FACULTY OF PHARMACEUTICAL SCIENCES

Factors associated with treatment response to inhaled corticosteroids:

insights from WTC-exposed and chronic users

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OVERVIEW OF PUBLICATIONS AND MANUSCRIPTS IN THIS THESIS

Chapter III.1
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Chapter III.2
Singh A, Liu C, Putman B, Zeig-Owens R, Hall CB, Schwartz T, Webber MP, Cohen, HW, Berger KI, Nolan A, Prezant DJ, Weiden MD. Predictors of Asthma/COPD Overlap in FDNY Firefighters With World Trade Center Dust Exposure. Chest. 2018 Dec;154(6):1301–10.

I contributed to the data analyses & interpretation and critically revised the manuscript.

Chapter III.3
Putman B, Lahousse L, Zeig-Owens R, Singh A, Hall CB, Liu Y, Schwartz T, Goldfarb D, Webber MP, Prezant DJ, Weiden MD. Low serum IgA and airway injury in World Trade Center-exposed firefighters: a 17-year longitudinal study. Thorax. 2019 Dec;74(12):1182–4.

Chapter III.4
Putman B, Lahousse L, Goldfarb DG, Zeig-Owens R, Schwartz T, Singh A, Vaeth B, Hall CB, Lancet EA, Webber MP, Cohen HW, Prezant DJ, Weiden MD. Factors Predicting Treatment of World Trade Center-Related Lung Injury: A Longitudinal Cohort Study. IJERPH. 2020 Dec 4;17(23):9056.

Chapter IV.1
Putman B, Lahousse L, Goldfarb DG, Zeig-Owens R, Lancet EA, Schwartz T, Hall CB, Webber MP, Cohen HW, Prezant DJ, Weiden MD. Effect of inhaled corticosteroids on FEV_1 trajectory in WTC-exposed firefighters: a 16-year longitudinal cohort study. *In preparation.*

Chapter IV.2
Putman B, Coucke L, Vanoverschelde A, Mehuys E, Lahousse L. Community pharmacist counseling improves adherence and asthma control: a nationwide study. *Submitted to BMC Health Services Research.*

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

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I would like to thank you. First of all because you have gotten to read until this page. This means you were able to get a copy of my research work. Additionally, you might feel sympathy for me somehow or you are really interested in my research topic.
Some of the most important goals in my life is to mean something for someone by helping people. That is why I became a physician. When I discovered I also love statistics, getting into medical research was a way to combine some things. I am very pleased that this research topic of analyzing disease and treatment was one my mentor's suggestions, so I got to study a clinically meaningful subject, that might have implications on real-life practice. That is how I found motivation to keep going, even on difficult moments.

The most important person is my 'personal driver', my husband Matthias. Without his pushes I would not have finished this project yet. He also taught me to be more realistic, of which one thing is planning (or when it is really is time to wrap up). We also share the passion for data analyses, which has led to some home-work nights exchanging SAS code. Our children, Cathaleya and Benjamin, also motivated me by just being kids and clearing my mind in the evening and weekends. One thing I like to share with them is that it is worth persevering, even though it is not always the easiest way. But the satisfaction afterwards makes it worth it. They will understand when they are all grown up.

Thanks to the open-minded and passionate promotor, professor Lies Lahousse, I was able to find a perfectly matching promotor with a background in epidemiology, big pulmonary data and medication adherence. Always enthusiastic to broaden her world, Lies gave me an additional support. Even before corona got to rule the world, we already had our biweekly video-call meetings to discuss the progress of my PhD and give me practical advice.

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Also, many thanks go to my parents for their unconditional love and support in whatever I do. They are always interested to hear what I'm doing and to know that everything is going well. To cite my father his speech on our wedding on how I modestly start many challenges 'I can try and see how it goes'. And that is also how this project started. But step by step I wanted to get more out of my research, and this is the result. Furthermore, I want to thank my parents-in-law, especially for letting us stay at their farm for 5 months when we escaped NYC because of corona. That way I was able to continue my research from remotely in a supportive environment.

Finally, I would like to thank my former and future patients, for giving me this drive and satisfaction. I am really looking forward to many more years of clinical work to come.

Barbara
November 6th, 2020

LIST OF ABBREVIATIONS

9/11	(disaster on) 11 September 2001
ACO	asthma/COPD overlap
BD-PFT	bronchodilator pulmonary function test
BMI	body mass index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
EMR	electronic medical record
FDNY	Fire Department of the City of New York
FEV_1	forced expiratory volume in 1 second
FEV_1/FVC	ratio of forced expiratory volume in 1 second on forced vital capacity
FVC	forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
HR	hazard ratio
ICS	inhaled corticosteroid
ICS/LABA	inhaled corticosteroids/long-acting beta-agonist
IgA	immunoglobulin A
IPTW	inverse probability of treatment weighting
IQR	inter-quartile range
LABA	long-acting beta-agonists
LAMA	long- acting muscarinic antagonist
mMRC	modified Medical Research Council
OCS	oral corticosteroids
OR	odds ratio
PFT	pulmonary function test
ROC	receiver-operator characteristic
RV	residual volume
SABA	short-acting beta-agonist
SEM	standard error of mean
T_h	T-helper cell
TLC	total lung capacity
WTC	(collapse of the) World Trade Center (towers)

I. Introduction

I.1. Pulmonary function and testing

I.1.1. Pulmonary function

I.1.1.1. Normal pulmonary function and defense

The lungs are the major organs of the respiratory system. Their vital function is to supply the body with oxygen from the air. Therefore, ventilation, which is the process of inspiration and expiration, is essential. When we breathe in, air flows through the nose or mouth, down the pharynx, into larynx, and down the trachea (Figure 1). The air then comes to the right and left main bronchi, which then branch into smaller and smaller airways, to finally form bronchioles.[1] The bronchioles are lined with a layer of smooth muscles.[2] Air continues through these small airways until it finally reaches the tiny balloon-like air sacs, the alveoli. At the level of the alveoli the gas exchange takes place, with diffusion of oxygen into capillary blood.

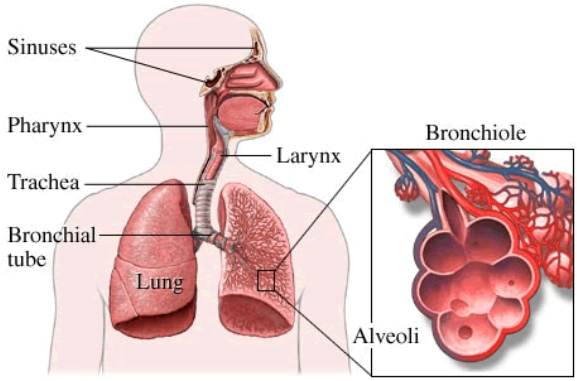


Figure 1 – Anatomy related to pulmonary function. When inhaling, air flows through the nose or mouth, down the pharynx, into larynx, down the trachea. The air then comes to the right and left main bronchi, which branch into smaller and smaller airways, to form bronchioles. Air continues through these small airways until it finally reaches the alveoli, where gas exchange takes place with the blood.

Figure adapted from website of the College of Medicine, University of Florida.[3]

To maintain its structure and function, immunological and defense mechanisms protect the respiratory system against microorganism and noxious gases and particles. First innate, intrinsic defense is activated, including anatomical barriers, mucociliary clearance and professional phagocytes cells.[4] These, at their turn, will activate several mediators, resulting in an inflammatory cascade of cytokines and chemokines.

Once innate host defense systems are activated, the adaptive, acquired immune response is regulated by B and T cells, which are lymphocytes.[5] The two major types of T cells are helper T cells (T_h) and cytotoxic T cells (T_C). T_h cells exist of three main subsets: T_h1, T_h2, and T_h17. Type 1 and type 2 immune responses that are mainly regulated by T_h1 and T_h2 cells, respectively.[6] T_h1 cells primarily secrete interferon-γ (IFN-γ) and stimulate type 1 immunity. By contrast, T_h2 cells mainly secrete the cytokines IL-4, IL-5 and IL-13, and stimulate type 2 immunity, which is characterized by high antibody titers and increased eosinophil counts. After antigen-dependent activation, B cells can develop into plasma cells, which secrete antibodies, or immunoglobulins (Ig) specialized to target that antigen.[5] IgA is the predominant type in secretions.[7]

I.1.1.2. Compromised pulmonary function

Lung function may be compromised in case of obstructive lung disease, such as asthma and chronic obstructive pulmonary disease (COPD). Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[8] Airway type 2 immune responses are mainly mediated by eosinophils, mast cells, basophils, T_h2 cells, group 2 innate lymphoid cells and IgE-producing B cells.[6] Asthma is often triggered by allergens or irritants in the air. When these irritants enter the bronchioles, mast cells release an inflammatory mediator histamine, which causes the smooth muscles of the bronchioles to contract. Narrowing of the airways, or bronchoconstriction, while meant to keep foreign substances from entering the lungs, can restrict breathing, sometimes severely.

This can happen during an exacerbation, which is an acute worsening of the patient's baseline respiratory symptoms. Exacerbations are caused or triggered by different factors including viruses, bacteria and air pollutants.[9] They are associated with acute, increased worsening of existing airway inflammation, causing deterioration of lung function.[9,10]

COPD is a common, preventable and treatable disease that is characterized by persistent, usually progressive respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development.[11] Included in those causing agents are environmental or occupational exposures to dust, as cigarette smoking but also exposure to organic and inorganic dust in non-smokers. [12–14] Increased airway smooth muscle in COPD patients with progressing disease is negatively correlated with lung function.[15,16] The term 'asthma-COPD overlap' (ACO) is used to describe patients who have persistent airflow limitation together with clinical features of both asthma and COPD.[8,17] ACO is associated with more frequent exacerbations and poorer quality of life.[18,19]

I.1.2. Pulmonary function tests

I.1.2.1. Spirometry

Spirometry is the most common test to evaluate pulmonary function and outputs physiologic measurements. It can be used for screening of high-risk populations or as work-up for individuals with respiratory symptoms. It is a physiological test that measures air volumes when exhaling with maximal effort after a deepest inhalation possible. The volume of air produced during the first second of this exercise, is called the FEV_1 (Figure 2). The total volume of air that can be forcibly exhaled, is the FVC. FEV_1 and FVC are often plotted on spirometric curves.[20] A frequently used ratio of those two is the FEV_1/FVC ratio, also named the Tiffeneau index, used to detect airflow limitation.[21] An obstructive disease is defined by a FEV_1/FVC ratio is below the cutoff of 0.7. However, because the ratio varies with ageing, it should be confirmed by post-bronchodilator FEV_1/FVC values below the lower limit of normal, especially in young individuals.[21,22] The severity of the disorder is determined by the FEV_1 % predicted based on reference values derived from population-based cross sectional studies.

A bronchodilator pulmonary function test (BD PFT) includes a spirometry before administration of a bronchodilator (pre-bronchodilator), followed by second spirometry after administration of a bronchodilator (post bronchodilator) such as salbutamol (albuterol). This test will assess bronchodilator responsiveness. A significant positive bronchodilator response is defined as a change in FEV_1 and/or FVC from baseline being >12% and 200 mL.[23]

Another test reversible airflow obstruction is a bronchial provocation test. This test measures reduction of FEV_1 in response to methacholine, histamine or exercise.[21,24]. The dose of methacholine or histamine producing a 20% reduction of FEV_1 is a measure of bronchial responsiveness.[25] A 15-20% reduction of FEV_1 during exercise or after a 10mg/mL doses of methacholine defines bronchial hyper-responsiveness.[26]

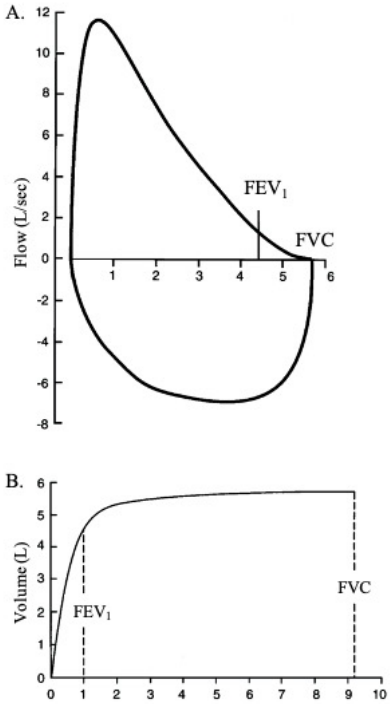


Figure 2 – Spirometric flow-volume (Panel A) and volume-time (Panel B) curves for a healthy 52-year-old male, who's 188cm tall. In the flow-volume curve the well-defined peak in expiratory flow represents good initial effort. The expiratory portion of the curve can be found at the top and closing the loop back to 0 flow shows the inspiratory portion (bottom). The Forced Expiratory Volume in 1 second (FEV_1) is indicated around 4.4L in the expiratory part of the flow-volume curve or at 1 second on the volume-time curve. The maximum volume of air that can be exhaled after a maximal inhalation, is the Forced Vital Capacity (FVC) of the spirometry. In the volume-time curve good initial effort is shown by a sharp increase in volume from time 0.

Figure adapted from Crapo, NEJM, 1994. Reproduced with permission from Crapo RO. Pulmonary-Function Testing. N Engl J Med. 1994 Jul 7;331(1):25–30. Copyright Massachusetts Medical Society.

I.1.2.2. Quality of pulmonary function test

Following American Thoracic Society/European Respiratory Society recommendations on standardized reporting for pulmonary function tests, spirometry measurements of FEV_1 and FVC are graded on a scale between A and F.[27] The grading system informs the interpreter about the acceptability and repeatability. The acceptability criteria define a minimum of quality standards the results of FEV_1 and FVC have to meet, including not being allowed to make certain critical errors. The repeatability criteria set maximum allowable differences between the two largest FVC values and the two largest FEV_1 values. Grades A through C are considered as clinically useful.

I.1.2.3. Screening spirometry testing

As for primary care setting, hand-held office spirometers have been used since many years as a screening tool.[27,28] They are user-friendly, but require trained personnel to provide reproducible results. Hand-held spirometers are useful in offices of general practices. Analogously, for the longitudinal follow-up of lung function, a handheld spirometer was used as part of the World Trade Center (WTC) health program at the Fire Department of the City of New York (FDNY).[29]

I.1.3. Lung function trajectories

I.1.3.1. FEV_1 trajectories

When collecting multiple spirometry measurements longitudinally, we can analyze a FEV_1 trajectory. Throughout childhood FEV_1 increases to a maximum at an age around 20 years. There is evidence that there is a plateau phase between age 20 until 30-35 years (Figure 3). From middle age adulthood, the FEV_1 declines around 30 mL/year in men and 25mL/year in women.[30] A greater than age-related (accelerated) decline in FEV_1 despite a normal lung function at early adulthood, is one of the pathways found to lead to COPD, visualized as a red trajectory on Figure 3.[31]

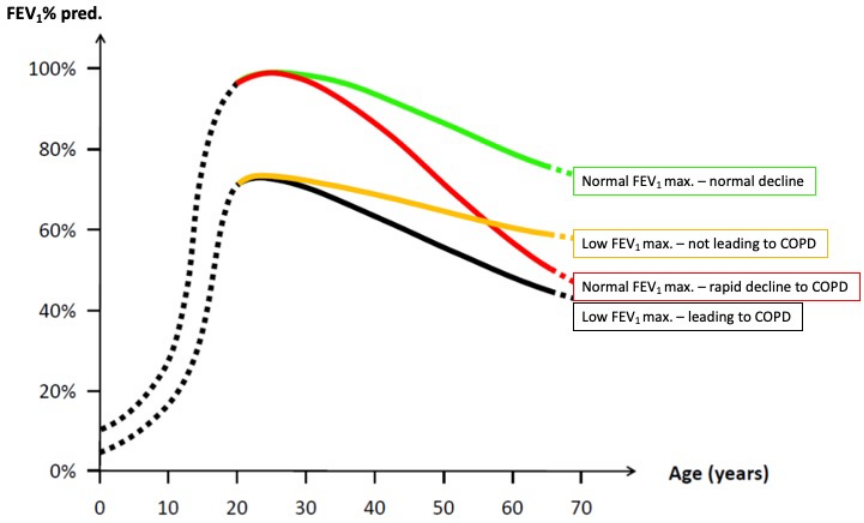


Figure 3 – Lung function trajectories leading to chronic obstructive pulmonary disease (COPD). When attenuating a maximal lung function at early adulthood, a normal decline will result in an age-related FEV_1 decline, whereas an accelerated, rapid decline will lead to COPD. In case of a lower maximum lung function at early adulthood, a moderate decline can preserve the lung function, but a greater decline will end in COPD.

Figure adapted from Lange et al. NEJM, 2015. Reproduced with permission from Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med 2015;373:111-22. Copyright Massachusetts Medical Society.

I.1.3.2. Risk factors for FEV_1 decline

As shown by the black trajectory of FEV_1 in Figure 3, impaired lung growth an early lung function might also be a risk factor for developing COPD.[32] Lung growth and lung function in early life is a result of both genetic mechanisms and complex interactions between genetic makeup and a large number of environmental factors. A large number of environmental toxic agents have been implicated as having the potential to adversely affect normal lung development. There is strong evidence that in utero exposure to environmental agents, specifically tobacco smoke, is associated with adverse

respiratory outcome and this appears to be influenced by genetic makeup. Evidence of a gene-environmental interaction is found by showing that infants from mothers carrying polymorphisms of the GST gene were more susceptible to the adverse effects of smoking.[33] Moreover, polymorphisms in GST-Omega genes interact with environmental tobacco smoke exposure both in utero and in adulthood and significantly affect FEV_1 in adulthood.[34] Population-based studies have connected genes important for lung growth, such as ADAM33, with susceptibility to chronic obstructive pulmonary disease. These have been confirmed by patient studies.[35,36] Another study showed that SOX5, a gene necessary for lung development, is associated with chronic obstructive pulmonary disease, which suggest the development of the disease being in utero.[37]

Risk factors for an accelerated decline in FEV_1 leading to COPD despite a normal maximum at early adulthood (red trajectory on Figure 3) , are smoking, occupational exposures and heterozygote alpha-1-anti-trypsin deficiency.[30,38] A greater decline in FEV_1 has also been observed in individuals with asthma.[39,31] Also, an increased frequency of pulmonary exacerbations was found to be associated with FEV_1 decline.[40,41]

I.2. WTC cohort

I.2.1. 9/11 disaster

The terrorist attack on 11 September 2001 (9/11) caused the WTC towers to explode and collapse. This produced a huge dust cloud in Lower Manhattan in the first days after 9/11, containing building debris and products of combustion.[42] Many individuals, from residents, to commuters, rescue- and recovery and cleanup workers, got massively exposed to this dust. The FDNY operated a continuous rescue and recovery effort at the WTC site, involving approximately 11 000 firefighters. An increase in symptoms and incidence of post-9/11 diseases was observed. Among the FDNY rescue- and recovery cohort, a raise in lower respiratory symptoms and obstructive airway disease was found, besides a significant drop in FEV_1 compared with pre-9/11 screening spirometry measurements.[43,44,29,45,46] Furthermore, comorbidities such as chronic rhinosinusitis, gastro-esophageal reflux disorder, post-traumatic stress disorder and depression have been noted.[47–51]

I.2.2. Monitoring program and data collection

Soon after 11 September 2001, the Fire Department of the City of New York (FDNY) instituted a medical monitoring program that performed screening spirometry tests (Figure 4). The program also collected demographic, exposure and respiratory symptom data via computer-based health questionnaires and body measurements form physical examination.[52] Additionally, FDNY began a treatment program at no cost to the participants. If indicated, individuals were sent to a hospital pulmonary laboratory for subspecialty pulmonary exams as post-bronchodilator pulmonary function test (PFT) or methacholine challenge test (MCT). Longitudinal data from these monitoring and treatment programs have gained insights in post-9/11 diseases

and treatment responses. A majority of FDNY firefighters also had pre-9/11 spirometry tests and blood work.

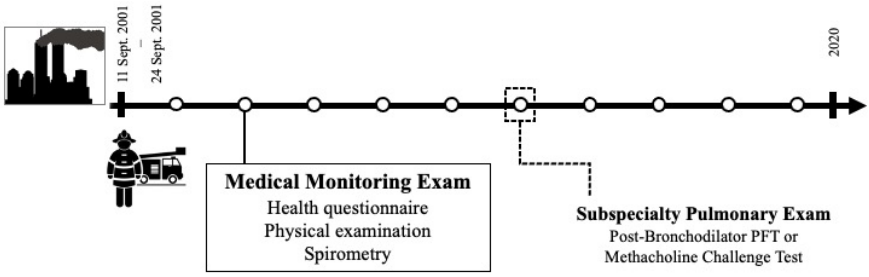


Figure 4 - Longitudinal data collection at Fire Department of the City of New York (FDNY) as part of the World Trade Center (WTC) Health Program. Soon after the disaster on 11 September 2001 (9/11) FDNY started a medical monitoring for rescue and recovery workers who were active at the WTC site between 11-24/09/2001. At the monitoring exams a physical exam, health questionnaire and spirometry test were performed. When indicated, patients underwent an additional subspecialty pulmonary exam as a post-bronchodilator pulmonary function test or methacholine challenge test to test for bronchodilator responsiveness or hyperresponsiveness, respectively.

I.2.3. Demographics of the FDNY WTC cohort

Of the FDNY rescue and recovery workers, approximately 11 000 were firefighters exposed to dust from working at the WTC site. Since the FDNY WTC-exposed firefighter cohort was less than 1% female, women were not included in most research studies.

Table 1 shows demographics of WTC-exposed male firefighters who had at least one post-9/11 monitoring spirometry. The mean age on 9/11 was about 40 years old. Two thirds never smoked. The majority race was white (94%). The proportion of individuals who had high intensity exposure, defined by arrival at the WTC site on the morning of 9/11, was about 17%, whereas 71% arrived the afternoon of 9/11 or the day after. The mean of first post-9/11 FEV_1 was 96.7 ± 13.8% predicted and the FEV_1/FVC was 0.84 ± 0.06. By 2020, a big proportion (77%) of the cohort has retired, with a mean age of 50 years at their retirement. The mean of most recent FEV_1 was 92.5 ± 14.5% predicted and the FEV_1/FVC was 0.78 ± 0.06.

Table 1 – Demographics of WTC-exposed male firefighters (n = 10 172) containing first post-9/11 characteristics and measurements

Variable	Population *n = 10 172*
Age on 9/11 (years), mean±SD	40.3 ± 7.4
BMI (kg/m^2), mean±SD	28.9 ± 3.5
Smoking status, n (%)	
Never smokers	7 500 (73.7)
Former smokers	1 453 (14.3)
Current smokers	1 218 (12.0)
Race, n (%)	
White	9 561 (94.0)
Black	255 (2.5)
Other	356 (3.5)
WTC exposure level	
Morning of 9/11	1 673 (16.5)
Afternoon of 9/11 or 12 September 2001	7 240 (71.2)
13 to 24 September 2001	1 259 (12.4)
Spirometry measurement, mean±SD	
FEV_1 % predicted	96.7 ± 13.8
Absolute FEV_1, L	4.00 ± 0.68
FEV_1/FVC ratio	0.84 ± 0.06

9/11 = 11 September 2001; SD = standard deviation; BMI = body mass index; WTC = World Trade Center; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity

I.2.4. WTC-exposure and other risk factors of disease

High WTC exposure, defined as initial arrival at the WTC site during the morning of 9/11, was found to be associated with a lower lung function (Figure 5).[45] WTC-exposure intensity, was also associated with physician-diagnosed obstructive airways disease until September 2008.[53] After the first 7 years, WTC-exposure intensity was no longer significantly associated with incident disease even though elevated incidence of physician diagnosed lower airways disease has persisted.

In sinus disease, high WTC exposure and elevated first post 9/11 blood eosinophil counts were found to be risk factors for chronic rhinosinusitis (CRS).[47] These factors also turned out to be predictors in CRS patients requiring sinus surgery. Furthermore, low IgA was associated with eosinophils in sinus surgery and not in individuals without sinus disease.[48]

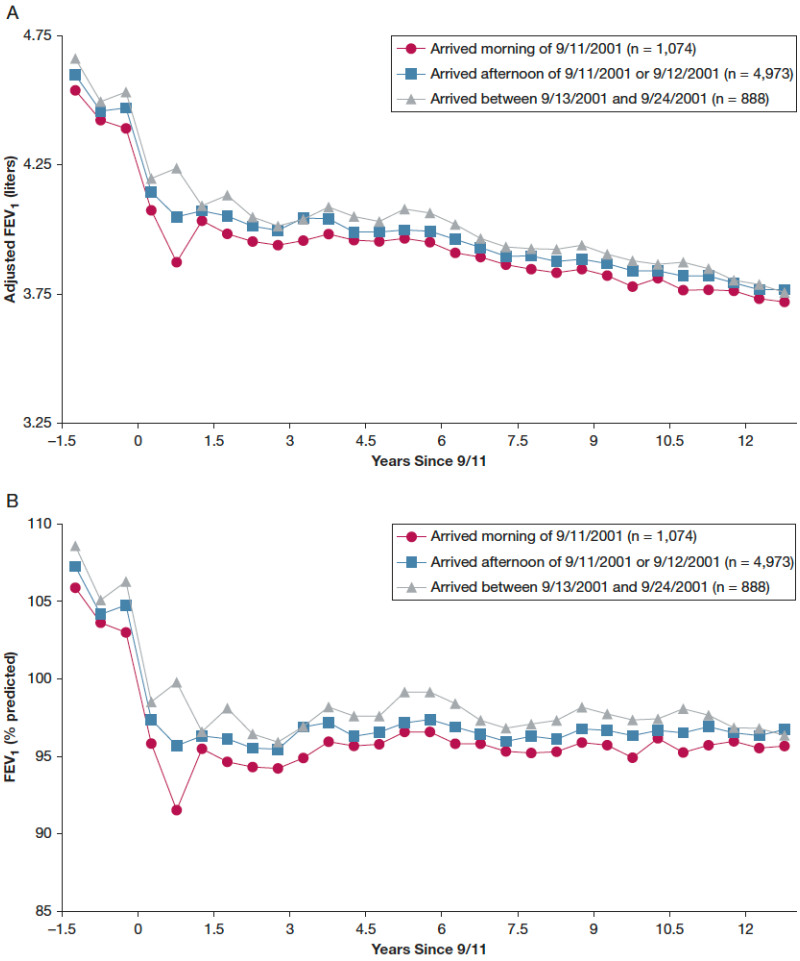


Figure 5 – Longitudinal FEV_1 trajectories stratified by WTC-exposure intensity. Individuals with high intensity exposure defined by arrival at the morning of 11 September 2001 (9/11) were showing lower FEV_1 values longitudinally. (Panel A) Actual FEV_1 adjusted by age on 9/11, height, weight, sex, and race. (Panel B) FEV_1 % predicted adjusted by age on 9/11, and weight. Only never-smokers at the end of the study were included.

Figure from Aldrich TK, Vossbrinck M, Zeig-Owens R, et al. Lung Function Trajectories in World Trade Center-Exposed New York City Firefighters Over 13 Years. Chest 2016;149:1419–27. Copyright Elsevier.

I.2.5. Classification of post-9/11 lung injury

When WTC-exposed firefighters had an abnormal screening FEV_1 or when they experienced persistent respiratory symptoms, they were referred for additional work-up at a hospital-based pulmonary laboratory. This subspecialty pulmonary testing most often included a bronchodilator PFT and/or MCT, checking for bronchodilator responsiveness or bronchial hyperresponsiveness, respectively.[24,54]

Bronchial hyperreactivity and obstructive airways disease (OAD) was a frequent finding post 9/11.[55,44] By 2008, 13% had received subspecialty pulmonary testing, with 59% having OAD based on meeting at least one of those criteria: an FEV_1/FVC <0.76 (LLN), bronchodilator responsiveness, hyperreactivity, or an RV>120% predicted. The type of asthma that was seen was an irritant-induced asthma likely related to the exposure to WTC dust, resulting in negative allergy testing most of the time. A smaller proportion of 44% of individuals with BD PFT showed an airflow limitation defined by $FEV_1/FVC<0.7$.[46] Higher eosinophil concentrations were associated with incident airflow limitation.

Categorizing all post-9/11 lung injury into a standard type of lung disease seems to be challenging. By 2014 only 1.6% of WTC-exposed firefighters had a persistent FEV_1 < 70% predicted (Figure 6). [29] Although a proportion of around 13% of WTC-exposed firefighters are experiencing an accelerated (loss >64 ml/y) FEV_1 decline by 2016 (red triangle curve on Figure 7). Higher blood eosinophil and neutrophil counts were both associated with accelerated FEV_1 decline.[46] Reduced lung growth will less likely have been the pathway (black trajectory on Figure 3) to the development of accelerated decline in WTC firefighters, since there is a high demanding physical testing before onboarding as a firefighter [56,57] Most individuals experiencing an accelerated FEV_1 decline still have an FEV_1 within the normal range and 2/3rd lack evidence of asthma on subspecialty testing.[46] This means this type of airways disease does not yet meet the definition of asthma or COPD.

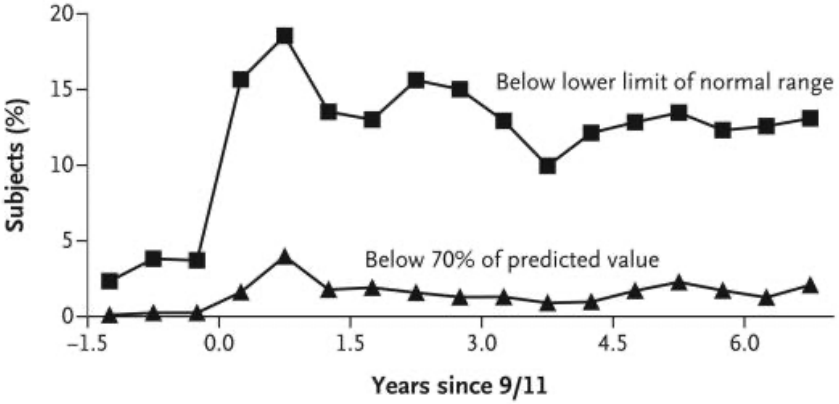


Figure 6 – Proportion of abnormal lung function in WTC-exposed Fire Department of New York City (FDNY) firefighters. Shown are data for nonsmoking FDNY firefighters who were at the World Trade Center site during the first 2 weeks after the attack of 11 September 2001 (9/11). The proportions of firefighters who had a forced expiratory volume in 1 second (FEV_1) under the lower limit of the normal range (=the lowest 5th percentile of a reference population) or less than 70% of the predicted value are indicated. Data are shown for white workers and black workers only, since reliable predicted normal values were not available for other groups.

