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Original Contribution

Estimating the Time Interval Between Exposure to the World Trade Center Disaster and Incident Diagnoses of Obstructive Airway Disease

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Respiratory disorders are associated with occupational and environmental exposures. The latency period between exposure and disease onset remains uncertain. The World Trade Center (WTC) disaster presents a unique opportunity to describe the latency period for obstructive airway disease (OAD) diagnoses. This prospective cohort study of New York City firefighters compared the timing and incidence of physician-diagnosed OAD relative to WTC exposure. Exposure was categorized by WTC arrival time as high (on the morning of September 11, 2001), moderate (after noon on September 11, 2001, or on September 12, 2001), or low (during September 13–24, 2001). We modeled relative rates and 95% confidence intervals of OAD incidence by exposure over the first 5 years after September 11, 2001, estimating the times of change in the relative rate with change point models. We observed a change point at 15 months after September 11, 2001. Before 15 months, the relative rate for the high- versus low-exposure group was 3.96 (95% confidence interval: 2.51, 6.26) and thereafter, it was 1.76 (95% confidence interval: 1.26, 2.46). Incident OAD was associated with WTC exposure for at least 5 years after September 11, 2001. There were higher rates of new-onset OAD among the high-exposure group during the first 15 months and, to a lesser extent, throughout follow-up. This difference in relative rate by exposure occurred despite full and free access to health care for all WTC-exposed firefighters, demonstrating the persistence of WTC-associated OAD risk.

change point model; latency; obstructive airway disease; occupational exposure; rescue/recovery workers; World Trade Center

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FDNY, Fire Department of the City of New York; OAD, obstructive airway disease; WTC, World Trade Center.

Tobacco use, infections, and the inhalation of chemicals, particulate matter (dusts and fibers), and the incomplete products of combustion during occupational and environmental disasters have long been associated with respiratory disorders, especially in those with genetic predispositions (1–3). There is also substantial literature on the association between chronic environmental exposures (4, 5) and obstructive airway diseases (OADs). Occupational exposures, such as to floor sealant, spray paint, metal coat remover, chlorine, sulphur dioxide, ammonia, isocyanates, Western red cedar (*Thuja plicata*), dusts, and fire/smoke, have been associated with increased risks of asthma and bronchial hyperreactivity (6–9). Dose-response relationships for asthma (allergic-immunologically mediated or irritant) have been well documented (6–8, 10), although there is insufficient understanding of the timing of disease onset relative to the timing of the triggering exposure (8, 10–13).

The World Trade Center (WTC) disaster presents a unique opportunity to describe the latency period (time interval between exposure and diagnosis) for OADs, such as asthma and

chronic bronchitis, after a major environmental catastrophe (14–23). Firefighters from the Fire Department of the City of New York (FDNY) who worked as rescue and recovery workers at the WTC site continue to show significantly elevated rates of incident OAD years after exposure (20, 21). The WTC rescue and recovery effort was unlike most other environmental and occupational exposure situations, in that the date of the disaster, the date that FDNY firefighters first worked at the WTC site, and the date of first OAD diagnosis are known. This gives us an opportunity to estimate the latency period between exposure and OAD onset in a previously healthy, well-described cohort of FDNY firefighters who had full and free access to health care from FDNY physicians. Additionally, we use an analytical method not previously used in WTC-exposed cohorts—parametric survival models with change points—to estimate the length of time that WTC exposure is associated with new-onset OAD.

The aim of this study was to assess whether the WTC exposure-response gradient observed for the cumulative incidence of OAD can be attributed entirely to higher incidence rates shortly after September 11, 2001, or if an exposure-response gradient for incident disease persists beyond the first year after September 11, 2001. Specifically, we analyzed whether firefighters with different levels of WTC exposure intensity were equally likely to develop incident OAD throughout the 5-year follow-up, or whether the association between WTC exposure and incident OAD attenuated over the study period.

