EXPOSURE TO CRUDE OIL CHEMICALS AND BURNING-RELATED $PM_{2.5}$ AMONG *DEEPWATER HORIZON* OIL SPILL WORKERS AND INCIDENT CORONARY HEART DISEASE

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ABSTRACT

Dazhe Chen: Exposure to crude oil chemicals and burning-related $PM_{2.5}$ among *Deepwater Horizon* oil spill workers and incident coronary heart disease
(Under the direction of Lawrence Engel)

No study to date has examined exposure to individual crude oil chemicals or fine particulate matter ($PM_{2.5}$) from burning of crude oil/natural gas in relation to coronary heart disease (CHD) among oil spill workers. During the 2010 *Deepwater Horizon (DWH)* disaster, oil spill response and cleanup (OSRC) workers were exposed to toxic volatile components of crude oil and increased $PM_{2.5}$ levels from burning of oil/gas.

In aim 1, we investigated the association of exposure to total petroleum hydrocarbons (THC) and several crude oil chemicals (benzene, toluene, ethylbenzene, xylene, n-hexane, i.e. BTEX-H) with incident CHD events among 22,655 *DWH* OSRC workers. In aim 2, we assessed burning-related $PM_{2.5}$ exposure in relation to CHD risk among 9,091 *DWH* water workers.

Exposures to THC, BTEX-H, and burning-related $PM_{2.5}$ were estimated via job-exposure matrices that linked air concentration data to self-reported OSRC work histories. We identified incident CHD events that occurred after each worker ended OSRC work from self-report and death certificates. We estimated hazard ratios (HR) and 95% confidence intervals (95%CI) for CHD associated with exposure to BTEX-H/THC (quintiles (Q)) and $PM_{2.5}$. We applied inverse probability weights to account for bias due to confounding and loss to follow-up. We also assessed the joint effect of the BTEX-H mixture using quantile g-computation.

Workers in the highest cumulative exposure category of each crude oil agent had modest increases in CHD risk compared to the referent group (Q1) of that agent (range of HR: 1.14-

1.44), although most associations were non-significant. No apparent association was observed for the overall effect of the BTEX-H mixture. Compared to workers not involved in or near the burning (ref), workers with in the highest *average* $PM_{2.5}$ exposure category had significantly elevated risk of CHD (HR=2.11, 95%CI: 1.08, 4.12). We also observed a monotonic, but non-significant, trend among workers with higher *cumulative* $PM_{2.5}$ exposure (low: HR=1.19, 95%CI: 0.68, 2.08; medium: HR=1.38, 95%CI: 0.88, 2.16; high: HR=1.44, 95%CI: 0.96, 2.14).

Higher exposures to volatile components of crude oil and $PM_{2.5}$ from burning of oil/gas were associated with a modest increase in risk of CHD among oil spill workers.

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TABLE OF CONTENTS

LIST OF TABLES 8

LIST OF FIGURES 11

LIST OF ABBREVIATIONS 12

CHAPTER 1: SPECIFIC AIMS 1

CHAPTER 2: BACKGROUND 4

2.1 The *Deepwater Horizon* Oil Spill and Cleanup Effort 4

2.2 Potential Exposures from OSRC Activities 5

2.2.1 VOC Exposure from Crude Oil 6

2.2.2 $PM_{2.5}$ Exposure from Controlled Burning 8

2.2.3 Exposure Monitoring during the *DWH* Oil Spill 11

2.2.4 Other Occupational Exposures 13

2.3 Cardiovascular Impacts of Exposure to $PM_{2.5}$ and Volatile Hydrocarbons 13

2.3.1 Health Effects Summarized in Existing Oil Spill Literature 14

2.3.2 Cardiovascular Effects of $PM_{2.5}$ 16

2.3.3 Cardiovascular Effects of BTEX-H and Other Volatile Hydrocarbons 22

CHAPTER 3: RESEARCH METHODS 27

3.1 Study Design and Data 27

3.1.1 Parent Study and Cohort Enumeration 27

3.1.2 Ascertainment of Exposures 28

3.1.3 Ascertainment of Outcome 33
3.1.4 Ascertainment of Covariates 35
3.2 Statistical Methods 36
3.2.1 Aim 1 Methods 36
3.2.2 Aim 2 Methods 40
CHAPTER 4: AIM 1 RESULTS 43
4.1 Introduction 43
4.2 Methods 44
4.3 Results 51
4.4 Discussion 54
4.5 Tables and Figures 63
CHAPTER 5: AIM 2 RESULTS 95
5.1 Introduction 95
5.2 Methods 97
5.3 Results 105
5.4 Discussion 107
5.5 Tables and Figures 115
CHAPTER 6: DISCUSSION 129
6.1 Summary of Objectives and Results 129
6.2 Strengths and Limitations 131
6.3 Directions for Future Research 135
6.4 Conclusions 135
REFERENCES 137

LIST OF TABLES

Table 1. Characteristics of DWH disaster oil spill workers who responded to the enrollment, first follow-up, and second follow-up interviews, respectively 63

Table 2. Associations between cumulative daily maximum exposures to crude oil chemicals and incident CHD events among *DWH* disaster oil spill workers (N=22,655), 2010-2019 65

Table 3. Associations between cumulative daily average exposures to crude oil chemicals and incident CHD events among DWH disaster oil spill workers (N=22,655), 2010-2019 67

Table 4. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by smoking status among *DWH* disaster oil spill workers (N=22,655), 2010-2019 69

Table 5. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by highest education attained among *DWH* disaster oil spill workers (N=22,655), 2010-2019..... 71

Table 6. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by obesity status among *DWH* disaster oil spill workers (N=22,655), 2010-2019 73

Table 7. Quantile g-computation estimates for the change in CHD events hazards for a one quintile increase in cumulative exposure to all crude oil chemicals (BTEX-H) among *DWH* disaster oil spill workers (N=22,655), 2010-2019 75

Table 8. Spearman correlation coefficients between cumulative exposure to oil-spill chemicals among *DWH* disaster oil spill workers (N=22,655)..... 77

Table 9. Distribution of stabilized inverse probability of exposure, censoring, and overall weights in analysis of cumulative daily maximum exposure to oil spill-related chemicals and coronary heart disease among *DWH* disaster oil spill workers (N=22,655), 2010-2019..... 78

Table 10. Associations between cumulative exposure to crude oil chemicals and incident CHD events among *DWH* disaster oil spill workers, additionally adjusting for prevalent hypertension (N=22,279), 2010-2019..... 79

Table 11. Associations between cumulative exposure to crude oil chemicals and incident non-fatal MI or fatal CHD (a *contributing/underlying* cause of death) among *DWH* disaster oil spill workers (N=22,655), 2010-2019 81

Table 12. Associations between cumulative exposure to crude oil chemicals and incident self-reported myocardial infarction among *DWH* disaster oil spill workers (N=22,655), 2010-2019 83

Table 13. Associations between cumulative exposure to crude oil chemicals and incident CHD events after *enrollment* among *DWH* disaster oil spill workers (N=22,526), 2010-2019 85

Table 14. Associations between cumulative exposure to crude oil chemicals and incident CHD events among *DWH* disaster oil spill workers who were not potentially exposed to $PM_{2.5}$ from controlled burning activities (N=20,658), 2010-2019 87

Table 15. Associations between maximum daily maximum exposure to crude oil chemicals and incident CHD events among DWH disaster oil spill workers (N=22,655), 2010-2016 and 2010-2019 89

Table 16. Associations between cumulative maximum exposures to crude oil chemicals and incident CHD events (self-reported MI, self-reported blockage in heart arteries, or fatal CHD) among *DWH* disaster oil spill workers (N=22,410), 2010-2019 90

Table 17. Marginal HRs of CHD comparing *DWH* oil spill workers who had high daily maximum daily exposures to spill-related chemicals (in the top 15th and 20th percentile of maximum daily maximum exposure) for a number of days (≥7 and ≥14 days) with workers whose daily maximum exposures were in the first quintile of the study population's maximum daily exposure, 2010-2019 92

Table 18. Characteristics of *DWH* disaster oil spill water workers who responded to the enrollment, first follow-up, and second follow-up interviews, respectively 115

Table 19. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill water workers, 2010-2019 (N=9,091). 117

Table 20. Association between $PM_{2.5}$ exposure and incident non-fatal CHD among *DWH* disaster oil spill workers, 2010-2019 (N=9,091). 118

Table 21. Average and cumulative $PM_{2.5}$ exposure among *DWH* disaster oil spill water workers (N=9,091) 119

Table 22. Distribution of stabilized inverse probability of exposure, censoring, and overall weights in analysis of $PM_{2.5}$ exposure and coronary heart disease among *DWH* disaster oil spill workers (N=9,067), 2010-2019 120

Table 23. Association between $PM_{2.5}$ exposure and incident CHD events (fatal events identified as CHD as a *contributing* cause of death) among *DWH* disaster oil spill water workers, 2010-2019 (N=9,091). 121

Table 24. Association between $PM_{2.5}$ exposure and incident CHD events events after *enrollment* among DWH disaster oil spill water workers, 2010-2019 (N=8,983). 122

Table 25. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill water workers, additionally adjusting for prevalent hypertension, 2010-2019 (N=8,941). 123

Table 26. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill water workers, additionally adjusting for cumulative daily maximum exposure to total hydrocarbons, 2010-2019 (N=9,091). 124

Table 27. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill water workers, excluding offshore workers who did not participate in in situ burning, 2010-2019 (N=7,960). 125

Table 28. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill worker, 2010-2019 (N=20,351). 126

LIST OF FIGURES

Figure 1. Possible biological mechanisms linking PM to MI (Brook et al., 2004) 22

Figure 2. Timeline of data collection 35

Figure 3. Directed acyclic graph that guided covariate selection for models estimating the relationship between crude oil chemical exposures and risk of coronary heart disease among *Deepwater Horizon* oil spill workers, 2010-2019 (N=22,809) 94

Figure 4. Distribution of cumulative daily maximum PM2.5 exposure among burning-exposed *Deepwater Horizon* oil spill workers (N=1,980). 127

Figure 5. Directed acyclic graph that guided covariate selection for models estimating the relationship between burning-related $PM_{2.5}$ exposure and incident coronary heart disease events among *Deepwater Horizon* oil spill workers, 2010-2019 (N=9,091). 128

LIST OF ABBREVIATIONS

BMI	Body mass index
BTEX-H	Benzene, toluene, ethylbenzene, xylene, n-hexane
CI	Confidence interval
CHD	Coronary heart disease
DAG	Directed acyclic graph
EMM	Effect measure modification
EPA	Environmental Protection Agency
GuLF	Gulf Long-term Follow-up
HR	Hazard ratio
IP	Inverse probability
IQR	Interquartile range
LOD	Limit of detection
MI	Myocardial infarction
NDI	National Death Index
NIOSH	National Institute for Occupational Safety and Health
PM2.5	Fine particulate matter
PPE	Personal protective equipment
QGC	Quantile g-computation
THC	Total hydrocarbons
U.S.	United States
VOC	Volatile organic compounds

CHAPTER 1: SPECIFIC AIMS

During the 2010 *Deepwater Horizon* (*DWH*) disaster, an estimated 4.9 million barrels of crude oil were released into the Gulf of Mexico (National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling 2011). Tens of thousands of oil spill response and cleanup (OSRC) workers were potentially exposed to a) volatile hydrocarbons from the crude oil and b) fine particulate matter ($PM_{2.5}$) generated by flaring and *in situ* burns of oil/natural gas during the cleanup operations (National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling 2011). Crude oil is a complex mixture of thousands of chemicals (ATSDR 1999a). Several volatile components of the crude oil, including benzene, toluene, ethylbenzene, xylene, and n-hexane (BTEX-H), are classified by the United States (U.S.) Environmental Protection Agency (EPA) as hazardous air pollutants for their environmental and health impacts (Batavia 1991). In addition to being components of the crude oil, BTEX-H are commonly found in tobacco smoke, vehicular exhaust, and many consumer products (Bolden et al. 2015). Similar to BTEX-H, $PM_{2.5}$ is an universal air pollutant and is regulated as a criteria pollutant for its hazardous health effects (U.S. EPA 2020). Air monitoring of benzene and $PM_{2.5}$ in Louisiana during the *DWH* disaster has shown that both pollutants exceeded health-based standards (Nance et al. 2016), raising concerns of spill-related inhalation exposures on human health.

