# A Dyadic Growth Modeling Approach to Examine Associations Between Weight Gain and Lung Function Decline: The NHLBI Pooled Cohorts Study

Talea Cornelius, Joseph E. Schwartz, Pallavi Balte, Surya P. Bhatt, Patricia A. Cassano, David Currow, David R. Jacobs, Jr., Miriam Johnson, Ravi Kalhan, Richard Kronmal, Laura Loehr, George T. O'Connor, Benjamin Smith, Wendy B. White, Sachin Yende, and Elizabeth C. Oelsner

Correspondence to Dr. Elizabeth C. Oelsner, Division of General Medicine, Columbia University Irving Medical Center, 622 West 168th Street, PH9E-105K, New York, NY, 10032 (email: eco7@cumc.columbia.edu)

This is a pre-copyedited, author-produced version of an article accepted for publication in American Journal of Epidemiology following peer review. The version of record Talea Cornelius, Joseph E Schwartz, Pallavi Balte, Surya P Bhatt, Patricia A Cassano, David Currow, David R Jacobs Jr, Miriam Johnson, Ravi Kalhan, Richard Kronmal, Laura Loehr, George T O'Connor, Benjamin Smith, Wendy B White, Sachin Yende, Elizabeth C Oelsner, A Dyadic Growth Modeling Approach to Examine Associations Between Weight Gain and Lung Function Decline: The NHLBI Pooled Cohorts Study, American Journal of Epidemiology, , kwaa059, is available online at: https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwaa059/5819837

Author affiliations: Columbia University Medical Center, Department of Medicine, New York, NY, USA (Talea Cornelius, Joseph E. Schwartz, Pallavi Balte, and Elizabeth C. Oelsner); Stony Brook School of Medicine, Stony Brook, NY, USA (Joseph E. Schwartz); University of Alabama at Birmingham, Division of Pulmonary, Allergy and Critical Care Medicine, Birmingham, AL, USA (Surya P. Bhatt); Cornell University, Division of Nutritional Sciences, Ithaca, NY, USA (Patricia A. Cassano); University of Technology Sydney, Sydney, AU (David Currow); University of Hull, Hull York Medical School, Hull, AU (David Currow and Miriam Johnson); University of Minnesota, School of Public Health, Minneapolis, MN, USA (David R. Jacobs, Jr.); Northwestern University, Feinberg School of Medicine, Chicago, IL, USA (Ravi Kalhan); University of Washington, School of Public Health, Seattle, WA, USA (Richard Kronmal); University of North Carolina, Gillings School of Global Public Health, Chapel Hill, NC, USA (Laura Loehr); Boston University, School of Medicine, Boston, MA, USA (George T. O'Connor); McGill University Health Centre, Québec, CA (Benjamin Smith); Tougaloo College, Tougaloo, MS, USA (Wendy B. White); University of Pittsburgh, Department of Critical Care Medicine, Pittsburgh, PA, USA (Sachin Yende)

This work was supported as follows by grants from the National Institutes of Health (NIH) and the U.S Environmental Protection Agency:

*NHLBI Pooled Cohorts Study*: NIH/NHLBI R21-HL121457, R21-HL-129924, K23-HL-130627.

*CARDIA*: The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201800005I & HHSN268201800007I), Northwestern University (HHSN268201800003I), University of

Minnesota (HHSN268201800006I), and Kaiser Foundation Research Institute (HHSN268201800004I). This manuscript has been reviewed by CARDIA for scientific content.

*CHS*: This research was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

*Framingham Offspring Study*: From the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195; HHSN268201500001I).

*Health, Aging and Body Composition Study*: This research was supported by National Institute on Aging (NIA) contracts #N01-AG-6-2101; N01-AG-6-2103; N01-AG-6-2106; NIA grant R01-AG028050; NINR grant R01-NR012459. This research was supported in part by the intramural research program at the NIA.

*MESA*: NIH/NHLBI R01-HL-077612, R01-HL-093081, RC1-HL-100543, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169. This publication was also developed under a STAR research assistance agreement, No. RD831697 (MESA Air), awarded

by the U.S Environmental Protection Agency. It has not been formally reviewed by the EPA. The views expressed in this document are solely those of the authors and the EPA does not endorse any products or commercial services mentioned in this publication.

Conflicts of Interest: Surya P Bhatt has received research grants from the NIH and from ProterixBio, consulting fees from Sunovion, and has served on the advisory boards for Sunovion and GlaxoSmithKline; Ravi Kalhan reports grants from NHLBI, Boehringer Ingelheim, PneumRx (BTG), Spiration, Astrazeneca, and GlaxoSmithKline, and personal/consulting fees from Boehringer Ingelheim, AstraZeneca, CVS Caremark, Aptus Health, GlaxoSmithKline, and Boston Scientific; GTO reports grants from Janssen Pharmaceuticals, and personal/consulting fees from Astra Zeneca; David Currow is a paid consultant and receives payment for intellectual property with Mayne Pharma. Talea Cornelius, Pallavi P Balte, Patricia Ann Cassano, David R Jacobs Jr., Miriam Johnson, Richard Kronmal, Joseph E. Schwartz, Benjamin Smith, Laura R Loehr, Wendy B. White, Sachin Yende, and Elizabeth Oelsner report no competing interests relevant to the present work.