METHODS

Population

The study population consisted of 10,671 FDNY firefighters who first arrived at the WTC site to participate in the rescue and recovery effort on or before September 24, 2001. Firefighters who retired after September 11, 2001, were included if they were active FDNY employees on September 11, 2001. We excluded data from the following subjects: 543 subjects with a diagnosis of OAD prior to September 11, 2001; women and nonwhites because of small numbers ($n = 657$); those who were present at the site but not on active duty for the FDNY on September 11, 2001 ($n = 258$); those missing information on smoking history ($n = 173$); and those who did not consent to have their data used for research ($n = 110$), leaving 8,930 male firefighters in the final analytical cohort. Study participants provided written informed consent. The study was approved by the institutional review board at Montefiore Medical Center (Bronx, New York).

Data sources

Demographic information came from the FDNY employee database. Beginning in 1996, the FDNY medical program, run by the FDNY Bureau of Health Services, transitioned to electronic medical records with diagnoses coded according to the *International Classification of Diseases, Ninth Revision*. Physician diagnoses were obtained from these electronic medical records. Since October 2001, the FDNY Bureau of Health Services also has collected data from self-administered health questionnaires completed during routine annual exams, from which we obtained information regarding WTC exposure, smoking status, and current lower respiratory symptoms of cough, shortness of breath, or wheeze.

Follow-up period

Because the primary purpose of this study was to determine whether the relative incidence of OAD diagnosis changed significantly during the follow-up period, it was essential that the opportunity to obtain an OAD diagnosis from a FDNY physician remained constant. This means that the likelihood of a physician visit must have been the same across all levels of exposure throughout the follow-up period after controlling for other factors. A programmatic change in January 2007 offered free prescription medications (without copay or deductibles) for all WTC-covered conditions, but it required a diagnosis from a FDNY physician. Because this increased the likelihood that firefighters would seek medical treatment at the FDNY, we limited the study analyses to the first 5 years following September 11, 2001.

FDNY physician diagnoses

FDNY physicians receive detailed instruction in diagnosing and treating respiratory diseases and are trained to use consistent diagnostic criteria (24). Examining physicians determine diagnoses after integrating information from patient history, physical examination, spirometry, other pulmonary function testing, and chest imaging.

We reviewed the FDNY electronic medical record database from September 11, 2001, through September 10, 2006, for any diagnosis of asthma, chronic bronchitis, or chronic obstructive pulmonary disease (COPD)/emphysema using the following *International Classification of Diseases, Ninth Revision*, codes for a diagnosis of asthma: 493.0, 493.00, 493.01, 493.02, 493.1, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.82, 493.9, 493.90, and 493.91. We used the following codes for nonasthma OAD (chronic bronchitis and COPD/emphysema): 491, 491.0, 491.1, 491.2, 491.20, 491.21, 491.22, 491.8, 491.9, 492.8, 494, 494.1, and 496. A person was considered to have new-onset OAD if they had the first diagnosis of asthma, chronic bronchitis, or COPD/emphysema within the study period (September 11, 2001–September 10, 2006). Our primary analyses used any diagnosis of OAD as the outcome; secondary analyses used either asthma or nonasthma OAD as outcomes. To increase the reliability of OAD diagnoses, we required that a diagnosis of asthma or COPD/emphysema be documented 2 or more times after September 11, 2001. When a first diagnosis occurred from September 11, 2001, to September 10, 2006, we allowed the second or confirmatory diagnosis to take place any time through September 10, 2012. Chronic bronchitis required 2 diagnoses within 1 year and at least 1 additional diagnosis in the following 3 years. Multiple visits with the same diagnosis within a 30-day period were counted only once because they were most likely related to a single episode. For all OAD diagnoses, the date of diagnosis used for analyses was the date it was first documented.

WTC exposure measurement

Intensity of exposure to the WTC rescue and recovery effort was based on initial arrival time as follows: arrival on the morning of September 11, 2001 (high-exposure group); arrival during the afternoon of September 11, 2001, through September 12, 2001 (moderate-exposure group); or arrival any day between September 13, 2001, and September 24, 2001 (low-exposure group) (18, 23, 25–27).

Smoking status

Smoking status was characterized by self-reports as of September 10, 2006. Participants were considered "ever smokers" if they reported ever smoking before September 11, 2006. Participants were considered "never smokers" if they consistently reported never smoking on all questionnaires. If smoking status during the study period was missing, but the participant later reported never smoking, he or she was considered a "never" smoker. As previously noted, those whose smoking status was consistently missing ($n = 173$) were excluded from the final analytical cohort.

