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WORLD TRADE CENTER (WTC) OCCUPATIONAL EXPOSURE

Association of World Trade Center (WTC) Occupational Exposure Intensity with Chronic Obstructive Pulmonary Disease (COPD) and Asthma COPD Overlap (ACO)

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Abstract

Introduction Reported associations between World Trade Center (WTC) occupational exposure and chronic obstructive pulmonary disease (COPD) or asthma COPD overlap (ACO) have been inconsistent. Using spirometric case definitions, we examined that association in the largest WTC occupational surveillance cohort.

Methods We examined the relation between early arrival at the 2001 WTC disaster site (when dust and fumes exposures were most intense) and COPD and ACO in workers with at least one good quality spirometry with bronchodilator response testing between 2002 and 2019, and no physician-diagnosed COPD before 9/11/2001. COPD was defined spirometrically as fixed airflow obstruction and ACO as airflow obstruction plus an increase of ≥ 400 ml in FEV_1 after bronchodilator administration. We used a nested 1:4 case-control design matching on age, sex and height using incidence density sampling.

Results Of the 17,928 study participants, most were male (85.3%) and overweight or obese (84.9%). Further, 504 (2.8%) and 244 (1.4%) study participants met the COPD and ACO spirometric case definitions, respectively. In multivariable analyses adjusted for smoking, occupation, cohort entry period, high peripheral blood eosinophil count and other covariates, early arrival at the WTC site was associated with both COPD (adjusted odds ratio $[OR_{adj}] = 1.34$, 95% confidence interval [CI] 1.01–1.78) and ACO ($OR_{adj} = 1.55$, 95%CI 1.04–2.32).

Conclusion In this cohort of WTC workers, WTC exposure intensity was associated with spirometrically defined COPD and ACO. Our findings suggest that early arrival to the WTC site is a risk factor for the development of COPD or of fixed airway obstruction in workers with pre-existing asthma.

Keywords Occupational lung disease · Smoke inhalation injury · Chronic obstructive pulmonary disease · World Trade Center Attack, 2001 · Longitudinal changes in lung function · Spirometry

Introduction

Occupational exposures at the World Trade Center (WTC) disaster site in 2001–2002 have been associated with a variety of adverse health effects [1], including a heterogeneous and often not easily classifiable group of chronic lower airway diseases (LAD) [1, 2]. In all surveillance cohorts with lung function data, the most frequently reported spirometric ventilatory impairment pattern has been reduced forced vital capacity (FVC), while airflow obstruction (characterized by a reduced FEV_1/FVC ratio) has been considerably less frequently demonstrated [1, 3–8].

A subgroup of WTC workers with LAD has been shown to have accelerated longitudinal lung function decline [7, 9], but it is still unclear whether occupational WTC exposures lead to disabling chronic lung diseases, as such exposures have been inconsistently associated with chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap (ACO), or with interstitial lung diseases.

A potential explanation for the discrepant findings of previous studies of WTC occupational exposure and COPD or ACO is limited phenotypic assessment (e.g., not including lung function measures) [10, 11]. We hypothesized that occupational exposures at the WTC site would be associated with COPD and ACO if these conditions were defined using objective spirometric data. We tested this hypothesis among participants in the Mount Sinai WTC General Responders

Extended author information available on the last page of the article

Cohort, the largest occupational cohort of WTC rescue and recovery workers with spirometric data and assessment of bronchodilator responsiveness regardless of clinical status.

