HEART ATTACK AMONG OIL SPILL WORKERS 5 YEARS AFTER *DEEPWATER HORIZON*

Jean Marie Strelitz

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology.

Chapel Hill
2018

Approved by:

Lawrence Engel

Marilie Gammon

Gerardo Heiss

David Richardson

Richard Kwok

ABSTRACT

Jean Marie Strelitz: Heart attack among oil spill workers 5 years after Deepwater Horizon
(Under the direction of Lawrence Engel)

Introduction: The *Deepwater Horizon* oil spill was the largest marine oil spill in history.

Exposures to total hydrocarbons from fresh and burning oil during clean-up of the oil spill, as

well as stress due to the oil spill, may have increased risk of coronary heart disease (CHD)

among clean-up workers and Gulf Coast communities.

Objective: Assess the associations of duration of clean-up work, residence proximity to the oil

spill, and total hydrocarbon (THC) exposure with heart attack over 5 years of follow-up.

Methods: The Gulf Long Term Follow-up (GuLF) STUDY is a cohort study of the human health

impact of the *Deepwater Horizon* oil spill. Among respondents with two GuLF STUDY

interviews (n=21,256), we estimated hazard ratios (HR) and 95% confidence intervals (95%CI)

for heart attack (self-reported myocardial infarction, or fatal CHD) associated with duration of

clean-up work, residence proximity to the spill, and total hydrocarbon (THC) exposure. We

weighted the study population to account for differences between those who did (n=21,256) and

did not (n=10,353) complete the second interview.

Results: Maximum THC exposure levels >0.30ppm were associated with heart attack [marginal

HR (95% CI) for ≥3.00ppm=1.81 (1.11, 2.95)], as was living in proximity to the oil spill (vs.

living further away) [1.30 (1.01-1.67)]. Work duration >180 days (vs. 1-30 days) was

suggestively associated with heart attack [1.41 (0.89-2.21)]. Associations were robust to censoring.

Conclusions: In this first study to assess heart attack risk in relation to oil spills, maximum THC exposure and living in proximity to the spill were associated with heart attack, and risks persisted across the 5-year study period.

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LIST OF ABBREVIATIONS

BP   British Petroleum

CI   Confidence interval

CHD   Coronary heart disease

DAG   Directed acyclic graph

ECG   Electrocardiogram

EPA   Environmental Protection Agency

GuLF   Gulf Long-term Follow-up

HR   Hazard ratio

IP   Inverse probability

MI   Myocardial infarction

NAAQS   National Ambient Air Quality Standards

NDI   National Death Index

NIEHS   National Institute of Environmental Health Sciences

NOAA   National Oceanic and Atmospheric Administration

PM   Particulate matter

RD   Risk difference

THC   Total hydrocarbon

US   United States

VOC   Volatile organic compound

CHAPTER 1: SPECIFIC AIMS

The *Deepwater Horizon* oil spill was the largest marine oil spill in US history (1). Workers involved in clean-up of the spill faced exposures to a number of chemicals, including volatile organic compounds and particulate air pollution generated by crude oil and burning oil (2). Ambient exposures to total hydrocarbons from particulate matter and volatile chemicals are associated with risk of coronary heart disease (CHD) (3-5). Short-term (24-hour) average elevations in ambient particulate matter increase incidence of myocardial infarction (MI) (3, 6). Exposures to hydrocarbons from working in proximity to crude oil and burning oil during the clean-up response may have impacted the risk of CHD among clean-up workers, but no previous study of oil spills has addressed this question. Apart from chemical exposures related to the spill, Gulf coast communities faced economic burdens and psychosocial stress due to disruption of the local tourism, fishing, and oil industries in the months following the oil spill (7, 8). Psychosocial stress can impact risk of cardiovascular diseases by accelerating progression of atherosclerotic plaques (9). Thus, the physical and emotional stress caused by the oil spill, in addition to exposure to hydrocarbons due to the spill, may impact incidence of CHD among clean-up workers and Gulf Coast residents.

The Gulf Long Term Follow-up (GuLF) STUDY is the largest study of the human health impact of oil spills and is the first to assess cardiovascular health outcomes among individuals exposed to oil spills (10). The GuLF STUDY collected information on health outcomes, including diagnoses of myocardial infarction, longitudinally during two telephone interviews

occurring two to three years apart. Of the 31,609 English or Spanish-speaking participants who completed the first study interview, 67% completed the second interview. We have assessed the associations of duration of clean-up work, total hydrocarbon exposure, and residence proximity to the oil spill with heart attack in the 5 years following the oil spill, accounting for predictors of non-response to the second study interview.

Aim 1**: (1) Determine predictors of non-response to the second study interview, and (2) assess associations between duration of clean-up work with heart attack, and residence proximity to the oil spill with heart attack up to 5 years after the spill, accounting for predictors of non-response.** Information on the exposures and first nonfatal heart attack were self-reported during the first and second study interviews; fatal coronary heart disease was ascertained from the National Death Index. We assessed factors associated with response to the second interview by determining the crude associations of lifestyle, demographic, and clean-up work characteristics with follow-up status. We estimated conditional and marginal hazards ratios using Cox regression models with inverse probability (IP) of censoring weights, and estimated cumulative incidence of heart attack using Nelson-Aalen survival estimation.

Aim 2: **Assess the association between total hydrocarbon exposure during clean-up work and heart attack up to 5 years after the oil spill.** Maximum and median total hydrocarbon (THC) exposure levels were determined using a job exposure matrix taking into account clean-up tasks, dates, and locations of work, and measurements of airborne THC taken throughout the clean-up. We estimated marginal hazard ratios for the associations of maximum and median total hydrocarbon exposures and heart attack in the 5-year follow-up period. We estimated cumulative incidence of heart attack at 1, 2, 3 and 4 years of follow-up.

CHAPTER 2: BACKGROUND

The *Deepwater Horizon* oil spill

The oil spill began April 20th 2010 when an explosion occurred at the *Deepwater Horizon* oil rig, roughly 50 miles offshore in the Gulf of Mexico. Over 200 million gallons of crude oil were released into the ocean before the oil well was eventually capped in July 2010 (11). A clean-up effort was launched immediately to decrease the volume of oil that had accumulated on the ocean surface and on shores. Oil management techniques such as 'controlled burns' of oil deposits and spraying dispersants were used throughout clean-up (1). These practices led to additional widespread chemical exposures among clean-up responders.

Over 100,000 workers and volunteers were involved in the cleanup effort. Workers included local fishermen and other Gulf residents working as contractors or subcontractors for British Petroleum (BP), oil and gas workers that were already employed on oil rigs in the Gulf, the US Coast Guard, and volunteers. Workers came from all over the US, though most were from the Gulf Coast region.

Those who were involved in clean-up or who lived in areas near to the oil spill faced potential exposures to air pollution from crude oil and burning oil, heat stress, chemical dispersants, and other pollutants from vehicles, boats or other sources related to the oil spill (12). Clean-up workers experienced differing spill-related exposures depending on their tasks, work locations, and dates that they worked (2, 13). Aside from clean-up related exposures, Gulf Coast

communities faced socioeconomic stress in the wake of the oil spill due to job loss and loss of income in the tourism, fishing and oil industries (8). Exposures to chemical pollutants and stress during the oil spill may have caused acute as well as longer-term health effects among workers and community members, however few epidemiologic studies have examined the physical health impacts of oil spills.

Characterizing public health concerns of the oil spill

Crude oil and burning oil

Nearly 5 million barrels of crude oil were released into the Gulf of Mexico following the explosion at the *Deepwater Horizon* drilling rig. During the clean-up, workers performed a variety of tasks to disperse, burn, or otherwise remove the oil from the ocean and along shorelines. Workers located on the water generally had the highest exposures to fresh crude oil, and the volatile chemicals present in fresh oil, while workers on shorelines were more likely to be exposed to weathered oil with decreased volatile constituents (2). The majority of fresh oil exposures occurred before the oil well was capped on July 15th 2010. Oil deposits on the ocean surface were burned, resulting in large plumes of smoke containing various hydrocarbon combustion products. Exposures to oil and combustion products during the clean-up effort varied temporally and spatially (2, 10).

Air pollution due to the spill

Throughout the oil spill, ambient levels of air pollutants were elevated across the Gulf Coast (14). Increases in ambient levels of hydrocarbons including particulate matter (PM) and volatile organic compounds have been associated with numerous adverse health outcomes, including cancer (15-18), cardiovascular disease (19-23), respiratory symptoms (24, 25) and other chronic diseases (18, 26, 27). While the average air pollutant exposures occurring during

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the spill were often higher than typical ambient levels (2), they were at the low end of

occupational levels for which exposure guidelines are often set. Particulate matter measurements

taken by the National Oceanic and Atmospheric Administration (NOAA) recorded

concentrations in the air directly over oil slicks in the Gulf of Mexico that were comparable to

ambient-level concentrations in urban U.S. areas, however concentrations increased in areas

downwind to the spill, where some workers may have been exposed (28). Short term (24-hour)

increases in ambient particulate matter increase risk of hospitalizations due to coronary heart

disease (CHD) (3) and acute myocardial infarction (29, 30). Research is needed to assess

whether these exposures, at concentrations present during the oil spill, impact CHD as well.

Physical and psychological stress

Many workers involved in the oil spill response and clean-up faced physical stress due to

high ambient temperatures and the manual labor that was required for many clean-up tasks,

which could contribute to coronary events. Clean-up tasks included carrying or lifting

equipment, working outdoors in high heat, and other physical labor (1, 2). Use of personal

protective equipment such as Tyvek suits and respirators may have also contributed to heat stress

and fatigue.

Aside from physical stress related to clean-up work, workers and other residents living in

areas that were impacted by the oil spill may have faced psychosocial stressors due to the spill

that were unrelated to clean-up work. Most clean-up workers resided in the Gulf coast region

where local industries including fishing and tourism were disrupted for months following the oil

spill (8). Surveys of Gulf coast residents showed decreases in income and increases in job loss

after the oil spill (7), which may have contributed to psychosocial stress in these communities.

Psychosocial stress can impact risk of cardiovascular disease by accelerating formation and

progression of atherosclerotic plaques (9). Acute stress elevates blood pressure and may impact cardiac arrhythmia and myocardial ischemia, which can result in onset of an acute MI (31) or contribute to an increased risk of a future CHD event by driving atherosclerotic progression and worsening cardiovascular disease states.

Evidence of the health impacts of oil spills

Several studies have examined acute health effects of general oil spill-related exposures (Table 1). These studies, which did not measure specific chemical exposures occurring during oil spill clean-up, relied on exposure proxies such as living in a community affected by the oil spill, or fact of participation in clean-up work. Some results from these studies indicate that oil spills may affect the long-term health of clean-up workers.

Four research articles were identified that have addressed longer-term health effects related to oil spills. Studies of fishermen involved in clean-up of the *Prestige* oil spill showed that respiratory symptoms among clean-up workers were increased at 1, 2 and 5 years after the spill, compared to fishermen who were not involved in cleanup (25, 32, 33). However, this association was not apparent at 6 years of follow-up (34). This study featured substantial attrition among unexposed fishermen who were healthier at baseline, thus the referent group in the study at 6 years of follow-up may have poorer health than the population that gave rise to the cases. In a small study (N=62) of the *Tasman Spirit* oil spill, Meo et al (2009) assessed pulmonary function in workers exposed to oil for at least 15 days, matched to unexposed community members. They showed reduced lung function among exposed workers compared to the referent group within 1-5 months of the oil spill (35). These studies provide some evidence to support the hypothesis that oil spill exposures may affect long-term respiratory health, however the limitations in study design complicate interpretation of the study results. Moreover, it remains

unknown whether other chronic disease outcomes may be elevated among individuals exposed to oil spills, and whether any such associations may be persistent over time.

Table 2.1. An abbreviated summary of the research on the physical health conditions associated with oil spills

Oil Spill	Title	Year	Journal	Authors	Methods	Results	Considerations/Limitations
Hebei Spirit	Respiratory effects of the Hebei Spirit oil spill on children in Taean, Korea.	2013	Allergy Asthma Immunol Res.	Jung SC et al.	Measured FEV1 in children living in areas exposed to the oil spill, compared to children living farther away. FEV1 measurements were taken ~1.5 years after the oil spill.	Increased prevalence of bronchial hyperresponsiveness among exposed children compared to controls. Decreased lung function among exposed children as well.	Crude exposure estimation (living near the spill vs. away from the spill) does not include measurement of air pollutant concentrations.
Hebei Spirit	Urinary metabolites before and after cleanup and subjective symptoms in volunteer participants in cleanup of the Hebei Spirit oil spill.	2012	Sci Total Environ.	Ha M et al.	Prospective study of short-term clean-up work and acute health effects. Surveyed volunteers involved in oil spill clean-up during the 2nd and 3rd week after the spill began. A subgroup provided urine at the start and end of a work day at the spill.	Most participants are young (20-30 yrs) and worked for only 1 day. Higher concentrations of metabolites of VOC and PAH in urine after work compared to before work. No associations were observed between urinary metabolites and physical symptoms.	Homogenous cohort with respect to demographic characteristics which may not be comparable to other worker cohorts. Exposure duration for most participants was very short (1 day); associations may differ for longer work durations.
Hebei Spirit	Hebei Spirit oil spill exposure	2011	Environ Health Toxicol.	Cheong HK et al.	Prospective study of oil spill exposure among residents near the spill who worked on clean-up. Assessed oil spill exposure	No difference in urinary PAH or VOC metabolites between workers and	Only measured acute symptoms, no information about chronic outcomes,

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	and subjective symptoms in residents participating in clean-up activities.				and acute outcomes among resident workers 2-8 weeks after the start of the oil spill. Assessed exposure by "degree of skin contamination". At 2-8 weeks post spill, also measured urinary metabolites of PAH and VOC.	nonworkers. Duration of clean-up work significantly associated with eye and nose irritation, headache, fatigue.	limited exposure assessment. Measured biomarkers several weeks after the spill, which would not capture spill-related PAH/VOC exposures.
Prestige	Evaluation of the persistence of functional and biological respiratory health effects in clean-up workers 6 years after the prestige oil spill.	2014	Environ Int.	Zock JP et al.	Followed a cohort of fisherman who participated in clean-up of the 2002 Prestige oil spill. Respiratory outcomes were assessed by the study at baseline and via telephone survey follow-ups.	There were no clear differences in respiratory health between exposed and unexposed fishermen.	The unexposed group had worsening health over time compared to the exposed, therefore controls may not represent the source population of the workers.
Prestige	Prolonged respiratory symptoms in clean-up workers of the	2007	Am J Respir Crit Care Med.	Zock JP et al.	Used questionnaires to ascertain self-reported respiratory symptoms among fisherman >1 year after they had participated in oil spill clean-up work, and among controls who are fishermen	Prevalence of lower respiratory tract symptoms significantly increased among clean-up workers compared to nonworkers. No dose-response for work	Self-reported health outcomes, and there may be issues with recall for cleanup work-related exposures reported >1 year after the spill. The Prestige study

	prestige oil spill.				that weren't involved in clean-up.	duration. Associations with nasal and respiratory symptoms attenuate with longer duration since clean-up and for wearing face mask vs not wearing face mask.	results may not be generalizable to the Deepwater Horizon spill due to differences in oil exposures (bunker oil vs crude oil).
Prestige	Health changes in fishermen 2 years after clean-up of the Prestige oil spill.	2010	Ann Intern Med.	Rodríguez-Trigo G et al.	Two years after the 2002 prestige oil spill, respiratory outcomes were assessed in a group of fishermen: respiratory symptoms; forced spirometry; markers of oxidative stress, airway inflammation, among others.	Oil-exposed fishermen were at increased risk for lower respiratory tract symptoms (risk difference, 8.0 [95% CI, 1.1-14.8]). Lung function did not significantly differ between the groups.	The Prestige study results may not be generalizable to the Deepwater Horizon spill due to differences in oil exposures (bunker oil vs crude oil).
Tasman Spirit	Effect of duration of exposure to polluted air environment on lung function in subjects exposed to crude oil spill into sea water.	2009	Int J Occup Med Environ Health.	Meo SA, et al.	A study of lung function among 31 men who worked on oil spill clean-up and 31 age-, height-, weight- and SES-matched controls living 15-20km from the spill area. Data collected within 1-5 months of the spill.	They detected poorer lung function among workers involved with clean-up compared to unexposed controls.	Very small sample size; there are only 8, 9, 14 participants in each respective exposure category.

Cardiovascular health risks of oil spills

No studies of oil spill-related exposures have addressed cardiovascular-related outcomes, and few have examined long-term health outcomes (as described in the previous section). Other studies of air pollution have shown associations with acute triggering of heart disease events, but these studies have mainly focused on short-term associations, and no studies have assessed changes in heart disease risk over time, nor the persistent effects of short-term pollution exposures (6, 23, 36).

Studies of stress and cardiovascular disease have shown that long-term psychological stress is associated with development of cardiovascular disease, and acute stressful events may trigger heart attacks (37). It is unclear whether stress related to living in an area impacted by the oil spill would affect risk of CHD acutely or for years following exposure, or how risk may change over time.

Petrochemical exposures among oil industry workers

The literature on the health effects of petrochemical exposures is limited. Many studies of oil refinery workers have been likely influenced by healthy worker bias (38, 39), and the fact that much of this research has been conducted within the oil industry raises concerns of conflicts of interest. However, one study has reported increased risk of heart disease, and other illnesses, among oil industry employees (40) and also increased blood pressure among children living near refineries (41). This limited body of research suggests that oil exposures may impact CHD, however it is not clear what the exposure thresholds for these associations are, or if there are similar associations for exposures experienced during an oil spill.

Other occupational hydrocarbon exposures

Occupational studies of cohorts with relatively high PM exposure (compared to ambient levels) have identified associations with heart disease. These associations have emerged despite the fact that workers are usually healthier than the general population and may have lower baseline heart disease risk. In an analysis of occupational fine PM exposures in a Swedish cohort study of manual workers, occupational exposure to fine particles <1µm and >1µm in diameter were determined based on a job exposure matrix, in reference to Swedish occupational exposure limits (42). Workers in the highest exposure category for ever being exposed to fine particles <1µm had increased hazard of hospitalizations for MI [hazard ratio (HR) 1.12 (95% CI 1.09 to 1.15)], as did workers who ever had high exposure to particles >1µm [HR 1.14 (95% CI 1.10 to 1.18)]. These associations were slightly strengthened among workers with exposure duration exceeding 5 years [HR 1.21 (95% CI 1.11 to 1.31)], but with no clear trend for intensity of exposure (42). A limitation of this study is that they did not measure cumulative exposure or intensity of exposure, so it is unclear what exposure thresholds may be responsible for the observed associations, or whether there are changes in risk over time. However, this research does support the hypothesis that particulate exposures may contribute to long-term heart attack risk.

A systematic review of the literature on occupational particulate matter exposures showed that 37 studies since 1990 have reported possible associations between occupational particulate exposures and CHD mortality as well as nonfatal MI. These studies also showed evidence of associations between PM and heart rate variability and systemic inflammation, which are potential intermediates between occupational PM exposure and CHD. The occupations and industries encompassed in this review include gold mining, trucking, heavy equipment

operations, asphalt workers, synthetic rubber industry workers, among others. There were no

studies included of petrochemical industry workers, who are understudied in regards to the

cardiovascular effects of workplace exposures. Of the studies included in the review, most used

external population-based control groups in their analyses, which may be problematic since

worker cohorts are typically healthier than the general population, leading to underestimation of

associations. Another issue is that the majority of the occupational studies did not directly

measure exposures; rather, they enumerated a cohort where exposures are known to be elevated,

and employment or job type served as a proxy for exposure (43). Even in light of these issues,

the occupational literature on PM exposures has consistently shown significant associations with

fatal and nonfatal coronary heart diseases in a number of exposure settings.

Environmental hydrocarbon exposures

Findings from the occupational literature have been substantiated in population-based

studies of ambient exposure levels. Exposure to ambient levels of air pollution over short time

periods as well as long-term have been associated with an increase in MI incidence, CHD-related

mortality and all-cause mortality (4, 23, 44-47). Many of the common air pollutants that are

thought to play a role in these associations are exposures of concern for oil spill clean-up

workers. Typical ambient-level exposures to $PM_{2.5}$ and benzene, which were exceeded in various

locations and time periods during the oil spill, have shown associations with increased short-term

risks of MI (29, 48).

Particulate matter

Fine particulate matter [$PM_{2.5}$: encompasses fine particles (diameter <2.5µm) and

ultrafine particles (diameter <1µm)] is a ubiquitous air pollutant that is primarily formed via

combustion of fossil fuels and other organic material. Studies of short-term and long-term

exposures to ambient $PM_{2.5}$ have shown associations with increases in cardiovascular morbidity and mortality (49). Typical concentrations of ambient PM were described in an American Heart Association statement on air pollution published by Brook et al (23). The authors reported average 24-hour concentration ranges of several hydrocarbons, including $PM_{2.5}$ and benzene, as well as typical 24-hour peaks in areas that are not concentrated plumes or areas with direct source emission impact. Results are shown in Table 2.2 below. The National Ambient Air Quality Standards (NAAQS), which set standards for permissible exposures to the EPA criteria air pollutants, set the annual mean standard for $PM_{2.5}$ to be 15 $\mu g/m^3$, and the daily standard, which is a 24 hour mean, to be ≤35 $\mu g/m^3$ (23).

Table 2.2 excerpt from Brook et al 2010. Typical 24-hour concentrations of criteria air pollutants in US (23)

Pollutant	US Average Range	US Typical Peak	Most Recent NAAQS for Criteria Pollutants
$PM_{2.5}$	5–50 $\mu g/m^3$ (Mean=13.4±5.6)	100 $\mu g/m^3$	15 $\mu g/m^3$ (Annual mean) 35 $\mu g/m^3$ (24 h)
Benzene	0.5–10 $\mu g/m^3$	100 $\mu g/m^3$	

A number of studies of ambient-level exposures have identified $PM_{2.5}$ as a risk factor for fatal and nonfatal MI and CHD, though there is heterogeneity in the findings of these studies indicating regional and possible temporal differences in associations. A systematic review published by Bhaskaran et al (2009) summarized the literature on air pollution and MI and showed disparate conclusions among studies in different populations and regions.

