsuperscript{20} Further, decrements in lung function tended to be associated with weight gain over the course of 10 years.\textsuperscript{20} In another study, highlighting the bidirectional relationship between BMI and lung function, baseline BMI predicted decline in lung function and, reciprocally, people considered to experience rapid decline in lung function had greater subsequent abdominal obesity.\textsuperscript{21}

Hence, to elucidate the dynamic interplay between weight/BMI and lung function as they change over time, it is critical to examine how obesity and lung function each impact change in the other. Whereas prior research has mainly examined a single outcome at a time (i.e., examining either lung function or weight-related outcomes separately), and has frequently used reductive categorizations of lung function (e.g., “rapid decline”)\textsuperscript{21} or BMI change (e.g., gain vs. loss),\textsuperscript{20} such methods cannot adequately address how BMI and lung function each change over time; how lung function and BMI influence change in the other; or, whether/how these relationships might vary across different categorizations of BMI and lung function impairment. We therefore propose to apply dyadic growth curve modeling and cross-lagged structural equation modeling to examine covariation of change in and reciprocal influences\textsuperscript{22} between BMI and lung function across different BMI categories and in persons with and without abnormal spirometry in a large US population-based sample of adults.\textsuperscript{23}

**Main study questions and hypotheses**

1. Do the rates of change (i.e., temporal trends) in BMI and in lung function (FEV1, FVC, FEV1/FVC) covary?

2. Does BMI (lung function) at a previous time point predict current lung function (BMI), after accounting for previous lung function (BMI)? (i.e., influence)

3. Is there effect modification for Questions 1 or 2 by:
   a. Baseline BMI categorization? (i.e., underweight, normal, overweight, obese)
   b. Baseline lung function? (e.g., presence/absence of airflow limitation)

**Data**

**Sample**

We will use data from five large cohorts which provide 3 or more spirometry assessments to allow sufficient data for stable growth curve estimates, that have been harmonized and pooled as part of the NHLBI Pooled Cohorts Study.\textsuperscript{23}

1. Atherosclerosis Risk in Communities (ARIC) Study
2. Coronary Artery Risk Development in Young Adults (CARDIA) Study
3. Cardiovascular Health Study (CHS)
4. Framingham Heart Study (FHS)
5. Health, Aging, and Body Composition (Health ABC) Study
We will exclude participants who:

- Provided < 3 spirometry readings
- Are not classified as White or Black (due to low numbers of other race/ethnicities represented in the 5 cohorts above)

We will also exclude observations that do not meet 2005 ATS/ERS spirometry quality standards.\(^\text{24}\)

The resulting total N is 13,729 participants and 54,916 observations. There are 2568 obese participants (BMI ≥ 30 kg/m\(^2\)), 4987 overweight participants (25 ≤ BMI < 30 kg/m\(^2\)), 5932 normal weight participants (18.5 ≤ BMI < 25 kg/m\(^2\)), and 242 underweight participants (BMI < 18.5 kg/m\(^2\)). Approximately 75% of the sample is White, and 25% is Black.

Outcomes

- Lung function
  - Repeat assessments of FEV\(_1\), FVC, and FEV\(_1\)/FVC, using spirometry data that has been validated, harmonized, and pooled by the NHLBI Pooled Cohorts Study.\(^\text{23}\)
  - Lung function impairment will be categorized according to the lower limit of normal (LLN), as defined by NHANES III reference equations.\(^\text{25}\)
    - Airflow limitation: FEV\(_1\)/FVC < LLN
    - Restrictive pattern: FEV\(_1\)/FVC ≥ LLN and FVC < LLN
    - Preserved spirometry: neither airflow limitation nor restrictive pattern
    - Of note, current guidelines support a fixed ratio for defining airflow limitation.\(^\text{26}\) Because this leads to differential rates of misclassification over the life course,\(^\text{27}\) we will use the age-specific LLN threshold for our primary endpoints. Fixed thresholds will be used in sensitivity analyses.
- Body mass index
  - Weight/height\(^2\) (kg/m\(^2\)), continuous.
  - Categorized by CDC category definitions specified above.\(^\text{28}\)

Covariates

- Socio-demographics: sex, race/ethnicity, educational attainment, birth year
- Anthropometric: time-varying height, time-varying height squared
- Smoking: time-varying smoking status, baseline pack-years
- Other: study
  *Note: Covariates will be entered as predictors of both slope and intercept. Continuous covariates will be mean-centered prior to analysis. Categorical covariates (e.g., education) will be centered around median reference values.*

Methods and Analytic Plan

- Baseline participant characteristics will be tabulated.
- **Question 1**: Dyadic models will be specified as multilevel, multivariate growth curve models. Data are structured so that there are two observations for each person-visit: one observation representing BMI as the outcome and the other observation representing...
Lung Function. Random intercepts and random slopes (using “age” as a time-varying covariate) will be specified separately for each outcome (4 random effects—2 intercepts and 2 coefficients for age—in total). The quadratic term for slope will be evaluated and included, if significant, as either a random or fixed effect. The residuals error structure will be specified to allow covariance between the errors for lung function and BMI at each time point, and different variances over time for lung function and BMI separately. The covariance/correlation of the age coefficients (average annual rates of change in BMI and lung function) will be compared qualitatively across the three separate models for FEV1, FVC, and FEV1/FVC. Models will be adjusted for the abovementioned covariates as predictors of both slopes and intercepts. Fixed effects will be reported, but the primary focus is on the covariance/correlation of the age coefficients (i.e., the degree of association between the average annual rate of change in BMI and in lung function), the intercept-slope covariance (i.e., how expected lung function /BMI at age X correlates with the average annual rate of change over time), intercept covariance (i.e., how expected BMI and expected lung function at age X relate), and the residual covariance (i.e., remaining interdependence in BMI and lung function).

- **Question 2:** We will estimate cross-lagged structural equation models with separate random intercepts for lung function and for BMI. For example, BMI at Time X will be predicted by BMI at Time X-1 (stability in BMI) and by lung function at Time X-1 (influence of lung function on BMI). The focus in these models are on fixed effects for stability and influence.

- **Question 3:** Effect modification by BMI category and initial lung function (i.e., airflow limitation, restriction, normal) will be assessed by multiplicative interaction terms and in stratified models.

- **Additional sensitivity analyses**
  - In order to examine potential differences in covariation of change trajectories and BMI/lung function at different points in the life-course (Question 1), we will examine the impact of centering age at 35, 45, 55, and 65.
  - We will also examine whether results are robust to the following adjustments:
    - BMI classification by quartiles, rather than CDC BMI cutoffs
    - Lung function impairment classification by fixed (versus LLN) thresholds
  - With respect to missing data and the potential for selection/attrition biases, we will consider several different approaches including relaxing selection criteria (e.g., including anyone who provides fewer than 3 observations), inverse probability weighting, and multiple imputation conditional on vital status. We will also perform sensitivity analyses stratifying by cohort, given differing rates of attrition by cohort.
References