Methods

Subject Recruitment and Study Procedures

All study subjects participated in the screening, surveillance, and clinical programs of the WTC Health Program Clinical Center of Excellence at Mount Sinai Medical Center in New York City [8]. Details on subject recruitment, eligibility criteria, and screening and surveillance protocols have been previously reported [4, 8]. In brief, the members of this open cohort were workers or volunteers who performed rescue, recovery, clean up, and service restoration duties at the WTC disaster site between 11-September-2001 and June 2002 [12]. Beginning in July 2002, all subjects underwent an initial screening evaluation, which included questionnaires on respiratory and general health, and WTC-related occupational exposures, as well as physical examination, laboratory testing, spirometry, and chest radiograph (the latter repeated on alternate visits). Subsequent ("monitoring") health surveillance visits included a similar evaluation at 12- to 18-month intervals, and clinical services were offered (often contiguously to the screening) for individualized diagnostic and treatment services [1, 13–17]. Inclusion into this study required that WTC workers did not report a physician's diagnosis of COPD before 11-September-2001, and that they had at least one screening and surveillance spirometry with adequate assessment of bronchodilator responsiveness (see below) between their baseline examination and 30-June-2019. We did not exclude subjects with pre-existing asthma from the current analysis, as fixed airflow obstruction and thus COPD or ACO could result from WTC exposures in those subjects.

All spirometries were performed using the EasyOne® portable flow device (ndd, Zurich, Switzerland). Bronchodilator response (BDR) was assessed at least once (most often at the baseline visit), irrespective of clinical status or indication, by repeating spirometry 15 min after administration of 180 µg of albuterol via metered dose inhaler and a dual-valve disposable spacer (LiteAire, Thayer Medical, Tucson, Arizona). BDR was calculated as change in FEV_1 and/or FVC following albuterol administration as both absolute volume and as a percentage of the respective pre-bronchodilator measurement. Clinically significant BDR was then defined as an increment in pre-bronchodilator FEV_1 or FVC $\geq$ 200 ml and $\geq$ 12% after bronchodilator administration. Of note, medication withholding was not required from those already on treatment. Predicted values for spirometric measurements were calculated for all subjects, based on reference equations from the third National Health and Nutrition Examination Survey (NHANES III) [18], and all testing, quality assurance, ventilatory impairment pattern definitions, bronchodilator response presence, and interpretative approaches followed American Thoracic Society recommendations [19, 20]. To be included in data analyses, spirometric maneuvers had to be acceptable and reproducible (based on a computer quality grade [21] of A or B, or C if at least 5 trials had been obtained), and a forced exhalatory time of at least 6 s.

Our exposure of interest was self-reported arrival at the WTC disaster site within 48 h (heretofore referred to as "early arrival") at the WTC site. While environmental sampling was extremely limited [22] due to risk underestimation [23], early arrival at the site was previously associated with higher toxic inhalant concentrations (based on limited air sampling reports [24, 25]), reduced respiratory personal protective equipment usage [26], and adverse post-disaster lower airway symptoms and diagnoses in several large occupational cohorts [1, 3, 8, 26]. Our main outcome of interest was COPD, defined spirometrically ($COPD_{spiro}$) as fixed air flow obstruction [27] (a postbronchodilator [post-BD] FEV_1/FVC ratio $<$ 0.7) in the absence of any subsequent spirometry with normal result or low FVC impairment pattern. As a secondary outcome, we defined a subgroup of those patients as asthma COPD overlap (ACO_{spiro}), requiring both evidence of COPD (as above) and a post-BD increase in $FEV_1 \geq 400$ ml [28].

For descriptive purposes, we categorized COPD severity using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification based on post-BD FEV_1 [27]: mild/GOLD 1 if $\geq$ 80%, moderate/GOLD 2 if $<$ 80% but $\geq$ 50%, severe/GOLD 3 if $<$ 50% but $\geq$ 30%, and very severe/GOLD 4 if $<$ 30%. Further, we report the prevalence of clinically significant exertional dyspnea (the most frequent respiratory symptom in this cohort), defined by level 2 ("I walk slower than people of my same age on the level because of breathlessness, or have to stop for breath when walking at my own pace on the level") or higher on the modified Medical Research Council (mMRC) breathlessness scale[29, 30] for each functional severity COPD category.