The authors identified 5 studies of $PM_{2.5}$ and MI and reported that 3 of the 5 studies showed statistically significant estimates of increased risks ranging from 5% to 17% per 10 $\mu g/m^3$ increase in PM exposure (50). These were case-crossover studies of acute MIs occurring on the same day or within 1 day of short windows of fine PM exposure, generally 24-hour averages. Of these studies, Barnett et al (2006) in New Zealand reported very small increases in

risk for an average 10 µg/m^3 increase in PM$_{2.5}$ 0-1 days before the MI [RR 1.07 (1.04 to 1.11)].

Two studies in Boston, MA looked at average 20 µg/m^3 increases in PM$_{2.5}$ 2 days before an MI

and found similarly small increased risks: Zanobetti et al (2005) [RR 1.05 (1.01 to 1.09)] and

Peters et al (2001) [RR 1.105 (0.987 to 1.226)]. Peters et al (2005), in Germany, and Sullivan et

al (2005), in Washington, report similar results, though they were not statistically significant (3,

6, 30, 51, 52). There was just one study of long-term fine PM exposure and MI; this was among

postmenopausal women and had null findings (53).

Overall, this review highlights the fact that associations may vary by region and results

from one study may not be generalizable to populations external to the study base. These

discrepancies in associations emphasize the need for research in understudied populations,

including the southern US. There is also a dearth of studies of the longer-term effects of PM

exposures on MI, and the lack of an overall consensus on the strength of these associations.

Short-term exposures of fine PM:

There is mixed evidence that short-term environmental PM$_{2.5}$ exposures are associated

with acute MI. The majority of studies of short-term exposures to PM use a time-series or case-

crossover approach to assess associations between short ranges of exposures and acute outcomes.

Studies have reported some increased risk of MI within hours to days of increased PM$_{2.5}$

exposures (29), and also that an average daily increase of 10 µg/m^3 is associated with a small yet

statistically significant increased risk of cardiovascular mortality and MI immediately following

exposure (21, 23, 54) and increased hospital admissions for nonfatal CHD (36). Table 3 below

summarizes studies of short-term PM exposures and cardiovascular disease outcomes and

demonstrates the heterogeneous associations that have been estimated from studies conducted in

different regions and exposure contexts.

Table 2.3. Short-term PM exposures and risk of ischemic heart disease(23)

Event/Study Area	Primary Source	Exposure Increment	% Increase (95% CI)
MI events–Boston, Mass	Peters et al 2001	20-25 µg/m^3 PM$_{2.5}$	20 (5.4–37)
MI, 1st hospitalization–Rome, Italy	D'Ippoliti et al 2003	30 µg/m^3 TSP	7.1 (1.2–13.1)
MI, emergency hospitalizations–21 US cities	Zanobetti and Schwartz 2005	20 µg/m^3 PM$_{10}$	1.3 (0.2–2.4)
Hospital readmissions for MI, angina, dysrhythmia, or heart failure of MI survivors–5 European cities	Von Klot et al 2005	20 µg/m^3 PM$_{10}$	4.2 (0.8–8.0)
MI events–Seattle, Wash	Sullivan et al 2005	10 µg/m^3 PM$_{2.5}$	4.0 (−4.0–14.5)
MI and unstable angina events–Wasatch Front, Utah	Pope et al 2006	10 µg/m^3 PM$_{2.5}$	4.8 (1.0–6.6)
Tokyo metropolitan area	Murakami et al 2006	TSP >300 µg/m^3 for 1 h vs reference periods <99 µg/m^3	40 (0–97)[*]
Nonfatal MI, Augsburg, Germany	Peters et al 2004	Exposure to traffic 1 h before MI (note: not PM but self-reported traffic exposure)	292 (222–383)
Nonfatal MI, Augsburg, Germany	Peters et al 2005	Ambient UFP**, PM$_{2.5}$, and PM$_{10}$ levels	No association with UFP or PM$_{2.5}$ on same day. Positive associations with PM$_{2.5}$ levels on 2 days prior

TSP indicates total suspended particulate matter.
*Adjusted rate ratio for MI deaths.
**Ultrafine particles

As shown in table 3, the associations between PM and CHD may vary depending on region, particulate constituents, and study design. Studies in the Northeastern US have shown small positive associations between increases in long-term particulate air pollution exposure and acute heart attack (6, 55), while a study in the Northwest reported a null association between PM$_{2.5}$ and MI (risk ratio= 1.01 (95% CI 0.98-1.05) (30). The differences in results from these

studies may be due to the fact that the Northeast studies both assessed $20\mu g/m^3$ increases in fine

PM concentrations, while the study in the Northwest assessed $10\mu g/m^3$ increases in fine PM.

Additionally, the studies did not measure particulate matter constituents, which are known to

vary geographically. A case-crossover study of short-term daily 24-h average $PM_{2.5}$ exposures

and cardiovascular-related emergency hospitalizations in several states across the US showed

significant effects of $PM_{2.5}$ during the cooler months across most disease categories. This

analysis looked at four different lag periods of exposure to hospitalization and found significant

associations for $PM_{2.5}$ exposures 0-1 days before the hospitalization. However, these associations

were region and climate-dependent: associations were strongest in cooler months for the

Northeast, but no associations of $PM_{2.5}$ exposure on hospitalization were observed in Washington

or New Mexico, neither for cool nor warm months. Although Florida showed no cooler month

effects, significant increases were noted in odds ratios for the warm weather months for acute

MI, CHD, circulatory disease in addition to other diagnoses (56). Another US multi-city time-

series study identified significant associations between $PM_{2.5}$ and all-cause mortality and stroke,

and null results for MI and other CVD-related mortality for a $10-\mu g/m^3$ increase in 2-day

averaged $PM_{2.5}$ concentration (57). These associations may also vary due to co-exposures, such

as noise or other stressors (58, 59). Little research has been conducted on the PM/CHD

association in Southern US populations, so it remains unclear what the environmental $PM_{2.5}$

exposure risks may be among individuals in the Gulf region, and if the trends for this region are

similar to or distinct from results shown in other geographies.

There is additional evidence that PM exposures may affect intermediate conditions that

increase risk for CHD. Increases in daily levels of $PM_{2.5}$ have been shown to be associated with

increased blood pressure (60); similar to the region-specific phenomena of $PM_{2.5}$/MI

associations, the associations with blood pressure also vary based on location, even within the same metropolitan region (61). A meta-analysis conducted by Liang et al showed that 10 $\mu g/m^3$ increases in $PM_{2.5}$ modestly elevate blood pressure, both for long-term and short-term PM exposures (60). It is plausible that blood pressure may, in part, mediate the relationship between PM exposures and CHD.

Long-term exposure to PM

The effects of long-term occupational and environmental exposures to PM have been studied much less extensively than short-term exposures. Analyses from the Women's Health Initiative showed significant increases in nonfatal stroke [HR 1.28 (1.02-1.61)], nonfatal CHD [HR 1.21 (1.04-1.42)], and fatal CHD [2.21 (1.17-4.16)] corresponding to an average annual increase in $PM_{2.5}$ of 10 $\mu g/m^3$ (53). A study of fatal and nonfatal MI hospitalizations in Massachusetts showed a 16% (4%-29%) increase in the odds of MI for an area $PM_{2.5}$ IQR increase of 0.59 $\mu g/m^3$ (62). A Japanese cohort study found a small increase in hazard of MI corresponding to an average annual increase of 10 $\mu g/m^3$ PM (63). Similarly, a study of long-term $PM_{2.5}$ exposure among a British cohort found only weak evidence for associations with myocardial infarction, stroke, or arrhythmia, but did find very small statistically significant associations between pollutant concentrations and incident cases of heart failure. For the British study, annual increases in PM exposures were averaged over a year, and an interquartile range change in PM_{10} of 3.0 $\mu g/m$ corresponded to a hazard ratio of 1.06 (95% CI 1.01-1.11) (64).

Biological mechanism

Exposures to PM may affect the initiation and progression of cardiovascular disease, and may also trigger the onset of acute events (65). The process by which PM exposure increases cardiovascular risk is largely via atherosclerosis, which can be affected by inflammatory

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processes initiated by inhaled PM (66). Fine and ultra-fine particles that have been inhaled into the lungs permeate the membranes of the alveoli and enter the bloodstream, where reactive intermediates can cause cellular and genetic damage (26, 67-69). Metabolites of these particles can also initiate pulmonary inflammation (70), systemic inflammation, platelet activation, and oxidative stress, thereby increasing risk of cardiovascular disease events (50, 65, 71). This state of oxidative stress can alter the blood vessels, contributing to initiation and progression of atherosclerosis and thrombosis (72).

Exposures to PM during cleanup work may cause short-term increases in inflammation of the vessels, contributing to both acute and delayed manifestations of coronary heart disease (4). Inflammation of the vessels can result in destabilization of an arterial plaque and onset of an acute MI if the artery had already reached an advanced state of atherosclerosis (44). Otherwise, the inflammation and oxidative stress caused by PM exposures (or other inhaled pollutants) may contribute to progression of an existing plaque, furthering the process of atherosclerosis and thereby increasing risk of a future heart attack or another symptomatic manifestation of coronary heart disease (44). Therefore, the length of time between PM exposure and detection of CHD may be very short (within a day) for triggering a heart attack or may be months to years for worsening of underlying conditions leading to an eventual event. For this reason, we hypothesize that oil spill-related air pollutant exposures may cause acute immediate cardiovascular events or may increase risk of events long-term.

Overall, the literature remains inconclusive on the details of the inflammatory cascades that may be triggered by PM exposure, since some biomarkers of inflammation are elevated along with increasing PM while others are depressed. A study of traffic police men in Shanghai, China measured 24-hour $PM_{2.5}$ exposures (using personal monitors), once in summer and once in

winter. Blood measurements were taken at the end of each air monitoring period. The results showed that a unit increase in $PM_{2.5}$ concentrations was associated with an increase in IgG, IgM and IgE, and decrease of IgA, and CD8 cells. When comparing seasonal biomarker levels, C-reactive protein, IgM and IgG were higher in winter than in summer, while IgA, CD4 and CD8 were lower in winter than in summer. Percent changes in biomarker levels between summer and winter were: CRP [1.1% (95% CI 0.6% to 1.5%)], IgM [11.2% (95% CI 10.9% to 11.6%)], IgG [6.7% (95% CI 6.4% to 7.1%)] and IgE [3.3% (95% CI 3.0% to 3.6%)] IgA [-4.7% (95% CI −5.6% to −4.2%)] and CD8 [−0.7% (95% CI −1.1% to −0.3%)] (71). This evidence supports the hypothesis that inflammation and immune system responses may be affected by changes in PM exposures, however it remains unclear how long these cascades of immunologic response last and for how long they are measureable, or if these responses affect cardiovascular outcomes. It is important to note that these processes are poorly understood, and the evidence thus far suggests that no single hypothesis is adequate to explain the effects that particulate matter can have on the cardiovascular system.

Volatile organic compounds

The hydrocarbons benzene, toluene, ethylbenzene and xylene (BTEX) are volatile organic compounds (VOCs) present in crude oil. Volatile organic compounds are used widely in industrial settings for chemical and materials synthesis. Benzene is released into the environment from its use in the production process of chemicals and plastics, as well as from gasoline vapors, vehicle emissions, combustion of organic material such as wood, and cigarette smoke. Aside from inhaled exposures, exposure to benzene also occurs via ingestion of processed foods (73). BTEX exposure can occur in the general environment, though air concentrations of VOCs are typically higher indoors than outdoors because they are released from cleaning supplies, paints,

lacquers and pesticides (74). Benzene, toluene and xylene are classified by IARC as carcinogens (75) but have shown associations with non-cancerous disease as well, including CVD (27).

Workers on boats, barges, rigs or otherwise in the presence of fresh oil may have experienced high exposures to BTEX and other VOCs. No previous studies have characterized exposures to VOCs during oil spill clean-up work, but the occupational and environmental literature have examined BTEX exposures in other contexts.

Occupational literature on BTEX

There is a limited literature on BTEX and cardiovascular diseases, consisting mostly of occupational cohorts and laboratory-based studies. A study of petrochemical factory workers examined the relationships between exposure to benzene, and joint exposure to benzene and xylene, with changes in electrocardiogram (ECG) and arterial hypertension. Both the benzene only and benzene + xylene groups showed associations with irregular ECG, as well as with hypertension (19). Increases in arterial hypertension have also been reported among workers with exposure to toluene, and this relationship may be modified by noise exposure (76).

Crude exposure assessment in occupational studies has limited the ability to assess dose-response trends or thresholds of exposure to BTEX that may cause CVD. In a case-control study of CHD nested within a cohort of over 6,000 workers at an aluminum smelter, there were 306 cases of heart disease diagnosed from 1975-1983, compared to 575 controls who were workers that did not develop CHD. Exposure to VOCs was not measured but approximated by using a crude categorization of "blue collar" vs "white collar" worker status; among blue collar workers, further classifications distinguished job type and location within the factory. Results showed that work location within the factory, a proxy for exposure to contaminants, was significantly associated with disease risk, but CHD risk did not increase with work duration (77).

Environmental exposure to volatile hydrocarbons

A limited number of studies have assessed associations between ambient benzene exposures and CHD. A case-crossover study of traffic-related air pollution in Strasbourg, France measured hourly benzene, nitrogen dioxide, ozone, carbon monoxide, and PM levels in block groups. This study looked at effects of average benzene concentrations on MI (after lag periods), compared with concentrations on the "control" days of the week during the same month as the event. The exposures were defined as average hourly concentrations on either the same day as the event, the day of the event and the prior day, or just the prior day. The results showed that a 1 $\mu g/m^3$ increase in benzene corresponds to a 10.4% (3.0-18.2%) increase in risk for same-day MI onset; a 1 $\mu g/m^3$ increase in benzene within 0-1 days corresponds to an 10.7% (2.7-19.2%) increase in risk for MI onset; a 1 $\mu g/m^3$ increase in benzene 1 day before the MI corresponds to a 7.2% (0.3-14.5%) increased risk (48). These results support what has been shown about the association of benzene and MI from the occupational literature and demonstrate that short-term exposures may have acute effects.

Results from a cross-sectional study of alkylbenzene exposure and CVD prevalence in the National Health and Nutrition Examination Survey (NHANES) showed higher prevalence of nonfatal CHD or stroke among individuals with higher blood levels of toluene, ethylbenzene, xylene and styrene (22).

Biological mechanism

There is evidence that the hypothesized relationship between exposure to BTEX chemicals and cardiovascular disease is biologically plausible. One study investigated the role of oxidative stress in the cardiovascular effects of BTEX in a cohort of occupationally exposed individuals. This study examined a number of oxidative stress biomarkers and changes in

expression of genes related to oxidative stress mechanisms. The authors identified several genes that had increased expression corresponding with higher exposures. These results indicated that oxidative stress can be induced by xylene and toluene exposure, and were strongest for toluene exposure (78).

Studies have also documented the immunologic effects of benzene exposure, showing increased concentrations of immune cells and decreases in DNA repair factors, suggesting that exposures to benzene may increase an individual's susceptibility to genetic mutations (79, 80). Other research has suggested that BTEX exposures may have endocrine disrupting properties, even at low exposures(81). It remains unclear how BTEX may biologically affect CHD, as the mechanisms remain poorly understood and unexplained in the literature. The associations that have been found between BTEX and cardiovascular risk do warrant further exploration, especially to address gaps regarding dose-response and exposure thresholds.

Stress and cardiovascular disease

Physical and psychosocial stress

Vigorous physical exertion increases risk of acute myocardial infarction (MI), particularly among adults who do not habitually participate in physical activity and/or who have atherosclerotic disease (82). Tasks that were common among oil spill clean-up workers, such as carrying or lifting equipment, working outdoors in high heat, and other manual labor, may have created an environment with increased risk of triggering acute cardiovascular events or exacerbating existing coronary disease conditions among workers. Furthermore, workers and other residents living in areas that were impacted by the oil spill may have faced decreases in income and increases in job loss after the oil spill (7), which may have contributed to psychosocial stress in these communities. Long-term elevations in emotional stress are

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associated with incidence of cardiovascular diseases and mortality, and acute increases in stress may trigger coronary events (37, 83, 84).

Biological mechanisms of the impact of stress on coronary disease

Stress can impact risk of cardiovascular disease by accelerating formation and progression of atherosclerotic plaques (9, 84). Acute stress elevates blood pressure and may impact cardiac arrhythmia and myocardial ischemia, which can result in onset of an acute MI (31) or contribute to an increased risk of a future CHD event by driving atherosclerotic progression.

The mechanism by which stress acts on heart disease is primarily through contributions to atherosclerosis, though there are distinct mechanisms through which chronic stress versus acute stress impact CHD (37). Broadly, stress results in elevated heart rate and increased vasoconstriction, which can impact CHD by increasing blood pressure, hemostasis, and endothelial dysfunction, and reducing insulin sensitivity (85). Chronic stress contributes to atherosclerotic progression via hypertension, which increases risk of vulnerable plaque development. Acute physical stress and psychosocial stress elicit similar endogenous responses (86). These forms of stress increase thrombosis and hypertension by triggering the sympathetic nervous system; this can, in turn, trigger an acute MI if vulnerable plaque is ruptured (84).

Conclusions for Chapter 2

This section has identified several gaps in the literature regarding what is known about the health effects of oil spills, and what is known about the associations between occupational and ambient hydrocarbon exposures, stress, and CHD. Few studies of the health effects of oil spills have assessed associations with chronic health outcomes, and no research has examined the cardiovascular disease impact of oil spills. This is the first study to have assessed whether oil

spill-related exposures impact CHD, and whether this association may persist in the 5 years following the spill. We sought to assess whether chemical exposures as well as physical and community-level stress related to the *Deepwater Horizon* oil spill may impact CHD. We have used longitudinal information from the Gulf Long-term Follow-up Study (GuLF STUDY) to assess associations between duration of clean-up work, living in an area impacted by the oil spill, total hydrocarbon exposure and fatal and self-reported myocardial infarction up to 5 years after the oil spill.

CHAPTER 3: RESEARCH METHODS

Study Design and Data

GuLF STUDY overview

The Gulf Long-term Follow-up (GuLF) STUDY is a prospective cohort study of individuals who were involved in, or had trained to participate in, clean-up of the 2010 *Deepwater Horizon* oil disaster. The goal of the GuLF STUDY is to investigate the acute and persistent health effects of a variety of exposures associated with the oil spill. Participants in the study include workers involved in a number of jobs at numerous locations during the clean-up response. This includes workers on the rigs who were involved with capping the oil well, collecting spilled oil, flaring oil and gas, and drilling relief wells. The study also includes workers on research vessels, barges, and re-purposed fishing boats who were tasked with collecting and corralling the oil; beach and wildlife cleanup workers; workers decontaminating vessels and equipment; and support workers for all of these activities, who may have not been in contact with any oil.

Source population and cohort enumeration

Participants for the GuLF STUDY were identified from multiple lists of people involved, or potentially involved, in the clean-up effort. These include rosters of individuals who had participated in safety training for clean-up work, rosters of government employees involved in the cleanup response, registries of volunteers, and security badge records. All available

information was used to identify the study base; however, it is likely that some eligible individuals were not identifiable from the available sources.

A total of 152,169 apparently unique names were identified from these lists. After excluding individuals with incomplete or outdated contact information, those known to be deceased or ineligible, and duplicates, there remained 58,925 individuals presumed eligible for the study (≥21 years old at time of enrollment; capable of completing an interview in English, Spanish, or Vietnamese).

Recruitment for the GuLF STUDY began approximately 11 months after the start of the oil spill, in March 2011. With a contact rate of 62%, a total of 32,608 (55% of potentially eligible participants; 90% of those contacted and confirmed to be eligible) completed the enrollment telephone interview between March 2011 and May 2013. Of these, 999 completed an abbreviated Vietnamese language interview and were not eligible for the current project because they were not asked about CHD diagnoses.

Full scale GuLF STUDY recruitment activities ended December 31, 2012, but efforts to enroll Spanish and Vietnamese speaking participants continued through May 2013. Figure 3.1 shows the timing of study recruitment in reference to the oil spill and cleanup effort.

Figure 3.1. Timeline of data collection
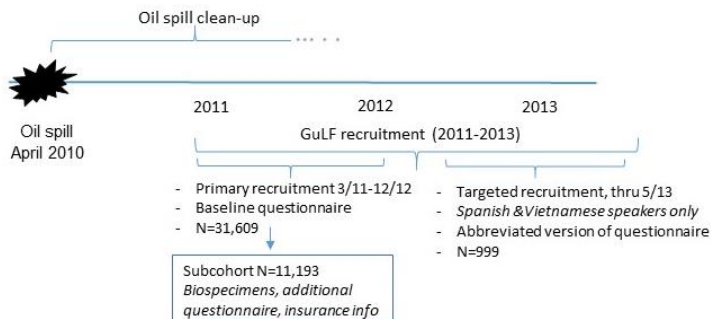
Participants were recruited and enrolled via a phone call from study staff. Eligible participants for the study were at least 21 years old, had a telephone number, spoke English, Vietnamese or Spanish and lived in the United States at the time of enrollment. A total of 32,608 participants were enrolled in the study, and this analysis

includes the 31,609 English and Spanish speaking participants who completed the full baseline interview.

Baseline data collection (interview #1)

During the enrollment interview, participants were asked about their demographic characteristics, details on their participation and tasks related to oil spill clean-up, about their personal health history, and about any first myocardial infarction diagnoses (MI) they have received. Information on first MI diagnosis was ascertained during the baseline interview and again at the second telephone interview. The questions used to assess the diagnoses were the same at both interviews: "Has a doctor ever told you that you have had a heart attack or myocardial infarction (MI)? What month and year were you first told that you had a heart attack or MI?"

Interview #2

Of the 31,609 participants who enrolled in the study, 21,256 (67%) completed a second telephone interview in 2014-2016, 2-3 years after their first interview. This interview confirmed some demographic and lifestyle characteristics that were assessed in the enrollment interview, and asked again about the occurrence and timing of a first diagnosis of nonfatal MI.