Running head: Modeling Weight Gain and Lung Function Decline

ABSTRACT

The relationship between body weight and lung function is complex. Using a dyadic multilevel linear modeling approach, treating body mass index (BMI) and lung function as paired, within-person outcomes, we test the hypothesis that individuals with more rapid increase in BMI exhibit more rapid decline in lung function: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and their ratio (FEV1/FVC). Models included random intercepts and slopes and were adjusted for socio-demographic and smoking-related factors. A sample of 9,115 adults with paired measurements of BMI and lung function at ≥3 visits were selected from a pooled set of 5 US population-based cohorts (1983 – 2018; mean age at baseline, 46 years; median follow-up, 19 years). At age 46, average annual rates-of-change in BMI, FEV1, FVC, and FEV1/FVC were 0.22 kg/m$^2$/year, -25.50 mL/year, -21.99 mL/year, and -0.24 percent/year, respectively. Individuals with steeper BMI increases had faster declines in FEV1 (r=-0.16) and FVC (r=-0.26), and slower declines in FEV1/FVC (r=0.11) (all P<0.0001). Results were similar in subgroup analyses. Residual correlations were negative (P<.0001), suggesting additional interdependence between BMI and lung function. Results show that greater rates of weight gain are associated with greater rates of lung function loss.

Keywords (3-8): BMI, cohort studies, COPD, dyadic models, longitudinal, lung function, obesity, spirometry

Abbreviations: CRD = Chronic Respiratory Diseases; COPD = Chronic Obstructive Pulmonary Disease; BMI = Body Mass Index; FEV1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital Capacity; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; FHS-O = Framingham Offspring Cohort; Health ABC = Health, Aging and Body Composition; MESA = Multi-Ethnic Study of Atherosclerosis

Obesity and chronic respiratory diseases (CRDs) have increased in prevalence and global public health impact over recent decades (1, 2). According to the Global Burden of Disease study, high body mass index (BMI) contributed to 4.0 million deaths in 2015, and chronic obstructive pulmonary disease (COPD) and asthma contributed to 3.6 million deaths (1). Understanding interrelationships between the obesity and CRD epidemics is therefore of great public health importance.

Obesity and low lung function are physiologically interdependent: obesity may restrict ventilatory capacity, reduce exercise capacity, and contribute to breathlessness, while low lung function may reinforce sedentary and obesogenic behavior (3-6). Elevated BMI and low lung function also have shared risk factors, such as aging, immune response, diet, physical inactivity, and the microbiome (7). These complex causal networks may engender correlations between within-person changes in BMI and lung function.

Dyadic growth modeling has been applied to understand associations in rates-of-change between paired individuals (e.g., couples, parent/child) (8, 9). To our knowledge, it has never been applied to paired, within-individual health outcomes such as BMI and lung function. Rather, prior research has relied on non-dyadic models that test associations between a given exposure and outcome—whether changes in BMI predict changes in lung function, or vice versa (10-32). Dyadic models are better suited for describing the association between rates-of-change for BMI and lung function because they provide estimates of the between-person association of the within-person long-term trends/trajectories in the two outcomes and, also, the pooled within-person association between the concurrent short-term deviations of each outcome from its

trajectory. Because neither outcome is predicting the other, dyadic models bypass concerns regarding causal ordering (e.g., confounding by prior exposure) (33).

We applied a dyadic growth modeling approach to examine concurrent rates-of-change in BMI and lung function in a large, US general population-based sample of adults (34). Treating BMI and lung function as a person-level "dyad," we tested the hypothesis that individuals with more rapid rates of gain in BMI would exhibit more rapid rates of lung function loss. We explored whether these associations varied over the life-course, across ranges of BMI and lung function at baseline, or according to socio-demographic and clinical factors.

## METHODS

### NHLBI Pooled Cohorts Study

The NHLBI Pooled Cohorts Study harmonized and pooled data from nine US epidemiologic cohorts that conducted lung function assessments over the last four decades (34). This report is limited to five cohorts that conducted three or more spirometry assessments between 1983 – 2018 (**Web Table 1**): Coronary Artery Risk Development in Young Adults (CARDIA) (35); Cardiovascular Health Study (CHS) (36); Framingham Offspring Cohort (FHS-O) (37); the Health, Aging and Body Composition (Health ABC) (38); and the Multi-Ethnic Study of Atherosclerosis (MESA) (39).

Primary analyses included participants with ≥3 valid spirometry exams with full data on BMI and covariates. The sample was restricted to participants of Non-Hispanic White or African-American race/ethnicity due to low numbers of participants in other race/ethnic groups (**Web Figure 1**).

All studies were approved by Institutional Review Boards at participating institutions and all participants provided written informed consent.

Lung function

Pre-bronchodilator lung function was measured using water-seal, dry-rolling-seal, or flow-sensing spirometers following American Thoracic Society (ATS) guidelines current at the time of assessment. To harmonize spirometry data, we applied a standardized quality grading system based upon 2005 ATS/European Respiratory Society guidelines, which define valid exams as two or more acceptable curves reproducible within 150 mL. Invalid exams were excluded (34, 40). This approach was previously found to reduce between-person and within-person variability, outliers, and lung-function trend irregularities.

Lung function outcomes were forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and their ratio (FEV1/FVC). Standardized Z-scores, generated using the Global Lung Function Initiative (GLI) equations (41) were used in sensitivity analyses.

Airflow limitation was defined as FEV1/FVC less than the lower-limit-of-normal (LLN), defined by the NHANES III reference equations (42). Restrictive pattern was defined as FEV1/FVC≥LLN and FVC<LLN. Preserved spirometry was defined as absence of airflow limitation or restrictive pattern.