Although BTEX-H chemicals have been investigated most extensively in relation to neurotoxicity (Niaz et al. 2015; Takeuchi 1993; Werder et al. 2019) and hematotoxicity (Bahadar et al. 2014; Doherty et al. 2017), there is accumulating evidence that they are deleterious to the

cardiovascular system. Studies of ambient air pollution exposure among the general population have associated one or more chemicals of BTEX-H with coronary heart disease (CHD) (Barceló et al. 2016; Ran et al. 2018b) or coronary deaths (Ran et al. 2018a; Tsai et al. 2010). The effect of $PM_{2.5}$ exposure on CHD is well-documented, with air pollution studies generally supporting a causal relationship (Brook et al. 2010). Putative mechanisms underlying the air pollution-CHD relationship include promotion of systemic inflammatory responses and disturbance of the autonomic nervous system (Brook et al. 2010; Rajagopalan et al. 2018).

Although dozens of oil spills have occurred around the globe in the past few decades (Aguilera et al. 2010), the cardiovascular effect of oil spill work has only been examined among the *DWH* disaster workers. These studies have associated increased risk of CHD with exposure to maximum total (petroleum) hydrocarbons (THC), a composite measure of the volatile components of crude oil (Strelitz et al. 2018; Strelitz et al. 2019b); however, it was unclear if any specific individual or mixtures of chemicals were responsible for the persistent cardiovascular effect. Also, few studies have examined controlled burning of oil/gas as a unique source of $PM_{2.5}$ exposure or the long-term cardiovascular impact of a transient $PM_{2.5}$ exposure among oil spill workers. I therefore propose to investigate these associations within the Gulf Long-term Follow-up Study, a prospective cohort of *DWH* disaster workers enrolled 1-3 years after the spill. My proposed study will focus on the 24,375 participants who engaged in spill-related activities. The ***long-term goal*** of this research is to identify the public health impact of oil spill-related exposures among OSRC workers. The ***overall objective*** of the proposed study is to rigorously evaluate the impact of BTEX-H/THC and $PM_{2.5}$ exposures on incident CHD events among these workers, using both single-pollutant regression models and a mixture model. My central hypothesis is that exposures to $PM_{2.5}$ and BTEX-H/THC are associated with higher incidence of

CHD. There are two aims to my study:

Aim 1: Assess associations of THC and BTEX-H with incident CHD events up to ten years after the *DWH* disaster. Exposure to these agents was estimated via a job-exposure matrix based on personal air measurements and self-reported OSRC work histories. CHD events were identified as the first self-reported physician-diagnosed myocardial infarction (MI) or a fatal CHD case that occurred after each worker's last day of work. Single-pollutant Cox proportional hazard models and quantile g-computation (QGC) model will be used to assess the effect of each agent and the joint effect of the BTEX-H mixture, respectively.

Aim 2: Assess association between burning-related $PM_{2.5}$ exposure and incident CHD events up to ten years after the *DWH* disaster. $PM_{2.5}$ exposure was estimated from a job-exposure matrix based on modelled $PM_{2.5}$ concentrations and self-reported work histories. CHD events were ascertained using self-reporting and death certificates and defined as the first self-reported CHD (physician-diagnosed MI or blockage in the arteries of the heart) or a fatal CHD case that occurred after each worker's last day of work. Single-pollutant Cox models will be used to examine $PM_{2.5}$ exposure in relation to incident CHD events.

This will be the first study to examine exposures to BTEX-H and $PM_{2.5}$ in relation to CHD events among OSRC workers. Understanding the cardiovascular effects of spill-related agents among OSRC workers may contribute evidence to support changes in workplace practices to better protect oil spill workers against these chemicals. Moreover, because exposure to these agents is widespread among the general population (Bolden et al. 2015; Rajagopalan et al. 2018), studying these relationships may help quantify the CHD risks from these exposures and inform interventions and policies to reduce the exposure in a broader population.

CHAPTER 2: BACKGROUND

2.1 The Deepwater Horizon Oil Spill and Cleanup Effort

The *Deepwater Horizon* (*DWH*) disaster is the largest marine oil spill in the United States (U.S.) history (National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling 2011). On the evening of April 20, 2010, an explosion occurred on the *Deepwater Horizon* rig in the Gulf of Mexico (National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling 2011). The explosion and ensuing fire destroyed the drilling rig, and crude oil gushed out of the Macondo well for 87 days before the well was capped on July 15, 2010 (U.S. Coast Guard 2011). In total, an estimated 4.9 million barrels of oil (~795 million liters) was released into the Gulf, prompting extended cleanup and response (National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling 2011). In addition to damaging the local ecosystem and economy, the spill threatened the health of workers involved in the cleanup efforts as well as local residents.

The cleanup effort of the spill was unprecedented in the scale of resources devoted, the complexity of tasks performed, and the duration of the operation. To mitigate damage to the environment, tens of thousands of workers and volunteers from the Gulf states and across the nation participated in various oil spill response and cleanup (OSRC) activities. At the height of the response, over 47,849 personnel and over 6,000 vessels were mobilized for response (U.S. Coast Guard 2011). To try to contain the spill at the source, rig vessels were deployed above the well to collect and burn oil and natural gas while a containment system was constructed (U.S.

Coast Guard 2011). To prevent oil from reaching the shores, dedicated special task forces applied dispersants and performed skimming, booming, and in situ burning to recover and/or remove oil from the sea surface (U.S. Coast Guard 2011). Even more joined in the collective effort to clean beaches and marshes, decontaminate vessels and equipment, and provide administrative support to operations (U.S. Coast Guard 2011). While cleanup on water was completed by December 2010, most tasks on land were not terminated until June 30, 2011, over a year after the spill occurred (Stewart et al. 2018).

2.2 Potential Exposures from OSRC Activities

During an OSRC, workers are exposed to various occupational hazards that may pose risks to their health (Kwok et al. 2017a). Inhalation hazards are pervasive and can originate either from the crude oil or from other cleanup activities. Crude oil as a mixture that contains thousands of chemicals, many of which, including benzene, alkylbenzenes, and n-hexane, are volatile organic chemicals (VOCs) that possess toxicological properties (Overton et al. 2016). When used as a spill mitigation method (Allen et al. 2011), controlled burning produces a significant amount of fine particulate matter (Nance et al. 2016) as well as other inhalation toxicants (Pratt et al. 2022). Operation of water vessels, land vehicles, and machinery also releases particulate matter and other pollutants in the engine exhaust. Other potential chemical hazards include dispersants and cleaning agents, and workers may also encounter heat stress, physical hazards, and/or psychosocial stressors during an oil spill cleanup (U.S. Coast Guard 2011).

2.2.1 VOC Exposure from Crude Oil

Crude oil is a complex mixture that consists of predominantly hydrocarbons: 1) saturated hydrocarbons (i.e. straight, branched, and cyclic alkanes), and 2) aromatic hydrocarbons (benzene, alkylbenzenes, naphthalenes and polycyclic aromatic hydrocarbons) (ATSDR 1999a). Its smaller non-hydrocarbon fraction includes trace metals and sulfur-, nitrogen-, and oxygen-containing compounds (ATSDR 1999a). The chemical composition and physical properties of each crude oil mixture varies by its source (Overton et al. 2016). Macondo crude oil (i.e. the oil released during the *DWH* disaster), for instance, originated from the deep sea (~5000 feet) and was considered "lighter" than other crude oils, containing more low-molecular-weight compounds (U.S. Coast Guard 2011). Many of those chemicals belong to a class of chemicals called VOCs, as their high vapor pressure allow them to vaporize into gases under ambient temperature and pressure. **Many VOCs released by the crude oil are known toxicants that exist at lower levels in many other settings. These chemicals include benzene, alkylbenzenes (e.g. toluene, ethylbenzene, xylene), and n-hexane.**

Benzene, toluene, ethylbenzene, and isomers (o-, m-, p-) of xylene constitute the lighter aromatic fractions of the crude oil (ATSDR 1999a). Because of their adverse health effects, these chemicals are regulated as hazardous air pollutants by the U.S. Environmental Protection Agency (EPA) (Batavia 1991). Referred to collectively as BTEX, these chemicals or various combinations of them often exist as a mixture in different sources (ATSDR 2004). After being isolated from the crude oil, BTEX are combined in specific proportions in gasolines and aviation fuel to elevate their octane rating (Bolden et al. 2015). In addition to being a component of refined petroleum products, BTEX are also used as solvents or raw materials in the manufacture of commonplace consumer products, including household cleaners, paints, fabric

and leather treatments, plastic and rubber products, and cosmetics and pharmaceuticals (Bolden et al. 2015; Lim et al. 2014). Those chemicals have been detected at relatively low levels (low $\mu g/m^3$ range) near sites of oil/gas operations (Gilman et al. 2013; Heibati et al. 2017) and gas stations (Xiong et al. 2016), in traffic emissions (Fujita et al. 2011; Ran et al. 2018a), and in tobacco smoke (Pazo et al. 2016).

n-Hexane is another constituent of crude oil and refined petroleum products (ATSDR 1999b) that is classified as a hazardous air pollutant (Batavia 1991). The chemical is widely used as an edible-oil extractant in the agriculture for various seed crops, such as soybeans, peanuts, cotton seeds, and corn germ (ATSDR 1999b). It is also applied as a special-purpose solvent and cleaning agent in industry for the manufacture of textiles, furniture, shoes/leather adhesives and sealants, tires, and pharmaceuticals (ATSDR 1999b). n-Hexane is released into the environment primarily from the combustion of petroleum products for heating and motor vehicle use, as well as from industrial processes. It has been detected at low levels in rural and urban air polluted with automobile emissions (ATSDR 1999b), and at higher levels in occupational settings (Committee on Acute Exposure Guideline et al. 2013; Perbellini et al. 1980; Wilson et al. 2007).

During an oil spill, workers may be exposed to moderate to high levels of VOCs from inhalation (Goldstein et al. 2011). As fresh oil weathers, the volatile components rapidly leave the mixture into the air through vaporization (Overton et al. 2016). Lighter oils like the Macondo oil can lose between 40% and 75% of its low-molecular-weight components to the air in a period of hours to days (Overton et al. 2016). The rapid influx of chemical vapors in the ambient air and the toxicity of these chemicals (e.g. BTEX and n-hexane) make lighter oils especially dangerous to workers immediately after a spill (Overton et al. 2016). Inhalation of

vapors and aerosols is the main process by which VOCs and larger chemicals enter humans (Overton et al. 2016). In the *DWH* disaster, response workers on vessels near the spill source were potentially exposed to moderate to high levels VOCs from the fresh oil, while workers farther away were exposed to weathered oil depleted to varying degrees of the more toxic components (U.S. Coast Guard 2011). Use of personal protective equipment (PPE), including respirators, was demonstrated in studies of previous oil spills to be effective in reducing chemical exposure (Laffon et al. 2016). However, wearing them could be physically taxing, especially under high heat and for new workers not used to them (Michaels and Howard 2012). A survey conducted by the National Institute for Occupational Safety and Health (NIOSH) before the cleanup showed that 32% of workers were expected to use respiratory protection, and only 28% had been fit-tested in the past year (NIOSH 2011). Thus, respirators were used situationally and sometimes only as a last resort during oil spill cleanup (Michaels and Howard 2012). Besides inhalation, workers may also have dermal contact with the oil while working at sea or on land (ATSDR 1999a). However, dermal absorption of most VOCs (in the liquid/solution form), including BTEX and n-hexane (BTEX-H), is found to be low and/or slow in animals and humans (ATSDR 1999b, 2004), and thus systemic health risks of dermal exposure are deemed low under normal working conditions (Jakasa et al. 2015).