National Death Index data

Deaths due to CHD were ascertained for the entire enrolled cohort from the National Death Index (NDI) through December 31st 2014, the latest date for which complete NDI data were available. Individuals with International Classification of Diseases, 10th Edition (ICD-10) codes indicating ischemic heart disease as a cause of death (codes I20-I25) were counted as cases

for this project. Eligible deaths occurred after enrollment in the GuLF STUDY until December 31st 2014.

Ascertainment of exposures

The main exposures of interest in aims 1 and 2 are duration of clean-up work, home residence proximity to the oil spill, and total hydrocarbon exposure levels during clean-up work. Duration of clean-up work was defined using self-reported start dates and end dates of clean-up work, ascertained during the first study interview. Residential proximity to the oil spill was defined as "direct or indirect" for participants living in or adjacent to a county that had coastline oiled from the spill; participants living "away from the spill" reported living elsewhere in the Gulf region or in other parts of the US. We grouped coastal and adjacent counties because these areas were likely to have been similarly impacted by loss of income and community stress due to the oil spill.

A job exposure matrix (JEM) was used to derive maximum and median THC exposure levels (2). The JEM was created using data from approximately 28,000 personal exposure monitoring measurements of THC collected during the oil spill response and clean-up, in addition to detailed self-reported data on clean-up work tasks, locations and dates. Maximum and median exposure scores were assigned for each vessel type (for clean-up work on the water), job type, and time period of clean-up work, as well as for each work activity in each time period throughout the clean-up response.

Many participants reported multiple work tasks throughout clean-up, and intensity of oil exposure varied between tasks, and within tasks over time. We defined a worker's maximum overall THC exposure level based on their highest exposure task at any time during clean-up. We defined median THC exposure by the median of exposure scores across all tasks performed

before the oil well was capped on July 15th, 2010 in order to capture workers' usual exposure during the period when oil exposures were highest (2). In the event that the participant could not recall the exact dates when they performed certain tasks, other data on the timing of clean-up tasks was used to identify the likely period that the participant worked, based on the job tasks that they reported.

Ascertainment of outcomes

Nonfatal myocardial infarction

Self-reported physician-diagnosed first myocardial infarction was assessed during the first and second study interviews. During these interviews, participants were asked if they had ever received a diagnosis of a heart attack or MI. The validity of self-reported MI has been published in other studies, with sensitivity of self-reported MI between 60%-80% (87-90). The period of recall and definitions of gold standards vary between validation studies. There are limitations to relying on non-validated self-reported outcomes in the GuLF STUDY, however the relatively short time period for recalling an incident diagnosis reduces concerns about recall.

Fatal CHD

Fatal CHD outcomes were ascertained from death certificate cause-of-death data. The majority of studies that examine mortality (all-cause or CHD-specific) rely on death certificate data for indication of an event and the cause. Use of the codes listed as cause-of-death in the death certificate has been validated against hospital records of cause-of-death in other population-based studies. These studies have found that, while the validity does vary between communities, sensitivity of death certificates is relatively high [81% (95% CI 79%-83%)]. However, CHD is over-reported on death certificates; there was a CHD mortality false-positive rate of 28% for death certificate cause-of-death among participants in the ARIC cohort (91).

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Ascertainment of covariates

Information on participant demographics and lifestyle characteristics were obtained during the baseline telephone interview. Age at baseline, gender, ethnicity, education attainment, 2010 household income, county of residence at enrollment, height/weight for BMI calculation, details regarding tobacco smoking, and health information were ascertained.

Aim 1 Methods

Aim 1: (1) Determine predictors of non-response to the second study interview and (2) assess associations between duration of clean-up work and heart attack, and home proximity to the oil spill and heart attack during the 5 years following the oil spill.

Defining exposures and outcomes

Dates of initiating and ending clean-up work were self-reported by participants, as was their county or parish of residence at the time of enrollment. Work duration was defined categorically as 1-30 days, 31-90 days, 91-180 days and >180 days. Residential proximity to the oil spill was defined as "direct or indirect" for participants living in or adjacent to a county that had coastline oiled from the spill; participants living "away from the spill" reported living elsewhere in the Gulf region or in other parts of the US. We grouped coastal and adjacent counties because these areas were most likely to have been similarly impacted by loss of income and community stress due to the oil spill.

The outcome of interest is the incident first occurrence of a heart attack, defined as a self-reported MI or a fatal CHD event. During the two study interviews, participants were asked if they had ever received a diagnosis of a heart attack or MI, and the month and year of their first MI diagnosis. Participants who reported an MI occurring prior to clean-up work (n=610) were excluded from the analyses.

Deaths due to CHD were ascertained for the entire enrolled cohort from the National Death Index (NDI) through December 31st 2014, the latest date for which complete NDI data were available. International Classification of Diseases, 10th Edition (ICD-10) codes indicating ischemic heart disease as a cause of death in any position were included (codes I20-I25).

Risk period for heart attack

The time at risk for a first heart attack (fatal or nonfatal) was based on calendar time and was determined differently for analyses including all study participants and for analyses among clean-up workers only. For analyses of residential proximity to the spill and heart attack, participants were at risk for a self-reported first MI from the date that the oil spill began (April 20th 2010); for analyses of work duration and heart attack, the risk period began at initiation of oil spill clean-up work, which was between April and July 2010 for most clean-up workers. For all analyses, the risk period for a self-reported MI ended at the first of either the date of diagnosis of a first MI or at the last GuLF STUDY interview that the participant completed. The risk period for a fatal CHD event began at the time of the enrollment interview and continued until December 31st 2014. Only a participant's first reported MI diagnosis or CHD event was counted in this study.

Statistical analyses

Time-to-heart attack analyses

Hazard ratios for the associations between duration of clean-up work and home proximity to the oil spill with heart attack were estimated using Cox Proportional Hazards regression models. The Cox model assumes non-informative censoring and proportional hazards, and features Kaplan Meier estimators to account for censoring. We assessed whether each covariate met the proportional hazards assumption visually by plotting the log of the negative log of the

probability of survival (determined by Kaplan-Meier estimation) by the log of time at risk (92). We assessed proportional hazards of each covariate statistically by modeling an interaction term between the log of time and each covariate in the model. We fit conditional Cox models with and without IP censoring weights, as well as marginal Cox models with and without IP censoring weights.

We used inverse probability (IP) of censoring weights to weight the population that completed the second interview with respect to predictors of non-response, in order to estimate associations that would be observed in the absence of censoring (93). The probabilities of censoring for the IP weights were determined from models conditional on predictors of non-response to the second study interview. We used a causal diagram (99) to determine the set of predictors to be included in the IP censoring weights model: age, education, residential proximity to the oil spill, duration of clean-up work, cigarette smoking, and maximum total hydrocarbon exposure during clean-up work. The probabilities output from the weights model served as the denominator for the IP censoring weights, and for stabilized weights, the numerator was the probability of being observed at follow-up (93).

We controlled for confounders using two separate methods: (1) by conditioning on the covariates in the regression model; and (2) by applying IP exposure weights. An adjustment set of confounders was determined using a directed acyclic graph (DAG) (99). For the analyses of work duration and heart attack, we adjusted for: gender, age, maximum education attainment, residential proximity to the oil spill and cigarette smoking. For the residential proximity to the spill analyses, we adjusted for gender, age, smoking, and maximum education attainment.

Cumulative incidence of heart attack

We generated IP exposure- and censoring-weighted cumulative conditional risk plots to illustrate changes in the risk of heart attack over the study period, and examine trends in hazards over time by exposure (94). The time scale for the risk curves was months since initiation of clean-up work for the work duration analyses, and months since April 20th 2010 for the proximity to the spill analyses. To assess whether associations with heart attack changed across the study period, we estimated risks and risk differences of heart attack at 12 months, 24 months, 36 months and 48 months of follow-up. The risks were defined as the proportion of cumulative cases at the given month, divided by the total number at risk for a heart attack at that time. Risks were determined from proportional hazards regression using Nelson-Aalen estimation of survival, with IP exposure and censoring weights to account for confounders and predictors of censoring (94).

Assessing and accounting for predictors of censoring

Differences among participants who did or did not participate in the second study interview were assessed by building a predictive model with response to the second interview as the dependent variable. We examined distributions of a broad range of factors, determined by literature review and dependent on availability of data, among those who did and did not complete the second interview. The factors that we assessed included demographic (age; gender; ethnicity), lifestyle (smoking; alcohol consumption) and socioeconomic (income; education; employment status) covariates, as well as factors related to health at enrollment (prevalent heart attack; prevalent hypertension; perceived health), and oil spill clean-up work characteristics (working on clean-up; duration of clean-up work; clean-up job type; exposure to burning oil;

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exposure to total hydrocarbons; and residential proximity the oil spill.) We compared crude proportions of censoring across levels of each predictor variable.

To describe the major predictors of non-response in our study, we fit a logistic regression model combined with a Least Absolute Shrinkage and Selection Operator (LASSO) approach (95). Briefly, LASSO is a regression penalization method that is often used for variable selection procedures. The level of penalization was selected using Akaike's Information Criterion (AIC) (96) using the SAS procedure HPGENSELECT (97). We began with a model that included potential predictors of loss to follow-up: gender, age, ethnicity, income, highest education attainment, tobacco smoking, current alcohol intake, heavy tobacco smoking, self-reported diagnosis of hypertension, residence proximity to the oil spill, maximum total hydrocarbon exposure during cleanup work, duration of clean-up work, employment status at the time of the first interview, clean-up of another oil spill, and ever enlisting in the military. We then fit a logistic regression model for non-response, conditional on the LASSO-selected variables, to determine the concordance statistic which indicates the predictive ability of the model (98).

Censoring, time at risk, and competing risks

In the GuLF STUDY, enrollment occurred approximately 1-3 years after the oil spill. Within this period before enrollment, nonfatal MI cases may have been subject to competing risks (left truncation). This time window was relatively short and we do not anticipate that this would meaningfully bias results. Nonfatal events may be censored among participants who did not respond to the second study interview (see figure 3.2 below), as nonfatal MI were ascertained during the first (2011-2013) and second (2014-2016) interviews.
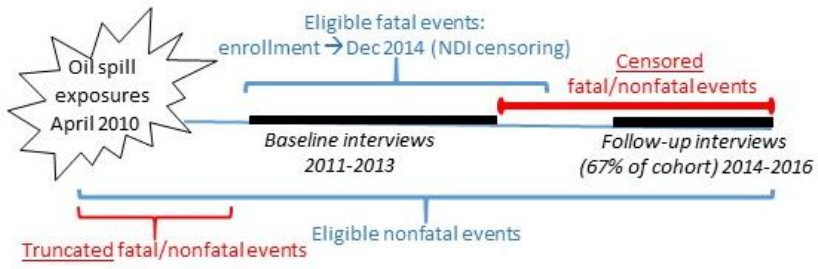
Figure 3.2. Truncation, censoring and differential risk periods for fatal and nonfatal events

Aim 2 Methods

Aim 2: Assess the association between total hydrocarbon exposure during clean-up work and heart attack up to 5 years after the oil spill.

Defining exposures and outcomes

The exposures of interest in aim 2 are maximum and median total hydrocarbon exposure during oil spill clean-up. The outcome of interest is first incident heart attack, defined as a first incident self-reported non-fatal MI occurring after initiation of clean-up work, or fatal CHD ascertained from the National Death Index occurring after enrollment in the study until December 31st 2014.

Estimates of hydrocarbon exposure were derived using a job exposure matrix. We defined a worker's maximum overall THC exposure based on their highest exposure task at any time during clean-up. We defined median THC exposure by the median of exposure scores across all tasks performed before the oil well was capped on July 15th, 2010 in order to capture workers' usual exposure during the period when oil exposures were highest (2). We categorized maximum THC levels, based on the distribution of the maximum exposure scores, as <0.30 ppm, 0.30-0.99 ppm, 1.00-2.99 ppm, and ≥3.00 ppm. Categories for median THC exposure levels prior to July 15th, 2010 were defined as <0.10 ppm; 0.10-0.29 ppm, 0.30-0.99 ppm, and ≥1.00 ppm, based on the distribution of the exposure scores. Analyses for maximum THC include all 24,375 clean-up workers, while analyses for median exposure include the 22,982 workers who initiated clean-up work before July 15th, 2010.

We compared distributions of a number of factors plausibly related to the outcome and non-response among those who did and did not complete the second interview. The factors that we assessed, determined by literature review and dependent on availability of data, included demographic, lifestyle and socioeconomic covariates, as well as factors related to health at enrollment, and oil spill clean-up work characteristics. We compared crude proportions of non-response across levels of each predictor variable, as was also done in the aim 1 analyses.

Statistical analyses

Time-to-heart attack analyses

We assessed the associations between total hydrocarbon exposure and heart attack in a time-to-event analysis (92). Person-time was accrued from the start of an individual's oil spill clean-up work until the earlier of their first MI event, they left the study, or were administratively censored.

We used inverse probability (IP) weights to weight the population that completed the second interview with respect to predictors of nonresponse, in order to estimate associations that would be observed in the absence of censoring (93). The IP censoring weights were estimated from models conditional on predictors of censoring. The variables we included in the censoring weights model were determined from a causal diagram (99): age (20-29; 30-39; 40-49; 50-59; 60-65; >65 years), maximum education attainment (less than high school; high school diploma/GED; some college/2 year degree; 4+ year college graduate), cigarette smoking (current; former; never), residential proximity to the oil spill ("direct/indirect": living in or adjacent to a county with coastline oiled during the spill; vs. "away from the spill"), and maximum total hydrocarbon exposure during clean-up work (<0.30 ppm, 0.30-0.99 ppm, 1.00-

2.99 ppm, ≥3.00 ppm). Stabilized IP censoring weights were determined by dividing the probability of being observed at the second interview by the probabilities output from the censoring weights model (93).

We controlled for confounders using IP exposure weights (100). The following adjustment set was determined using a directed acyclic graph (DAG) (99): gender (male; female), age (20-29; 30-39; 40-49; 50-59; 60-65; 65+ years), tobacco smoking (current; former; never), maximum education attainment (less than high school; high school diploma/GED; some college/2 year degree; 4+ year college graduate), and residential proximity to the oil spill ("direct/indirect": living in or adjacent to a county with coastline oiled during the spill; vs. "away from the spill"). Stabilized IP exposure weights were obtained by fitting a logistic regression model for the exposure with confounders as independent variables; the probability output from the model served as the denominator, and the numerator was the probability of exposure (93).

Cox Proportional Hazards models (92) with a robust variance estimator were fit to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) (101). We assessed whether each covariate met the proportional hazards assumption visually by plotting the log of the negative log of the probability of survival (determined by Kaplan-Meier estimation) by time at risk (92), and statistically by modeling an interaction term between the natural log of time and each covariate.

Cumulative incidence of heart attack

To assess whether associations with heart attack changed across the study period, we estimated conditional risks of heart attack at yearly intervals throughout the follow-up period. We generated weighted cumulative risk plots using proportional hazards regression with Nelson-

Aalen survival estimation, where the time scale was months since initiation of clean-up work.

We accounted for confounders and predictors of censoring using the same IP weights (94) as we

used in the Cox regression models.

CHAPTER 4: AIM 1 RESULTS

Title: Heart attack among clean-up workers and community members 5 years after the

Deepwater Horizon oil spill

Introduction

The 2010 *Deepwater Horizon* oil disaster was the largest marine oil spill in US history. The spill began April 20th, 2010 when a pipeline burst at the *Deepwater Horizon* drilling rig. Over 200 million gallons of crude oil spilled into the Gulf of Mexico in the following months. The clean-up response, which involved more than 100,000 workers, began at the start of the oil spill and continued through the end of 2010 (Kwok et al. 2017).

During the oil spill clean-up, workers may have faced physical stress as well as chemical exposures from hydrocarbons volatilizing from fresh oil, combustion products from burning crude oil and flaring natural gas, emissions from the equipment and machinery used during the clean-up, and chemical dispersants (Kwok et al. 2017; Middlebrook et al. 2012; Stewart et al. 2017). Exposures to some of these pollutants, including particulate matter and volatile organic chemicals, have shown associations with coronary heart disease (CHD) in environmental and occupational exposure studies (Bahadar et al. 2014; Brook et al. 2010; Peters 2005; Stewart et al. 2017). Airborne particulate levels during oil spill clean-up were elevated in coastal communities and around clean-up sites compared to typical ambient levels in these regions (Nance et al. 2016).

Apart from chemical exposures related to the spill, Gulf coast communities faced economic burdens and increases in psychosocial stress in the wake of the oil spill (Gould et al. 2015; Peres et al. 2016). Local industries including fishing and tourism were disrupted for months following the spill (Shultz et al. 2015), and loss of income may have contributed to psychosocial stress in these communities. Psychosocial stress can impact risk of cardiovascular diseases by accelerating progression of atherosclerotic plaques (Rozanski et al. 1999). Thus, the physical and emotional stress caused by the oil spill may have contributed to an increased risk of future CHD.

It is unknown whether exposures to pollutants or physical stressors during the oil spill may affect risk of heart disease over time. Short-term increases in ambient particulate matter concentrations increase risk of cardiovascular events and overall mortality acutely, but the persistence of these associations remains unexplored (Brook and Rajagopalan 2010; Brook et al. 2010). A prior study of the *Prestige* oil spill found that respiratory symptoms among clean-up workers persisted up to 5 years after the spill (Zock et al. 2012). However, no research has examined cardiovascular diseases or other chronic health outcomes among oil-exposed populations.

The Gulf Long Term Follow-up (GuLF) STUDY is the largest study of the health impact of oil spills (Kwok et al. 2017) and is the first study to assess heart disease among individuals exposed to oil spills. We have used longitudinal information from the GuLF STUDY to assess associations between duration of clean-up work, living in an area impacted by the oil spill, and fatal and self-reported myocardial infarction up to 5 years after the oil spill. We also assessed predictors of non-response to the GuLF STUDY second interview, and accounted for this attrition in our analyses.

Methods

2.1 Study population

The GuLF STUDY is a prospective cohort study of individuals who worked on, or had trained to work on, clean-up of the 2010 *Deepwater Horizon* oil spill disaster (Kwok et al. 2017). Participants in the study include individuals aged ≥21 years who completed mandatory oil spill safety training in order to take part in oil spill response and clean-up as well as government workers and oil professionals who were living in the United States at the time of enrollment.

Study recruitment began approximately 11 months after the start of the oil spill, in March 2011, and continued until May 2013. From a list of 62,803 presumably unique names with sufficient contact information, a total of 32,608 participants were enrolled and completed the first study interview. Of the enrolled participants, we excluded from the present analyses 999 individuals who completed a Vietnamese language abbreviated version of the questionnaire that did not collect complete information on oil spill clean-up jobs, leaving 31,609 participants who completed their interviews in English or Spanish. Of the 31,609 participants who enrolled in the study, 21,256 (67%) completed a second telephone interview in 2014-2016, two to three years after their first interview.

2.2 Exposure and outcome measures

All oil spill-related exposures and clean-up tasks were assessed during the first interview. Health outcomes were assessed during the first and second interviews. The exposures of interest in the present analyses are duration of participation in oil spill clean-up work and home residence in an area impacted by the oil spill. Dates of initiating and ending clean-up work were self-

reported by participants, as was their county or parish of residence at the time of enrollment. Work duration was defined categorically as 1-30 days, 31-90 days, 91-180 days and >180 days. Residential proximity to the oil spill was defined as "direct or indirect" for participants living in or adjacent to a county that had coastline oiled from the spill; participants living "away from the spill" reported living elsewhere in the Gulf region or in other parts of the US. We grouped coastal and adjacent counties because these areas were likely to have been similarly impacted by loss of income and community stress due to the oil spill.

The outcome of interest is the incident first occurrence of a heart attack, defined as a self-reported myocardial infarction (MI), or a fatal CHD event ascertained from death certificates. During the first and second interviews, participants were asked if they had ever received a diagnosis of a heart attack or MI and, if so, the month and year of their first MI diagnosis. Participants who reported an MI occurring before clean-up work (n=610) were not included in this analysis.

Deaths due to CHD were ascertained for the entire enrolled cohort from the National Death Index (NDI) through December 31st 2014, the latest date for which complete NDI data were available. International Classification of Diseases, 10th Edition (ICD-10) codes indicating ischemic heart disease as a cause of death (I20-I25) were counted as fatal CHD cases.

2.3 Risk period for heart attack

The time at risk for an MI was based on calendar time, and was determined differently for analyses including all study participants and for analyses among clean-up workers only. For analyses of residential proximity to the spill and heart attack, participants were at risk for a self-reported first MI from the date that the oil spill began (April 20, 2010); for analyses of work

duration and heart attack, the risk period began at initiation of oil spill clean-up work, which was between April and July 2010 for most participants. For all analyses, the risk period for a self-reported MI ended at the earlier of the date of diagnosis of a first MI or the last GuLF STUDY interview that the participant completed. The risk period for a fatal CHD event began at the time of the enrollment interview and continued until December 31, 2014. Only a participant's first reported MI diagnosis or CHD event was counted in this study.

2.4 Statistical methods

2.4.1 Censoring and predictors of loss to follow-up

Nonfatal MIs were censored if a participant who was at risk for a first MI, i.e. did not report an MI at the first interview, did not complete the second interview. We compared distributions of a broad range of factors plausibly related to the outcome and non-response, between those who did and did not complete the second interview. The factors that we assessed, determined by literature review and dependent on availability of data, included demographic (age; gender; ethnicity), lifestyle (cigarette smoking; alcohol consumption) and socioeconomic (income; education; employment status) covariates, as well as factors related to health at enrollment (prevalent heart attack; prevalent hypertension; perceived health), and oil spill clean-up work characteristics (working on clean-up; duration of clean-up work; clean-up job type; exposure to burning oil; exposure to total hydrocarbons; and residential proximity the oil spill.)

We compared crude proportions of censoring across levels of each predictor variable. The magnitude and precision of these estimates were considered in order to assess the ability of each variable to predict non-response.

