ORIGINAL ARTICLE

Dynamic Metabolic Risk Profiling of World Trade Center Lung Disease: A Longitudinal Cohort Study

Sophia Kwon[1]*, Myeonggyun Lee[2]*, George Crowley[1], Theresa Schwartz[3], Rachel Zeig-Owens[3,4], David J. Prezant[3,5], Mengling Liu[2,6], and Anna Nolan[1,3,6]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, [2]Division of Biostatistics, Department of Population Health, and [6]Department of Environmental Medicine, New York University School of Medicine, New York, New York; [3]Bureau of Health Services and Office of Medical Affairs, Fire Department of New York, Brooklyn, New York; and [4]Department of Epidemiology and Population Health and [5]Pulmonary Medicine Division, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York

ORCID IDs: 0000-0003-3639-5107 (S.K.); 0000-0002-0473-6934 (G.C.); 0000-0002-0631-1171 (A.N.).

Abstract

Rationale: Metabolic syndrome (MetSyn) increases the risk of World Trade Center (WTC) lung injury (LI). However, the temporal relationship of MetSyn, exposure intensity, and lung dysfunction is not well understood.

Objective: To model the association of longitudinal MetSyn characteristics with WTC lung disease to define modifiable risk.

Methods: Firefighters, for whom consent was obtained ($N = 5{,}738$), were active duty on September 11, 2001 (9/11). WTC-LI ($n = 1{,}475$; FEV_1% predicted <lower limit of normal [LLN]) and non–WTC-LI ($n = 4{,}263$; FEV_1% predicted ≥LLN at all exams) was the primary outcome, and FVC% predicted <LLN and FEV_1/FVC <0.70 were secondary outcomes. We assessed *1*) the effect of concurrent MetSyn on longitudinal lung function by linear mixed models, *2*) the temporal effect of MetSyn and exposure by Weibull proportional hazards, *3*) the effects of MetSyn's rate of change by two-stage models, and *4*) the nonlinear joint effect of longitudinal MetSyn components by a partially linear single-index model (PLSI).

Measurements and Main Results: WTC-LI cases were more often ever-smokers, arrived in the morning (9/11), and had MetSyn. Body mass index ≥30 kg/m^2 and high-density lipoprotein <40 mg/dl were most contributory to concurrent loss of FEV_1% predicted and FVC% predicted while conserving FEV_1/FVC. Body mass index ≥30 kg/m^2 and dyslipidemia significantly predicted WTC-LI, FVC% predicted <LLN in a Weibull proportional hazards model. Dynamic risk assessment of WTC-LI on the basis of MetSyn and exposure showed how reduction of MetSyn factors further reduces WTC-LI likelihood in susceptible populations. PLSI demonstrates that MetSyn has a nonlinear relationship with WTC lung disease, and increases in cumulative MetSyn risk factors exponentially increase WTC-LI risk. An interactive metabolic-risk modeling application was developed to simplify PLSI interpretation.

Conclusions: MetSyn and WTC exposure contribute to the development of lung disease. Dynamic risk assessment may be used to encourage treatment of MetSyn in susceptible populations. Future studies will focus on dietary intervention as a disease modifier.

Keywords: metabolic syndrome; dynamic risk model; World Trade Center lung injury; World Trade Center lung disease; World Trade Center

(Received in original form August 30, 2020; accepted in final form July 26, 2021)

*These authors contributed equally to this work.

Supported by the NHLBI (R01HL119326), CDC/NIOSH (U01-OH11300 and U01-OH011855), National Institute for Occupational Safety and Health Contracts (Clinical Center of Excellence 200-2017-93426, and Data Center 200-2017-93326), and National Institute of Environmental Health Sciences R01ES032808.

Author Contributions: S.K. and A.N. participated in study conception and design; A.N. was the primary investigator; D.J.P., S.K., and A.N. were responsible for data collection; S.K., M. Lee, G.C., T.S., R.Z.-O., and A.N. were responsible for data validation; S.K., M. Lee, G.C., M. Liu, and A.N. participated in data analysis. G.C. created the interactive Shiny App. All authors participated in data interpretation, writing, and revision of the report and approval of the final version.

Correspondence and requests for reprints should be addressed to Anna Nolan, M.D., M.S., Professor of Medicine and Environmental Medicine, New York University School of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, New Bellevue, 7N Room 24, 462 1st Avenue, New York, NY 10016. E-mail: anna.nolan@med.nyu.edu.

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 204, Iss 9, pp 1035–1047, Nov 1, 2021

Originally Published in Press as DOI: 10.1164/rccm.202006-2617OC on September 2, 2021
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Globally, air pollution contributes to pulmonary and/or vascular disease, yielding a devastating 7 million annual deaths. Particulate matter (PM) is a significant component of air pollution and a prominent component of the World Trade Center (WTC) exposure. Furthermore, the prevalence of metabolic syndrome (MetSyn) has rapidly increased globally and is a risk factor for WTC-PM–associated lung disease. Dynamic risk profiling of MetSyn has been used to predict the development of cardiovascular injury but has not yet been extended to predict pulmonary outcomes in a susceptible population. Understanding the interaction between PM and MetSyn will provide new disease insights and further our understanding of risk prediction.

What This Study Adds to the Field: Our study leverages the longitudinally phenotyped, PM-exposed Fire Department of New York WTC cohort. Dynamic risk assessment allows us to define susceptibility to the development of WTC-associated lung disease based on the multicollinear MetSyn phenotypic characteristics, smoking history, and exposure intensity. Our findings include that body mass index and dyslipidemia imparted more risk of the development of WTC lung disease than smoking and that improving MetSyn characteristics can decrease the risk of developing WTC lung disease. We have proposed a novel method of characterizing risk due to MetSyn components and developed an interactive application to simplify interpretation and visualization of this model. Our novel assessment may direct further treatment modalities to mitigate risk of disease.

Introduction

The events of September 11, 2001 (9/11) exposed thousands to particulate matter (PM) (1–3). Fire Department of New York (FDNY) first responders in the World Trade Center (WTC)-Health Program (HP) had serum banked after 9/11 and continued longitudinal medical monitoring over the subsequent 20 years (4, 5). Early metabolic syndrome (MetSyn) biomarkers predicted WTC lung injury (WTC-LI; FEV_1 percent predicted <lower limit of normal [LLN]) (1–14). MetSyn characteristics are routinely measured, generalizable, and validated biomarkers of cardiovascular disease (CVD) (15, 16).

Our work has focused on FEV_1% predicted as a primary endpoint, as it characterizes severity of obstructive airways disease (OAD) (17–24). We also examine secondary endpoints of FVC% predicted and FEV_1/FVC, which facilitate restrictive and obstructive phenotyping (25, 26). Although spirometry lacks defining measures of restriction, it remains important to define its association with MetSyn. Obesity can reduce lung volumes consistent with restrictive patterns, increase airway resistance, and lead to ventilatory heterogeneity (27–36). Adiposity also has endocrine functions that induce airway smooth muscle proliferation and subepithelial fibrosis that contribute to OAD (27, 37–41). OAD patients with comorbid CVD, diabetes, and hypertension have a higher risk of hospitalization and death (42, 43). Elevated triglycerides and insulin resistance have also been associated with OAD (44).

Although cross-sectional studies have explored the role of MetSyn, air pollution, and comorbid respiratory disease, few longitudinal studies establish the timing of disease onset (45–48). In a prospective cohort without baseline MetSyn, poor lung function was an independent risk factor of developing MetSyn (49). We validated that a one-time diagnosis of MetSyn soon after WTC-PM exposure can predict WTC-airway hyperreactivity and WTC-LI (5, 50, 51). Pathways of MetSyn-induced respiratory disease are poorly understood (52–54).

We now seek to investigate the association of MetSyn risk, exposure, and time with longitudinal measures of FEV_1% predicted, FVC% predicted, and FEV_1/FVC (Figure 1). First, the temporal contribution of MetSyn on spirometry as a continuous variable was used to identify MetSyn's effect on concurrent spirometry as a marker of severity of disease. Next, we examined the effect of MetSyn on WTC-LI disease-free survival and used dynamic MetSyn measurements to predict time to WTC lung disease, allowing us to identify those at high risk, thereby encouraging aggressive treatment of risk factors contributing to future disease. Modeling potential risk reduction by reversing MetSyn was also examined.

The complex multicollinear relationships of MetSyn necessitate the use of novel statistical methodology and computational modeling algorithms. Thus, to understand the potential nonlinear associations of longitudinal MetSyn and WTC-LI, we applied a novel partially linear single-index (PLSI) hazards model with time-dependent covariates. This model possesses the advantage of reducing dimensionality of multiple covariates into a single index and allowing flexible, nonlinear effects (55, 56). Moreover, it addresses multicollinearity that can arise in the examination of comorbid MetSyn characteristics (57). PLSI modeling also enables us to rank the contributions by individual MetSyn characteristics to the risk of developing WTC-LI, an important step toward the treatment of modifiable MetSyn factors in those at risk of developing WTC-LI. Some results have been previously reported in abstracts (58–60).

Methods

Study Design

WTC-exposed rescue and recovery workers (N = 13,954) enrolled in the WTC-HP (N = 12,781) were included in our baseline cohort (N = 6,498) if they were active duty on 9/11 and consented to research (Figure 2). Firefighters with MetSyn and initial spirometry data within 180 days of 9/11 were assessed and yielded a source cohort (N = 5,738). All clinical information, including serial spirometry and blood tests, were obtained from the FDNY electronic medical record in compliance with Code of Federal Regulations Title 21 Part 11 and were approved by the Albert Einstein College of Medicine (#07-09-320) and New York University (#s16-01412/18-00474) Institutional Review Boards (61).