Adapted from Aldrich et al., NEJM, 2010. Reproduced with permission from Aldrich TK, Gustave J, Hall CB, Cohen HW, Webber MP, Zeig-Owens R, Cosenza K, Christodoulou V, Glass L, Al-Othman F, Weiden MD, Kelly KJ, Prezant DJ. Lung function in rescue workers at the World Trade Center after 7 years. N Engl J Med. 2010 Apr 8;362(14):1263-72. Copyright Massachusetts Medical Society.

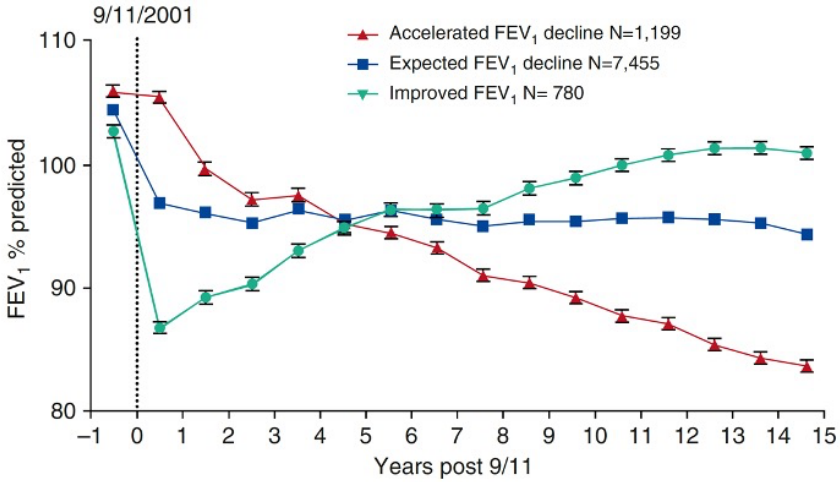


Figure 7 – Longitudinal FEV_1 trajectories stratified by rate of FEV_1 decline. A subgroup of WTC-exposed workers experiencing accelerated FEV_1 decline defined by a loss >64 ml/year (red line with triangles).

Adapted with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved. Zeig-Owens R, Singh A, Aldrich TK, Hall CB, Schwartz T, Webber MP, Cohen HW, Kelly KJ, Nolan A, Prezant DJ, Weiden MD. 2018. Blood Leukocyte Concentrations, FEV_1 Decline, and Airflow Limitation. A 15-Year Longitudinal Study of World Trade Center–exposed Firefighters. Annals of the ATS. 15:173–83. Annals of the American Thoracic Society is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at https://doi.org/10.1513/AnnalsATS.201703-276OC. The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations.

I.3. Treatments containing inhaled corticosteroids (ICS)

I.3.1. Inhaled corticosteroid (ICS) and inhaled corticosteroids / long-acting beta-agonist (ICS/LABA)

Corticosteroids are the most frequently prescribed anti-inflammatory therapy for obstructive airway disease.[58] The corticosteroid binds to the cytoplasmic glucocorticoid receptor, present in many cells of the lung. Consequently, the activated glucocorticoid receptor binds to DNA at the glucocorticoid response elements located on steroid-sensitive genes, inhibits transcription and synthesis of many proinflammatory cytokines (transrepression) and promotes synthesis of anti-inflammatory proteins (transactivation).[59,60] At a cellular level, corticosteroids reduce the number of eosinophils, T-lymphocytes, mast cells and dendritic cells in the airways (Figure 8) and reduce inducible nitric oxide production.[61] Since corticosteroids can interfere with the multiple inflammatory pathways, systemic administration has a lot of side effects. Topical application of corticosteroids via inhalation (ICS) has a better therapeutic index and is the cornerstone in current pharmacotherapy of asthma patients. [62–65] ICS is a controller therapy that reduces airway inflammation and hyperresponsiveness by altering the production of mediators associated with inflammatory cells in the airways.[66,67] Even in mild asthma a low dose ICS is recommended and recently there became more evidence to shift to as-needed low dose ICS combined with the long-acting beta-agonist (LABA) formoterol.[8,68] Inhaled corticosteroids and long-acting beta-agonist (ICS/LABA) combination is the preferred therapy for moderate asthma and COPD with frequent exacerbations.[8,11]

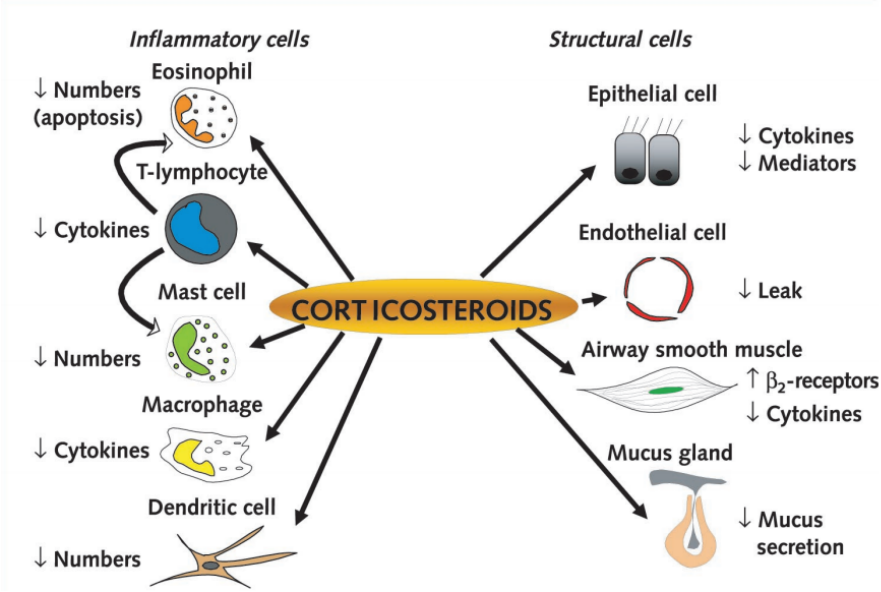


Figure 8 – *Action mechanisms of corticosteroids. Corticosteroids suppress the inflammation in the airways. They inhibit the recruitment of inflammatory cells into the airway by suppressing the production of chemotactic mediators and adhesion molecules and inhibit the survival in the airways of inflammatory cells, such as eosinophils, T cells and mast cells and dendritic cells.*

Figure adapted from Barnes PJ and Adcock IM. How do corticosteroids work in asthma?Annals of Internal Medicine. 2003;139:359. Copyright American College of Physicians.

Beta-2-agonists are effective bronchodilators primarily to their ability to relax airway smooth muscle.[69] They exert their effects via their binding to the active site of beta-2-adrenoceptors on the smooth muscle, which triggers a signaling cascade that results in a number of events, all contributing to relaxation of the airway smooth muscle.[70] LABA's are long-acting agents (duration of action more than 12 hours), which result in long-term improvement in lung function and are ideally suited as maintenance treatment. The working mechanisms of bronchodilators are to reduce airflow obstruction and decrease respiratory symptoms by reducing dynamic hyperinflation.[71]

I.3.2. Treatment for post-9/11 lung injury

The data sources used for most post-9/11 treatment analyses in the FDNY WTC cohort consisted of electronic medical record (EMR) notes and pharmacy claims. Analyses of those data revealed 40% of WTC-exposed firefighters were prescribed an ICS/LABA combination by 2020. A proportion of 25% used an inhaler for at least 2 years post 9/11 (Figure 9). The majority of those (86%) was on an inhaler containing ICS and LABA combination and 12% an ICS monotherapy.

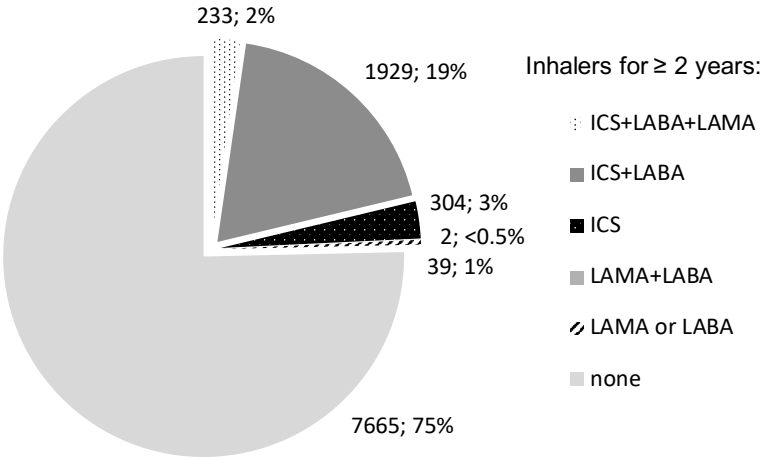


Figure 9 – Distribution of inhaler use for at least 2 years in WTC-exposed firefighters (N =10 172). A proportion 25% of WTC-exposed firefighters used an inhaler for at least 2 years post-9/11. The majority of inhaler users was on a combination of inhaled corticosteroids and long-acting beta-agonist (ICS/LABA) (77%), 12% on ICS and 9% on triple combination.

I.3.3. Treatment response

I.3.3.1. Outcome measures

There are several respiratory outcomes that can be examined to evaluate the effect of a particular treatment. The choice of the outcome measure(s) depends on the model of action or the indication of the treatment. Often assessed in obstructive lung diseases are spirometric endpoints, such as FEV_1. When lung function has been monitored longitudinally, FEV_1 trajectory measuring a change in FEV_1 over time (slope), is another important outcome (Figure 3, Figure 5 and Figure 7). Other possible outcomes are rate of yearly exacerbations or change in respiratory symptoms. The latter one belongs to the group of patient-reported outcomes (PROs). PROs are directly reported by the patient without interpretation of the patient's response by a clinician or anyone else. Despite being a subjective outcome, PROs gained importance since they reflect the patient's health, quality of life, or functional status associated with health care or treatment.[72] Patient reported outcome measures (PROMs) are the tools or instruments used to measure PROs. Those often include validated questionnaires or scales. Well known in pulmonary medicine are the Asthma Control Test/Asthma Control Questionnaire in asthma and COPD Assessment Test, modified Medical Research Council dyspnea scale and Saint George's Respiratory Questionnaire in COPD.[73,74] In the WTC health program, a baseline demographic and exposure questionnaire was hand out first and followed by psychical and mental health questionnaire at each monitoring exam.

I.3.3.2. Factors affecting treatment response

Treatment response is the results of a multifactorial play of host factors, environmental factors, the drug-related factors. Host factors include many components such as the disease entity and patient-specific characteristics (age, race, sex, weight, genetics).[75] Disease entities are often classified by endotypes, that will classify patient in different categories based on their underlying molecular mechanisms.[76] Patient characteristics also contain

factors that determine the pharmacokinetics of the drug, such as genetic polymorphisms for drug-metabolizing enzymes and liver and kidney function.[77,78]

The environmental factors are modifiable components that mostly alter the intensity of the response, include allergens, smoking or exposure to noxious particles, infections, exercise, physiological impact, comorbidities, comedication and diet.[75]

Among the drug-related factors, are the specific characteristics of the drug and adherence to the prescribed treatment. Drug characteristics will also contribute to the pharmacokinetics, such as the formulation determining the lung deposition, which is important in inhaler therapies.[79] Adherence to treatment will be discussed in more detail in section 3.4.

I.3.3.3. Biomarkers of treatment response

Given the heterogeneity of clinical presentation, disease course and response to therapy, a targeted and more personalized approach is recommended. To better understand treatment effects and to improve the effectiveness of treatments, big data analyses and the identification of biomarkers are highly important. This led to the field of 'precision medicine', where treatments target the needs of individual patients based on certain characteristics, such as biomarkers, that distinguish a particular patient from other patients with similar clinical presentations.[80] The identification of endotypes, based on common biological mechanisms of disease, in obstructive lung disease, allowed the development of targeted therapies.[81] The recognition of two major asthma endotypes T_h2-high (eosinophilic) and T_h2-low (noneosinophilic) led to specific asthma treatments, such as anti-IgE, anti-IL5 and anti-IL5R.[82] Although blood eosinophil count appears to be a promising biomarker for corticosteroid response in COPD, the selection of patients with a beneficial response to specific interventions is generally still unsatisfactory.[83] More steps to move towards precision medicine in COPD need to be taken.[84]

In the WTC cohort, a subgroup of WTC-exposed firefighters is experiencing accelerated decline in FEV_1, with a substantial number having continuing deterioration of lung function. To improve the effectiveness of treatments, it is crucial to identify characteristics or markers of individuals that can be targeted by certain treatments.

I.3.3.4. Response to ICS containing therapies

In COPD studies a favorable effect of ICS/LABA was seen on the annual exacerbation rate and health status defined by Sint-Georges respiratory questionnaire.[85] A recent trial studying COPD patients with exacerbations showed that triple therapy caused a reduction in mortality compared with long- acting muscarinic antagonist (LAMA)/LABA but not with ICS/LABA.[86,87] In asthma, ICS/LABA combination was found to improve overall asthma control, measured by improved symptoms, lung function and reduced exacerbations, and to improve quality of life.[88,89] Analyses of

databases suggest an important role for ICS containing therapies in reducing mortality in asthma.[90,91]
The effect of pharmacotherapy on FEV_1 decline has been questioned for over decades.[92] Two randomized controlled trials (RCTs) studying pharmacotherapeutic effects in COPD patients included FEV_1 decline as a secondary endpoint. The post-hoc analyses showed a limited effect on the rate of FEV_1 decline. The analyses from the TORCH (TOwards a Revolution in COPD Health) data showed an effect of ICS/LABA of 16 mL/year and these from the SUMMIT (Study to Understand Mortality and Morbidity in COPD) 8 mL/year compared with placebo, respectively.[93,94] In asthma, hard evidence that ICS prevents long-term decline in lung function occurring in subgroup of asthma patients, is lacking.[91]

I.3.4. Adherence to inhaler and other treatments

Medication adherence is defined as the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider.[95] Adherence to a drug will highly influence the expected pharmacological effect of that drug and the ability to treat the patient's disease.[96,97] There are different ways to measure adherence such as medication questionnaires, clinical assessments, objective measurements as drug (metabolite) testing in blood/urine or pill counts, or calculated ratios, based on the sum of days for which the medication is dispensed, such as 'proportion days covered'.[98] A questionnaire often used to estimate the adherence to inhaler treatment is the Test of the Adherence to Inhalers® (TAI) questionnaire.[99] Non-adherence can be intentional or non-intentional, when the patient is willing but not able to take the medication.[100]

Non-adherence leads to adverse outcomes. Poor medication adherence as evaluated using a dose counter on the returned inhaler device, was associated with increased hospital admission and mortality in moderate to severe COPD.[101] Poor adherence, combining intentional and unintentional measures, has also been associated with low lung function, reduced cognition and advanced age.[102] A correct inhaler technique was found to be

fundamental for a good adherence.[96] The inhaler technique will also contribute to which fraction of the inhaled medication is deposited in the lungs.[78] The fraction not entering the lungs may lead to side effects, which can adversely affect the adherence. A Belgian pharmaceutical intervention trial resulting in an improved inhaler technique, had a positive effect on disease control in patients with asthma.[103] Better asthma control scores were also reported by patients with higher ICS adherence studied in a prospective cohort study.[104] In clinical setting, objective prescription refill data are used to estimate patients' adherence. While imperfect, low adherence defined by pharmacy prescription data, was associated with increased exacerbation rates, health care costs and mortality in COPD.[105]

II. AIMS

Once a patient has been diagnosed with a certain disease, prescribing the recommended treatment may seem like a guarantee for clinical improvement. However, the patient's response is unique and is not entirely predictable from previously reported performances of the prescribed drug or treatment. Instead, the treatment response is the result of a complex interaction of host factors, environmental factors, and drug-related factors. Within the field of precision medicine, we aim to integrate these factors to improve patient outcomes. Focusing on lung diseases, **the overall aim of this thesis is therefore to identify optimal treatment response to inhaled corticosteroids (ICS).** The various factors contributing to this treatment response and assessed in this thesis have been graphically represented in Figure 10. A first focus was on host factors. More specifically, the disease type (endotype) has been characterized and screening parameters for individuals at risk have been identified. Second, the impact of environmental factors was studied, namely World Trade Center (WTC) exposure, defined by arrival at the WTC site and firefighting duty. In a third part, an important drug-related factor was studied, namely the impact of adherence to the prescribed treatment.

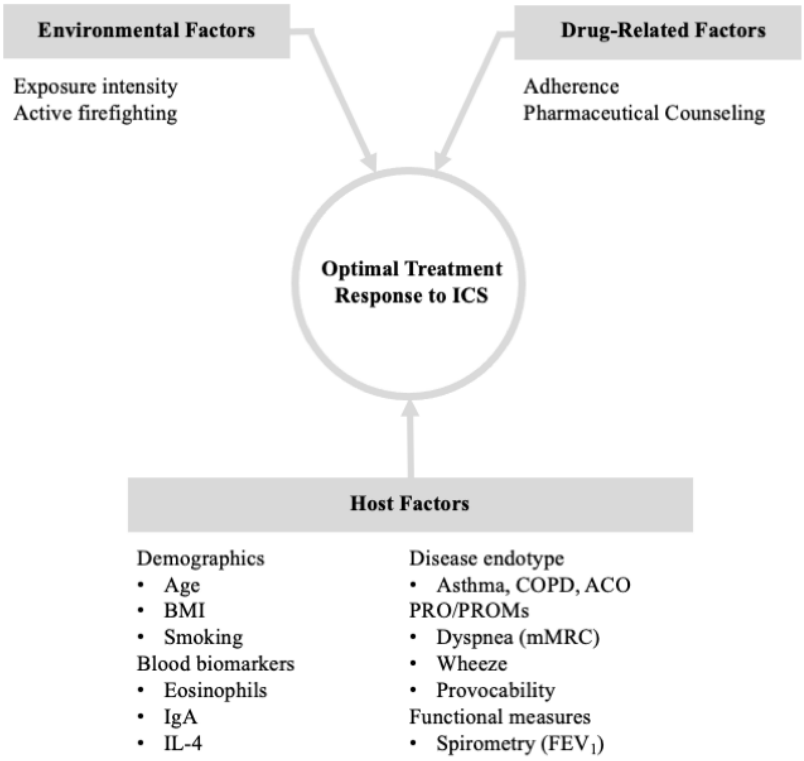


Figure 10 – Schematic overview of factors affecting treatment response to inhaled corticosteroids (ICS) that have been evaluated in the scope of this thesis

As the first focus was on host factors, the disease entity and its underlying pathological mechanisms have been assessed. A first specific aim was to further characterize the type of lung injury of WTC-exposed firefighters and identify individuals at risk. Hereby, we targeted to link early biomarkers with subsequent disease risk. In **Chapter III.1,** we intended to identify early post-9/11 characteristics identifying individuals at risk for developing WTC-related lung injuries. Lung injuries were thereby defined by the initiation of prolonged ICS/long-acting beta-agonist (LABA) treatment. Blood eosinophil count was previously identified as a biomarker for airway inflammation and a risk factor for WTC-related chronic rhinosinusitis[48]. We therefore studied blood eosinophils and their predictive power for WTC-related lung injuries. By assessing disease entities and clustering WTC-exposed firefighters, we aimed to identify characteristics associated with isolated asthma, isolated chronic obstructive pulmonary disease (COPD) and Asthma/COPD overlap (ACO) in **Chapter III.2**. Furthermore, we studied various blood biomarkers, including eosinophils, IgE and cytokines, and their relation to asthma, COPD or ACO, respectively.

Immunoglobulin A (IgA) has an important role in airway immunity to defend against pathogens or foreign agents. Since low IgA is known to increase the risk for airway inflammation and COPD exacerbations,[106,107] we hypothesized that reduced serum IgA soon after WTC exposure was associated with subsequent airway injury. To evaluate this hypothesis, we studied the lung function in relation to counts of antibiotic and oral steroid courses. The lung function was thereby characterized by FEV_1 trajectories and airflow obstruction. The medication usage was seen as a proxy for exacerbations of lung injury. (**Chapter III.3**)

Longitudinal data leading up to the disease diagnosis is scarce. During 15-year follow-up, a subgroup of WTC-exposed firefighters showed an accelerated FEV_1 decline compared to their peers. The majority of this subgroup still has screening spirometry measurements within normal limits, even though the trajectory indicates that abnormal values are to be expected.[46] This can impact clinical decision making through the identification of at-risk individuals, in turn allowing to start treatment prior to

development of abnormal lung function. Therefore, we aimed to identify patient characteristics that predict WTC-related lung injury. These characteristics are based on the data collected during longitudinal routine medical monitoring. Lung injury was defined by initiation of prolonged ICS/LABA treatment. (**Chapter III.4**) Since patient-reported outcomes measures (PROMs) gain importance, longitudinal data on questionnaire-based, patient-reported respiratory symptoms were analyzed, evaluating changes in dyspnea before and after ICS/LABA initiation. We thereby hypothesized that treatment initiation soon after WTC exposure would improve the trajectory of dyspnea. (**Chapter III.1**)

A second specific aim of this thesis was to assess the impact of patient's adherence to treatment response. The adherence is a very important factor since it will highly influence the desired pharmacological effect of the drug.[96,97] First, a longitudinal study was performed to quantify adherence to ICS and the effects of ICS adherence on lung function trajectory. The pharmacotherapeutic effect on long term lung function decline remains questionable and the previously established effects have been rather small.[93,94] However, since acute exacerbations are associated with lung function decline and ICS is effective in treating acute exacerbations, it was hypothesized that ICS treatment decreases the rate of lung function decline in WTC-exposed firefighters. (**Chapter IV.1**) Eventually, examining how this important drug-related factor is translated into clinical practice, the impact of an intervention in Belgian asthma patients was studied. Pharmaceutical counseling (PC) intervention trials have proven to improve adherence to controller medication and asthma control.[108–110] Our goal was to analyze national-level pharmacy claims data one year prior and one year after a pharmaceutical counseling intervention, looking at adherence to ICS and asthma control. The former was thereby defined by the change in ICS usage, the latter by use of other asthma-related drugs. We hypothesized that individuals with difficult-to-control asthma who received a PC intervention experienced an increase in ICS adherence and an improvement in asthma control. (**Chapter IV.2**)

III. HOST-FACTORS

III.1. Course of dyspnea before and after initiation of inhaled corticosteroid/long-acting beta-agonist treatment

III.1.1. Introduction

Inhaled corticosteroids in combination with long-acting beta-agonists (ICS/LABA) are commonly used to treat fixed and variable obstructive lung diseases.[88,111–115] Current treatment guidelines are based on clinical trials with restricted data before ICS/LABA initiation. Research on the trajectories of respiratory symptoms before and after ICS/LABA initiation is limited. FDNY rescue/recovery workers experienced a massive irritant exposure after the collapse of the World Trade Center (WTC) on September 11, 2001 (9/11), resulting in increased rates of respiratory symptoms, as well as an acute drop in lung function associated with reactive airway disease and fixed airflow obstruction.[29,42,44,46,116–118] Using longitudinal data on respiratory symptoms, the aims of the present study were to analyze changes in dyspnea before and after ICS/LABA initiation and to determine whether time between WTC exposure and treatment initiation was associated with treatment response.

III.1.2. Methods

The source population consisted of 9 638 male firefighters who were employed by FDNY on 9/11, first arrived at the WTC site between 11 and 24 September 2001, and underwent at least three routine medical monitoring examinations between 11 September 2001 and 10 September 2018. The study population (N = 1 073; 11% of the source population) consisted of those who had ICS/LABA treatment for longer than 2 years after 9/11 and had at least one modified Medical Research Council (mMRC) dyspnea scale score [119] before and at least two mMRC scores after ICS/LABA initiation. The study

population completed 7 835 medical monitoring questionnaires, including mMRC scores, between 1 August 2005 and 10 September 2018. Written informed consent was provided by all participants.

Demographics, height, weight, smoking status, initial arrival time at the WTC site (WTC exposure level), and spirometric measurements were retrieved from the FDNY employee database and/or assessed during routine medical monitoring examinations. Medication data were obtained from the FDNY electronic medical record and/or pharmacy claims data. Treatment duration was defined as the interval between first and latest fill dates of ICS/LABA. Multivariable-adjusted logistic regression determined variables associated with being in the study population of ICS/LABA-treated individuals versus not receiving ICS/LABA treatment (N = 6 721). Individuals classified as "responders" to ICS/LABA were those who had an mMRC slope less than 0 after treatment initiation; "nonresponders" had an mMRC slope greater than or equal to 0. Longitudinal mMRC scores in responders and nonresponders were estimated using linear mixed effects models with random intercepts, with categorized year from ICS/LABA initiation, age, body mass index (BMI), and race as fixed effects. Multivariable logistic regression assessed pretreatment mMRC and time from 9/11 to treatment initiation as predictors for treatment response, adjusting for age and BMI pretreatment, race, ever smoking status, and WTC exposure level.

Data analyses were performed using SAS version 9.4 software (SAS Institute). Figures were created with Prism 8 software (GraphPad Software).

III.1.3. Results

The study population included 1 073 individuals who received ICS/LABA therapy for more than 2 years and had at least one mMRC score before and two mMRC scores after ICS/LABA initiation. The mean (± standard deviation) numbers of mMRC scores were 4 (± 2) before ICS/LABA initiation and 6 (± 3) after ICS/LABA initiation. Individuals from the study population had higher WTC exposure, first post-9/11 mMRC score, blood eosinophils, and BMI and lower first post-9/11 lung function than those who did not receive ICS/LABA treatment (Figure 11).

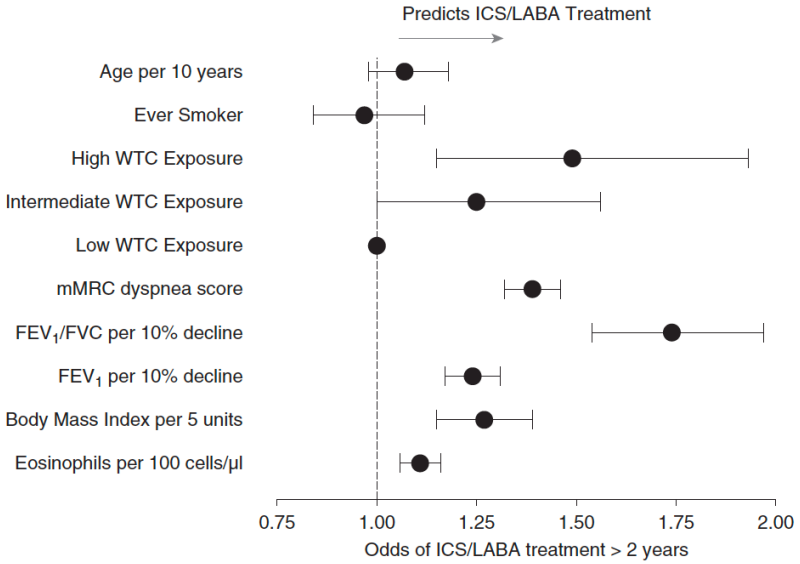


Figure 11 – Forest plot showing variables associated with being included in the study population and receiving inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) treatment for longer than 2 years versus not receiving ICS/LABA treatment (N = 7 777). Results shown are from a multivariable logistic regression analysis performed to determine the associations between first post-9/11 medical monitoring data and ICS/LABA treatment for longer than 2 years (odds ratios and 95% confidence intervals [bars]); data are also adjusted for race.

Responders (571 of 1 073; 53%) were more likely to be ever smokers (36% vs. 33%) but had pretreatment lung function similar to that of nonresponders (FEV_1 % predicted, 89.3 ± 4% vs. 89.2 ± 13.7%; FEV_1/FVC ratio, 77.3 ± 6.0% vs. 76.8 ± 6.4%). Nonresponders (502 of 1 073; 47%) had a gradual rise in mMRC scores starting 11 years after WTC exposure (Figure 12A), culminating in worse dyspnea score at the end of longitudinal follow-up (1.55; 95% CI from 1.40 to 1.70; vs. 0.79; 95% CI from 0.64 to 0.94, respectively). When we assessed dyspnea trajectory relative to treatment initiation (Figure 12B), we observed that responders had a sharp increase in mMRC scores before treatment and a subsequent decrease. Non-responders, however, had a gradual rise in mMRC scores before treatment initiation, which continued to increase during treatment.

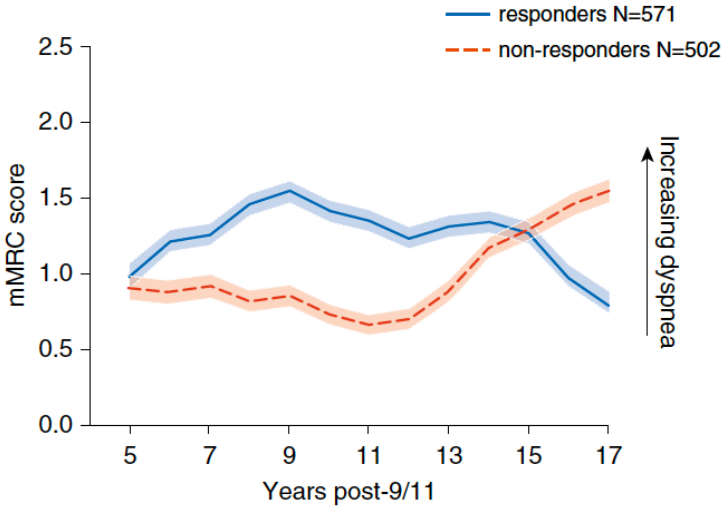
In an adjusted multivariable model, increased time between 9/11 and treatment initiation was a strong predictor of nonresponse to therapy (Table 2). A higher pretreatment mMRC, however, was significantly associated with a favorable response to treatment.