2.2.2 $PM_{2.5}$ Exposure from Controlled Burning

Controlled burning is an efficient oil mitigation method sometimes used in conjunction with mechanical means to remove oil from the environment (U.S. EPA 1999). In the *DWH* disaster, two burning techniques were used: 1) *in situ* burning of surface oil offshore and 2) flaring of oil and/or natural gas captured by vessels at the spill source. Because of toxic

emissions and the unique environmental and oil conditions required for a successful burn (Pacific Northwest 1979; U.S. EPA 1999), *in situ* burning has seen limited use in previous spill cleanups. The decision to use *in situ* burning in the *DWH* disaster was based on the inadequacy of skimming alone to stop oil from reaching shores, the amenable combustibility of the oil, and the ability to conduct most burns far away from populated areas (U.S. Coast Guard 2011). From April 28 to July 19, 2010, the *in situ* burn (ISB) taskforce conducted 376 large burns to remove an estimated 220,000-310,000 barrels of oil (Ramseur 2010). Flaring was the other burning method, which played a large role in removing oil at the wellhead. From May 17 to July 11, 2010, a rig vessel, *the Discoverer Enterprise*, processed ~18,000 barrels of oil per day by recovering oil and flaring the natural gas separated from the oil (U.S. Coast Guard 2011). The other rig vessel, *the Helix Q4000*, and a production/offloading vessel, *the Helix Producer I*, were not capable of processing the oil and flared the oil/gas mixture at rates of ~10,000 and ~25,000 barrels per day, respectively (U.S. Coast Guard 2011). **Both flaring and *in situ* burning generated substantial particulate and gaseous emissions that could be inhaled by workers near sites of burning.**

One emission of particular concern is fine particulate matter (PM), particles with aerodynamic diameter of 2.5 microns or less ($PM_{2.5}$), which are considered by health professionals as the main toxicant to investigate in controlled burns (Barnea 2011). $PM_{2.5}$ is a universal air pollutant and one of six criteria pollutants whose outdoor levels are regulated by the U.S. EPA because of their harmful effects on human health and the environment (Batavia 1991). A primary source of $PM_{2.5}$ emission is incomplete combustion of fuels. During combustion, $PM_{2.5}$ is either released directly from the source (primary emissions) or formed in the atmosphere through chemical reactions that involve gaseous pollutants generated by the

burning (secondary emissions/aerosols) (Middlebrook et al. 2012). The chemical composition of $PM_{2.5}$, which partly dictates its health impacts, differs by the fuel type and environmental conditions, but numerous studies have shown that organic carbon, sulfates, and nitrates predominate its composition (Cheng et al. 2016; Cusack et al. 2012; Dabek-Zlotorzynska et al. 2011; Malm et al. 2004; Putaud et al. 2010; Wang et al. 2016). Common anthropogenic sources of $PM_{2.5}$ emissions include vehicles and engines, power plants, other industrial processes, and indoor use of fireplaces and woodstoves (Gullett et al. 2003). The pollutant has been detected both indoors and outdoors, with levels varying across geographic regions and seasons (Cusack et al. 2012; Dabek-Zlotorzynska et al. 2011; Malm et al. 2004; Wang et al. 2016).

In the *DWH* disaster, a subset of OSRC workers were exposed to high levels of $PM_{2.5}$ from controlled burning. Emissions from flaring were relatively uniform in the two months of mid-May to mid-July in 2010. Response workers aboard the vessels stationed in the wellhead area were at risk of inhaling high levels of $PM_{2.5}$ for days or weeks during this period. On the other hand, emissions from *ISBs* were highly episodic. Throughout the two months, the *ISB* taskforce conducted 1 to 26 burns per day, with each combustion lasting between 4 min and 23 hours (Allen et al. 2011). These workers were potentially exposed to high levels of $PM_{2.5}$ in some days but not others. In order to protect *ISB* workers from emissions, protocols were established to detail the burning procedure, and PPEs (flame resistant clothing and respirators) were provided when necessary (U.S. Coast Guard 2011). However, given the burden of wearing full protective gear and the high temperature in the summer and near burning sites, it is unknown how many workers wore a respirator during the operations. Besides workers in the wellhead area and the *ISB* taskforce, the remainder of the workforce were also exposed to $PM_{2.5}$ from these burning sources, albeit at much lower levels. For them, background emissions from water

vessels, land vehicles, and land equipment likely constituted a larger source of $PM_{2.5}$ exposure.

2.2.3 Exposure Monitoring during the *DWH* Oil Spill

Emissions from crude oil and burning activities were monitored at the source and in the air throughout the Gulf region during the *DWH* oil spill and cleanup. Samples of smoke plumes were collected during controlled burning, and laboratory analysis of the composition showed high levels of PM (mostly black carbon) and low concentrations of other gaseous emissions (polycyclic aromatic hydrocarbons, dioxins/furans, and metals) (Gullett et al. 2016; Perring et al. 2011). Concentration of various gas and aerosol species around, downwind, and away from the *DWH* site were measured on an aircraft on June 8 and 10 of 2010 (Middlebrook et al. 2012). Measurements showed that volatile hydrocarbons from the crude oil constituted the largest fraction of air emissions by mass (Middlebrook et al. 2012). To assess the types and levels of airborne chemical exposures experienced by OSRC workers, NIOSH performed personal breathing zone and area air monitoring on selected vessels (King and Gibbins 2012). Although concentrations of hazardous emissions were well below the occupational exposure limits, the small number of samples collected on a few vessels and days could not completely capture workers' exposure across the entire work period (King and Gibbins 2012). Outside the working zones, one study measured concentrations of benzene and $PM_{2.5}$ in coastal/urban areas of Louisiana and observed elevated levels during the spill (Nance et al. 2016). Although these studies provided evidence of inhalation exposures that were experienced by OSRC workers during the *DWH* disaster, individual estimates of volatile hydrocarbons and $PM_{2.5}$ exposures were only recently developed by industrial hygienists (Pratt et al. 2022; Stewart et al. 2022).

Individual exposure estimates showed that many *DWH* oil spill workers were

exposed to $PM_{2.5}$ from burning of oil/gas for a number of days and volatile hydrocarbons from the crude oil for many months (Pratt et al. 2022; Stewart et al. 2022). Industrial hygienists estimated workers' exposures to volatile components of the crude oil and burning-related $PM_{2.5}$ using job-exposure matrices based on air concentration data and workers' self-reported OSRC work histories (Pratt et al. 2022; Stewart et al. 2022). Measurement data for volatile hydrocarbons came primarily from ~28,000 personal air samples collected on some workers during their work shifts from April 2010 to June 2011. These samples were analyzed for total petroleum hydrocarbons (THCs), a composite measure of the volatile components of crude oil, as well as BTEX-H. Concentrations of $PM_{2.5}$ were estimated from May 15 to July 15, 2010, the period where most flaring/ISBs were conducted, using a Gaussian plume dispersion model (AERMOD) (Pratt et al. 2022). On some days, workers were exposed to BTEX-H at levels higher than those found in gas stations (Xiong et al. 2016) and manufacturing factories (Attarchi et al. 2013); however, exposure levels were substantially lower than the threshold limits established by the American Conference of Governmental Industrial Hygienists (ACGIH 2012). The median duration of crude oil exposure was four months among workers. On the other hand, the highest burning-related $PM_{2.5}$ exposure for workers who performed work in the wellhead area reached up to 545.03 $\mu g/m^3$ in an hour or 96.93 $\mu g/m^3$ over a 12-hour shift. These estimates exceeded the U.S. National Ambient Air Quality Standards for $PM_{2.5}$ (24-hour average of 35 $\mu g/m^3$) designed for the general population (Batavia 1991). Exposure levels for those who worked in the offshore, nearshore, and land areas were much lower and well below the standard. Most workers were exposed to $PM_{2.5}$ from burning of oil/gas for only a few days or weeks.

2.2.4 Other Occupational Exposures

Another source of inhalation exposure that workers may encounter in an oil spill cleanup is chemical dispersants (COREXIT 9500A and COREXT 9527A) used for breaking the oil into small droplets (U.S. Coast Guard 2011). Besides inhalation exposures, workers also faced other work-related hazards, including heat stress, physical hazards, and psychosocial stressors. Heat stress was an important health concern for the *DWH* oil spill workers. Temperatures often reached above 100 Fahrenheit during the summer, and the use of PPE accelerated fatigue (King and Gibbins 2012). Workers were also prone to acute injuries from physical hazards while engaging in physically demanding cleanup activities and operating heavy equipment or motor vehicles (NIOSH 2010, 2020). Lastly, workers and local residents faced various psychosocial stressors from the disaster, including disruption of local industries (e.g. fisheries, oil and gas exploration, and tourism), concerns about the health effects of the spill, and damage to the ecosystem and wildlife (Kwok et al. 2017b). **Acting alone or together, these exposures could induce short- and long-term adverse health effects among OSRC workers (Aguilera et al. 2010; Laffon et al. 2016).**

2.3 Cardiovascular Impacts of Exposure to $PM_{2.5}$ and Volatile Hydrocarbons

Also known as ischemic heart disease, coronary heart disease (CHD) is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart (Nowbar et al. 2019). Currently, CHD stands as the top cause of mortality in the U.S. and many parts of the world (Nowbar et al. 2019). In 2016 alone, heart attack and other complications of CHD were responsible for over 9 million deaths globally (Nowbar et al. 2019). Numerous studies have associated ambient exposure to $PM_{2.5}$ with increased incidence of CHD (Alexeeff et al. 2021;

Farhadi et al. 2020), and there is increasing evidence from occupational (Attarchi et al. 2013; Kotseva and Popov 1998; Strelitz et al. 2019b) and ambient air pollution literature (Barceló et al. 2016; Bard et al. 2014; Tsai et al. 2010) that points to volatile hydrocarbons exposure as a risk factor for cardiovascular diseases. Biological mechanisms by which these air pollutants induce CHD include promotion of systemic inflammatory responses and disturbance of the autonomic nervous system (Brook et al. 2004; Brook 2008). In this section, we review the current evidence on the association of $PM_{2.5}$ and volatile hydrocarbons exposures with CHD.

2.3.1 Health Effects Summarized in Existing Oil Spill Literature

Over the past century, dozens of major oil spills have occurred between 1967 and 2010, but few studies have ascertained the long-term human health effects from these spills. Among the major oil spills, only nine (*Exxon Valdez*, *MV Braer*, *Sea Empress*, *Nakhodka, Erika*, *Prestige*, *Tasman Spirit*, *Hebei Spirit*, and *Deepwater Horizon*) have been studied for their health effects among OSRC workers or nearby residents (Laffon et al. 2016). Most of the studies were cross-sectional and explored acute physical or physiological effects of exposures (Aguilera et al. 2010; Laffon et al. 2016). Some studies examined health effects by comparing OSRC workers with non-worker controls (Meo et al. 2009a; Zock et al. 2014), while others examined cleanup-related exposures among workers only (Chen et al. 2022; Cheong et al. 2011). Although a few studies measured levels of spill-related chemicals in environmental samples or biospecimens and examined them in relation to health outcomes (Cheong et al. 2011; Gam et al. 2018c; Ha et al. 2012; Noh et al. 2015), most characterized OSRC-related exposures using self-reported duration of cleanup, contact with oil, and/or participation in specific OSRC activities (Gam et al. 2018b; Kwok et al. 2017b; Meo et al. 2009b; Perez-Cadahia et al. 2008; Strelitz et al. 2019a). Around

half of the studies assessed health outcomes using self-reported symptoms, while the other half used more objective clinical measures (e.g. spirometry, serum biomarkers) (Laffon et al. 2016). Overall, studies have associated higher occurrence of mental health and acute physiological effects (e.g. airway and skin irritation, neurological impairment, genotoxicity, immunotoxicity) with participating in OSRC work (Aguilera et al. 2010; Laffon et al. 2016).

