Low serum IgA and airway injury in World Trade Center-exposed firefighters: a 17-year longitudinal study

Barbara Putman,[1,2] Lies Lahousse,[2] Rachel Zeig-Owens,[3,4] Ankura Singh,[3,5] Charles B Hall,[4] Yang Liu,[3,5] Theresa Schwartz,[3,5] David Goldfarb,[3,5] Mayris P Webber,[3,4] David J Prezant,[3,5] Michael D Weiden[1,3]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2019-213715).

[1]Department of Medicine, New York University School of Medicine, New York, New York, USA
[2]Department of Bioanalysis, Ghent University, Gent, Belgium
[3]The Bureau of Health Services, Fire Department of the City of New York, Brooklyn, New York, USA
[4]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, USA
[5]Department of Medicine, Montefiore Medical Centre, Bronx, New York, USA

Correspondence to
Dr Michael D Weiden, Department of Medicine, New York University School of Medicine, New York, NY 10016, USA;
Michael.Weiden@nyumc.org

Received 14 June 2019
Revised 19 August 2019
Accepted 17 September 2019
Published Online First 14 October 2019

To cite: Putman B, Lahousse L, Zeig-Owens R, *et al*. *Thorax* 2019;**74**:1182–1184.

ABSTRACT

Serum IgA ≤70 mg/dL (low IgA) is associated with exacerbations of chronic obstructive pulmonary disease. The association of low IgA with longitudinal lung function is poorly defined. This study included 917 World Trade Center (WTC)-exposed firefighters with longitudinal spirometry measured between September 2001 and September 2018 and IgA measured between October 2001 and March 2002. Low IgA, compared with IgA >70 mg/dL, was associated with lower forced expiratory volume in 1 s (FEV_1) % predicted in the year following 11 September 2001 (94.1% vs 98.6%, p<0.001), increased risk of FEV_1/FVC <0.70 (HR 3.8, 95% CI 1.6 to 8.8) and increased antibiotic treatment (22.5/100 vs 11.6/100 person-years, p=0.002). Following WTC exposure, early IgA ≤70 mg/dL was associated with worse lung function and increased antibiotic treatment.

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 forced expiratory volume in 1 s (FEV_1).[1] Accelerated FEV_1 decline is a risk factor for fixed and variable airflow obstruction.[2] 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.[3] Secretory IgA is reduced in those with damaged airways.[4 5] 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.

METHODS

The source population contained 9638 WTC-exposed male Fire Department of the City of New York (FDNY) firefighters (online supplementary-figure 1). 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.

Statistical analyses

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/forced vital capacity (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 11/9, 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.

RESULTS

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 (online supplementary-table 1). 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 11/9 (online supplementary-figure 2). 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 (online supplementary-table 2).

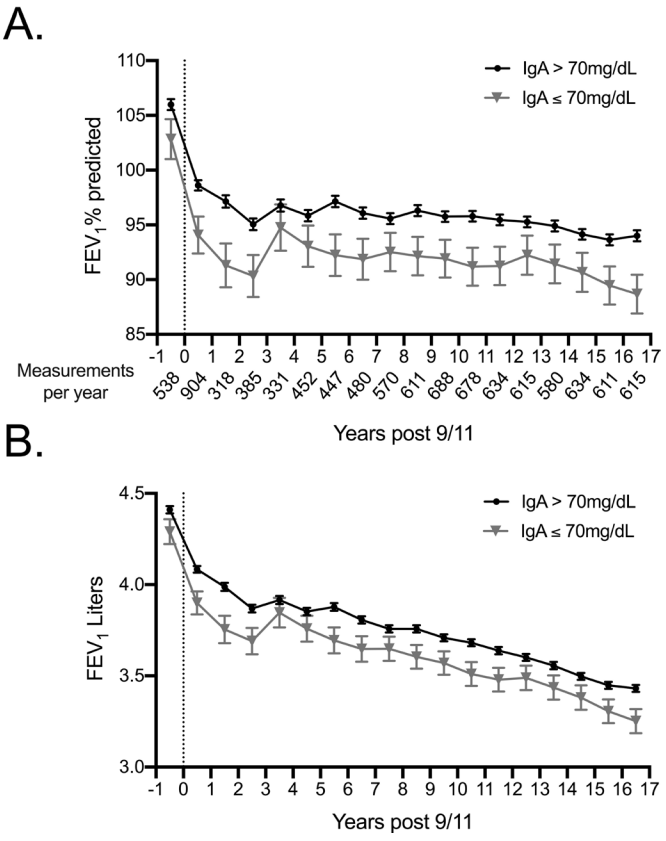

Figure 1 Lung function over time stratified by IgA measured on 11 September 2001 to 10 March 2002. (A) shows the mean (±SEM); SEM not shown if it is smaller than the size of the symbol) FEV_1 % predicted in each year between 11 September 2000 and 10 September 2018. The triangles correspond to the IgA ≤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. (B) Shows the mean absolute FEV_1 in the above groups in each year, adjusted for age, race and height, using the same spirometry measurements as in (A). FEV_1, forced expiratory volume in 1 s; SEM, SE of mean.