Table 2 – Multivariate logistic regression predicting response to ICS/LABA treatment (N = 1 073)

Variable	OR	95% CI		P Value
Time from 9/11 to treatment initiation, per 5 years	0.43	0.34	0.55	<0.001
mMRC score[a], per 1 point	1.21	1.10	1.33	<0.001
Age[a], per 10 years	1.06	0.87	1.28	0.60
Smoking, ever vs. never	1.17	0.89	1.53	0.26
BMI[a], per 5 units	1.05	1.01	1.08	0.005
WTC-exposure, high exposure (Ref: low)	0.74	0.45	1.22	0.24
intermediate exposure (Ref: low)	0.74	0.48	1.13	0.16

[a]pre-treatment

(A)


responders N=571
non-responders N=502
mMRC score
2.5
2.0
1.5
1.0
0.5
0.0
5
7
9
11
13
15
17
Years post-9/11
Increasing dyspnea

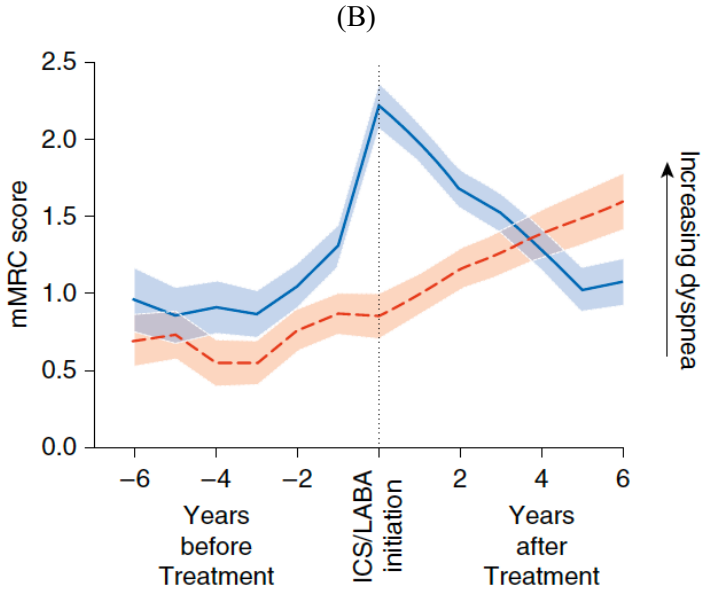


Figure 12 – Longitudinal modified Medical Research Council (mMRC) dyspnea scale scores and 95% confidence intervals in linear mixed effects models, stratified by responder type. mMRC scores were estimated using linear mixed effects models with random intercepts, with categorized year, age, body mass index, and race as fixed effects. The trajectory of the responder group is shown as a solid blue line, and the trajectory in the non-responders is shown as a broken red line. (A) Trajectories of mMRC scores relative to 11 September 2001 (9/11). Non-responders had a gradual rise in mMRC scores starting 11 years after WTC exposure, culminating in worse dyspnea score at the end of longitudinal follow-up. (B) Trajectories of mMRC scores relative to treatment initiation. Responders had a sharp increase in mMRC scores before treatment, followed by a subsequent decrease. Non-responders, however, had a gradual rise in mMRC scores before treatment initiation, which continued to increase after inhaled corticosteroid/long-acting b-agonist (ICS/LABA) initiation.

III.1.4. Discussion & Conclusion

This study produced longitudinal, patient-reported data on dyspnea from 1 073 previously healthy WTC-exposed firefighters who received more than 2 years of ICS/LABA treatment. The risk factors for treatment were similar to risk factors for obstructive airway disease in this cohort.[29,44,46,116] We observed heterogeneity in dyspnea response, with only 53% of treated individuals responding to treatment. We found that responders had rapidly increasing dyspnea, as defined by mMRC score, in the 3 years before treatment initiation. Notably, in responders, dyspnea improved for 5 years after treatment initiation, returning to a level similar to baseline. Non-responders had gradually increasing dyspnea in the 3 years before treatment, which continued to increase during the first 5 years after treatment initiation. This finding suggests that clinical trials with patient-reported outcomes may benefit from longer follow-up than that used in most randomized clinical trials. Our study revealed pronounced differences in the trajectory of dyspnea in responders and non-responders to ICS/LABA treatment. Responders presented earlier after WTC exposure, and higher pre-treatment mMRC score predicted favorable treatment response, whereas non-responders had a longer time between WTC exposure and symptom onset or treatment initiation. This difference in onset of symptoms suggests that non-responders might have a different endotype of obstructive airway disease that is less responsive to ICS/LABA therapy. The lack of response to ICS/LABA therapy in those with later-onset dyspnea might be indicative of a less inflammatory type of disease.

One limitation of this study may include generalizability to other affected individuals, because this single-center study of a massively dust-exposed cohort included only previously healthy males. We also acknowledge that there may be unmeasured confounding, which is possible in all observational studies. In addition, although regression to the mean might also contribute to the difference in symptom score trajectories between responders and non-responders, the greater symptom burden of non-responders at the end of follow-up suggests that regression to the mean is unlikely to be the sole or even main explanation for the observed effect.

In conclusion, this longitudinal study showed that almost half of irritant-exposed patients had worsening dyspnea after ICS/LABA initiation. Treatment benefited more symptomatic individuals who initiated ICS/LABA treatment sooner after WTC exposure.

III.2. Characterization of asthma, COPD and asthma/COPD overlap in World Trade Center-exposed firefighters

III.2.1. Introduction

The collapse of the World Trade Center (WTC) on 11 September 2001 (9/11), exposed the FDNY rescue and recovery workers to caustic dust and products of combustion.[42] Subsequently, WTC-exposed rescue and recovery workers had high rates of airway injury, including excessive loss of lung function,[29] obstructive ventilatory defect,[44] and airway hyperreactivity.[45] Firefighters with elevated post-exposure blood eosinophil concentrations were at increased risk of developing COPD.[46]

Asthma/COPD overlap is a recently defined endotype of COPD,[120–122] with patients experiencing a poorer quality of life and higher mortality compared with patients who have either isolated-COPD or isolated asthma.[123–125] Risk factors for asthma/COPD overlap are poorly defined, but among those with smoking-related COPD, elevated eosinophils in sputum and blood are biomarkers for this condition.[126,127] Longitudinal studies are needed to define risk factors for asthma/COPD overlap.[128]

The aim of the present study was to determine early predictors of asthma/COPD overlap among WTC-exposed firefighters with at least one post-9/11 clinically indicated pulmonary function test (PFT) with bronchodilator (BD) measurement (N = 2 137). The main predictors of interest were blood biomarkers collected during participants' post-9/11 FDNY medical monitoring examination. We also examined these measurements in association with isolated-asthma and with isolated-COPD as a way to understand the unique predictors of asthma/COPD overlap.

III.2.2. Methods

III.2.2.1. Study population

The source population consisted of 9 598 male firefighters who were actively employed by the FDNY on 9/11; first arrived at the WTC between 11 September 2001 and 24 September 2001; and had ≥ 3 post-9/11 FEV_1 measurements from routine medical monitoring PFTs taken at FDNY.[46] A subset of this population received at least one clinically indicated BD-PFT performed according to American Thoracic Society standards[129] at a hospital-based pulmonary function laboratory between 11 September 2001 and 10 September 2017. We excluded 57 participants whose BD-PFT occurred before their first post-9/11 medical monitoring examination. The final study population included 2 137 firefighters (Figure 13).

Participants provided written informed consent. The Montefiore Medical Center (FWA #00002558)/Albert Einstein College of Medicine (FWA #00023382) Institutional Review Board approved this study.

III.2.2.2. Baseline characteristics

Demographic data were retrieved from the FDNY employee database. Participants' height, weight, self-reported smoking status (current, former, or never-smoker), and time of initial arrival at the WTC site were assessed during routine medical monitoring examinations at FDNY (both active duty firefighters and WTC-exposed retirees are scheduled to have a monitoring examination once every 12 to 18 months). Individuals were classified as having high (morning of 11 September 2001), moderate (afternoon on 11 September 2001 to 12 September 2001), or low (13 September 2001 to 24 September 2001) WTC exposure based on their WTC site arrival time.[45] Current and former smokers were grouped together as ever-smokers in these analyses. Those who consistently self-reported no cigarette smoking were classified as never-smokers.

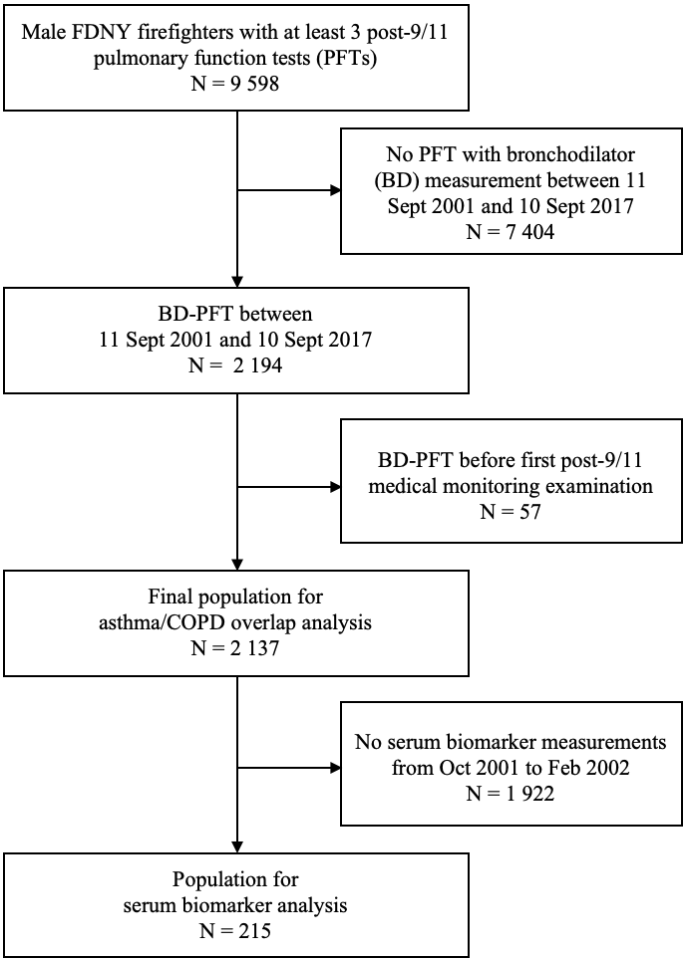


Figure 13 – Firefighters who participated in the asthma/COPD overlap study. Shown is the source population of male firefighters who were employed by the FDNY on 11 September 2001 (9/11), present at the WTC site between 11 September 2001 and 24 September 2001, and had at least three routine monitoring PFTs taken between 11 September 2001 and 10 September 2017 for FEV_1 slope measurement. The final study population included those who had received a post-9/11 clinically indicated PFT with BD measurement. The serum biomarker population was a subgroup who had biomarkers measured on serum drawn between Oct 2001 and Feb 2002

III.2.2.3. Blood and serum biomarkers

Eosinophil concentration was measured from blood drawn shortly after 9/11, during the first post-9/11 monitoring examination. The median first post-9/11 blood draw date was 10 January 2002 (interquartile range: 26 November 2001 to 27 December 2002). We also had pre-9/11 blood data (eosinophil concentration) for the 1 008 participants who had blood drawn at a pre-9/11 monitoring examination. Serum biomarkers from the first post-9/11 blood draw, including IgE and cytokines, were available for a subgroup of the study cohort (N = 215). Serum was stored at –80°C; IL-4 and interferon (IFN)- γ were assayed with Millipore Sigma HSTCMAG28SPMX21 and IgE with HGAMMAG-303E.

III.2.2.4. Pulmonary Function

Participants' most recent BD-PFT from the 11 September 2001 to 10 September 2017 period provided the pre- and post-BD FEV_1 and FVC measurements used to define our main outcome. A BD response of > 12% and 200 mL increase from baseline FEV_1 diagnosed asthma.[130] COPD was defined according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria, which requires a FEV_1/FVC ratio < 0.7 on a post-BD PFT.[121] We classified individuals who had a BD response and FEV_1/FVC ≥ 0.7 as having isolated-asthma, and those who had FEV_1/FVC < 0.7 and no BD response as having isolated-COPD. Individuals who met the criteria for both asthma and COPD had asthma/COPD overlap.

Total lung capacity (TLC) and residual volume (RV) measurements were also available from the BD-PFT data; these were measured prior to BD administration. We used spirometric measurements from 22 737 routine monitoring PFTs (always done without BD) taken between 11 September 2001 and 10 September 2017 to assess post-9/11 FEV_1 trajectories. FEV_1 values from post-9/11 monitoring PFTs that occurred prior to the BD-PFT were used to determine whether patients with asthma and/or COPD had accelerated (> 64 mL/y) or expected (≤ 64 mL/y) FEV_1 decline post-9/11 but prior to our outcome determination; for individuals who had neither diagnosis,

all post-9/11 FEV_1 values were included in the FEV_1 decline rate calculation. Pre-9/11 FEV_1 and FVC measurements. were available from 1 265 spirometries performed at FDNY monitoring in the year prior to 9/11 (11 September 2000 to 10 September 2001).

III.2.2.5. Statistical Analysis

Demographic and other characteristics of the study population and serum biomarker subgroup were assessed as proportions and means ± SD, with independent sample Student t tests or χ^2 tests used to evaluate differences, as appropriate. Longitudinal FEV_1 % predicted, FEV_1/FVC ratio, and post-9/11 rate of FEV_1 change were estimated in four subsets of the population defined according to outcome (isolated-asthma, isolated-COPD, asthma/COPD overlap, or neither condition) using linear mixed effects models with random intercepts. Participants' age on 9/11, height, and race were included as fixed effects in the models with the absolute FEV_1 or FEV_1/FVC ratio as the outcome. Mean FEV_1 % predicted and FEV_1/FVC ratio values in the four groups were estimated for each 1-year period between 11 September 2000 and 10 September 2017, and mean rates of FEV_1 change were determined by using the post-9/11 spirometry data.

Log-rank Mantel-Cox tests were performed to examine the univariable associations of post-9/11 FEV_1 trajectory (accelerated vs expected FEV_1 decline), eosinophil concentration, and smoking status with incident asthma/COPD overlap, followed by multivariable marginal Cox regression models for multiple events to evaluate shared and distinct risk factors for isolated-asthma, isolated-COPD, and asthma/COPD overlap. Censoring occurred at the time of the BD-PFT. Blood eosinophil concentration was assessed first as a binary variable (≥ 300 cells/μL vs < 300 cells/μL) and then as a continuous variable. Two sensitivity analyses were conducted: one that excluded individuals with an FEV_1/FVC ratio < 0.7 on a pre-9/11 monitoring PFT (N = 69) and another that examined the relationship between pre-9/11 eosinophil concentration and the outcomes of interest (N = 1 008). Absolute

change in eosinophil concentration from pre-9/11 to post-9/11 was also investigated.

A multivariable-adjusted Cox regression analysis for multiple events data was also performed in the serum biomarker subpopulation (N = 215) to determine whether log_2-transformed serum IgE and 21 cytokines were associated with isolated-asthma, isolated-COPD, or asthma/COPD overlap. After Bonferroni correction, the significance cutoff for the serum biomarker analyses was set at a two-sided P value of 0.0024. For all other analyses, reported P values are two-sided and considered significant at the < 0.05 level. Multivariable models included age, race, smoking status, WTC exposure, first post-9/11 FEV_1/FVC ratio, and BMI as covariates. Covariates were selected based on theory. Data analyses were performed by using SAS version 9.4 (SAS Institute, Inc). Figures were created by using Prism 7 (GraphPad Software).

III.2.3. Results

III.2.3.1. Baseline characteristics

Demographic and other characteristics of the 2 137 firefighters with clinically indicated post-9/11 BD-PFT in the final study population (Figure 13) and those without BD-PFT are presented in Table 3. Compared with WTC-exposed firefighters who did not have a BD-PFT, the study population was slightly different in that it was older, had a higher BMI and post-9/11 blood eosinophil
concentration, and a greater proportion of ever-smokers.

These differences were more pronounced in those who would develop a post-BD FEV_1/FVC ratio < 0.70. The serum biomarker subgroup was similar to the study population, with the exception of having a smaller proportion of ever-smokers.

III.2.3.2. Lung function on monitoring and BD-PFTs

Clinically indicated BD-PFT diagnosed isolated-asthma in 202 individuals (9.5%), isolated-COPD in 215 (10.1%), and asthma/COPD overlap in 99 (4.6%) (Figure 14). At the time of BD-PFT, the asthma/COPD overlap subgroup had a lower pre-BD FEV_1 % predicted, lower pre-BD FEV_1/FVC ratio, and higher RV/TLC ratio than any other diagnostic category (Table 4). BD response was similar in patients with asthma/COPD overlap and isolated-asthma (22.6 ± 13.3% vs 19.9 ± 12.8% increase in FEV_1, respectively; P = 0.09).

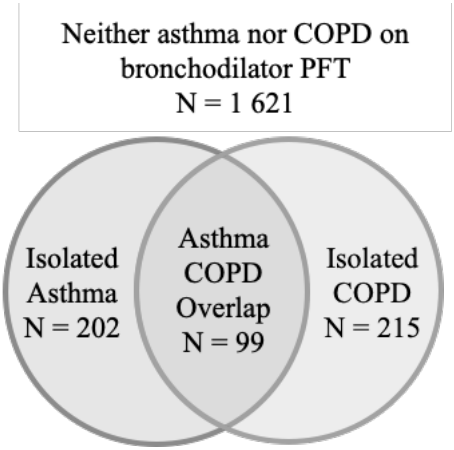


Figure 14 – Asthma/COPD overlap in WTC-exposed firefighters who had a BD-PFT. The Venn diagram demonstrates abnormalities on BD-PFTs obtained via the WTC treatment program. Isolated-asthma was diagnosed in 202 individuals who had FEV_1 BD response of > 12% and 200 ml. Isolated-COPD was diagnosed in 215 individuals who had a post-BD FEV_1/FVC ratio < 0.70. Asthma/COPD overlap was diagnosed in 99 who had both an FEV_1 BD response > 12% and 200 ml, and an FEV_1/FVC ratio < 0.70. The remainder of the study population (N = 1 621) did not have a BD response or airflow limitation.

Table 3 – Population characteristics and longitudinal lung function

Variable	WTC-Exposed No BD-PFT N = 7 404	BD-PFT Study Population N = 2 137		Sub-population with serum biomarkers N = 235	P Value
		Post-BD $FEV_1/FVC \geq 0.7$ N = 1 823	Post-BD $FEV_1/FVC < 0.7$ N = 314		
Age on 9/11, y [b]	39.9 ± 7.6	40.5 ± 6.7	44.0 ± 6.8	41.0 ± 6.8	< 0.001
BMI, kg/m^2 [b,c]	28.7 ± 3.4	29.2 ± 3.5	28.5 ± 3.3	28.7 ± 3.3	< 0.001
Smoking status, n (%) [c]					
Never	5 031 (67.9)	1 229 (67.4)	142 (45.2)	185 (86.0)	< 0.001
Former	2 143 (28.9)	542 (29.7)	148 (47.1)	22 (10.2)	
Ever	230 (3.1)	52 (2.9)	24 (7.6)	8 (3.7)	
Race, n (%)					
White	6 971 (94.2)	1 719 (94.3)	299 (95.2)	208 (96.7)	< 0.001
Black	174 (2.3)	36 (2.0)	10 (3.2)	4 (1.9)	
Hispanic	234 (3.2)	66 (3.6)	5 (1.6)	3 (1.4)	
Other	25 (0.3)	2 (0.1)	0	0	
WTC arrival time, n (%)					
Morning of 9/11	1 129 (15.3)	366 (20.1)	52 (16.6)	37 (17.2)	< 0.001
Afternoon on 9/11-12 Sept 2001	5 322 (71.9)	1 295 (71.0)	223 (71.0)	168 (78.1)	
13-24 Sept 2001	953 (12.9)	162 (8.9)	39 (12.4)	10 (4.7)	

Variable	WTC-Exposed No BD-PFT N = 7 404	BD-PFT Study Population N = 2 137		Sub-population with serum biomarkers N = 235	P Value
		Post-BD $FEV_1/FVC \geq 0.7$ N = 1 823	Post-BD $FEV_1/FVC < 0.7$ N = 314		
Pre-9/11 spirometry					
FEV_1, L [b]	4.43 ± 0.68[d]	4.38 ± 0.69[e]	3.94 ± 0.74[f]	4.32 ± 0.69[g]	< 0.001
FEV_1 % predicted [b]	105.9 ± 13.3[d]	104.3 ± 13.7[e]	95.2 ± 15.4[f]	103.3 ± 14.2[g]	< 0.001
FEV_1/FVC [b]	0.85 ± 0.05[d]	0.85 ± 0.05[e]	0.78 ± 0.07[e,f]	0.84 ± 0.05[g]	< 0.001
Post-9/11 spirometry					
FEV_1, L [b,c]	4.05 ± 0.65	3.96 ± 0.65	3.46 ± 0.73	3.92 ± 0.70	< 0.001
FEV_1 % predicted [b,c]	97.8 ± 12.9	95.4 ± 13.5	85.2 ± 15.3	94.4 ± 14.4	< 0.001
FEV_1/FVC [b,c]	0.84 ± 0.05	0.84 ± 0.05	0.74 ± 0.07	0.83 ± 0.06	< 0.001
Post-9/11 FEV^1 slope, mL/y[b]	-35.1 ± 30.8	-37.8 ± 32.4	-47.5 ± 36.3	-41.1 ± 37.0	< 0.001
Blood eosinophil concentration					
Pre-9/11 cells / µL	154 ± 109[h]	162 ± 117[i]	186 ± 144[j]	153 ± 104[k]	< 0.001
Post-9/11 cells / µL	184 ± 126[l]	194 ± 136[m]	231 ± 175[n]	198 ± 132	< 0.001

[a]ANOVA or 2 test comparing values in first three columns
[b]Mean ± SD
[c]Value on first post-9/11 monitoring examination
[d]N = 6 836 [e]N = 1 686 [f]N = 285 [g]N = 209 [h]N = 3 295 [i]N = 857 [j]N = 151 [k]N = 109 [l]N = 1 815 [m]N = 1 815
[n]N = 314

Both the pre-9/11 and first post-9/11 FEV_1 % predicted in each subgroup were on average ≥ 80% on monitoring PFTs but were lowest in those who went on to develop asthma/COPD overlap (Figure 15A). The FEV_1/FVC ratio on the first post-9/11 monitoring PFT was also lowest in this subgroup (Figure 15B). The annual post-9/11 FEV_1 loss in individuals with asthma/COPD overlap was similar to that of the COPD subgroup (47.6 mL/y [95% CI from 43.5 to 51.6] and 47.2 mL/y [95% CI from 44.7 to 49.6], respectively), and greater than the rate of FEV_1 loss in those with isolated-asthma (43.4 mL/y; 95% CI from 40.7 to 46.2) or neither outcome (36.8 mL/y; 95% CI from 35.9 to 37.6).

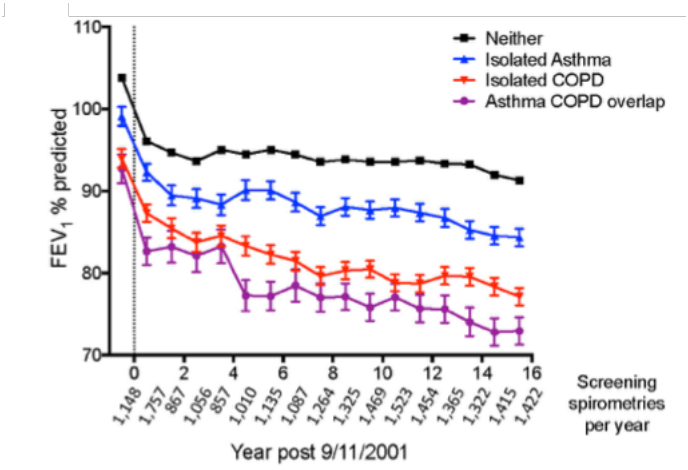
Table 4 – Bronchodilator PFT Results

Variable	Asthma/COPD Overlap	Isolated-Asthma	Isolated-COPD	Neither Diagnosis
Pre-BD FEV1 % Predicted	67.3 ± 14.8	80.9 ± 13.5[a]	82.3 ± 15.2[a]	96.9 ± 13.2[a]
Post-BD FEV1 % Predicted	81.3 ± 14.5	96.2 ± 13.7[a]	85.9 ± 15.0[a]	100.5 ± 13.5[a]
Pre-BD FVC % Predicted	93.3 ± 15.8	87.1 ± 13.91	101.2 ± 15.1[a]	98.3 ± 12.9[a]
Post-BD FVC % Predicted	101.8 ± 14.0	96.0 ± 13.3[a]	103.4 ± 15.1	98.5 ± 12.9[a]
Pre-BD FEV_1 / FVC	0.56 ± 0.08	0.73 ± 0.07[a]	0.62 ± 0.07[a]	0.77 ± 0.05[a]
Post-BD FEV_1 / FVC	0.62 ± 0.07	0.78 ± 0.05[a]	0.64 ± 0.06[a]	0.80 ± 0.05[a]
Pre-BD RV / TLC	0.40 ± 0.10	0.33 ± 0.09[a]	0.33 ± 0.08[a]	0.28 ± 0.07[a]

Data are expressed as mean ± SD

[a]$P < 0.05$ vs asthma / COPD overlap subgroup

(A)



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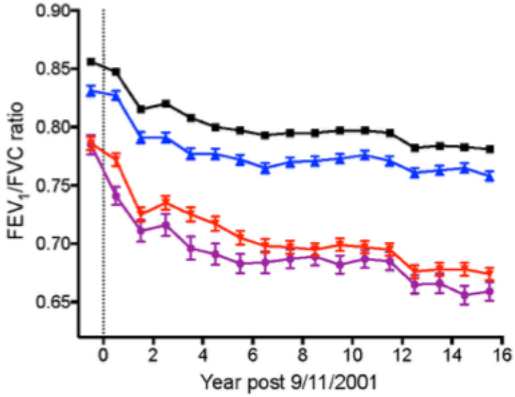


Figure 15 – Lung function over time. (A) Mean ± SEM (SEM not shown if it is smaller than the size of the symbol) FEV_1 % predicted in each year between 11 September 2000 and 10 September 2017 in the asthma/COPD overlap (orange), isolated-COPD (gray), isolated-asthma (blue), and asthma-free and COPD-free (red) groups. The vertical line at 0 represents 11 September 2001. The number of spirometries per year is shown below the x-axis. (B) Mean FEV_1/FVC ratio in the aforementioned groups in each year, adjusted for race, height, and age, using the same number of spirometries per year as shown in panel A.

III.2.3.3. Risk factors for asthma/COPD overlap

Univariable analyses showed that the incidence of asthma/COPD overlap was elevated in participants with post-9/11 eosinophil concentration ≥ 300 cells/μL (HR, 1.69; 95% CI from 1.00 to 2.81; P < 0.05) (Figure 16A), those with a history of smoking (HR, 1.67; 95% CI from 1.11 to 2.50; P = 0.02) (Figure 16B), and those experiencing post-9/11-accelerated FEV_1 decline (HR, 2.05; 95% CI from 1.22 to 3.43; P = 0.006) (Figure 16C). In multivariable marginal Cox regression models for multiple events, asthma/COPD overlap was predicted by eosinophil concentration ≥ 300 cells/μL (Table 5). Eosinophil concentration was not significantly associated with isolated-asthma or isolated-COPD. When isolated asthma and asthma/COPD overlap were compared directly, asthma/COPD overlap was still associated with elevated eosinophils (Table 6). Results were similar if analyses were restricted to those who had eosinophils measured < 15 months following 9/11 (data not shown). A unique risk factor for isolated asthma was high-intensity WTC exposure, and for isolated-COPD, it was ever-smoking. Post-9/11 accelerated FEV_1 decline was associated with all three outcomes. The observed associations did not change when eosinophil concentration was assessed as a continuous variable (data not shown).

To confirm that elevated post-9/11 eosinophil concentration and accelerated FEV_1 decline were associated with incident asthma/COPD overlap, a sensitivity analysis was conducted excluding patients with a pre-exposure PFT that showed a FEV_1/FVC ratio < 0.7 (N = 69). First post-9/11 eosinophil concentration ≥ 300 cells/μL and accelerated FEV_1 decline both remained significant predictors of asthma/COPD overlap (HR, 1.67 [95% CI from 1.03 to 2.71], P = 0.03; and HR, 2.15 [95% CI from 1.35 to 3.43], P = 0.001, respectively). To assess if pre-exposure blood eosinophil levels were indicative of a predisposition to asthma/COPD overlap, another sensitivity analysis was performed by using pre-9/11 eosinophil concentration in place of the post-9/11 measurement. The subgroup of participants who had had a pre-9/11 blood draw (N = 1 008) had baseline characteristics and lung function similar to those of the full study population (data not shown). We found that

pre-9/11 eosinophil concentration ≥ 300 cells/μL was also associated with the outcome (HR, 1.42; 95% CI from 1.22 to 1.66; P < 0.001). Change in eosinophil concentration from pre-9/11 to post-9/11 was not associated with asthma/COPD overlap (data not shown).

To gain further insight into the immunologic pathways associated with isolated-asthma, isolated-COPD, and asthma/COPD overlap, we examined serum T-helper cell type 1, T-helper cell type 17 (T_h17), and T-helper cell type 2 (T_h2) biomarkers obtained within 6 months of 9/11. A multivariable marginal Cox regression analysis for multiple events in the serum biomarker subpopulation (N = 215) found that higher early post-9/11 IgE was associated with incident asthma/COPD overlap, but this result was not significant after adjustment for multiple comparisons (Table 7). We found that elevated IL-4 predicted asthma/COPD overlap and elevated IL-21 predicted both isolated-asthma and isolated-COPD; elevated IFN-γ was a protective factor for isolated-asthma and isolated-COPD. Early post-9/11 levels of IL-5, IL-13, IL-17, IL-23, and IL-6 were not associated with any of the three mutually exclusive outcomes (data not shown).