To describe the major predictors of non-response in our study, we fit a logistic regression model combined with a Least Absolute Shrinkage and Selection Operator (LASSO) approach (Tibshirani 1996). Briefly, LASSO is a penalized regression method that is often used for variable selection. The level of penalization was selected using Akaike's Information Criterion (AIC) (Akaike 1992) using the SAS procedure HPGENSELECT (Yuan and Lin 2006). We began with a full model that included the following covariates: gender (male; female), age (20-29, 30-39, 40-49, 50-59, 60-65, >65 years), ethnicity (white; black; Asian; other/multi-racial), income (≤$20,000; $20,001-$50,000; >$50,000), highest education attainment (less than high school; high school diploma/GED; some college/2 year degree; 4+ year college graduate), smoking (current; former; never), current alcohol intake (yes; no), heavy cigarette smoking (currently smokes ≥1 pack per day; smokes <1 pack per day or non-smoker), self-reported physician diagnosis of hypertension (yes; no), residence proximity to the oil spill (direct/indirect; away from the spill), maximum total hydrocarbon exposure during cleanup work (<0.30 ppm; 0.30-0.99 ppm; 1.00-2.99 ppm; >3.00 ppm), duration of clean-up work (1-30 days; 31-90 days; 91-180 days; >180 days), employment status at the time of the first interview (working; temporarily laid off, sick leave or maternity leave; looking for work or unemployed; retired; disabled; keeping house; student; other), previous work on clean-up of another oil spill (yes; no), and ever being enlisted in the military (yes, now on active duty; yes, on active duty during the last 12 months, but not now; yes, on active duty in the past, but not during the last 12 months; no, training for Reserves or National Guard only; no, never served in the military). We then fit a logistic regression model with non-response as the dependent variable, conditional on the variables selected by the LASSO procedure. We used this logistic model to estimate the

concordance statistic, which quantifies the predictive accuracy of the model (Austin and Steyerberg 2012).

2.4.2 Estimating hazard ratios

We assessed the associations between work duration, residential proximity to the oil spill and heart attack in a time-to-event analysis (Cox 1992). We used inverse probability (IP) of censoring weights to weight the population that completed the second interview with respect to predictors of censoring, in order to estimate associations that would be observed in the absence of censoring (Cole and Hernan 2008). Each individuals' probability of censoring for the IP weights was estimated using a logistic model with censoring as the dependent variable and predictors of censoring as the independent variables. We used a causal diagram (Greenland et al. 1999) to determine the minimally sufficient set of predictors to be included in the IP censoring weights model (Howe et al. 2016): age, education, residential proximity to the oil spill, duration of clean-up work, smoking, and maximum total hydrocarbon exposure during clean-up work (which was determined from a job exposure matrix described by Stewart and colleagues) (Stewart et al. 2017). The probabilities output from the weights model served as the basis for the denominator for the IP censoring weights, and for stabilized weights, the numerator was the probability of being observed at follow-up (Cole and Hernan 2008).

We controlled for confounders using two separate methods: (1) by conditioning on the covariates in the regression model; and (2) by applying IP exposure weights. An adjustment set of confounders was determined using a directed acyclic graph (DAG) (Greenland et al. 1999). For the analyses of work duration and heart attack, we adjusted for: gender (male; female), age (20-29; 30-39; 40-49; 50-59; 60-65; >65 years), maximum education attainment (less than high

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school; high school diploma/GED; some college/2 year degree; 4+ year college graduate),

residential proximity to the oil spill (direct/indirect; away from the spill) and cigarette smoking

(current; former; never). For the residential proximity to the spill analyses, we adjusted for

gender, age, smoking, and maximum education attainment. We were unable to control for finer

categories of smoking because of a substantial amount of missing data for pack-years of smoking

among former smokers. Body mass index and self-reported prevalent hypertension were

determined to not be confounders, and we did not adjust for these in any of the models; in

addition, adjusting for these variables did not meaningfully change results (<10% change in beta

estimates).

The IP exposure weights were obtained by fitting a logistic regression model (for the

categorical work duration variable, we used a multinomial logistic regression model) for the

exposure with confounders as independent variables. We used stabilized weights, where the

numerator was the probability of exposure, and the denominator was the probability output from

the model (Cole and Hernan 2008).

Cox proportional hazards models (Cox 1992) with a robust variance estimator were fit to

estimate hazard ratios (HRs) and 95% confidence intervals (CIs) (Williamson et al. 2014). We

assessed whether each covariate met the proportional hazards assumption visually by plotting the

log of the negative log of the probability of survival (determined by Kaplan-Meier estimation) by

time at risk (Cox 1992). We assessed proportional hazards of each covariate statistically by

modeling an interaction term between the natural log of time and each covariate in the model.

We fit conditional Cox models with and without IP censoring weights, as well as marginal Cox

models, which controlled for confounders using IP exposure weights, with and without IP

censoring weights.

To account for the fact that NDI data were censored before some participants had their second study interviews, we performed a sensitivity analysis where we administratively censored all participants on December 31st 2014 (the date of last available NDI data); this analysis excluded 47 participants who gave their second interview on or after January 1st 2015. We also performed a sensitivity analysis to assess associations with non-fatal MI only, in order to create a more uniform follow-up period. This analysis included 353 incident non-fatal heart attacks that were reported during the first or second study interviews, excluding fatal events (n=48).

2.4.3 Cumulative incidence of heart attack

We generated IP exposure- and censoring-weighted cumulative risk plots to illustrate changes in the risk of heart attack over the study period, for the exposures of interest (Cole and Hernán 2004). The time scale for the risk curves was months since initiation of clean-up work for the work duration analyses, and months since April 20th 2010 for the proximity to the spill analyses. To assess whether associations with heart attack changed across the study period, we estimated risks and risk differences of heart attack at 12 months, 24 months, 36 months and 48 months of follow-up. The risks were defined as the proportion of cumulative cases at the given month, divided by the total number at risk for a heart attack at that time. Risks were determined from proportional hazards regression using the complement of the Nelson-Aalen estimate of survival, with IP exposure and censoring weights to account for confounders and predictors of censoring (Cole and Hernán 2004).

Results

There were 31,609 participants who entered the cohort by completing the enrollment interview, including 24,375 clean-up workers. A total of 21,256 participants, including 16,814

clean-up workers, completed the second interview. Among the 21,256 participants who completed the second interview, 12,699 (59.7%) reported, at enrollment, that they lived in a county that we defined as proximal to the oil spill. Among the 16,814 clean-up workers who completed the second interview, 2,063 (12.3%) worked for 1-30 days, 5,293 (31.5%) worked for 31-90 days, 5,735 (34.1%) worked for 91-180 days, and 3,723 (22.1%) worked >180 days.

Those who completed the second interview were more likely to be older, white, have a 2010 household income >$50,000, and were more likely to have completed 4 years of college (table 4.1). There were no differences in perceived health between those who did and did not complete the second interview, however those who completed the interview were slightly more likely to have reported a diagnosis of hypertension, to have reported a diagnosis of MI, to be a current drinker, and were less likely to be current smokers (table 4.2). Those who completed the second interview were also more likely to have worked on oil spill clean-up and were slightly more likely to have low total hydrocarbon exposure during clean-up, but there were no differences with respect to clean-up work tasks or job characteristics (table 4.3). Participants who had served on active duty in the military were also slightly more likely to complete the second interview. Neither duration of clean-up work nor exposure to burning oil was associated with participation.

The LASSO selection method determined a final model that included covariates for age, completing 4+ years of college, and former smoking. The concordance statistic was 0.621, indicating moderate ability for this model to predict non-response.

3.1 IP censoring and exposure weights

For the work duration analyses (clean-up workers only), the mean and range of the stabilized IP censoring weights was 1.00, 0.62-2.85 with standard deviation 0.22. For the residence proximity to the spill analyses (workers and non-workers), the mean of the stabilized IP censoring weights was 1.00 and the range was 0.55-2.61, with a standard deviation of 0.22.

The stabilized IP exposure weights for work duration had a mean of 1.00 and a range of 0.48 to 2.72 with standard deviation 0.16. The stabilized IP exposure weights for residential proximity to the spill had a mean of 1.00 and a range of 0.54 to 5.67, with a standard deviation of 0.39.

3.2 Heart attack outcomes

Among 31,609 study participants, 355 reported incident first MI diagnoses that occurred after the participant began clean-up work (or after the start of the oil spill, for non-workers). Among clean-up workers who worked >30 days, 9 reported an incident nonfatal MI within the first 30 days of clean-up work. In a sensitivity analysis, excluding these 9 cases from the analyses did not meaningfully impact results. There were 347 deaths among the cohort during the study period. Of the total deaths, 316 were among participants who had not already reported a first nonfatal MI; 40 of these deaths were due to CHD. The fatal CHD cases included the following ischemic heart disease ICD-10 codes: I110, I119, I219, I250, I251, and I259. This analysis included a total of 395 first MI events, 355 of which were nonfatal and 40 which were fatal.

3.3 Time-to-heart attack analysis

Hazard ratios assessing associations between home proximity to the spill, work duration and heart attack are presented in table 4.4. We saw positive associations between residential proximity to the oil spill and heart attack [marginal HR= 1.29 (95% CI: 1.00, 1.65)]. This association remained after accounting for censoring with IP weights [1.30 (1.01, 1.67)]. There were suggestive positive associations between work duration >180 days (vs 1-30 days) and heart attack [1.36 (0.88, 2.11)], and these associations also did not meaningfully change after applying censoring weights [1.43 (0.91, 2.25)]. Adjusting for having had to stop clean-up work due to heat did not meaningfully change the observed associations. Visual assessment of plots of the log of the negative log of survival vs time in study showed some small departures from proportional hazards for some variables; however, the Wald test for a product term between time in study and each covariate showed no significant departures from proportional hazards (p>0.10, results not shown).

Cumulative risk curves for work duration and heart attack showed that risk was similar across the categories of work duration, especially during the earlier months of follow-up (figure 1). The work duration categories 31-90 days, 91-180 days and >180 days did not diverge substantially over time, but those who worked 1-30 days consistently had the lowest risk of heart attack across the study period. The risk difference for >180 days of work (vs 1-30 days) ranged from 2 cases per 1000 workers at 12 months to 6 cases per 1000 workers at 48 months (table 4.5). When examining risk of heart attack by home proximity to the spill, risks appeared to be higher in the group living in proximity to the spill (figure 4.2). The risk difference for living in proximity to the oil spill (vs living farther away) and heart attack was 1 case per 1000 workers at 12 months, and 5 cases per 1000 workers at 48 months (table 4.5).

Sensitivity analyses where we censored the cohort after December 31st 2014 showed no meaningful change in associations for work duration and heart attack [marginal HR for >180 days of work (vs 1-30 days): 1.45 (0.90-2.34)], or for residential proximity to the spill and heart attack [marginal HR: 1.39 (1.06-1.83)] (supplemental table 4.S1), compared to the main results in table 4. Risk differences for work duration and heart attack, and proximity to the oil spill and heart attack were also unchanged (supplemental table 4.S2). Analyses that excluded fatal CHD outcomes also did not show any meaningfully changes in the observed associations for work duration [marginal HR for >180 days of work (vs 1-30 days): 1.47 (0.91-2.36)], or for residential proximity to the spill [marginal HR for direct/indirect proximity to the spill (vs away from spill): 1.28 (0.98-1.67)] (supplemental table 4.S3).

In a sensitivity analysis, we removed US Coast Guard and other federal employees who worked on oil spill clean-up from the analyses, as these workers may be more physically fit or have more access to health care services compared to non-federally-employed workers. After first excluding the 2,653 US Coast Guard, and then the total 4,640 federally employed workers from the cohort, we did not see any meaningful changes in the HR estimates for work duration and heart attack [marginal HR for >180 days (vs 1-30 days): 1.43 (0.91-2.24) excluding Coast Guard; 1.48 (0.92-2.40) excluding all federal employees]. We similarly did not see changes in the associations between residential proximity to the spill and heart attack [marginal HR for direct/indirect proximity to the spill (vs away from spill): 1.27 (0.99-1.64) excluding Coast Guard; 1.22 (0.95-1.58) excluding all federal employees], though the confidence intervals were wider compared to the analyses that included all participants (supplemental tables 4.S4 and 4.S5).

Discussion

This study, conducted among a cohort of trained workers in the clean-up of the *Deepwater Horizon* oil spill, along with others who had registered for training but did not ultimately work on the clean-up, showed hazards of heart attack 29% to 43% higher for living in proximity to the oil spill and duration of clean-up work >180 days. Risk differences for these associations ranged from 1 to 6 excess cases per 1000 workers. We assessed predictors of non-response to the second interview for the GuLF STUDY, and used IP weights to account for these factors in our models. Those who completed the second interview were more likely to be white, older age, nonsmokers, to have completed at least some college, have income >$50,000, and to have worked on oil spill clean-up compared to participants who did not complete the second interview. However, there were no particularly strong predictors of non-response, and hazard ratios appeared to be robust to censoring. Though applying IP censoring weights did not meaningfully change our results, weighting the cohort to resemble the full enrollment cohort addresses potential bias due to informative censoring.

This study showed a positive association between living in proximity to the spill and heart attack. This association may be driven by psychosocial stress caused by the oil spill, pollutant exposures, or other spill-related environmental factors. Other research studies have shown that living in proximity to the Gulf oil spill is associated with acute health symptoms, and that affected communities faced economic and social hardships following the spill (Gould et al. 2015). A study of women living in Southeast Louisiana who were physically, environmentally or economically exposed to the oil spill showed elevations in acute symptoms including wheezing and nausea, compared to unexposed women (Peres et al. 2016). Increased stress, anxiety, or

other health symptoms may increase risk of an acute or future heart disease manifestation (Steptoe and Kivimaki 2012).

Work duration showed a suggestive positive association with heart attack, however there was no clear exposure-response relationship. Oil spill clean-up work was often highly physically demanding, and workers endured hot temperatures and strenuous conditions. Workers who were, perhaps, less physically capable of this work or who had health limitations may have been more likely to work a short duration, or not at all. This could lead to differences in physical fitness between those with shorter work duration compared to those with longer work duration. Similarly, those who remained in the work force for longer may be healthier and less predisposed to CHD than those who worked shorter duration. If this were to be the case, the associations with heart attack observed in our study for workers in the longer duration categories would be attenuated due to healthy worker survivor bias (Arrighi and Hertz-Picciotto 1994; Buckley et al. 2015).

Despite ~33% non-response to the first follow-up phone interview for the GuLF STUDY and differences between cohort members who did and did not complete the interview, we observed negligible impact of these differences on the estimated associations for duration of clean-up work and residential proximity to the oil spill in relation to heart attack. This is in accordance with what we anticipated, based on the fact that the associations between each predictor and loss to follow-up were generally weak (tables 1-3). The censoring weights would be expected to have more influence on effect estimates in the presence of stronger predictors of loss to follow-up (Howe et al. 2011). For the conditional HRs, censoring weights may also not affect the estimates if the strong predictors of censoring are already adjusted for in the

proportional hazards model. The robustness of our results to potential bias due to nonresponse increases our confidence in the generalizability of our results to the full GuLF STUDY cohort.

There are limitations of the IP censoring weights approach to address bias due to censoring, and we acknowledge that our results are specific to our chosen approach and the required modeling assumptions. One important assumption of our approach was that missing outcome data occurred at random within strata of the predictors included in the censoring weights models. Other unmeasured factors that we did not account for may have been associated with non-response. However, if non-response were random with respect to unmeasured factors within strata of the adjustment set for our censoring weights model, failure to account for unmeasured predictors would not bias our estimates (Westreich 2012). Overall, we believe it is unlikely that unmeasured factors would contribute substantial bias. Despite the fact that results were generally robust to censoring, use of IP censoring weights has been recommended as a means to interpret results as representative of the full cohort in the presence of non-random censoring of outcomes, a benefit of IP weighting that has been demonstrated in other work (Buchanan et al. 2014).

This study relied on self-reported information on nonfatal heart attack, which is subject to errors in recall. Previous research in other populations has shown that recall of an MI diagnosis may be poorer among individuals >75 years old, or those with less education (Yasaitis et al. 2015), however the majority of the GuLF STUDY cohort was <60 years old at enrollment, and more than half attended at least 2 years of college. Though agreement varies by study and by population, self-report of MI has shown moderate agreement with hospital discharge data (kappa=0.64), and is more reliably reported than other cardiovascular diseases (Heckbert et al. 2004). Recall is also dependent on the time period for which disease is being ascertained. This

study focuses on a relatively short time period (~5 years) during which a new diagnosis can occur, so there is less concern about a participants' ability to recall the occurrence and timing of a diagnosis. Misreport of MI diagnoses would be expected to be non-differential with respect to the exposures of interest, and would then bias results toward the null.

This study used National Death Index death certificate data to determine total mortality and CHD-related mortality in the cohort. Previous studies that have validated CHD-related cause of death in death certificates have found that sensitivity compared to cause-of-death determined by medical records varies between communities, but is generally relatively high [81% (95% CI: 79%-83%)]. However, there was a 28% false-positive rate of classification of CHD mortality by death certificate cause-of-death among participants in the ARIC cohort (Coady et al. 2001). Misclassification of CHD-related deaths may impact results from this study, however we do not expect that misclassification would be differential with respect to the exposures of interest for this analysis, and therefore bias due to outcome misclassification would most likely be towards the null.

Deaths prior to the start of follow up were excluded. Thus, our results are conditional on surviving to the beginning of follow-up. If deaths occurred more often among those with longer work duration or among those who lived closer to the spill, some of these higher risk individuals in the higher exposure groups would not have survived to be included in our study. This may have resulted in a lower observed risk of heart attack than what would be seen in the underlying target population of all *Deepwater Horizon* clean-up workers.

During the study there were 276 participants who were at risk for a first MI and died of non-CHD causes. At the time of death, these participants had been followed by the study for a

period of 10-58 months, and 60 had completed the follow-up interview for the study and reported

to have not received a diagnosis of an MI. The 216 who did not complete the follow-up interview

were censored either due to death or our inability to reach them for an interview. We assessed

crude risk differences of non-CHD deaths by duration of clean-up work and residence proximity

to the spill. While work duration was not associated with non-CHD death, living in proximity to

the oil spill had a small positive association with non-CHD death. Previous work has

demonstrated that unmeasured confounders of the competing risk-exposure relationship can bias

the unconditional risk difference estimates but not the conditional HR and conditional risk

differences (Lesko and Lau 2017). Therefore, we do not think that bias related to non-CHD death

has impacted our estimates, which are based on conditional HRs and conditional risk differences.

This feature is a relative advantage of our approach, versus estimating unconditional risk

differences.

We assessed crude risk differences of non-CHD deaths by duration of clean-up work and

residence proximity to the spill. While work duration was not associated with non-CHD death,

living in proximity to the oil spill had a small positive association with non-CHD death.

Confounding of the relationship between proximity to the oil spill and non-CHD death is

unlikely, however, since we could not identify any confounders of this relationship beyond what

we already had adjusted for in the conditional Cox models. Therefore, we do not think that bias

related to non-CHD death has impacted the conditional risk or hazard ratio estimates.

This study showed positive associations between duration of clean-up work, residential

proximity to the oil spill up and heart attack up to 5 years after the *Deepwater Horizon* oil spill.

These associations persisted across the follow-up period, and were also robust to censoring.

Future research may investigate whether specific exposures, such as stress or individual chemical exposures, are driving the observed associations.

Tables and figures

Table 4.1. Participant demographic characteristics for enrollment cohort (N=31,609) and follow-up cohort (N=21,256). GuLF STUDY 2010-2016

	Interview #1 (N=31,609)	Interview #2 (N=21,256)	Did not complete interview #2 (N=10,353)	Risk difference for non-response
	n (%)	n (%)	n (%)	RD (95%CI)
Gender				
Male	25502 (80.7)	17031 (80.1)	8471 (81.8)	ref
Female	6105 (19.3)	4224 (19.9)	1881 (18.2)	0.0241 (0.0111, 0.037)
Missing	2 (0.0)	1 (0.0)	1 (0.0)	
Age category (years)				
20-29	6226 (19.8)	3529 (16.6)	2697 (26.2)	-0.0529 (-0.0695, -0.0364)
30-39	7340 (23.3)	4549 (21.5)	2791 (27.1)	ref
40-49	7709 (24.5)	5302 (25.0)	2407 (23.4)	0.068 (0.0528, 0.0832)
50-59	7019 (22.3)	5294 (25.0)	1725 (16.7)	0.1345 (0.1195, 0.1495)
60-65	1849 (5.9)	1442 (6.8)	407 (3.9)	0.1601 (0.1382, 0.182)
>65	1364 (4.3)	1085 (5.1)	279 (2.7)	0.1757 (0.1516, 0.1998)
Missing	102 (0.3)	55 (0.3)	47 (0.5)	
Ethnicity				
White	20688 (65.8)	14134 (66.9)	6554 (63.7)	ref
Black	7425 (23.6)	4836 (22.9)	2589 (25.2)	-0.0319 (-0.0444, -0.0193)
Asian	326 (1.0)	186 (0.9)	140 (1.4)	-0.1126 (-0.1668, -0.0585)
Other/multi-racial	2990 (9.5)	1985 (9.4)	1005 (9.8)	-0.0193 (-0.0374, -0.0012)
Missing	180 (0.6)	115 (0.5)	65 (0.6)	
Hispanic				
Yes	2115 (6.7)	1357 (6.4)	758 (7.3)	-0.0332 (-0.0543, -0.0121)
No	29400 (93.3)	19840 (93.6)	9560 (92.7)	ref
Missing	94 (0.3)	59 (0.3)	35 (0.3)	
Education completed				
Less than high school	5099 (16.2)	3161 (14.9)	1938 (18.8)	-0.014 (-0.0305, 0.0025)
High school diploma/GED	9436 (30.0)	5982 (28.2)	3454 (33.5)	ref
Some college/2 year degree	9382 (29.8)	6339 (29.9)	3043 (29.5)	0.0417 (0.0281, 0.0553)
4+ year college graduate	7584 (24.1)	5709 (26.9)	1875 (18.2)	0.1188 (0.1051, 0.1326)
Missing	108 (0.3)	65 (0.3)	43 (0.4)	

Income				
≤ $20,000	8260 (29.2)	5187 (27.0)	3073 (33.6)	-0.0331 (-0.0473, -0.0188)
$20,001 To $50,000	9060 (32.0)	5989 (31.2)	3071 (33.6)	ref
More Than $50,000	11001 (38.8)	8007 (41.7)	2994 (32.8)	0.0668 (0.054, 0.0796)
Missing	3288 (10.4)	2073 (9.8)	1215 (11.7)	
Proximity to the spill				
Direct/indirect	19354 (61.2)	12699 (59.7)	6655 (64.3)	-0.0421 (-0.0526, -0.0316)
Away from spill	12255 (38.8)	8557 (40.3)	3698 (35.7)	ref
Missing	0 (0.0)	0 (0.0)	0 (0.0)	

Proximity to the oil spill is defined as living in, or adjacent to, a county or parish with coastline oiled during the spill.