Statistical analyses

Follow-up time started on September 11, 2001, and ended on the earliest date of the following events: first OAD diagnosis, last FDNY physician visit, or September 10, 2006. WTC exposure was modeled by arrival time (3 groups), as described above, and was used in all relative rate analyses. Both moderate- and low-exposure groups were used as the reference population in separate analyses. Smoking was modeled as smoking status as of the end of the study. Age on September 11, 2001, was included in all models. Retirement from active service at the FDNY was modeled as a time-dependent variable.

We estimated relative rates and 95% confidence intervals for OAD incidence as a function of exposure group (high, moderate, low) over the first 5 years after September 11, 2001. These models were run first for an outcome of OAD and then as a sensitivity analysis using an asthma or nonasthma OAD outcome. In analyses by asthma or nonasthma OAD subtype, patients diagnosed with both asthma and nonasthma OAD on the same day ($n = 6$) were considered to have asthma alone. We used piecewise exponential survival models with 3-month increments as the time interval, allowing for a new baseline incidence rate at each 3-month interval, and the models were fit by maximum likelihood. This method results in estimates of relative rates that are almost always similar to the relative hazards obtained from Cox regression models (and have relative hazard interpretation) but with the advantage of having a full likelihood available to measure goodness-of-fit. Change point analyses were used within the models to estimate the 3-month interval (quarter) for which the relative incidences significantly changed (decreased or increased) from 1 quarter to the next (28). The goal of the analyses was to identify a change point after which relative incidences did not differ significantly from 1, which would show that the exposure-response relationship between WTC exposure and incident OAD was limited to the period prior to the change point.

Change points were determined using profile likelihood (29). First, we fit a model without change points that assumed constant incidence rates for each exposure group throughout the follow-up period. We then fit a succession of models with a single change point, allowing each model to change incidence rates at a different follow-up time, at 3-month intervals, with change points varying from 3 months to 57 months after September 11, 2001, resulting in a total of 19 possible models. The maximized likelihood for each model as a function of the change point forms the profile likelihood, and the maximum likelihood across all 19 models determined the best fitting model; the change point associated with that model is the maximum likelihood estimate for the change point that we report (29). The same process was used for models with 2 or 3 change points, in which each combination of change points was run in separate models and then compared via maximum likelihood. Likelihood ratio tests were used to determine the model with the proper number of change points. To avoid the potential for overfitting with too many change points over the follow-up time, successively more stringent criteria to include more change points were used. In comparing a model with p change points to a model with $p - 1$ change points, a P value of $(0.05) \times (0.5)^p$ was used as a threshold for selecting the larger model. Thus, to compare a model with 1 change point to a model with 0 change points, a P value threshold of 0.025 was used; to compare a model with 2 change points to a model with 1 change point, a P value threshold of 0.0125 was used, and so on. This sequential testing procedure controls the maximum type I error rate for all tests involving change points at 0.05 regardless of the number of change points considered (28).

WTC exposure was also modeled as an ordinal predictor (coded 0 for the low-exposure group, 1 for the moderate-exposure group, and 2 for the high-exposure group) to test the hypothesis of a linear trend in exposure-response relationship and to describe how that linear trend varied over the follow-up time using similar change point analyses. Detailed descriptions of the models are included in the Appendix.

RESULTS

There were 962 confirmed cases of OAD during the course of the study, which included 537 cases of asthma and 425 of nonasthma OAD, 417 of which were chronic bronchitis and 8 of which were COPD/emphysema. The median number of FDNY physician visits and the timing of the first visit were nondifferential by exposure group; therefore, they were not included in final models. The only variable that differed by exposure group was OAD incidence (Table 1); differences between exposure groups were significant for any OAD and for both subtypes (likelihood ratios based on Poisson model χ^2 statistics of 53.02, 31.63, and 21.49 for any OAD, asthma, and nonasthma OAD, respectively, all with 2 degrees of freedom, and all $P < 0.001$).