Definitions

Similar to prior papers, MetSyn diagnosis was defined based on National Cholesterol Education Program Adult Treatment Panel III guidelines and optimized for this study cohort by requiring at least three of the following five criteria: systolic blood pressure (SBP) ⩾130 mm Hg or diastolic blood pressure (DBP) ⩾85 mm Hg; high-density

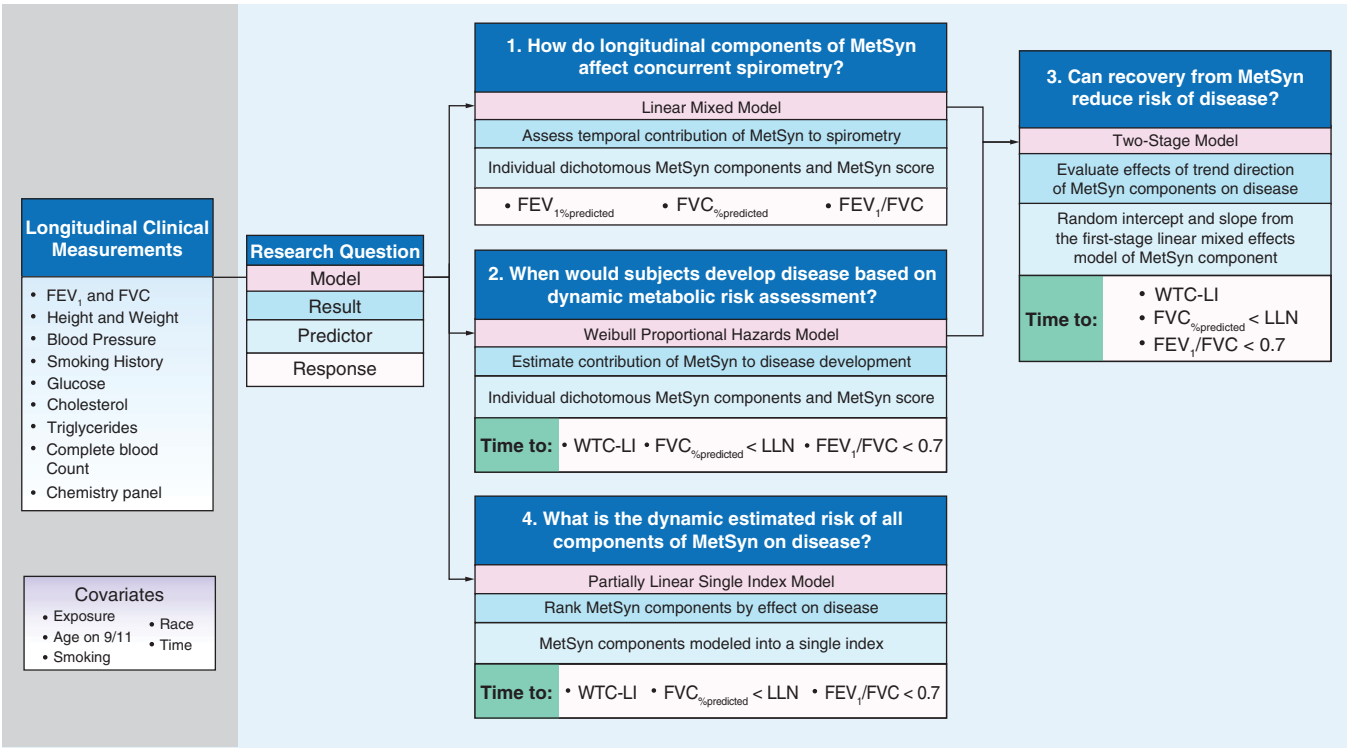

Figure 1. Investigation overview. Four complementary models were used to explore MetSyn and its associations with our primary and secondary outcomes. They include a linear mixed model (1.1), a Weibull proportional hazards model (1.2), a two-stage model (1.3), and a partially linear mixed model (1.4). For each model, we summarize the study question, longitudinal clinical measurements used, intended model interpretation (result), covariates, predictors, and response variable (outcomes). 9/11 = September 11, 2001; LI = lung injury; LLN = lower limit of normal; MetSyn = metabolic syndrome; WTC = World Trade Center.

lipoprotein (HDL) <40 mg/dl; triglycerides ⩾150 mg/dl; glucose ⩾100 mg/dl; or body mass index (BMI) ⩾30 kg/m^2 at the WTC-HP entry, used as a surrogate for central adiposity (5, 15, 16, 50, 51, 62–66). BMI clinical cut-points of overweight and obesity classes I–III were assessed (67, 68).

Outcomes

WTC-LI (primary outcome) was defined at the first post-9/11 spirometry where the FEV_1% predicted was <LLN (n = 1,475) (8). Control subjects were subjects without WTC-LI (n = 4,263) and had FEV_1 ⩾LLN at all spirometry. FVC% predicted <LLN and FEV_1/FVC <0.70 were secondary outcomes (25, 26).

Statistical Analysis

SPSS version 25 (IBM) and R (version 3.6.3)—including packages openxlsx-4.2.2, nlme 3.1.150, tableone-0.12.0, plyr-1.8.6, ggplot2-3.3.2, survival-3.2.7, eha-2.8.1, and splines2-0.3.1—were used for primary data storage, handling, and analyses. Continuous variables were compared by two-sample t test.

Complementary modeling investigated relationships between longitudinally collected MetSyn and spirometry. All models were adjusted for age, self-identified race, smoking history, and exposure levels (28, 69–77).

Model 1: Effect of Longitudinal MetSyn Components on Concurrent Spirometry as an Assessment of Disease Severity

Linear mixed effects modeling (LME) was used to identify the temporal contribution of longitudinal MetSyn to longitudinal FEV_1% predicted, FVC% predicted, and FEV_1/FVC (Figure 1.1) (78, 79). MetSyn components dichotomized into clinical cutoffs and composite MetSyn score were assessed in separate LME models adjusted for intercept, time (year-scale), exposure, ever-smoking, race, age on 9/11, and the interaction between smoking and time. A random intercept was assumed to account for interindividual variation at baseline. The interaction term accounted for smoking's known acceleration of lung function decline. Time was assumed to have a linear effect.

Model 2: Effect of Longitudinal MetSyn on Time to Onset of Disease

Weibull proportional hazards (Weibull-PH) modeling with time-dependent covariates was used to assess the dynamic risk of MetSyn on the hazard functions of time to disease onset (Figure 1.2) (78–80). MetSyn score and dichotomized components were fit in separate PH models adjusted for age on 9/11, race, smoking history, and exposure. The estimated hazard ratios (HRs) and Weibull baseline hazard function were used to plot a survival curve to visualize results. The PH assumption was examined using cumulative sums of martingale-based residuals (81). Dynamic prediction incorporates time-dependent MetSyn scores accrued during the follow-up to improve the prediction of the risk of developing disease (78). Given each assumed MetSyn history, we computed the probabilities of disease development (79, 80).

Model 3: Assessment of Recovery of MetSyn and Risk of Future Disease

We assessed the effect of rate of change of MetSyn on the onset time of disease to study whether MetSyn recovery could reduce lung

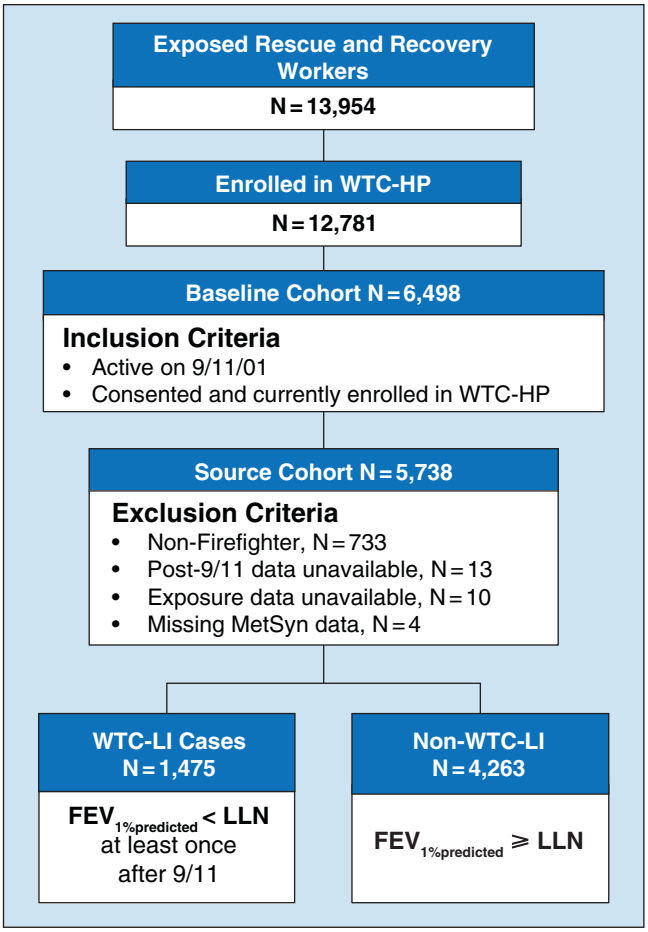

Figure 2. Study population. Consort diagram for primary outcome of WTC-LI. 9/11 = September 11, 2001; HP = Health Program; LI = lung injury; LLN = lower limit of normal; MetSyn = metabolic syndrome; WTC = World Trade Center.

disease risk (Figure 1.3) (82, 83). Two-stage models fit using LME and Weibull-PH regression to identify the hazard of change with respect to individual MetSyn component patterns. In the first stage, LME was modeled as a linear function of time for each MetSyn component (82, 83). In the second stage, standardized best linear unbiased predictor estimates of these random coefficients were used as predictors in the Weibull-PH model. HR associated with the rate of change of each MetSyn component reflects how the change in directionality of each component influences disease-free survival.

Model 4: Joint Effects of MetSyn Components Were Modeled into a Single Index (Dynamic Risk)

PLSI delineates the relative contribution of multiple time-dependent MetSyn components to the risk of developing disease and can be used to identify the patient-specific prognosticating trajectory (Figure 1.4) (55, 56, 84) Maximum partial likelihood estimates were obtained and standard errors were estimated using 5,000 bootstrap samples (84). Longitudinal triglycerides and glucose were logarithmically transformed owing to right-skewed distributions, and MetSyn components were standardized to 0 mean and 1 SD.