BMI

Height and weight were measured using standard techniques at each spirometry exam. BMI was defined as weight/height-squared ($kg/m^2$).

BMI was categorized according to the Centers for Disease Control (CDC) definitions (43): obesity (≥30), overweight (≥25-<30), normal weight (≥18.5-<25), and underweight (<18.5).

Covariates

Sex, race/ethnicity, educational attainment, birth year, and pack-years of smoking history were self-reported at the baseline exam. Smoking status was self-reported at each spirometry exam; biochemical verification by cotinine was available for two cohorts, in which 2% to 4% were reclassified as current smokers based on cotinine discordance (44, 45). Baseline clinical CRDs were self-reported COPD, emphysema, chronic bronchitis, and/or asthma; or, inhaler use, defined by self-report or medication inventory (34).

Statistical analyses

Data were structured so that there were two observations for each person-visit: one observation representing BMI as the outcome, and the other representing lung function (FEV1, FVC, or FEV1/FVC) as the outcome. Using mixed linear models (PROC MIXED, SAS Version 9.4, Cary, NC), a random intercept and random slope for the effect of time were specified separately for each outcome to account for individual differences in within-person rates-of-change for each outcome. The repeated statement was used to account for unexplained within-person variance in lung function and BMI (residuals), as well as any covariance between concurrent (i.e., same exam) lung function and BMI residuals.

Separate dyadic models were specified for the relationships between rate-of-change in BMI with rates-of-change in each of the three lung function measures (**Figure 1**). First, we examined predicted BMI and lung function levels over the life course, together with estimates of the predicted rate-of-change (slope) at specific ages. Second, we examined the degree of association between individuals' average rate-of-change in BMI and their average rates-of-change in lung function, specifically the correlations (*r*) and their standard errors (*se*). To visualize the bivariate distribution of these two rates-of-change, estimates of each participants' random effect for rates-of-change in BMI and lung function were plotted, along with 95% confidence ellipses. Third, "residual correlations" were examined; this indicates additional, short-term association between individuals' BMI and lung function, independent of their shared temporal patterns (46).

All models treated biological age-at-measurement as the time scale and were adjusted for the following covariates, entered as predictors of both intercept and slope: time-varying age-squared, height, height-squared, and smoking status; and time-invariant (baseline) gender, educational attainment, birth-year, race/ethnicity, study, and pack-years. Height and height-squared were included as covariates since they are major determinants of predicted lung function (42). Sensitivity analyses were performed using weight (kg) and waist circumference as outcomes, rather than BMI, among participants without baseline clinical CRDs, and including all participants with two or more valid spirometry measures.

Stratified analyses were performed to identify differences by baseline BMI and lung function categories, as well as by baseline age group, birth cohort, study cohort, sex, race/ethnicity, and smoking status. Meta-analysis was performed to test for the presence of heterogeneity in slope correlations within each set of stratified analyses using the *Q* statistic.

For comparison, associations between BMI and lung function were tested using six non-dyadic models (**Figure 1**): baseline BMI and rate-of-change in BMI (i.e., last BMI minus baseline BMI, divided by last age minus baseline age) as predictors of (1) FEV1, (2) FVC, and (3) FEV1/FVC, and baseline and rates-of-change in (4) FEV1, (5) FVC, and (6) FEV1/FVC as predictors of BMI. In these models, the parameter of interest was the impact of change in the predictor on change in the outcome (e.g., the association of change in BMI with the FEV1 slope—the change-by-age interaction). Estimating both the effect of BMI on lung function and vice versa violates the assumption that the residuals are independent of the predictors; hence, this is done only for illustrative purposes.

RESULTS

There were 9,115 participants (**Table 1**) with a median of 4 (interquartile range [IQR] 3—5) observations over a median follow-up of 19 years (IQR 10—28; **Web Table 2**). Fifty-seven percent were women, 73% were non-Hispanic White, and 27% were African-American. At the baseline exam, 49% were never-smokers, 31% were former smokers, and 19% were current smokers; among ever-smokers, the median pack-years was 9 (IQR 2—25). At baseline, 4% and 6% reported prior physician diagnosis of COPD and asthma, respectively.

Median BMI was 25 at the baseline exam; 18% were obese, 34% were overweight, 46% were normal weight, and 2% were underweight (**Table 1**). Among participants at normal weight at the baseline exam, 34% and 15% transitioned to overweight and obesity, respectively, by the time of their last spirometry visit (**Web Table 3**).

At baseline, mean percent predicted FEV1 was 96, mean percent predicted FVC was 99, mean FEV1/FVC was 0.78 and the prevalences of airflow limitation and restrictive spirometry were 11% and 5%, respectively. (**Table 1**). As of the last spirometry visit, the proportions with incident airflow limitation and restrictive spirometry were 7% and 6%, respectively (**Web Table 4**).

Changes in BMI and lung function over follow-up

On average, BMI increased over time, although the rate of increase decelerated with age (**Figure 2A**). The predicted BMI slope was 0.33 /year at age 35, but only 0.03 /year at age 65. By contrast, lung function decreased over time at an accelerating rate (**Figure 2B, 2C, 2D**). At 35 years old, the predicted FEV1 and FVC slopes were -18.98 mL/year and -10.38 mL/year, respectively; at 65 years old, the predicted FEV1 and FVC slopes were -36.77 mL/year and -42.05 mL/year, respectively. Consistent with a relatively greater acceleration in FVC versus FEV1 decline with increasing age, the rate of FEV1/FVC decline decelerated at later ages: -0.29 percent/year at age 35, and -0.15 percent/year at age 65.

