

FINAL RESEARCH REPORT

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Assessing the Impacts of Epidemiologic Biases in WTC Health Studies

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ABSTRACT

This project aimed to assess the impact of epidemiologic biases in World Trade Center (WTC) health studies by identifying the presence of bias and subsequently quantifying and adjusting for the bias effects. Main methods used in the project are: 1) Quantitative bias evaluation with a systematic review of the literature related to WTC exposure and asthma incidence; 2) hypothetical bias assessment and adjustment; and 3) Heckman selection correction using empirical data collected from the WTC general responder cohort (GRC). The key findings from this study are: 1) Qualitative presence and the impact of potential biases in the context of WTC-related studies, and 2) a quantitative assessment of the presence of selection bias from existing literature and bias-corrected the association between WTC exposure and health outcome. This project introduced methods for bias identification and qualitative and quantitative adjustments in WTC cohorts. These methods will benefit the researchers in evaluating biases in their studies and in correcting the bias effect in causal inference. Our study findings can serve as a guideline to avoid biases from the study design phase in future disasters.

RESEARCH AIMS/PROJECT OVERVIEW

The main objective of the project was to assess the impacts of epidemiologic biases in WTC health studies by identifying the presence of bias and then by quantifying and adjusting for the bias effects. To achieve this goal, we proposed to conduct three specific aims as below:

***Aim 1.** Identify potential biases and use the WTC responder cohort data to provide evidence of the strength and direction of these biases in the use of WTC responder cohort data;*

***Aim 2.** Quantify the effects of likely biases in risk estimates for the four proposed health outcomes, and produce bias-adjusted estimates of the effects of various WTC exposures on health outcomes; and*

***Aim 3.** Develop recommendations for bias adjustment in WTC health studies and future disaster studies.*

All three aims have been achieved.

AIM 1 MAIN FINDINGS:

This aim qualitatively assessed the presence of biases and their impact in WTC health studies. In doing so, we have performed a systematic literature review of articles referring to asthma among WTC responders in order to identify potential bias. Currently, we are in the final stage of writing an article for journal submission.

From initial review of literature on this topic, 75 articles were identified from PubMed search, but only five articles came to be relevant for the final evaluation. The selection criteria were to include those articles reporting asthma incidence and those reporting association with WTC exposure among WTC responders. Responders included general responders enrolled in the GRC, New York City WTC Health Registry (WTCHR), and firefighters from Fire Department of New York (FDNY). The qualitative evaluation included the following – source of bias in exposure and outcome measurement, different types of bias (including selection bias, exposure misclassification, reporting bias, and unmeasured confounding), and the impact of these biases. Our assessment was done with respect to each WTC cohort and the results were compared against each other.

Our main findings confirm the presence of a number of different types of biases in each WTC cohorts, which could have potentially resulted in bias in observed associations. In conducting this aim, we have learned that there exists only one article published by FDNY, and two from each of the remaining two cohorts, respectively, regarding asthma and WTC exposure association. This sparsity in the number of studies on this topic was surprising because asthma is one of the most publicized health problems from the WTC exposure. Among these, three of five papers that we have examined either did not discuss any biases or only briefly stated such biases. Only two article performed a quantitative bias analysis. Brackbill et al. tested for selection bias

by comparing self-identified and list-identified participants to WTCHR (Brackbill et al. 2009). Kim et al. identified health worker effects and adjusted the effect by matching occupation (Kim et al. 2012). The remaining 70 studies that are outside the scope of asthma and WTC association do not quantitatively assess potential biases at all.

In addition to a literature review, we have performed internal-data validation for bias using the GRC dataset. First, we have checked for inconsistency of repeated self-reported asthma diagnosis (Yes/No) among those who participated in at least one follow-up visit. Second, we have examined the data quality on date of diagnosis of asthma. The date of diagnosis is a very important piece of information in identifying the incidence of outcome. In any WTC study, to identify the incidence of a health outcome, diagnosis date must be obtained and incidence cases must have been diagnosed on September 11, 2001 or after.

Table 1. Frequency distribution of reported asthma date by day, month, and year.