Visualization and Interpretation of PLSI (Model 4)

Model characteristics can be interpreted using our novel Shiny App "Interactive Metabolic Risk Modeling Application" (https://med.nyu.edu/nolanlab). This was built using R 4.0.3, RStudio 1.3.1093, shiny 1.5.0, shinydashboard 0.7.1, and tidyverse 1.3.0 for data management and graphical displays. This shows how clinical parameters are incorporated into the MetSyn single index score and further used to calculate an HR of disease development (*see* Figure E2 and Appendix E.3A–E.3D in the online supplement for detailed methods and instructions).

Results

Baseline Characteristics and Demographics

A total of $N = 52,355$ serial PFTs were collected from 9/11 to time of extraction of data, which occurred on August 1, 2017, with an average of 9.12 (SD, 2.66) measures/subject. Clinical measures were assessed for the baseline cohort ($N = 5,738$). WTC-LI cases ($n = 1,475$) were not significantly different from non–WTC-LI cases ($n = 4,263$) in age, sex, race, or duration at site. Cases were more likely to be ever-smokers (35.25% vs. 31.29%, $P = 0.006$) and have high exposure compared with control subjects (19.73% vs. 15.72%, $P < 0.001$). Cases also had a lower mean FEV_1% predicted at baseline before 9/11 than control subjects (97.05 vs. 109.75, respectively) but were clinically disease-free and active-duty firefighters. WTC-LI cases had higher BMI and higher amounts of SBP, DBP, and triglycerides than control subjects, whereas glucose, total cholesterol, and low-density lipoprotein were not significantly different. Cases also had lower HDL than control subjects (50.36 vs. 52.15 mg/dl). A higher percentage of cases had MetSyn than control subjects (21.56% vs. 16.94%, $P < 0.001$) (Table 1).

Similarly, cases with FVC <LLN ($n = 2,043$) had a lower FVC value at baseline and were more likely highly exposed; had higher BMI and higher amounts of SBP, DBP, triglycerides, and glucose; and had less HDL than cases with FVC ⩾LLN ($n = 3,695$). Cases with FEV_1/FVC <0.70 ($n = 852$) were more likely smokers with a lower BMI and lower amounts of triglycerides and higher amounts of HDL than cases with FEV_1/FVC ⩾0.70 ($n = 4,886$). Amounts of SBP, amounts of DBP, and percentage with MetSyn were not significantly different among them. Full demographics of secondary endpoints are available in Table E1.

Elevated BMI Has a Larger Effect on FEV_1% Predicted and WTC-LI Diagnosis than Smoking

MetSyn components with clinical cut-points were evaluated by LME and Weibull-PH and

Table 1. Baseline Clinical Measures

Clinical Measure	Baseline Cohort ($N = 5,738$)	Control ($n = 4,263$)	Cases ($n = 1,475$)	P Value
Sex, M	5,725 (99.77)	4,256 (99.84)	1,469 (99.60)	0.170
Age on 9/11, yr	40.09 ± 7.51	40.20 ± 7.58	39.77 ± 7.30	0.054
White race	5,379 (93.74)	3,999 (93.81)	1,380 (93.56)	0.782
Ever-smoker	1,854 (32.31)	1,334 (31.29)	520 (35.25)	0.006
Duration, mo	3.71 ± 2.70	3.69 ± 2.68	3.76 ± 2.75	0.333
Arrived morning of 9/11	961 (16.75)	670 (15.72)	291 (19.73)	<0.001
Pre-9/11				
FEV_1% predicted	106.54 ± 12.86	109.75 ± 12.09	97.05 ± 10.09	<0.001
FVC% predicted	99.98 ± 11.98	102.34 ± 11.64	92.98 ± 10.09	<0.001
FEV_1/FVC	85.19 ± 4.98	85.73 ± 4.66	83.59 ± 5.54	<0.001
WTC-HP entry				
FEV_1% predicted	96.66 ± 12.06	100.58 ± 10.10	85.31 ± 9.90	<0.001
FVC% predicted	94.74 ± 11.31	97.61 ± 10.21	86.38 ± 10.16	<0.001
FEV_1/FVC	80.73 ± 5.64	81.510 ± 4.97	78.458 ± 6.76	<0.001
MetSyn components				
BMI, kg/m^2	29.59 ± 3.62	29.43 ± 3.47	30.070 ± 3.96	<0.001
SBP, mm Hg	123.17 ± 13.06	122.95 ± 13.18	123.819 ± 12.70	0.041
DBP, mm Hg	76.72 ± 8.39	76.56 ± 8.51	77.180 ± 8.02	0.023
Glucose, mmol/L	93.59 ± 19.60	93.31 ± 18.20	94.399 ± 23.19	0.067
Triglycerides, mg/dl	161.90 ± 127.49	157.63 ± 119.00	174.28 ± 148.79	<0.001
HDL, mg/dl	51.69 ± 12.82	52.15 ± 12.89	50.36 ± 12.55	<0.001
LDL, mg/dl	122.61 ± 32.86	123.04 ± 32.63	121.36 ± 33.50	0.099
Total cholesterol	204.48 ± 37.36	204.70 ± 37.03	203.86 ± 38.32	0.461
Diagnosis	1,040 (18.13)	722 (16.94)	318 (21.56)	<0.001

Definition of abbreviations: 9/11 = September 11, 2001; BMI = body mass index; DBP = diastolic blood press; HDL = high-density lipoprotein; HP = Health Program; LDL = low-density lipoprotein; MetSyn = metabolic syndrome; SBP = systolic blood pressure; WTC = World Trade Center. Values are displayed as mean ± SD or *n* (%). *P* values are for comparisons between control subjects and cases by Student's *t* test or Pearson's chi-square test where appropriate.

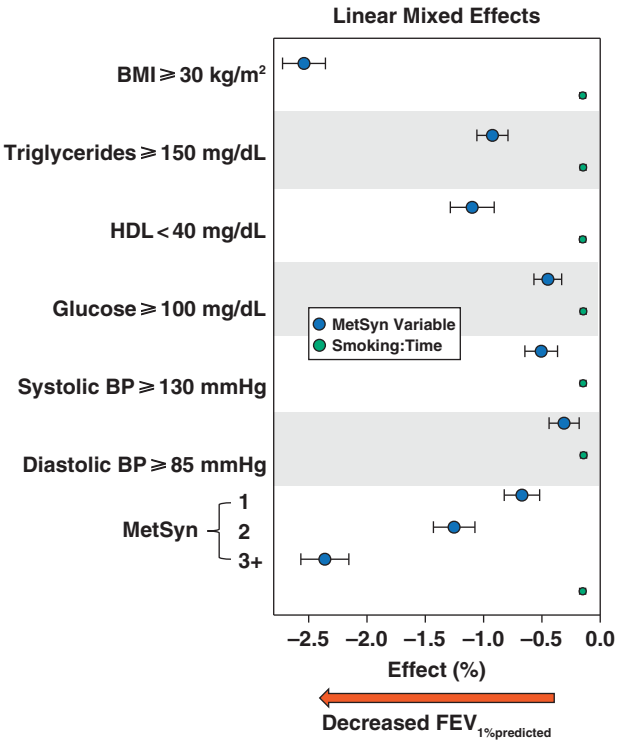

Figure 3. Effect of MetSyn components on FEV_1% predicted assessed by linear mixed effects models. BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; MetSyn = metabolic syndrome.

displayed in a forest plot (Figures 3 and 4A). Full data of models using all longitudinal data can be found in Tables E2–E5. Although smoking did not show a significant baseline effect in LME models of FEV_1% predicted, there was significant interaction between smoking and time in all MetSyn models ($P < 0.001$). Therefore, smokers had a greater decrease in FEV_1% predicted than nonsmokers over time. The interaction between WTC-PM and time was not significant and was not included in final LME models. BMI ⩾30 kg/m^2 expresses the highest effect on concurrent FEV_1% predicted longitudinally, with an effect of −2.54% (95% confidence interval, −2.72 to −2.36; $P < 0.001$). When examining the effect of increasing cumulative MetSyn risks on longitudinal FEV_1% predicted, a dose–response was observed. Compared with having no MetSyn risks, having one, two, or three or more additional risk factors had effects of −0.67% (−0.82% to −0.52%), −1.25% (−1.43% to −1.07%), and −2.36% (−2.57% to −2.15%), respectively, on longitudinal FEV_1% predicted (Figure 3). In order of decreasing magnitude of effect size, HDL, triglycerides, DBP, SBP, and glucose had significant effects on the reduction of

FEV_1% predicted. Age, race, and exposure were not significant risks.

A BMI dose–response was also seen in models of longitudinal FEV_1% predicted, with effects of −1.48%, −3.55%, and −6.64% for having overweight, having class I obesity, or having class II/III obesity, respectively (Table E2) (85). Compared with normal-weight nonsmokers, class-II-obesity smokers had −8.34% lower FEV_1% predicted 10 years after 9/11.

Similar patterns were seen when examining FVC% predicted. Obesity had the most deleterious effect on longitudinal FVC% predicted—a value of −2.89%. There was also a BMI-dependent dose–response similar to FEV_1% predicted. Again, HDL, triglycerides, DBP, SBP, and glucose had significant effect sizes on FVC% predicted, conserving the order of decreasing magnitude size.

When investigating the effect of MetSyn on FEV_1/FVC, BMI ⩾30 kg/m^2, amount of triglycerides ⩾150 mg/dl, and amount of HDL <40 mg/dl were significantly associated with increased FEV_1/FVC. Insulin resistance and hypertension did not have significant effects.