Covariates assessed at the baseline examination included age (divided into 5-year intervals), self-identified sex and ethnicity/race (Latino of any race, non-Latino White, non-Latino Black, and others), measured height, self-reported cumulative WTC exposure duration ($<$ 60 vs. $\geq$ 60 days), occupation before 11-September-2001 (protective services; construction; building cleaning and maintenance, and electrical, telecommunications, and other installation and repair group [BCM&IRG]; and all others), date of entry into the cohort (2002–2005, 2006–2008, and 2009 and later)[12], and both smoking status (former or not), and smoking intensity (in pack-years). A subject was considered a never smoker if (s)he had smoked less than 20 packs of cigarettes (or 12 oz. of tobacco) in a lifetime, or less than 1 cigarette/day (or 1 cigar/week) for one year. A minimum of 12 months without tobacco use was required to deem a subject a former smoker[31]. Weight was measured and body mass index (BMI) recorded at each visit and classified as normal ($18 < BMI < 25$ kg/m^2), overweight ($25 \leq BMI < 30$ kg/m^2), and obese ($BMI \geq 30$ kg/m^2). Covariates assessed at any visit included: BDR, highest recorded diastolic blood pressure (dichotomous, with 90 mm Hg as cut point), highest recorded serum glucose (whether fasting or not, dichotomous, with 200 mg/dl as cut point), highest serum triglycerides (whether fasting or not, dichotomous, with 300 mg/dl as cut point), highest peripheral blood eosinophil count (BEC, dichotomous, with 300/mcl as cut point)[32] and neutrophil count (dichotomous, with 6,000/mcl as cut point), and lowest HDL cholesterol (dichotomous, with 40 and 50 mg/dl as cut points for men and women, respectively). As in our previous study[8], we used HDL, glucose, triglycerides, and diastolic blood pressure as surrogate indicators of probable metabolic syndrome (MetSyn), categorized as 0–1 and 2–4 indicators.

The Mount Sinai Program for the Protection of Human Subjects (HS 17-01098) approved this study, and participants consented to have their data aggregated for research.

Statistical Analyses

We employed a nested 1:4 [33] case-control design matching on age (within ± 2 years), sex and height (within 5 cm), using incidence density sampling [34], where we matched each case to a sample of those who were at risk at the time of case occurrence, and a control subject could provide a matched comparison to more than one case. We used multiple imputation with fully conditional specification to address missing responses among the independent variables, and performed sensitivity analyses without multiple imputation as a comparison. The results with the complete and imputed data sets were essentially identical, and we thus present only the latter. Collinearity among variables was excluded by a variance inflation factor of 5. We examined standardized differences (StD) [35] to compare subjects included and excluded from the study, and those with $COPD_{spiro}$ and with self-reported diagnosis of COPD (and no $COPD_{spiro}$). We deemed a standardized difference ≥ 0.2 as suggestive of a potentially significant difference in a covariate. Conditional logistic regression was used for the multivariable analyses, with fully specified models with covariates selected based on known, detected, or potential associations and confounding, and models are presented for $COPD_{spiro}$ and for the ACO_{spiro} subgroup. In sensitivity analyses, we considered other WTC exposure indicators, particularly work on the pile resulting from the destructed WTC towers, and cumulative self-reported exposure duration, and tested the association of our main exposure variable and self-reported physician diagnoses of COPD and ACO. We also tested for interactions between the exposure of interest and selected covariates (age, smoking, and BEC), and between BEC and smoking. Lastly, we modeled FEV_1 and FVC trajectories across time for subjects with 2 or more available good quality pre-bronchodilator spirometries during the study period, using linear mixed models with a random intercept to account for within-subject correlation between visits. We categorized time in one-year intervals between 1-July-2002 and 30-June-2019 and treated them as a classification variable. Models were adjusted for sex, age at time of spirometry, ethnicity/race and height. We created separate models for (1) ACO_{spiro}, (2) COPD alone (i.e., excluding ACO), and (3) the rest of the cohort (NoCOPD).

A two-sided p value below 0.05 defined statistical significance, and we used the SAS program version 9.4 (SAS Institute, Cary, NC) for all analyses.

Results

After excluding 6074 subjects because of either low-quality spirometries ($n = 5821$) or pre-WTC self-reported physician-diagnosed COPD ($n = 253$), our study population consisted of 17,928 subjects. Compared to subjects excluded from this analysis, those included were more likely to be early entrants into the cohort (between 2002 and 2005) and to have a high BEC, but otherwise had very similar characteristics (Table OS1).