On the basis of the profile likelihood, the change point from a single change point model was determined to be 15 months after September 11, 2001. A single change point improved model fit over a model without any change points ($P < 0.001$). Adding a second change point did not improve model fit ($P = 0.338$); therefore, a 3-change-point model was

Table 1. Characteristics of the FDNY Firefighter Population by Exposure Level to the World Trade Center Disaster, New York City, New York, September 11, 2001–September 10, 2006

Characteristic	Exposure Level[a]									
	High Exposure ($n = 1,425$)			Moderate Exposure ($n = 6,437$)			Low Exposure ($n = 1,068$)			Total ($n = 8,930$)		
	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%
Age on September 11, 2001, years	39.5 (34.7–44.8)			39.2 (34.3–44.5)			40.6 (35.1–45.7)			39.4 (34.5–44.7)		
Ever smoker		415	29.1		1,855	28.8		335	31.4		2,605	29.2
Retired during study		257	18.0		1,120	17.4		236	22.1		1,613	18.1
No. of physician visits	21 (11–33)			19 (11–31)			17 (9–29)			19 (10–31)		
OAD diagnosis		222	15.6		668	10.4		72	6.7		962	10.8
Asthma		125	8.8		373	5.8		39	3.7		537	6.0
Nonasthma OAD		97	6.8		295	4.6		33	3.1		425	4.8
Overall OAD incidence per 100-person-years		3.60			2.28			1.49			2.39	
Total person-time, months		71,341.2			339,200.6			55,826.6			466,368.4	
Person-time, months	50.1 (16.8)[b]			52.7 (13.8)[b]			52.3 (14.2)[b]			52.2 (14.4)[b]		

Abbreviations: FDNY, Fire Department of the City of New York; IQR, interquartile range; OAD, obstructive airway disease.

[a] High exposure denotes those who arrived at the WTC site on the morning of September 11, 2001. Moderate exposure denotes those who arrived after noon on September 11, 2001, or on September 12, 2001. Low exposure denotes those who arrived during the period September 13–24, 2001.

[b] Values expressed as mean (standard deviation).

not considered. Analysis of the linear trend in exposure response found the same change point at 15 months, and that model fit significantly better than the corresponding model with no change points ($P < 0.001$). We also found no improvement in fit by adding a second change point ($P = 0.442$) compared with a 1-change-point model.

The relative rates of developing OAD for the most highly exposed group compared with the least exposed group were 3.96 (95% confidence interval (CI): 2.51, 6.26) during the first 15 months after September 11, 2001, and 1.76 (95% CI: 1.26, 2.46) after 15 months (Table 2). These pre– versus post–change point differences were statistically significant both for the high-exposure versus the low-exposure comparison ($P = 0.005$) and the high-exposure versus the moderate-exposure comparison ($P < 0.001$). In the final linear trend model, higher WTC exposure level was a significant predictor of OAD, both before ($P < 0.001$) and after ($P = 0.001$) the 15-month change point. Sensitivity analyses by OAD subtype showed similar results. The best fitting model for those with asthma was a single change point at 15 months. Before 15 months, the most highly exposed had a relative rate of 4.61 (95% CI: 2.43, 8.73) compared with the least exposed. After 15 months, the relative rate was 1.78 (95% CI: 1.14, 2.79). The 15-month change point model for nonasthma OAD had similar results (Table 2). Although contrasts between high and moderate exposures were nonsignificant both for any OAD and the subtypes, and the contrasts between moderate and low exposures were nonsignificant for the subtypes, the trend tests for asthma and nonasthma OAD were significant both before ($P < 0.001$) and after ($P = 0.013$ for asthma; $P = 0.030$ for nonasthma OAD) the 15-month change point.

More than 88% of the cohort had their first FDNY physician visit for any reason by the 15-month change point, and this rate did not differ significantly by exposure group ($P = 0.109$). All individuals diagnosed before the 15-month change point reported at least 1 lower respiratory symptom during that period. Of those diagnosed after the 15-month change point ($n = 599$), 71.8% ($n = 430$) reported at least 1 lower-respiratory symptom before the change point.