Emerging evidence suggests that oil spill workers are at elevated risks of long-term cardiorespiratory effects from cleanup work. Compared to non-worker controls, workers have shown worse respiratory health (symptoms, lung function, respiratory biomarkers) up to 5 years after the *Prestige* oil spill (Rodriguez-Trigo et al. 2010; Zock et al. 2007; Zock et al. 2012) and lower lung function several months after the *Tasman Spirit* spill (Meo et al. 2009a). Improving upon the previous studies, investigation of the *DWH* oil spill workers examined specific cleanup activities and exposure agents in relation to cardiorespiratory outcomes. Studies have found lower lung function 1-3 years after the spill among workers with stressful work experiences (Gam et al. 2018a), self-reported burning exposures (Gam et al. 2018b), and higher burning-related $PM_{2.5}$ exposure (Chen et al. 2022). *DWH* disaster was also the first oil spill in which cardiovascular effects of OSRC work were examined. Stretliz et al. (2018) have observed slightly higher risks of self-reported MI among workers compared to non-workers up to 3 years post-spill. Among workers, longer duration of work was associated with almost twice the risk of MI, while exposure to maximum daily THC only marginally increased risk of MI (Strelitz et al. 2018). When considering the first self-reported MI or fatal CHD event as the outcome, workers in the top THC exposure group had significantly higher risk of MI [hazard ratio (HR) = 1.81, 95%CI: 1.11, 2.95] compared to the lowest exposed group up to 6 years after the spill (Strelitz et al. 2019b). Despite the suggestive associations observed with maximum daily THC exposure

among *DWH* oil spill workers, it remains unclear if any specific chemicals were responsible for the effect and if the effect would persist over a longer follow-up time. Given $PM_{2.5}$ is a well-established cardiovascular risk factor (U.S. EPA 2020), it is also worth examining whether workers with higher $PM_{2.5}$ exposure from flaring/ISBs were at elevated risk of CHD.

2.3.2 Cardiovascular Effects of $PM_{2.5}$

The deleterious impact of $PM_{2.5}$ on the cardiovascular system has been documented in numerous studies. After an extensive review of literature, the Integrated Science Assessment for Particulate Matter has concluded a causal relationship of short- and long-term $PM_{2.5}$ exposure with adverse cardiovascular effects, including higher incidence of CHD (U.S. EPA 2020). The strongest evidence came from studies of cardiovascular disease-driven emergency department visits and hospital admissions (Alexeeff et al. 2021; Farhadi et al. 2020).

Short-term $PM_{2.5}$ exposure

The short-term effect of ambient $PM_{2.5}$ exposure on CHD has been examined in various time-series and case-crossover studies. Earlier multi-city studies that leveraged Medicare data have found consistent evidence associating $PM_{2.5}$ concentrations with CHD-induced hospital admissions or emergency department visits among elderly participants. In the Medicare Air Pollution Study, a 10 $\mu g/m^3$ increase in daily $PM_{2.5}$ (at lag of 2 days) was associated with a 0.44% [95%CI: 0.02, 0.86] increase in daily hospital admissions for CHD among the 11.5 million Medicare beneficiaries (Dominici et al. 2006). $PM_{2.5}$ concentrations were also associated with a 2.25% [95%CI: 1.10, 3.42 per 10 $\mu g/m^3$ increase] increase in emergency department admissions for MI in another study of Medicare enrollees (Zanobetti et al. 2009).

Subsequent studies have expanded the study population to all adults. A study conducted across multiple U.S. states have observed increased CHD hospitalizations following short-term $PM_{2.5}$ exposure for three Northeast states during cooler months, and for Florida during warmer months (Talbott et al. 2014). Positive associations were also found between short-term $PM_{2.5}$ exposure and CHD hospitalizations in certain regions of New York State (Hsu et al. 2017). In a recent meta-analysis of 26 studies conducted around the world, 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure (lag of 0 or 1 day) was associated with a statistically significant increase in risk of MI hospitalization (RR = 1.02; 95%CI: 1.01, 1.03).

Literature on the short-term effect of $PM_{2.5}$ on fatal CHD is more limited but also generally supports a relationship (Luo et al. 2015; Mustafic et al. 2012). Two U.S. multi-city studies found similar increases (1.18% [95% CI: 0.48, 1.89] and 1.22% [95% CI: 0.62, 1.82]) in MI deaths for a 10 $\mu g/m^3$ increase in daily $PM_{2.5}$ (Dai et al. 2014; Zanobetti and Schwartz 2009). A study conducted in Japan found a marginally significant association, which became significant after additionally adjusting for coarse PM: 2.5% [95% CI: 0.3, 4.6] increase in CHD mortality per 10 $\mu g/m^3$ increase in daily $PM_{2.5}$ (Michikawa et al. 2019). Using improve exposure assessment methods, Dabass et al. (2016) examined $PM_{2.5}$ exposure in relation to CHD mortality in a city in Pennsylvania and found a 2.1% [95% CI: 0.2, 4.1] increase in mortality per 10 $\mu g/m^3$ increase in daily $PM_{2.5}$ (lag of 5 days). Outside of the U.S., Chen et al. investigated air pollution-related mortality in 272 Chinese cities, where level of $PM_{2.5}$ exposure was higher (average of 56 $\mu g/m^3$) than that in developed countries, and found a 0.30% [95%CI: 0.19, 0.40] increase in CHD mortality for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Chen et al. 2017).

Long-term $PM_{2.5}$ exposure

The relationship of long-term $PM_{2.5}$ exposure with CHD and MI have been explored in numerous prospective studies. Evidence is mixed among studies that examined non-fatal or overall (i.e. fatal and non-fatal) incidence of events. In a recent meta-analysis, a 10 μg/m^3 increase in long-term $PM_{2.5}$ exposure was associated with a non-significant increase in risk of MI (8% [95% CI: -1, 18]) (Alexeeff et al. 2021). This meta-analysis included a large study of residents in Massachusetts where an interquartile range (IQR) increase (0.59 μg/m^3) in annual $PM_{2.5}$ was linked to a significant increase in MI risk [odds ratio (OR)=1.05, 95%CI: 1.00, 1.11] (Madrigano et al. 2013). In the Women's Health Initiative Study, where researchers obtained adjudicated cardiovascular outcomes among post-menopausal women, a 10 μg/m^3 increase in annual total $PM_{2.5}$ was associated with higher risks of overall CHD [HR=1.21, 95%CI: 1.04, 1.42], fatal CHD [HR=2.21, 95%CI: 1.17, 4.16], but not with MI (Miller et al. 2007). In a meta-analysis of 11 European cohorts, a positive association was observed between annual $PM_{2.5}$ concentration and hazard of acute coronary events (Cesaroni et al. 2014). Effects persisted at exposure levels below the standards set by the European Union (<25 μg/m^3) and the U.S. (<15 μg/m^3), suggesting that $PM_{2.5}$ exposures could elicit adverse cardiovascular effects at low levels (Cesaroni et al. 2014).

Evidence is also inconsistent among several American occupational cohorts of men or women. In the California Teachers Study Cohort, a 10 μg/m^3 increase in annual $PM_{2.5}$ was associated with elevated HR of fatal CHD [HR=1.20, 95%CI: 1.02, 1.41] among the female teachers, but no association was found for overall MI (Lipsett et al. 2011). In the Nurses' Health Study, no association was found between annual $PM_{2.5}$ exposure and non-fatal MI or overall CHD among female nurses in 13 Northeast and Mid-west states (Puett et al. 2009), although an

updated analysis that extended to nurses across all U.S. regions found a significant association with CHD among women with pre-existing diabetes (Hart et al. 2015). In the Health Professionals Follow-up Study, no apparent association was found between annual $PM_{2.5}$ concentration and non-fatal MI among male medical professionals (Puett et al. 2011). Given the potential differences between workers and the general population, these occupational studies might serve as better comparisons to our study of oil spill workers. However, because these studies were restricted to either male or female workers, our analyses should explore sex-specific effects (assuming we are sufficiently powered).

On the other hand, studies investigating cause-specific cardiovascular mortality provided the stronger evidence for the long-term effect of $PM_{2.5}$ on CHD. A recent meta-analysis has shown a statistically significant increase in fatal CHD risk (23% [95% CI: 15, 31]) corresponding to a 10 $\mu g/m^3$ increase in long-term $PM_{2.5}$ exposure (Alexeeff et al. 2021). Evidence summarized by the meta-analysis included two large U.S. population-based studies that found elevated HRs of fatal CHD of 1.14 [95%CI: 1.10, 1.18] and 1.16 [95% CI 1.09-1.22] for every 10 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations (Hayes et al. 2019; Pope et al. 2015). In contrast, a meta-analysis of 22 European cohorts did not find an association of long-term $PM_{2.5}$ with fatal CHD or fatal MI (Beelen et al. 2014). One limitation of this study is outcome misclassification from use of mortality registries and non-standardized coding of death certificates between different countries, which added uncertainty to the results (Beelen et al. 2014). Among the occupational cohorts, annual $PM_{2.5}$ exposure was associated with increased risk of fatal CHD in the California Teachers Study Cohort (HR=1.55, 95% CI: 1.43, 1.69 per IQR increase) (Ostro et al. 2010) and the Nurses' Health Study (HR=2.02, 95% CI: 1.07, 3.78 per 10 $\mu g/m^3$ increase) (Puett et al. 2009). However, no association was found in the Health

Professionals Follow-up Study (Puett et al. 2011). In a study of agricultural workers and their families, increased mortality from CHD was found among men [HR=2.68, 95% CI: 1.04, 6.87] but not among women exposed to a 10 $\mu g/m^3$ increase in annual concentrations of $PM_{2.5}$ (Weichenthal et al. 2014).

Biological mechanism

Although mechanisms underlying the air pollution–mediated CHD association are still evolving, two major biological pathways have been proposed based on existing evidence. 1) One involves activation of pulmonary and systemic inflammatory responses by inhaled pollutants (U.S. EPA 2020). 2) The other mechanism involves modulation of the autonomic nervous system by pollutants trapped in the respiratory tract (U.S. EPA 2020). Once these pathways are initiated, various pathophysiological responses that ensue can either predispose individuals to CHD or trigger an acute CHD event (e.g. MI) among high-risk individuals (e.g. those with atherosclerosis).

1) Promotion of inflammatory response and oxidative stress

Inhaled $PM_{2.5}$ can trigger inflammatory responses and oxidative stress in the respiratory tract (Brook et al. 2004). This can occur because transition metals, organic chemicals, or endotoxins contained in PM are oxidizing agents and can contribute to the formation of reactive oxygen species (Brook et al. 2004). Oxidative stress can activate specific transcription factors that upregulate the genes to produce cytokines and other pro-inflammatory mediators (Shukla et al. 2000; Sorensen et al. 2003). Once these agents (e.g. IL-6) enter the circulatory system, they can stimulate the liver to secrete inflammatory proteins (e.g. C-reactive protein) and coagulation factors (e.g. fibrinogen) (Hajat et al. 2015; Hennig et al. 2014) that increase blood viscosity.