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 11/9 and throughout follow-up (figure 1A,B). Pre-11/9 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-11/9 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-11/9 FEV_1 slopes (figure 1B and online supplementary-table 2). Low IgA increased the risk of postbronchodilator FEV_1/FVC <0.70 by 3.8-fold (95% CI 1.6 to 8.8) (table 1).

Table 1 Multivariable COX model examining the association between serum IgA ≤70 mg/dL and postbronchodilator FEV_1/FVC ratio less than 0.70* †

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

*Time from 11September 2001 to BD-PFT, median (IQR): 5.9 years (3.6–9.9).
†n=284; also adjusted for race, WTC exposure and BMI.
BD-PFT, bronchodilator pulmonary function test; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; WTC, World Trade Center.

Table 2 Multivariable Poisson model examining the association between serum IgA ≤70 mg/dL and courses of antibiotic treatment after 1 January /2007*

Variable	Rate ratio	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

*n=914; also adjusted for race, WTC exposure and BMI.
BMI, body mass index; WTC, World Trade Center.

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 2). Oral steroid use, however, was not significantly associated with IgA level (online supplementary-table 3).

DISCUSSION

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.[3 4]

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.[3] These observations are consistent with suppression of production of IgA or increased degradation of IgA by proteases such as neutrophil elastase.[6] Local IgA deficiency has been associated with smoking-related COPD and increased susceptibility to smoking-related lung injury.[7] 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.[3] 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 generalisability 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-11/9 predicted antibiotic use years later. Since IgA was measured shortly after 11/9 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 11/9, this suggests that recurrent infection could have impacted lung function during development and/or adulthood.[8 9] Since low maximally-attained FEV_1 is a risk factor for obstructive lung disease, even in individuals with expected FEV_1 decline,[10] further research should test if IgA levels are associated with maximally attained FEV_1 and fixed airflow obstruction in other populations.

Contributors MDW had full access to all of the data in the study and agrees to be accountable for all aspects of the work so that questions related to the accuracy and integrity of the research are appropriately investigated and resolved. MDW conceived of the study, and designed it in conjunction with BP, LL, RZ-O, CBH and DJP. MDW, BP, AS, RZ-O, TS, YL and DG analysed and interpreted the data. MDW and BP drafted the first manuscript with critical revisions from LL, AS, RZ-O, CBH, DJP, MPW and TS. All authors approved the final manuscript.

Funding This research was funded by National Institute for Occupational Safety and Health, grant number U01 OH011302, U01OH011682 and contracts #200-2011-39383, #200-2011-39378, #200-2017-93426 and #200-2017-93326.

Competing interests BP, RZ-O, AS, CBH, YL, TS, DG, MPW, DJP and MDW report grants and/or contracts from the National Institute of Occupational Safety and Health, during the conduct of the study and outside the submitted work. LL reports grants from AstraZeneca and Chiesi (both awards), and expert consultation for Boehringer Ingelheim GmbH and Novartis outside the submitted work.

Patient consent for publication Not required.

Ethics approval The Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board approved this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Author note The sponsors had no role in the design and conduct of the study, the collection, management, analysis and interpretation of the data, the preparation, review and approval of the manuscript, or the decision to submit the manuscript for publication.

REFERENCES

1 Zeig-Owens R, Singh A, Aldrich TK, *et al*. Blood Leukocyte Concentrations, FEV_1 Decline, and Airflow Limitation. A 15-Year Longitudinal Study of World Trade Center-exposed Firefighters. *Ann Am Thorac Soc* 2018;15:173–83.
2 Singh A, Liu C, Putman B, *et al*. Predictors of Asthma/COPD overlap in FDNY firefighters with world Trade center dust exposure: a longitudinal study. *Chest* 2018;154:1301–10.
3 Putcha N, Paul GG, Azar A, *et al*. Lower serum IgA is associated with COPD exacerbation risk in SPIROMICS. *PLoS One* 2018;13:e0194924.
4 Polosukhin VV, Cates JM, Lawson WE, *et al*. Bronchial secretory immunoglobulin A deficiency correlates with airway inflammation and progression of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011;184:317–27.
5 Polosukhin VV, Richmond BW, Du R-H, *et al*. Secretory IgA deficiency in individual small airways is associated with persistent inflammation and remodeling. *Am J Respir Crit Care Med* 2017;195:1010–21.
6 Pilette C, Ouadrhiri Y, Dimanche F, *et al*. Secretory component is cleaved by neutrophil serine proteinases but its epithelial production is increased by neutrophils through NF-kappa B- and p38 mitogen-activated protein kinase-dependent mechanisms. *Am J Respir Cell Mol Biol* 2003;28:485–98.
7 Richmond BW, Brucker RM, Han W, *et al*. Airway bacteria drive a progressive COPD-like phenotype in mice with polymeric immunoglobulin receptor deficiency. *Nat Commun* 2016;7:11240.
8 Chan JYC, Stern DA, Guerra S, *et al*. Pneumonia in childhood and impaired lung function in adults: a longitudinal study. *Pediatrics* 2015;135:607–16.
9 Habibi MS, Jozwik A, Makris S, *et al*. Impaired antibody-mediated protection and defective IgA B-cell memory in experimental infection of adults with respiratory syncytial virus. *Am J Respir Crit Care Med* 2015;191:1040–9.
10 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.