DISCUSSION

We found an association between WTC exposure and new diagnoses of OAD that lasted throughout the 5-year post–September 11, 2001, follow-up period. This conclusion is supported by the statistically significant trend tests, the continued significant differences between the high- and low-exposure groups, and the nonexistence of a significant change point past 15 months. The increased relative rates demonstrate that this occupational/environmental exposure influenced diagnoses of OAD for longer than has previously been suspected. Although the relative rates remained elevated throughout the study period, the magnitude became attenuated at 15 months after September 11, 2001. The pre– and post–15-month change point relative rates were similar when analyzing OAD by asthma and nonasthma subtypes, suggesting that the observed association was not driven by a specific diagnosis.

In multivariable analyses, the associations we reported between WTC exposure and OAD were similar, regardless of

Table 2. Change Point Models for OAD, Asthma, and Nonasthma OAD in FDNY Firefighters, New York City, New York, September 11, 2001–September 10, 2006[a]

WTC Exposure Level[b]	Relative Rate	95% CI	*P* Value
OAD			
<15 Months			
High vs. low exposure	3.96	2.51, 6.26	<0.001
High vs. moderate exposure	2.21	1.76, 2.77	<0.001
Moderate vs. low exposure	1.79	1.16, 2.77	0.009
15–60 Months			
High vs. low exposure	1.76	1.26, 2.46	0.001
High vs. moderate exposure	1.21	0.98, 1.48	0.079
Moderate vs. low exposure	1.46	1.09, 1.96	0.011
Asthma			
<15 Months			
High vs. low exposure	4.61	2.43, 8.73	<0.001
High vs. moderate exposure	2.15	1.60, 2.90	<0.001
Moderate vs. low exposure	2.14	1.16, 3.95	0.015
15–60 Months			
High vs. low exposure	1.78	1.14, 2.79	0.012
High vs. moderate exposure	1.22	0.92, 1.61	0.170
Moderate vs. low exposure	1.46	0.99, 2.17	0.059
Nonasthma OAD			
<15 Months			
High vs. low exposure	3.29	1.71, 6.35	<0.001
High vs. moderate exposure	2.30	1.62, 3.26	<0.001
Moderate vs. low exposure	1.43	0.77, 2.68	0.258
15–60 Months			
High vs. low exposure	1.76	1.06, 2.90	0.028
High vs. moderate exposure	1.20	0.88, 1.63	0.254
Moderate vs. low exposure	1.47	0.94, 2.28	0.088

Abbreviations: CI, confidence interval; FDNY, Fire Department of the City of New York; OAD, obstructive airway disease; WTC, World Trade Center.

[a] Best-fitting models had 1 change point at 15 months. Analyses control for age on September 11, 2001, retirement status as a time-dependent covariate, and smoking status as ever versus never.

[b] High exposure denotes those who arrived at the WTC site on the morning of September 11, 2001. Moderate exposure denotes those who arrived after noon on September 11, 2001, or on September 12, 2001. Low exposure denotes those who arrived during the period September 13–24, 2001.

which covariates were included in the models. We included smoking status and retirement in the final models because in previous studies, including our own, they were shown to be associated with an increased risk of OAD (2, 14, 21, 30).

Most of the cohort reported symptoms referable to the lower respiratory tract before the 15-month change point, including 72% of those who did not receive a diagnosis until after the change point. This is consistent with our prior report of highly prevalent lower respiratory symptoms in the first year after September 11, 2001 (26), followed by a decline in some symptom categories. For example, prevalence of cough declined from 54% in the first year after September 11, 2001, to 16% in the second year. Early symptom reports may represent acute inflammation, which resolved for some, was more troublesome for others leading to an early diagnosis, and yet for others, either waxed and waned or persisted, progressing at a slower rate and leading to a diagnosis at a later date. Early symptoms without an early diagnosis, however, may also occur, because some firefighters may have wished to continue working at the FDNY, despite symptoms. OAD diagnoses can lead to mandatory retirement, because these conditions potentially limit the safe performance of firefighting. Consequently, firefighters may try to avoid OAD diagnoses to allow them to continue employment. Nevertheless, we observed a consistent exposure-response gradient throughout the follow-up period, with the highest OAD incidence in the high-exposure group, suggesting that WTC exposure continued to influence OAD diagnoses throughout the 5-year follow-up period.