Day	N	%	Month	N	%	Year	N	%
1	2,542	84.5	1	1,251	41.6	Prior to 2001	765	26.4
2	29	1.0	2	178	5.9	2001	75	2.5
3	11	0.4	3	177	5.9	2002	260	8.6
4	15	0.5	4	148	4.9	2003	360	12.0
5	13	0.4	5	143	4.8	2004	252	8.4
6	18	0.6	6	164	5.5	2005	177	5.9
7	23	0.8	7	126	4.2	2006	366	12.2
8	21	0.7	8	141	4.7	2007	340	11.3
9	8	0.3	9	164	5.5	2008	167	5.6
10	13	0.4	10	184	6.1	2009	140	4.7
11	16	0.5	11	151	5.0	2010	78	2.6
12	21	0.7	12	183	6.1			
13	12	0.4						
14	23	0.8						
15	17	0.6						
16	16	0.5						
17	18	0.6						
18	11	0.4						
19	8	0.3						
20	35	1.2						
21	14	0.5						
22	15	0.5						
23	10	0.3						
24	11	0.4						
25	19	0.6						
26	10	0.3						
27	14	0.5						
28	16	0.5						
29	9	0.3						
30	15	0.5						
31	7	0.2						

In this process, we have found that less than 1% of asthma diagnosis were inconsistent. These cases were directly corrected by replacing the value to “yes”, when other asthma diagnosis-related questions were answered, such as the date of asthma diagnosis, and replacing the value to “No” when no other related questions were provided. Missing or incomplete date of diagnosis was not imputable without any supporting information. However, the magnitude of problem from the GRC data was ignorable.

We found that 85% and 42% of reported asthma diagnosis date were the 1st day of the month and January, respectively, as shown in Table 1. However, the day of month can be ignorable for incidence ascertainment because it is also highly likely to be inaccurate due to recall problem. It may be significant only if a substantial number of cases reported September 1 of 2001 as the diagnosed date, but only 11 reported this as the diagnosis date. The month of diagnosis is important and less likely to have been contaminated by recall bias. However, we have observed that 42% of the cases reported January as diagnosis date and this is highly likely to be erroneous. Nevertheless, only 23% (n=17) reported January when the diagnosed year was 2001 and only 17 cases reported January of 2001, so this does not affect any statistical association between asthma and WTC exposure.

Validation test for other data was not performed because most of non-health outcome data were measured only once and internal validation requires repeated measures. To perform validation of these data, one must collect them again during follow-up visits or perform external validation. An example of external validation is comparing this non-health outcome data, such as smoking status, with other record such as medical chart that contains same information. We were not allowed to obtain personal identifiers and consequently, were not able to obtain any other data for validation.

AIM 2 MAIN FINDINGS:

With respect to Aim 2, we have employed two approaches. First is a hypothetical bias analysis for multiple biases adjustment, and second is an empirical bias analysis for selection bias using Heckman selection correction.

The hypothetical bias analysis was published in *Annals of Epidemiology* (Jurek 2016). This study described the theoretical mechanism of bias generation process and simulates a range of bias effect. This study also demonstrated bias adjustment in Odds Ratio (OR) estimation. It found multiple biases adjusted ORs for WTC exposure and asthma ranged from 1.3 to 3.8. The bias analysis demonstrated with hypothetical data in this study is a useful tool to determine what data should be collected for bias analysis for a future disaster cohort.

In the empirical bias analysis, we have adopted the Heckman correction analysis, to examine presence of selection bias by using three separate selection models, using data from different temporal stages. James Heckman developed a two-stage sample selection model in 1979 (Heckman 1979). The concept behind this method is to treat unselected population as omitted

variance in selected population, so that adjusting for unselected population variance in selected population can produce unbiased association. In our study, we have created three potential selection processes as illustrated in Figure 1 and 2: 1) adjusting for the GRC participants who dropped out at the follow-up visit 1 and only participated baseline visit (selection model 1), 2) adjusting for those who dropped at follow-up visit 2 or later (selection model 2), and 3) adjusting for those who enrolled in 2006 or later (selection model 3). The underlying hypothesis for each selection model is that the participants who dropped out at follow-up visit 1 or at the later follow-up visits are different from those who continued to participate until the final scheduled visits. In addition, we have found that the participant group who enrolled in 2006 or later are also different from those who enrolled earlier than 2006. Figure 1 describes such conceptual selection processes. Note, however, that “Selection stage 1” has been excluded from Figure 1 because the Selection stage 1 occurs at the moment of deciding to enroll to the cohort, and we do not have any information on those who did not enroll. However, necessary data for bias analysis to test Selection stage 2 and 3 were collected and included in the analysis. In 2006, GRC aggressively expanded their outreach program to recruit more participants. From this outreach activity, a large number of police officers joined with the benefit of a paid day off in order to visit WTC Health Program. Figure 2 shows enrollment frequency by occupation and by enrolled year. It shows large increase of protective service workers (i.e., police) enrollment from 2006.