A total of 40,814 spirometries were available on 17,928 subjects (mean ± standard deviation [SD] = 2.28 ± 1.60] spirometries per subject), who were followed until 30-June-2019 for 4.28 ± 5.09 years since their first visit spirometry, 11 ± 5.55 years since 11-September-2001. Table 1 shows the main characteristics of the study participants, who had a mean (SD) age of 38.8 (8.8) years on 11-September-2001, and were predominantly male (85.3%), and overweight/obese (84.9%), consistent with previous reports in the WTC occupational cohorts [8, 36]. Through screening and surveillance, we identified 504 cases of COPD (2.8% of the total) a median of 4.93 (IQR 2.05–7.33) years after 11-September-2001, and most often (72.4%) at their baseline spirometry. Of the 504 subjects with COPD, 244 (48.4%, 1.4% of the study population) also met the study spirometric case definition of ACO. Of note, 2171 subjects reported a physician diagnosis of COPD, more than four times the number of $COPD_{spiro}$ cases. Compared to $COPD_{spiro}$ subjects, those individuals with self-reported physician diagnosed COPD seemed more likely to be of Latino/any race ethnicity and to work in construction or protective services, and much less likely to demonstrate bronchodilator responsiveness

Table 1 Characteristics of 17,928 World Trade Center (WTC) rescue and recovery workers and volunteers, as well as those meeting the spirometric case definition of chronic obstructive pulmonary disease ($COPD_{spiro}$, $n = 504$) and Asthma COPD overlap (ACO_{spiro}, $n = 244$), and their control ($n = 1682$) subgroups

Characteristic	value	Entire group		$COPD_{spiro}$ subgroup		ACO_{spiro} subgroup		Control subgroup	
		n or mean	% or SD	*n* or mean	% or SD	*n* or mean	% or SD	*n* or mean	% or SD
Arrival at WTC disaster site	≤ 48 h	11841	66.0	339	67.3	171	70.1	1074	65.4
	> 48 h	5947	33.2	160	31.7	71	29.1	595	33.8
	Missing	140	0.8	5	1.0	2	0.8	13	0.7
Age on 9/11	Years	38.8	8.8	44.7	9.9	43.1	10.0	43.5	8.7
Gender	Female	2630	14.7	56	11.1	20	8.2	189	10.9
	Male	15,298	85.3	448	88.9	224	91.8	1493	89.1
Ethnicity/race	Non-Latino/Black	2099	11.7	61	12.1	28	11.5	248	14.3
	Non-Latino/White	9994	55.7	321	63.7	153	62.7	1019	58.4
	Latino/any race	4927	27.5	82	16.3	46	18.9	332	22.0
	Non-Latino/Other	371	2.1	7	1.4	3	1.2	26	2.2
	Missing	537	3.0	33	6.5	14	5.7	57	3.1
Height	cm	174.4	9.1	175.6	8.5	176.6	8.2	175.5	8.2
Body mass index (BMI) category	Normal	2668	14.9	94	18.7	31	12.7	252	13.6
	Overweight	8039	44.8	199	39.5	97	39.8	792	48.2
	Obese	7181	40.1	206	40.9	115	47.1	637	38.0
	Missing	40	0.2	5	1.0	1	0.4	1	0.2
Cohort entry period	2002–2005	8946	49.9	284	56.3	144	59.0	757	42.8
	2006–2008	4809	26.8	123	24.4	59	24.2	464	27.0
	2009–2019	4173	23.3	97	19.2	41	16.8	461	30.1
Smoking status	Never smoker	10,737	59.9	172	34.1	93	38.1	915	63.4
	Former smoker	4379	24.4	171	33.9	79	32.4	556	23.7
	Current smoker	2586	14.4	151	30.0	63	25.8	165	10.8
	Missing	226	1.3	10	2.0	9	3.7	46	2.1
Smoking intensity	Pack-years	4.4	9.9	12.6	18.8	10.5	16.8	5.8	12.5
Pre-WTC occupation group	Construction	4270	23.8	146	29.0	69	28.3	432	22.4
	BCM&IRG†	1719	9.6	52	10.3	25	10.2	166	8.3
	Other	3700	20.6	167	33.1	73	29.9	383	17.7
	Protective	8239	46.0	139	27.6	77	31.6	701	51.6
WTC exposure duration	< 60 days	8905	49.7	255	50.6	124	50.8	890	52.7
	≥ 60 days	8902	49.7	246	48.8	119	48.8	781	46.5
	Missing	121	0.7	3	0.6	1	0.4	11	0.7
Bronchodilator response	Absent	14,308	79.8	201	39.9	12	4.9	1409	85.4
	Present	2519	14.1	303	60.1	232	95.1	141	8.1
	Missing	1101	6.1	–	–	–	–	132	6.6
Metabolic syndrome (MetSyn) criteria	0–1 criteria	15,033	83.9	403	80.0	194	79.5	1435	86.3
	2–4 criteria	2221	12.4	64	12.7	33	13.5	208	11.5
	Missing	674	3.8	37	7.3	17	7.0	39	2.2
Blood eosinophil count	≤ 300/mcl	14,180	79.1	355	70.4	161	66.0	1390	83.4
	> 300/mcl	3053	17.0	111	22.0	65	26.6	249	14.4
	Missing	695	3.9	38	7.5	18	7.4	43	2.3
Blood neutrophil count	≤ 6000/mcl	13,084	73.0	335	66.5	162	66.4	1283	75.4
	> 6000/mcl	4159	23.2	131	26.0	64	26.2	360	22.4
	Missing	685	3.8	38	7.5	18	7.4	39	2.2