Table 5 – Marginal Cox regression models predicting isolated-asthma, isolated-COPD, and asthma/COPD overlap

	Asthma/COPD Overlap vs Neither			Isolated-Asthma vs Neither			Isolated-COPD vs Neither		
Variable	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**
Eosinophils ≥ 300 cell / μL[a]	1.85	1.16 – 2.95	0.009	0.93	0.63 – 1.36	0.69	1.16	0.82 – 1.64	0.39
Accelerated FEV_1 decline	2.17	1.40 – 3.35	< 0.001	2.12	1.54 – 2.91	< 0.001	2.18	1.59 – 2.99	< 0.001
Ever-smoker	0.92	0.58 – 1.44	0.70	0.77	0.56 – 1.05	0.09	1.60	1.18 – 2.17	0.003
WTC exposure morning of 9/11	1.40	0.84 – 2.32	1.58	1.58	1.14 – 2.20	0.006	0.86	0.59 – 1.26	0.44

The total N value was 2 124 due to missing covariates. Data were adjusted for age, race, BMI, and first post-9/11 FEV_1/FVC measurement.

[a]First post-9/11 measurement

Table 6 – Marginal Cox regression models predicting isolated-asthma, isolated-COPD, and asthma/COPD overlap

	Asthma/COPD Overlap vs Isolated-Asthma			Asthma/COPD Overlap vs Isolated-COPD		
Variable	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**
Eosinophils ≥ 300 cell / μL[a]	2.00	1.11 – 3.62	0.02	1.60	0.89 – 2.85	0.12
Accelerated FEV_1 decline	1.02	0.60 – 1.74	0.94	0.99	0.60 – 1.65	0.98
Ever-smoker	1.19	0.69 – 2.05	0.52	0.57	0.34 – 0.98	0.04
WTC exposure morning of 9/11	0.88	0.49 – 1.61	0.68	1.62	0.88 – 3.01	0.12

The total N value was 2 124 due to missing covariates. Data were adjusted for age, race, BMI, and first post-9/11 FEV_1/FVC measurement.

[a]First post-9/11 measurement

Table 7 – Marginal Cox regression models predicting isolated-asthma, isolated-COPD, and asthma/COPD overlap in the subpopulation with serum drawn between 11 September 2001 and 10 September 2002

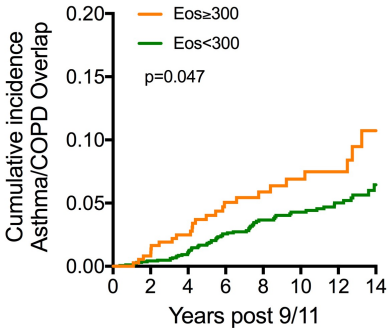
	Asthma/COPD Overlap vs Neither			Isolated-Asthma vs Neither			Isolated-COPD vs Neither		
Variable	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**
IgE [a]	2.31	1.14 – 4.67	0.02[b]	1.21	0.92 – 1.58	0.16	1.14	0.81 – 1.62	0.45
IFN- γ [a]	0.42	0.22 – 0.81	0.01[b]	0.48	0.32 – 0.70	< 0.001	0.45	0.28 – 0.70	< 0.001
IL-21a	1.33	0.89 – 1.98	0.17	1.73	1.27 – 2.35	< 0.001	2.06	1.31 – 3.23	0.002
IL-4 substituted for IL-21 in marginal Cox regression model									
IL-4[a]	1.51	1.17 – 1.95	0.002	1.68	1.08 – 2.61	0.02[b]	1.35	0.96 – 1.91	0.08

The total N value was 215. Data were adjusted for age, race, BMI, smoking status, WTC exposure level, and first post-9/11 FEV_1/FVC measurement.

[a]One $\log_2$ increase (doubling) of cytokine concentration.

[b]A P value of .0024 was considered significant after Bonferroni correction.

(A)



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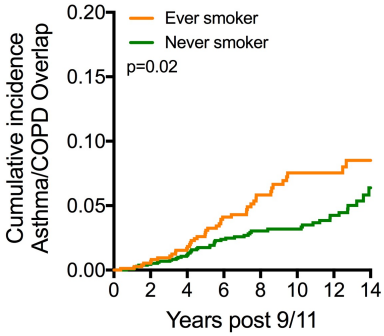

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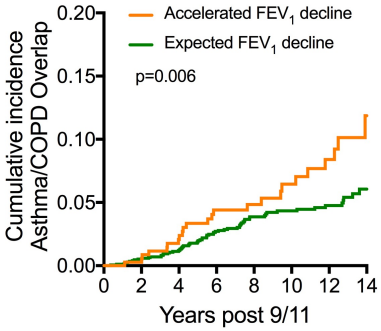


Figure 16 – Cumulative incidence of asthma/COPD overlap in WTC-exposed firefighters who had a BD PFT. (A) Cumulative incidence of asthma/COPD overlap in participants with blood EOS concentration ≥ 300 cells/μL (orange) and < 300 cells/μL on first post-9/11 medical monitoring examination (green). The level of significance shown in each panel was determined by using the log-rank test. (B) Cumulative incidence in those who reported ever smoking (orange) and never smoking (green). (C) Cumulative incidence in participants who had an accelerated rate of post-9/11 FEV_1 decline > 64 mL/y (orange) and those with expected FEV_1 decline ≤ 64 mL/y (green).

III.2.4. Discussion & Conclusion

The WTC-exposed FDNY firefighter population is a cohort comprising previously healthy male subjects. Importantly, asthma documented during preemployment medical evaluation precludes employment as a FDNY firefighter. Those who develop reactive airways disease during their career are removed from active duty[131]; therefore, the prevalence of pre-9/11 asthma in this cohort was low. The massive irritant exposure at the WTC site resulted in an acute drop in lung function, with rescue/recovery workers going on to experience air trapping, as well as fixed and reversible airflow obstruction.[29,44,45] In the present study, we observed that elevated early post-9/11 blood eosinophil concentration predicted irritant-associated asthma/COPD overlap but not isolated-asthma or isolated-COPD. A sensitivity analysis noted that pre-9/11 elevated eosinophils were a risk factor for asthma/COPD overlap. This finding suggests a pre-WTC exposure predisposition to irritant-associated fixed and reversible airway injury. Although we found some overlapping biomarkers of these outcomes, the observation that there are unique biomarkers of vulnerability to asthma/COPD overlap, isolated-asthma, and isolated-COPD suggests the potential for different pathologic processes for these three diagnoses; this topic could be explored in future studies.

The FDNY WTC-exposed cohort has advantages for investigating irritant-associated airways disease. Data from a centralized post-WTC medical treatment program enabled explicit diagnostic criteria for incident isolated-asthma, isolated-COPD, and asthma/COPD overlap. Pre-9/11 lung function and blood data were available for a large subset of the cohort, enabling assessment of early indicators of susceptibility to subsequent airway injury. Our observation that pre-exposure eosinophil concentration was associated with later asthma/COPD overlap suggests patient-intrinsic vulnerability to the damaging effects of WTC dust exposure. How much the exposure itself contributed to the presentation is limited because not every assessment was performed pre-exposure.

Compared with those who developed isolated-asthma or isolated-COPD, patients with asthma/COPD overlap had a lower post-exposure FEV_1 and FEV_1/FVC ratio. An investigation in a cohort without WTC exposure found that low lung function in childhood was a risk factor for subsequent asthma/COPD overlap,[132] and thus our observed associations between early lung function measurements and this outcome may be evidence of similar biological mechanism(s). Both the asthma/COPD overlap, and isolated-COPD subgroups have progressive airway injury, with greater post-9/11 FEV_1 rates of decline than individuals with isolated-asthma or neither diagnosis. The asthma/COPD overlap subgroup also experienced more air trapping, shown by higher RV/TLC at the time of BD-PFT. This finding is consistent with previous investigation of asthma/COPD overlap in never-smokers[133] and could be evidence of the severity of small airways dysfunction associated with WTC exposure.[134]

Eosinophils and IgE are two T_h2 mediators that have been extensively studied as risk factors for asthma, COPD, and asthma/COPD overlap.[126,135–139] In the present investigation, serum IgE was associated with asthma/COPD overlap but did not achieve significance after Bonferroni adjustment for multiple comparisons. We did observe a significant association between serum levels of the T_h2 cytokine IL-4 and this outcome. IL-4 may be a biomarker on the causal pathway to irritant-associated asthma/COPD overlap because inhibiting it with dupilumab reduced asthma severity in non-WTC-exposed patients with or without high eosinophil levels.[140,141] Further investigation is required to assess the T_h2 pathways that are associated with FEV_1 decline, airflow limitation, and BD response following an intense irritant exposure.

The incident asthma observed in the present study is a variant of irritant-induced asthma.[142] The fact that it was associated with high-intensity WTC exposure but not eosinophil concentration suggests that airway reactivity in this cohort is a form of non-eosinophilic asthma.[143] IFN-γ was a protective biomarker for this condition and also for isolated-COPD. High IFN-γ is

associated with low IL-4 in modulation of pulmonary lymphocyte-mediated innate immunity.[144] Furthermore, asthma is associated with blunted IFN-g response.[145,146]

The balance between T_h2 and T_h17 cytokines in airway inflammation is under active investigation.[147–149] IL-21, which was found to significantly predict isolated-asthma and isolated-COPD in the present cohort, is a component of the T_h17 pathway that is produced by innate lymphoid cells which regulate airway inflammation.[150] Elevated levels are associated with airway inflammation in mouse models and humans.[151–153] The data from the WTC-exposed FDNY cohort are consistent with a T_h2 and T_h17 response predicting
airway remodeling and reactivity. These data support further investigation of the innate T_h17 response to pulmonary irritants.

In univariable analyses, we found that in addition to high eosinophil concentration and accelerated FEV_1 decline, ever-smoking was associated with asthma/COPD overlap. After adjusting for confounders, such as post-9/11 lung function, smoking was a unique risk factor for isolated-COPD but not isolated-asthma or asthma/COPD overlap. Therefore, the relationship between smoking and asthma/COPD overlap in this cohort was confounded by the other covariates. High WTC exposure level was not associated with isolated-COPD or asthma/COPD overlap, which suggests that an intense but brief irritant exposure did not increase risk of airway remodeling. In this cohort, isolated-COPD was not associated with eosinophil levels. In a population with smoking-related COPD, however, elevated blood eosinophil concentration was a biomarker of increased exacerbation.[154] The variability of eosinophil effect reported in the literature may be related to the proportion of the study cohorts with an asthma component.[155,156]

There are several limitations to this investigation. The FDNY firefighters are overwhelmingly white, male, and experienced a massive irritant exposure, potentially limiting generalizability of these findings; however, most findings

from the FDNY cohort have been replicated in other WTC-exposed cohorts. Our definitions of isolated asthma, asthma/COPD overlap, and isolated COPD depend on results from the most recent BD-PFT. It is possible that those with isolated COPD, defined as $FEV_1/FVC < 0.7$ and no BD response in this study, have asthma/COPD overlap because we did not proceed to methacholine challenge testing in the subgroup. Similarly, those with asthma/COPD overlap, defined as $FEV_1/FVC < 0.7$ and a BD response, may not have persistent $FEV_1/FVC < 0.7$ with permanent airway remodeling. A third limitation may be the use of eosinophils ≥ 300 cells/μL or < 300 cells/μL in our analyses. We modeled post-9/11 eosinophils as a continuous variable and still observed a significant association with asthma/COPD overlap. This method suggests that cut-point selection did not drive the analyses. Lastly, this study was vulnerable to selection bias. The study population with clinically indicated BDPFT was systematically different from those without BDPFT, with more intense WTC exposure, higher eosinophil levels, and post-WTC exposure lower lung function. This outcome precludes assessment of rates of asthma/COPD overlap in the entire cohort because undiagnosed cases are likely. Nevertheless, analyses within the BD-PFT population provide a valid assessment of risk factors for specific diagnoses within a symptomatic subgroup.

In conclusion, the data from the FDNY WTC Health Program are a valuable resource for understanding irritant-associated airways disease in a previously healthy population. High eosinophil concentrations, uniquely associated with asthma/COPD overlap in this population, may reflect biological pathways that predispose one to exaggerated inflammation and/or poor counterregulatory responses to inflammation, leading to reversible and fixed airflow obstruction. There may be potential for early interventions that involve targeting specific inflammatory pathways in an attempt to improve lung function outcomes.

The article was published in Chest. 2018. Volume 154(6). Singh A, Liu C, Putman B, Zeig-Owens R, Hall CB, Schwartz T, Webber MP, Cohen, HW, Berger KI, Nolan A, Prezant DJ, Weiden MD. Predictors of Asthma/COPD Overlap in FDNY Firefighters With World Trade Center Dust Exposure. Page 1301–10. Copyright © Elsevier 2021.

III.3. Low serum IgA and airway injury

III.3.1. Introduction

The collapse of the World Trade Center (WTC) exposed rescue/recovery workers to an intense dust cloud, causing airway inflammation and subsequent accelerated decline in FEV_1.[157] Accelerated FEV_1 decline is a risk factor for fixed and variable airflow obstruction.[116] IgA protects airways from immunological, infectious or toxic injury. Serum IgA ≤ 70 mg/dL increases risk for acute exacerbations of chronic obstructive pulmonary disease (COPD) treated with antibiotics.[158] Secretory IgA is reduced in those with damaged airways.[159,160] We aimed to determine if reduced serum IgA ≤ 70 mg/dL soon after WTC exposure was associated with subsequent airway injury, defined by worse lung function and increased antibiotic treatment.

III.3.2. Methods

III.3.2.1. Clinical Data

The source population contained 9 638 WTC-exposed male FDNY firefighters (Figure 17). The study population consisted of 917 firefighters with baseline serum drawn between October 2001 and March 2002 and immunoglobulin concentrations (including IgA) assayed with HGAMMAG-301K (EMD Millipore). Antibiotic and oral steroid courses per person, at least 6 weeks apart, were obtained from a billing database initiated on 1 January 2007. Three persons were lost to follow-up before 2007 and excluded from the medication analyses. Spirometric measurements were collected during routine medical monitoring examinations between 11 September 2000 and 10 September 2018. Clinically indicated bronchodilator pulmonary function tests (BD-PFTs) were performed on a subpopulation of 284 individuals between February 2002 and August 2018. FDNY databases contributed demographic and smoking status data.

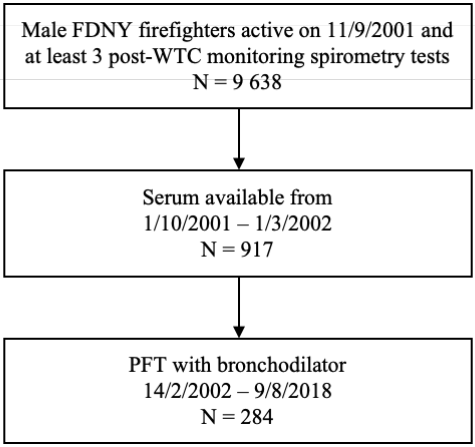


Figure 17 – Flow diagram of study population

III.3.2.2. Statistical Analysis

Longitudinal FEV_1 and rates of FEV_1 decline were estimated in the IgA ≤ 70 mg/dL and IgA > 70 mg/dL subgroups using random intercept linear mixed-effects models. Participants' age on 11 September 2001, height and race were included as fixed effects in the models for FEV_1 absolute and FEV_1 decline. Mean ± SEM FEV_1 and FEV_1 % predicted were estimated for each 1–year period between 11 September 2000 and 10 September 2018. Multivariable Cox regression assessed the association between IgA and fixed airflow obstruction characteristic of COPD (post-BD $FEV_1/FVC < 0.70$) on the last BD-PFT. Follow-up time started 11 September 2001 and ended at the last BD-PFT. Multivariable Poisson models compared rates of antibiotic courses in IgA ≤ 70 mg/dL and IgA > 70 mg/dL subgroups.

To avoid immortal time bias, follow-up time for medication use started 1 January 2007 and ended at the latest of the following dates for retirees: last medication prescription date or last medical exam; and on 10 September 2018 for active firefighters. All models were adjusted for age on 9/11, race, body mass index, smoking status and WTC exposure. Covariates were selected based on theory. Data analyses were performed using SAS V.9.4 and figures created using Prism V.8.

III.3.3. Results

III.3.3.1. Demographics

The study population was slightly older (41.4 ± 7.4 vs 40.1 ± 7.4 years) and had fewer ever-smokers (16% vs 35%) than the firefighters without IgA measured (Table 8). IgA ≤ 70 mg/dL (low IgA) was present in 9% of the study population (83/917), but the proportion of IgA measurements ≤ 70 mg/dL was highest in those with measurements closest to 9/11 (Figure 18). The low-IgA subgroup had similar levels of IgE and IgM as the IgA > 70 mg/dL group, but lower levels of certain IgG concentrations (Table 9).

III.3.3.2. Early IgA and lung function

The low-IgA subgroup had lower FEV_1 % predicted and absolute FEV_1 than the IgA > 70 mg/dL subgroup before 9/11 and throughout follow-up (Figure 19 and Figure 20). Pre-9/11 FEV_1 % predicted in those with low IgA was 102.8% (95%CI 99.3% to 106.4%) vs 106.0% (95%CI 105.0 to 107.0) in those with IgA >70 mg/dl; first post-9/11 FEV_1 % predicted was 94.1% (95% CI 90.7 to 97.4) compared with 98.6% (95% CI 97.7% to 99.5%) and last FEV_1 % predicted was 88.6% (95% CI 85.1% to 92.1%) compared with 94.0% (95% CI 93.0% to 95.0%). The subgroups had similar post-9/11 FEV_1 slopes (Figure 20 and Table 9). Low IgA increased the risk of postbronchodilator FEV_1/FVC <0.70 by 3.8-fold (95% CI 1.6 to 8.8) (Table 10).

Table 8 – Baseline characteristics and longitudinal FEV_1

Variable	No serum IgA measured N = 8 721	IgA study population N = 917	Bronchodilator PFT with IgA N = 284
Age on 9/11, y [a,b]	40.1 ± 7.4	41.4 ± 7.4	41.0 ± 6.5
BMI, kg/m^2 [b]	28.9 ± 3.4	28.5 ± 3.2	28.6 ± 3.3
Smoking status, n (%)			
Never	5 687 (65.2)	770 (84.0)	250 (88.0)
Ever	3 034(34.8)	147 (16.0)	34 (12.0)
Race, n (%)			
White	8 201 (94.0)	878 (95.8)	277 (97.5)
Black	210 (2.4)	15 (1.6)	4 (1.4)
Hispanic	285 (3.3)	23 (2.5)	3 (1.1)
Other	25 (0.3)	1 (0.1)	0
WTC arrival time, n (%) [c]			
Morning of 9/11	1 428 (16.4)	148 (16.1)	48 (16.9)
Afternoon on 9/11 or 12/9/2001	6 199 (71.1)	707 (77.1)	224 (78.9)
13/9 - 24/9/2001	1094 (12.5)	62 (6.8)	12 (4.2)
Spirometry			
FEV_1 (l) [b,c]	4.00 ± 0.67	4.06 ± 0.70	3.96 ± 0.71
FEV_1 % predicted [b,c]	96.9 ±13.6	98.2 ± 14.6	94.9 ± 15.0
FEV_1 slope ml/y [b]	-36.3 ± 27.7	-38.9 ± 29.8	-41.2± 35.5

[a]11 September 2001
[b]Mean ± standard deviation
[c]Value on first post-9/11 monitoring exam

Table 9 – Baseline characteristics and longitudinal FEV_1 by IgA subgroups

Variable	IgA > 70 mg/dl N = 834	IgA ≤ 70 mg/dl N = 83
Age on 9/11, y [a,b]	41.5 ± 7.5	40.8 ± 6.7
BMI, kg/m^2 [b]	28.5 ± 3.2	28.8 ± 3.4
Smoking status, n (%)		
Never	703 (84)	69 (83)
Ever	131 (16)	14 (17)
Race, n (%)		
White	793 (95)	79 (96)
Black	19 (2.2)	1 (1.1)
Hispanic	21 (2.5)	3 (3.3)
Other	1 (0.1)	0
WTC arrival time, n (%)		
Morning of 9/11	135 (16)	17 (21)
Afternoon on 9/11 or 12/9/2001	636 (76)	63 (77)
13/9 - 24/9/2001	62 (7.5)	2 (2.2)
Spirometry		
FEV_1 (L) [b,c]	4.05 ± 0.67	3.89 ± 0.65
FEV_1 % predicted [b,c]	98.2 ±13.5	94.1 ± 15.4
FEV_1 slope ml/y [b]	-38.4 ± 34.0	-38.5 ± 37.2
Serum immunoglobulin mg/dl		
IgE	0.51 ± 0.73	0.46 ± 0.51
IgM	143 ± 83	143 ± 200
IgG_1	466 ± 213	383 ± 191
IgG_2	329 ± 183	251 ± 184
IgG_3	208 ± 375	86 ± 76
IgG_4	103 ± 265	64 ± 46

[a]11 September 2001
[b]Mean ± standard deviation
[c]Value on first post-9/11 monitoring exam

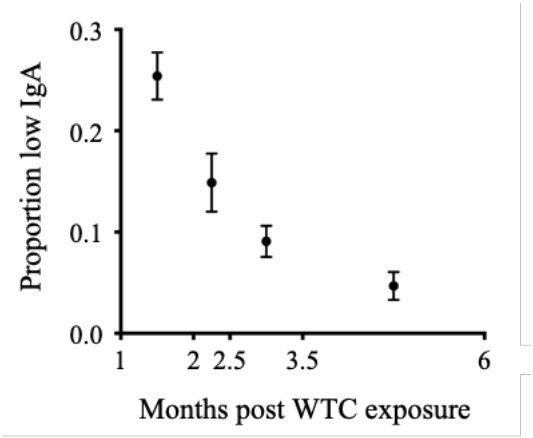


Figure 18 – Low serum IgA over time. The proportion of IgA measurements that were ≤70mg/dl (low IgA) is shown in each of 4 time intervals post-WTC exposure: 1-2 months, 2 to 2.5 months, 2.5 to 3.5 months and 3.5-6 months. The proportion of individuals with low IgA declined as time post-WTC exposure increased (p < 0.001Chi-square trend). Mean and SEM are shown.

III.3.3.3. Early IgA and antibiotic treatment

After 1 January 2007, the rate of antibiotic use was 22.5 antibiotic courses / 100 person-years in those with low IgA, compared with 11.6 antibiotic courses / 100 person-years in those with IgA > 70 mg/dl (unadjusted p=0.002). The low-IgA subgroup had a 1.9-fold increased rate of antibiotic treatment (95% CI 1.2 to 2.9) in multivariable Poisson regression, adjusted for potential confounders (Table 11). Oral steroid use, however, was not significantly associated with IgA level (Table 12).

Table 10 – Multivaraible Cox model examining the association between serum IgA ≤ 70 mg/dl and postbronchodilator FEV_1/FVC ratio less than 0.70 [a,b]

Variable	HR	95% CI	P value
IgA ≤ 70 mg/dl	3.75	1.59 to 8.83	0.0025
Age	1.10	1.04 to 1.16	0.0008
Ever smoker	4.58	2.06 to 10.20	0.0002

[a]Time from 11 September 2001 to BD-PFT, median (IQR): 5.9 years (3.6–9.9).

[b]N = 284; also adjusted for race, WTC exposure and BMI.

Table 11 – Multivariate Poisson model examining the association between serum IgA ≤ 70 mg/dl and courses of antibiotic treatment after 1 January 2007 [c]

Variable	HR	95% CI	P value
IgA ≤ 70 mg/dl	1.90	1.24 to 2.90	0.003
Age	0.99	0.97 to 1.02	0.63
Ever smoker	0.68	0.41 to 1.12	0.13

[c]N = 914; also adjusted for race, WTC exposure and BMI.

Table 12 – Multivariate Poisson model examining the association between serum IgA ≤ 70 mg/dl and courses of oral steroid treatment [d]

Variable	HR	95% CI	P value
IgA ≤ 70 mg/dl	1.47	0.78 to 2.75	0.23
Age	0.99	0.96 to 1.02	0.64
Ever smoker	0.52	0.24 to 1.10	0.09

[d]N = 914; also adjusted for race, WTC exposure and BMI.

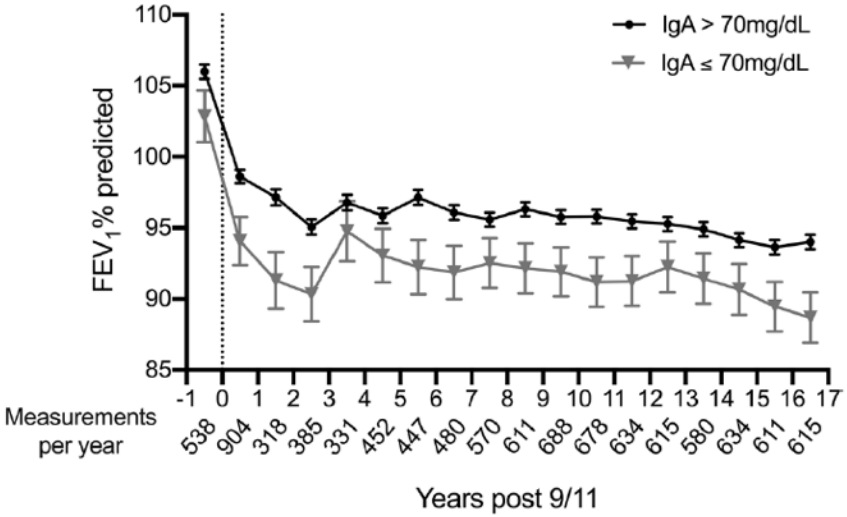


Figure 19 – Lung function over time stratified by IgA measured on 11 September 2001 to 10 March 2002. The mean (±SEM) FEV_1 % predicted is shown in each year between 11 September 2000 and 10 September 2018. The triangles correspond to the IgA ≤70 mg/dL subgroup (N = 83). Dots correspond to the IgA >70 mg/dL subgroup (n=834). The number of spirometric measurements in each year is shown below the X axis

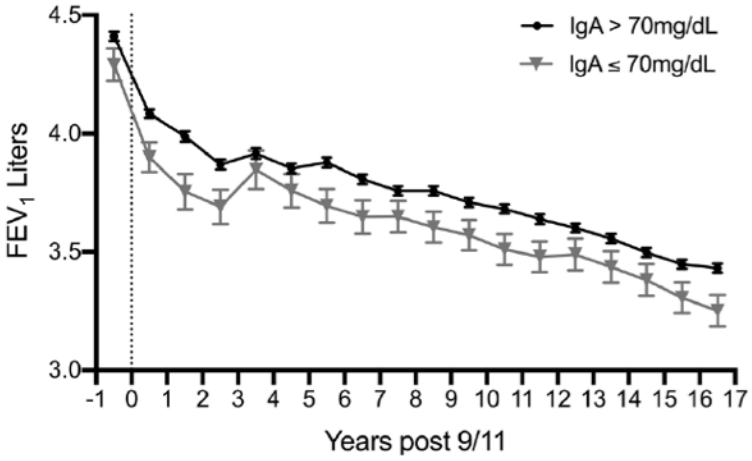


Figure 20 – Lung function over time stratified by IgA measured on 11 September 2001 to 10 March 2002. The mean absolute FEV_1 is shown in the groups with higher resp. lower than 70 mg/dL IgA in each year, adjusted for age, race and height, using the same spirometry measurements as in Figure 19.

III.3.4. Discussion & Conclusion

In an occupational cohort with low smoking prevalence and preserved lung function, low IgA (IgA ≤ 70 mg/dl) soon after an intense irritant exposure was associated with lower FEV_1 measurements throughout longitudinal follow-up and increased antibiotic treatment. Low IgA was also associated with development of fixed airflow obstruction. These data build on recent reports demonstrating that low IgA is a risk factor for COPD exacerbation and airway injury in current and former smokers with reduced lung function.[158,159]

Low IgA was observed as part of an intense, but transient inflammatory response to inhaled particulates. This may account for the high prevalence of low IgA in this cohort when compared with the SPIROMICS cohort.[158] These observations are consistent with suppression of production of IgA or increased degradation of IgA by proteases such as neutrophil elastase.[161] Local IgA deficiency has been associated with smoking-related COPD and increased susceptibility to smoking-related lung injury.[161] Low IgA soon after irritant exposure may serve as a proxy for increased susceptibility to lung injury.

There are several limitations to this study. This study employed an arbitrary cut point to define low IgA, although one consistent with prior literature.[158] Nevertheless, the results support the conclusion that 70 mg/dl represents a reproducible threshold for outcomes relevant to lung injury. The unusual nature of the massive irritant exposure that produced lung injury in this cohort could limit generalizability of these data, although our findings are consistent with other observations in smoking-related lung injury. Finally, since this was an observational study, it may be subject to unmeasured confounding and selection bias.

IgA ≤ 70 mg/dl in the first 6 months post-9/11 predicted antibiotic use years later. Since IgA was measured shortly after 9/11 and prior to disease presentation, it is unlikely that low IgA is a consequence of abnormal lung function. Since reduced FEV_1 in the low-IgA subgroup was persistent throughout follow-up, including before 9/11, this suggests that recurrent infection could have impacted lung function during development and/or adulthood.[162,163] Since low maximally-attained FEV_1 is a risk factor for obstructive lung disease, even in individuals with expected FEV_1 decline,[164] further research should test if IgA levels are associated with maximally attained FEV_1 and fixed airflow obstruction in other populations.