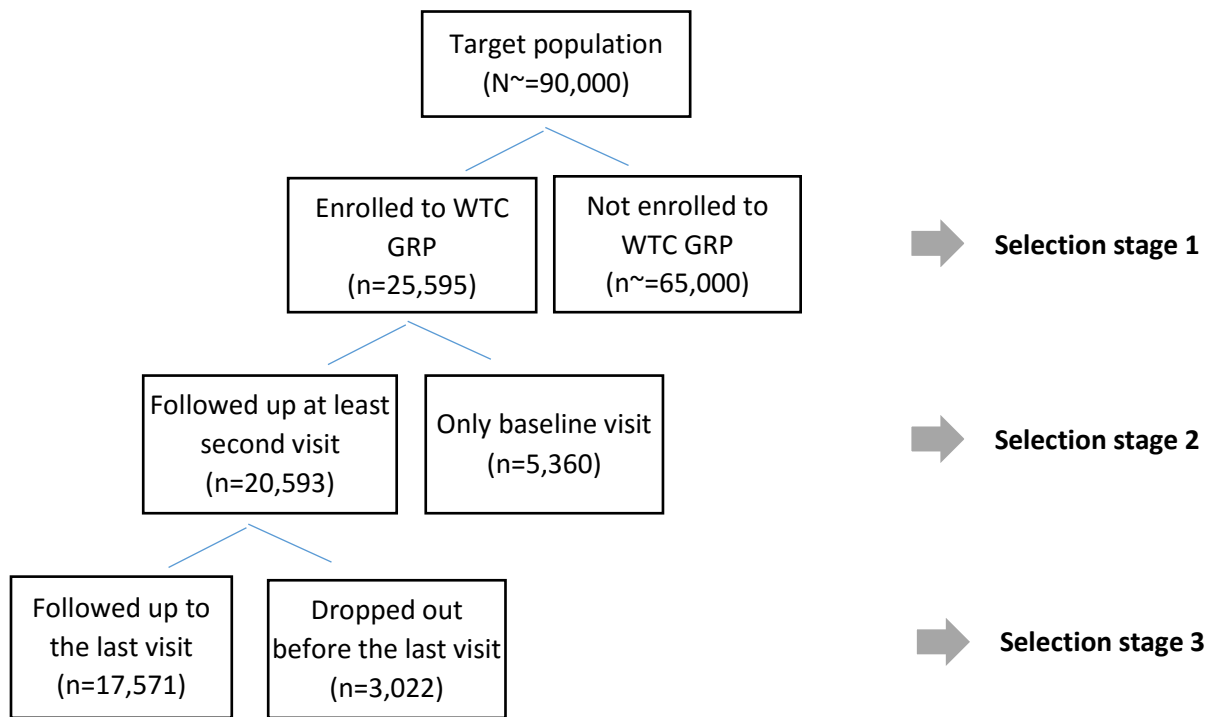


Figure 1. Conceptual selection process of WTC general responder cohort.

After applying the Heckman correction analysis, all three selection models that we have tested statistically demonstrated presence of selection bias. We have observed that the GRC participants who participate longer in the follow-up visits were those that had more WTC

exposure (arrive at the site earlier than 9/14/2001), never smoked, married, and when have been diagnosed some other health problems. A similar pattern was found among those who enrolled in 2006 or later, but the diagnosed health problems prior to the baseline visit were the main reasons for this post-2006 group.