Dyslipidemia and Obesity Contribute the Largest Risk to Time to WTC-LI

When investigating the temporal effects of MetSyn components on the risk of developing WTC-LI, triglycerides ⩾150 mg/dl had the highest HR (1.48 [95% confidence interval (CI), 1.32–1.65]), followed by HDL <40 mg/dl, at 1.39 (95% CI, 1.21–1.59), and BMI ⩾30 kg/m^2, at 1.37 (95% CI, 1.23–1.53) (Figure 4A and Table E3).

Similar patterns were seen for the FVC% predicted <LLN endpoint. Triglycerides ⩾150 mg/dl again had the highest HR (1.64 [95% CI, 1.49–1.81]), followed by BMI ⩾30 kg/m^2, at 1.60 (95% CI, 1.45–1.77), and HDL <40 mg/dl, at 1.56 (95% CI, 1.38–1.76). When examining FEV_1/FVC <0.70 as an endpoint, BMI ⩾30 kg/m^2, amount of triglycerides ⩾150 mg/dl, and amount of HDL <40 mg/dl were less likely to have resulted in an obstructive pattern.

High exposure to PM (being present on the morning of 9/11) was a significant risk factor in all Weibull-PH models for the onset of WTC-LI and even exceeded the risk incurred by smoking. For example, the HR of exposure in the triglycerides model was 1.24 (95% CI, 1.08–1.42; $P = 0.002$), whereas the HR of smoking in the same model was 1.21 [95% CI, 1.08–1.36) (Table E3). WTC-LI disease-free survival probabilities were estimated in strata defined by number of MetSyn points, smoking, and exposure history (Figure 4B). Increasing number of MetSyn points, smoking, and high exposure (by being present on the morning of 9/11) had the highest risk of WTC-LI compared with their respective reference categories. Smokers with high WTC-PM exposure and MetSyn (⩾3 criteria) had the lowest survival probability. Smokers with high WTC-PM exposure but no MetSyn risks had similar survival curves to never-smoking, low-exposure individuals who had two MetSyn points as a significant risk factor (black-dotted and solid-blue lines are overlying).

Dynamic Risk Assessment of WTC-LI Development Created on the Basis of the Fitted Weibull-PH Model

This parametric modeling can capture prediction for at least the subsequent 5 years. Dynamic risk profiling of WTC-LI will provide the probability of risk and potential risk reduction with resolution of MetSyn risk factors. To demonstrate the utility of this model, we used the Weibull-PH model as a survival function formula (Appendix E.2B) to compute the expected survival probabilities for two hypothetical subjects who both start with two MetSyn risk factors at the first visit but differ at the second visit (Figure E1). Subject 1 develops MetSyn criteria on the subsequent visit, whereas subject 2 recovers from all MetSyn risk factors. The projected risk of WTC-LI diverges at each subsequent visit and shows that subject 2, who recovered from MetSyn risks, is less likely to develop WTC-LI than subject 1.

Recovery from MetSyn Can Decrease Risk of WTC-LI

On the basis of the two-stage models, we showed that the positive annual rate of change of BMI, glucose, SBP, and DBP increased the risk of WTC-LI (Figure 5). HDL also had a significant inverse relationship with WTC-LI, with increasing HDL reducing the HR of developing WTC-LI. Conversely, reductions of BMI, glucose, SBP, and DBP were associated with a decreased risk of WTC-LI, whereas individuals with decreased HDL would be more likely to develop WTC-LI. If assuming that a subject has the average height of the cohort, a 1 kg/m^2 reduction in BMI is equivalent to approximately a 7-lb weight loss and reduced risk of WTC-LI by 20.38%. An increase of 10 mg/dl in HDL reduced risk by 89.00%; a decrease of 10 mmol/L in fasting blood glucose reduced risk by 72.36%; and a reduction of 10 mm Hg in SBP and DBP reduced risk by 74.93% and 136.44%, respectively (Figure 5A).

The risk of FVC% predicted <LLN was similarly reduced with a weight loss of 7 lb (19.81%), an increase of 10 mg/dl in HDL (52.00%), a decrease of 10 mmol/L in glucose (56.60%), and a decrease of 10 mm Hg in DBP (116.61%). FEV_1/FVC had a reduced risk of falling below 0.70 with a decrease of 10 mmol/L in glucose (66.29%) and of 10 mm Hg in DBP (107.94%) (Figures 5B and 5C and Table E4).

Triglyceride change did not affect the HR of WTC-LI, likely because of the relative lack of dynamic change and near-zero slope in the two-stage model (Stage 1). Improvement in BMI, HDL, glucose, and DBP reduced the risk of FVC% predicted <LLN. For FEV_1/FVC, only reductions in glucose and DBP significantly reduced the risk of obstruction. A reduction of SBP and triglycerides did not reduce the risk of FVC% predicted <LLN. BMI, triglycerides, HDL, and SBP change similarly did not affect the outcome of FEV_1/FVC <0.70.

Assessment of the Nonlinear Relationship of Concurrent MetSyn and Onset of WTC-LI

The PLSI hazards model identified a nonlinear relationship with a concurrent joint effect of standardized MetSyn and WTC-lung-disease–free survival (Figures 6A–6C). The contribution of each MetSyn component (estimates in Table E5, or β_i in Appendix E.2D [Model 4]) into a cumulative risk score (single index) is reported in Table E5, and the overall effect of the MetSyn single index is shown in Figure 6. BMI had the largest-magnitude weight—0.73—in the estimated MetSyn single index, followed by log(triglycerides) with 0.51 and HDL with −0.42. The overall effect of the MetSyn single index was nonlinear. Because the estimated link function was monotone, the joint effect of MetSyn components in the single index can be interpreted qualitatively (55). When examining the extremes of the link function for WTC-LI, having fewer MetSyn characteristics, and thereby being on the negative end of the spectrum of MetSyn single indices, had modest effects on the risk of developing WTC-LI (Figure 6A). In contrast, when examining positive MetSyn single indices, the risk increased exponentially. The estimated link function

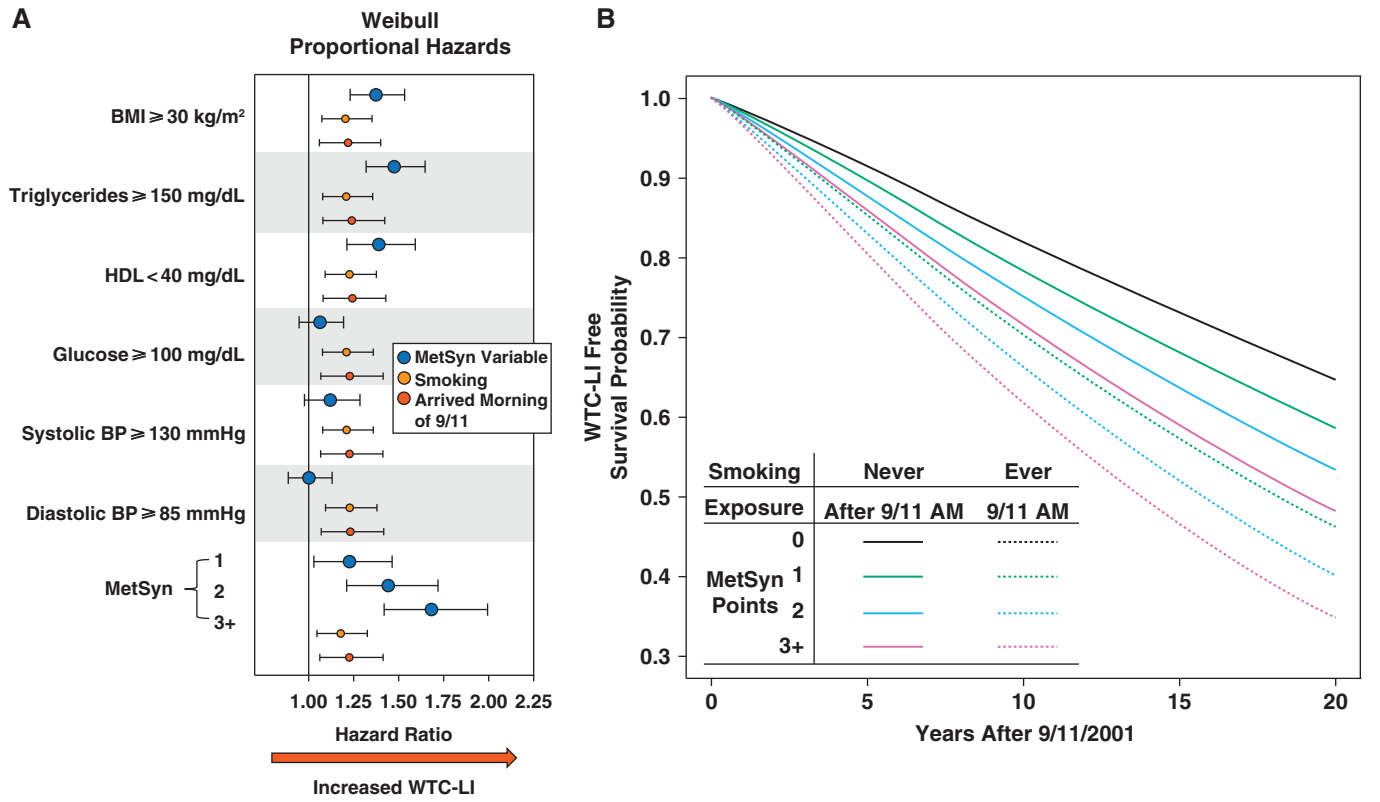

Figure 4. Effect of metabolic syndrome (MetSyn) components on hazard of developing World Trade Center lung injury (WTC-LI) assessed by Weibull proportional hazards models. (*A*) Hazard ratios of dichotomous MetSyn components, as well as MetSyn score. (*B*) WTC-LI–free survival probability, stratified by MetSyn, exposure, and smoking. Reference (solid, black) represents the survival probability of a never-smoking subject with zero MetSyn points and exposure after the morning of September 11, 2001 (9/11). Solid green, blue, and red lines represent survival probability of never-smokers who arrived after the morning of 9/11 with $n = 1$, 2, or 3+ MetSyn risk factors, respectively. Dashed lines represent the survival probability of each MetSyn risk factor adjusted for positive smoking history and exposure during the morning of 9/11. Note that the dashed black and solid blue lines overlap. Covariates age and race were held constant at the mean and at White, respectively. BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein.

for FVC <LLN similarly showed a decreased likelihood of disease with negative MetSyn single indices and an increased risk with positive values (Figure 6B). For FEV_1/FVC <0.70, negative MetSyn single indices were associated with more risk (Figure 6C). The interpretation of positive MetSyn single indices is more difficult owing to insignificant 95% confidence interval.