Correlations between rates-of-change in BMI and lung function

Those with a steeper rate of increase in BMI over time tended to have a steeper rate of decline in FEV1 ($r$=-0.16, $se$=0.02, $P$<0.001; **Figure 3A**). The correlation of within-person slopes was even more negative with respect to the FVC ($r$=-0.26, $se$=0.02, $P$<0.001; **Figure 3B**). Consistent with these relationships, a steeper BMI gain was associated with a more gradual FEV1/FVC decline (i.e., less negative slope), as indicated by a positive correlation of within-person slopes ($r$=0.11, $se$=0.02, $P$<0.001; **Figure 3C**). Results when BMI was replaced by weight (FEV1: $r$=-0.17, $P$<0.001; FVC: $r$=-0.27, $P$<0.001; FEV1/FVC: $r$=0.11, $P$<0.001; **Web Figure 2**) or waist circumference (FEV1: $r$=-0.25, $P$<0.001; FVC: $r$=-0.35, $P$<0.001; FEV1/FVC: $r$=0.17, $P$<0.001) were similar.

Residual correlations

Correlations between residuals for BMI and those for lung function outcomes were consistently negative (FEV1: $r$=-0.25, $se$=0.01, $P$<0.001; FVC: $r$=-0.23, $se$=0.01, $P$<0.001; FEV1/FVC: $r$=-0.02, $se$=0.01, $P$<0.001; **Web Figure 3**). This indicates that, on those exams when a participant's BMI was higher (lower) than predicted from her/his covariate-adjusted BMI trajectory, s/he tended to have a lower (higher) lung function than predicted.

Stratified analyses

There was no evidence of heterogeneity in the correlation between individuals' rates-of-change in BMI and lung function in analyses stratified by baseline BMI or lung disease (**Figure 4**). However, there were differences by baseline lung function ($Q$=10.46, $P$=.005). Participants with initial airflow limitation exhibited a near-zero correlation between BMI and FEV1 rates-of-change, even as the inverse correlation with FVC rate-of-change remained, resulting in the BMI rate-of-change exhibiting an even greater correlation with FEV1/FVC rate-of-change (not shown).

Correlations between rates-of-change for BMI and lung function also differed by smoking status (FEV1: $Q$=14.49, $P$<.001; FVC: $Q$=9.76, $P$=.008), with the strongest correlations observed among never smokers and the weakest correlations among former smokers (**Figure 4**).

Correlations of BMI and FVC rates-of-change were stronger in males versus females ($Q$=4.12, $P$=.042). Correlations of rate-of-change for BMI with those for FEV1 and FVC were stronger in Black versus White participants (FEV1: $Q$=14.70, $P$<.001; FVC $Q$=11.17, $P$<.001), more recent generations (FEV1: $Q$=26.88, $P$<.001; FVC: $Q$=12.79, $P$<.001), and more contemporary study cohorts (FEV1: $Q$=24.71, $P$<.001; FVC: $Q$=17.74, $P$<.001)) (**Web Figure 4**).

Re-analysis including participants with two or more valid spirometry measures (N=13,332) somewhat attenuated correlations between rates-of-change in BMI and lung function (FEV1: $r$=-0.12; FVC: $r$=-0.19; FEV1/FVC: $r$=0.08; all $P$<0.0001).

Comparisons with non-dyadic models

Non-dyadic models supported similar conclusions to our dyadic models (**Web Table 5**), although some results were relatively difficult to interpret or misleading. For example, the estimated effect of change in BMI on FVC intercept was positive, suggesting that those with more rapid increase in BMI had a higher FVC; however, the estimated effect of change in BMI on FVC slope was negative, suggesting that more rapid BMI increase was associated with more rapid rate of decline in FVC. Contradictory intercept and slope estimates also emerged in the non-dyadic models predicting FEV1 and FEV1/FVC from change in BMI.

DISCUSSION

More rapid rates of increase in BMI were associated with greater rates of decline in FEV1 and especially FVC in a large, US general population-based sample of adults. These correlations were present across the range of baseline BMI values, consistent with underlying physiologic interdependence between weight gain and lung function loss.

This is the first study to apply dyadic growth modeling to characterize relationships between weight gain and lung function loss, and to compare these to single-outcome growth models. In our data, non-dyadic results were inconsistent, complicating their interpretation. Non-dyadic models also did not quantify the strength of the association between rates-of-change in BMI and lung function (i.e., the correlation between the slopes representing their respective rates-of-change), and were unable to differentiate these long-term associations from correlated residuals. Importantly, if causal relationships are bidirectional, non-dyadic models suffer from time-varying confounding by prior exposure (33) and lack of independence of residuals. By contrast, our dyadic growth models identified correlations between rates-of-change in continuous measures of BMI and lung function that bypassed issues regarding causal ordering, were internally consistent and consistent with our hypotheses (based on physiologic and epidemiologic literature), and were straightforward to interpret. Rather than using change scores as a predictor, which is commonly done but inherently introduces error, treating within-person trajectories as latent variables accounts for differential uncertainty in rates-of-change across participants and increases the precision of estimated correlations between individuals' rates-of-change in BMI and lung function (46). Furthermore, our analysis estimated correlations between BMI and lung function residuals, suggesting interdependence between concurrently assessed

measures of BMI and lung function that is not accounted for by correlated rates-of-change or other time-varying covariates.