Table 4.2. Participant health and lifestyle characteristics among participants who completed the first (N=31,609) and second (N=21,256) study interviews. GuLF STUDY 2010-2016

	Interview #1 (N=31,609)	Interview #2 (N=21,256)	Did not complete interview #2 (N=10,353)	Risk difference for non-response
	n (%)	n (%)	n (%)	RD (95%CI)
Report of ever having had a nonfatal MI				
Yes	724 (2.3)	548 (2.6)	176 (1.7)	0.0863 (0.0546, 0.118)
No	30783 (97.7)	20643 (97.4)	10140 (98.3)	ref
Missing	102 (0.3)	65 (0.3)	37 (0.4)	
Nonfatal MI/fatal CHD since the oil spill/study enrollment				
Yes	395 (1.9)	314 (1.5)	81 (0.8)	-0.2051 (-0.2472, -0.1629)
No	20299 (98.1)	20299 (98.5)	10112 (99.2)	ref
Missing	10915 (34.5)	643 (3.0)	160 (1.5)	
Hypertension				
Yes	8573 (27.2)	6135 (29.0)	2438 (23.6)	0.0591 (0.0477, 0.0705)
No	22927 (72.8)	15052 (71.0)	7875 (76.4)	ref
Missing	109 (0.3)	69 (0.3)	40 (0.4)	
Perceived health				
Excellent	5353 (17.0)	3526 (16.7)	1827 (17.7)	-0.0104 (-0.0261, 0.0053)
Very good	10102 (32.1)	6857 (32.4)	3245 (31.5)	0.0096 (-0.0033, 0.0226)
Good	10010 (31.8)	6698 (31.7)	3312 (32.2)	ref
Fair	4510 (14.3)	3061 (14.5)	1449 (14.1)	0.0096 (-0.0069, 0.026)
Poor	1478 (4.7)	1017 (4.8)	461 (4.5)	0.019 (-0.0064, 0.0443)
Missing	156 (0.5)	97 (0.5)	59 (0.6)	
Health compared to several years ago				
Better	2664 (8.5)	1787 (8.5)	877 (8.5)	0.0035 (-0.0156, 0.0225)
Worse	9432 (30.1)	6454 (30.6)	2977 (28.8)	0.017 (0.0055, 0.0285)
About The Same	19269 (61.4)	12859 (60.9)	6410 (62.0)	ref
Missing	244 (0.8)	155 (0.7)	89 (0.9)	
Smoker				
Current	9449 (30.1)	5884 (27.9)	3565 (34.8)	-0.0676 (-0.0798, -0.0554)
Former	6777 (21.6)	4785 (22.7)	1992 (19.4)	0.0158 (0.0026, 0.0289)
Never	15144 (48.3)	10454 (49.5)	4690 (45.8)	ref
Missing	239 (0.8)	133 (0.6)	106 (1.0)	
Heavy smoker (>1 pack per day)				
Yes	3178 (10.2)	1979 (9.4)	1199 (11.8)	-0.0569 (-0.0746, -0.0392)
No	27966 (89.8)	19006 (90.6)	8960 (88.2)	ref
Missing	465 (1.5)	271 (1.3)	194 (1.9)	
Current drinker				

Yes	23774 (75.8)	16098 (76.2)	7676 (74.9)	0.0159 (0.0037, 0.0281)
No	7593 (24.2)	5021 (23.8)	2572 (25.1)	ref
Missing	242 (0.8)	137 (0.6)	105 (1.0)	

Table 4.3. Participant clean-up work and employment characteristics among participants who completed the first (N=31,609) and second (N=21,256) study interviews. GuLF STUDY 2010-2016

	Interview #1 (N=31,609)	Interview #2 (N=21,256)	Did not respond to interview #2 (N=10,353)	Risk difference for non-response
Worked on cleanup	n (%)	n (%)	n (%)	RD (95% CI)
Yes	24375 (77.1)	16814 (79.1)	7561 (73.0)	0.0758 (0.0631, 0.0884)
No	7234 (22.9)	4442 (20.9)	2792 (27.0)	ref
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Work duration				
1-30 days	2998 (12.3)	2063 (12.3)	935 (12.4)	ref
31-90	7669 (31.5)	5293 (31.5)	2376 (31.4)	0.0021 (-0.0175, 0.0216)
91-180	8363 (34.3)	5735 (34.1)	2628 (34.8)	-0.0024 (-0.0217, 0.017)
>180	5345 (21.9)	3723 (22.1)	1622 (21.5)	0.0084 (-0.0122, 0.0291)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Worked before the well was capped				
Yes	20950 (85.9)	14362 (85.4)	6588 (87.1)	-0.0304 (-0.0467, -0.014)
No	3425 (14.1)	2452 (14.6)	973 (12.9)	ref
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Clean-up job type				
Response work	4462 (18.3)	3048 (18.1)	1414 (18.7)	-0.0252 (-0.0442, -0.0062)
Operations work	4371 (17.9)	2946 (17.5)	1425 (18.8)	-0.0343 (-0.0535, -0.0152)
Water cleanup	3803 (15.6)	2620 (15.6)	1183 (15.6)	-0.0194 (-0.0392, 0.0004)
Decontamination	3555 (14.6)	2455 (14.6)	1100 (14.5)	-0.0177 (-0.0379, 0.0024)
Land cleanup	3631 (14.9)	2520 (15.0)	1111 (14.7)	-0.0143 (-0.0343, 0.0057)
Support work	4553 (18.7)	3225 (19.2)	1328 (17.6)	ref

Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Potential exposure to burning/flaring				
Unknown	502 (2.1)	356 (2.1)	149 (2.0)	0.0143 (-0.0259, 0.0546)
No	21625 (88.7)	15010 (89.3)	6724 (88.9)	ref
Yes	2248 (9.2)	1448 (8.6)	688 (9.1)	-0.0127 (-0.0335, 0.008)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Maximum total hydrocarbon exposure				
None (nonworkers)	7234 (22.9)	4442 (20.9)	2792 (27.0)	-0.0959 (-0.1123, -0.0794)
Very low	5443 (17.2)	3864 (18.2)	1579 (15.3)	ref
Low	7984 (25.3)	5519 (26.0)	2465 (23.8)	-0.0186 (-0.0344, -0.0029)
Medium	7476 (23.7)	5094 (24.0)	2382 (23.0)	-0.0285 (-0.0446, -0.0125)
High	3445 (10.9)	2313 (10.9)	1132 (10.9)	-0.0385 (-0.0583, -0.0187)
Missing	27 (0.1)	24 (0.1)	3 (0.0)	
Employment status				
Working Now Only	20758 (66.0)	13994 (66.1)	6764 (65.7)	ref
Temporarily Laid Off, Sick Leave Or Maternity Leave	586 (1.9)	391 (1.8)	195 (1.9)	-0.0069 (-0.0456, 0.0318)
Looking For Work Or Unemployed	5865 (18.6)	3764 (17.8)	2101 (20.4)	-0.0324 (-0.0462, -0.0185)
Retired	1511 (4.8)	1198 (5.7)	313 (3.0)	0.1187 (0.0973, 0.1401)
Disabled, Permanently Or Temporarily	1016 (3.2)	689 (3.3)	327 (3.2)	0.004 (-0.0254, 0.0334)
Keeping House	284 (0.9)	192 (0.9)	92 (0.9)	0.0019 (-0.0529, 0.0567)

				-0.076 (-0.1142, -0.0378)
Student	652 (2.1)	390 (1.8)	262 (2.5)	
				0.0274 (-0.0053, 0.06)
Other	784 (2.5)	550 (2.6)	234 (2.3)	
Missing	153 (0.5)	88 (0.4)	65 (0.6)	
Other oil spill cleanup				
				0.0591 (0.0435, 0.0747)
Yes	3578 (11.3)	2594 (12.2)	984 (9.5)	
No	27934 (88.4)	18601 (87.5)	9333 (90.2)	ref
				0.0204 (-0.1071, 0.1478)
Don't Know	51 (0.2)	35 (0.2)	16 (0.2)	
				-0.0659 (-0.2413, 0.1095)
Refused	30 (0.1)	18 (0.1)	12 (0.1)	
Missing	16 (0.1)	8 (0.0)	8 (0.1)	
Served on active duty				
				0.0216 (0.0025, 0.0407)
Yes, Now On Active Duty	2563 (8.1)	1735 (8.2)	828 (8.0)	
Yes, On Active Duty During The Last 12 Months, But Not Now	567 (1.8)	424 (2.0)	143 (1.4)	0.0924 (0.0562, 0.1287)
Yes, On Active Duty In The Past, But Not During The Last 12 Months	4553 (14.4)	3400 (16.0)	1153 (11.1)	0.0914 (0.0774, 0.1054)
No, Training For Reserves Or National Guard Only	271 (0.9)	192 (0.9)	79 (0.8)	0.0531 (-0.0013, 0.1076)
No, Never Served In The Military	23565 (74.6)	15444 (72.7)	8121 (78.5)	ref
Don't Know	29 (0.1)	23 (0.1)	6 (0.1)	0.1377 (-0.0098, 0.2853)
Refused	44 (0.1)	29 (0.1)	15 (0.1)	0.0037 (-0.1365, 0.1439)
Missing	17 (0.1)	9 (0.0)	8 (0.1)	

Table 4.4. The association of work duration and self-reported MI/fatal CHD: conditional and marginal hazard ratios (HR). GuLF STUDY 2010-2016

	Cases / total N**	Conditional model* HR (95% CI)	IP exposure weighted HR (95% CI)
Exposure: Residential proximity to the spill		Among workers and nonworkers	
No censoring weights			
Away from spill	100/11872	ref	ref
Direct/indirect proximity	292/18590	1.37 (1.09, 1.74)	1.29 (1.00, 1.65)
IP censoring weighted			
Away from spill	99/11859	ref	ref
Direct/indirect proximity	291/18577	1.39 (1.09, 1.78)	1.30 (1.01, 1.67)
Exposure: Work duration		Among clean-up workers only	
No censoring weights			
1-30 days	29/2877	ref	ref
31-90 days	86/7385	1.23 (0.81, 1.88)	1.27 (0.83, 1.94)
91-180 days	121/8091	1.48 (0.99, 2.22)	1.43 (0.95, 2.15)
>180 days	73/5193	1.43 (0.93, 2.21)	1.36 (0.88, 2.11)
IP censoring weighted			
1-30 days	29/2873	ref	ref
31-90 days	85/7374	1.19 (0.78, 1.84)	1.23 (0.79, 1.90)
91-180 days	121/8086	1.44 (0.95, 2.18)	1.38 (0.91, 2.10)
>180 days	72/5187	1.49 (0.95 2.33)	1.43 (0.91, 2.25)

HR= Hazard Ratio; 95% CI= 95% Confidence Interval

Proximity to the oil spill is defined as living in, or adjacent to, a county or parish with coastline oiled during the spill.

*Adjusts for gender, age, smoking, and education

**Total N for non-censoring-weighted models is where all confounders (gender, age, smoking, education) are nonmissing. Work duration models also adjusted for home proximity to the spill. Total N for IP censoring-weighted-models is where all confounders and predictors of censoring (gender, age, smoking, education, maximum total hydrocarbon exposure, and work duration) are nonmissing.

Table 4.5. Risk of self-reported MI/fatal CHD by residence proximity to the spill and work duration. GuLF STUDY, 2010-2016

Duration of follow-up:	12 months		24 months		36 months		48 months	
	Risk*	RD	Risk*	RD	Risk*	RD	Risk*	RD
Residential proximity to the oil spill	Among the full study cohort (N=31,609)							
Away from the spill	0.003	ref	0.007	ref	0.009	ref	0.012	ref
Direct/indirect	0.004	0.001	0.009	0.001	0.013	0.004	0.018	0.005
Work duration	Among clean-up workers only (n=24,375)							
1-30 days	0.002	ref	0.006	ref	0.010	ref	0.011	ref
31-90 days	0.004	0.002	0.008	0.002	0.012	0.002	0.014	0.003
91-180 days	0.004	0.002	0.008	0.002	0.011	0.002	0.018	0.007
>180 days	0.004	0.002	0.010	0.003	0.013	0.003	0.017	0.006

Risks are equal to the proportion of the number of cumulative cases at the indicated point in time divided by the total number of study participants at risk at that time.

Proximity to the oil spill is defined as living in, or adjacent to, a county or parish with coastline oiled during the spill

*The risks are weighted for confounders (gender, age, smoking, and education) and predictors of censoring (max THC exposure, age, education, proximity to the spill, work duration, and smoking). Models for work duration also controlled for home proximity to the oil spill as a confounder
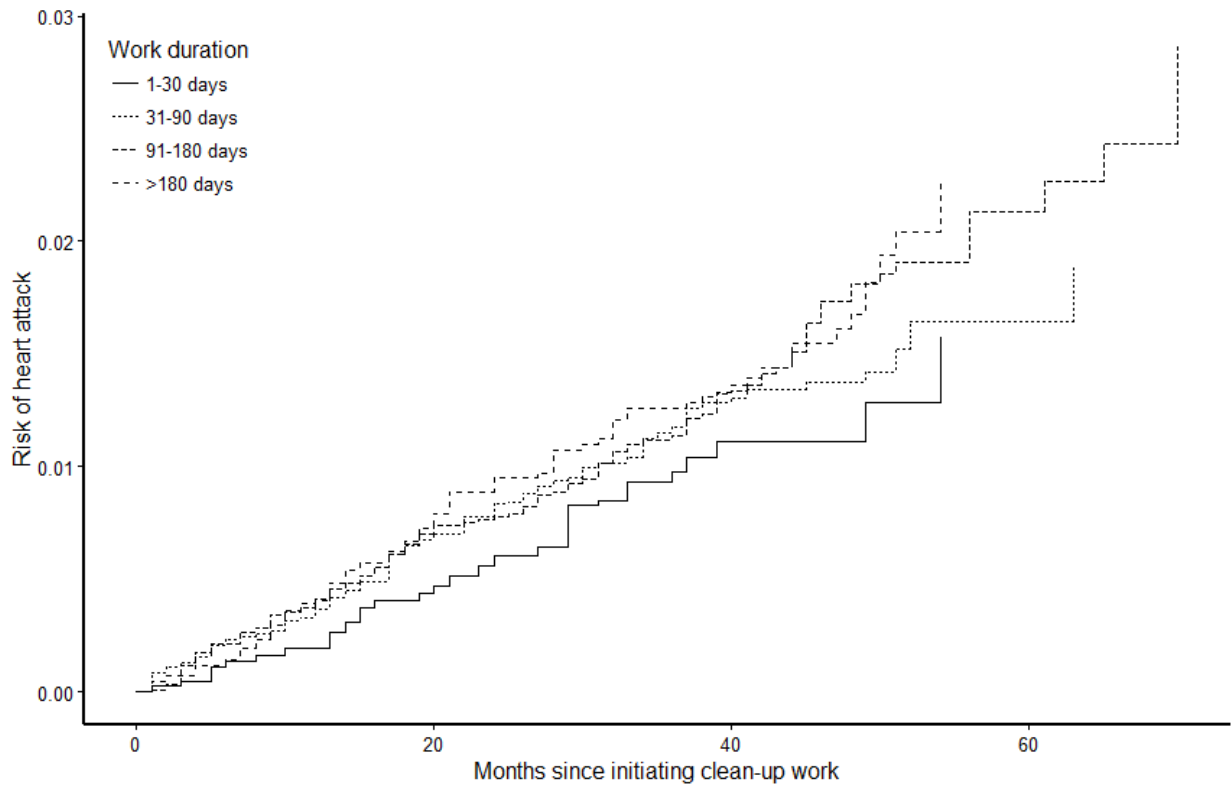
Figure 4.1. Cumulative risk curves for clean-up work duration and self-reported MI/ fatal CHD with IP exposure and censoring weights to account for gender, age, smoking, education, maximum total hydrocarbon exposure, and residential proximity to the oil spill
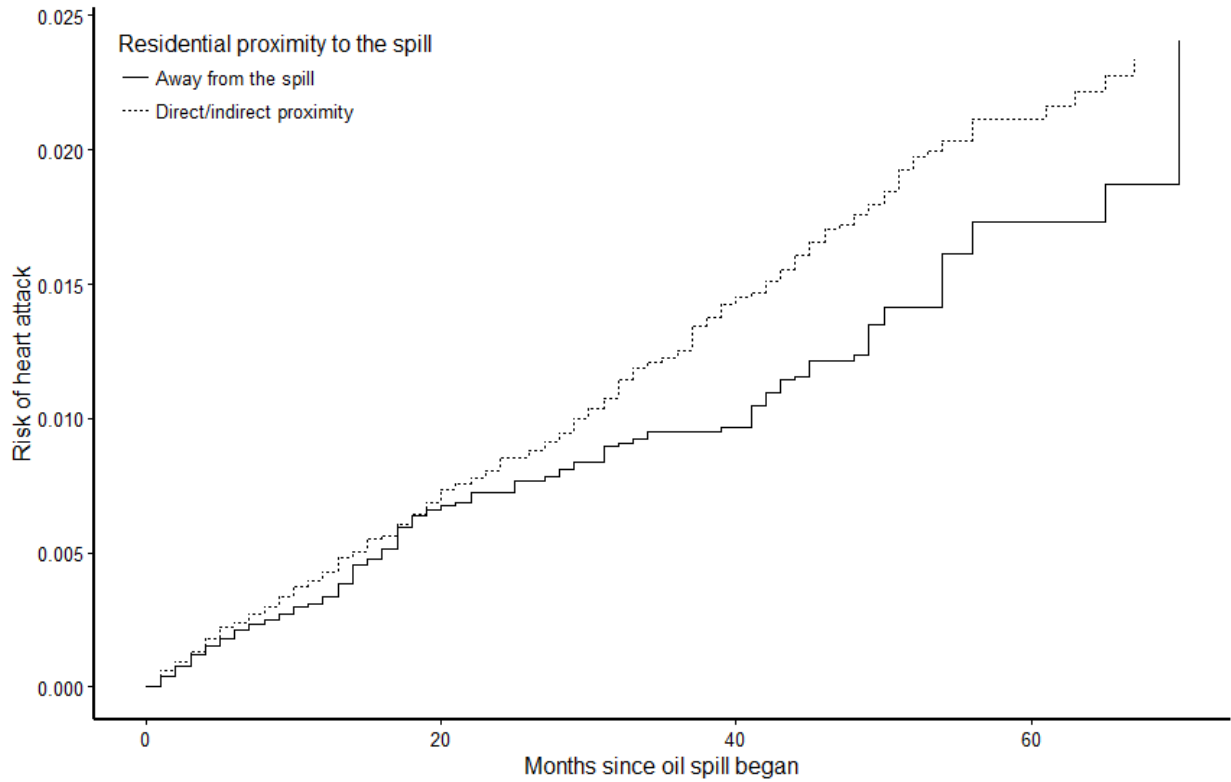
Figure 4.2. Cumulative risk curves for residence proximity to the oil spill and self-reported MI/ fatal CHD, with IP exposure and censoring weights to account for gender, age, smoking, education, maximum total hydrocarbon exposure, and work duration.

Supplemental Tables

Table 4.S1. Sensitivity analysis: The associations of residential proximity to the spill, work duration, and self-reported MI/fatal CHD, administratively censored at December 31st 2014: conditional and marginal model results. GuLF STUDY 2010-2016

Control for confounding:		Conditional model*	IP exposure weighted
	Cases/ total N**	HR (95% CI)	HR (95% CI)
Exposure: Residential proximity to the oil spill		Among workers and non-workers (n=28,854)	
No censoring weights			
Away from the spill	87/10989	ref	ref
Direct/indirect	258/16834	1.45 (1.12, 1.86)	1.37 (1.10, 1.72)
IP censoring weighted			
Away from the spill	86/10977	ref	ref
Direct/indirect	257/16824	1.47 (1.13, 1.93)	1.39 (1.06, 1.83)
Exposure: Work duration		Among clean-up workers only (n=22,251)	
No censoring weights			
1-30 days	26/2666	ref	ref
31-90 days	74/6763	1.20 (0.76, 1.87)	1.19 (0.77, 1.84)
91-180 days	109/7356	1.49 (0.97, 2.28)	1.41 (0.92, 2.16)
>180 days	68/4711	1.50 (0.95, 2.36)	1.40 (0.90, 2.19)
IP censoring weighted			
1-30 days	26/2662	ref	ref
31-90 days	73/6754	1.15 (0.72, 1.82)	1.14 (0.72, 1.82)
91-180 days	109/7353	1.43 (0.92, 2.22)	1.35 (0.87, 2.11)
>180 days	67/4705	1.56 (0.97, 2.51)	1.45 (0.90, 2.34)

Proximity to the oil spill is defined as living in, or adjacent to, a county or parish with coastline oiled during the spill.

*Adjusts for gender, age, education, smoking and residential proximity to the oil spill

**Total N for non-censoring-weighted models is where all confounders (gender, age, smoking, education) are nonmissing. Total N for IP censoring-weighted-models is where all confounders and predictors of censoring (gender, age, smoking, education, maximum total hydrocarbon exposure, and work duration) are nonmissing.