Whether and for how long latency periods occur following irritant exposures remains unknown. Studies of latency are difficult to find. When available, they may be limited by small numbers; imprecise measures of exposure; measurement only of duration of direct exposure, but not of the time interval between exposure cessation and disease diagnosis; and undocumented or unknown health care access that could have contributed to an observed long latency (10, 11, 13). Following the WTC disaster, we found a relationship between WTC exposure and newly diagnosed OAD that persisted for at least the first 5 years. The existence of a latency period for WTC-related irritant OAD in this cohort may be due to multiple simultaneous or sequential exposures to noxious gas, vapor, fumes, and particle forms (31–33) that were inhaled on numerous occasions. Additionally, immunologically mediated mechanisms have been shown to play a role in the development of OAD following WTC exposure in this cohort (34–36), although it is not known if they can differentiate between those with early versus late onset. Longer latency periods between exposure and the diagnosis of new-onset asthma might be expected for immunologically mediated asthma because time is needed to acquire "sensitization" to the causal agent (12) or for chronic inflammation or airway remodeling to occur. It is also possible that some of those diagnosed with OAD have an underlying case of bronchiolitis, similar to that reported in workers exposed to butter flavoring volatiles including diacetyl (37–43), in which latency ranged from 9 months to 14 years after exposure (37–43).

There are some potential limitations to this study. As mentioned above, given this cohort's continued participation in the WTC rescue and recovery effort through July 24, 2002, it is possible that diagnoses might have been postponed in nonseriously ill firefighters. Additionally, there could have been an interaction between initial WTC exposure and subsequent or ongoing firefighting exposures for those, comprising most of the cohort, who did not retire shortly after September 11, 2001. We believe, however, that this issue is mitigated by the fact that retirement status was not significantly associated with OAD incidence and by our finding of a statistically significant WTC exposure-response gradient throughout the

study period, indicating that WTC exposure continued to be associated with OAD diagnoses even during later periods. Further, there is no evidence that the high-exposure group had differential firefighting exposures after the WTC disaster. Nonetheless, it remains possible that OAD latency was a response to cumulative exposures, albeit driven by WTC exposure, and was influenced by an individual firefighter's exposure to, for example, the number or type of non-WTC fires or to nonoccupational exposures for which data are not available. Likewise, there could be an interaction with nonoccupational events such as respiratory viral infections (44). Finally, we acknowledge that, beyond the WTC disaster and other exposures, the susceptibility to develop OAD, like any disease, is, in part, influenced by genetic predispositions (3).

This study has numerous strengths. We were able to successfully implement a statistical method not previously used in the analysis of WTC-exposed cohorts to estimate the amount of time that WTC exposure was associated with new-onset OAD. This has broad applications for future WTC studies and for analyses of other exposure-response relationships that are not immediately obvious. In fact, we are hopeful that this technique can facilitate a better understanding of the relationship between acute or chronic occupational exposures and subsequent illness. Another strength is limited participation bias, because we knew the exposure status of all cohort members, and almost all were included in the study. Further, because this cohort did not have OAD prior to September 11, 2001, we are confident that these are incident diagnoses. All firefighters had free and unlimited access to medical treatment during this study period, which contributed to very limited loss to follow-up (6.4%) and provided an unparalleled opportunity for them to obtain a diagnosis without delay across all exposure levels. Because analyses focused on relative rates, our results were unaffected by potential confounders, such as the timing and initiation of treatment or season of diagnosis. Further, our results consistently showed a significant WTC exposure-response relationship with increased rates of OAD throughout the study period in all models. In future studies, we plan to use similar methodology to analyze OAD incidence beyond the first 5 years to determine if there are additional change points and to study post–WTC exposure symptom development and persistence.

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(Appendix follows)

APPENDIX

Detailed Description of the Models Included in the Analyses for Estimating the Time Interval Between World Trade Center Exposure and Incident Diagnoses of Obstructive Airway Disease

In the model equations for analyses that compare the 3 exposure groups (low, moderate, high), low-exposure intensity is assumed to be the reference group. These models are piecewise exponential survival models with change points included to model the changing relative rate over time.