Our results confirm and extend previously reported associations between increasing weight and decreasing lung function, particularly FVC (24, 26, 28, 47, 48). Our findings are also consistent with cross-sectional data linking metabolic syndrome to increased prevalence of restrictive lung disease, the hallmark of which is low FVC (49), as well as longitudinal studies showing stronger associations of weight gain with FVC loss than with FEV1 loss (21-31).

Whereas some have argued that the adverse effects of increased BMI on lung function are limited to those who are already overweight or obese (25, 29), our findings clearly show that the correlation between rate of BMI gain and lung function loss is consistent across categories of baseline body BMI. This suggests that alterations in lung mechanics previously associated with massive obesity (50) impact individual lung function trajectories in the context of weight gain across the continuum of weight status. Physiological mechanisms for the observed associations between rate of weight gain and rate of FVC decline may include decreased lung compliance via micro-atelectasis and/or decreased chest-wall compliance and reduced diaphragmatic excursion due to abdominal fat (4, 51-55). With respect to FEV1 decline, increased airway resistance may be one of the adverse physiologic impacts of the shallower breathing favored by decreased lung compliance (11, 56, 57). Furthermore, weight gain is bi-directionally linked with pro-inflammatory markers (58, 59), which are implicated in airway remodeling and FEV1 decline (60, 61).

Our finding of preserved FEV1 despite weight gain in persons with initial airflow limitation provides some support for the "obesity paradox" wherein overweight and obesity have been linked with favorable outcomes in COPD, while underweight has been more strongly linked with emphysema (16-20). Physiologically, the "strapping effect" may help to explain our results. Chest wall strapping in experimental paradigms promotes breathing at smaller lung volumes. In those with airflow obstruction in particular, strapping may raise FEV1 due to increased elastance or increased dilation of small airways (62). Our finding of no association between BMI and FEV1 rates-of-change in participants with airflow limitation may reflect a lesser decline in FEV1 due to "strapping" by obesity (62-64). That said, our results were non-paradoxical among persons with and without self-reported CRDs. It is also important to consider whether the "paradox" may be explained by smoking. Smoking cessation reduces the rate of lung function decline and promotes weight gain (65). Consistent with this, correlations of rates of BMI gain with decline in FEV1 and FVC were most negative in never smokers, and most attenuated in former smokers.

Strengths of this work include the application of a novel, robust analytic method to analyze the association between rates-of-change in BMI and lung function. We used rigorously quality-controlled, harmonized data from five large, US general population-based cohort studies with excellent long-term follow-up.

There were nonetheless a number of limitations. This was a descriptive analysis, so direct clinical applicability is limited. However, results are consistent with prior work showing that an intensive weight loss program was associated with improved lung function in obese women (13,

66) and that weight loss improves asthma control in obese individuals with severe asthma (67). There is also limited evidence to suggest that inhaler use, which improves lung function, may promote weight loss, although the hypothesized mechanisms for this response relate to metabolic pathways (68).

Restricting the sample to participants with at least three observations improved estimation of parameters pertaining to individuals' rates-of-change at the expense of potential selection bias. At baseline, participants excluded from the primary analyses were older and had higher BMI and lower lung function. Including participants with two or more measures attenuated the associations, but associations persisted.

We did not have measures of abdominal adiposity, which were more strongly associated with lung function than BMI or weight in some prior work (69). Similarly, other lung volumes, such as total lung capacity and expiratory reserve volume, have been more strongly associated with obesity in some prior studies (12), but were not available in this study. Other covariates, such as physical activity, diet, or other environmental exposures, were unavailable in this study and should be included in future research.

In conclusion, this is the first study to apply dyadic growth modeling to estimate correlations between within-person rates-of-change in BMI and lung function, showing that individuals with more rapid rates of increase in BMI exhibited more rapid rates of decrease in FEV1 and particularly FVC. Residual correlations between BMI and lung function suggested negative associations between BMI and lung function not accounted for by the model. Thus, in addition to

showing that increased rates of weight gain are associated with increased rates of lung function decline in the general population, this study demonstrates that dyadic growth models are a promising approach to examine associations between interdependent health outcomes.