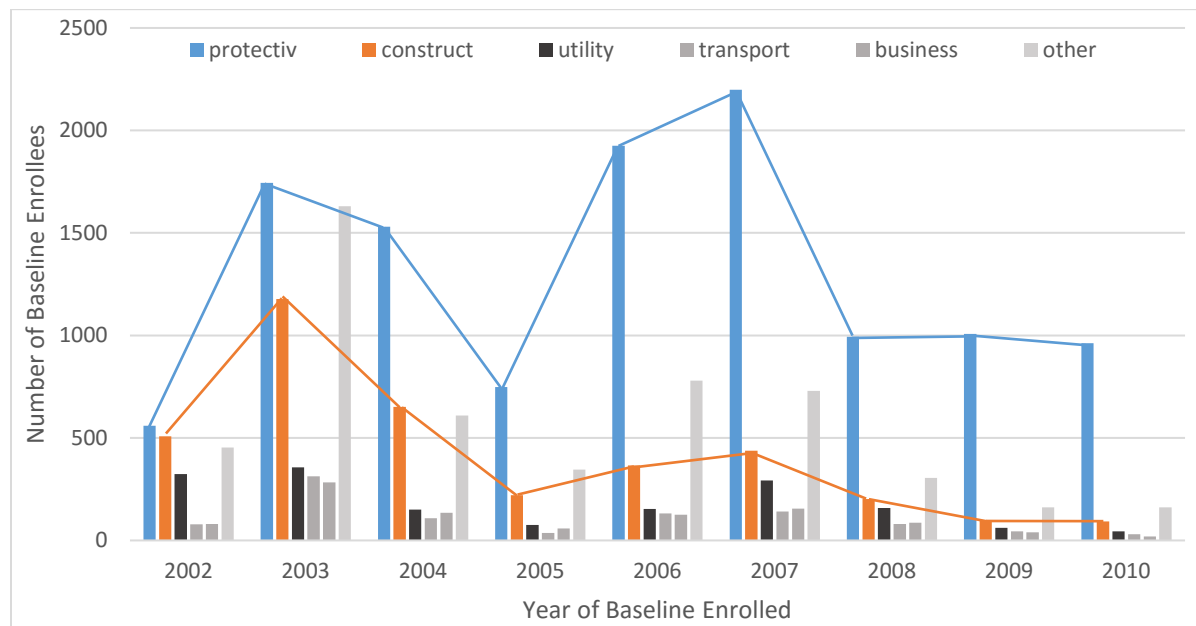


Figure 2. Baseline enrollment by occupational groups

After adjusting for the selection bias, Heckman model adjusted Risk Ratios significantly compared to no-bias correction model. In Selection Model 1 correction, when compared against no-correction model, the GRC participants who were widowed, non-Hispanic, and current smoker experienced a higher risk of asthma while these variables *prevented* asthma before the correction. Factors such as the degree of WTC exposures, arriving on 9/11 AM and more working hours, became non-significant after adjusting for selection bias while these variable significantly increased asthma risk before adjusting for selection bias. In Selection Model 2 correction, having occupations other than protective service workers became a significant risk factor for asthma. The same pattern was observed in Selection Model 3 – this reflects that the effect of a large number of police officers enrollment from 2006. One may infer from this that protective service officers who enrolled later experienced less asthma than the other occupational groups. Interestingly, WTC exposures remained at similar strength and direction of association in respect of asthma, regardless of correction of selection bias.

Nearly half of the GRC population is protective service workers and over half of those protective service workers enrolled to the GRC in 2006 or later (Figure 2). Those that enrolled later had more health problems than those enrolled before 2006 while exposure status remained similar between the two groups. The conclusion that can be drawn is that severe selection bias was introduced by including a large group of protective service workers, and this may be due to the

distinct characteristics of the occupational groups. Therefore, these findings suggest employing stratification analysis by occupation to remove selection bias effect from specific occupational groups, such as the protective service workers.

Final findings from this bias analysis was the observed association between probable Post Traumatic Stress Disorder (PTSD) and asthma. Brackbill et al (2009) observed significant association between the two health outcomes. We have included PTSD in our bias analysis as a source of selection bias rather than as a risk factor with the hypothesis that people with PTSD participate more or enroll earlier. However, the analysis showed that PTSD is the sole risk factor for asthma or *vice versa* even after controlling for selection bias.

AIM 3 MAIN FINDINGS:

Results from Aims 1 and 2 signal certain methodological improvements to minimize and correct biases, if applicable. Such recommendations are to 1) understand potential biases in the unique setting of disaster study or cohort, 2) design data collection tools to obtain bias factors for evaluation of presence and adjustment, if present, and 3) present the findings with either a qualitative or quantitative bias analysis.