†BCM&IRG: buildings and grounds cleaning and maintenance, and electrical, telecommunications and other installation and repair groups

(see Table OS2). Also of note, and similar to our previous study on the WTC Chest CT Imaging subcohort [37], 34.1% of subjects with $COPD_{spiro}$ reported having never smoked tobacco products. Confirming also previous findings in that subcohort [37], annual cross-sectional prevalence of current tobacco smoking steadily decreased from 19.3% to 5.6% among all subjects examined within the years ending on 30-June-2003 to 30-June-2019, respectively.

Based on post-BD FEV_1, COPD was classified mostly as moderate/GOLD 2 (62.1%) or mild/GOLD 1 (27.6%), with few cases of severe/GOLD 3 (9.9%) or very severe/GOLD 4 (0.4%) COPD (Table OS3). This distribution of COPD severity did not differ by diagnostic subgroup (COPD excluding ACO vs. ACO). Table 2 also shows the count and proportion of subjects who reported level 2 or higher breathlessness on the mMRC breathlessness scale [29, 30].

In bivariate analyses, age, tobacco smoking, early entry into the cohort (2002–2008), and high peripheral blood eosinophil and neutrophil counts were associated with increased odds of $COPD_{spiro}$ and ACO_{spiro}. On the other hand, protective services (law enforcement) occupation was associated with reduced odds of $COPD_{spiro}$ and ACO_{spiro}, and so was overweight status with $COPD_{spiro}$. Table 2 shows the results of the multivariable analysis of early arrival at the WTC disaster site and COPD or ACO. In this analysis, early arrival at the WTC disaster site was associated with 34% increased odds of $COPD_{spiro}$ (95% CI for $OR_{adj} = 1.01$ to 1.78, $p = 0.04$). Further, smoking intensity, high BEC, early entry into the cohort, and occupation other than law enforcement were also associated with increased odds of COPD. Also in a multivariable analysis, early arrival at the WTC site was also associated with 55% increased odds of ACO_{spiro} ($OR_{adj} = 1.55$, 95% CI 1.04 to 2.32, $p = 0.03$). There was no association between early arrival at the WTC site and self-reported physician-diagnosed COPD or ACO (data not shown). Our findings were unchanged in a sensitivity analysis with additional adjustment for other WTC exposure indicators (e.g., work on the towers pile, cumulative exposure duration).