Additionally, oxidative stress can impair endothelial and vascular functions by decreasing the bioavailability of NO and enhancing the systemic release of vasoconstrictors (Kampfrath et al. 2011; Lawal et al. 2016). Increased release of coagulation factors and inflammatory proteins, coupled with vascular dysfunction, may promote or enhance the progression of atherosclerosis, leading to a higher risk of thrombosis and subsequent CHD events (Brook et al. 2004). Endothelial dysfunction and vasoconstriction are also thought to trigger acute CHD events among susceptible people by destabilizing atherosclerotic plaques (Gutiérrez et al. 2013).

2) Dysregulation of the autonomic nervous system

$PM_{2.5}$ deposited in the lungs can activate sensory nerves via irritant receptors to disturb the autonomic nervous system (Brook et al. 2004). Because heart rate variability and blood pressure are mediated through a balance between the sympathetic and parasympathetic nervous systems, a shift of the autonomic balance towards the sympathetic tone can result in increased blood pressure, decreased heart rate variability, and impaired vascular function (Brook et al. 2004). Hypertension can induce endothelial dysfunction, contribute to atherosclerotic progression, and destabilize existing atherosclerotic plaques, all of which have been associated with a higher risk of CHD (Escobar 2002). Additionally, both hypertension and decreased heart rate variability have been linked to cardiac arrhythmias (Ferrari and Fox 2016; Lip et al. 2017), which can contribute to myocardial ischemia among people with or without atherosclerotic plaques (Liang and Wang 2021).

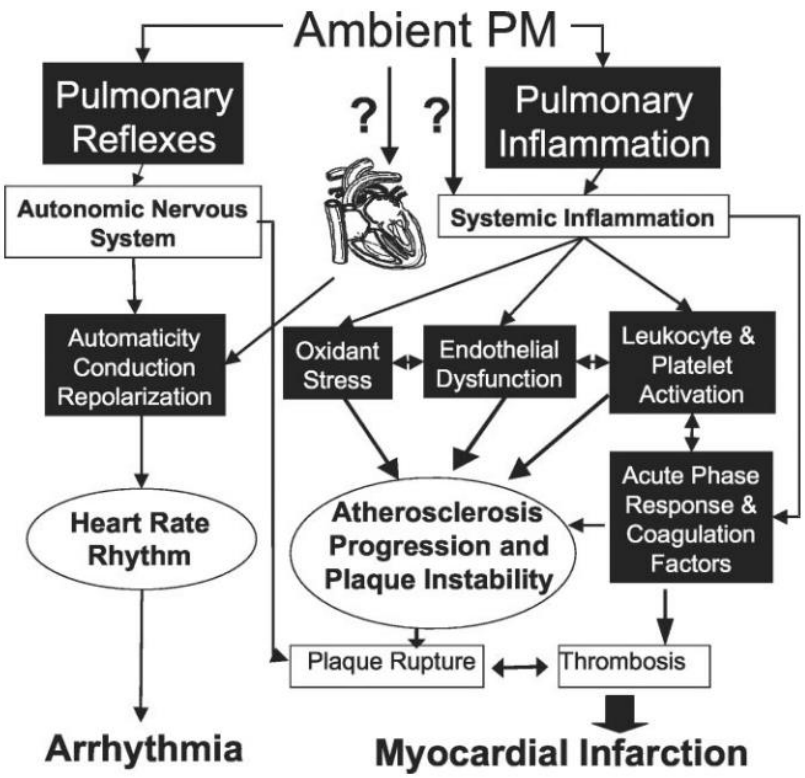

Figure 1. Possible biological mechanisms linking PM to MI (Brook et al., 2004)

2.3.3 Cardiovascular Effects of BTEX-H and Other Volatile Hydrocarbons

Among volatile hydrocarbons contained in the crude oil, BTEX-H are among the most well-studied toxic components (ATSDR 1999b, 2000, 2007a, b, 2010). These chemicals have been associated with impairments in the central and peripheral nervous system (ATSDR 1999b, 2000, 2007a, b, 2010; Burbacher 1993; Kim and Kang 2010) and hematological toxicities (Niaz et al. 2015; Smith 1996). Benzene and ethylbenzene have also been classified as known (Group 1) and potential carcinogens (Group 2B), respectively (IARC 2000, 2018). In ambient air pollution and occupational studies, one or more chemicals of BTEX-H have been associated with MI (Barceló et al. 2016; Bard et al. 2014), circulatory mortality (Ran et al. 2018a; Tsai et al. 2010), and other cardiovascular endpoints (Attarchi et al. 2013; Chang et al. 2009; Kotseva and Popov 1998), as described below.

Occupational literature on BTEX-H

A few occupational studies have assessed exposure to organic solvents that contained one or more chemicals of BTEX-H in relation to cardiovascular health. In a study of 345 petrochemical workers, higher prevalence of arterial hypertension (AH) and irregular electrocardiography were observed among those working in environments with high concentrations of benzene and xylene compared to a control group with no occupational exposure to chemical solvents (Kotseva and Popov 1998). The joint effect of noise and organic solvent exposure on AH has been investigated in two studies of manufacturing workers (Attarchi et al. 2013; Chang et al. 2009). To ascertain exposure to organic solvents, the most common VOCs present in the work environments were measured: N,N-dimethylformamide and toluene in Chang et al., and benzene, toluene, xylene, acetone, and tetrachloroethylene in Attarchi et al. Indexes were developed to represent co-exposure to the chemical mixtures. Both studies found workers with higher exposure to the VOC mixtures had higher prevalence of AH compared to workers with lower exposure, with the effect modified by exposure to noise (Attarchi et al. 2013; Chang et al. 2009). Taken together, evidence from the occupational literature demonstrated the potential of volatile hydrocarbons to induce cardiovascular changes. However, because most studies examined a mixture of chemicals, it is unclear which etiologic agents were responsible for the adverse effects. Additionally, the cross-sectional study design of these studies added difficulty to establish temporality for causal interpretation of the results.

Environmental exposure to BTEX-H

Quantitatively assessed benzene, alkylbenzenes, and alkanes have been examined in relation to cardiovascular morbidity and mortality in a few air pollution studies. Barceló et

al. (2016) assessed the long-term effects of air pollution on cause-specific mortality in a case-control study. An IQR increase in annual levels of benzene was associated with a higher risk of MI mortality among the elderly subgroups only (male: OR = 4.74, 95% CI: 2.00, 11.33; female: OR = 3.26, 95% CI: 1.45, 7.34). Self-reported MI was also associated with annual concentrations of benzene among residents of an industrial area in Estonia, but interpretation of the findings was limited by the cross-sectional study design (Orru et al. 2018).

Other studies have focused on short-term volatile hydrocarbon exposures and shown a modest acute effect on cardiovascular health. In a French case-crossover study, significant associations were observed between onset of MI and benzene concentration over the past two days (Bard et al. 2014). Specifically, a 1 ug/m^3 increase in benzene concentration on the same day and averaged over the past two days was associated with a 10.4 [95%CI: 3, 18.2] and 10.7 [95%CI: 2.7, 19.2] percent increase in risk, respectively (Bard et al. 2014). In a study conducted in Hong Kong, cumulative exposure to benzene across several days was associated with emergency hospitalizations for heart failure (Ran et al. 2018b), and both benzene and the alkylbenzene group were associated with circulatory mortality but not with CHD mortality (Ran et al. 2018a). An association between short-term benzene exposure and cardiovascular mortality was also observed in a Taiwan study (Tsai et al. 2010). The studies above have also associated acute cardiovascular events with alkanes (Ran et al. 2018b; Tsai et al. 2010), but no study that we are aware of have examined n-hexane specifically.

One study used a biomarker-based approach to assess alkylbenzene exposure and cardiovascular disease among participants of the National Health and Nutrition Examination Survey (Xu et al. 2009). Markers of several alkylbenzenes were assayed in blood samples, and cardiovascular disease was defined based on self-reported physician diagnosis of

any of the following conditions: CHD, MI, stroke, angina, or heart failure. Statistically significant associations were observed for toluene, ethylbenzene, xylene, and styrene. However, given the short half-life of alkylbenzene chemicals (< 0.5 hour for most) (Ashley et al. 1996; Ashley and Prah 1997), it is unclear whether the biomarker measurements reflected a recent exposure or a stable long-term exposure.

Because BTEX-H and other crude oil chemicals often arise from a single emission source (e.g. vehicular exhaust, oil/gas operations) (Dehghani et al. 2018; Gilman et al. 2013), it is useful to assess the joint effect of the exposure mixture to support interventions that target the exposure source. To our knowledge, only one study has examined the joint effect of crude oil chemicals in relation to acute cardiovascular events. Ye et al. (2017) investigated emergency department visits for cardiovascular diseases in Atlanta and same-day exposure to pre-specified pollutant groups. Joint effects were examined by modelling the effect corresponding to one IQR increase in all exposures in the group. While alkanes and most other hydrocarbon groups were associated with increased visits, the aromatic group (which contained BTEX) was not.

Biological mechanism

The biological mechanisms underlying the association between BTEX-H and CHD are not fully understood. However, studies on other air pollutants (e.g. PM) suggest that the same mechanisms could explain the relationship between BTEX-H and CHD.

1) Promotion of inflammatory response and oxidative stress

One suggested biological pathway involves activation of pulmonary and systemic inflammatory responses by inhaled pollutants (Brook et al. 2004; U.S. EPA 2020). The

inflammation and associated oxidative stress can impair endothelial function and stimulate the circulatory release of inflammatory proteins and coagulation factors, which can either predispose individuals to a future CHD event by promoting atherosclerosis or trigger an acute CHD event by destabilizing existing plaques (Brook et al. 2004; U.S. EPA 2020). Indeed, elevated levels of oxidative stress and inflammation have been found in animals or humans exposed to BTEX-H (Khedun et al. 1996; Moro et al. 2010; Shima et al. 2006; Uzma et al. 2010; Xiong et al. 2016).

2) Dysregulation of the autonomic nervous system

The other mechanism involves modulation of the autonomic nervous system by pollutants in the respiratory tract (Brook et al. 2004; U.S. EPA 2020). A shift of the system towards the sympathetic tone increases blood pressure, which can increase the risk of CHD by exacerbating atherosclerosis, impairing vascular function, and promoting arrhythmia (U.S. EPA 2020). Consistent with the mechanism, occupational studies have associated hypertension and electrocardiographic abnormalities with working in an environment that exposed workers to BTEX-H chemicals (Attarchi et al. 2013; Chang et al. 2009; Kotseva and Popov 1998). Among GuLF Study participants, cumulative THC exposure has been associated with increased risks of hypertension 1-3 years after the spill (Kwok et al. 2022).

CHAPTER 3: RESEARCH METHODS

3.1 Study Design and Data

3.1.1 Parent Study and Cohort Enumeration

The GuLF Study (Gulf Long-Term Follow-up Study) is a prospective cohort study of workers and volunteers who participated in the response and cleanup of the 2010 *DWH* disaster (Kwok et al. 2017a). Led by the National Institute of Environmental Health Sciences (NIEHS), the main purpose of the study is to investigate relationships of oil spill exposures with potential acute and chronic health effects. Potential participants were identified from a master recruitment list assembled from training and badge records, BP (the Responsible Party for the spill) contractors, a NIOSH Roster, and local, state, and federal workers. Eligible individuals included anyone ≥21 years of age at the time of enrollment, with contact information, and who had either participated in the OSRC for at least one day (workers) or completed OSRC safety training but were not hired (non-workers). These individuals were mailed a packet containing an invitation letter, a brochure explaining the study, and a privacy statement and given 2 weeks to opt out of the study. Those who did not opt out received a postcard and were encouraged to call the study toll-free number on the card to enroll.