Visualization and Interpretation of the PLSI Model

Because data visualization is key to facilitating clinical understanding and implementation, we developed the "Interactive Metabolic Risk Modeling Application" for model interpretation (86). This application facilitates the interpretation of complex dynamic models such as our PLSI model and allows for further assessment of how the individual components of MetSyn impact the MetSyn single index and HR (Figures 6A–6C, Table E5, Figures E2–E5, and Appendix E.3A–E.3D).

Discussion

Complementary modeling facilitated our understanding of the longitudinal MetSyn/PM exposure phenotype by leveraging the FDNY-WTC cohort's 20-year data set. Dynamic assessment allowed us to define the risk of the development of WTC-associated lung disease based on multicollinear MetSyn characteristics, smoking, and WTC exposure. BMI and dyslipidemia imparted more risk of WTC lung disease development than smoking. Furthermore, mitigating MetSyn can decrease the risk of WTC lung disease.

Dyslipidemia, a MetSyn component, is linked to vascular disease and consequential FEV_1 loss (4, 5, 9, 13, 50, 51, 87–89). Exposure to PM significantly increases low-density lipoprotein, cholesterol, and triglycerides and decreases HDL in rats and their offspring (90). Additionally, females exposed to tobacco smoke *in utero* have higher triglycerides, lower HDL, and a significantly higher BMI/waist circumference than unexposed females (91, 92). Recent studies have focused on the systemic effects of obesity/MetSyn's hormonal/immune-inflammatory biomarkers in the context of pollution and respiratory compromise (29, 32, 36, 93–96). Surfactant disruption has been linked to acute respiratory distress syndrome, OAD, vaping lung injury, pulmonary fibrosis, and infectious disease (39). The growing body of literature linking OAD and MetSyn suggests dyslipidemia-related inflammation as contributory (36). Cardiovascular Health Study subjects with a SBP > 160 mm Hg had significantly lower FEV_1 values (97).

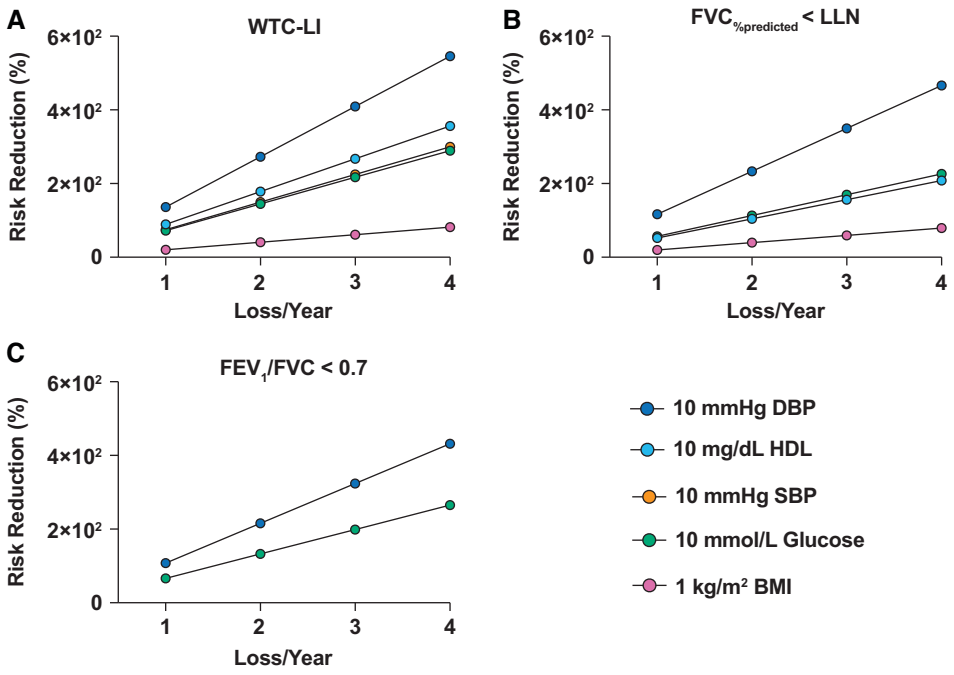

Figure 5. Two-stage model interpretation. The two-stage model shows how a unit rate of change in a clinical parameter affects disease-free survival. (*A*) WTC-LI, (*B*) FVC% predicted <LLN, and (*C*) FEV_1/FVC <0.70. Only significant variables are shown. BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LI = lung injury; LLN = lower limit of normal; SBP = systolic blood pressure; WTC = World Trade Center.

Our longitudinal study examines the temporal relationship of PM exposure, abnormal lung function, and MetSyn. Mechanistic studies linking MetSyn and airway disease suggest biologic plausibility (12, 98–101). Our work supports the literature of obesity's adverse effect on the lung and builds on a shift in traditional views of MetSyn as a purely cardiovascular risk factor. However, there are conflicting data on the relationship of obesity and OAD (102, 103). Although obesity can have FVC loss consistent with a restrictive phenotype, FEV_1 dysfunction could be a better predictor of WTC-associated disease

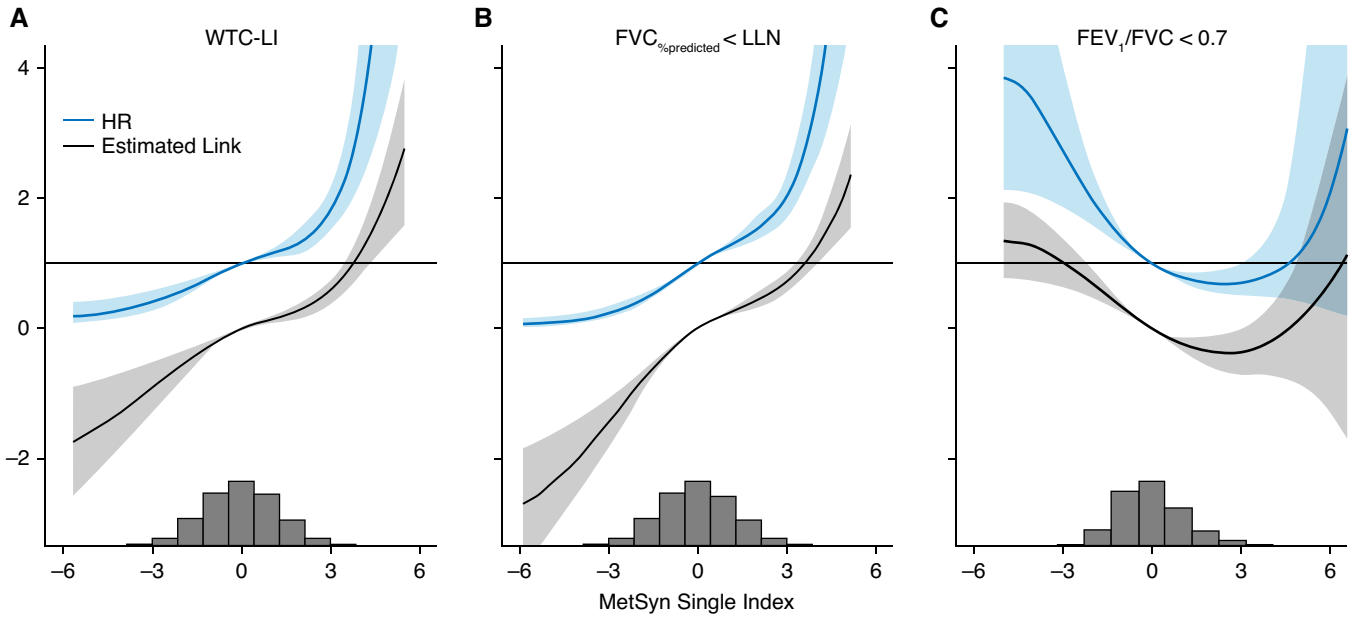

Figure 6. Estimated joint effect of metabolic syndrome (MetSyn) on the risk of developing (*A*) WTC-LI, (*B*) FVC% predicted <LLN, and (*C*) FEV_1/FVC <0.70. The black line is the estimated link function, and the blue line is the hazard ratio as a function of the estimated link function; 95% confidence intervals are represented as shaded areas surrounding each curve. Histograms on the horizontal axis show frequency of observed points of the MetSyn single index. HR = hazard ratio; LI = lung injury; LLN = lower limit of normal; WTC = World Trade Center.

severity (2, 104, 105). In addition, concurrent MetSyn has significant impact on survival risk of WTC lung disease. When investigating time to survival, dyslipidemia and BMI $\geq$30 kg/m^2 imparted the highest risk of WTC-LI and FVC <LLN, even compared with smoking. Exposure also exhibited a near-equivalent effect to smoking history in both Weibull-PH and PLSI modeling. This bolsters our understanding that MetSyn and relatively higher WTC-PM exposure continue to influence the morbidity of WTC lung disease and may contribute to persistent symptoms in these FDNY workers. Furthermore, the Weibull-PH model offers dynamic risk assessment of the WTC-exposed individuals based on their history of all MetSyn components. This is particularly useful as metabolic disease can differ within the same patient over time.