Let $(t_{k-1}, t_k]$ define the kth interval of follow-up, with $t_0 = 0$ at September 11, 2001; in our analyses, we had twenty 3-month time intervals. Also, let i index all the combinations of covariates that exist for the time interval k. The null model, assuming constant relative rates of incidence over the entire follow-up period and, therefore, containing no change points, can be expressed as follows:

$$\log(Y_{ik}) = \log(T_{ik}) + \sum_{k=1}^{k=20} \alpha_k w_{ik} + \beta_1 x_{i1} + \beta_2 x_{i2} + \sum_l \gamma_l z_{il}. \quad (1)$$

The meanings of the data and parameters in model 1 are as follows: Y_{ik} is the number of incident cases of disease, modeled to follow a Poisson distribution given the covariates. T_{ik} is the total person-time at risk for a particular stratum corresponding to the time interval k and the exposures indicated by the values of x_{i1}, x_{i2}. The α_k's in model 1 represent the log of the baseline incidence (i.e., the incidence for the low-exposure group for individuals with the z_{il}'s all taking the value 0 and the w_{ik}'s as dummy variables that indicate the time interval for the stratum). As stated above, x_{i1} and x_{i2} are dummy exposure variables, with x_{i1} taking the value 1 for moderate exposure and 0 otherwise, and x_{i2} taking the value 1 for high exposure and 0 otherwise; β_1 is thus the log relative hazard between the moderate- and low-exposure groups, and β_2 is the log relative hazard between the high- and low-exposure groups. The z_{il}'s are the additional covariates included in the model, and the γ_l's are the log relative hazard for the additional covariates. A Poisson likelihood, mathematically equivalent to that of the exponential survival model, was used for the model fit and as the goodness-of-fit measure.

In the nonnull model, change points are introduced to allow the relative hazards between exposure groups to vary over the follow-up time. This is shown in the following expression for a model with p distinct nontrivial change points:

$$\begin{aligned}\log(Y_{ik}) = \log(T_{ik}) &+ \sum_{k=1}^{k=20} \alpha_k w_{ik} \\ &+ \sum_{j=1}^{p+1} \beta_{1j} x_{i1} 1(\tau_{j-1} < t_{ik} \le \tau_j) \\ &+ \sum_{j=1}^{p+1} \beta_{2j} x_{i2} 1(\tau_{j-1} < t_{ik} \le \tau_j) \\ &+ \sum_l \gamma_l z_{il}.\end{aligned} \quad (2)$$

In model 2, β_{1j} and β_{2j} are the log relative hazards (moderate vs. low exposure, and high vs. low exposure, respectively), for the jth period of follow-up $(t_{j-1}, t_j]$, defined as between the change points at time τ_{j-1} and τ_j, with $\tau_0 = 0$ and $\tau_{p+1} = 60$ months from September 11, 2001, and the time variable t_{ik} defined similarly. $1(-)$ is a dummy variable function taking the value 1 when the argument is true and 0 otherwise.

For $p \ge 1$, $\tau_1, \tau_2, \ldots, \tau_p$ would be nontrivial change points. For $p = 1$, model 2 reduces to model 1. Models with different numbers of change points can be compared by using likelihood ratios. A significantly better fit to a model with 1 or more change points indicates that the exposure-response relationship changes over time. If, after some time, τ_j, neither $\beta_{1,j+1}$ or $\beta_{2,j+1}$ is significantly different from 1, that would show that the exposure-response relationship between World Trade Center exposure and incident obstructive airway disease is limited to the first τ_j months of follow-up.

For the analyses examining the trend in exposure-response relationship, there is only 1 exposure variable, as indicated in this model:

$$\begin{aligned}\log(Y_{ik}) = \log(T_{ik}) &+ \sum_{k=1}^{k=20} \alpha_k w_{ik} \\ &+ \sum_{j=1}^{p+1} \beta_j x_i 1(\tau_{j-1} < t_{ik} \le \tau_j) + \sum_l \gamma_l z_{il}.\end{aligned} \quad (3)$$

Here, x_i takes the value 0 for low exposure, 1 for moderate exposure, and 2 for high exposure. If, after some time, τ_j, β_{j+1} is not significantly different from 0, then the monotonic exposure-response relationship between World Trade Center exposure and incident obstructive airway disease is limited to the first τ_j months of follow-up.