Table 4.S2. Sensitivity analysis: Risk of self-reported MI/fatal CHD by residence proximity to the spill and work duration, administratively censoring data at December 31st 2014. GuLF STUDY, 2010-2016

Duration of follow-up:	12 months		24 months		36 months		48 months	
	Risk*	RD	Risk*	RD	Risk*	RD	Risk*	RD
Proximity to the oil spill	Among the full study cohort (N=31,609)							
Away from the spill	0.004	ref	0.007	ref	0.009	ref	0.011	ref
Direct/indirect	0.004	0.001	0.009	0.001	0.013	0.004	0.018	0.007
Work duration	Among clean-up workers only (n=24,375)							
1-30 days	0.002	ref	0.006	ref	0.010	ref	0.012	ref
31-90 days	0.004	0.002	0.008	0.002	0.012	0.001	0.013	0.002
91-180 days	0.004	0.003	0.008	0.002	0.012	0.001	0.019	0.007
>180 days	0.004	0.003	0.010	0.004	0.013	0.003	0.018	0.006

Proximity to the oil spill is defined as living in, or adjacent to, a county or parish with coastline oiled during the spill.

*Risks are equal to the proportion of the cumulative number of cases at the point in time divided by the total number of study participants at risk at that time. The risks are weighted for confounders (gender, age, smoking, education) and predictors of censoring (max THC exposure, age, education, proximity to the spill, work duration, and smoking). Models for work duration also controlled for home proximity to the oil spill as a confounder

Table 4.S3. Sensitivity analysis: The association of home proximity to the spill and self-reported myocardial infarction: conditional and marginal model results. GuLF STUDY 2010-2016

Control for confounding:		Conditional model*	IP exposure weighted
	Cases/ total N**	HR (95% CI)	HR (95% CI)
Exposure: Residential proximity to the oil spill		Among workers and non-workers	
No censoring weights			
Away from the spill	91/11872	ref	ref
Direct/indirect	262/18590	1.35 (1.05, 1.73)	1.28 (0.99, 1.66)
IP censoring weighted			
Away from the spill	90/11859	ref	ref
Direct/indirect	261/18577	1.35 (1.04, 1.76)	1.28 (0.98, 1.67)
Exposure: Work duration		Among clean-up workers only	
No censoring weights			
1-30 days	26/2877	ref	
31-90 days	82/7385	1.31 (0.84, 2.04)	1.38 (0.88, 2.16)
91-180 days	107/8091	1.46 (0.95, 2.24)	1.44 (0.93, 2.22)
>180 days	65/5193	1.42 (0.90, 2.25)	1.35 (0.85, 2.15)
IP censoring weighted			
1-30 days	26/2873	ref	
31-90 days	81/7374	1.31 (0.83, 2.05)	1.38 (0.88, 2.17)
91-180 days	107/8086	1.45 (0.94, 2.23)	1.43 (0.93, 2.22)
>180 days	64/5187	1.53 (0.95, 2.44)	1.47 (0.91, 2.36)

Proximity to the oil spill is defined as living in, or adjacent to, a county or parish with coastline oiled during the spill.

*Adjusts for gender, age, smoking, and education

**Total N for non-censoring-weighted models is where all confounders (gender, age, smoking, education) are nonmissing. Total N for IP censoring-weighted-models is where all confounders and predictors of censoring (gender, age, smoking, education, maximum total hydrocarbon exposure, and work duration) are nonmissing.

Table 4.S4. Sensitivity analysis: The associations of residential proximity to the spill, work duration, and heart attack excluding 2,653 Coast Guard employees: conditional and marginal model results. GuLF STUDY 2010-2016

Control for confounding:		Conditional model*	IP exposure weighted
	Cases/ total N**	HR (95% CI)	HR (95% CI)
Exposure: Residential proximity to the spill		Among clean-up workers and non-workers	
No censoring weights			
Away from spill	95/9626	ref	ref
Direct/indirect	292/18241	1.32 (1.04, 1.68)	1.26 (0.98, 1.62)
IP censoring weighted			
Away from spill	94/9616		ref
Direct/indirect	291/18228	1.34 (1.04, 1.72)	1.27 (0.99, 1.64)
Exposure: Work duration		Among clean-up workers only	
No censoring weights			
1-30 days	29/2641	ref	ref
31-90 days	85/6392	1.25 (0.82, 1.90)	1.27 (0.83, 1.95)
91-180 days	120/7591	1.46 (0.97, 2.20)	1.42 (0.94, 2.15)
>180 days	73/4972	1.42 (0.92, 2.18)	1.37 (0.88, 2.13)
IP censoring weighted			
1-30 days	29/2638	ref	ref
31-90 days	84/6382	1.21 (0.78, 1.86)	1.23 (0.79, 1.90)
91-180 days	120/7587	1.43 (0.94, 2.16)	1.39 (0.91, 2.11)
>180 days	72/4966	1.47 (0.94, 2.30)	1.43 (0.91, 2.24)

Proximity to the oil spill is defined as living in, or adjacent to, a county or parish with coastline oiled during the spill.

*Adjusts for gender, age, smoking, and education. Models for work duration also adjusted for residential proximity to the oil spill.

**Total N for non-censoring-weighted models is where all confounders (gender, age, smoking, education) are nonmissing. Total N for IP censoring-weighted-models is where all confounders and predictors of censoring (gender, age, smoking, education, maximum total hydrocarbon exposure, and work duration) are nonmissing.

Table 4.S5. Sensitivity analysis: The associations of residential proximity to the spill, work duration, and self-reported MI/fatal CHD excluding 4,640 federal employees: conditional and marginal model results. GuLF STUDY 2010-2016

Control for confounding:		Conditional model*	IP exposure weighted
	Cases/ total N**	HR (95% CI)	HR (95% CI)
Exposure: Residential proximity to the spill		Among clean-up workers and non-workers	
No censoring weights			
Away from spill	87/8015	ref	ref
Direct/indirect	288/17918	1.27 (0.99, 1.62)	1.21 (0.94, 1.56)
IP censoring weighted			
Away from spill	86/8009	ref	ref
Direct/indirect	287/17906	1.27 (0.99, 1.64)	1.22 (0.95, 1.58)
Exposure: Work duration		Among clean-up workers only	
No censoring weights			
1-30 days	25/2140	ref	ref
31-90 days	77/5444	1.27 (0.81, 2.00)	1.28 (0.81, 2.03)
91-180 days	120/6987	1.59 (1.03, 2.44)	1.54 (0.99, 2.38)
>180 days	70/4467	1.50 (0.95, 2.37)	1.45 (0.91, 2.31)
IP censoring weighted			
1-30 days	25/2137	ref	ref
31-90 days	76/5438	1.23 (0.77, 1.95)	1.23 (0.77, 1.96)
91-180 days	120/6984	1.54 (0.99, 2.40)	1.49 (0.96, 2.34)
>180 days	69/4461	1.55 (0.96, 2.49)	1.48 (0.92, 2.40)

Proximity to the oil spill is defined as living in, or adjacent to, a county or parish with coastline oiled during the spill.

*Adjusts for gender, age, education, and smoking. Models for work duration also adjust for residential proximity to the spill.

**Total N for non-censoring-weighted models is where all confounders (gender, age, smoking, education) are nonmissing. Total N for IP censoring-weighted-models is where all confounders and predictors of censoring (gender, age, smoking, education, maximum total hydrocarbon exposure, and work duration) are nonmissing.

CHAPTER 5: AIM 2 RESULTS

Title: Exposure to total hydrocarbons during clean-up of the *Deepwater Horizon* oil spill and risk of heart attack across 5 years of follow-up

Introduction

Workers involved in response and clean-up of the 2010 *Deepwater Horizon* oil spill faced exposures to a number of chemicals and air pollutants generated by crude oil, burning oil and clean-up efforts. Some of these pollutants, including particulate matter (PM), polycyclic aromatic hydrocarbons (PAHs), and some volatile organic compounds, have been associated with coronary heart disease (CHD) (1-4). Working in proximity to oil spill chemical stressors and air pollutants may impact the risk of CHD among clean-up workers, but no previous study of oil spills has addressed this question.

Exposure to particulate matter and organic chemicals via air pollution has been shown to be associated with cardiovascular disease risk (4-8). Short-term (24-hour) average increases in ambient particulate matter are associated with increased incidence of myocardial infarction (2, 9). Air concentrations of PM, PAHs, and total hydrocarbons varied spatially and temporally over the course of the *Deepwater Horizon* oil spill (10). Particulate matter concentrations exceeded typical ambient levels (11), which range from 0.02-1.00 µg/m³ in the Southern United States (US) (12). It is unknown whether these exposures, at levels present during the spill, could have impacted cardiovascular health among workers and whether any such effects would be acute or persistent.

Several studies have examined acute health effects associated with oil spills, but there has been relatively little research into longer-term health effects following these events. Zock and colleagues observed that respiratory symptoms were elevated among fishermen involved in clean-up of the *Prestige* oil spill for 5 years after the spill (13). In a study of the *Tasman Spirit* oil spill, clean-up workers had reduced lung function up to 5 months after the spill, compared to community members who were not involved with clean-up (14). Although these studies did not examine the effects of specific oil spill-related chemical exposures, results are consistent with the hypothesis that short-term exposures may elicit biological changes that persist after exposure to the oil spill has ended.

We hypothesized that total hydrocarbon exposures during *Deepwater Horizon* oil spill clean-up increases risk of coronary heart disease and aimed to assess whether these associations, if present, persist over time.

The Gulf Long Term Follow-up (GuLF) STUDY is the largest study of the health impacts of oil spills and is the first study to assess heart disease among individuals exposed to oil spills (15). We used information from two sequential GuLF STUDY interviews to examine relationships between total hydrocarbon exposure and risk of first heart attack up to 5 years after the oil spill.

Methods

Study Population

The GuLF STUDY is a longitudinal cohort study of the health impacts of the *Deepwater Horizon* oil spill. Participants include individuals who completed mandatory oil spill safety training in order to take part in the oil spill response and clean-up, as well as government

workers and oil industry professionals (15). Study enrollment began 11 months after the start of the oil spill, in March 2011, and continued until May 2013. A total of 32,608 individuals enrolled in the cohort; this report includes 24,375 English and Spanish speaking participants who worked on oil spill clean-up for at least one day. Among these, 16,814 (69%) completed a second telephone interview in 2014-2016, two to three years after the enrollment interview.

Exposure measures

The exposure of interest is maximum and median level of total hydrocarbon (THC) exposure (as a general marker of oil exposure) during clean-up work. A job-exposure matrix (JEM) was used to assign estimated levels of THC exposure to workers (16). Exposure groups were formed, which were expected to have similar distributions of exposure based on clean-up activities, locations, and dates of work. Participants reported complex work patterns (e.g., performing multiple activities sometimes at the same time), and were assigned to multiple exposure groups. Arithmetic means of THC exposure were calculated for each exposure group (17).

We defined workers' maximum THC exposure as their highest intensity exposure at any time during clean-up and categorized this based on the distribution of the maximum exposure estimates, as <0.30 ppm, 0.30-0.99 ppm, 1.00-2.99 ppm, and ≥3.00 ppm. We defined a participant's median THC exposure as the median of the exposure estimates across all his/her exposure groups before the oil well was capped on July 15th, 2010, the period when oil exposures were generally highest (16). Categories for the median THC exposure were defined as <0.10 ppm; 0.10-0.29 ppm; 0.30-0.99 ppm; ≥1.00 ppm, based on the distribution of these scores. Maximum THC scores were available for all 24,375 clean-up workers, and median exposure scores were available for the 22,982 workers who initiated clean-up before July 15th, 2010.

Outcome measure

The outcome of interest is the first occurrence of an incident heart attack, defined as either a self-reported physician-diagnosed myocardial infarction (MI) or a fatal CHD event. During the study interviews, participants were asked if they had ever received a diagnosis of a heart attack or MI, and the month and year of their first MI diagnosis. Deaths due to CHD were ascertained from the National Death Index (NDI) from the date of enrollment in the cohort through December 31st 2014, the latest date for which complete NDI data were available. International Classification of Diseases, 10th Edition (ICD-10) codes in any position indicating ischemic heart disease as a cause of death (codes I20-I25) were included.

Risk period for heart attack

The risk period for a nonfatal MI began at initiation of oil spill clean-up work and ended at the first of either the date of diagnosis of a first MI or at the last GuLF STUDY interview that the participant completed. The risk period for a fatal CHD event began at the date of the enrollment interview and continued until December 31st 2014. Only a participant's first reported MI or CHD event was counted in this study. Participants who reported a first MI occurring prior to initiation of clean-up work (n=452) were excluded.

Among the 23,923 clean-up workers remaining after excluding prevalent cases, there were 253 deaths during the study period, including 36 CHD-related deaths. Incident nonfatal MI were reported by 282 participants. Of the 36 CHD-related deaths, six were among individuals who had already reported an incident first MI diagnosis; only the earlier, non-fatal MI was included in these analyses. Thus, a total of 312 first heart attack cases were included in this report.

Censoring and predictors of censoring

Self-reported MI may have been censored among study participants who did not complete the second interview but were at risk for a first MI. We compared distributions of a number of factors plausibly related to the outcome and non-response, for their associations with completion of the second interview. These factors included demographic, lifestyle and socioeconomic characteristics, factors related to health at enrollment, and clean-up work characteristics. We compared crude proportions of censoring across levels of each predictor variable. The magnitude and precision of these estimates were considered to assess the ability of each variable to predict non-response.

To reduce the impact of potential selection bias, we weighted the population that completed the second interview with respect to predictors of censoring; this approach allowed us to estimate associations that would be observed in the absence of censoring (18). Inverse probability (IP) of censoring weights were estimated from models conditional on predictors of censoring. The variables (derived from information collected at the first interview) we included in the censoring weights model were determined from a causal diagram (19): age (20-29; 30-39; 40-49; 50-59; 60-65; >65 years), maximum education attainment (less than high school; high school diploma/GED; some college/2 year degree; 4+ year college graduate), cigarette smoking (current; former; never), residential proximity to the oil spill ("direct/indirect": living in or adjacent to a county with coastline oiled during the spill; vs. "away from the spill"), and maximum THC exposure during clean-up work (<0.30 ppm, 0.30-0.99 ppm, 1.00-2.99 ppm, ≥3.00 ppm). We calculated stabilized IP censoring weights by dividing the marginal probability of being observed at the second interview by the conditional probabilities of being observed output from the censoring weights model.

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Time-to-heart attack analyses

We assessed the associations between THC exposure and time-to-incident first heart attack using Cox proportional hazards models (20). Person-time was accrued from the start of an individual's oil spill clean-up work until the earlier of first MI event, leaving the study, or administrative censoring at the end of NDI follow-up.

We controlled for confounders using IP exposure weights (21). The following adjustment set (based on information collected at the first interview) was determined using a directed acyclic graph (19): gender (male; female), age at enrollment (20-29; 30-39; 40-49; 50-59; 60-65; >65 years), cigarette smoking (current; former; never), maximum education attainment at enrollment (less than high school; high school diploma/GED; some college/2 year degree; 4+ year college graduate), and residential proximity to the oil spill at enrollment ("direct/indirect": living in or adjacent to a county with coastline oiled during the spill; vs. "away from the spill"). We did not adjust for body mass index or self-reported prevalent hypertension because these were not associated with THC exposure. Stabilized IP exposure weights were obtained by fitting a multinomial logistic regression model for the exposure with confounders as independent variables; the denominator was based on the probability output from the model, and the numerator was based on the marginal probability of exposure (18). As a sensitivity analysis, we controlled for confounders conditionally in the Cox models.

Cox proportional hazards models (20) with a robust variance estimator were fit to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) (22). We assessed whether each covariate met the proportional hazards by modeling an interaction term between the natural log of time and each covariate; we also assessed this assumption visually by plotting the log of the negative log of the Kaplan-Meier estimator of heart attack risk by time at risk (20). Tests of the

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proportional hazards assumption did not indicate any significant departures from proportional hazards (all p>0.10, results not shown).

The NDI mortality data were censored on December 31, 2014, before some participants had completed their second study interviews. To account for this, we performed a sensitivity analysis where we excluded the 2,124 participants who gave their second interview after December 31, 2014. We also performed a sensitivity analysis to assess associations for nonfatal MI only; this analysis included the 282 incident nonfatal heart attacks that were reported during the first or second study interviews. In separate analyses, we controlled for work duration to assess the possible impact of a healthy worker survivor bias, as healthier workers may have worked longer on the clean-up. To assess the possible impact of heat stress during clean-up work on the observed results, we adjusted for whether the participant reported having to stop clean-up work activities due to the heat. In another sensitivity analysis, we removed the US Coast Guard and other federal employees from the analyses (n=4,640), as these workers may be more physically fit and/or have more access to health care services compared to non-federally-employed workers.

Cumulative incidence of heart attack

To assess whether associations with heart attack changed across the study period, we estimated cumulative risks of heart attack at yearly intervals throughout the follow-up period. We generated weighted, cumulative conditional risk plots with proportional hazards regression using the Nelson-Aalen survival estimator (23), with months since initiation of clean-up work as the time scale. We accounted for confounders and predictors of censoring using the same IP weights as were included in the Cox regression models (24).

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Results

Table 5.1 shows distributions of demographic characteristics among the 24,375 clean-up workers who completed the first interview, and the 16,814 (69%) who completed the first and second interviews. Participants who completed both interviews, as compared with those who only completed the first, were more likely to be older, white, nonsmokers, to have attended or graduated from college, and to have a 2010 household income >$50,000 (Table 5.1). Distributions of demographic, health, and oil spill exposure characteristics by heart attack status among the 23,923 workers with no prevalent MI diagnosis are shown in in Table 5.2.

IP censoring and exposure weights

After excluding prevalent MI cases, censoring weights were determined separately for the full cohort (N=23,923) and for those who began clean-up work before July 15, 2010 (n=22,550). For the full cohort, the mean and range of the stabilized censoring weights was 1.00 (0.52-2.61) with standard deviation 0.21, the stabilized exposure weights had a mean and range of 1.00 (0.32-7.05) with standard deviation 0.48, and the final weight (exposure weight multiplied by censoring weight) had a mean and range of 1.00 (0.25-13.40) with a standard deviation of 0.55. For the 22,550 workers who started clean-up work before July 15 2010, the mean and range of the stabilized censoring weights was 1.00 (0.55-2.68) with standard deviation 0.21, the stabilized exposure weights had a mean and range of 1.00 (0.31-4.47) with a standard deviation of 0.39, and the final weight had a mean and range of 1.00 (0.25-6.33) with a standard deviation of 0.47.

Hazard ratios for heart attack and total hydrocarbon exposure

Risks of heart attack were elevated for maximum THC exposure levels in excess of 0.30 ppm (Table 5.3). Maximum THC exposure ≥3.00 ppm (vs <0.30 ppm) showed the strongest

association with risk of heart attack [marginal HR(95%CI)=1.81(1.11, 2.95)], though hazard ratios were also significantly elevated for exposure levels 0.30-0.99 ppm [1.66(1.09, 2.53)] and 1.00-2.99 ppm [1.62(1.06, 2.47)]. There was no clear exposure-response relationship across exposure groups. Results were robust to factors associated with non-response to the second interview, as hazard ratios without IP censoring weights were not meaningfully changed, though they did decrease slightly in magnitude [marginal HR(95%CI) for maximum THC exposure ≥3.00 ppm=1.70(1.05, 2.74)]. Hazard ratios for the associations of median THC exposure before the oil well was capped and heart attack were attenuated compared to the associations with maximum THC exposure (Table 5.4). Hazard ratios were similar using the conditional Cox models (Supplemental Table 5.S1).

Sensitivity analyses that censored all participants on December 31, 2014, the last date of available NDI data, showed similar but slightly strengthened results across all levels of maximum THC exposure; the marginal HR(95%CI) for maximum THC ≥3.00 ppm (vs <0.30 ppm) was 2.01(1.21, 3.34) (Supplemental Table 5.S2). Analyses that excluded fatal CHD outcomes were slightly weakened in magnitude and precision but were overall not meaningfully different from the results in Table 5.3 (Supplemental Table 5.S3). Hazard ratios adjusting for heat stress during clean-up work were also not meaningfully changed compared to the main results (results not shown).

Workers with the maximum THC exposure <0.30ppm had the lowest cumulative risk of heart attack across follow-up (Table 5.5; Figure 5.1). The IP censoring- and confounding-weighted risk differences for maximum THC exposure ≥3.00ppm (vs <0.30 ppm) and heart attack showed elevated risks from 4 cases per 1000 workers at 12 months of follow-up, to 9 cases per 1000 workers at 48 months of follow-up (Table 5.5). Results from the sensitivity

analyses that censored all participants on December 31, 2014 also yielded similar risk differences (Supplemental Table 5.S4). The risk differences for median THC exposure ≥1.00 ppm (vs <0.10 ppm) ranged from 2 excess cases per 1000 workers to 5 excess cases per 1000 workers (Figure 5.2; Table 5.6).

Findings from the sensitivity analyses where we excluded 4,640 federally employed workers from the cohort showed slightly increased hazard ratios for maximum THC exposure levels >0.30ppm. The marginal HR(95%CI) for maximum THC exposure ≥3.00 ppm (vs 0.30 ppm) was 1.94(1.16, 3.26) (Supplemental Table 5.S5). In an additional sensitivity analysis that controlled for work duration, we also observed slightly strengthened associations between total hydrocarbon exposure and heart attack (Supplemental Table 5.S6).

Discussion

This study of *Deepwater Horizon* oil spill response and clean-up workers showed 62-81% higher hazards for heart attack among those with estimated maximum THC exposure levels in excess of 0.30 ppm. Risk differences comparing those with the highest to the lowest level of exposure were small in magnitude but showed persistent associations across follow-up. Accounting for differences in characteristics of those who completed the second interview using IP censoring weights showed that results were generally robust to censoring, though the magnitudes of the observed associations were slightly attenuated when IP censoring weights were not applied.

Associations between median exposures before the well was capped and heart attack were weaker than the associations with maximum exposure levels. We had hypothesized that exposures during the period before the oil well was capped would have greater cardiovascular

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impact than exposures after the well was capped as most fresh oil was present during this time (16). However, the maximum exposure categorizations better captured the highest intensity of exposures among workers. It may have been the case that median exposures were generally not high enough to elicit an observable association with heart attack.

We observed persistence of the association between maximum THC exposure and heart attack risk across the follow-up period. Most studies of air pollutant exposures and heart disease have focused on short temporal periods between exposure and outcome (4, 25), and we are unaware of any studies that assessed persistent effects of short-term pollution exposures. Considering other research on the health impacts of oil spills, our results are consistent with studies that identified persistent respiratory health problems up to 5 years after oil spill clean-up (13), though our study is the first to consider persistence of coronary heart disease among oil spill workers.