Participant enrollment started in March 2011, approximately 8 months after the spill, in the form of a 30- to 60-min computer-assisted telephone enrollment interview conducted in English or Spanish. The interview asked detailed sociodemographic, occupation, lifestyle, and health information, as well as details on the OSRC work they had performed. Enrollment was

largely completed by December 2012, but efforts continued until May 2013 to increase recruitment of Vietnamese-speaking participants and oil/gas industry professionals with high exposure. The full cohort consists of 31,609 English- or Spanish-speaking participants who completed the full telephone interview and 999 Vietnamese-speaking participants who completed an abbreviated interview.

Enrolled participants were followed every 2-3 years via telephone interviews, in which questions about changes in health status and other important factors since the previous interview were asked. Among the remaining 31,609 participants, 21,256 (67%) and 14,187 (45%) completed the first and second follow-up interviews, respectively. Response rates were over 88% in both follow-ups among those who could be reached.

For both aims, we restricted our study population to the 24,375 workers, as non-workers did not have an opportunity to be directly exposed during *DWH* cleanup. Additional inclusion criteria were applied to aim 2: 1) We restricted our analysis to the 21,195 workers who worked at least one day between May 15 and July 15, 2010, the primary period in which burning occurred. 2) We further restricted our main analysis to the 9,457 workers who conducted any response or cleanup activities on water (i.e. water workers), excluding 11,738 land workers because workers on land were additionally exposed to $PM_{2.5}$ emissions from land vehicles and equipment engines, for which we lacked information to characterize this background exposure.

3.1.2 Ascertainment of Exposures

BTEX-H and THC exposures assessment

Cumulative exposures to five spill-related chemicals (BTEX-H) and THC across each worker's cleanup period were estimated via a job-exposure matrix that linked air measurement

data with detailed work histories (Stewart et al. 2022). Measurement data came primarily from ~28,000 personal air samples collected on OSRC workers using organic vapor passive dosimeters during their work shifts from April 2010 to June 2011. These samples were analyzed for THC and BTEX-H, resulting in over 143,000 chemical measurements of THC (as petroleum hydrocarbons) and BTEX-H (Stenzel et al. 2022a). A substantial percentage of measurements were at or below the laboratory reported limits of detection (LOD). Because these LODs were developed by the laboratories to reflect occupational exposure limits, the study industrial hygienists recalculated the measurements to reflect the analytic methods' true LODs and reduced the number of left-censored measurements (Stenzel et al. 2021). These personal measurements were supplemented by over 26 million direct-reading volatile organic compound (VOC) area measurements collected on 38 vessels involved in the OSRC to develop THC and BTEX-H estimates (Groth et al. 2022a; Ramachandran et al. 2022).

To estimate exposures for the full cohort, the study industrial hygienists created exposure groups (EGs) identified from three exposure determinants: job/work activity, location, and time period (Stenzel et al. 2022b). Each EG was a unique combination of these determinants and represented workers who, based on these determinants, were expected to have similar distributions of exposures. Using these determinants, industrial hygienists assigned air measurements to each EG and estimated exposure averages for the EGs (Groth et al. 2017; Groth et al. 2022b; Huynh et al. 2022a, b; Huynh et al. 2022c). For THC, estimates for each EG were calculated using a univariate Bayesian framework that accounted for measurements below the LOD. Because a large proportion of BTEX-H measurements were below the LOD (even after accounting for the analytic methods' true LODs), BTEX-H estimates below the LOD for each EG were predicted from the THC estimates using a bivariate Bayesian regression framework

(Groth et al. 2017; Groth et al. 2021).

Workers were matched to the appropriate EGs based on their reported OSRC work history (Stewart et al. 2022). Because many workers reported multiple work activities across the cleanup, two daily exposure estimates were created: 1) the daily maximum, the value corresponding to the highest-exposed activity on a day, and 2) the daily average, the average of the exposure estimates across all jobs/activities on each day. To examine the total burden of exposure received by each worker during the cleanup, two cumulative exposure metrics were created across all workdays: 1) *cumulative* daily maximum, the sum of daily maximum exposure estimates, and 2) *cumulative* daily average, the sum of daily average exposure estimates. These measures are the primary exposure estimates examined in the current analyses. We also considered as each worker's exposure the highest daily maximum exposure estimate (*maximum* daily maximum exposure) across their OSRC period in a sub-analysis. In secondary analyses, we explored the health impacts among workers who had multiple unusually high daily exposures to BTEX-H or THC by comparing them with workers with lower daily maximum exposure estimates in all days of their cleanup period (as described in *statistical methods* below).

$PM_{2.5}$ exposure assessment

The method for developing $PM_{2.5}$ exposure estimates for workers in the GuLF Study has been described elsewhere (Pratt et al. 2020). While working on water, workers were potentially exposed to three sources of $PM_{2.5}$ emissions: flaring at the wellhead, *in situ* burning offshore, and operation of thousands of mostly diesel-powered vessel engines. However, because of uncertainties in the locations of workers and vessels, it was not possible to consider background emissions from the vessel exhaust or other sources in the development of individual exposure

estimates. Here, we summarize the approach by which $PM_{2.5}$ exposure from controlled burning of oil and gas was assessed.

Potential exposure to $PM_{2.5}$ from burning activities was estimated from May 15 to July 15, 2010. Emissions for each ISB or flaring episode were calculated based on emission factors reported in previous studies (Fingas et al. 1995; U.S. EPA 2017) and the estimated volume of oil/gas burned. The resulting primary emissions data were used along with meteorological data and source characterizations as inputs in the Gaussian air dispersion model, AERMOD (Cimorelli et al. 2005), to estimate air concentrations of $PM_{2.5}$ across the Gulf. Meteorological data were obtained from meteorological stations in the Gulf area, and emission sources were optimized by comparing potential AERMOD simulation options with photographs/videos of plumes recorded during the *DWH* cleanup to see which options best represented the photographic evidence. Using AERMOD, hourly $PM_{2.5}$ concentrations were modeled for 3,960 geospatial model receptors in the Gulf area for each day that burning occurred. From the modelled hourly concentrations, two daily air concentration estimates at each receptor were retained in the exposure assessment database: the maximum 1-hour concentration (to represent peak concentrations) and the maximum of two 12-hour (0:00-11:59 and 12:00-23:59) average concentrations (to represent work shift concentrations).

To link workers with these concentration estimates, industrial hygienists created exposure groups based on work locations in the Gulf: hot zone (≤1 nautical mile (nmi) from the wellhead), source (>1 and ≤5 nmi from the wellhead), offshore (>5 nmi from the wellhead to >3 nmi from shore), near shore (≤3 nmi from shore), and land. These areas were delineated by 10x10 nmi grid squares, along with a finer grid of 1x1 nmi squares in the 10x10 nmi square containing the wellsite for higher resolution in the hot zone and source areas. Workers in the offshore exposure

group were further divided by their reported activity into *ISB* workers and non-*ISB* offshore workers to underscore the higher exposure experienced by the *ISB* Group from *in-situ* burning. A job-exposure matrix was created by assigning each exposure group an exposure estimate that represented a spatiotemporal average of the daily maximum concentrations across all days of burning over the period of May 15 to July 15, 2010 (i.e. average daily maximum exposure). For *ISB* workers, industrial hygienists first averaged daily concentrations (either maximum 1-hour or maximum 12-hour average) across receptors within grid squares that contained *ISBs* on each burn day, and then took the (arithmetic) mean of these area-average daily estimates across all *ISB* days (N=30). For the other exposure groups (i.e. non-*ISB* workers), exposure was calculated by first averaging daily concentrations across all receptors in the grid squares that delineated the work location on each burn/flaring day, and then averaging these daily values across all 57 days during which *ISB*/flaring occurred.

To match individual workers to the exposure groups and the corresponding average daily maximum exposure estimates, industrial hygienists relied on work histories obtained from the enrollment interview and external administrative data maintained by BP, p.l.c. and its contractors. Participants who worked in multiple locations and/or performed multiple activities (i.e. *ISB* and others) were matched to the exposure group with the highest exposure estimate. Besides average daily maximum exposure, industrial hygienists also created "cumulative daily maximum exposure" estimates, a proxy for the total exposure burden received in the exposure period, by multiplying average daily maximum exposure by the number of days exposed to $PM_{2.5}$. To estimate days of exposure, the number of days worked in the exposure period was multiplied by the proportion of (either flare or *ISB*) burn days in the exposure period. By applying the two exposure metrics (i.e. average and cumulative) to each of the two daily

concentration estimates (i.e. maximum 1-hour, maximum 12-hour average), four measures of $PM_{2.5}$ exposure were available for analysis. Exposure estimates using the maximum 1-hour daily concentration and the maximum 12-hour average daily concentration had nearly identical distributions (Pearson r>0.99), so we chose to examine only the average maximum 12-hour exposure ($\mu g/m^3$) and the cumulative maximum 12-hour exposure ($\mu g/m^3$-day) (henceforth, average daily maximum and cumulative daily maximum exposures) in all analyses.

3.1.3 Ascertainment of Outcome

The outcome of interest was the first occurrence of a CHD event after the last day of each worker's OSRC work. For aim 1, the outcome is defined as the first self-reported physician-diagnosed MI or an International Classification of Disease (ICD)-coded fatal CHD event. For aim 2, we also included as events workers who self-reported being diagnosed with a blockage in the arteries of the heart after their last day of work to increase statistical power in analyses.

Self-reported MI and blockage in the arteries of the heart

Physician-diagnosed MI was assessed at enrollment and in the two follow-up interviews. Participants were asked the question "*Has a doctor ever told you that you had a heart attack, also called a myocardial infarction or 'MI'?*" In these interviews, participants were also asked "*Has a doctor ever told you that you had a blockage in the arteries of the heart?*" Those who responded "yes" to each question were asked to provide the month and year of, or the age at, the event.

Validity of self-reported CHD

Because we were not able to obtain medical records for the majority of participants who reported an MI diagnosis, we did not perform a validation analysis of self-reported MI. Instead, we performed a literature review to identify studies published after the 1980s that assessed the accuracy of self-reported MI. In general, studies that validated MI against medical record reviews or hospital discharge diagnoses have indicated moderate-to-high levels of accuracy, with sensitivities ranging from 0.82 to 0.98, and specificities close to 1.0 (Barr et al. 2009; Eliassen et al. 2016; Machón et al. 2013; Okura et al. 2004; Yamagishi et al. 2009). Some of these studies have associated lower accuracy with older age (Okura et al. 2004; Yamagishi et al. 2009). Compared to participants examined in these validation studies, workers in our study were younger, and most were < 60 years old at enrollment, so we expect a lower degree of outcome misclassification in our population.

Fatal coronary heart disease

Fatal CHD events were ascertained via linkage with the National Death Index (NDI) through December 31, 2019. We included deaths attributed to ischemic heart disease (ICD-10 code I20-I25) as an underlying cause. We also identified deaths with ischemic heart disease as a contributing / underlying cause to be examined in a sensitivity analysis.

Validity of death certificate diagnosis of CHD

We performed a literature review of studies published after 1980s that assessed the accuracy of death certificate diagnosis of CHD. We restricted studies to those conducted in the U.S., given potential differences in assigning causes of death and quality of cause of death data

between countries (Iburg et al. 2020; Pagidipati and Gaziano 2013). In studies that evaluated death certificate diagnoses of CHD against clinician adjudicated cause of death (Coady et al. 2001; Folsom et al. 1987; Goraya et al. 2000; Lloyd-Jones et al. 1998; Olubowale et al. 2017), we found sensitivities ranging from 0.54 to 0.91 and specificities varying from 0.72 to 0.90. Older age was associated with worse reliability in using death certificate data to classify CHD deaths (Lloyd-Jones et al. 1998; Olubowale et al. 2017). Again, we expect a lower degree of outcome misclassification in our study given that the GuLF Study population was younger at enrollment compared to populations in these validation studies.