REFERENCES


1. Collaborators GBDO, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13-27.
2. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.
3. Jakes RW, Day NE, Patel B, Khaw KT, Oakes S, Luben R, et al. Physical inactivity is associated with lower forced expiratory volume in 1 second : European Prospective Investigation into Cancer-Norfolk Prospective Population Study. Am J Epidemiol. 2002;156(2):139-47.
4. Koenig SM. Pulmonary complications of obesity. Am J Med Sci. 2001;321(4):249-79.
5. Currow DC, Dal Grande E, Sidhu C, Ekström M, Johnson MJ. The independent association of overweight and obesity with breathlessness in adults: a cross-sectional, population-based study. European Respiratory Journal. 2017;50(3):1700558.
6. Vermeulen F, Garcia G, Ninane V, Laveneziana P. Activity limitation and exertional dyspnea in adult asthmatic patients: what do we know? Respiratory medicine. 2016;117:122-30.
7. Peters U, Suratt BT, Bates JH, Dixon AE. Beyond BMI: Obesity and Lung Disease. Chest. 2017;153(3):702-09.
8. Cornelius T, Gettens K, Gorin AA. Dyadic dynamics in a randomized weight loss intervention. Annals of Behavioral Medicine. 2016;50(4):506-15.
9. Kashy DA, Donnellan MB, Burt SA, McGue M. Growth curve models for indistinguishable dyads using multilevel modeling and structural equation modeling: The case of adolescent twins' conflict with their mothers. Developmental Psychology. 2008;44(2):316-29.
10. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. Jama. 1999;282(16):1523-9.
11. Rubinstein I, Zamel N, DuBarry L, Hoffstein V. Airflow limitation in morbidly obese, nonsmoking men. Annals of internal Medicine. 1990;112(11):828-32.
12. Jones RL, Nzekwu M-MU. The effects of body mass index on lung volumes. Chest. 2006;130(3):827-33.
13. Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. Chest. 2004;125(6):2046-52.
14. Hakala K, Stenius-Aarniala B, Sovija A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. Chest. 2000;118(5):1315-21.
15. Tantisira K, Weiss S. Complex interactions in complex traits: obesity and asthma. Thorax. 2001;56(suppl 2):ii64-ii74.
16. Hanson C, Rutten EP, Wouters EF, Rennard S. Influence of diet and obesity on COPD development and outcomes. International journal of chronic obstructive pulmonary disease. 2014;9:723-33.

17. Eriksson B, Backman H, Bossios A, Bjerg A, Hedman L, Lindberg A, et al. Only severe COPD is associated with being underweight: results from a population survey. ERJ open research. 2016;2(3):00051-2015.
18. Poulain M, Doucet M, Major GC, Drapeau V, Sériès F, Boulet L-P, et al. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. Canadian Medical Association Journal. 2006;174(9):1293-9.
19. Zammit C, Liddicoat H, Moonsie I, Makker H. Obesity and respiratory diseases. International journal of general medicine. 2010;3:335-43.
20. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1989;139(6):1435-8.
21. Wang ML, McCabe L, Petsonk EL, Hankinson JL, Banks DE. Weight gain and longitudinal changes in lung function in steel workers. Chest. 1997;111(6):1526-32.
22. Chinn DJ, Cotes JE, Reed JW. Longitudinal effects of change in body mass on measurements of ventilatory capacity. Thorax. 1996;51(7):699-704.
23. Chen Y, Horne SL, Dosman JA. Body weight and weight gain related to pulmonary function decline in adults: a six year follow up study. Thorax. 1993;48(4):375-80.
24. Wise RA, Enright PL, Connett JE, Anthonisen NR, Kanner RE, Lindgren P, et al. Effect of weight gain on pulmonary function after smoking cessation in the Lung Health Study. American journal of respiratory and critical care medicine. 1998;157(3 Pt 1):866-72.
25. Carey IM, Cook DG, Strachan DP. The effects of adiposity and weight change on forced expiratory volume decline in a longitudinal study of adults. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 1999;23(9):979-85.
26. Bottai M, Pistelli F, Di Pede F, Carrozzi L, Baldacci S, Matteelli G, et al. Longitudinal changes of body mass index, spirometry and diffusion in a general population. The European respiratory journal. 2002;20(3):665-73.
27. van Oostrom SH, Engelfriet PM, Verschuren WM, Schipper M, Wouters IM, Boezen M, et al. Aging-related trajectories of lung function in the general population—The Doetinchem Cohort Study. PloS one. 2018;13(5):e0197250.
28. Moualla M, Qualls C, Arynchyn A, Thyagarajan B, Kalhan R, Smith LJ, et al. Rapid decline in lung function is temporally associated with greater metabolically active adiposity in a longitudinal study of healthy adults. Thorax. 2017;72(12):1113-20.
29. Thyagarajan B, Jacobs DR, Apostol GG, Smith LJ, Jensen RL, Crapo RO, et al. Longitudinal association of body mass index with lung function: the CARDIA study. Respiratory research. 2008;9(1):31.
30. Abramson MJ, Kaushik S, Benke GP, Borg BM, Smith CL, Dharmage SC, et al. Symptoms and lung function decline in a middle-aged cohort of males and females in Australia. International journal of chronic obstructive pulmonary disease. 2016;11:1097-103.
31. Rossi A, Fantin F, Di Francesco V, Guariento S, Giuliano K, Fontana G, et al. Body composition and pulmonary function in the elderly: a 7-year longitudinal study. International journal of obesity (2005). 2008;32(9):1423-30.
32. Wu TD, Ejike CO, Wise RA, McCormack MC, Brigham EP. Investigation of the Obesity Paradox in Chronic Obstructive Pulmonary Disease, According to Smoking Status, in the United States. American Journal of Epidemiology. 2019;188(11):1977-83.