We found no evidence of a significant interaction between early arrival at the WTC disaster site and smoking status, age, or evidence of high BEC on $COPD_{spiro}$ or ACO_{spiro},

Table 2 Simple and multivariable conditional logistic regression models of spirometrically defined chronic obstructive pulmonary disease ($COPD_{spiro}$, $n = 504$) and asthma COPD overlap subgroup (ACO_{spiro}, $n = 244$) vs. early arrival (within 48 h) at the World Trade Center (WTC) disaster site in a 1:4 nested case–control study of WTC rescue and recovery workers, matched on age (within 2 years), sex, and height (within 5 cm)

Variable	Value	$COPD_{spiro}$				ACO_{spiro}			
		OR	95% CI	OR_{adj}	95% CI	OR	95% CI	OR_{adj}	95% CI
Arrival at WTC disaster site	≤ 48 h	1.09	0.86, 1.38	1.34	1.01, 1.78	1.21	0.85, 1.72	1.55	1.04, 2.32
	> 48 h	Ref		Ref		Ref		Ref	
Body mass index category	Normal	Ref		Ref		Ref		Ref	
	Overweight	0.6	0.42, 0.86	0.73	0.48, 1.09	0.8	0.50, 1.28	0.87	0.52, 1.46
	Obese	0.74	0.53, 1.02	0.87	0.6, 1.25	1.16	0.72, 1.86	1.22	0.72, 2.07
Cohort entry period	2009+	ref		Ref		Ref		Ref	
	2006–2008	1.54	1.12, 2.13	1.38	0.95, 1.98	1.75	1.06, 2.90	1.5	0.86, 2.59
	2002–2005	2.42	1.84, 3.20	1.76	1.26, 2.46	2.9	1.84, 4.57	2.14	1.27, 3.60
Smoking intensity	Pack-year	1.06	1.04, 1.07	1.05	1.04, 1.07	1.05	1.03, 1.06	1.04	1.03, 1.06
Former smoking status	No	Ref		Ref		Ref		Ref	
	Yes	1.42	1.12, 1.80	0.84	0.63, 1.12	1.51	1.08, 2.11	0.97	0.63, 1.50
Pre-WTC occupation group	Protective	ref		ref		ref		ref	
	BCM&IRG†	2.65	1.76, 4.00	2.16	1.36, 3.45	2.35	1.34, 4.12	2.17	1.14, 4.14
	Other	3.46	2.49, 4.81	2.97	2.09, 4.22	2.93	1.92, 4.47	2.77	1.74, 4.42
	Construction	2.63	1.96, 3.54	2.03	1.42, 2.91	2.49	1.58, 3.93	1.99	1.17, 3.39
Metabolic syndrome criteria	0–1 criteria	Ref		Ref		Ref		Ref	
	2–4 criteria	1.24	0.89, 1.75	1.2	0.79, 1.84	1.37	0.84, 2.23	1.16	0.65, 2.07
Blood eosinophil count	≤ 300/mcl	Ref		Ref		Ref		Ref	
	> 300/mcl	1.65	1.25, 2.17	1.56	1.13, 2.17	2.22	1.52, 3.24	2.15	1.43, 3.23
Blood neutrophil count	≤ 6000/mcl	Ref		Ref		Ref		Ref	
	> 6000/mcl	1.5	1.15, 1.96	1.09	0.8, 1.48	1.6	1.13, 2.27	1.2	0.81, 1.76

The two multivariable models were adjusted for all the listed covariates

†BCM&IRG: buildings and grounds cleaning and maintenance, and electrical, telecommunications and other installation and repair groups.

or between smoking status and intensity and high BEC ($p \geq 0.10$ in all instances). Table OS4 and Figure OS1 show the mean yearly pre-bronchodilator FEV_1 and FVC declines for subjects with 2 or more good quality pre-bronchodilator spirometries by group (median was 3 spirometries/subject), namely $COPD_{spiro}$ (without ACO, $n = 130$), ACO_{spiro} ($n = 123$), and the rest of the cohort (NoCOPD, $n = 9{,}806$) over the study period. As expected, the mean yearly pre-bronchodilator expiratory flow declines were larger for $COPD_{spiro}$ than for NoCOPD, but not when compared with ACO_{spiro}, in all likelihood due to sample size limitations and the use of pre-bronchodilator spirometric values.