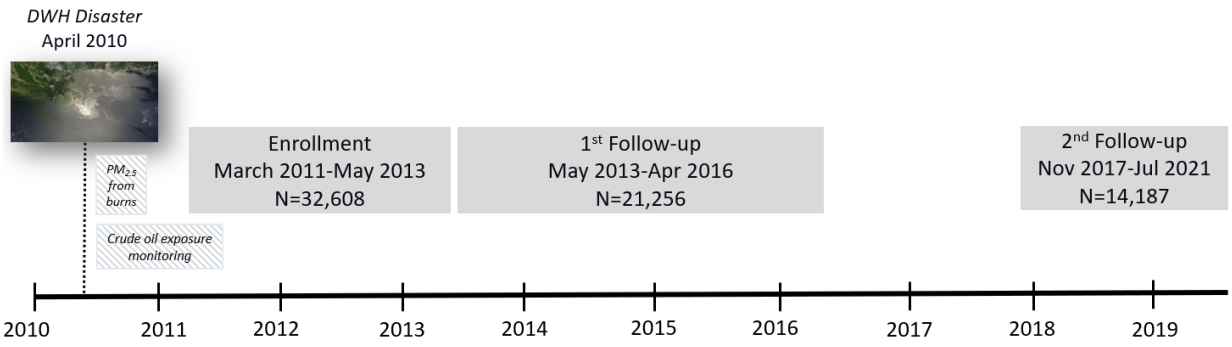

Figure 2. Timeline of data collection

3.1.4 Ascertainment of Covariates

We selected covariates based on a directed acyclic graph (DAG) and included the minimally sufficient adjustment set and predictors of the outcome that are not descendants of the exposure in the model (Greenland et al. 1999). The same set of covariates were accounted for in analyses of aim 1 and aim 2, which included: age (in years: 20-29, 30-39, 40-49, 50-59, ≥60), sex (male; female), self-reported race (White; Black; other/multi-racial ("American Indian or Alaskan Native", "Asian", "Native Hawaiian or Pacific Islander", "other races")), Hispanic ethnicity (Hispanic; non-Hispanic), cigarette smoking status (current heavy (≥20 cigarettes/day);

current light (<20 cigarettes/day); former; never), highest educational attainment (less than high school; high school diploma or general equivalency diploma; some college or 2-year degree; 4-year college graduate or more), body mass index (BMI; in kg/m^2: underweight or normal [<25], overweight [25-<30], obese I [30-<35], obese II ≥35]), previous oil spill cleanup experience (yes; no), previous oil industry experience (yes; no), pre-cleanup diabetes diagnosis (yes; no), and residential proximity to the spill (living in a coastal county directly affected by the spill or a county adjacent to the impacted counties; living in a Gulf state further from the spill; living in a non-Gulf state). All covariates were ascertained at enrollment.

3.2 Statistical Methods

3.2.1 Aim 1 Methods

Aim 1: Assess the relationship of THC and BTEX-H exposures with CHD events that occurred after the last day of OSRC work among the DWH workers. In a sub-aim, examine the joint effect of the BTEX-H mixture in relation to incident CHD events.

Defining exposures and outcomes

In aim 1, we examined cumulative exposure to THC and BTEX-H, estimated via a job-exposure matrix that linked air measurement data to *DWH* spill work histories provided by study participants. Because many participants worked on multiple jobs/tasks during the cleanup and we do not have information on which days and how much time in a day they spent on each job/task, we examined both cumulative daily *maximum* and cumulative daily *average* exposures in the analyses. In an exploratory analysis, we also considered the impact of short-term exposure to higher exposure levels by exploring risks associated with having exposures in the top 20th and 15th percentile of maximum daily maximum exposure for a minimum of 7 or 14 days compared to having daily maximum exposures in the first quintile of the study population's maximum daily

maximum exposure in all days of the cleanup.

The outcome of interest in aim 1 was the first occurrence of a CHD event after the last day of each worker's OSRC work, defined as either a self-reported physician-diagnosed MI or an ICD-coded fatal CHD event. Because some participants completed the second follow-up interview after the last available date of the NDI data (Dec 2019), we administratively censored the study on Dec 31, 2019 to keep the risk period consistent for all workers. Time at risk was measured in months from the last date of each worker's OSRC work to the first of non-fatal or fatal CHD event, death from other causes, withdrawal from the study, or end of follow-up (December 31, 2019).

Single-pollutant time-to-event analyses

In aim 1, we used Cox proportional hazards models to estimate HRs for first incident CHD events associated with increasing cumulative exposure to each BTEX-H chemical and THC (Cox 1972). Tied event times were handled by the Efron's approximation method. We used quintiles of exposure levels for analysis, with workers in the lowest quintile (Q1) of an exposure agent as the referent group. We also investigated exposure-response trends by examining ln-transformed continuous exposure levels.

We used inverse probability (IP) of exposure weighting to control for confounders identified in the DAG (see section "Ascertainment of Covariates") (Cole and Hernan 2004). Compared to the traditional method of conditioning on confounders, IP-exposure weighted analysis is more interpretable as it produces marginal effects that compare the outcome for a defined population under different counterfactuals (Cole and Hernan 2008). We obtained stabilized weights by fitting a multinomial logistic regression model for each *categorical*

exposure with respect to selected covariates. In analysis of ln-transformed *continuous* exposures, we generated weights for each exposure agent using a quantile binning approach (Naimi et al. 2014).

To account for informative censoring due to loss to follow-up, we used IP censoring weights (Hernán et al. 2004; Howe et al. 2016). Under a set of assumptions, the weighted results can be interpreted as associations that would be observed in the absence of censoring (Hernán et al. 2004; Howe et al. 2016). Participants were considered censored if they 1) did not complete a follow-up interview or completed the first but not the second interview and 2) had not experienced a CHD event prior to being lost to follow-up. Censoring was modelled as a function of its predictors in a pooled logistic regression, and weights were stabilized by the marginal probability of censoring. Covariates in the IP-censoring weights were determined from a DAG (different from the DAG for IP-exposure weights) (Brookhart et al. 2006) and included: exposure(s) (THC for model of THC, all chemicals of BTEX-H for each model of BTEX-H), age, sex, self-reported race, Hispanic ethnicity, cigarette smoking, highest educational attainment, previous oil spill cleanup experience, and residential proximity to the spill. The finalized weights applied to the models were the product of the IP-exposure and the IP-censoring weights. Cox proportional hazards models with a robust variance estimator were fitted to estimate HRs and 95% confidence intervals (CIs). IP-exposure and IP-censoring weights were applied to the main analysis and sub-analyses.

In single-pollutant analyses, we investigated potential effect measure modification (EMM) by cigarette smoking status (ever vs. never), obesity (obese vs. non-obese), and educational attainment (high school or less vs. more than high school) at enrollment to see whether there was heterogeneity among associations. We assessed EMM by including a product

term between quintile exposure and the modifier in the model and reported the p-value for the joint Wald test. To address potential co-pollutant confounding from exposure to higher levels of $PM_{2.5}$ from controlled burning activities, we reran the analysis excluding the *ISB* taskforce and workers in the source and hot zone to see if results differed.

Quantile g-computation mixture analysis

We performed a mixture analysis using quantile g-computation (QGC) (Keil et al. 2020) to estimate the joint effect of BTEX-H as a mixture on the risk of CHD events. For time-to-event outcomes, this method is a semi-parametric model-based implementation of g-computation to estimate the expected change in outcome corresponding to a simultaneous increase in all of the mixture components by one quantile (White et al. 2020). To implement this method, we first categorized exposure components into quintiles and assigned each quintile an integer score (Q1=1, …, Q5=5). Then, we fit a Cox proportional hazards model of CHD against the quintile scores (treated as continuous variables) and conditional on the same covariates used in single-agent IP-exposure weight models. This construction allows a weight for each BTEX-H component to represent a component's relative contribution to positive associations (positive weights), or relative contribution to inverse associations (negative weights). Positive and negative weights sum to 1 and -1, respectively. Under assumptions of linearity and additivity of the effects of BTEX-H, the joint effect equals the sum of generalized linear model coefficients for all of the transformed exposures. As in single-pollutant analyses, we applied IP-censoring weights to the mixture model. QGC was performed using R 4.0.4 package "qgcomp".

3.2.2 Aim 2 Methods

Aim 2: Assess the relationship of average and cumulative $PM_{2.5}$ exposures with CHD events that occurred after the last day of OSRC work among DWH water workers.

Defining exposures and outcomes

The exposure of interest in aim 2 was $PM_{2.5}$ from controlled burning, estimated via a job-exposure matrix that linked modelled concentrations data to detailed OSRC work histories reported by the participants. We examined two exposure metrics in all analyses: the average daily maximum exposure and the cumulative daily maximum exposure.

For average daily maximum exposure, the referent group consisted of the combined group of nearshore and non-*ISB* offshore workers, whose burning-related $PM_{2.5}$ exposure was substantially lower than those of the other water workers who had higher exposure (i.e. "burning-exposed workers"). We also combined the groups of *ISB* workers (10.4 $\mu g/m^3$) and workers at the source (28.7 $\mu g/m^3$) due to the small number of *ISB* workers (N=41). Average daily maximum exposure then became a three-level categorical variable: referent (0.8 $\mu g/m^3$), low (10.4-28.7 $\mu g/m^3$), and high (96.9 $\mu g/m^3$, corresponding to the exposure level for hot zone workers).

The cumulative daily maximum exposure, which was determined by both the exposure level and the exposure duration (range=0-49 days), had greater individual variability. To model it in the analysis, we employed the same referent group and categorized the remainder of workers (i.e. burning-exposed group) into tertiles by the exposure distribution to create a four-level categorical variable: the referent group (<10 $\mu g/m^3$-days), low (10-679 $\mu g/m^3$-days), medium (689-1378 $\mu g/m^3$-days), and high (1406-4071 $\mu g/m^3$-days). Because of numerous tied values at the tertile cutoffs, the number of burning-exposed workers in each tertile is not evenly

distributed.

The outcome of interest for aim 2 was CHD events that occurred after each participant ended their OSRC work. CHD events included workers who reported a physician-diagnosed MI, a blockage in the arteries of the heart, or an ICD-coded fatal CHD event. Similar to the aim 1 analysis, we administratively censored the study on Dec 31, 2019 to keep the risk period consistent for all workers. Time at risk was measured in months from the earlier date of each worker's last date of cleanup work and July 15, 2010 to the first of non-fatal or fatal CHD event, death from other causes, withdrawal from the study, or end of follow-up (December 31, 2019).

Statistical analyses

We used Cox proportional hazards models with a robust variance estimator to estimate HRs and 95%CIs for first incident CHD event associated with increasing average and cumulative daily maximum $PM_{2.5}$ exposures (Cox 1972). Average and cumulative daily maximum exposures were coded as categorical variables, as described above, with nearshore and non-*ISB* offshore workers as the referent group. In addition to the categorical exposure models, we also investigated exposure-response trends by assessing continuous exposures in relation to CHD risk in models. Exposure-response trends were analyzed separately for average (per 10 $\mu g/m^3$ increase) and cumulative daily maximum exposures (per 100 $\mu g/m^3$-day increase).

Similar to aim 1, we applied inverse probability weights to account for bias due to confounding and loss to follow-up (Cole and Hernan 2004; Hernán et al. 2004). To construct the IP-exposure weights, we fitted a multinomial logistic regression model for the categorical exposure with respect to covariates selected from the DAG. We obtained stabilized weights, where the denominator of the weights was the probability of exposure conditional on covariates,

and the numerator was the marginal probability of exposure. To estimate censoring weights, censoring was modelled as a function of its predictors (determined from a DAG) in a pooled logistic regression, and weights were stabilized by the marginal probability of censoring. The finalized weights applied to the models were the product of the IP-exposure and the IP-censoring weights.