We evaluated the extent to which other factors such as heat stress associated with clean-up work explained the observed associations. Heat stress was common among clean-up workers, and heat stress or other physical stress can increase risk of heart attack (26, 27). Adjusting for heat stress did not lead to meaningful changes in the associations between THC exposure and heart attack. We were unable to account for any heat stress-related fatalities occurring during the oil spill clean-up or prior to the enrollment interviews, as participants had to be alive at enrollment. Truncation of deaths prior to enrollment may have resulted in underestimation of heart attack risk as less healthy workers would not have been included in our cohort, as well as underestimation of acute effects of spill-related exposures on heart attack.

Healthier or more physically fit clean-up workers may have been less predisposed to heart attack compared to less fit workers and may have worked longer durations, leading to

possibly higher cumulative THC exposures. These differences may have resulted in healthy worker survivor bias (28, 29). When we controlled for work duration, we saw only a slight strengthening in the observed associations between THC exposure and heart attack, which is consistent with no appreciable healthy worker survivor bias but may not have captured this bias if exposure strongly predicted retention in clean-up activities.

In a sensitivity analysis where we excluded the 4,640 federally-employed workers, the HRs for maximum THC exposure were slightly stronger compared to results in the full cohort. Federal workers may have more access to health care services compared to less stably-employed oil spill workers. Furthermore, federally-employed workers had lower prevalence of self-reported physician-diagnosed hypertension compared to the remainder of the cohort (16% vs 29%). These differences likely explain why associations were attenuated when federal workers were included.

This study relied on self-reported information on nonfatal physician-diagnosed MI, which is subject to errors in reporting. Self-reported MI has shown moderate sensitivity (61%) when compared against adjudicator diagnosis (30). Recall of MI is also dependent on the time period for which disease is being ascertained, but the 5-year period of this study is a relatively short period to recall a serious event such as an MI. There is also possibility for competing risks (non-CHD death) to introduce bias in our conditional risk estimates. However, non-CHD death was rare during the study period (0.82% prevalence) and was not associated with THC exposure, therefore bias due to competing risks is unlikely.

In summary, the GuLF STUDY is the largest study of the human health impact of oil spills and is the first to investigate the association between THC exposure and heart attack risk among oil spill workers. Our study improves on exposure assessment methods used in past

studies of oil spills by utilizing job exposure matrix-based estimates of THC exposure, which

incorporated detailed self-reported data on clean-up activities as well as airborne THC

measurements. Our study showed positive associations between the estimated maximum THC

exposure during oil spill clean-up work and risk of heart attack up to 5 years after the spill, with

more equivocal evidence of associations in relation to median THC exposures. Additional

research should assess possible heterogeneity of the observed associations by factors such as

tobacco smoking, or other risk factors for CHD. Future studies can also make use of planned

subsequent follow-up interviews to further assess longitudinal changes in these associations.

Figures and tables

TABLES

Table 5.1. Demographic and Oil Spill Work Characteristics at Enrollment (except where noted) Among Those Who Completed (n=16,814) and Did Not Complete (n=7,561) the Second Study Interview. GuLF STUDY 2010-2016

	Completed interview #2 (N=16,814)	Did not complete interview #2 (N=7,561)		
	N(%)	N(%)	RD	95% CI
Gender				
Male	13,747 (81.8)	6,335 (83.8)	ref	
Female	3,067 (18.2)	1,226 (16.2)	0.0299	0.0149, 0.0448
Missing	0 (0.0)	0 (0.0)		
Age category (years)				
20-29	2,936 (17.5)	2,063 (27.4)	-0.0489	-0.0673, -0.0306
30-39	3,745 (22.3)	2,141 (28.4)	ref	
40-49	4,245 (16.8)	1,726 (7.6)	0.0747	0.0579, 0.0915
50-59	4,018 (16.8)	1,188 (5.5)	0.1355	0.1188, 0.1523
60-65	1,071 (4.6)	256 (1.3)	0.1708	0.1463, 0.1954
>65	753 (3.4)	153 (0.9)	0.1949	0.1676, 0.2222
Missing	46 (0.3)	34 (0.4)		
Ethnicity				
White	11,270 (67.4)	4,827 (64.2)	ref	

Black	3,767 (22.5)	1,859 (24.7)	-0.0306	-0.0447, -0.0164
Asian	132 (0.8)	87 (1.2)	-0.0974	-0.1626, -0.0322
Other/multi-racial	1554 (9.3)	743 (9.9)	-0.0236	-0.044, -0.0032
Missing	91 (0.6)	45 (0.6)		
Hispanic				
Yes	1,112 (6.6)	599 (7.9)	-0.0431	-0.0664 ,-0.0197
No	15,659 (93.4)	6,938 (92.1)	ref	
Missing	43 (0.3)	24 (0.3)		
Education completed				
Less than high school	2,446 (14.6)	1,376 (18.3)	-0.0129	-0.0317, 0.0059
High school diploma/GED	4,673 (27.9)	2,485 (33.0)	ref	
Some college/2 year degree	5,032 (30.0)	2,269 (30.1)	0.0364	0.0211, 0.0517
4+ year college graduate	4,618 (27.5)	1,408 (18.7)	0.1135	0.0982, 0.1289
Missing	45 (0.3)	23 (0.3)		
2010 Household Income				
≤ $20,000	3,960 (25.9)	2,114 (31.3)	-0.0208	-0.037, -0.0045
$20,001-$50,000	4,748 (31.1)	2,310 (34.2)	ref	
> $50,000	6,581 (43.0)	2,330 (34.5)	0.0658	0.0516, 0.0801
Missing	1525 (9.1)	807 (10.7)		
Residential proximity to the spill				
Direct/indirect	9,688 (57.6)	4,723 (62.5)	-0.0429	-0.0546, -0.0312
Away from the spill	7,126 (42.4)	2,838 (37.5)	ref	
Missing	0 (0.0)	0 (0.0)		
Clean-up work duration (days)				
1-30	2,063 (12.3)	935 (12.4)	ref	
31-90	5,293 (31.5)	2,376 (31.4)	0.0021	-0.0175, 0.0216
91-180	5,735 (43.8)	2,628 (44.2)	-0.0024	-0.0217, 0.017
>180	3,723 (22.1)	1,622 (21.5)	0.0084	-0.0122, 0.0291
Missing	0 (0.0)	0 (0.0)		
Worked before the well was capped				
Yes	14,362 (85.4)	6,588 (87.1)	-0.0304	-0.0467 ,-0.014
No	2,452 (14.6)	973 (12.9)	ref	
Missing	0 (0.0)	0 (0.0)		
Maximum total hydrocarbon exposure (ppm)				
<0.30	3,864 (23.0)	1,579 (20.9)	ref	
0.30-0.99	5,519 (32.9)	2,465 (32.6)	-0.0186	-0.0344, -0.0029
1.00-2.99	5,094 (30.3)	2,382 (31.5)	-0.0285	-0.0446, -0.0125

			RD	95% CI
≥3.00	2,313 (13.8)	1,132 (15.0)	-0.0385	-0.0583, -0.0187
Missing	24 (0.1)	3 (0.0)		
Report at interview #1 or #2 of ever having had a nonfatal MI				
Yes	416 (2.5)	126 (1.7)	0.0795	0.0434, 0.1155
No	16,350 (97.5)	7,413 (98.3)	ref	
Missing	48 (0.3)	22 (0.3)		
Report of first nonfatal MI/fatal CHD after the oil spill/study enrollment				
Yes	250 (1.5)	62 (0.8)	-0.0201	-0.0878, 0.0477
No	16,089 (98.5)	7,392 (99.2)	ref	
Missing	475 (2.8)	107 (1.4)		
Self-reported physician-diagnosed hypertension before study enrollment				
Yes	4,716 (28.1)	1,701 (22.6)	0.0591	0.0477,0.0705
No	12,053 (71.9)	5,839 (77.4)	ref	
Missing	45 (0.3)	21 (0.3)		
Perceived health				
Excellent	2,689 (16.1)	1,279 (17.0)	-0.013	-0.0308, 0.0048
Very good	5,383 (32.2)	2,350 (31.3)	0.0054	-0.0091, 0.02
Good	5,352 (32.0)	2,397 (31.9)	ref	
Fair	2,471 (14.8)	1,132 (15.1)	-0.0049	-0.0232, 0.0135
Poor	841 (5.0)	360 (4.8)	0.0096	-0.0183, 0.0375
Missing	78 (0.5)	43 (0.6)		
Tobacco smoking				
Current	4,710 (28.2)	2,635 (35.2)	-0.0681	-0.0818, -0.0544
Former	3,713 (22.2)	1,452 (19.4)	0.0095	-0.0052, 0.0243
Never	8,300 (49.6)	3,401 (45.4)	ref	
Missing	91 (0.5)	73 (1.0)		
Current drinker				
Yes	12,852 (76.9)	5,677 (75.7)	0.0135	-0.0003, 0.0274
No	3,871 (23.1)	1,821 (24.3)	ref	
Missing	91 (0.5)	63 (0.8)		
BMI (kg/m^2) at enrollment				
<25	4,365 (26.2)	2,140 (28.7)	ref	
25-29.9	6,911 (41.5)	3,078 (41.3)	0.0208	0.0063, 0.0354
≥30	5,365 (32.2)	2,236 (30.0)	0.0348	0.0195, 0.0501
Missing	173 (1.0)	107 (1.4)		

95% CI: 95% confidence interval; BMI: Body Mass Index; RD: Risk difference.

Residential proximity to the spill is defined as living in, or adjacent to, a county with coastline that was oiled during the spill

Table 5.2. Demographic and Oil Spill Work Characteristics at Baseline Among Enrolled Clean-up Workers Without Prevalent Nonfatal Heart Attack (N=23,923), by Incident Heart Attack. GuLF STUDY 2010-2016

	Cases n (%) (N=312)	Total N (%) (N=23,923)
Gender		
Male	284 (91.0)	19585 (82.2)
Female	28 (9.0)	4244 (17.8)
Missing		0 (0.0)
Age (years)		
20-29	6 (1.9)	4985 (21.0)
30-39	30 (9.6)	5850 (24.6)
40-49	94 (30.1)	5865 (24.7)
50-59	118 (37.8)	5012 (21.1)
60-65	37 (11.9)	1245 (5.2)
>65	27 (8.7)	793 (3.3)
Missing		173 (0.7)
Ethnicity		
White	199 (63.8)	15708 (66.6)
Black	77 (24.7)	5543 (23.5)
Asian	5 (1.6)	213 (0.9)
Other/multi-racial	31 (9.9)	2132 (9.0)
Missing		227 (1.0)
Education		
Less than high school	78 (25.0)	3702 (15.6)
High school diploma/GED	108 (34.6)	6987 (29.4)
Some college/2 year degree	83 (26.6)	7149 (30.1)
4+ year college graduate	43 (13.8)	5925 (24.9)
Missing		160 (0.7)
Household income		
≤ $20,000	102 (34.9)	5917 (27.4)
$20,001-$50,000	102 (34.9)	6905 (32.0)
> $50,000	88 (30.1)	8748 (40.6)
Missing		2353 (9.8)
Residence proximity to the oil spill		
Direct/indirect	231 (74.0)	14019 (58.8)
Away from the spill	81 (26.0)	9810 (41.2)
Missing		94 (0.4)
Duration of clean-up work(days)		
1-30	29 (9.3)	2920 (12.3)
31-90	88 (28.2)	7488 (31.4)
91-180	122 (39.1)	8178 (34.3)

>180	73 (23.4)	5243 (22.0)
Missing		94 (0.4)
Maximum total hydrocarbon exposure (ppm)		
<0.30	42 (13.5)	5342 (22.4)
0.30-0.99	106 (34.2)	7801 (32.8)
1.00-2.99	114 (36.8)	7283 (30.6)
≥3.00	48 (15.5)	3377 (14.2)
Missing		120 (0.5)
Median total hydrocarbon exposure (ppm)		
<0.10	41 (14.0)	4460 (19.9)
0.10-0.29	106 (36.3)	7792 (34.7)
0.30-.99	128 (43.8)	9035 (40.2)
≥1.00	17 (5.8)	1173 (5.2)
Missing		1463 (6.1)
Self-reported prevalent hypertension		
Yes	199 (64.4)	6092 (25.6)
No	110 (35.6)	17689 (74.4)
Missing		142 (0.6)
Cigarette smoking		
Current	120 (38.8)	7140 (30.2)
Former	88 (28.5)	4989 (21.1)
Never	101 (32.7)	11547 (48.8)
Missing	(0.0)	247 (1.0)
BMI		
<25	63 (20.2)	6401 (27.2)
25-29.9	110 (35.3)	9785 (41.5)
≥30	139 (44.6)	7376 (31.3)
Missing		361 (1.5)

BMI: Body Mass Index (Underweight or Healthy weight: <24.9;
Overweight: 25.0–29.9; Obese: >=30.0); ppm: parts per million.
Residential proximity to the spill is defined as living in, or adjacent to, a
county with coastline that was oiled during the spill.

Table 5.3. Marginal Hazard Ratios of the Association of Maximum Total Hydrocarbon (THC) Exposure and Self-Reported MI/Fatal CHD. GuLF STUDY 2010-2016

Max THC exposure (ppm)	Cases/Total N[a] (307/23,520)	HR[b]	95% CI
No censoring weights			
<0.30	41/5,246	ref	
0.30-0.99	105/7,719	1.60	1.07, 2.41
1.00-2.99	114/7,209	1.45	0.96, 2.18
≥3.00	47/3,346	1.70	1.05, 2.74
IP censoring weighted[c]			
<0.30	41/5,215	ref	
0.30-0.99	105/7,682	1.66	1.09, 2.53
1.00-2.99	114/7,178	1.62	1.06, 2.47
≥3.00	47/3,334	1.81	1.11, 2.95

CHD: coronary heart disease; HR: Hazard ratio; IP: Inverse probability; Max THC exposure: Maximum total hydrocarbon exposure during clean-up work; MI: myocardial infarction; ppm: parts per million

[a]Total N for models without censoring weights is where median oil exposure, gender, age, smoking, education, residential proximity to the spill are non-missing; total N for models with censoring weights is where ethnicity is also non-missing

[b]Models control for gender, age, smoking, education, residence proximity to the oil spill

[c]Censoring weights account for age, ethnicity, education, residential proximity to the oil spill, smoking, and maximum total hydrocarbon exposure

Table 5.4. Marginal Hazard Ratios of the Association of Median Total Hydrocarbon (THC) Exposure Before the Oil Well Was Capped and Self-Reported MI/Fatal CHD. GuLF STUDY 2010-2016

Median THC exposure (ppm) before July 15, 2010	Cases/Total N[a] (289/22,200)	HR[b]	95% CI
No censoring weights			
<0.10	40/4,386	ref	
0.10-0.29	106/7,715	1.44	1.01, 2.06
0.30-0.99	126/8,940	1.27	0.89, 1.80
≥1.00	17/1,159	1.35	0.75, 2.43
IP censoring weighted[c]			
<0.10	40/4,363	ref	
0.10-0.29	106/7,682	1.58	1.04, 2.40
0.30-0.99	126/8,904	1.32	0.88, 2.00
≥1.00	17/1,154	1.47	0.78, 2.78

CHD: coronary heart disease HR: Hazard ratio; IP: Inverse probability; Max THC exposure: Maximum total hydrocarbon exposure during clean-up work; MI: myocardial infarction; ppm: parts per million.
[a]Total N for models without censoring weights is where median oil exposure, gender, age, smoking, education, residential proximity to the spill are non-missing; total N for models with censoring weights is where ethnicity is also non-missing
[b]Models control for gender, age, smoking, education, residence proximity to the oil spill
[c]Censoring weights account for age, ethnicity, education, residential proximity to the oil spill, smoking, and maximum total hydrocarbon exposure

Table 5.5. Risk of self-reported MI/fatal CHD by maximum THC exposure by time since initiating oil spill work. GuLF STUDY, 2010-2016 (N=24,375)

Time since initiating clean-up:	12 months		24 months		36 months		48 months	
Max THC exposure (ppm)	Risk[a]	RD	Risk[a]	RD	Risk[a]	RD	Risk[a]	RD
<0.30	0.002	ref	0.005	ref	0.007	ref	0.010	ref
0.30-0.99	0.004	0.002	0.010	0.004	0.012	0.005	0.017	0.007
1.00-2.99	0.003	0.001	0.007	0.002	0.012	0.004	0.015	0.005
≥3.00	0.006	0.004	0.010	0.005	0.013	0.006	0.019	0.009

CHD: coronary heart disease; Max THC exposure: Maximum total hydrocarbon exposure during clean-up work; MI: myocardial infarction; ppm: parts per million; RD: Risk difference
[a]Risk estimates account for confounders (age, gender, education, smoking, home proximity to the spill) and predictors of censoring (age, education, ethnicity, smoking, clean-up work duration, home proximity to the spill) using inverse probability weights

Table 5.6. Risk of Self-Reported MI/fatal CHD by Median THC Exposure Before the Oil Well Was Capped, By Time Since Initiating Oil Spill Clean-Up. GuLF STUDY, 2010-2016 (N=22,982)

Time since initiating clean-up:	12 months		24 months		36 months		48 months	
Med THC exposure (ppm)	Risk[a]	RD	Risk[a]	RD	Risk[a]	RD	Risk[a]	RD
<0.10	0.003	ref	0.006	ref	0.009	ref	0.011	ref
0.10-0.29	0.003	0.001	0.009	0.002	0.012	0.003	0.017	0.006
0.30-0.99	0.004	0.001	0.008	0.001	0.011	0.002	0.015	0.005
≥1.00	0.005	0.002	0.009	0.002	0.013	0.004	0.016	0.005

CHD: coronary heart disease; Med THC exposure: Median total hydrocarbon exposure before the oil well was capped on July 15 2010; MI: myocardial infarction; ppm: parts per million; RD: Risk difference

[a]Risk estimates account for confounders (age, gender, education, smoking, home proximity to the spill) and predictors of censoring (age, education, ethnicity, smoking, clean-up work duration, home proximity to the spill) using inverse probability weights

Figures

Figure 5.1. Cumulative risk of self-reported myocardial infarction/fatal coronary heart disease by maximum total hydrocarbon exposure during clean-up work. Risks are weighted using IP exposure and censoring weights to account for gender, age, ethnicity, smoking, education, and residential proximity to the oil spill. GuLF STUDY, 2010-2016 (N=23,923).

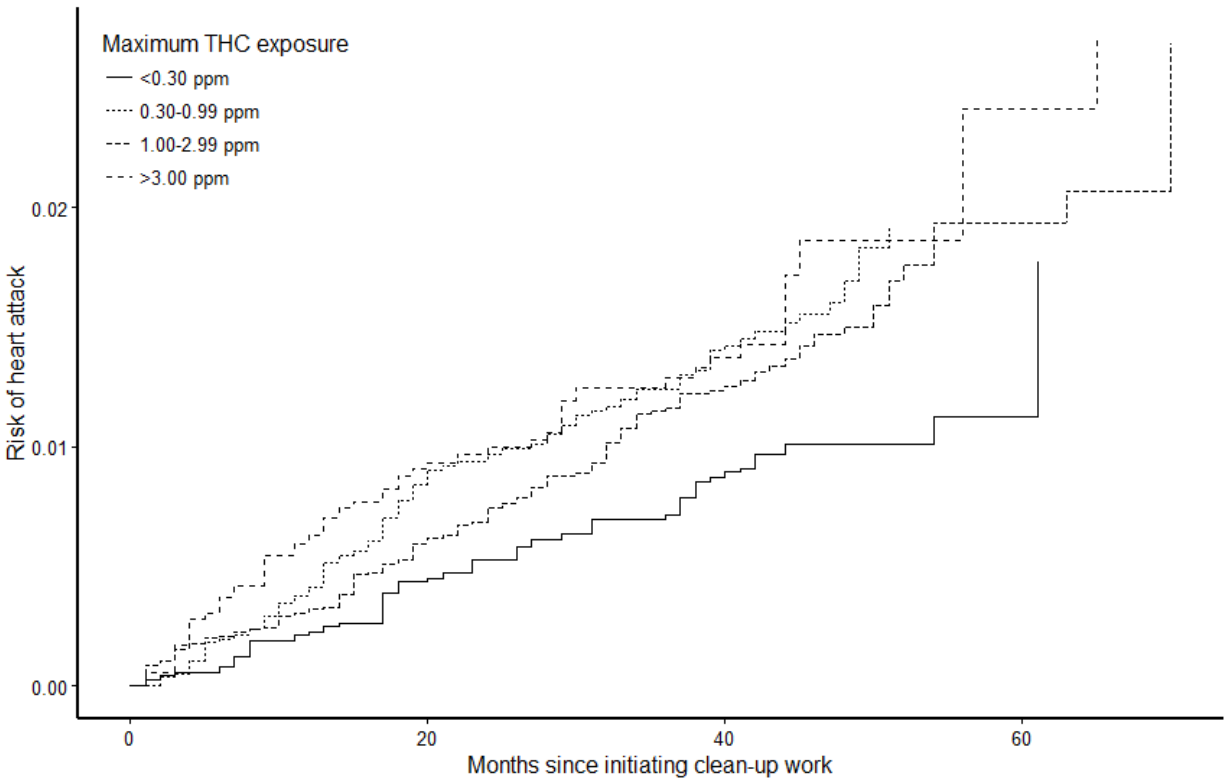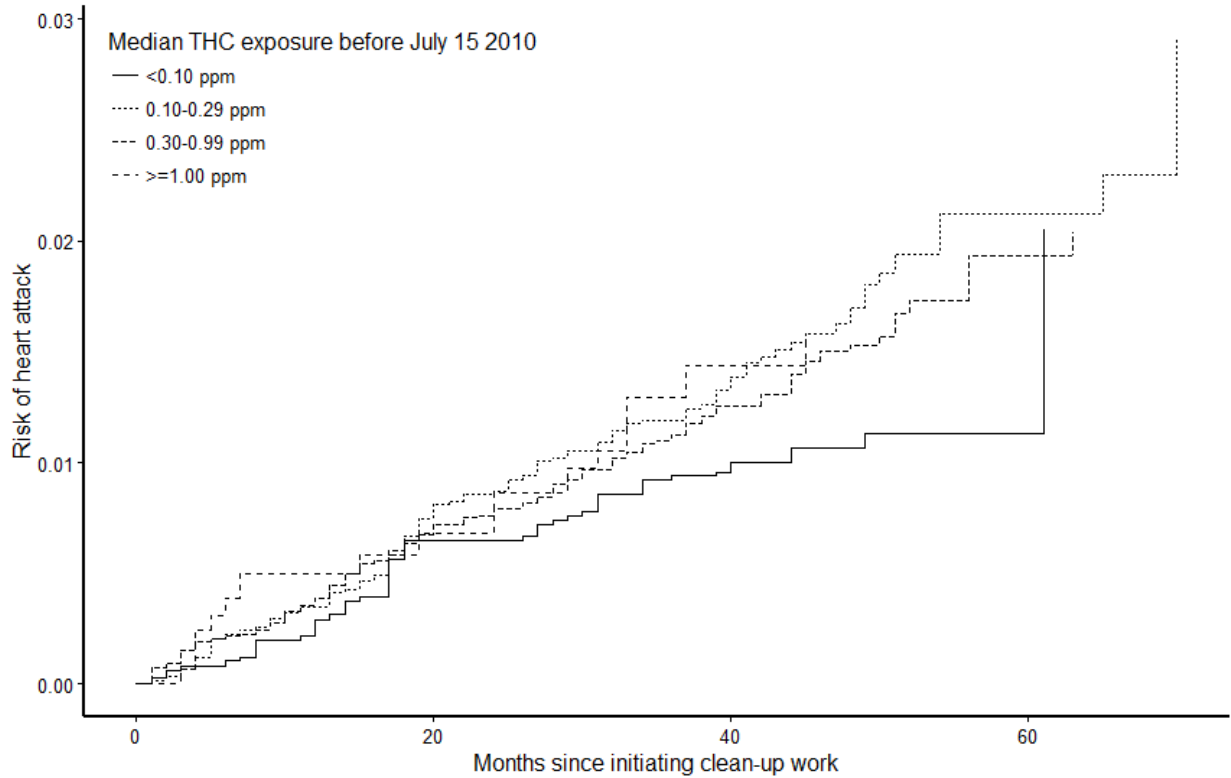Figure 5.2. Cumulative risk of self-reported myocardial infarction/fatal coronary heart disease by median total hydrocarbon exposure during clean-up work, before the oil well was capped on July 15, 2010. Risks are weighted using IP exposure and censoring weights to account for gender, age, ethnicity, smoking, education, and residential proximity to the oil spill. GuLF STUDY, 2010-2016 (N=22,550).