Interestingly, reversal of MetSyn could also decrease the subsequent risk of WTC Lung Disease, thereby providing therapeutic potential through MetSyn mitigation. Although a reduction of triglycerides was not significantly associated with WTC-LI risk reduction, elevated triglycerides have intrinsic risk and impart a significant effect on WTC-LI over time. This finding is consistent with the literature investigating OAD and statins—that target triglycerides and increase HDL. Although many studies have shown that statins could improve symptoms and health-related quality of life in OAD patients, this effect was mostly limited to those with OAD and comorbid CVD and did not impact mortality (106). Nevertheless, pathways of cholesterol dysregulation are actively studied as potential pharmacologic targets in asthma, acute lung injury, and fibrosis (27, 37–41, 107, 108). Further investigation could determine whether statin therapy would benefit comorbid WTC-LI and CVD.

The novel PLSI hazards model allows for linear and nonlinear time-dependent covariate effects on the log hazard function by the flexible functional form and uses a weighted sum of risk from each component of MetSyn to calculate a cumulative risk score. This may also be interpreted as a surrogate of severity of MetSyn using actual values and preserving information, as opposed to using the at-least-three components of MetSyn. Although MetSyn severity scores have been explored in prior studies, this is the first (to our knowledge) application of this method to model its effect on lung function (109, 110). Furthermore, there is an additional advantage over traditional PH modeling in providing the joint effect of all MetSyn components without risk of multicollinearity and interaction between potentially highly correlated characteristics such as SBP and DBP. The developed application can be used to quickly identify the risk of WTC-related lung function decline with user-inputted MetSyn components. The cumulative risk score includes information from exposure, smoking history, and MetSyn (single index) to derive an HR.

This study has several limitations. The lack of a complete assessment of lung volumes, specifically total lung capacity, limits our ability to fully define a restrictive phenotype; normal FEV_1/FVC does not exclude obesity-induced restriction (25). Therefore, the authors caution interpretation of models using FVC and FEV_1/FVC because they may be affected by potential misclassification. Although we have assessed the relative effects of WTC exposure not only in prior work but also in our current manuscript, we are unable to quantify the isolated pulmonary dysfunction from non-WTC exposure. Furthermore, distinguishing the contribution of WTC exposure independent of other firefighting or innate risk factors is also not possible because we do not compare our participants with an unexposed cohort. Although all subjects in our study were WTC exposed and were of a similar age at 9/11, the WTC-LI cases had a significantly greater percentage of individuals who were highly exposed to WTC particulates than the subjects who did not develop WTC-LI (1, 2, 4–6, 8–13). The effect of WTC exposure on lung dysfunction is further evident in prior studies (1, 2, 4–6, 8–13). In several of this study's models, WTC exposure was found to be a significant contributor.

The cohort is also not designed to examine the contribution from non–WTC-exposure-related factors such as genetics, childhood lung development, childhood exposures, or non-WTC occupational exposures to firefighting. At baseline, all firefighters have occupational exposure that is a risk to their lung health. Under the guidance of the National Fire Protection Association (NFPA) Standards, the FDNY evaluates the lung function of all firefighters annually. Pulmonary symptoms or the need for inhalational therapy, per NFPA standards, precludes performing the duties of an active-duty firefighter (111). Rigorous preemployment medical and fitness evaluation as required by the NFPA limits the inclusion of those with active pulmonary dysfunction prior to exposure (111). Our cohort used active-duty status as an inclusion criterion, which limits the inclusion of subjects with active pulmonary dysfunction prior to exposure. Specifically, before 9/11, few firefighters had spirometry results below the LLN (112). After 9/11, approximately 13% of firefighters had an FEV_1 value below the LLN, and even fewer had an FEV_1 value <70% predicted. Furthermore, lung function loss lacked recovery, and the trajectory differed by exposure level (113). Retirement, disability, and pension benefits—although present before 9/11—also increased after 9/11, primarily because of respiratory illness (114). Because smoking and exposure history are self-reported, misclassifications may occur. Traditional measures of smoking history, such as pack-years, or measures of concurrent use, such as cotinine levels, are not available. Dichotomized smoking status to ever or never may lead to recall and/or self-reporting bias, but more often bias toward the null, and studies have supported the sensitivity and reliability of these measurements (113, 115–117). Additional measures of WTC-PM exposure, such as days at the WTC site and direct personal measures of PM exposure, are not available. However, the use of WTC site arrival time has been associated with a higher risk of WTC-LI, airway hyperreactivity, and chronic rhinosinusitis (5, 50, 51, 118). Although duration of exposure (months at the WTC site) has been assessed in prior work, its lack of temporal granularity fails to capture the gradation of exposure intensity that includes the intense 9/11 morning exposure (5, 50, 51, 119).

Although these models can perform dynamic assessments, they assume that MetSyn risk is constant over time. In line with other studies, our models support that MetSyn risk factors occur prior to onset of WTC-LI (120). Further investigation of other spirometric values strengthens our findings. We elected to focus on FEV_1 because of its stronger implications for severity compared with FVC, but future studies can investigate the impact of MetSyn on restrictive disease in a subcohort with additional lung function definition (106, 107). The current dynamic risk assessment models are more clinically

relevant to subjects who have not yet developed WTC lung disease. Further investigation is needed on the impact of MetSyn recovery on reversing WTC lung disease. We also do not correct for multiple comparisons because this was a hypothesis-driven analysis. However, when using a multiple-comparison correction (e.g., Bonferroni), MetSyn would be still significant in LME models, thereby minimizing that these components of MetSyn would be significant by chance.

In summary, dynamic risk assessment has important therapeutic implications. Recently, the effect of dynamic MetSyn on the risk of major adverse cardiovascular events showed that not only was MetSyn itself a risk factor but recovery from MetSyn lowered future cardiovascular event susceptibility (121). This supports our proposed risk stratification models to target those who have not yet developed WTC-LI with earlier therapy against MetSyn. These findings also reinforce the importance of long-term monitoring of disaster survivors. Finally, individual MetSyn components being highly correlated has impeded the investigation of MetSyn as a predictor of CVD and comorbidities. Whereas the PLSI was fitted to cohort-specific pulmonary disease definitions, the MetSyn single index is a novel method of quantifying the impact of MetSyn and its components on morbidity/mortality. The MetSyn single index could be used to derive an improved definition of MetSyn with respect to pulmonary and vascular outcomes. Our novel assessment may direct future studies on mitigating MetSyn as a disease-modifying risk factor of future PM-associated lung disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors dedicate their work to the FDNY first responders and thank them for their sacrifice in the line of duty.

References

1. Prezant DJ, Weiden M, Banauch GI, McGuinness G, Rom WN, Aldrich TK, *et al.* Cough and bronchial responsiveness in firefighters at the World Trade Center site. *N Engl J Med* 2002;347:806–815.
2. Weiden MD, Kwon S, Caraher E, Berger KI, Reibman J, Rom WN, *et al.* Biomarkers of World Trade Center particulate matter exposure: physiology of distal airway and blood biomarkers that predict FEV_1 decline. *Semin Respir Crit Care Med* 2015;36:323–333.
3. Rom WN, Reibman J, Rogers L, Weiden MD, Oppenheimer B, Berger K, *et al.* Emerging exposures and respiratory health: World Trade Center dust. *Proc Am Thorac Soc* 2010;7:142–145.
4. Nolan A, Naveed B, Comfort AL, Ferrier N, Hall CB, Kwon S, *et al.* Inflammatory biomarkers predict airflow obstruction after exposure to World Trade Center dust. *Chest* 2012;142:412–418.
5. Naveed B, Weiden MD, Kwon S, Gracely EJ, Comfort AL, Ferrier N, *et al.* Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study. *Am J Respir Crit Care Med* 2012;185:392–399.
6. Tsukiji J, Cho SJ, Echevarria GC, Kwon S, Joseph P, Schenck EJ, *et al.* Lysophosphatidic acid and apolipoprotein A1 predict increased risk of developing World Trade Center-lung injury: a nested case-control study. *Biomarkers* 2014;19:159–165.
7. Cho SJ, Nolan A, Echevarria GC, Kwon S, Naveed B, Schenck E, *et al.* Chitotriosidase is a biomarker for the resistance to World Trade Center lung injury in New York City firefighters. *J Clin Immunol* 2013;33:1134–1142.
8. 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;159:179–187.
9. Weiden MD, Naveed B, Kwon S, Cho SJ, Comfort AL, Prezant DJ, *et al.* Cardiovascular biomarkers predict susceptibility to lung injury in World Trade Center dust-exposed firefighters. *Eur Respir J* 2013;41:1023–1030.
10. Weiden MD, Ferrier N, Nolan A, Rom WN, Comfort A, Gustave J, *et al.* Obstructive airways disease with air trapping among firefighters exposed to World Trade Center dust. *Chest* 2010;137:566–574.
11. Kwon S, Weiden MD, Echevarria GC, Comfort AL, Naveed B, Prezant DJ, *et al.* Early elevation of serum MMP-3 and MMP-12 predicts protection from World Trade Center-lung injury in New York City Firefighters: a nested case-control study. *PLoS One* 2013;8:e76099.
12. Caraher EJ, Kwon S, Haider SH, Crowley G, Lee A, Ebrahim M, *et al.* Receptor for advanced glycation end-products and World Trade Center particulate induced lung function loss: a case-cohort study and murine model of acute particulate exposure. *PLoS One* 2017;12:e0184331.
13. Crowley G, Kwon S, Haider SH, Caraher EJ, Lam R, St-Jules DE, *et al.* Metabolomics of World Trade Center-Lung Injury: a machine learning approach. *BMJ Open Respir Res* 2018;5:e000274.
14. de la Hoz RE, Jeon Y, Reeves AP, San José Estépar R, Liu X, Doucette JT, *et al.* Increased pulmonary artery diameter is associated with reduced FEV_1 in former World Trade Center workers. *Clin Respir J* 2019;13:614–623.
15. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, *et al.*; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–2752.
16. Grundy SM. Metabolic syndrome update. *Trends Cardiovasc Med* 2016; 26:364–373.
17. Menezes AM, Pérez-Padilla R, Wehrmeister FC, Lopez-Varela MV, Muiño A, Valdivia G, *et al.*; PLATINO team. FEV_1 is a better predictor of mortality than FVC: the PLATINO cohort study. *PLoS One* 2014;9:e109732.
18. Puddu PE, Menotti A, Tolonen H, Nedeljkovic S, Kafatos AG. Determinants of 40-year all-cause mortality in the European cohorts of the Seven Countries Study. *Eur J Epidemiol* 2011;26:595–608.
19. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313:711–715, discussion 715–716.
20. Jenkins C, Rodríguez-Roisin R. Quality of life, stage severity and COPD. *Eur Respir J* 2009;33:953–955.
21. Tojo N, Ichioka M, Chida M, Miyazato I, Yoshizawa Y, Miyasaka N. Pulmonary exercise testing predicts prognosis in patients with chronic obstructive pulmonary disease. *Intern Med* 2005;44:20–25.
22. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. *Eur Respir J* 2009;33:262–272.
23. Montes de Oca M, Tálamo C, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, *et al.*; PLATINO Team. Chronic obstructive pulmonary disease and body mass index in five Latin America cities: the PLATINO study. *Respir Med* 2008;102:642–650.
24. Osman IM, Godden DJ, Friend JA, Legge JS, Douglas JG. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. *Thorax* 1997;52:67–71.
25. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26:948–968.
26. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, *et al.* Standardization of Spirometry 2019 Update: an Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med* 2019;200:e70–e88.
27. Mafort TT, Rufino R, Costa CH, Lopes AJ. Obesity: systemic and pulmonary complications, biochemical abnormalities, and impairment of lung function. *Multidiscip Respir Med* 2016;11:28.
28. Liao W, Zhou J, Zhu S, Xiao A, Li K, Schauer JJ. Characterization of aerosol chemical composition and the reconstruction of light extinction coefficients during winter in Wuhan, China. *Chemosphere* 2020;241: 125033.