III.4. Factors predicting treatment of World Trade Center-related lung injury

III.4.1. Introduction

Rescue and recovery workers suffered a massive exposure to dust and products of combustion after the collapse of the WTC twin towers.[165] This resulted in increased rates of respiratory symptoms, as well as an acute drop of lung function and subsequent high incidence of reactive airways disease and fixed airflow obstruction.[116,117,157,166–169] Immediately after 11 September 2001 (9/11), the FDNY instituted a medical monitoring program that performed screening pulmonary function tests and collected respiratory symptom data via computer-based questionnaires.[170] Additionally, FDNY began a treatment program at no cost to the participants. Longitudinal data from these monitoring and treatment programs have identified WTC-related diseases and treatment responses. We previously found that initiation of treatment with inhaled steroids combined with long-acting beta agonists (ICS/LABA) sooner after WTC exposure was more likely to result in improvement of dyspnea in the FDNY cohort than initiation of treatment years after WTC exposure.[171]

ICS/LABA is the standard of care for asthma and COPD with exacerbations.[111,112] Current guidelines on obstructive airway diseases recommend that physicians evaluate lung function, respiratory symptoms, and frequency of exacerbations to inform treatment strategies.[172,173] In the era of telemedicine, web-based symptom monitoring, wearable devices, and data transmission technology are becoming more widely used.[174,175] Predictive models using these data will help detect individuals with undiagnosed disease who may benefit from early interventions such as subspecialty testing and treatment.

It remains unclear which factors identify at-risk individuals prior to the development of abnormal lung function on screening spirometry exams. A subgroup of individuals has experienced an accelerated decline of lung function, but the majority still have spirometry measurements within normal limits.[157] The objective of this study was therefore to identify patient characteristics collected on routine medical monitoring that would predict WTC-related lung injury defined by initiation of ICS/LABA treatment for more than 2 years.

III.4.2. Materials and Methods

III.4.2.1. Source population and data sources

The source population included 10 168 World Trade Center (WTC)-exposed male firefighters who were actively employed by FDNY on 11 September 2001, consented to research, and had at least one routine medical monitoring exam between 11 September 2001 and 1 July 2018 (Figure 21). Since the FDNY WTC-exposed firefighter cohort was less than 1% female, women were not included from the source population into our study.

Data on demographics, height, weight, smoking status, WTC exposure level (defined by initial arrival time to work at the WTC site), spirometry measurements, and respiratory symptoms were retrieved from the FDNY employee database (race, sex, and age) or were assessed during routine medical monitoring exams. Spirometry measurements included FEV_1 and FEV_1/FVC ratio. Respiratory symptoms included self-reported wheeze, dyspnea, and provocability. Provocability was evaluated by asking about symptoms of cough, wheeze, dyspnea, or chest tightness when exposed to smoke, fumes, odors, dust, allergens, temperature or humidity extremes, or physical activity. When individuals reported at least one respiratory symptom of provocability on the medical monitoring questionnaire, they were considered as having provocability.

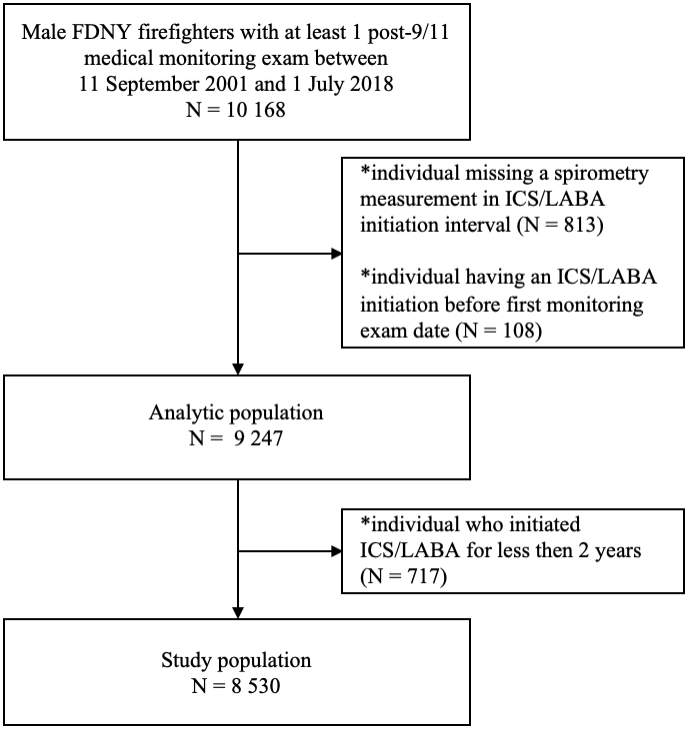


Figure 21 – Flowchart of the study population. The source population included 10 168 World Trade Center (WTC)-exposed male firefighters who were actively employed by FDNY on 11 September 2001, consented to research, and had at least one routine medical monitoring exam between 11 September 2001 and 1 July 2018. After applying exclusion criteria for individuals missing a spirometry in the initiation interval or having inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) initiation before first monitoring date, the analytic population included 9 247 firefighters. Excluding individuals who initiated ICS/LABA for ≤ 2 years, a study population of 8 530 firefighters was established to perform the main analyses.

III.4.2.2. ICS/LABA treatment

Medication data were obtained from the FDNY electronic medical record (EMR) and the FDNY WTC health program claims database. The date of treatment initiation was defined as the earliest of either the first note in the EMR or the first prescription billed. Treatment duration was defined as the interval between first and most recent prescription fill dates of ICS/LABA. Individuals were considered as having been treated with ICS/LABA therapy when the duration was at least 2 years (N = 2 162).

III.4.2.3. Dataset structure and exclusions

Analytic datasets were organized into 2-year time intervals, starting 11 September 2001 and ending 1 July 2018. When multiple visits occurred in the same 2-year time interval, the first visit with available data was used. Individuals missing a spirometry measurement in their ICS/LABA initiation interval (N = 813) were excluded from the analyses. As shown in Figure 21, an additional 108 individuals who had an ICS/LABA initiation date before their first monitoring exam date were also excluded. After applying those exclusion criteria, the analytic population included 9 247 firefighters. Additionally, 717 individuals who initiated ICS/LABA for ≤ 2 years were excluded (Figure 21). Among the remaining study population of 8530 firefighters, 1 629 individuals initiated ICS/LABA for > 2 years between 11 September 2001–1 July 2018. During the subsequent intervals, individuals missing spirometry data on a particular visit were excluded from that interval (total of 1 496 visits). The follow-up time ended at either date of ICS/LABA initiation, participants' last monitoring exam (if retired), or the end of the study period (1 July 2018), whichever came first. Missing respiratory symptom data were imputed by using symptom data from the prior interval.

III.4.2.4. Statistical analysis

Descriptive statistics were reported as proportions for categorical variables and means (with SD) for continuous variables, all of which met normality assumptions. Differences between groups were evaluated by chi-squared and t-tests, respectively.

Multinomial logistic model assessed the associations of the number of respiratory symptoms of wheeze, dyspnea, or provocability with ICS/LABA treatment (> 2y, ≤ 2y vs. no ICS/LABA) as the outcome. The four-level symptom variable compared those that had one, two, or three respiratory symptoms versus none of those three. The models were adjusted for age, WTC exposure, retirement status and FEV_1. Multivariable logistic regression was used to determine covariates associated with initiation of ICS/LABA treatment versus no ICS/LABA treatment, for each 2-year interval. Individuals who had already been prescribed ICS/LABA treatment were excluded from the analyses of the later intervals. We performed receiver operating characteristic (ROC) analysis for the logistic models, calculating the area under the curve (AUC). The covariates were chosen based on theory and different models were evaluated using the AUC of the model.

Cox proportional hazards regression was used to assess the validity of the probability of ICS/LABA initiation generated by the earlier logistic models to predict future ICS/LABA initiation. The upper 10th percentile of the probability from a 2-year interval was used as the exposure variable. The follow-up time started the beginning of the intervals tested (2007 and 2015, respectively) and ended at the earliest actual ICS/LABA initiation, last monitoring exam, or the end of the intervals tested (11 September 2011 or 1 July 2018), whichever came first. We tested the proportional hazard assumption and all models met the assumption.

In a sensitivity analysis, we used only complete data available for the logistic models, without imputing missing data for respiratory symptoms from the prior interval (N = 8 466).

In a second sensitivity analysis we included individuals that had ICS/LABA treatment for less than 2 years (N = 717 after exclusions) in the ICS/LABA treatment group (total N = 9 247).

Data analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, NC). Figures were made using SAS and R v3.6.0.2 (R Core Team. R: A Language and Environment for Statistical Computing, 2019; https://www.R-project.org).

III.4.3. Results

III.4.3.1. ICS/LABA use in population

During the study period, 6 901 individuals never initiated ICS/LABA and 1 629 received ICS/LABA treatment for more than 2 years. The median treatment duration of this treated group was 8.5 years (IQR 5.0–12.5). The proportion of individuals that was persistent in ICS/LABA use > 2 years out of all ICS/LABA initiators was 1 629/2 346 (69.4%).

The number of individuals who initiated ICS/LABA in each 2-year time interval ranged between 34 and 292 (median 184 IQR 205–163) (Figure 22). The mean FEV_1 around the time of ICS/LABA initiation was 87.7 ± 14.1% predicted and the FEV_1/FVC ratio was 0.78 ± 0.07. Compared with nontreated individuals, a greater proportion of individuals who received ICS/LABA for more than 2 years arrived at the WTC site on the morning of 9/11 (19.5% vs. 15.0%) (Table 13). The 717 WTC exposed firefighters who were treated with ICS/LABA for ≤ 2 years had intermediate WTC exposure intensity, with 17.9% of treated individuals arriving on morning of 9/11.

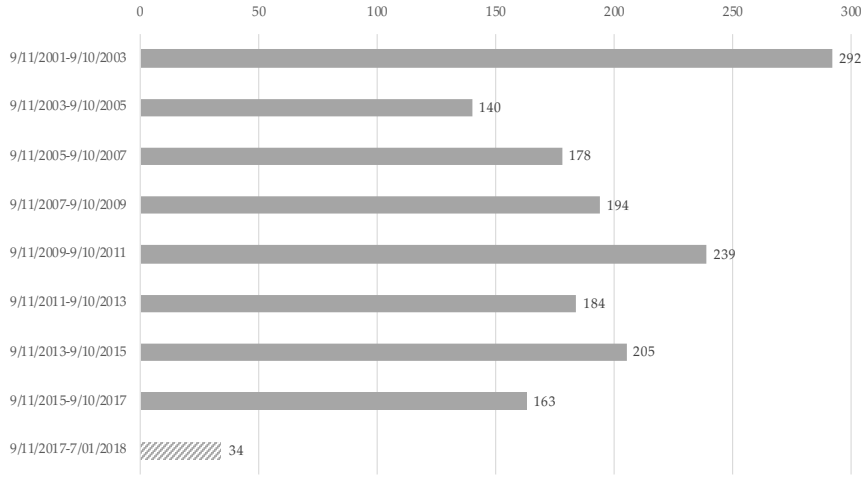


Figure 22 – Distribution of individuals initiating ICS/LABA for more than 2 years (N = 1 629) per time interval. The first interval, 11 September 2001 – 10 September 2003, with 292 individuals starting ICS/LABA treatment, had the highest number. In the other, full 2-year intervals the numbers of individuals initiating ranged from 139 to 239 per 2-year time interval. The last interval 11 September 2017 – 1 July 2018, which was not a full 2-year interval (striped filling pattern), contained 34 individuals with ICS/LABA initiation.

Table 13 – Demographics comparing full study population with ICS/LABA-treated population

Variable	Study Population N = 8 530	ICS/LABA non-treated N = 6 910	ICS/LABA treated > 2 y N = 1 629	ICS/LABA treated ≤ 2 y N = 717
Age on 9/11, y	40.5 ± 7.5	40.4 ± 7.7	40.8 ± 6.8	39.8 ± 7.3
Height, cm	177.1 ± 6.4	177.0 ± 6.4	177.2 ± 6.6	177.5 ± 6.6
Smoker, ever [a]	2 195 (25.7)	1 754 (25.4)	441 (27.1)	199 (27.8)
Race, n (%)				
White	8 008 (93.9)	6 464 (93.7) [b]	1 544 (94.8) [b]	677 (94.4)
Black	221 (2.6)	198 (2.9) [b]	23 (1.4) [b]	12 (1.7)
Other	301 (3.5)	239 (3.5) [b]	62 (3.8) [b]	28 (3.9)
WTC exposure level, n (%)				
Morning of 9/11	1 352 (15.9)	1 034 (15.0) [b]	318 (19.5) [b]	128 (17.9)
Afternoon on 9/11 to 12 Sept 2001	6 065 (71.1)	4 908 (71.1) [b]	1 157 (71.0) [b]	524 (73.1)
13 Sept to 24 Sept 2001	1 113 (13.1)	959 (13.9) [b]	154 (9.5) [b]	65 (9.1)
Baseline FEV_1, L [a]	4.01 ± 0.68	4.06 ± 0.66 [b]	3.80 ± 0.68 [b]	3.97 ± 0.68
Baseline FEV_1 % predicted [a]	97.3 ± 13.6	98.6 ± 13.1 [b]	91.8 ± 14.1 [b]	95.2 ± 14.2
Baseline wheeze [a]	1 797 (21.1)	1 210 (17.6) [b]	587 (36.0) [b]	216 (30.2)
Baseline dyspnea [a]	2 454 (28.9)	1 720 (25.0) [b]	734 (45.1) [b]	272 (38.0)

[a]At first post-9/11 exam

[b]$P < 0.01$ on t-tests and chi-squared

III.4.3.2. Concurrent symptoms and ICS/LABA treatment duration

We hypothesized that duration of treatment was associated with lung function and symptoms at the time of ICS/LABA initiation. To assess if patients with > 2 years of ICS/LABA treatment were different from those with ≤ 2 years of ICS/LABA treatment, we performed multinomial logistic regression. As shown in Table 14, smaller expiratory lung volumes (FEV_1) were more strongly associated with > 2 years of ICS/LABA treatment than with ≤ 2 years of ICS/LABA treatment (OR 2.36 per L less, 95% CI 2.10–2.67 vs. 1.52, 95% CI 1.52–1.77). We also observed that concurrent symptoms were more strongly associated with > 2 years of ICS/LABA treatment than with ≤ 2 years of ICS/LABA treatment. Compared with an asymptomatic patient, a patient with symptoms of wheeze, dyspnea, and provocability was 28-fold more likely (95% CI 23.2–35,8) to be treated with ICS/LABA for > 2 years and 10-fold more likely (95% CI 7.6–13.3) to be treated with ICS/LABA for ≤ 2 years.

Table 14 – Multinomial logistic regression[a] for ICS/LABA treatment (N = 9 018)[b]

	ICS/LABA Treated > 2y N = 1 570 [b]				**ICS/LABA Treated ≤ 2y N = 690 [b]**			
Variable	**OR**	**95% CI**		**P Value**	**OR**	**95% CI**		**P Value**
FEV_1 absolute[c], per -1, L	2.36	2.10	2.67	<0.001	1.52	1.31	1.77	<0.001
Respiratory symptoms[d]								
1 vs. 0	3.68	3.06	4.42	<0.001	2.57	2.07	3.20	<0.001
2 vs. 0	10.04	8.37	12.05	<0.001	5.47	4.38	6.83	<0.001
3 vs. 0	28.80	23.19	35.76	<0.001	10.06	7.60	13.32	<0.001

[a]Adjusted for age, WTC exposure, and retirement status.

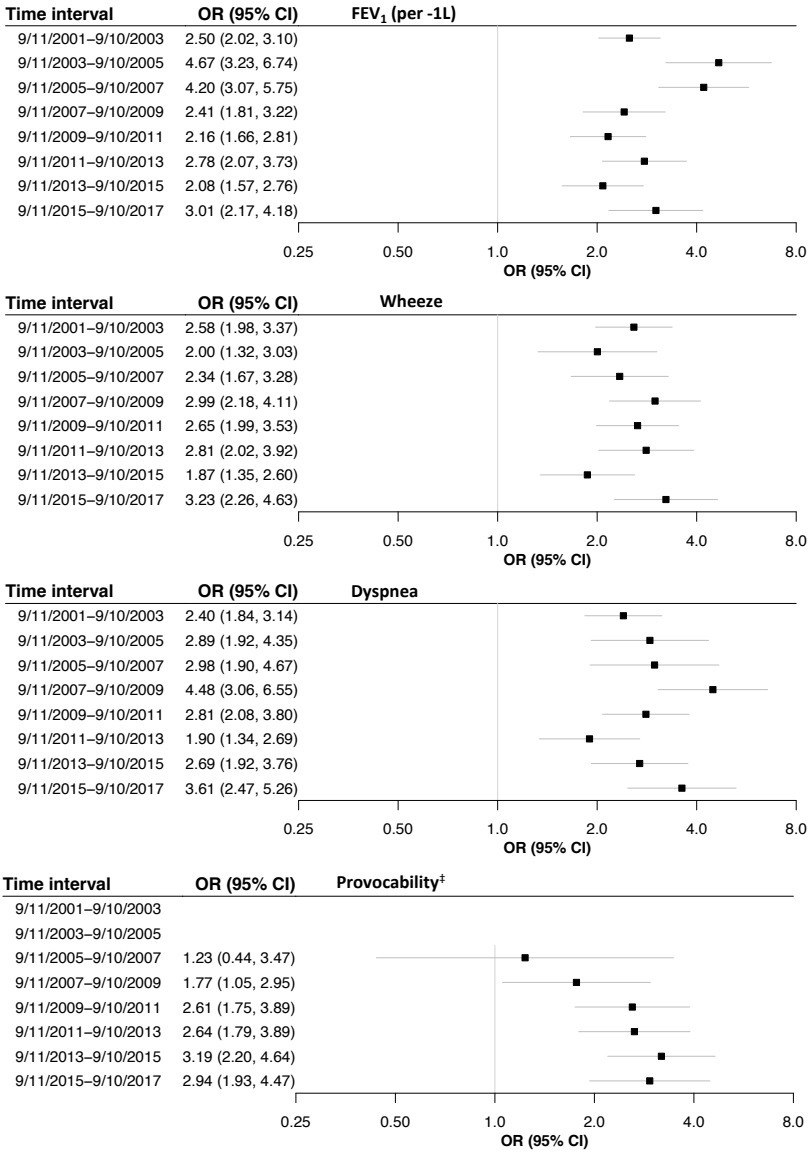
[b]N = 228 were excluded from the analysis due to missing covariates. (142 in ICS/LABA nontreated, 59 in > 2y and 27 in ≤ 2y group). ICS/LABA nontreated (N = 6 759) as the reference group

[c]On medical monitoring exam closest to ICS/LABA initiation or most recent for non-ICS/LABA.

[d]Numbers of (concurrent) symptoms of wheeze, dyspnea, and/or provocability

III.4.3.3. Initiation of prolonged ICS/LABA treatment over time

After excluding the 717 individuals who were treated for ≤ 2 years and using patient characteristics measured on routine monitoring exams from each 2-year time interval over 16 years, we tested if factors associated with prolonged ICS/LABA treatment changed over time. Multivariable logistic regression demonstrated that wheeze, dyspnea, and lower FEV_1 were persistent and independent correlates of ICS/LABA treatment (Figure 23). Symptoms of provocability were associated with ICS/LABA treatment after 11 September 2007. High-intensity WTC exposure, defined as arriving at the WTC site on the morning of 9/11, was associated with ICS/LABA treatment from 11 September 2001–10 September 2003 but not significantly thereafter. Age was not a meaningful predictor of treatment in any of the intervals (Table 15).


Time interval
OR (95% CI)
FEV1 (per -1L)
9/11/2001–9/10/2003 2.50 (2.02, 3.10)
9/11/2003–9/10/2005 4.67 (3.23, 6.74)
9/11/2005–9/10/2007 4.20 (3.07, 5.75)
9/11/2007–9/10/2009 2.41 (1.81, 3.22)
9/11/2009–9/10/2011 2.16 (1.66, 2.81)
9/11/2011–9/10/2013 2.78 (2.07, 3.73)
9/11/2013–9/10/2015 2.08 (1.57, 2.76)
9/11/2015–9/10/2017 3.01 (2.17, 4.18)
0.25 0.50 1.0 2.0 4.0 8.0
OR (95% CI)
Time interval
OR (95% CI)
Wheeze
9/11/2001–9/10/2003 2.58 (1.98, 3.37)
9/11/2003–9/10/2005 2.00 (1.32, 3.03)
9/11/2005–9/10/2007 2.34 (1.67, 3.28)
9/11/2007–9/10/2009 2.99 (2.18, 4.11)
9/11/2009–9/10/2011 2.65 (1.99, 3.53)
9/11/2011–9/10/2013 2.81 (2.02, 3.92)
9/11/2013–9/10/2015 1.87 (1.35, 2.60)
9/11/2015–9/10/2017 3.23 (2.26, 4.63)
0.25 0.50 1.0 2.0 4.0 8.0
OR (95% CI)
Time interval
OR (95% CI)
Dyspnea
9/11/2001–9/10/2003 2.40 (1.84, 3.14)
9/11/2003–9/10/2005 2.89 (1.92, 4.35)
9/11/2005–9/10/2007 2.98 (1.90, 4.67)
9/11/2007–9/10/2009 4.48 (3.06, 6.55)
9/11/2009–9/10/2011 2.81 (2.08, 3.80)
9/11/2011–9/10/2013 1.90 (1.34, 2.69)
9/11/2013–9/10/2015 2.69 (1.92, 3.76)
9/11/2015–9/10/2017 3.61 (2.47, 5.26)
0.25 0.50 1.0 2.0 4.0 8.0
OR (95% CI)
Time interval
OR (95% CI)
Provocability‡
9/11/2001–9/10/2003
9/11/2003–9/10/2005
9/11/2005–9/10/2007 1.23 (0.44, 3.47)
9/11/2007–9/10/2009 1.77 (1.05, 2.95)
9/11/2009–9/10/2011 2.61 (1.75, 3.89)
9/11/2011–9/10/2013 2.64 (1.79, 3.89)
9/11/2013–9/10/2015 3.19 (2.20, 4.64)
9/11/2015–9/10/2017 2.94 (1.93, 4.47)
0.25 0.50 1.0 2.0 4.0 8.0
OR (95% CI)

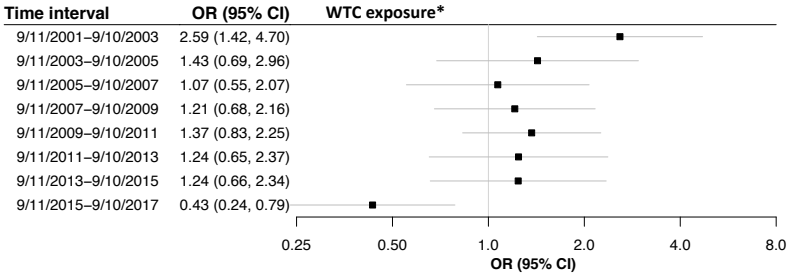


*Figure 23 - Forest plots showing variables associated with the initiation of inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) treatment > 2 years between 11 September 2001 and 10 September 2017 (N = 1 629) versus not initiating ICS/LABA treatment (N = 6 901), created from multivariable logistic regression models examining the associations between medical monitoring exam covariates and initiation of prolonged ICS/LABA treatment (odds ratios (diamonds) and 95% confidence intervals (bars)). The models were adjusted for age and retirement status. Respiratory symptoms, such as wheeze, dyspnea, provocability, and lower FEV_1, consistently predicted the early onset of lung injury defined by ICS/LABA treatment. High-intensity Word Trade Center exposure, based on arrival time, was strongly associated with ICS/LABA initiation soon after exposure. ‡ missing first two intervals because provocability data was not collected; * WTC exposure based on arrival at the WTC site: Morning of 11 September 2001 vs. 13 September 2001 or later.*

Table 15 - Results from multivariable logistic regression models examining the associations between medical monitoring exam covariates and initiation of inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) treatment >2 years between 11 September 2001 and 10 September 2017 (N = 1 629) versus not initiating ICS/LABA treatment (N = 6 901).

	Odds ratios[a] from logistic regression per 2-year interval[b]							
Variable	**11 Sep 2001-10 Sep 2003**	**11 Sep 2003-10 Sep 2005**	**11 Sep 2005-10 Sep 2007**	**11 Sep 2007-10 Sep 2009**	**11 Sep 2009-10 Sep 2011**	**11 Sep 2011-10 Sep 2013**	**11 Sep 2013-10 Sep 2015**	**11 Sep 2015-10 Sep 2017**
Total N used in model[c]	7 045	4 737	4 632	6 032	6 510	6 074	5 789	5 688
N initiated ICS/LABA treatment[c]	278	116	171	190	236	180	201	162
FEV_1 absolute, per -1L	2.50	4.67	4.20	2.41	2.16	2.78	2.08	3.01
Wheeze	2.58	2.00	2.34	2.99	2.65	2.81	1.87	3.23
Dyspnea	2.40	2.89	2.98	4.48	2.81	1.90	2.69	3.61
Provocability	na	na	(1.23)	1.77	2.61	2.64	3.19	2.94
WTC exposure, early vs. late[d]	2.59	(1.43)	(1.07)	(1.21)	(1.37)	(1.24)	(1.24)	0.43
WTC exposure, intermediate vs. late[d]	(2.21)	(0.92)	(1.23)	(0.98)	(1.00)	(1.39)	(1.64)	(0.53)
Age	(1.01)	(0.98)	(1.00)	(0.99)	(0.99)	(0.98)	(1.00)	(0.99)
Active status[e]	[f]	(0.41)	(0.87)	(1.10)	1.54	1.91	3.11	4.74

[a]Odds Ratio when P < 0.05; (Odds Ratio) when P > 0.05

[b]different intervals result from separate models

[c]individuals might be excluded from the analysis due to missing covariates

[d]WTC exposure based on arrival at the WTC site: morning 9/11(early), afternoon 9/11 or 12 September 2001 (intermediate) and 13 September 2001 or later (late)

[e]not having retired in previous interval

[f]estimate is 0 since all individuals were active on 9/11

We assessed ROC curves resulting from the models of each 2-year time interval. The AUC from the logistic models ranged from 0.77 (95% CI 0.73–0.80) to 0.85 (95% CI 0.81–0.88).

We then tested if high probability of ICS/LABA treatment, based on the logistic regression model results, increased the hazard of ICS/LABA initiation in subsequent time intervals using Cox proportional hazards models (Table 16). The upper 10th percentile of risk for ICS/LABA initiation during the period 11 September 2005–10 September 2007 increased actual ICS/LABA treatment in the next interval by 3.32-fold (95% CI 2.58–4.26; $P < 0.001$) and in the 11 September 2015–1 July 2018 interval by 2.13-fold (95% CI 1.37-3.32; $P \leq 0.001$).

Table 16 – Cox regression models for ICS/LABA treatment

Probability[a] on ICS/LABA treatment	Predicting	HR	95% CI		P Value
11 Sep 2005–10 Sep 2007	11 Sep 2007–10 Sep 2011	3.32	2.58	4.26	<0.001
11 Sep 2005–10 Sep 2007	11 Sep 2015–1 July 2018	2.13	1.37	3.32	<0.001

[a]Top 10th percentile of probability on ICS/LABA treatment

III.4.3.4. Sensitivity analysis

The results of the sensitivity analysis using only complete data for the logistic model (N = 8 466) were similar to the primary analyses (Table 17).

A sensitivity analysis comparing individuals with ICS/LABA treatment of any duration (N = 2 346) with never-treated individuals (N = 6 901) demonstrated similar findings as the primary analyses (Table 18).

Table 17 – Results from first sensitivity analysis using only complete data, not imputing missing data for respiratory symptoms from the prior interval (N = 8 466). Multivariable logistic regression models examining the associations between medical monitoring exam covariates and initiation of inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) treatment >2 years between 11 September 2001 and 10 September 2017 (N = 1 629) versus not initiating ICS/LABA treatment (N = 6 837).

	Odds ratios[a] from logistic regression per 2-year interval[b]							
Variable	**11 Sep 2001-10 Sep 2003**	**11 Sep 2003-10 Sep 2005**	**11 Sep 2005-10 Sep 2007**	**11 Sep 2007-10 Sep 2009**	**11 Sep 2009-10 Sep 2011**	**11 Sep 2011-10 Sep 2013**	**11 Sep 2013-10 Sep 2015**	**11 Sep 2015-10 Sep 2017**
Total N used in model[c]	7054	184	4630	6012	6469	6014	5729	5648
N initiated ICS/LABA treatment[c]	278	0[g]	171	189	228	163	186	159
FEV_1 absolute, per -1L	2.50	-	4.21	2.46	2.06	2.77	1.99	2.95
Wheeze	2.58	-	2.34	3.03	2.75	3.09	2.05	3.22
Dyspnea	2.40	-	2.98	4.61	3.00	2.00	2.70	3.60
Provocability	na	-	(1.23)	1.72	2.48	2.80	3.11	3.08
WTC exposure, early vs. late[d]	2.59	-	(1.07)	(1.15)	(1.39)	(1.27)	(1.27)	(0.43)
WTC exposure, intermediate vs. late[d]	(2.21)	-	(1.23)	(0.96)	(1.01)	(1.47)	1.61	(0.51)
Age	(1.01)	-	(1.00)	(0.99)	(0.99)	(0.98)	(1.00)	(0.99)
Active status[e]	[f]	(0.87)	(1.07)	1.51	1.72	3.06	4.65	(0.87)

[a]Odds Ratio when P < 0.05; (Odds Ratio) when P > 0.05

[b]different intervals result from separate models

[c]individuals might be excluded from the analysis due to missing covariates

[d]WTC exposure based on arrival at the WTC site: morning 9/11(early), afternoon 9/11 or 12 September 2001 (intermediate) and 13 September 2001 or later (late)

[e]not having retired in previous interval

[f]estimate is 0 since all individuals were active on 9/11

[g]no individuals who initiated ICS/LABA having complete data, thus no model possible

Table 18 – Results from second sensitivity analysis including individuals that had inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) treatment for less than 2 years (N = 717) to the ICS/LABA treatment group. Multivariable logistic regression models examining the associations between medical monitoring exam covariates and initiation of ICS/LABA treatment (N = 2 346) between 11 September 2001 and 10 September 2017 versus not initiating ICS/LABA treatment (N = 6 901).