Discussion

In this large cohort of WTC workers, WTC exposure intensity (as suggested by early arrival at the WTC disaster site) [1, 8] was significantly associated with spirometrically defined COPD and ACO, independently of age, tobacco smoking, peripheral BEC, and occupational classification. To our knowledge, this is the first study to focus on fixed airflow obstruction as a spirometric impairment pattern in WTC responders irrespective of clinical indication and to restrict the analyses to spirometries with a minimum forced exhalatory time of 6 s, besides acceptable reproducibility criteria (quality grades).

Previous studies had limited assessment of COPD and/or ACO. In a study of a subgroup of 2,137 New York City firefighters (out of a cohort of 9,598 exposed to the WTC 2001 disaster), who underwent complete pulmonary function testing, including clinically indicated post-bronchodilator spirometric testing, COPD was diagnosed in 314 subjects (14.7%), including 99 (4.6% of the total) who also met the standard definition of a positive BDR [38], were deemed to also have asthma, and thus ACO. Defining ACO based on the standard definition of BDR would grossly misclassify ACO patients, given its presence in a very large percentage (38–52%) of COPD patients [39]. Unsurprisingly, neither COPD nor ACO thus defined were significantly associated with higher WTC-related exposures, as indicated by early arrival at the site [11]. On the other hand, in a study from the WTC Health Registry, a closed cohort that includes 14,168 rescue and recovery workers, 5.9 and 7% self-reported physician diagnoses of COPD and ACO, respectively, and ACO was associated with higher occupational WTC exposures [10]. The severe limitations of self-reported diagnosis [40] or claims data [41] definitions of COPD and/or ACO are well known. There is, however, no fully satisfactory definition of ACO, and asthma with fixed airway obstruction [42] cannot be easily excluded by our spirometric one. Self-reported physician diagnoses of COPD and ACO were not significantly correlated with $COPD_{spiro}$ and ACO_{spiro} in the current analysis or associated with our main WTC-related occupational exposure variable, strongly supporting the use of spirometric evidence for research on COPD in WTC workers.

Our study further underscores the non-negligible proportion of COPD cases occurring among nonsmokers, exposed in this case to occupational toxicants. Our findings agree with those of a recently published report of a significantly increased odds of $COPD_{spiro}$ among nonsmokers in a population-based study of individuals exposed to fine particles from a coal mine fire in Australia [43]. These two reports suggest the importance of discrete episodes of airway inhalation injuries (such as the WTC disaster, or the Hazlewood, Australia, coal mine explosion) in the evolution towards COPD in some individuals. These add to the emerging evidence for the effect of longer term exposures, such as vapors, gases, dusts and fumes in longest held occupation [44–46], and environmental air pollutants [47] on the incidence of COPD.

Quantitative computed tomography (QCT) data from our WTC Chest CT Imaging subgroup of this same cohort, indicated that only about 9.6% of all study subjects [9], and 24% of 59 subjects with $COPD_{spiro}$ [37] had emphysema, as indicated by a low attenuation volume percent at 950 HU (LAV%, also known as EI950) exceeding the maximum of 2.5% reported in a nonsmoking healthy multiethnic population [48] and only 4% exceeding LAV% 5% (unpublished data). Our imaging data also revealed QCT evidence of both proximal (wall area percent, WAP), and (indirectly) distal airway involvement (expiratory-inspiratory mean lung density, MLD_{EI}) in WTC workers with $COPD_{spiro}$ [37]. Further research is needed to investigate whether a chronic bronchitis COPD phenotype [49] predominates in this occupationally exposed cohort.