Supplemental Tables

Table 5.S1. Conditional Hazard Ratios for the Associations of Overall Maximum Total Hydrocarbon (THC) Exposure and Median THC Exposure Before the Oil Well was Capped with Self-Reported MI/Fatal CHD. GuLF STUDY 2010-2016

Max THC exposure (ppm)	Cases/Total N[a] (307/23,520)	HR[b]	95% CI
No censoring weights			
<0.30	41/5,246	ref	
0.30-0.99	105/7,719	1.40	0.97, 2.03
1.00-2.99	114/7,209	1.34	0.92, 1.94
≥3.00	47/3,346	1.51	0.98, 2.33
IP censoring weighted[c]			
<0.30	41/5,215	ref	
0.30-0.99	105/7,682	1.49	1.03, 2.16
1.00-2.99	114/7,178	1.51	1.04, 2.20
≥3.00	47/3,334	1.66	1.08, 2.56
Median THC exposure (ppm) before July 15, 2010	Cases/Total N[a] (289/22,200)	HR[b]	95% CI
No censoring weights			
<0.10	40/4,386	ref	
0.10-0.29	106/7,715	1.28	0.88, 1.86
0.30-0.99	126/8,940	1.12	0.77, 1.62
≥1.00	17/1,159	1.03	0.58, 1.85
IP censoring weighted[c]			
<0.10	40/4,363	ref	
0.10-0.29	106/7,682	1.43	0.98, 2.09
0.30-0.99	126/8,904	1.21	0.84, 1.73
≥1.00	17/1,154	1.16	0.64, 2.10

CHD: coronary heart disease; HR: Hazard ratio; IP: Inverse probability; Max THC exposure: Maximum total hydrocarbon exposure during clean-up work; MI: myocardial infarction; ppm: parts per million
[a]Total N for models without censoring weights is where maximum THC exposure, gender, age, smoking, education, residential proximity to the spill are non-missing; total N for models with censoring weights is where ethnicity is also non-missing
[b]Models control for gender, age, smoking, education, residence proximity to the oil spill
[c]Censoring weights account for age, ethnicity, education, residential proximity to the oil spill, smoking, and maximum total hydrocarbon exposure

Table 5.S2. Marginal hazard Ratios of the Association of Maximum Total Hydrocarbon (THC) Exposure and Self-Reported MI/Fatal CHD Until December 31 2014. GuLF STUDY 2010-2016

Max THC exposure (ppm)	Cases/Total N[a] (275/21,474)	HR[b]	95% CI
No censoring weights			
<0.30	36/4,837	ref	
0.30-0.99	95/7,033	1.7	1.11, 2.60
1.00-2.99	101/6,566	1.49	0.98, 2.28
≥3.00	43/3,038	1.82	1.10, 3.00
IP censoring weighted[c]			
<0.30	36/4,810	ref	
0.30-0.99	95/6,998	1.82	1.18, 2.81
1.00-2.99	101/6,537	1.78	1.15, 2.76
≥3.00	43/3,027	2.01	1.21, 3.34

CHD: coronary heart disease; HR: Hazard ratio; IP: Inverse probability; Max THC exposure: Maximum total hydrocarbon exposure during clean-up work; MI: myocardial infarction; ppm: parts per million

[a]Total N for models without censoring weights is where maximum THC exposure, gender, age, smoking, education, residential proximity to the spill are non-missing; total N for models with censoring weights is where ethnicity is also non-missing

[b]Models control for gender, age, smoking, education, residence proximity to the oil spill

[c]Censoring weights account for age, ethnicity, education, residential proximity to the oil spill, smoking, and maximum total hydrocarbon exposure

Table 5.S3. Marginal Hazard Ratios of the Association of Maximum Total Hydrocarbon (THC) Exposure and Self-Reported Nonfatal MI. GuLF STUDY 2010-2016

Max THC exposure (ppm)	Cases/Total N[a] (278/23,520)	HR[b]	95% CI
No censoring weights			
<0.30	40/5,246	ref	
0.30-0.99	96/7,719	1.49	1.04, 2.12
1.00-2.99	99/7,209	1.29	0.90, 1.87
≥3.00	34/3,346	1.59	1.05, 2.40
IP censoring weighted[c]			
<0.30	40/5,215	ref	
0.30-0.99	96/7,682	1.57	1.02, 2.40
1.00-2.99	99/7,178	1.43	0.93, 2.22
≥3.00	43/3,334	1.68	1.02, 2.76

HR: Hazard ratio; IP: Inverse probability; Max THC exposure: Maximum total hydrocarbon exposure during clean-up work; ppm: parts per million
[a]Total N for models without censoring weights is where maximum THC exposure, gender, age, smoking, education, residential proximity to the spill are non-missing; total N for models with censoring weights is where ethnicity is also non-missing
[b]Models control for gender, age, smoking, education, residence proximity to the oil spill
[c]Censoring weights account for age, ethnicity, education, residential proximity to the oil spill, smoking, and maximum total hydrocarbon exposure

Table 5.S4. Risk of Self-Reported MI/Fatal CHD by Maximum Total Hydrocarbon (THC) Exposure by Time Since Initiating Oil Spill Clean-Up, Censoring Follow-Up on December 14 2014. GuLF STUDY, 2010-2016 (n=22,251)

Time since initiating clean-up:	12 months		24 months		36 months		48 months	
Max THC exposure (ppm)	Risk[a]	RD	Risk[a]	RD	Risk[a]	RD	Risk[a]	RD
<0.30	0.002	ref	0.005	ref	0.007	ref	0.011	ref
0.30-0.99	0.004	0.002	0.010	0.005	0.013	0.005	0.018	0.007
1.00-2.99	0.003	0.001	0.008	0.002	0.012	0.004	0.015	0.004
≥3.00	0.006	0.004	0.010	0.005	0.014	0.006	0.020	0.009

CHD: coronary heart disease; Max THC exposure: Maximum total hydrocarbon exposure during clean-up work; MI: myocardial infarction; ppm: parts per million; RD: Risk difference
[a]Risk estimates account for confounders (age, gender, education, smoking, home proximity to the spill) and predictors of censoring (age, education, ethnicity, smoking, clean-up work duration, home proximity to the spill) using inverse probability weights

Table 5.S5. Marginal Hazard Ratios of the Association of
Maximum Total Hydrocarbon (THC) Exposure and Self-Reported
MI/Fatal CHD, Among Non-Federally-Employed Clean-Up
Workers. GuLF STUDY 2010-2016 (N=19,756)

Max THC exposure (ppm)	Cases/Total N[a] (290/19,020)	HR[b]	95% CI
No censoring weights			
<0.30	30/3,137	ref	
0.30-0.99	101/6,652	1.63	1.05, 2.54
1.00-2.99	113/6,439	1.51	0.97, 2.34
≥3.00	46/2,792	1.80	1.08, 2.99
IP censoring weighted[c]			
<0.30	30/3,126	ref	
0.30-0.99	101/6,625	1.69	1.08, 2.66
1.00-2.99	113/6,416	1.68	1.07, 2.64
≥3.00	46/2,785	1.94	1.16, 3.26

CHD: coronary heart disease; HR: Hazard ratio; IP: Inverse
probability; Max THC exposure: Maximum total hydrocarbon
exposure during clean-up work; MI: myocardial infarction; ppm:
parts per million; RD: Risk difference
[a]Total N where maximum oil exposure, gender, age, smoking,
education, residential proximity to the spill are non-missing
[b]Models control for gender, age, smoking, education, residence
proximity to the oil spill
[c]Censoring weights account for age, ethnicity, education,
residential proximity to the oil spill, smoking, and maximum total
hydrocarbon exposure

Table 5.S6. Marginal Hazard Ratios for the Association of Maximum Total Hydrocarbon (THC) Exposure with Self-reported MI/Fatal CHD, adjusting for duration of clean-up work. (N=23,923) GuLF STUDY 2010-2016

Max THC exposure (ppm)	Cases/Total N[a] (307/23,520)	HR[b]	95% CI
No censoring weights			
<0.30	41/5,246	ref	
0.30-0.99	105/7,719	1.76	1.16, 2.68
1.00-2.99	114/7,209	1.50	0.99, 2.28
≥3.00	47/3,346	1.86	1.04, 3.33
IP censoring weighted[c]			
<0.30	41/5,215	ref	
0.30-0.99	105/7,682	1.82	1.18, 2.79
1.00-2.99	114/7,178	1.68	1.09, 2.59
≥3.00	47/3,334	2.12	1.12, 4.03

HR: Hazard ratio; IP: Inverse probability; Max THC exposure: Maximum total hydrocarbon exposure during clean-up work; ppm: parts per million
[a]Total N for models without censoring weights is where maximum oil exposure, gender, age, smoking, education, residential proximity to the spill and work duration are non-missing; total N for models with censoring weights is where ethnicity is also non-missing
[b]Models control for gender, age, smoking, education, residence proximity to the oil spill and work duration
[c]Censoring weights account for age, education, residential proximity to the oil spill, smoking, and maximum THC exposure

CHAPTER 6: DISCUSSION

Summary of Objectives and Results

The aims of this research were to 1) determine any predictors of non-response to the second GuLF STUDY interview and assess the associations between duration of clean-up work, residence proximity to the oil spill, and heart attack, and 2) assess the associations between total hydrocarbon (THC) exposure during clean-up work with heart attack, in the 5 years following the *Deepwater Horizon* oil spill.

In the results presented in **Chapters 4 and 5**, we observed higher hazards of heart attack by 30% for living in proximity to the oil spill and by 43% for duration of clean-up work >180 days. We also observed increased hazards of heart attack for maximum THC exposure in excess of 0.30 ppm, however there was not a clear dose-response trend. Compared to those with maximum THC exposure <0.30 ppm, hazards were 66% higher for exposure 0.30-0.99 ppm, 62% higher for exposures 1.00-2.99 ppm, and 81% higher for exposure ≥3.00 ppm. Associations for median THC exposure and heart attack were attenuated compared to what was observed for maximum THC exposure. There was a 32-58% suggestive increased hazard of heart attack for those with median THC exposure >0.10 ppm (vs <0.10 ppm), but no clear exposure-response relationship, as higher median exposure levels were associated with smaller, nonsignificant increases in hazard. Risk differences for these associations were small in magnitude but persistent across the follow-up period.

Those who completed the second interview were more likely to be white, older age, nonsmokers, to have completed at least some college, have income >$50,000, and to have worked on oil spill clean-up compared to participants who did not complete the second interview. However, there were no particularly strong predictors of non-response, and results appeared to be robust to censoring. Accounting for predictors of non-response using IP weights only slightly strengthened the magnitudes of the observed associations. Sensitivity analyses that accounted for a shorter follow-up period for NDI data showed similar associations as with the full cohort data, as did analyses restricting to nonfatal MI events.

The positive associations between living in proximity to the spill and heart attack may be driven by psychosocial stress caused by the oil spill, pollutant exposures, or other spill-related environmental factors. Other research has shown that living in proximity to the Gulf oil spill is associated with acute health symptoms, and that affected communities faced economic and social hardships following the spill (7). A study of women living in Southeast Louisiana who were environmentally or economically exposed to the oil spill (determined based on self-reported exposure to oil or ability to smell oil from home, and self-reported financial information) showed elevations in acute symptoms including wheezing and nausea, compared to unexposed women (103). Increased stress and anxiety due to the spill may have increased risk of an acute or future coronary event (31).

Work duration and maximum THC exposure showed apparent positive associations with heart attack; however, these associations did not appear to strengthen with increasing work duration or increasing THC exposure. Oil spill clean-up work was often highly physically demanding, and workers endured hot temperatures and strenuous conditions. Workers who were, perhaps, less physically capable of this work or who had health limitations may have been more

likely to work a short duration, or not at all. Differences in physical fitness and health between those with shorter work duration compared to those with longer work duration may attenuate observed associations with heart attack for workers in the longer duration categories, a form of healthy worker survivor bias (105, 106). In a sensitivity analysis in **Chapter 5**, we assessed whether work duration may confound the relationship with maximum THC exposure and heart attack. Adjusted analyses appeared to show slight strengthening in the associations between maximum THC exposure and heart attack. We also performed a sensitivity analysis where we adjusted for having to stop clean-up work due to heat; this heat stress measure was not associated with THC exposure and adjusting for this did not show meaningful changes to the associations between THC exposure and heart attack, indicating little impact of healthy worker bias.

Although 33% of enrolled participants did not complete the second interview for the GuLF STUDY, we observed negligible impact of factors related to non-response on the estimated hazard ratios. This is in accordance with what we anticipated, based on the fact that the associations between each predictor and loss to follow-up were generally weak (tables 4.1-4.3). The censoring weights would be expected to have more influence on effect estimates in the presence of stronger predictors of loss to follow-up (107). The robustness of our results to potential bias due to non-response increases our confidence in the generalizability of our results to the full GuLF STUDY cohort.

Limitations

A job exposure matrix for total hydrocarbon exposure during the oil spill response and clean-up work was used in the GuLF STUDY to derive estimates of maximum and median THC exposure levels. Estimates of maximum THC exposure were determined based on self-reported tasks with the highest exposure and do not account for duration of that exposure nor for

cumulative exposure across tasks. These estimates are derived from self-reported clean-up

activities, which were assessed during the baseline telephone interview. It follows that the

exposure estimates are subject to measurement error, and there may be some misclassification

between exposure groups, if work tasks were not reported fully accurately. However, we do not

anticipate that there would be differences in reporting with respect to case status. Nonetheless,

these exposure estimates were derived from detailed self-reported data on clean-up tasks and

from monitoring data of airborne THC concentrations collected during the oil spill clean-up (2),

providing more detailed exposure data than has been available in previous studies of oil spill

workers.

This study relied on self-reported information on nonfatal MI, which is subject to errors

in reporting. Outcome misclassification may be due to misreport or failure to recall a past

diagnosis, sub-clinical disease (silent MI), or under-diagnosis due to poor access to healthcare.

Agreement between self-reported MI and hospital records has been shown to vary by study and

by population, however self-report of MI has shown moderate agreement with hospital discharge

data (kappa=0.64), and has been more reliably reported than other cardiovascular diseases (113).

Recall of MI is also dependent on the time period for which the disease is being ascertained, and

this study focuses on only a relatively short 5-year risk period.

This study did not account for any ambient exposures to hydrocarbons unrelated to the oil

spill. Environmental exposure to hydrocarbons in particulate air pollution is ubiquitous and may

affect CHD outcomes. We do not have data on traffic-related exposures (or exposures from other

sources) and were unable to account for these in our analyses. However, we did measure

cigarette smoking, which is a dominant source for particulate matter and benzene exposures in

the general population (114). We adjusted for self-reported tobacco use to reduce possible

confounding by environmental hydrocarbon exposures. Aside from smoking and age, we did not

control for other factors associated with coronary heart disease. We did not adjust for prevalent

hypertension or BMI as these were determined to not be confounders. Sensitivity analyses

adjusting for hypertension or BMI resulted in no meaningful change in beta estimates (<10%

change).

The oil spill was an unexpected disaster, which poses many logistical difficulties for

planning and launching an epidemiologic study. The GuLF STUDY began data collection 11

months after the oil spill, which resulted in 1-3 years of immortal person-time between when the

oil spill began and when study enrollment ended. This study did not include any potentially

eligible individuals who died before enrolling in the cohort, which resulted in truncation of

CHD-related deaths occurring before enrollment. Similarly, nonfatal MI occurring after the oil

spill began but prior to recruitment in the study may have been unascertained due to competing

risks (death) occurring before enrollment. If deaths occurred more often among those with longer

work duration, those with higher THC exposure levels, or among those who lived closer to the

spill, this may have resulted in a attenuated associations with risk of heart attack than compared

to what would be seen in the full target population.

There are limitations of the IP censoring weights approach that we used in order to

address bias due to censoring, and we acknowledge that our results are specific to our chosen

approach and the required modeling assumptions. One important assumption of our approach

was that missing outcome data occurred at random within strata of the predictors included in the

censoring weights models. Other unmeasured factors that we did not account for may have been

associated with non-response. However, if non-response were random with respect to

unmeasured factors within strata of the adjustment set for our censoring weights model, failure to

account for unmeasured predictors would not bias our estimates (108). Given that we accounted for several predictors of non-response, it is unlikely that unmeasured factors would contribute substantial bias.

Strengths

This research uses data from the GuLF STUDY, which is the largest study of the impact of an oil spill on human health, and the first to assess heart disease among oil spill-exposed populations. The GuLF STUDY features detailed assessment of clean-up-related tasks, and improves upon exposure estimation from previous oil spill studies by incorporating semi-quantitative exposure estimates of total hydrocarbon exposure among clean-up workers, which are based on detailed self-reported data on clean-up work activities as well as air monitor THC measurements taken throughout the oil spill response (2). The longitudinal design of the study has allowed us to assess changes in the observed associations with heart attack over time.

This is the first research project to investigate the longitudinal association between oil spill exposures and heart attack. We showed that associations with total hydrocarbon exposure and heart attack persisted across the five-year study period. This result is also pertinent to ambient air pollution research, as we showed that a relatively short-term increase in exposure to common constituents of air pollution resulted in higher hazard of heart attack over a prolonged period, which has not been previously assessed.

This research fills critical gaps in the occupational health literature and has potential to help influence policies to protect worker health. Oil spills are frequent events with enormous environmental impacts. Despite this, little research has examined the physical health effects of spills. This study has contributed to our understanding of the health impact of oil spills, and

hopefully results from this research can help shape future policies to reduce oil exposures among clean-up workers.

Future directions

One of the benefits of this research is the ability to improve worker protection in the event of future oil spills. Additional research should assess possible heterogeneity of the observed associations in order to identify potentially more susceptible subgroups of workers. This may include assessment of heterogeneity of the hazard ratios by lifestyle factors such as cigarette smoking, or other risk factors for heart attack, such as prevalent hypertension.

The GuLF STUDY is currently developing quantitative estimates of worker exposures to particulate matter and volatile organic compounds during the oil spill. These estimates will provide more detailed information on specific chemical exposures compared to the job exposure matrix-based estimates of total hydrocarbon exposure that were used in the present study. Future analyses can make use of the quantitative exposure data in order to assess whether specific chemical exposures may drive the associations that we observed between total hydrocarbon exposure and heart attack. This information would be useful to identify specific worker groups with higher-risk exposures, so that interventions can target these groups to reduce exposure and overall excess heart attack.

Future analyses can also make use of additional interview data from the GuLF STUDY in order to assess longer-term associations with heart attack. We observed positive associations between residence proximity to the oil spill and maximum total hydrocarbon exposure with heart attack in the 5 years following the spill, whereas future studies will be able to incorporate additional years of interview data and mortality data from the NDI. Future studies featuring

longer follow-up periods and larger numbers of outcomes may also be able to explore temporal variations in the hazard ratios, using a time-stratified analysis approach to assess changes in associations over time.

Conclusions

The GuLF STUDY is the largest study of the human health impact of oil spills, and is the first to investigate heart attack risk among oil spill workers. Our study showed positive associations in relation to maximum THC exposure during oil spill clean-up work, living in proximity to the oil spill, and risk of heart attack up to 5 years after the spill. We observed suggestive associations between duration of clean-up work and heart attack, as well as with median THC exposure and heart attack. These associations persisted across the follow-up period. Future research with additional GuLF STUDY follow-up data should assess longer-term changes in these associations, and possible heterogeneity of the observed associations by other risk factors for coronary heart disease.

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