	Odds ratios[a] from logistic regression per 2-year interval[b]							
Variable	**11 Sep 2001-10 Sep 2003**	**11 Sep 2003-10 Sep 2005**	**11 Sep 2005-10 Sep 2007**	**11 Sep 2007-10 Sep 2009**	**11 Sep 2009-10 Sep 2011**	**11 Sep 2011-10 Sep 2013**	**11 Sep 2013-10 Sep 2015**	**11 Sep 2015-10 Sep 2017**
Total N used in model[c]	7 672	5 111	4 947	6 397	6 865	6 353	6 023	5 867
N initiated ICS/LABA treatment[c]	436	168	222	243	309	234	257	233
FEV_1 absolute, per -1L	2.15	2.89	3.20	2.76	1.80	2.20	1.78	2.46
Wheeze	2.27	2.17	2.18	2.38	2.58	3.04	1.87	2.82
Dyspnea	2.45	2.21	2.37	3.58	2.93	1.88	2.62	3.18
Provocability	na	na	(1.18)	1.87	1.98	2.14	2.49	2.41
WTC exposure, early vs. late[d]	1.84	(1.16)	(1.47)	(1.26)	(1.42)	(1.16)	(1.46)	(0.58)
WTC exposure, intermediate vs. late[d]	(1.61)	(0.93)	(1.33)	(1.13)	(1.09)	(1.39)	(1.65)	(0.67)
Age	1.02	(1.01)	(1.00)	(0.98)	(0.99)	(0.98)	(1.01)	0.97
Active status[e]	[f]	(0.32)	(0.96)	(1.01)	1.37	1.79	2.98	3.81

[a]Odds Ratio when P < 0.05; (Odds Ratio) when P > 0.05

[b]different intervals result from separate models

[c]individuals might be excluded from the analysis due to missing covariates

[d]WTC exposure based on arrival at the WTC site: morning 9/11(early), afternoon 9/11 or 12 September 2001 (intermediate) and 13 September 2001 or later (late)

[e]not having retired in previous interval

[f]estimate is 0 since all individuals were active on 9/11

III.4.4. Discussion & Conclusion

This retrospective cohort study identified factors predicting prolonged ICS/LABA treatment among WTC-exposed firefighters who were previously healthy when appointed to FDNY. Using longitudinal data from routine medical monitoring exams, we observed that wheeze, dyspnea, provocability, and lower FEV_1 were independent risk factors for the early onset of lung injury defined by prolonged ICS/LABA treatment in patients with normal FEV_1. There was a multiplicative increase in risk when two and three of the above symptoms co-occurred. We also demonstrated that factors present early in longitudinal follow-up increased the hazard for treatment initiation years later, suggesting that individuals with disease may have remained undiagnosed and untreated for significant periods of time. The diagnosis of occult disease as soon as possible is important, because in this cohort, delayed treatment was associated with poorer symptom control.[171]

Wheeze and dyspnea, and lower FEV_1 consistently predicted ICS/LABA initiation. Other factors, such as arrival at the WTC site on the morning of its collapse, provocability, and retirement status, changed over time. Using change-point models, we previously observed that the association of WTC exposure and obstructive airways disease have become attenuated over time.[176] Our observation that WTC exposure more strongly predicted ICS/LABA initiation shortly after is consistent with our prior studies.

The respiratory symptoms assessed in the study were derived from self-administered questionnaires and FEV_1 measured with a handheld spirometer. These simple screening tests could be adapted to a telemedicine format. The importance of lung function and respiratory symptoms was recently studied with peak expiratory flow and asthma symptom scores in home telemonitoring to predict asthma exacerbations using machine learning algorithms.[177] As patient-reported outcomes, respiratory symptoms are gaining interest in clinical research.[178] Our observation that routine monitoring data predicted

ICS/LABA treatment supports the utility of telemonitoring as a method to study pulmonary outcomes.

Patients who initiated ICS/LABA treatment but did not prolong it after 2 years were different than those who continued for more than 2 years, but these patients are interesting subgroup of individuals to further explore as well. Whereas reasons for their discontinuation are unclear, our results suggest this subgroup might also have increased risk for poor health outcomes based on their increased intensity of WTC exposure, wheeze, dyspnea, and lower lung volumes. It is also possible that this group consisted of both individuals who recovered well from their lung disease and therefore no longer needed treatment and individuals who would benefit of prolonged ICS/LABA treatment but failed to adhere to their chronic treatment. This latter group of individuals might especially benefit from increased monitoring of their symptoms and lung function over time to prevent further deterioration.

A potential weakness of our study is limited generalizability, because the FDNY cohort experienced a massive dust exposure and only included previously healthy males. We also acknowledge there may be unmeasured confounds, which is possible in all observational research. A strength of this investigation is comprehensive longitudinal data with little loss to follow-up, reducing the potential for selection bias. Drug use was objectively measured and the proportion of individuals who were persistent in ICS/LABA use > 2 years was 69%. This is slightly better than a study of real-world use of ICS/LABA in UK asthma patients, which found a proportion of patient persistence between 53% and 69% after only 1 year.[179] This slightly better adherence could be due to the increased monitoring and reimbursement of treatment within the WTC program.

Further research in occupational cohorts is needed to assess if routine respiratory symptom monitoring and hand-held spirometry can identify at-risk individuals who would benefit from subspecialty testing for obstructive airway disease.

In summary, we identified patient characteristics associated with ICS/LABA treatment. We observed that increased respiratory symptoms and lower FEV_1 are persistent factors associated with treatment. Occupational cohorts that experience irritant exposures may require screening for obstructive airway disease with the goal to treat lung injury before development of abnormal lung function.

IV. DRUG-RELATED FACTORS

IV.1. Effect of inhaled corticosteroids on FEV_1 trajectory in WTC-exposed firefighters: a 16-year longitudinal cohort study

IV.1.1. Introduction

In healthy individuals, normal aging affects pulmonary function, resulting in reduction in lung function but seldom leading to symptoms. The expiratory volume exhaled during the first second of a forced breath (FEV_1) declines around 30 mL/year in men and 25mL/year in women from middle age adulthood onwards.[30] A greater than age-related decline in FEV_1 is called an accelerated decline. Depending on the degree of decline, respiratory symptoms and general impact might be present.[180] Despite normal lung function at early adulthood, an accelerated decline in lung function is one of the pathways found to lead to chronic obstructive pulmonary disease (COPD).[31]

Exposure to dust and products of combustion at the collapse of the World Trade Center (WTC) resulted in an acute drop of lung function and high incidence of reactive airways disease (asthma) in rescue and recovery workers.[29,43,44] Immediately after 9/11/2001, the Fire Department of the City of New York (FDNY) instituted a longitudinal medical monitoring program that performed screening pulmonary function tests and collected health information via computer-based questionnaires.[52] Furthermore, FDNY resourced a treatment program staffed with pulmonologists to provide subspecialty pulmonary evaluation and treatment at no cost to the participants. Longitudinal data from these monitoring and treatment programs has identified a subgroup of WTC-exposed firefighters with an accelerated decline in FEV_1.[46] Importantly, accelerated FEV_1 decline in itself is not an indication for treatment according to guidelines for asthma or COPD.[8,11]

The effect of pharmacotherapy on FEV_1 decline has been questioned for over decades.[92] Post-hoc analyses of randomized controlled trial data showed the largest effect for ICS/LABA compared to placebo on the rate of FEV_1 decline

in COPD patients.[93,94] In asthma, there is no conclusive evidence that ICS prevents long-term accelerated decline in lung function and mortality, occurring in a subgroup of asthma patients.[91] Furthermore, there is a lack of real-life evidence from observational studies analyzing the effect of inhaled steroids (ICS) on lung function over time. Since a proportion of WTC-exposed firefighters are suffering from continued accelerated FEV_1 decline, we aimed to analyze the effect of ICS-containing treatment on FEV_1 trajectory in this WTC-exposed cohort.

IV.1.2. Methods

IV.1.2.1. Source population and data sources

The source population included 10,166 World Trade Center (WTC)-exposed male firefighters who were actively employed by FDNY on 11 September 2001 (9/11), consented to research and had at least one post-9/11 monitoring exam between 11 September 2001 and 10 September 2017. Since individuals were active firefighters on 9/11, who are banned from the job when they develop asthma, we assumed they were not on an ICS-containing inhaler on 9/11.

Data on demographics, height, weight, smoking status, WTC exposure level (defined by initial arrival time at the WTC site), spirometry measurements, respiratory symptoms and blood eosinophil counts were retrieved from the FDNY employee database and/or were assessed during the first routine medical monitoring exam post 9/11.

IV.1.2.2. Study population and exclusions

Figure 24 shows the flow chart of the study population, excluding individuals limited by longitudinal data and therefore not eligible for the calculation of time-varying propensity scores.

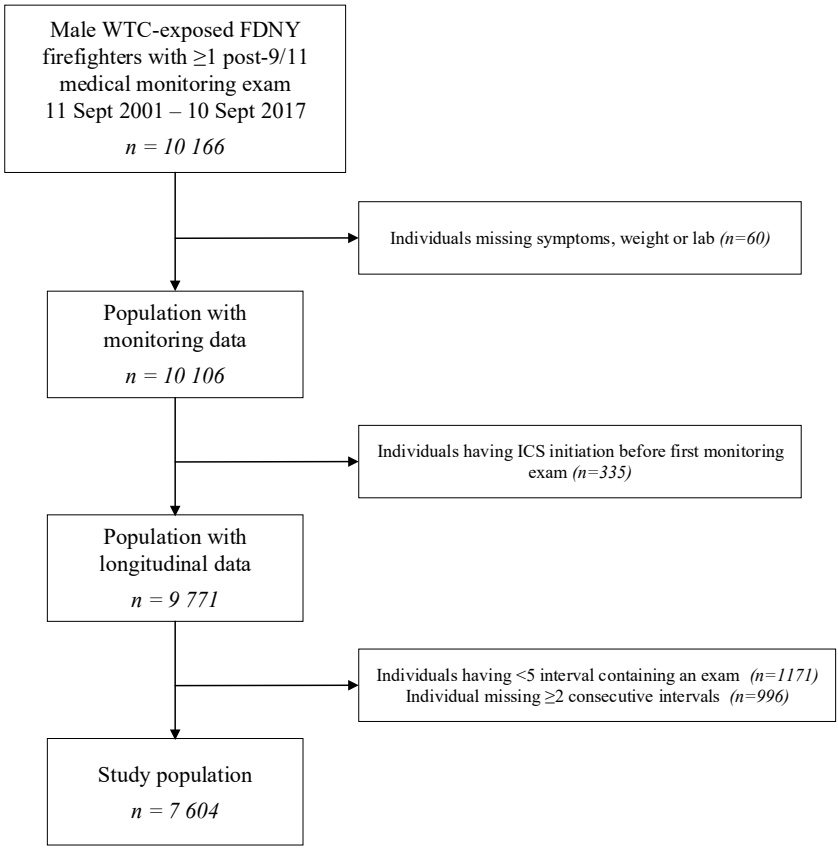


Figure 24 – Flow chart of the study population. The source population included 10 166 World Trade Center (WTC)-exposed male firefighters who were actively employed by Fire Department of the City of New York (FDNY) on 11 September 2001, consented to research, and had at least one routine medical monitoring exam between 11 September 2001 and 10 September 2017. After applying exclusion criteria, a study population of 7 604 firefighters was composed.

IV.1.2.3. ICS treatment exposure

The exposure of ICS-containing treatment, versus no ICS-containing treatment was studied. ICS-treatment was defined as ICS monotherapy or combination with LABA or LAMA/LABA, the majority in multiple devices. Medication data were obtained from the FDNY electronic medical record (EMR) and the pharmacy claims database. The initiation date was defined as the date of the first recorded prescription claim or EMR note, whichever occurred first. Once initiated, individuals were considered as staying on the ICS-treated trajectory until the end of study (n=2,593) but their actual days covered by ICS was calculated by proportion days covered (PDC) per 2-year interval.[181] Their adherence was approximated by the sum of days supplies of the pharmacy claims, divided by the total of days per 2-year interval. The highest PDC over all treated intervals in an individual defined the ICS adherence type of that individual: <50% as very low adherent (n=1050), 50- 80% as low adherent (n=333), 80-120% as ICS adherent (n=721), >120% as overuser (n=285). Before the time claims data was available (December 2006), adherence was calculated based on the EMR notes. The PDC was estimated for each distinct 270-day course in which ICS treatment was reported in the EMR notes. This duration was based on the extrapolation of EMR notes to claims data after December 2006.

A sensitivity analysis of the main analysis used pharmacy claims data as the primary medication data source. Before claims data was available (December 2006), medication use was estimated based on the EMR notes.

IV.1.2.4. Outcome

The main outcome of interest was FEV_1 trajectory over time (mL/year).

IV.1.2.5. Statistical analyses

Descriptive statistics are reported as proportions (%) for categorical variables and means (with SD) for continuous variables. Differences between groups were evaluated by chi-squared and t tests, respectively.

Propensity scores

Propensity scores for ICS initiation were calculated per 2-year interval post 9/11 using logistic regression models. When multiple exams occurred in the same 2-year time interval the first exam with complete data was used. Time-independent variables as age, race, height, baseline FEV_1 and WTC exposure level were included. In addition, time-dependent covariates as smoking and retirement status, weight, respiratory symptoms, blood eosinophil count and co-medications potentially impacting on FEV_1 trajectory (oral corticosteroids, short-acting or long-acting bronchodilators, leukotriene receptor antagonists, theophylline or biologicals) were included in the models. Respiratory symptoms of cough, wheeze, dyspnea and provocability were combined as a 5-level variable, comparing those that had one, two, three or four respiratory symptoms versus none of those four. Provocability was evaluated by asking about symptoms of cough, wheeze, dyspnea, or chest tightness when exposed to smoke, fumes, odors, dust, allergens, temperature or humidity extremes, or physical activity. When individuals reported at least one respiratory symptom of provocability on the medical monitoring questionnaire, they were considered as having provocability. Missing covariates were imputed by data from the most recent observed prior interval.[182]

Inverse probability of treatment weighting (IPTW) analysis

Inverse probability of treatment weighting (IPTW) was used to control for possible time-varying confounding of covariates associated with both outcome and initiation of ICS-containing treatment.[183] First, inverse probability of treatment weights were assigned, based on the inverse of their probability of initiating treatment, as estimated by the propensity score.[183] Weights in the first 2-year interval, considered as baseline, were one for all individuals, but could change over time dependent on the probability of ICS initiation. In ICS-treated individuals, once ICS was initiated, weights were set to one in the subsequent intervals.

Second, FEV_1 trajectories were estimated for ICS-users versus no ICS users, using linear mixed effects models with random intercepts. The first model estimated mean absolute FEV_1 values for the ICS-treated versus the non-treated group for each 2-year interval between 11 September 2001 and 10

September 2017, weighted for the propensity score weights per interval. A separate model estimated an average FEV_1 slope throughout follow-up, also weighted for the propensity score weights per interval.

Propensity score matched analysis

Propensity score matched analyses were additionally performed to confirm that the ICS effect was not driven by differences in baseline lung function. Matches were created within a subgroup of individuals with similar baseline lung function and early initiation of ICS, defined by start of an ICS-containing treatment between 11 September 2001 and 10 September 2005, and controls in the same time period (n=1814). The earliest lung function exam was used for the propensity score matching. The optimal matching method was used with 1:1 matching and a caliper around 0.2 times the SD of logit of the propensity score.[184] The baseline characteristics were assessed for balance through the appropriate testing procedure for the matched dataset. Linear mixed effects models estimated mean absolute FEV_1 for ICS-treated versus non-treated. A separate model estimated a mean FEV_1 yearly slope throughout follow-up.

Characteristics of response to ICS-containing treatment were assessed within this subset of users with early initiation post-9/11 of ICS treatment. Therefore, ICS-treated individuals of the matched analyses were grouped into responders and non-responders. Responders were defined as having an individual FEV_1 slope after treatment initiation calculated by mixed effects models greater than or equal to the group median slope for ICS-initiated individuals (-33.0 mL/y), which means an FEV_1 decline less than the median. Baseline characteristics and early biomarkers were compared. The biomarker analysis included blood eosinophil counts before the ICS initiation date, after excluding individuals who already received oral steroids (n=42). A subgroup had also immunoglobulin concentrations (including IgA) assayed with HGAMMAG-301K (EMD Millipore) on serum drawn between October 2001 and March 2002 and (n=147). Last, systemic antibiotic and oral corticosteroid use before the date of ICS initiation was assessed, as proxies for respiratory exacerbations.

Sensitivity analyses

Data analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, NC). Figures were made using SAS and Microsoft Excel.

IV.1.3. Results

IV.1.3.1. Descriptive Statistics

Table 19 shows the baseline characteristics of the study population which are comparable of those of the source population. Among the study population, the ICS treated group has a non-significant larger proportion of ever smokers ($p=0.23$), significant larger proportion of individuals with high WTC exposure level ($p<0.001$) and significant lower baseline FEV_1 values ($p<0.001$) compared with the non-ICS treated group.

Table 19. Demographics of the study population, comparing the ICS non-treated with the ICS-treated population

Variable	Source population *n=10,166*	Study population *n=7,604*	Non-ICS treated *n=5,011*	ICS treated *n=2,593*
Age on 9/11	40.4 ± 7.4	39.5 ± 7.2	39.1 ± 7.5	40.1 ± 6.7
Height	177.2 ± 6.4	177.0 ± 6.4	176.9 ± 6.3	177.2 ± 6.5
Smoker, ever*	2669 (26.3)	1849 (24.3)	1197 (23.9)	652 (25.1)
Race				
White	9557 (94.0)	7190 (94.6)	4723 (94.3)	2467 (95.1)
Black	254 (2.5)	148 (2.0)	114 (2.3)	34 (1.3)
Other	355 (3.5)	266 (3.5)	174 (3.5)	92 (3.6)
WTC exposure level				
Morning of 9/11	1671 (16.4)	1199 (15.8)	691 (13.8)	508 (19.6)
Afternoon of 9/11 or 12/9/2001	7237 (71.2)	5509 (72.5)	3651 (72.9)	1858 (71.7)
13/9-24/9/2001	1258 (12.4)	896 (11.8)	669 (13.4)	227 (8.8)
Baseline FEV_1 (L)*	3.99 ± 0.68	4.05 ± 0.66	4.11 ± 0.65	3.92 ± 0.66
Baseline FEV_1 % pred*	96.7 ± 13.8	97.4 ± 13.4	99.0 ± 12.9	94.3 ± 13.9

*First post 9/11

IV.1.3.2. IPTW analysis of ICS treatment versus no ICS

The average slope throughout 16 years of follow-up after 9/11 was -33.8 mL/year (95% CI -34.5; -33.1) when non-ICS treated versus -31.4 mL/year (95% CI -32.8; -30.0) when ICS-treated. ICS demonstrated a significant improvement in FEV_1 decline with an average slope of 2.4 mL/year (95% CI 0.9; 3.9 p=0.002). Figure 25 shows the trajectories by 2-year intervals throughout follow-up.

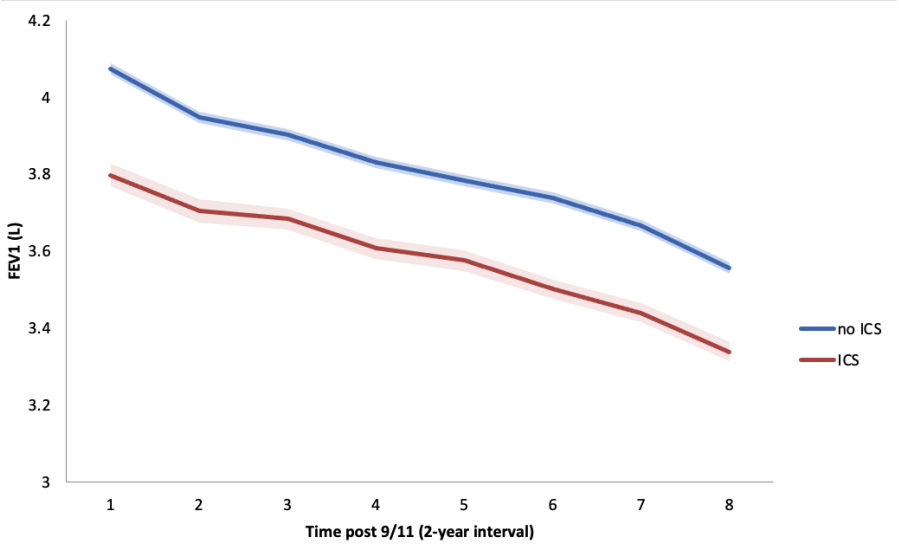


Figure 25 – FEV_1 trajectory by ICS-treatment weighted for inverse probability of treatment weights. The mean (±95% CI) trajectory of absolute FEV_1 is shown in each 2-year interval between 11 September 2001 and 10 September 2017. The blue graph corresponds to the ICS non-treated subgroup (n = 6808) and the red to the ICS-treated subgroup (n=2584). In the first two 2-year intervals, the decline is rather steeper in the non-treated ICS group compared with the ICS-treated. Thereafter both trajectories remain about parallel over time.

The results of the sensitivity analysis using pharmacy claims data as the primary medication data source, were similar to the primary analyses. The average slope throughout 16 years of follow-up after 9/11 was -33.7 mL/year (95% CI -34.4; -33.0) when non-ICS treated versus -31.6 mL/year (95% CI -33.0; -30.1) when ICS-treated. The effect of ICS, primary based on claims data, showed a significant improvement in FEV_1 decline with an average slope of 2.1 mL/year (95% CI 0.6; 3.7 p=0.006).

After adjusting for adherence to ICS, measured as proportion days covered (PDC) per interval, the average effect of ICS was estimated on 4.6 mL/year throughout 16 years of follow-up post-9/11. When stratifying treated individuals by ICS adherence type, defined by the highest PDC per interval, those who were very low adherent (PDC <50%) had a worsening in FEV_1 decline of 12.1 mL/year, low adherent (PDC 50-79%) had an improvement in FEV_1 decline of 4.0 mL/year, adherent (PDC 80-120%) had an improvement in FEV_1 decline of 13.0 mL/year and overusers (PDC >120%) an improvement in FEV_1 decline of 9.6 mL/year (Figure 26).

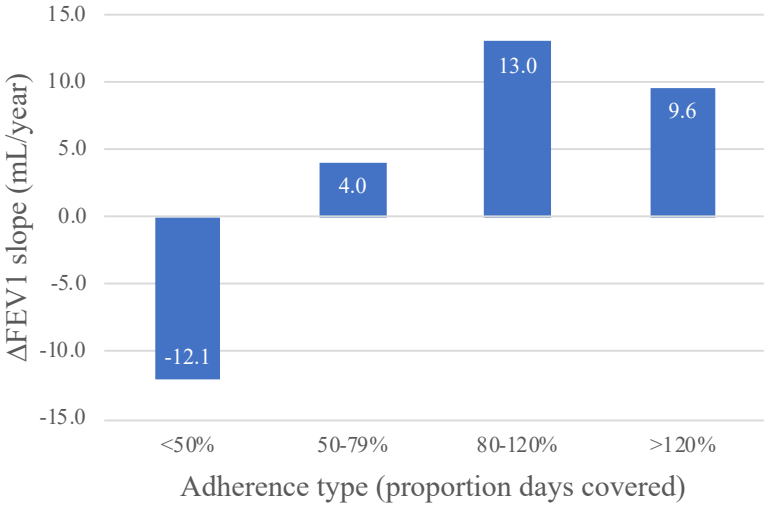


Figure 26. Change in FEV_1 slope stratified by adherence type, defined by highest proportion days covered per interval.

IV.1.3.3. Propensity score matched analyses

Using propensity score matching, we examined whether the ICS effect was driven by differences in baseline lung function. A subgroup of individuals with similar baseline lung function and with ICS initiation between 11 September 2001 and 10 September 2005 (n=907) was matched with control individuals in that time period (n= 907). The average FEV_1 slope throughout follow-up was -31.9 mL/year (95% CI -33.7; -30.1) for non-ICS treated versus -33.9 mL/year (95% CI -35.6; -32.3) for ICS-treated, including spirometry measurements from ICS initiation throughout follow-up. There was a non-significant worsening in FEV_1 slope of 2.0 mL/y (95% CI -4.5; 0.4 p=0.10) in the overall ICS-treated group, which was -1.4 mL (95% CI -3.9; 1.1 p=0.28)

in non-adherent users (PDC<80%; n=1375) and +10.7 mL (95% CI 1.5; 19.8 p=0.02) in adherent users (PDC ≥80%; n=439).

Among this earliest matched group, responders on ICS treatment were defined as having an individual mixed effect modeled FEV_1 slope greater than the mean group slope for ICS-initiated individuals (n=475). Their early characteristics were compared with non-responders defined as ICS-treated individuals with a slope less than the average of those treated (n=432). ICS responders were younger, had a significantly smaller proportion of ever smokers, lower baseline FEV_1 % predicted, a significantly lower proportion of adherent individuals and shorter average treatment duration (Table 20).

Table 20. Characteristics of responders versus less-responders to ICS-containing treatment for ICS treatment initiation in intervals 1-2

Variable	ICS responder[¶] n=475	ICS non-responder[¶] n=432
Age on 9/11	39.4 ± 6.2	42.1 ± 6.9[¥]
Height	177.4 ± 6.6	177.5 ± 6.8
Smoker, ever*	87 (18.3)	122 (28.2)[¥]
Race		
White	452 (95.2)	409 (94.7)
Black	5 (1.1)	4 (0.9)
Other	18 (3.8)	19 (4.4)
WTC exposure level		
Morning of 9/11	113 (23.8)	100 (23.2)
Afternoon of 9/11 or 12/9/2001	327 (68.8)	297 (68.8)
13/9-24/9/2001	35 (7.4)	35 (8.1)
FEV_1 absolute (L)*	3.87 ± 0.64	3.89 ± 0.68
FEV_1 % predicted*	92.3 ± 13.6	94.3 ± 14.1[¥]
Cough*	339 (71.4)	297 (68.8)
Wheeze*	175 (36.8)	174 (40.3)
Shortness of breath*	232 (48.8)	230 (53.2)
Blood eosinophils (cells/μL) *[$]	193.7 ± 124.1	210.4± 126.4
Low serum IgA, n (%)*[#]	12 (14.8)	9 (13.6)
Antibiotic use pre ICS initiation, n (%)	106 (22.3)	106 (24.5)
Oral steroid use pre ICS initiation, n (%)	23 (4.8)	20 (4.6)
ICS adherence type[‡], PDC≥80%, n (%)	140 (29.5)	172 (39.8)[¥]
ICS duration (years)	3.4 ± 5.1	4.2 ± 5.6[¥]

[¶] Responders: FEV_1 post initiation slope >=-33.0 mL/y and non-responders <-33.0 mL/y; [¥]$p<0.05$ between 2 groups *first post-9/11 exam; [$] n=213 missing eosinophil count before ICS initiation date, n=42 excluded because of oral steroid treatment; [#]serum IgA ≤ 70 mg/dL in subgroup (n=147) ; [‡]defined by the highest proportion days covered (PDC) of ICS per interval

IV.1.4. Discussion

In this previously healthy, WTC-exposed firefighter cohort, the effect of ICS-containing treatment on FEV_1 trajectory was studied. A longitudinal analysis using IPTW, showed that ICS-containing treatment altered lung function trajectory. We observed an average improvement in FEV_1 decline of 2.4 mL/year compared with no ICS treatment, and even 4.6 mL/year when adjusting for adherence to ICS.

The 9/11 disaster causing an intense dust cloud led to a transient inflammatory reaction to the inhaled dust, associated with an acute drop in lung function.[29,43,44] This inflammation could be targeted with ICS, since ICS reduce airway inflammation and hyperresponsiveness by altering the production of mediators associated with inflammatory cells in the airways.[66,67] However, there might be different underlying disease endotypes with variances in ICS responsiveness, as suggested by earlier observations among WTC-exposed firefighters responding better to ICS/LABA treatment when initiated sooner after 9/11.[185] Additionally, the ICS responder characterization showed that responders had a smaller proportion of ever smokers. Smoking is a known modifier of ICS response, leading to a reduced effect in asthma and COPD cohorts.[186,187] Interestingly, blood eosinophils count appeared not-significantly different in responders versus ICS-non responders. We therefore could not replicate in our firefighter cohort the beneficial response to ICS associated with high blood eosinophils observed in patients with asthma and COPD.[188–190]. The lacking availability of a blood eosinophil count close before ICS initiation might have played a role here. Alternately, WTC-related irritant-associated lung injury disease might have another underlying disease endotype, with different factors predicting ICS response. Pharmacogenomics studies showed genetic variants might also lead to a different response to ICS.[191–193]

We observed an average improvement in FEV_1 decline of 2.4 mL/year among ICS treated compared with non-treated individuals, with an effect of 4.6 mL/year when taking adherence into account. This effect is in line with

the effect observed in populations with chronic, ongoing exposure and inflammation due to noxious particles, such as smoking. In a recent systematic review, only including larger trials with at least 1 year follow-up, concluded to a 5.0 mL/year reduction in FEV_1 decline for active COPD treatments and 7.3 mL/year in a subgroup analysis of ICS-containing therapies.[194] The two largest randomized controlled trials (RCTs) were TORCH (TOwards a Revolution in COPD Health) and SUMMIT (Study to Understand Mortality and Morbidity in COPD), which showed a reduction of ICS/LABA on FEV_1 decline of 16 mL/year and 8 mL/year compared with placebo and an effect of ICS monotherapy of 13 mL/year and 8 mL/year compared with placebo, respectively.[93,94] Lung function was studied as a secondary endpoint, therefore post-hoc analyses were used to study the effect of ICS, LABA, ICS/LABA vs placebo on the rate of FEV_1 decline. Looking in detail at these short-term trajectories, first a big volume effect at 3-6 months is observed, with thereafter a decline in FEV_1 slope which is more parallel with control groups. This volume effect can partially be explained by relieving the chronic bronchoconstriction in those COPD patients.[195] The applicability of these results towards subjects heavily exposed to noxious particles or gases but not (yet) diagnosed with COPD, was unknown. The observed effect of ICS when stratified by adherence type, can be seen as a dose-response effect. However, overuse of ICS might have the risk of systemic side effects without a more pronounced effect. Our overall observed ICS effects are lower than those found in the TORCH and SUMMIT trials. When stratifying by adherence type, the effect is in the same range seen as the trials' effect. This can be explained by the fact that the adherence achieved in clinical trials was not reached in real life.