Our study had the added advantage of examining the largest, and most sociodemographically diverse occupational WTC cohort [12]. This cohort has the richest spirometry data set and is unique in that more than 80% of the subjects had bronchodilator responsiveness testing since 2002, usually at the baseline examination and, importantly, irrespective of clinical status or indications. The spirometry quality requirements for this study excluded suboptimal performance, reproducibility, expiratory effort, and (uniquely in the occupational WTC studies to date) short (< 6 s) forced exhalatory time. We also adjusted for substantial and highly prevalent potential confounders (notably, age and smoking), and for metabolic and other risk factors that have been reported in association with adverse respiratory outcomes in other cohort studies [50–55]. Selection bias due to differential loss to follow-up is a possible but unlikely explanation for our findings, given the minimal observed differences between subjects who were and were not included in this analysis, and our multivariable model adjustments. We can perhaps not completely exclude, however, participation bias, in that both the healthiest and the sickest individuals may have chosen not to participate.

Study limitations include the lack of pre-WTC lung function data in the vast majority of subjects, as well as a suitable unexposed control population. Similar to essentially all WTC-related studies, we lack direct toxicant measurement data, as the exposures were understudied [22], and detailed exposure studies were very limited in size and duration [22, 24, 25]. Limited data indicated, however, that fine particulate matter (< 2.5 µm in aerodynamic diameter, $PM_{2.5}$) increased 2.5 fold in the area [24], and the dust contained high concentrations of Calcium sulfate and carbonate [24, 56], $PM_{2.5}$ samples reaching considerable alkalinity [56], and sharply decreasing concentrations after September 2001 [24, 25]. Additionally, respiratory personal protective equipment use was lowest within the first 48 h after the attack among all occupational groups and began improving afterwards [26]. Several studies in different occupational cohorts demonstrated increased adverse respiratory health effects within the first hours to days of the towers' collapse [1, 3, 8, 26]. Those data support our empirically derived higher WTC-related occupational exposure indicator. In our studies thus far, adding other exposure indicators has not altered the association estimates. As these workers, aged in their early forties on 11-September-2001 had also been occupationally exposed to other vapors, dust, gas, and fumes [6], future studies might attempt to discern the effect of those pre-WTC occupational exposures. We lack data on post-WTC exposures, but we would expect those to have decreased, as a result of retirement, disability, and occupation changes for a substantial proportion of the cohort members [57]. We also lack data on other possibly relevant exposures, such as air pollution and biomass burning smoke [58]. We have data to suggest, on the other hand, that tobacco smoke exposure decreased very markedly and very early during the 2002–2019 surveillance period [8, 37]. Our study is based on screening and surveillance spirometry and may have missed some cases detectable with more detailed pulmonary function laboratory testing, and bronchodilator testing was infrequently performed after the baseline examination, and without requiring medication withholding, all of which may have contributed to an underestimation of the incidence of COPD over time. Repeat testing, particularly after treatment implementation, could have also excluded cases with "unstable" spirometric diagnosis of COPD, more likely in mild to moderate cases [59], such as most of our cases. On the other hand, our data confirmed the unreliability of self-reported diagnosis of COPD, and generally of questionnaire-based definitions of the disease[40].

Given the proportion of subjects with ACO and of nonsmokers, and the significance of early cohort entry in the adjusted associations (most excess asthma diagnoses were observed within a year after 11-September-2001 [26]), we suspect that a substantial proportion of our COPD cases were due to asthma developing fixed obstruction and thus meeting the COPD spirometric definition. Future investigations may help confirm or refute this.

In conclusion, we demonstrated in this large and diverse cohort of WTC workers and volunteers that occupational WTC exposure intensity, as indicated by early arrival at the disaster site, was associated with spirometrically defined COPD and that the association was stronger for the subgroup with ACO, independently of age, tobacco smoking and other risk factors.

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Author Contributions RED, MS, and JCC designed and oversaw the study and selected analytical strategies. MS performed all statistical analyses. All authors contributed to writing, reviewed, and revised the drafts, and approved the final manuscript.

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Declarations

Conflict of interest The authors had no other relevant financial conflict of interest to disclose. The contents of this article are the sole responsibility of the authors, and do not represent the official views of the CDCP/NIOSH.

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