29. Peters U, Suratt BT, Bates JHT, Dixon AE. Beyond BMI: obesity and lung disease. *Chest* 2018;153:702–709.
30. Dixon AE, Peters U. The effect of obesity on lung function. *Expert Rev Respir Med* 2018;12:755–767.
31. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol (1985)* 2010;108:206–211.
32. Leone N, Courbon D, Thomas F, Bean K, Jégo B, Leynaert B, *et al.* Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009;179:509–516.
33. McClean KM, Kee F, Young IS, Elborn JS. Obesity and the lung: 1. Epidemiology. *Thorax* 2008;63:649–654.
34. Franssen FM, O'Donnell DE, Goossens GH, Blaak EE, Schols AM. Obesity and the lung: 5. Obesity and COPD. *Thorax* 2008;63:1110–1117.
35. Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. *Thorax* 2008;63:1018–1023.
36. Baffi CW, Wood L, Winnica D, Strollo PJ Jr, Gladwin MT, Que LG, *et al.* Metabolic syndrome and the lung. *Chest* 2016;149:1525–1534.
37. Vijayakanthi N, Greally JM, Rastogi D. Pediatric obesity-related asthma: the role of metabolic dysregulation. *Pediatrics* 2016;137:e20150812.
38. Chen H, Li Z, Dong L, Wu Y, Shen H, Chen Z. Lipid metabolism in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2019;14:1009–1018.
39. Agudelo CW, Samaha G, Garcia-Arcos I. Alveolar lipids in pulmonary disease: a review. *Lipids Health Dis* 2020;19:122.
40. Chen K, Kolls JK. Good and bad lipids in the lung. *Nat Med* 2010;16: 1078–1079.
41. Butland BK, Fehily AM, Elwood PC. Diet, lung function, and lung function decline in a cohort of 2512 middle aged men. *Thorax* 2000;55:102–108.
42. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;32:962–969.
43. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, *et al.*; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:155–161.
44. Cottrell L, Neal WA, Ice C, Perez MK, Piedimonte G. Metabolic abnormalities in children with asthma. *Am J Respir Crit Care Med* 2011;183:441–448.
45. Kim J, Yoo JY, Kim HS. Metabolic syndrome in South Korean patients with chronic obstructive pulmonary disease: a focus on gender differences. *Asian Nurs Res (Korean Soc Nurs Sci)* 2019;13:137–146.
46. Xuan L, Han F, Gong L, Lv Y, Wan Z, Liu H, *et al.* Association between chronic obstructive pulmonary disease and serum lipid levels: a meta-analysis. *Lipids Health Dis* 2018;17:263.
47. James BD, Jones AV, Trethewey RE, Evans RA. Obesity and metabolic syndrome in COPD: is exercise the answer? *Chron Respir Dis* 2018;15: 173–181.
48. Ye L, Huang X, Wang Q, Yang H, Cai D, Wang Z. PRISMA-compliant meta-analysis: association of metabolic syndrome and its components with the risk of chronic obstructive pulmonary disease. *Biosci Rep* 2018;38:BSR20181199.
49. Hsiao FC, Wu CZ, Su SC, Sun MT, Hsieh CH, Hung YJ, *et al.* Baseline forced expiratory volume in the first second as an independent predictor of development of the metabolic syndrome. *Metabolism* 2010;59:848–853.
50. Kwon S, Crowley G, Mikhail M, Lam R, Clementi E, Zeig-Owens R, *et al.* Metabolic syndrome biomarkers of World Trade Center airway hyperreactivity: a 16-year prospective cohort study. *Int J Environ Res Public Health* 2019;16:1486.
51. Kwon S, Crowley G, Caraher EJ, Haider SH, Lam R, Veerappan A, *et al.* Validation of predictive metabolic syndrome biomarkers of World Trade Center lung injury: a 16-year longitudinal study. *Chest* 2019; 156:486–496.
52. Canoy D, Luben R, Welch A, Bingham S, Wareham N, Day N, *et al.* Abdominal obesity and respiratory function in men and women in the EPIC-Norfolk Study, United Kingdom. *Am J Epidemiol* 2004;159:1140–1149.
53. Lin WY, Yao CA, Wang HC, Huang KC. Impaired lung function is associated with obesity and metabolic syndrome in adults. *Obesity (Silver Spring)* 2006;14:1654–1661.
54. Tan DBA, Armitage J, Teo TH, Ong NE, Shin H, Moodley YP. Elevated levels of circulating exosome in COPD patients are associated with systemic inflammation. *Respir Med* 2017;132:261–264.
55. Huang JZ, Liu L. Polynomial spline estimation and inference of proportional hazards regression models with flexible relative risk form. *Biometrics* 2006;62:793–802.
56. Sun J, Kopciuk KA, Lu XW. Polynomial spline estimation of partially linear single-index proportional hazards regression models. *Comput Stat Data Anal* 2008;53:176–188.
57. Naik P, Tsai CL. Partial least squares estimator for single-index models. *J R Stat Soc B* 2000;62:763–771.
58. Kwon S, Lee M, Schwartz T, Zeig-Owens R, Prezant D, Liu M, *et al.* 4088 Longitudinal assessment of metabolic syndrome as a modifiable risk factor of World Trade Center particulate matter exposure associated lung disease. *J Clin Transl Sci* 2020;4:49–50.
59. Kwon S, Lee M, Liu M, Prezant D, Nolan A. Assessing the temporal relationship of metabolic syndrome, a modifiable risk factor of World Trade Center particulate exposure associated lung injury: a longitudinal case-cohort study [abstract]. ATS International Conference. May 15, 2020–May 20, 2020, Philadelphia, PA. *Am J Respir Crit Care Med* 2020;201:A7125.
60. Lee M, Kwon S, Troxel A, Nolan A, Liu M. Partially linear single index hazards regression with time-dependent covariates. 30th International Biometric Conference. July 5, 2020–July 10, 2020, Seoul, Korea.
61. Edelman P, Osterloh J, Pirkle J, Caudill SP, Grainger J, Jones R, *et al.* Biomonitoring of chemical exposure among New York City firefighters responding to the World Trade Center fire and collapse. *Environ Health Perspect* 2003;111:1906–1911.
62. Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech* 2009;2:231–237.
63. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–3421.
64. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, *et al.*; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–3167.
65. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition: a Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006;23:469–480.
66. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization; 1999 [accessed 2 April 2019]. Available from: https://apps.who.int/iris/bitstream/handle/10665/66040/WHO_NCD_NCS_99.2.pdf;jsessionid=9CC692F8D168C27C8070D5BC89F1A05C?sequence=1.
67. Freedman DS, Horlick M, Berenson GS. A comparison of the Slaughter skinfold-thickness equations and BMI in predicting body fatness and cardiovascular disease risk factor levels in children. *Am J Clin Nutr* 2013;98:1417–1424.
68. Defining adult overweight and obesity. Atlanta, GA: Centers for Disease Control and Prevention; 2021 [updated 7 Jun 2021; accessed 2021 Jul 5]. Available from: https://www.cdc.gov/obesity/adult/defining.html.
69. Leem AY, Park B, Kim YS, Chang J, Won S, Jung JY. Longitudinal decline in lung function: a community-based cohort study in Korea. *Sci Rep* 2019;9:13614.
70. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645–1648.
71. Pauwels RA, Löfdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, *et al.*; European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999;340:1948–1953.
72. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1: the Lung Health Study. *JAMA* 1994;272:1497–1505.
73. Halpin DMG, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ, *et al.* Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease: the 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2020;203:24–36.