A strength of this investigation is the comprehensive longitudinal data with little loss to follow-up reducing the potential for selection bias. Another strength is the objective measure of the treatment exposure. A weakness of our cohort is the specific setting of a massively dust-exposed cohort including only previously healthy males, which limits the generalizability. Inverse probability of treatment weighting, a type of propensity score method, was

used to analyze treatment effects from these observational data. Propensity scores are used to reduce selection bias by equating groups based on observed, time-varying confounders related to treatment assignment.[183] Selection bias is a discrepancy between the estimated treatment effect and the true treatment effect due to systematic pre-intervention differences between members of treated and untreated groups.[196] In observational studies, when participants are not randomly assigned to groups, observed pre-intervention differences cannot be assumed to be random and selection bias is highly likely when analyzing treatment effects. Unfortunately, the inverse probability of treatment weighting method also has its limitations. Propensity scores are valuable in controlling for measured confounding, but cannot control for unmeasured confounding either.[197] Using a mixed effects model as the outcome model, a possible effect might also be averaged out in the overall, average FEV_1 trajectory. Concerned about differences in baseline lung function, we performed a matched analysis for early ICS initiation to evade regression to the mean. This analysis was performed in a subgroup, because for the most extreme values of FEV_1, we were not able to find a match for every ICS-treated individual. Therefore, the resulting ICS effect is not representative of the entire group of ICS-treated individuals, since the individuals with worse baseline lung function were less presented in this analysis. The observed effect was therefore probably underestimated. Furthermore, due to the lack of statistical power in this subgroup analysis, we cannot state these associations of potential biomarkers and ICS response on FEV_1 decline are final. More research is needed to further explore the associations of these potential biomarkers and ICS response. Ideally, there should always be a systematic baseline blood drawn should prior to ICS initiation.

In conclusion, the effect of ICS treatment resulted in a 2.4 mL average reduction in FEV_1 decline over 16 years of follow-up. When taking adherence to ICS into account, the effect improved to 4.6 mL/year. More observational research in general cohorts is needed to further assess the effect of ICS on FEV_1 decline.

IV.2. Impact of community pharmacist counseling on adherence to inhaled corticosteroids and asthma control

IV.2.1. Introduction

Asthma is a prevalent chronic airway disease, often starting during childhood and affecting individuals of all ages.[198] Its worldwide prevalence was around 300 million individuals in 2016 according to the World Health Organization, with an estimated rise to 400 million expected by 2025.[199] In Belgium, the prevalence is around 7%.[200] Despite the wide range of adequate asthma medication available, only 50% of patients benefit sufficiently from it. Inhaled corticosteroids (ICS) are the cornerstone of asthma therapy.[65,201] However, adherence to controller medications and inhaler technique, remains low.[96] Uncontrolled asthma can lead to exacerbations, disability, and even death, with a large socio-economic burden associated. Therefore, asthma requires global attention and appropriate patient education, to improve patient's outcomes.[202]

Pharmaceutical counseling (PC) interventions have proven to improve adherence to controller medication and asthma control, reducing emergency department visits and hospital admissions and so decreasing total health costs.[108,109,203,204] In addition, one recent meta-analysis confirmed that PC interventions can effectively contribute to improved medication adherence in asthma patients[110], but another meta-analysis could only confirm an improved inhaler technique and not adherence in asthma patients.[205] However, data on real-life impact of these PC interventions are lacking, particularly in difficult-to-control and severe asthma patients, which are associated with a substantial health and economic burden.[206,207]

The overall aim of this study was to evaluate whether PC interventions improve adherence to chronic inhaler therapy among difficult-to-control asthma patients using real-world, nationwide data. We hypothesized that PC interventions improve ICS adherence and improved adherence results in a better asthma control.

IV.2.2. Methods

The source was the BelPhar database, which monthly collects reimbursement claims and patients' demographics from all community pharmacies affiliated with the Association of Pharmacists Belgium (APB; the Belgian federation of independent community pharmacies). At national level, the registered data represents around 85% of all Belgian community pharmacies and corresponds to approximately 78% of all national reimbursed community pharmaceutical dispenses.

The source population contained all patients aged 5+ in the BelPharData with at least one ICS dispensing in the period 1/1/2017-31/12/2017, with the date of first dispensing in 2017 defining the reference date. The asthma-related drug use (detailed in Table 21) of this population was extracted from exactly one year before to exactly one year after the reference date. The method used for the data extraction is illustrated in Figure 27. Chronic ICS users were defined as patients in the source population who had at least one ICS dispensing in the 12 months before and in the 12 months after the reference date. The study population, most representative of an asthmatic population, included chronic ICS users aged 5-40 years. Index patients received at least one PC intervention within 90 days after ICS dispensing, as recorded by the database. The protocol-based PC intervention consisted of two counseling interviews offered by the community pharmacist and targeted both incident asthma patients starting ICS treatment and prevalent asthma patients with difficult-to-control disease despite chronic ICS treatment. Our study population derived from this latter group with difficult-to-control asthma prescribed long-term ICS therapy, who received a PC intervention. Asthma control was assessed by the occurrence of nocturnal awakening ('how often did you wake up at night or early in the morning earlier than usual because of asthma symptoms?') and reliever use ('how often have you used your inhaler with fast-acting medication?') in the past 4 weeks, according to GINA guidelines.[65] In case of any nocturnal awakening in the past 4 weeks and/or reliever use more than twice a week, the asthma was considered poorly controlled and an interview was scheduled at the community pharmacy. In a first interview the pharmacist assessed patients' expectations, disease control

using Asthma Control Test, knowledge about asthma and medications, inhaler technique, adherence and the importance of adherence, side effects or corticophobia. Furthermore, the patient was educated about medication use (purpose, mechanisms of action, side effects, use of inhalers) and risks of non-adherence and overuse of reliever medication, and possible questions were answered. A follow-up interview was offered three to six weeks later, to assess patient's experience, detect remaining problems and check the evolution in patient's medication use and knowledge. A sensitivity analysis stratified on the number of PC interventions compared ICS usage between patients who received 1 PC intervention (n=1119) with patients who received two or more interventions (n=231), both within 90 days after ICS dispensing.

Table 21. The most commonly used drugs for the treatment of asthma are subdivided by chemical subgroup, active substance and ATC code.

Group	Active substance	ATC code
Antibiotics	Antibacterials for systemic use	J01
Biologicals	Omalizumab	R03DX05
Biologicals	Mepolizumab	R03DX09
Biologicals	Benralizumab	R03DX10
ICS	Salmeterol and fluticasone	R03AK06
ICS	Formoterol and budesonide	R03AK07
ICS	Formoterol and beclometasone	R03AK08
ICS	Vilanterol and fluticasone furoate	R03AK10
ICS	Formoterol and fluticasone	R03AK11
ICS	Vilanterol, umeclidinium bromide a fluticasone furoate	R03AL08
ICS	Formoterol, glycopyrronium bromide and beclometasone	R03AL09
ICS	Beclomethasone	R03BA01
ICS	Budesonide	R03BA02
ICS	Fluticasone	R03BA05
LABA/LAMA	Indacaterol, formoterol or olodaterol and/or aclinidinium, glycopyrronium, tiotropium or umeclidinium	R03BB04-07, R03AL04-06
OCS	Methylprednisolone	H02AB04
SABA/SAMA	Salbutamol	R03AC02
SABA/SAMA	Fenoterol and ipratropium bromide	R03AL01
SABA/SAMA	Salbutamol and ipratropium bromide	R03AL02

ATC, anatomical therapeutic chemical; ICS, inhaled corticosteroids: LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; OCS, oral corticosteroids; SABA, short-acting beta-agonists; SAMA, short-acting muscarinic antagonists.

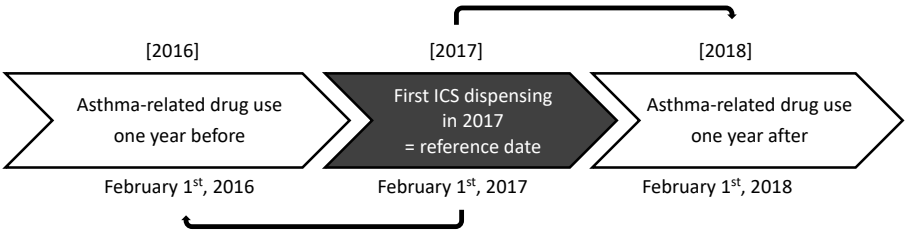


Figure 27 – An example of how the BelPharData was extracted for a fictional patient receiving the first ICS dispensing in 2017 on February 1st, 2017 (= reference date). The asthma-related drug history one year before ICS dispensing (February 1st, 2016) was observed in comparison to the drug use exactly 12 months after the reference date.

The change in drug use from one year before to one year after the PC intervention was analyzed (Figure 27). Asthma-relevant drug use was the main outcome of interest, reported as drug usage for ICS and proportion of drug users for the other asthma medications. Drug usage for ICS was defined as the proportion of total Defined Daily Dose (DDD) of ICS and the number of patients receiving ICS. Proportion of drug users was defined as the number of patients receiving an asthma-related drug of interest divided by the total number of ICS patients. For SABA, antibiotics and OCS, the proportion drug users from one year before first ICS dispensing in 2017 (reference period) was compared with one year after. The ratio of controller-to-total (CTT) asthma medications, an overall proxy for adherence and asthma control, was derived from the reported drug use.[208,209] The CTT ratio was calculated by dividing the sum of prescription DDDs for controller medication (ICS, long-acting beta-agonists [LABA]/long-acting muscarinic antagonists and biologicals) by total asthma medication (controller medication plus SABA). Since omalizumab was the only reimbursed asthma biological available on the Belgian market until the end of 2016 and more became available during 2017, we only analyzed the proportion of biological users post PC intervention. Controls for this analysis were defined as chronic ICS users aged 5-40 years who did not receive a PC intervention (n=50 477).

Confidence intervals for the group means were computed by the assumed mean method. Confidence intervals for the difference between two proportions were calculated using the Newcombe method.[210] P value <0.05 was considered significant. Data analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, NC). Figures were made using Microsoft Excel 16.45.

IV.2.3. Results

The BelPharData-based source population included 922 943 patients having an ICS dispensing recorded in 2017. Of this source population, 288 069 (31%) were chronic ICS users, of which 56 582 (20%) was aged 5 to 40 years. Among these 5-to-40-year-old asthma patients on chronic ICS therapy, about half (54%) were women and 6% received at least one PC intervention. Furthermore, 49% were SABA users, 51% were antibiotic users and 8% OCS users. The average ICS adherence was 36%, based on their DDD coverage in 2017. The study population consisted of difficult-to-control asthma patients identified by the pharmacist in this group of chronic ICS users aged 5-40 years, with at least one PC intervention within 90 days after the reference date (n=1350). Among those, 83% (n=1119) received one PC intervention and 17% (n=231) received more than one intervention.

IV.2.3.1. Impact on asthma controller medication

The primary analysis showed a significant increase of 43.3 DDD/patient in ICS usage with 125.9 DDD/patient (95% Confidence Interval [CI] 124.9-126.9) in the year following the PC intervention compared with a usage of of 82.6 DDD/patient (95% CI 82.0-83.2) the year before. (Figure 28). The CTT ratio went from 0.671 before to 0.749 after PC intervention, representing an increase of 0.078 (95% CI 0.075-0.081, $p<0.05$).

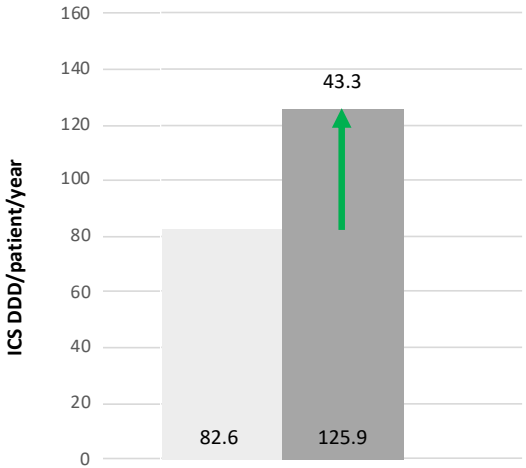


Figure 28 – Bar chart showing results of the primary analysis of inhaled corticosteroids (ICS) usage one year pre-intervention (light gray filled) and one year post-intervention (dark gray filled) in 5-40 year-old difficult-to-control asthma patients with at least one PC intervention in 2017. This corresponds with an increased ICS usage of 43.3 DDD per patient per year.

A sensitivity analysis on the number of interventions showed a similar, significant increase in ICS usage in patients who received one PC intervention (n=1119; 83%) of 39.3 DDD/patient (Figure 29). Patients who received two or more interventions (n=231; 17%) showed a significant gain of even greater magnitude in ICS usage of 62.1 DDD/patient.

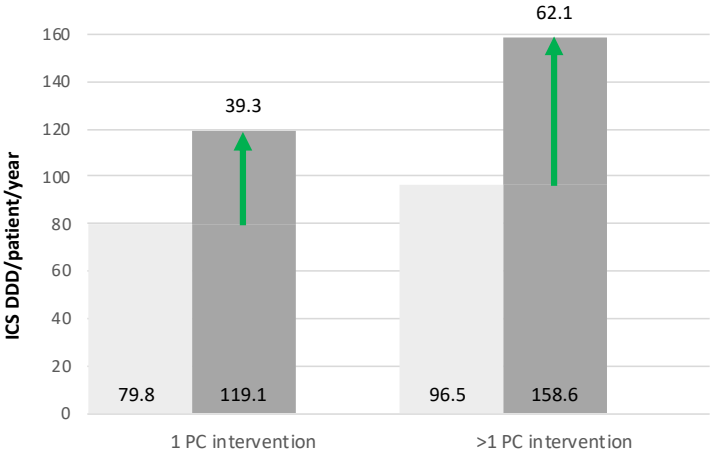


Figure 29 – Bar chart graphs showing results of the sensitivity analysis of ICS usage among difficult-to-treat asthma patients when stratifying by the number of pharmaceutical counseling (PC) interventions. The subgroup of patients who received 1 PC intervention (n=1119) had an evolution in ICS usage one year pre-intervention (light gray filled) from 79.8 to one year post-intervention (dark gray filled) of 119.1 Defined Daily Dose (DDD) per patient. This resulted in an increased usage of 39.3 DDD per patient. In addition, the subgroup of patients who received two or more interventions (n=231) showed an even a greater gain in ICS usage of 62.1 DDD per patient, going from 96.5 to 158.6.

IV.2.3.2. Impact on short-acting beta-agonist (SABA), antibiotic and oral corticosteroid (OCS) use

Difficult-to-control 5-40-year-old asthma patients who received a PC intervention in 2017 experienced a reduction in reliever use. The proportion of SABA users decreased from 48.0% in the year before the intervention to 46.2% in the year after the intervention, leading to a 1.8% (95% CI -2.0, 5.5%; p>0.05) lower proportion of SABA users (Figure 30). The proportion of antibiotic users was pronounced with 54.5% in the reference period. After the intervention a proportion of 52.7% was observed, leading to a 1.8% (95% CI -2.0,5.5%; p>0.05) lower proportion of antibiotic users compared with the reference period. Regarding the OCS use, there was a 1.1% (95% CI -1.1,3.3%; p>0.05) higher proportion of OCS users, going from 9.0% in the year before to 10.1% the year after the intervention.

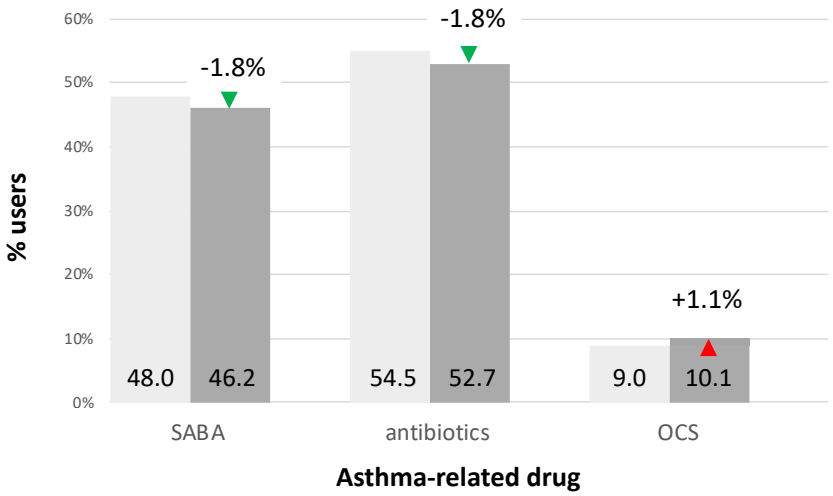


Figure 30 – Bar chart graphs representing the proportion of users of asthma-related drugs among difficult-to-control 5-40-year-old asthma patients who received at least one PC intervention in 2017. The proportion short-acting beta-agonist (SABA) users decreased from 48.0% pre-(light gray filled) to 46.2% post-(light gray filled) intervention, resulting in a 1.8% drop. The proportion antibiotic users decreased with 1.8%, from 54.5% one year before the intervention (light gray filled) to 52.7% one year after the (light gray filled). Regarding the recorded oral corticosteroids (OCS) use, the proportion users increased with 1.1% from one year before the intervention (light gray filled) to one year after the intervention (dark gray filled).

IV.2.3.3. Impact on biological use

The proportion of biological users was 0.22% when analyzing biological use in the year after the reference date among difficult-to-control 5–40-year-old asthma patients who had a PC intervention. In chronic ICS patients aged 5-40 years who never had an intervention (control group) on the other hand, the proportion of biological use was 0.30%. This indicates a 0.08% (95% CI -0.36%,0.23%; p>0.05) lower absolute proportion of biological use in the study population receiving at least one PC intervention compared with a similar, chronic ICS user group never receiving this PC intervention.

IV.2.4. Discussion

We conducted a nationwide, observational study to investigate whether real-world evidence can extrapolate the positive effect of PC interventions on adherence and asthma control in difficult-to-control asthma patients aged 5-40 years. As a first part, the adherence to asthma controller medication, represented by ICS usage per year and CTT ratio, significantly increased in the year after the intervention. Furthermore, a nominal decrease in the number of SABA and antibiotic users was observed compared to their own reference period. Additionally, a lower proportion of biological users was seen in the intervention group compared with a control group in the post-intervention period.

Our findings of an improved adherence to ICS and higher CTT ratio after PC intervention when using real-life data, is supporting earlier trial results on community pharmacy interventions.[108,204,211] However, in only one trial focused primarily on patients with difficult-to-control asthma, a community pharmacy intervention improved adherence.[203] The PC intervention in our study included an interview in which the community pharmacist assessed the patient's disease control, knowledge and expectations, inhaler technique and adherence. A follow-up interview was offered routinely, but only happened in 17%. Multiple interventions did lead to a higher increase in ICS usage, which

is in line with studies showing follow-up led to improved outcomes.[212,213] Adherence is of major importance because it will highly influence the expected pharmacological effect of that drug and the ability to treat the patient's disease.[96,97] Since adherence often remains low, improving adherence is fundamental to the success of asthma management.[65] A systematic review concluded that better adherence to asthma controllers is associated with fewer severe asthma exacerbations.[214] Better asthma control scores were also reported by patients with better ICS adherence in a prospective cohort study.[104] Non-adherence leads to adverse outcomes, as higher healthcare utilization and costs, and reductions in health-related quality of life.[215] Besides better adherence, the observed increase in CTT ratio also reflects improved asthma control.[208] An earlier observation study found an 0.1-unit increase in the ratio to result in a significant risk reduction of asthma exacerbations.[216] A higher CTT ratio is also associated with better asthma quality of life.[208]

The findings that PC interventions improved medication adherence and asthma control highlights the role of the pharmacist in improving patients' adherence in the healthcare system. Clinical pharmacist services delivered through telemedicine also positively impacted disease management and adherence.[217] With this increasingly central role that pharmacists play today, they could be seen as the guardian of adherence in chronic patients. This can be fulfilled in several ways, with or without using novel technologies. Regardless, the community pharmacist has the potential to further increase its impact on patients' health through such interventions.

Regarding reliever use, the amount of SABA users was found to be reduced in the pharmacist intervention group compared to their own reference period. These real-life observations are also in line with RCTs observing a decline in reliever medication use in the intervention arm.[108,203] This observed decline in reliever medication likely reflects the desirable improvement in asthma control. In literature, excessive use of SABA has been associated with insufficient controlled asthma, health-related costs and ultimately a higher mortality risk.[218,219] It has been shown that a significant number of these

health problems could be avoided. Appropriate use of maintenance medication is key in successful asthma management and optimal control reduces the need for reliever medication. In addition, the role of community pharmacies in supporting the asthma management plan was confirmed in a recent study.[220]

As the severity of asthma increases, the patient may need OCS therapy more often to adequately manage the disease and associated exacerbations.[221,222] The percentage of OCS users in our study population of 9-10% was much lower than found in a recent review about difficult-to treat and severe asthma patients reporting OCS use ranging from 45-90% over one year.[201] This can be explained by some differences with these studies such as the age difference between our study population aged 5-40 years and several studies with a mean age above 50 years, use of self-reported OCS use and a focus on patients with severe asthma, which is a 'truly severe' subgroup of around 20% of the difficult-to-treat patients.[221]

Moreover, the total percentage of biological users among the studied difficult-to-treat asthma patients was low during the entire follow-up period. This can partially be explained by the fact that omalizumab was the only reimbursed biological available on the Belgian market until the end of 2016. This means that it was being implemented in common pulmonary practice in 2017. The low observed use of these add-on drugs is also in line with their proven efficacy within a very specific target group of very severe asthma, the high costs and under-studied long-term side effects in a young to adult population.[33] Another reason for the low number can be explained by the fact that some biologicals need to be administered in hospital setting and BelPharData is not capturing hospital pharmacy claims. It is important to avoid adding biologicals to the treatment regimen of all difficult-to-control asthma patients. If the inhaler technique and adherence are optimized according to GINA guidelines, the vast majority of asthma patients in the general population can be treated with conventional therapy.[65,223] Although an apparently small absolute decline of 0.08% was observed in the proportion of biological users in cases compared with controls, avoiding unnecessary and potential ineffective initiation of biologicals may reduce substantial drug costs.[224] This is the

main objective of asthma management in this target population. By improving adherence to controller medication, the group of difficult-to-control asthma patients is reduced to a small group of patients with truly severe asthma where biologicals can be considered.

The main strength of this research is the large number of patients using ICS therapy registered in the database. This provided a recent and general picture of the current asthma burden on a national, Belgian level. We defined our study population as difficult-to-control asthma patients among chronic ICS users aged between 5-40 years. A higher prevalence of ICS usage in our population among patients aged 40 years and over suggested a higher proportion of COPD treated with ICS-containing therapy or asthma/COPD overlap, and therefore was considered not most representative for an asthma population.[65] Chronic ICS users per definition, would already be on ICS treatment the year before the intervention and continue at least until the year after. Therefore, they are representative for patients with asthma, which is a chronic disease. In addition, the database contains extensive information that offered the opportunity to observe various factors related to disease control. This included objective medication data, such as the use of reliever medication, medications treating exacerbations and add-on drugs. Additionally, using the BelPharData had the great advantage of observing a large amount of PC interventions and patient data in the general population. This database also created the opportunities to perform longitudinal analyses of unidentified asthma patients and their corresponding drug profile.
An important limitation of this study is the difficulty to clearly identify asthma patients, especially for a control group. The well-considered study design made it possible to not only to do an intra-patient comparison, taking their own period of time before the PC intervention as reference, but also to compare between patients receiving and not receiving the pharmacist intervention, to account for possible time-trend bias. The control patients used for the analysis of biologicals never received an intervention, meaning that there was no pharmacist assessment as to whether these ICS users were actually patients with asthma. These probably different patient groups make

comparative research challenging. Another limitation is ICS usage as a measure of adherence. We assumed that an increase in ICS usage reflected improved adherence through the PC intervention, but theoretically it could also be due to the need for a higher ICS dose in uncontrolled disease. Moreover, the observed differences in proportion of users of asthma-related drugs were rather small. This may be caused by a lower number of patients in the study population by limiting the definition to only difficult-to-control asthma patients among chronic ICS users aged 5-40 year. In addition, there was no control over the quality of the way the intervention was carried out, since this was a real-life observation. Although, participating pharmacists were offered training, there is undoubtedly a difference in the way pharmacists conduct the counseling interviews and how much time and effort they had invest in it. Nevertheless, the study results suggest that the intervention generally contributes to an average improvement in the asthma patients' health. Finally, there are some limitations on using CTT ratio as a measure for adherence and asthma control. First, a short beta-agonist might be used before exercising, which reflects a good health and disease control. This will overestimate the use of reliever medication taken for poor asthma control and so underestimate the CTT and asthma control. Second, there will be asthma patients on low dose ICS combined with the LABA formoterol as 'maintenance and rescue therapy'. This would mean that the ICS and LABA do not always reflect a good asthma control, since they could also be used as relievers, but would sometimes have been misclassified as controllers when calculating a CTT ratio. Since 2019, GINA guidelines recommends all individuals with asthma receiving ICS-containing controller treatment with for mild asthma as-needed low dose ICS combined with the LABA formoterol.[65,68] However, this was not yet the case in 2017, when our data was collected.

In summary, the results of this real-world observational study indicate that PC intervention improves adherence to ICS controller therapy and asthma control in difficult-to-treat asthma patients. This study suggests that community pharmacist counseling benefits the management of patients' asthma on a

national level and supports a follow-up interview, especially in all difficult-to-control asthma patients.

V. Discussion and Conclusion

To improve response to inhaled corticosteroids (ICS), host factors, drug-related and environmental factors influencing treatment response, were analyzed. Host factors included characterization of disease type and identification of individuals at risk for the development of World Trade Center (WTC)-related lung injury. Early blood biomarkers, such as high eosinophils and low IgA, were found to be risk factors for irritant-associated lung injury years later. Additionally, lower spirometric values and respiratory symptoms were associated with ICS/LABA treatment. As drug-related factors studied, an improved adherence among ICS-treated individuals resulted in better asthma control. Furthermore, ICS treatment among WTC-exposed individuals led to an average 2.4 mL/year improvement in FEV_1 decline compared with non-treated. Finally, regarding environmental factors, we observed that an increased level of WTC exposure was associated with ICS/LABA treatment shortly after 9/11 and active firefighting later in the follow-up. In addition, smoking was a predictor of a poorer response to ICS treatment on FEV_1 decline.

V.1. Effect of ICS treatment on FEV_1 decline

An average improvement in FEV_1 slope of 2.4 mL per year resulting from ICS-containing treatment, might seem small. However, when putting it in relevance of the average age-related decline, a proportion of 2.4 mL over an age-related decline of 25 mL to 30 mL is about an 8-10% slowing of longitudinal FEV_1 loss, which might be clinical meaningful. Furthermore, it is the overall average result of the entire study population. This means on an individual level, there will be people with worsening accelerated decline and there will be people with a far more pronounced beneficial effect, where ICS was able to close the gap again after initial lung function loss. This was clear when analyzing the average change in FEV_1 post-initiation compared with pre-initiation stratified by initiation time related to the 9/11 disaster. Initiation of ICS between 11 September 2001- 10 September 2005 led to a pronounced improvement in FEV_1 decline, whereas initiation between 11 September 2009- 10 September 2017 was not effective. This remarkable finding is of

clinical relevance in today's practice, almost 20 years after the 9/11 disaster. If ICS-containing treatment does not slow FEV_1 decline in a subset of patients developing COPD due to accelerated FEV_1 decline, research into alternative treatments seems appropriate.

V.2. Host-intrinsic predisposition

We assessed whether biomarkers as high blood eosinophils and low IgA could predict a beneficial response on ICS treatment. Low IgA tended to be predictive, but blood eosinophils were not predictive. The heterogeneity of clinical presentation and disease course makes the evaluation of treatment response difficult. Identifying biomarkers to better predict treatment response is a crucial step to improve the selection of a treatment matching the individual patient's needs. We observed high eosinophils and low IgA were associated with elevated risk on lung injury years later. Also, elevated IgE and IL-4 were associated with post-9/11 lung injury. The finding that high eosinophils were already higher pre-9/11 suggest the presence of patient-intrinsic susceptibility to developing obstructive airway disease. Similarly, low IgA drawn soon after 9/11 was identified as a risk factor for the development of lung injury years later. Our longitudinal observation reveals that the FEV_1 of this low IgA subgroup was already lower pre-9/11 and remained lower throughout follow-up after 9/11. This can also suggest a patient-intrinsic susceptibility for patients with low IgA as a result of an intense, but transient inflammatory response to inhaled particulates.

Eosinophils are the best studied biomarker in obstructive airway diseases, with testing of eosinophils count in blood being widely available. Elevated blood eosinophil count is a biomarker of increased exacerbation rate after ICS withdrawal in COPD patients.[154,225] Although blood eosinophil count appears to be a promising biomarker for corticosteroid response in COPD, the selection of patients with a beneficial response to specific interventions is generally still unsatisfactory.[83,189,226] There might also be underlying genetic factors associated with the inflammatory response to WTC exposure, explaining the difference in response to ICS for the treatment of

post-9/11 lung injury. Genetic variations also influence the response to ICS treatment, which has been examined by genome wide association studies (GWAS) examining ICS response.[191,227] In COPD, the identification of the pharmacogenomic factors determining the response of patients to ICS may guide its use of clinical practice.[192]

V.3. Environmental factors

The environmental factors are modifiable components that can alter the intensity of the treatment effect. We identified smokers having a poorer ICS response on FEV_1 trajectory. This corresponds with a reduced ICS effect when asthma and COPD patients continued smoking.[186,187,228] This reduced effect could be extrapolated to other noxious particles, such as chronic occupational exposures. Active firefighting might have acted as a modifier of ICS response, since active firefighting duty became stronger associated with ICS/LABA treatment the longer after 9/11.