TRANSLATION OF RESEARCH FINDINGS

In epidemiology, bias is one of the most significant challenges, especially in observational studies where eliminating all bias is nearly impossible. Bias is by definition the difference (error) between the measurement and the truth. Avoiding and controlling these biases are often viewed as the overarching goal of epidemiology. Nevertheless, most epidemiologic analyses either assume that error is absent or, if present, that such errors are random. For example, most conventional statistical methods require the strong assumption that the data were generated in a randomized experiment with perfect compliance. These methods include chi-square test, t-test, and most type of regressions. When this assumption is false, the interpretation of “statistical significance” can be highly misleading. While epidemiologic studies often discuss the potential sources and effects of bias (commonly three types: selection bias, information bias, and uncontrolled confounding), the impacts of these biases on study findings are rarely quantified. One of the main reasons for not quantifying bias is because the process requires specifying values (bias parameters) when little or no data are available, and this generally requires advanced statistical techniques such as multiple simulations. However, the failure to account for the effects of bias can distort study findings and lead to incorrect conclusions about causal inference.

This project demonstrated how to evaluate potential biases and how to correct such defects. Three different methods have been introduced based on the research findings – qualitative assessment, quantitative hypothetical and empirical analyses. The qualitative method is considerably beneficial at the study design stage. Understanding potential biases will help designing studies to minimize biases or at least design data collection to obtain bias information for future bias correction. The hypothetical approach demonstrated correcting multiple biases is a strong tool to correct bias effect when all required bias parameters were collected. Heckman selection bias correction method is a population approach in the field of economics, but it has not yet been adopted in public health. It is a very powerful tool to correct selection bias and also to

understand what factors affect people to determine to join study or not, or to be followed or dropped. This is critical in planning recruitment strategies and selection bias can be significantly avoided. Our study found that intensive recruitment of protective service workers four year from the inception of cohort strongly biased entire cohort.

PUBLIC HEALTH RELEVANCE AND IMPACT

Despite the breadth and scope of the potential impact of biases, this project is the only study of this kind which investigates bias effect in WTC health studies. Researchers trained in epidemiology are aware of the importance of avoiding biases and the serious impact. However, in reality, eliminating biases is almost impossible and even assessing the presence of any biases is difficult without having data on source of potential biases. This project provided several feasible approaches to identify, eliminate, and correct biases. By correcting these biases, more accurate causal relationships can be identified.

Disregarding the bias effect entirely or making inadequate effort to avoid and correct potential biases is a great loss, especially for a large cohort like WTC. Huge amount of financial support and other resources have been provided to recruit and to follow a large population overtime – there are a lot of lessons and findings that can be drawn from these researches and the need to avoid biased results is clearly evident.

We hope that the three bias analysis methods presented in this project are widely considered, applied and adopted by other WTC researchers and that the accuracy of causal inference among the WTC exposed population is improved. In the long-term, we expect that bias corrected causal inference will help identify better interventions with respect to WTC-related health problems and improve early detection of emerging health problems.

PUBLICATIONS

Peer-review Journal

Published:

Jurek AM, Maldonado G. Quantitative bias analysis in an asthma study of rescue-recovery workers and volunteers from the 9/11 World Trade Center attacks. *Annals of epidemiology*. 2016 Nov 30;26(11):794-801.

Submitted:

Kim H, Kriebel D, Liu B, Baron S, Mongin S, Baidwan NK, Moline J. Standardized Morbidity Ratios of four chronic health conditions among World Trade Center responders: Comparison to National Health Interview Survey. *American Journal of Industrial Medicine*. Under-review

In progress:

Kim H, Kriebel D, Cifuentes M, Baidwan NK, Baron S. Qualitative assessment of epidemiologic biases in World Trade Center health studies. (*expected to submit to journal in November 2017*)

Kim H, Baron S, Cifuentes M, Baidwan NK, Kriebel D. Quantitative selection bias assessment in World Trade Center general responder cohort using Heckman sample selection correction method. (*expected to submit to journal in November 2017*)

Conference Presentation:

Riester S, Kim H. Incidence of Rheumatoid Arthritis among World Trade Center Responder. American Occupational Health Conference, Denver, CO, 2017

Kim H, Baron S, Cifuentes M, Jurek A, Maldonado G, Kriebel D. World Trade Center Disaster and the Health of Responders: Surveillance, Epidemiology, and Biases. The 25th International Conference on Epidemiology in Occupational Health, Barcelona, Spain, 2016

Jurek A, Mongin S, Kriebel D, Cifuentes M, Baron S, Kim H. Epidemiologic Biases in Asthma Studies of the 9/11 World Trade Center Attack: Disaster Epidemiology Needed. Society for Epidemiologic Research, Miami, USA, 2016

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