33. Mansournia MA, Etminan M, Danaei G, Kaufman JS, Collins G. Handling time varying confounding in observational research. Bmj. 2017;359:j4587.
34. Oelsner EC, Balte PP, Cassano PA, Couper D, Enright PL, Folsom AR, et al. Harmonization of Respiratory Data From 9 US Population-Based Cohorts: The NHLBI Pooled Cohorts Study. Am J Epidemiol. 2018;187(11):2265-78.
35. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs Jr DR, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. Journal of clinical epidemiology. 1988;41(11):1105-16.
36. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The cardiovascular health study: design and rationale. Annals of epidemiology. 1991;1(3):263-76.
37. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. American journal of epidemiology. 1979;110(3):281-90.
38. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol (1985). 2001;90(6):2157-65.
39. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. American journal of epidemiology. 2002;156(9):871-81.
40. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. European respiratory journal. 2005;26(2):319-38.
41. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respiratory Soc. 2012;40:1324-43.
42. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(1):179-87.
43. Centers for Disease Control and Prevention (CDC). Healthy Weight: About Adult BMI [updated 2017]. Available from: https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html. Accessed January 1, 2019.
44. Rodriguez J, Jiang R, Johnson WC, MacKenzie BA, Smith LJ, Barr RG. The association of pipe and cigar use with cotinine levels, lung function, and airflow obstruction: a cross-sectional study. Ann Intern Med. 2010;152(4):201-10.
45. Wagenknecht LE, Burke GL, Perkins LL, Haley NJ, Friedman GD. Misclassification of smoking status in the CARDIA study: a comparison of self-report with serum cotinine levels. Am J Public Health. 1992;82(1):33-6.
46. Kenny DA, Kashy DA, Cook WL. Dyadic analysis. New York: Guilford Press; 2006.
47. Lazarus R, Gore CJ, Booth M, Owen N. Effects of body composition and fat distribution on ventilatory function in adults. The American journal of clinical nutrition. 1998;68(1):35-41.
48. Wannamethee SG, Shaper AG, Whincup PH. Body fat distribution, body composition, and respiratory function in elderly men. The American journal of clinical nutrition. 2005;82(5):996-1003.

49. Ford ES, Cunningham TJ, Mercado CI. Lung function and metabolic syndrome: Findings of National Health and Nutrition Examination Survey 2007-2010. J Diabetes. 2014;6(6):603-13.
50. Ray CS, Sue DY, Bray G, Hansen JE, Wasserman K. Effects of obesity on respiratory function. Am Rev Respir Dis. 1983;128(3):501-6.
51. Lourenco RV. Diaphragm activity in obesity. J Clin Invest. 1969;48(9):1609-14.
52. Naimark A, Cherniack RM. Compliance of the respiratory system and its components in health and obesity. J Appl Physiol. 1960;15:377-82.
53. Hedenstierna G, Santesson J. Breathing mechanics, dead space and gas exchange in the extremely obese, breathing spontaneously and during anaesthesia with intermittent positive pressure ventilation. Acta Anaesthesiol Scand. 1976;20(3):248-54.
54. Sharp JT, Henry JP, Sweany SK, Meadows WR, Pietras RJ. The Total Work of Breathing in Normal and Obese Men. J Clin Invest. 1964;43:728-39.
55. Pelosi P, Croci M, Ravagnan I, Vicardi P, Gattinoni L. Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. Chest. 1996;109(1):144-51.
56. Zerah F, Harf A, Perlemuter L, Lorino H, Lorino AM, Atlan G. Effects of obesity on respiratory resistance. Chest. 1993;103(5):1470-6.
57. Watson RA, Pride NB. Postural changes in lung volumes and respiratory resistance in subjects with obesity. J Appl Physiol (1985). 2005;98(2):512-7.
58. Cottam DR, Mattar SG, Barinas-Mitchell E, Eid G, Kuller L, Kelley DE, et al. The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. Obesity surgery. 2004;14(5):589-600.
59. Duncan BB, Schmidt MI, Chambless LE, Folsom AR, Carpenter M, Heiss G, et al. Fibrinogen, Other Putative Markers of Inflammation, and Weight Gain in Middle-aged Adults—The ARIC Study. Obesity Research. 2000;8(4):279-86.
60. Donaldson GC, Seemungal TA, Patel IS, Bhowmik A, Wilkinson TM, Hurst JR, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. Chest. 2005;128(4):1995-2004.
61. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma: from bronchoconstriction to airways inflammation and remodeling. American journal of respiratory and critical care medicine. 2000;161(5):1720-45.
62. Taher H, Bauer C, Abston E, Kaczka DW, Bhatt SP, Zabner J, et al. Chest wall strapping increases expiratory airflow and detectable airway segments in computer tomographic scans of normal and obstructed lungs. Journal of Applied Physiology. 2018;124(5):1186-93.
63. Abston E, Comellas A, Reed RM, Kim V, Wise RA, Brower R, et al. Higher BMI is associated with higher expiratory airflow normalised for lung volume (FEF25–75/FVC) in COPD. BMJ open respiratory research. 2017;4(1):e000231.
64. Eberlein M, Schmidt GA, Brower RG. Chest wall strapping. An old physiology experiment with new relevance to small airways diseases. Annals of the American Thoracic Society. 2014;11(8):1258-66.
65. O'Hara P, Connett JE, Lee WW, Nides M, Murray R, Wise R. Early and late weight gain following smoking cessation in the Lung Health Study. American journal of epidemiology. 1998;148(9):821-30.

66. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. BMJ. 2000;320(7238):827-32.
67. Dias-Júnior SA, Reis M, de Carvalho-Pinto RM, Stelmach R, Halpern A, Cukier A. Effects of weight loss on asthma control in obese patients with severe asthma. European Respiratory Journal. 2014;43(5):1368-77.
68. Liu AG, Arceneaux KP, 3rd, Chu JT, Jacob G, Jr., Schreiber AL, Tipton RC, et al. The effect of caffeine and albuterol on body composition and metabolic rate. Obesity (Silver Spring). 2015;23(9):1830-5.
69. Ochs-Balcom HM, Grant BJ, Muti P, Sempos CT, Freudenheim JL, Trevisan M, et al. Pulmonary function and abdominal adiposity in the general population. Chest. 2006;129(4):853-62.