V.4. Drug-related factors

As a drug-related factor, improved adherence to ICS after PC intervention when using real-life pharmacy claims data, led to a beneficial response to ICS in asthma patients. The results are in line with earlier trial results on community pharmacy interventions.[108,211,204,110] This confirms our hypothesis that adherence is an important factor for ICS response as it affects the expected pharmacological effect of the drug and thus the ability to treat the underlying disease.[97] Since adherence is a remaining hurdle in inhaler treatment, improving the adherence lead to more successful management of obstructive airway diseases, such as asthma.[8] Better asthma control scores were also observed in prospective research in patients with better ICS adherence.[104]

Interestingly, in the WTC cohort we found that individuals with a favorable response of ICS on FEV_1 decline had a shorter treatment duration compared with non-responders. In this cohort, this observed difference may be due

confounding by indication. Individuals with improved FEV_1 and symptoms, might have discontinued their treatment. In this subgroup analysis to define ICS responder was done on individuals who initiated ICS in the first 4 years after 9/11, there might also be individuals with a different, more acute disease endotype. In that case, a shorter duration of treatment was justified. In contrast, in asthma patients, most patients require continued treatment as asthma is a chronic disease.

V.5. ICS treatment on different outcomes

The responses of ICS-containing treatments have been studied on different outcomes. We studied lung function decline as primary outcome, which serves as a risk for mortality.[229] The choice of FEV_1 trajectory as the outcome was also based on availability of robust longitudinal data in this population. A proportion of WTC-exposed firefighters is experiencing a continuous accelerated decline in lung function without having a clear indication for inhaler treatment following asthma or COPD guidelines for the management for asthma or COPD. Therefore, our research findings are important for guiding the decision-making process in clinical practice in these patients. An increased frequency of pulmonary exacerbations was associated with accelerated FEV_1 decline.[40,41] Since ICS treatment is effective in preventing exacerbations,[85,88,230] ICS use may reduce accelerated lung function decline.[231] However, real-life data supporting that theoretical logic is scarce. The effect of pharmacotherapy on FEV_1 decline has been debated for over 20 years.[92] An important insight gained is that not only the trajectory of accelerated lung function decline can lead to COPD, but also the trajectory of reduced lung growth but age-related lung function decline.[31] However, we focused on accelerated FEV_1 decline since at study entry WTC-firefighters had an average FEV_1 % predicted of over 100%.[46] Analyses from TORCH and SUMMIT trials showed an effect of ICS monotherapy resulting in an improvement of FEV_1 decline of 13 mL/year and these from the SUMMIT 8 mL/year compared with placebo over the relatively short time span of the trials.[93,94] In TORCH ICS/LABA combination therapy had an

even greater beneficial effect of 16 mL/year compared with placebo.[93] Our observed average effect of ICS of an improvement of 2.4 mL/year on FEV_1 decline from our large observational cohort study with long term follow-up is less pronounced than these randomized placebo controlled trials. This is not a surprise since these trials studied populations with chronic, ongoing exposure and inflammation by smoking, which are different than the previously healthy WTC-exposed firefighter cohort with a proportion of ever smokers around 25%. A recent systematic review concluded that trials up to one year of follow-up were more likely to report an increase in FEV_1, with the general trend favoring ICS-containing medications compared to non-ICS-containing medications.[227] Studies with more than a year follow-up were more likely to report a decline in FEV_1 with little evidence of a treatment difference between ICS and non-ICS containing medications. These findings highlight the importance of sufficient long follow-up, which was certainly the case in our studies with over 16 years follow-up.

We chose asthma control as another outcome to assess the effect of community pharmaceutical counseling (PC) interventions. Asthma control can be measured by respiratory symptoms and reliever use, whether or not using a standardized questionnaires and spirometry result. Poor symptom control is a proxy for the risk of worse outcomes, such as increased need for medications, hospitalization and death. In our study, the ratio of controller-to-total (CTT) was calculated using pharmacy claims data before and after the PC intervention. This ratio reflects the proportion of controller medications by total asthma medication, including reliever therapy.[208,209] The higher this ratio, the better the expected asthma control. An advantage of CTT is its objective measuring which does not require additional participation, testing or time from the patient. The downside might be misclassification produced by poor adherence to dispensed medications. However, this would not be the preferred approach in US populations where automatic refill is standard, while we conducted this study in Belgium, where prescriptions need to be filled at the pharmacy. On the other hand, a short beta-agonist might be used before exercising, a manifestation of health. This will overestimate the use of reliever medication taken for poor asthma control and so underestimate the CTT and

asthma control. Another limitation of using the CTT is the fact that 2019 asthma guidelines added as-needed low dose ICS combined with the long-acting beta-agonist (LABA) formoterol for the treatment of mild asthma.[8,68] This would mean that the ICS and LABA do not reflect a good asthma control, since they were being used as relievers, but would have been misclassified as controllers when calculating a CTT ratio. However, this was not yet the case in 2017, when our data was collected.

Other outcomes are mortality and exacerbation rate. Mortality rate, which is a hard end point, can be directly related to respiratory disease, but it can also be due to comorbidities influencing mortality independently. The IMPACT and ETHOS trials, studying COPD with exacerbation history, showed that triple therapy caused a reduction in all-cause mortality compared with LAMA/LABA but not with ICS/LABA.[86,87,232] Analyses of databases suggest an important role for ICS containing therapies in reducing mortality in asthma, which is challenging to proof in prospective research.[90,91] Patients selected with more severe disease, such as history of exacerbations, are expected to have a higher number of expected deaths associated. This study design will serve to the aim of proving a reduction in mortality. In the ETHOS trial, only COPD patients with a history of exacerbations were included to proof mortality effect.[86] Since the WTC cohort fortunately has a low death rate, it would be difficult to study mortality as an outcome. Similarly, this is the case in asthma nowadays, whereas the improvement of controller therapies led to a lower mortality rate.[91] Moreover, exacerbation rate has also been studied as an outcome, with a favorable effect of ICS/LABA seen in COPD patients.[85] In asthma, ICS/LABA combination was found to improve overall asthma control, including symptoms, lung function and reduced exacerbations.[88]

V.6. Strengths

The WTC-exposed cohort has the advantage of environmental exposure at a specific, well-defined time point. This offered us the unique opportunity to investigate the role of time between exposure and initiation of therapy in

response to treatment. Accurately estimating exposure is often challenging in other cohorts, such as for smoking. This can also be complicated by a long time window in chronic exposures. Another strength of the WTC cohort is the wealth of longitudinal data with little loss to follow-up, reducing the potential for selection bias. Using this longitudinal data, we could analyze spirometry and symptoms pre- but also post-initiation of treatment. In RCTs such as TORCH and SUMMIT, on the other hand, there are no data prior to baseline assessment at trial entry. Also, the duration of follow-up without significant dropout is quite short.[93,94] Another limitation is that these RCTs were not powered for the analysis of FEV_1 decline because lung function was prespecified as a secondary outcome.[85,233] Since the treatment effect on the primary endpoint was not statistically significant, the statistical testing of FEV_1 decline should be interpreted as descriptive only. Furthermore, real-life observational studies analyzing the effect of ICS treatment on lung function trajectory are lacking. Our research estimated the effect of ICS treatment on FEV_1 trajectory using longitudinal, observational data.

V.7. Limitations

There is a limitation in generalizability with respect to the WTC cohort analyzed, which contained only males, who were exposed to WTC dust and who were active and healthy before 2002 at the time of FDNY enrollment. This implies that the results should be interpreted with caution for women or individuals with comorbidities that would preclude FDNY employment. Also, extrapolating the results of individuals exposed to this unique, massive dust exposure of 9/11 to lung injury from other causes, such as air pollution, biomass exposure or cigarette smoking, should be done with caution.

Furthermore, there are some limitations to the completeness of data and data availability for observational research. Studying biomarkers in observational cohorts, the analyzed are limited on the number of blood draws done and stored serum. Despite standard blood tests including eosinophils are incorporated in the WTC monitoring exams, there are more lab values missing

than spirometries or questionnaires. Some possible explanations include that labs are sometimes scheduled on a different day and therefore might get forgotten. Also, blood draws are a little more invasive and some people might have anxiety to perform this test. In addition, there is a chance of uninterpretable lab results due to pre-analytic errors, such as wrong storage of the specimen, or technical errors to perform the test, such as blood cloths in the sample. This explains the larger numbers of missing blood eosinophils. For specific tests, such as IgA and IL-4, it is even more obvious that the number of patients with these tests, is low. This made it more challenging to identify biomarkers. We ended up with a very low number of people with IgA tested among the individuals having sufficient longitudinal spirometry measurement. This resulted in low power to proof an association between low IgA and ICS response. Finally, there might be unmeasured confounding, as in all observational research, due to the lack of (detail in) some data. Regarding active firefighting, we included active duty vs retired status as a covariate for the initiation for ICS-containing treatments. However, to study the actual influence of active firefighting as an environmental factor, we would have a surrogate of firefighting exposure. This could have been the number fires or frequency firefighters are called to a big fire, for example. Other variables that would ideally be of better quality are smoking, including a more accurate amount of pack-years. Another variable is adherence to treatment, which is probably overestimated as it is mainly based on pharmacy claims data with automated refills trough mailing. These would only stop if firefighters acknowledged they were not using the medication sent by mail during a monitoring exam. Therefore, we used a threshold of 2-year treatment duration in a lot of the analyses.

Other limitations to the data availability, are the medication data sources, as in most pharmaco-epidemiologic research. First, data on pharmacy claims, billed through the WTC health program, was not electronically available until December 2006. The claim's prescription date is the date a medication was filled, and is not necessarily the date of treatment administration, as assumed in this study. We used prescription refill as a surrogate marker for medication

adherence, but we had no information if and how patients took their inhaler or medication in the 9/11 cohort. As a second source, we used data from an automated search through EMR notes describing medication use. This data source does not capture every single time medication was taken or dispensed, and thus, will be specific but not sensitive in estimating the duration of treatment exposure.

Also, the medication adherence calculated was dependent on the data sources available. As adherence measures in the Belgian nationwide study, we used cumulative defined daily dose (DDD)s over a year period. We compared the cumulative DDDs of ICS, being asthma controller medication, per patient one year before to the year after a pharmaceutical counseling intervention. Analyzing cumulative DDDs is analogous to proportion days covered, a commonly used parameter for adherence from pharmacy claim databases.[181] If the cumulative DDDs of controller medication improves, it can be used as a surrogate for adherence to this maintenance treatment. Since we did not have data on an individual level, another limitation is that we cannot guarantee that the gain in cumulative DDDs was exclusively due to increased frequency of their ICS dose (indicative for an improved overall adherence to ICS) and not influenced by higher doses of ICS prescribed (indicative for worsening severity).

Finally, there are also limitations to the inverse probability of treatment weighting (IPTW) model used to estimate the overall effect of ICS on lung function trajectory. This type of propensity score method used for estimating the treatment effect, also has its limitations. Propensity scores are valuable in controlling for measured confounding in observational studies of medical treatments or risk factors. However, this propensity score method cannot control for unmeasured confounding.[197] This might explain why the ICS effect resulted from the IPTW model differs from the effect estimated by the pre-post initiation analyses. Despite the weighting, the treated and non-treated groups had a different average FEV_1 throughout follow-up. To check if a different baseline FEV_1 played a role in the calculated treatment effect using IPTW, we also performed an analysis matched on baseline covariates, during

the first 4 years post-9/11. Another challenge using IPTW, was estimating the use of other medication that could have influence on the FEV_1 trajectory, such as oral steroids and LABAs. We added the use of those medications in the propensity score as a time-varying confounder. Moreover, choosing a time period to perform the time-varying modeling by IPTW was done arbitrary. We chose a 2-year period, assuming patients would have a monitoring exam every 2 year on average. Unfortunately, we still had to deal with missing data in those intervals, mainly for respiratory symptoms and blood eosinophil counts in particular intervals. To deal with this missing data, we used imputations. Unfortunately, there were still many missing eosinophils counts in a certain time period for which we performed sensitivity analyzes without eosinophils in the propensity score, which did not change the overall result. In future research it would be important to carefully estimate the adherence to dispensed medicines. Preferably this would not only include the treatment exposure that is being studied, but all comedications that potentially alter the outcome as well.

V.8. Conclusions

Host, environmental and drug-related factors predictive for an optimal response to ICS are identified. Individuals at risk for treatment of post-9/11 lung injury have a lower baseline FEV_1 and worse respiratory symptoms. Also, the potentially more reversible disease endotype developed early after 9/11 seems most ICS-responsive. Furthermore, blood biomarkers, such as eosinophils and IgA, drawn soon after irritant exposure may serve as a surrogate for host-intrinsic predisposition to develop irritant-associated lung injury years later. However, these biomarkers did not significantly predict response of ICS on accelerated lung function decline. As an environmental factor, continued occupational exposures may reduce the effect of response to ICS, when acting as modifiers. Among the drug related factors, an improved adherence leads to a beneficial ICS response, reflected in better disease control. Finally, ICS treatment among WTC-exposed individuals leads to a modest improvement in yearly FEV_1 decline compared with non-treated.

To further improve the selection of a treatment to the individual patient's needs, more determinants of the multifactorial interaction resulting in an overall ICS response need to be unraveled trough big, longitudinal data analyzes.

VI. BROADER INTERNATIONAL CONTEXT, RELEVANCE, AND FUTURE PERSPECTIVES

VI.1. Broader, international perspective – generalizability

The 9/11 disaster is an exceptional disaster, but it was luckily accompanied by an excellent monitoring program and meticulous data collection. This allowed studying research hypotheses in a very well-phenotyped cohort with well-documented exposure time. The very low death rate in the FDNY WTC-exposed cohort resulted moreover in many person years of longitudinal data and minimized risk of survival bias. It remains a challenge to proof causality of 9/11 and health effects as there is no similar non-WTC-exposed FDNY cohort as a comparison group. The observation of an acute drop in FEV_1 strongly suggests an impact of the disaster on the lower respiratory system.[29,46] Our research findings may also be useful in predicting health consequences in future events exposing individuals to dust produced by catastrophes and in certain occupations. Additionally, the effect of active firefighting by itself is also important to take into account, since it may act as a modifier for ICS response. Firefighting duty has found to be associated with decreased pulmonary function.[234] In that perspective our findings might be important for all firefighters, even those without WTC exposure.

Some key messages based on our research can be taken to the field of obstructive lung diseases. First, to study lung function decline, a long-term follow-up is recommended. This is also based on a systematic review examining ICS response on lung function decline, observing different effects in shorter follow-up studies (less than one year) compared with the effects in longer follow-up studies.[227] Additionally, in a subgroup analysis, younger age and lower baseline FEV_1 % predicted were identified as host factors and never smoking as an environmental factor, were associated with beneficial ICS response on FEV_1 trajectory. Blood eosinophils and IgA were considered potential biomarkers indicative of host susceptibility, but did not significantly identify ICS responders after WTC exposure. Given the limitations regarding the availability of blood data and the lack of statistical power, we cannot state these findings are final. Therefore, more research is needed to further explore these associations of potential biomarkers and lung injury. Ideally, there should always be a systematic baseline drawn of potential blood biomarkers,

including eosinophils, IgA, IgE, IL-4, prior to the initiation of ICS. It also highlights the challenge but continued importance of biomarker research and in expanding to all factors that contribute to the ultimate treatment response. Therefore, big data collections from treated patients, including potential biomarkers, remain essential to study the interplay of host, environmental and drug-related factors.

Inverse probability of treatment weighting (IPTW) was the method used to analyze ICS effects from the observational data of the WTC cohort. It is a method that is gaining importance, since the value of observational research and real-world data analyses is growing. Despite the complexity and limitations, it reduces selection bias by equating groups based on time-varying confounders when analyzing treatment effects in observational data.[196] In addition, IPTW could also be applied to study any outcome of interest, such as patient reported outcome measures. In the absence of real-world studies on the effects of pharmacotherapy in asthma and COPD, this method could also be applied to cohorts of patients with asthma or COPD.

VI.2. Socio-economic impact

Medication adherence remains a persistent challenge within respiratory care. Since primary care physicians and pulmonologists often rely on each other, additional support from the pharmacist has an important place in the healthcare system. Pharmaceutical counseling interventions are found to be effective in improving controller adherence and asthma control. This leads to a better health outcome and consequently a decrease in the economic burden. Additionally, clinical pharmacist services delivered via telemedicine, mainly telephonic interactions, had a positive impact on disease management and adherence.[217] With this increasing central role pharmacists are playing nowadays in Anglo-Saxon countries and beyond, they can be seen as the guardian of medication adherence, especially in chronic respiratory patients. This role can be fulfilled in various ways, with or without using novel

technologies. Either way, the community pharmacist has the potential to have even more impact on patient's health through such interventions.

VI.3. Clinical relevance

WTC-exposed firefighters with accelerated FEV_1 decline especially seemed to benefit from ICS treatment when they initiated shortly after WTC exposure. This may also have therapeutical consequences for the current management of WTC-related lung injury. Physicians who treat WTC-exposed patients might consider an add-on treatment or therapeutic switch in certain individuals. Those could include patients with ongoing accelerated FEV_1 decline who do not experience a clinical benefit, reflected by ongoing respiratory symptoms, frequent exacerbations or low quality of life. Given the observed association of IL-4 with obstructive airways disease, therapies targeting IL-4 may be an alternative treatment. Dupilumab, an IL- 4/IL-13 inhibitor, would be a reasoned choice as it showed a beneficial effect on lung function and exacerbations in asthma patients.[235] Studies to further exploring this biological are being conceptualized.

VI.4. Future

If exposure cannot be reduced to one event, or if an insidiously declining lung function pattern is not directly related to respiratory symptoms, identifying response to treatment can be challenging. Longitudinal monitoring through wearable devices and app- /web-based platform could collect all relevant, possible time-varying factors. Continuous development of new technologies and tools is shifting healthcare for the next generation respiratory patients towards e-health. Those patients are grown up with smartphones and electronic platforms, so that these technologies could be used. Based on our findings, respiratory symptoms, adherence to treatment and exposure to noxious particles such as smoking or occupational exposures are of interest. FEV_1 as an important factor could be added by a handheld spirometry screening. In combination with biomarker data, this could facilitate

longitudinal data collections and the identification of more disease phenotypes and endotypes. In chronic patients with obstructive lung diseases, those new technologies could become a standard follow-up tool as part of their disease management.

The role of inhaled corticosteroids could extend in the future to areas of application outside the WTC-exposed cohort or obstructive lung diseases. In severe pneumonia, preliminary findings that early treatment with a combination of an inhaled corticosteroid and a beta-agonist reduces the risk of respiratory failure are being examined by a multicentric clinical trial.[236] Furthermore, inhaled corticosteroid treatment has potentially beneficial effects in COVID-19, with is further investigated to date in different trials all over the world.[237–239]

VII. SUMMARY - SAMENVATTING

VII.1. Summary (EN)

Treatment response is the result of a complex interaction between host factors, environmental factors and drug-related factors. Those factors were studied separately in order to obtain the best possible picture of the optimal response to inhaled corticosteroids (ICS).

First, we characterized the type of lung injury of World Trade Center (WTC)-exposed firefighters, identifying individuals and their characteristics. In **Chapter III.1**, host factors associated with prolonged ICS / long-acting beta-agonist (LABA) treatment were body mass index, lower first post-11 September 2001 (9/11) spirometry measurements and first post-9/11 modified Medical Research Council (mMRC) dyspnea score. These observations were confirmed in the longitudinally analyses of **Chapter III.4** with as host characteristics lower forced expiratory volume in 1 second (FEV_1) and symptoms of wheeze and dyspnea associated with prolonged ICS/LABA treatment. Worse baseline FEV_1 and respiratory symptoms are host factors that predict response to ICS (**Chapter IV.2**).

Regarding biomarkers, a higher blood eosinophil count and increase in IL- 4 were associated with an increased risk of irritant-induced airflow obstruction (**Chapter III.2)**. Furthermore, low immunoglobulin A (IgA) soon after WTC exposure in **Chapter III.3** was associated with lower longitudinal FEV_1 measurements, increased risk of airflow obstruction and increased antibiotic treatment. However, blood eosinophils and IgA did not significantly predict the response to ICS on lung function decline, but low IgA tends to a beneficial response (**Chapter IV.2**).

Second, the environmental factor associated with prolonged ICS/LABA treatment was high intensity WTC exposure defined by arrival the morning of 9/11 (**Chapter III.1)**. In **Chapter III.4,** this association was only observed when treatment was initiated early after 9/11, leading to the conclusion that determinants of treatment response may change over time.

Last, drug-related factors associated with response to ICS treatment were assessed. In a longitudinal study in **Chapter IV.1**, ICS treatment improved lung function decline in individuals with WTC-related lung injury. This improvement was more pronounced when WTC-exposed firefighters were more adherent to ICS. Pharmaceutical counseling interventions, analyzed through nation-wide pharmacy data in **Chapter IV.2**, led to a marked improvement in the adherence of asthma patients to ICS. This also resulted in an improved controller-to-total-ratio and a trend towards a reduction in the number of patients requiring rescue inhalers and antibiotics, indicating an improvement in asthma control and a lower exacerbation rate.

In conclusion, to improve response to ICS, host factors and drug-related factors were studied. The former included characterization of disease type and identification of individuals at risk, and the latter included studying the impact of adherence. First, lower lung function and worse respiratory symptoms are host factors associated with ICS/LABA treatment, of which a lower FEV_1 predicts a better response to ICS. Subsequently, blood biomarkers, such as eosinophils and IgA, drawn soon after irritant exposure may serve as a surrogate for the patient-intrinsic predisposition to develop irritant-associated lung injury years later. However, these biomarkers do not predict the response of ICS on lung function decline, but low IgA tends to a beneficial response. Finally, improved adherence to ICS treatment leads to reduced lung function decline and better asthma control.

VII.2. Samenvatting (NL)

De respons op behandeling is het resultaat van een complex samenspel tussen gastheerfactoren, omgevingsfactoren en geneesmiddelgerelateerde factoren. Deze factoren werden afzonderlijk bestudeerd om een zo goed mogelijk beeld te krijgen van de optimale respons op inhalatiecorticosteroïden (ICS).

Ten eerste hebben we het type longaandoening van aan 11 september 2001 (9/11)-blootgestelde brandweermannen gekarakteriseerd door individuen en hun kenmerken te identificeren. In **Hoofdstuk III.1** waren gastheerfactoren geassocieerd met langdurige behandeling met ICS/langwerkende bèta-agonisten (LABA), de body mass index, lagere eerste post-9/11 spirometriewaarden en gemodificeerde *Medical Research Council* (mMRC) score voor kortademigheid. Deze waarnemingen werden bevestigd in de longitudinale analyses van **Hoofdstuk III.4** met als gastheerkarakteristieken een lagere éénsecondewaarde en symptomen van piepende ademhaling en kortademigheid die geassocieerd waren met langdurige ICS/LABA behandeling. Slechtere baseline éénsecondewaarde en ademhalingssymptomen zijn gastheerfactoren die de respons op ICS voorspellen (**Hoofdstuk IV.2**).

Wat betreft bloedbiomarkers waren een hoger aantal bloed-eosinofielen en een toename van IL-4 geassocieerd met een verhoogd risico op sommige endotypes van irritatie-geïnduceerde luchtwegobstructie (**Hoofdstuk III.2**). Bovendien was verlaagd immunoglobuline A (IgA) kort na 9/11 blootstelling in **Hoofdstuk III.3** geassocieerd met een lagere longitudinale éénsecondewaarde, een verhoogd risico op luchtwegobstructie en meer antibioticabehandeling. Blood eosinofielen en IgA werden echter niet significant bevonden in het voorspellen van de ICS respons op longfunctie achteruitgang, maar verlaagd IgA neigde wel tot een gunstige respons. (**Hoofdstuk IV.2**).

Ten tweede was blootstelling aan 9/11 met hoge intensiteit, gedefinieerd door aankomst de ochtend van 9/11, de omgevingsfactor geassocieerd met langdurige ICS/LABA behandeling (**Hoofdstuk III.1**). In **Hoofdstuk III.4**

werd deze associatie alleen bevestigd als de behandeling kort na 9/11 werd gestart, wat leidde tot de conclusie dat determinanten van respons op behandeling in de loop van de tijd kunnen veranderen.

Als laatste werden geneesmiddelgerelateerde factoren geassocieerd met de respons op ICS behandeling, beoordeeld. In een longitudinale studie in **Hoofdstuk IV.1**, verbeterde ICS behandeling de achteruitgang van de longfunctie bij personen met 9/11-gerelateerde longaandoeningen. Deze verbetering was meer uitgesproken wanneer de brandweermannen meer therapietrouw waren. Farmaceutische counseling-interventies, geanalyseerd aan de hand van nationale apotheekgegevens in **Hoofdstuk IV.2**, resulteerden in een duidelijke verbetering van de therapietrouw aan ICS in astmapatiënten. Dit resulteerde ook in een verbeterde *controller-to-total* ratio en een trend in de richting van een vermindering van het aantal patiënten dat noodmedicatie en antibiotica nodig heeft, hetgeen duidt op een verbetering van de astmacontrole en een daling in exacerbaties.

Concluderend dat, ter verbetering van de respons op ICS, gastheerfactoren en geneesmiddelgerelateerde factoren werden bestudeerd. De eerste betrof karakterisering van onderliggende ziekte en identificatie van personen die risico lopen, en de laatste betrof het bestuderen van de impact van therapietrouw. Ten eerste zijn een lagere longfunctie en meer respiratoire klachten, gastheerfactoren die geassocieerd zijn met ICS/LABA behandeling, waarvan een lagere éénsecondewaarde voorspellend is voor een betere respons op ICS. Vervolgens kunnen bloedbiomarkers, zoals eosinofielen en IgA, kort na 9/11 blootstelling afgenomen, dienen als een surrogaat voor de intrinsieke aanleg van de patiënt om jaren later een longaandoening te ontwikkelen. Deze biomarkers voorspellen echter niet de respons van ICS op longfunctie achteruitgang, hoewel IgA neigt naar een gunstige respons. Ten slotte leidt een betere therapietrouw aan ICS behandeling tot een verminderde achteruitgang van de longfunctie en een betere astma controle.

VIII. List of Peer-Reviewed Publications

Putman B, Lahousse L, Goldfarb DG, Zeig-Owens R, Schwartz T, Singh A, Vaeth B, Hall CB, Lancet EA, Webber MP, Cohen HW, Prezant DJ, Weiden MD. Factors Predicting Treatment of World Trade Center-Related Lung Injury: A Longitudinal Cohort Study. IJERPH. 2020 Dec 4;17(23):9056.

Vanoverschelde A, van der Wel P, **Putman B,** Lahousse L. A pragmatic randomized controlled trial to improve inhaler technique using mHealth. Clin Transl Allergy. 2020 Dec;10(1):59.

Putman B, Lahousse L, Singh A, Zeig-Owens R, Hall CB, Fazzari MJ, Schwartz T, Webber MP, Cohen HW, Prezant DJ, Weiden MD. Dyspnea and Inhaled Corticosteroid and Long-acting β-Agonist Therapy in an Occupational Cohort: A Longitudinal Study. Annals ATS. 2020 Jun;17(6):770–3.

Putman B, Lahousse L, Zeig-Owens R, Singh A, Hall CB, Liu Y, Schwartz T, Goldfarb D, Webber MP, Prezant DJ, Weiden MD. Low serum IgA and airway injury in World Trade Center-exposed firefighters: a 17-year longitudinal study. Thorax. 2019 Dec;74(12):1182–4.

Putman B*, Liu C*, Singh A, Zeig-Owens R, Hall CB, Schwartz T, Webber MP, Cohen HW, Fazzari MJ, Prezant DJ, Weiden MD. Abnormalities on Chest Computed Tomography and Lung Function Following an Intense Dust Exposure: A 17-Year Longitudinal Study. IJERPH. 2019 May 13;16(9):1655.

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Putman B, Zeig-Owens R, Singh A, Hall CB, Schwartz T, Webber MP, Cohen HW, Prezant DJ, Bachert C, Weiden MD. Risk factors for post-9/11 chronic rhinosinusitis in Fire Department of the City of New York workers. Occup Environ Med. 2018 Dec;75(12):884–9.

Singh A, Liu C, **Putman B,** Zeig-Owens R, Hall CB, Schwartz T, Webber MP, Cohen, HW, Berger KI, Nolan A, Prezant DJ, Weiden MD. Predictors of

Asthma/COPD Overlap in FDNY Firefighters With World Trade Center Dust Exposure. Chest. 2018 Dec;154(6):1301–10.

Zeig-Owens R, Nolan A, **Putman B,** Singh A, Prezant DJ, Weiden MD. Biomarkers of patient intrinsic risk for upper and lower airway injury after exposure to the World Trade Center atrocity: Biomarkers of Risk After WTC Exposure. Am J Ind Med. 2016 Sep;59(9):788–94.

Kwon S, **Putman B,** Weakley J, Hall CB, Zeig-Owens R, Schwartz T, Olivieri B, Singh A, Huie M, Morrison D, Webber MP, Cohen, HW, Kelly KR, Aldrich, TK, Nolan A, Prezant DJ, Shohet MR, Weiden MD. Blood Eosinophils and World Trade Center Exposure Predict Surgery in Chronic Rhinosinusitis. A 13.5-Year Longitudinal Study. Annals ATS. 2016 Aug;13(8):1253–61.

Depuydt P, **Putman B,** Benoit D, Buylaert W, De Paepe P. Nursing home residence is the main risk factor for increased mortality in healthcare-associated pneumonia. Journal of Hospital Infection. 2011 Feb;77(2):138–42.

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