74. Tantucci C, Modina D. Lung function decline in COPD. *Int J Chron Obstruct Pulmon Dis* 2012;7:95–99.
75. Liao YX, Chen YH. Twenty years of changes in the disease assessment method of the Global Initiative for Chronic Obstructive Lung Disease. *Chin Med J (Engl)* 2020;133:2098–2103.
76. Albitar HAH, Iyer VN. Adherence to Global Initiative for Chronic Obstructive Lung Disease guidelines in the real world: current understanding, barriers, and solutions. *Curr Opin Pulm Med* 2020;26: 149–154.
77. Casanova C, de Torres JP, Aguirre-Jaíme A, Pinto-Plata V, Marin JM, Cordoba E, *et al.* The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. *Am J Respir Crit Care Med* 2011;184:1015–1021.
78. van Houwelingen H, Putter H. Dynamic prediction in clinical survival analysis. Boca Raton, FL: CRC Press; 2011.
79. Therneau T, Grambsch P. Modeling survival data: extending the Cox model. New York, NY: Springer; 2000.
80. Broström G. Event history analysis with R. Boca Raton, FL: CRC Press; 2018.
81. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of Martingale-based residuals. *Biometrika* 1993;80:557–572.
82. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982;38:963–974.
83. Lindstrom MJ, Bates DM. Newton-Raphson and Em algorithms for linear mixed-effects models for repeated-measures data. *J Am Stat Assoc* 1988;83:1014–1022.
84. Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001;54:774–781.
85. Keating C, Backholer K, Gearon E, Stevenson C, Swinburn B, Moodie M, *et al.* Prevalence of class-I, class-II and class-III obesity in Australian adults between 1995 and 2011-12. *Obes Res Clin Pract* 2015;9: 553–562.
86. Criscuolo NG, Angelini C. StructuRly: a novel shiny app to produce comprehensive, detailed and interactive plots for population genetic analysis. *PLoS One* 2020;15:e0229330.
87. Tiengo A, Fadini GP, Avogaro A. The metabolic syndrome, diabetes and lung dysfunction. *Diabetes Metab* 2008;34:447–454.
88. Crowley G, Kwon S, Haider S, Caraher EJ, Lam R, Liu M, *et al.* Metabolite and biomarker predictors of World Trade Center-Lung Injury: an integrated multiplatform machine learning approach [abstract]. *Am J Respir Crit Care Med* 2018;197:A2588.
89. Jung W, Park T, Kim Y, Park H, Han Y, He J, *et al.* Validation of a nomogram to predict the risk of cancer in patients with intraductal papillary mucinous neoplasm and main duct dilatation of 10 mm or less. *Br J Surg* 2019;106:1829–1836.
90. Wei Y, Zhang JJ, Li Z, Gow A, Chung KF, Hu M, *et al.* Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: findings from a natural experiment in Beijing. *FASEB J* 2016; 30:2115–2122.
91. Cupul-Uicab LA, Skjaerven R, Haug K, Travlos GS, Wilson RE, Eggesbø M, *et al.* Exposure to tobacco smoke in utero and subsequent plasma lipids, ApoB, and CRP among adult women in the MoBa cohort. *Environ Health Perspect* 2012;120:1532–1537.
92. Stevens DR, Malek AM, Laggis C, Hunt KJ. In utero exposure to tobacco smoke, subsequent cardiometabolic risks, and metabolic syndrome among U.S. adolescents. *Ann Epidemiol* 2018;28:619–624.e1.
93. Wallwork RS, Colicino E, Zhong J, Kloog I, Coull BA, Vokonas P, *et al.* Ambient fine particulate matter, outdoor temperature, and risk of metabolic syndrome. *Am J Epidemiol* 2017;185:30–39.
94. Brook RD, Sun Z, Brook JR, Zhao X, Ruan Y, Yan J, *et al.* Extreme air pollution conditions adversely affect blood pressure and insulin resistance: the Air Pollution and Cardiometabolic Disease Study. *Hypertension* 2016;67:77–85.
95. Fiordelisi A, Piscitelli P, Trimarco B, Coscioni E, Iaccarino G, Sorriento D. The mechanisms of air pollution and particulate matter in cardiovascular diseases. *Heart Fail Rev* 2017;22:337–347.
96. Zammit C, Liddicoat H, Moonsie I, Makker H. Obesity and respiratory diseases. *Int J Gen Med* 2010;3:335–343.
97. Griffith KA, Sherrill DL, Siegel EM, Manolio TA, Bonekat HW, Enright PL. Predictors of loss of lung function in the elderly: the Cardiovascular Health Study. *Am J Respir Crit Care Med* 2001;163:61–68.
98. Cunningham TJ, Ford ES, Rolle IV, Wheaton AG, Croft JB. Associations of self-reported cigarette smoking with chronic obstructive pulmonary disease and co-morbid chronic conditions in the United States. *COPD* 2015;12:276–286.
99. Bowler RP, Jacobson S, Cruickshank C, Hughes GJ, Siska C, Ory DS, *et al.* Plasma sphingolipids associated with chronic obstructive pulmonary disease phenotypes. *Am J Respir Crit Care Med* 2015;191: 275–284.
100. Hoonhorst SJ, Lo Tam Loi AT, Hartman JE, Telenga ED, van den Berge M, Koenderman L, *et al.* Advanced glycation end products in the skin are enhanced in COPD. *Metabolism* 2014;63:1149–1156.
101. Yonchuk JG, Silverman EK, Bowler RP, Agustí A, Lomas DA, Miller BE, *et al.* Circulating soluble receptor for advanced glycation end products (sRAGE) as a biomarker of emphysema and the RAGE axis in the lung. *Am J Respir Crit Care Med* 2015;192:785–792.
102. Iyer AS, Dransfield MT. The "obesity paradox" in chronic obstructive pulmonary disease: can it be resolved? *Ann Am Thorac Soc* 2018;15: 158–159.
103. 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. *Am J Epidemiol* 2019;188:1977–1983.
104. Menezes AMB, Pérez-Padilla R, Wehrmeister FC, Lopez-Varela MV, Muiño A, Valdivia G, *et al.*; PLATINO team. FEV_1 is a better predictor of mortality than FVC: the PLATINO cohort study. *PLoS One* 2014;9: e109732.
105. Jakeways N, McKeever T, Lewis SA, Weiss ST, Britton J. Relationship between FEV_1 reduction and respiratory symptoms in the general population. *Eur Respir J* 2003;21:658–663.
106. Zhang W, Zhang Y, Li CW, Jones P, Wang C, Fan Y. Effect of statins on COPD: a meta-analysis of randomized controlled trials. *Chest* 2017; 152:1159–1168.
107. Gowdy KM, Fessler MB. Emerging roles for cholesterol and lipoproteins in lung disease. *Pulm Pharmacol Ther* 2013;26:430–437.
108. Keddissi JI, Younis WG, Chbeir EA, Daher NN, Dernaika TA, Kinasewitz GT. The use of statins and lung function in current and former smokers. *Chest* 2007;132:1764–1771.
109. Wiley JF, Carrington MJ. A metabolic syndrome severity score: a tool to quantify cardio-metabolic risk factors. *Prev Med* 2016;88:189–195.
110. DeBoer MD, Filipp SL, Sims M, Musani SK, Gurka MJ. Risk of ischemic stroke increases over the spectrum of metabolic syndrome severity. *Stroke* 2020;51:2548–2552.
111. Standard on comprehensive occupational medical program for fire departments [serial online]. Quincy, MA: National Fire Protection Association; 2021 [accessed 30 April 2021]. Available from: https://www.nfpa.org/codes-and-standards/all-codes-and-standards/list-of-codes-and-standards/detail?code=1582.
112. Aldrich TK, Gustave J, Hall CB, Cohen HW, Webber MP, Zeig-Owens R, *et al.* Lung function in rescue workers at the World Trade Center after 7 years. *N Engl J Med* 2010;362:1263–1272.
113. Aldrich TK, Vossbrinck M, Zeig-Owens R, Hall CB, Schwartz TM, Moir W, *et al.* Lung function trajectories in World Trade Center-exposed New York City firefighters over 13 years: the roles of smoking and smoking cessation. *Chest* 2016;149:1419–1427.
114. Niles JK, Webber MP, Gustave J, Zeig-Owens R, Lee R, Glass L, *et al.* The impact of the World Trade Center attack on FDNY firefighter retirement, disabilities, and pension benefits. *Am J Ind Med* 2011;54:672–680.
115. Gu F, Derkach A, Freedman ND, Landi MT, Albanes D, Weinstein SJ, *et al.* Cigarette smoking behaviour and blood metabolomics. *Int J Epidemiol* 2016;45:1421–1432.
116. Benowitz NL, Dains KM, Dempsey D, Yu L, Jacob P III. Estimation of nicotine dose after low-level exposure using plasma and urine nicotine metabolites. *Cancer Epidemiol Biomarkers Prev* 2010;19:1160–1166.

117. Cohen HW, Zeig-Owens R, Joe C, Hall CB, Webber MP, Weiden MD, *et al.* Long-term cardiovascular disease risk among firefighters after the World Trade Center disaster. *JAMA Netw Open* 2019;2: e199775.
118. Kwon S, Putman B, Weakley J, Hall CB, Zeig-Owens R, Schwartz T, *et al.* Blood eosinophils and World Trade Center exposure predict surgery in chronic rhinosinusitis: a 13.5-year longitudinal study. *Ann Am Thorac Soc* 2016;13:1253–1261.
119. Crowley G, Kwon S, Ostrofsky DF, Clementi EA, Haider SH, Caraher EJ, *et al.* Assessing the protective metabolome using machine learning in World Trade Center particulate exposed firefighters at risk for lung injury. *Sci Rep* 2019;9:11939.
120. Molina-Luque R, Romero-Saldaña M, Álvarez-Fernández C, Rodríguez-Guerrero E, Hernández-Reyes A, Molina-Recio G. Waist to height ratio and metabolic syndrome as lung dysfunction predictors. *Sci Rep* 2020; 10:7212.
121. Park S, Lee S, Kim Y, Lee Y, Kang MW, Han K, *et al.* Altered risk for cardiovascular events with changes in the metabolic syndrome status: a nationwide population-based study of approximately 10 million persons. *Ann Intern Med* 2019;171:875–884.