**Table 1. Baseline characteristics of participants in the NHLBI pooled cohorts study (1983 – 2018)**

| Characteristic | Total (N=9,115) | % |
|---|---|---|
| Age (years) [a] | 45.66 (20.36) | |
| Sex | | |
| *Female* | 5220 | 57.3% |
| *Male* | 3895 | 42.7% |
| Race | | |
| *African-American* | 2497 | 27.4% |
| *Non-Hispanic White* | 6618 | 72.6% |
| Education | | |
| *Grades 1-8* | 178 | 2.0% |
| *Grades 9-11* | 635 | 7.0% |
| *High School* | 2558 | 28.1% |
| *Some College* | 2543 | 27.9% |
| *Bachelor's Degree* | 1576 | 17.3% |
| *Graduate Degree* | 1625 | 17.8% |
| Birth Year [b] | 1949 (33) | |
| Height (meters) [b,c] | 1.68 (0.09) | |
| Smoking Status | | |
| *Never* | 4499 | 49.4% |
| *Former* | 2866 | 31.4% |

| | | |
|---|---|---|
| *Current* | 1750 | 19.2% |
| Pack Years (current/former smokers only)[b,c] | 9.00 (22.7) | |
| Lung Function[c] | | |
| *FEV1 (L)* [a] | 3.01 (0.91) | |
| *FVC (L)* [a] | 3.85 (1.07) | |
| *FEV1/FVC* [a] | 78.03 (8.29) | |
| *Airflow Limitation*[d] | 1021 | 11.2% |
| *Restrictive Pattern*[e] | 440 | 4.8% |
| *Preserved Spirometry*[f] | 7654 | 84.0% |
| *Percent Predicted FEV1* [a] | 95.75 (14.7) | |
| *Percent Predicted FVC* [a] | 98.51 (13.21) | |
| BMI [a, c] | 25.96 (5.00) | |
| *Underweight* | 206 | 2.3% |
| *Normal Weight* | 4194 | 46.0% |
| *Overweight* | 3111 | 34.1% |
| *Obese* | 1604 | 17.6% |
| Study | | |
| *CARDIA* | 4083 | 44.8% |
| *CHS* | 1280 | 14.0% |
| *FHS-O* | 2237 | 24.5% |
| *Health ABC* | 948 | 10.4% |
| *MESA* | 567 | 6.2% |

BMI = Body Mass Index; FEV1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital Capacity; *CARDIA*=Coronary Artery Risk Development in Young Adults; *CHS*=Cardiovascular Health Study; *FHS-O*=Framingham Offspring Cohort; *Health ABC*=Health, Aging and Body Composition; *MESA*=Multi-Ethnic Study of Atherosclerosis

[a]Mean (standard deviation)
[b]Median (interquartile range)
[c]For time-varying covariates, the baseline observation was reported
[d]Defined as FEV1/FVC less than the lower-limit-of-normal (LLN), as defined by NHANES III reference equations (42)
[e]Defined as FEV1/FVC ≥ LLN and FVC<LLN
[f]Defined as the absence of airflow limitation or a restrictive pattern
[g]Weight (kg)/height $(m)^2$

**Figure 1.** Diagram depicting conceptual distinctions between dyadic growth models (panel A) and non-dyadic growth models (panels B and C). Rectangles represent observed variables and circles represent latent variables. Curved lines represent covariances and straight lines represent regression parameters. Fixed parameters are denoted by *. The arrow representing the parameter of interest is bolded in each; in dyadic models, the focus is on the covariation between simultaneous rates-of-change in Body Mass Index (kg/m$^2$; BMI) and lung function. In non-dyadic models, the focus is on the estimated (presumed causal) effect of change in BMI on lung function, or the estimated effect of change in lung function on BMI.

**Figure 2.** Predicted Levels of Body Mass Index (BMI; kg/m$^2$) (panel A; Age 35, $B = 0.33$; Age 65, $B = 0.03$), FEV1 (panel B; Age 35, $B = -18.98$; Age 65, $B = -36.77$), FVC (panel C; Age 35, $B = -10.38$; Age 65, $B = -42.05$), and FEV1/FVC (panel D; Age 35, $B = -0.29$; Age 65, $B = -0.16$) between Ages 25—75. Dotted and dashed lines show slopes portraying predicted annual rate-of-change for those at ages 35 and 65, respectively. Results for BMI use parameter estimates from the dyadic model with FEV1.

BMI = Body Mass Index; FEV1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital Capacity

**Figure 3.** Scatterplots of Individuals' Estimated Slope Coefficients for Body Mass Index (BMI; kg/m$^2$) with FEV1 ($r = -0.16$; panel A), FVC ($r = -0.26$; panel B), and FEV1/FVC ($r = 0.11$; panel C). Coefficients for FEV1 and FVC are in deciliters per year.

BMI = Body Mass Index; FEV1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital Capacity

**Figure 4.** Forest Plot of Correlated Rates-of-Change and 95% Confidence Intervals Between Individual Slope Coefficients for Body Mass Index (BMI; $kg/m^2$) with FEV1 (panel A) and FVC (panel B). Heterogeneity with $P<.05$ is noted by *.

BMI = Body Mass Index; FEV1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital Capacity; COPD = Chronic Obstructive Pulmonary Disease