To account for co-pollutant confounding from crude oil exposures that were examined in aim 1, we additionally adjusted for cumulative THC exposure in a sensitivity analysis to see if results differed. Because workers were also exposed to the $PM_{2.5}$ from engine exhaust, which could not be quantified, we assessed the potential impact of this bias by performing sensitivity analyses that excluded non-*ISB* offshore workers, the group with the largest potential vessel exhaust exposure variability, and separately, that included land workers as an additional exposure category to quantify the potential bias from land equipment emissions.

CHAPTER 4: AIM 1 RESULTS

Title: Oil spill-related volatile hydrocarbon exposures and incident coronary heart disease events among *Deepwater Horizon* oil spill workers

4.1 Introduction

The 2010 *Deepwater Horizon* (*DWH*) disaster is the largest marine oil spill in U.S. history (National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling 2011). An estimated 4.9 million barrels of crude oil were discharged into the Gulf of Mexico before the wellhead was mechanically capped on July 15, 2010 (National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling 2011). Shortly after the spill began, an extensive oil spill response and cleanup (OSRC) operation was launched to stop the spill and remove the crude oil from the environment. Tens of thousands of workers and volunteers participated in this operation, with most efforts completed by June 2011 (U.S. Coast Guard 2011).

During the OSRC, workers were exposed to a range of inhalation hazards, including volatized crude oil hydrocarbons (Kwok et al. 2017a). These hydrocarbons were a significant contributor to air emissions in the *DWH* Disaster (Middlebrook et al. 2012). Many of these components, including benzene, some alkylbenzenes, and hexane, are classified as hazardous air pollutants because of their toxicological properties (Batavia 1991). Studies have associated short-term ambient exposure to benzene and alkylbenzenes with acute onset of coronary heart disease (CHD) (Bard et al. 2014) or coronary death (Ran et al. 2018a; Tsai et al. 2010). Chronic benzene exposure has also been linked to persistent myocardial infarction (MI) mortality in a Spanish case-control study; however, the study failed to account for important confounders, including

smoking and socioeconomic status (Barceló et al. 2016). Persistent respiratory effects have been observed among workers who participated in cleanup of the *Prestige*, *Hebei Spirit*, or *DWH* oil spills (Chen et al. 2022; Gam et al. 2018b; Meo et al. 2008; Zock et al. 2012); however, associations between oil spill exposures and cardiovascular health were previously assessed only among the *DWH* oil spill workers. In the analysis, ordinal categories of workers' maximum exposure to total (petroleum) hydrocarbons (THC), a measure of volatile components of the crude oil, were associated with higher incidence of CHD up to six years after the spill (Strelitz et al. 2019b).

These studies provided some evidence that exposure to crude oil chemicals may be related to increased risk of CHD over time. Recently, quantitative estimates of several cumulative oil-related exposures [THC, benzene, toluene, ethylbenzene, xylene (all isomers combined), and n-hexane (BTEX-H)] were developed from personal measurements and self-reported OSRC activities for the *DWH* OSRC workers, providing an opportunity to study health effects associated with these exposures (Stewart et al. 2022). Given that BTEX-H also arise from a single emission source in other environments (e.g. vehicular exhaust, oil/gas operations) (Dehghani et al. 2018; Gilman et al. 2013), it is useful to assess the joint effect of the exposure mixture to support interventions that target the exposure source. The objective of this study was to assess quantitative oil-related exposures, individually and as a mixture, in relation to incident CHD events among *DWH* OSRC workers.

4.2 Methods

Study population

The GuLF Study (Gulf Long-Term Follow-up Study) is a prospective cohort study of the potential health effects of the *DWH* disaster (Kwok et al. 2017a). Participants included anyone

≥21 years of age at enrollment who either had participated in OSRC work for at least one day (workers) or had completed safety training but were not hired (non-workers). Enrollment started in March 2011 and continued through May 2013. A total of 32,608 participants were enrolled. At enrollment, all participants completed a computer-assisted telephone interview in which they provided information on socio-demographics, lifestyle, health, and a detailed history of *DWH* OSRC activities. Two rounds of follow-up interviews (May 2013-Apr 2016 and November 2017-July 2021) were conducted via telephone to ascertain changes in health status and other important factors since the previous interview. We excluded from the current analysis 999 Vietnamese only-speaking participants who completed only an abbreviated enrollment interview. Among the remaining 31,609 participants, 21,256 (67%) and 14,187 (45%) completed the first and second follow-up interviews, respectively. Response rates were over 88% in both follow-ups among those who could be reached.

For all analyses, we restricted the study population to 24,375 workers. Since non-workers were not directly exposed during *DWH* cleanup, exposure estimates were not generated. We excluded 21 workers who did not provide information on MI diagnoses in any of the interviews. We restricted our analysis to incident cases. By beginning follow-up at the *end* of each worker's cleanup work time, we excluded 489 workers who reported an MI diagnosis before the start of follow-up. While MIs that occurred *during* clean-up would be informative, it is also likely that those who had such an event might have stopped working and were not enrolled in our study; thus, including the person-time before the end of clean-up could lead to immortal time bias. Of the remaining 23,865 workers, we restricted our analysis to 23,664 workers who had complete THC and BTEX-H exposure estimates. Finally, we excluded 1,009 workers with missing covariates needed for analysis and reached a final analytical sample of 22,655 workers. All

participants provided informed consent prior to participating in the GuLF Study. The Institutional Review Board of the National Institute of Environmental Health Sciences approved this study.

Exposure assessment

Cumulative exposures to five spill-related chemicals (BTEX-H) and THC across each participant's work period were estimated via a job-exposure matrix that linked air measurement data with detailed work histories. Measurement data came primarily from ~28,000 personal air samples collected on OSRC workers using organic vapor passive dosimeters during their work shifts from April 2010 to June 2011 (Stewart et al. 2022). These samples were analyzed for THC and BTEX-H, resulting in over 143,000 measurements of THC (as petroleum hydrocarbons) and BTEX-H (Stenzel et al. 2022a; Stewart et al. 2022). These personal measurements were supplemented by over 26 million direct-reading volatile organic compound (VOC) area measurements collected on 38 vessels involved in the OSRC to develop THC and BTEX-H estimates (Groth et al. 2022a; Ramachandran et al. 2022).

To estimate exposures for the full cohort, the study industrial hygienists created exposure groups (EGs) identified from three exposure determinants: job/work activity, location, and time period (Stenzel et al. 2022b). Each EG was a unique combination of these determinants and represented workers who, based on these determinants, were expected to have similar distributions of exposures. Using these determinants, industrial hygienists assigned air measurements to each EG and estimated exposure averages for the EGs (Groth et al. 2017; Groth et al. 2022a; Groth et al. 2022b; Huynh et al. 2022a, b; Huynh et al. 2022c; Ramachandran et al. 2022).

Workers were matched to the appropriate EGs based on their reported *DWH* OSRC work history. Because many workers reported multiple work activities across the cleanup, two daily

exposure estimates were created for each day worked: 1) the daily maximum, the value corresponding to the highest-exposed activity on a day, and 2) the daily average, the average of the exposure estimates across all jobs/activities on each day. To examine the total burden of exposure received by each worker during the cleanup, two cumulative exposure metrics were created across all workdays: 1) *cumulative* daily maximum, the sum of daily maximum exposure estimates, and 2) *cumulative* daily average, the sum of daily average exposure estimates. These measures are the primary exposure estimates examined in the current analyses. We also considered as each worker's exposure the single highest daily maximum exposure estimate (single maximum exposure) over the entire work period in a sub-analysis. In secondary analyses, we explored the health impacts among workers who had multiple unusually high daily exposures to BTEX-H or THC by comparing them with workers who exclusively had only lower daily maximum exposure estimates (as described in the *statistical modelling* below).

Outcome assessment

The outcome of interest was the first occurrence of a CHD event after the last day of each participant's OSRC work, defined as either a self-reported physician-diagnosed MI or an International Classification of Disease (ICD)-coded fatal CHD event. At each interview, participants were asked "*Has a doctor ever told you that you had a heart attack, also called a myocardial infarction or 'MI'?*" Those who responded "*yes*" were asked to provide the month and year of, or the age at, the event. Fatal CHD events were ascertained via linkage with the National Death Index through December 31, 2019, and we included deaths attributed to ischemic heart disease (ICD-10 code I20-I25) as an underlying cause. Time at risk was measured in months from the date after each participant ended cleanup work to the first of non-fatal or fatal CHD event, death from other causes, withdrawal from the study, or end of follow-up (December

31, 2019).

Statistical modeling

We used Cox proportional hazards models to estimate hazard ratios (HRs) for the first incident CHD event associated with increasing cumulative exposure to each BTEX-H chemical and THC (Cox 1972). We used quintiles of exposure levels for analysis, with workers in the lowest quintile (Q1) of an exposure agent as the referent group. We also investigated exposure-response trends by examining ln-transformed continuous exposure levels.

We adjusted for potential confounding using inverse probability (IP) weighting (Cole and Hernan 2004). We selected covariates based on a directed acyclic graph (DAG) and included the minimally sufficient adjustment set and predictors of the outcome that are not descendants of the exposure in the IP-exposure weights (Brookhart et al. 2006; Greenland et al. 1999) (Figure S1). Because of high correlations among exposures (range: 0.84-0.96) (Table 8), we were not able to account for co-exposures in the weights. We obtained stabilized weights by fitting a multinomial logistic regression model for each *categorical* exposure with respect to selected covariates. In analysis of ln-transformed *continuous* exposures, we generated weights for each exposure agent using a quantile binning approach (Naimi et al. 2014).

All covariates were ascertained at enrollment and included the following: age (in years: 20-29, 30-39, 40-49, 50-59, ≥60), sex (male; female), self-reported race (White; Black; other/multi-racial ("American Indian or Alaskan Native", "Asian", "Native Hawaiian or Pacific Islander", "other races")), Hispanic ethnicity (Hispanic; non-Hispanic), cigarette smoking status (current heavy (≥20 cigarettes/day); current light (<20 cigarettes/day); former; never), highest educational attainment (less than high school; high school diploma or general equivalency diploma; some college or 2-year degree; 4-year college graduate or more), body mass index

(BMI; in kg/m²: underweight or normal [<25], overweight [25-<30], obese I [30-<35], obese II ≥35]), previous oil spill cleanup experience (yes; no), previous oil industry experience (yes; no), pre-cleanup diabetes diagnosis (yes; no), and residential proximity to the spill (living in a coastal county directly affected by the spill or a county adjacent to the impacted counties; living in a Gulf state further from the spill; living in a non-Gulf state).

To account for informative censoring due to loss to follow-up, we used IP-censoring weighting (Hernán et al. 2004; Howe et al. 2016). Participants were considered censored if they 1) did not complete a follow-up interview or completed the first but not the second interview and 2) had not experienced a CHD event prior to being lost to follow-up. Censoring was modelled as a function of its predictors in a pooled logistic regression, and weights were stabilized by the marginal probability of censoring. Covariates in the IP-censoring weights were determined from a DAG (Brookhart et al. 2006) and included: exposure(s) (THC for model of THC, all chemicals of BTEX-H for each model of BTEX-H), age, sex, self-reported race, Hispanic ethnicity, cigarette smoking, highest educational attainment, previous oil spill cleanup experience, and residential proximity to the spill. The finalized weights applied to the models were the product of the IP-exposure and the IP-censoring weights. Cox proportional hazards models with a robust variance estimator were fitted to estimate HRs and 95% confidence intervals (CIs). IP-exposure and IP-censoring weights were applied to the main analysis and sub-analyses.

In single-agent analyses, we investigated potential effect measure modification (EMM) by cigarette smoking status (ever vs. never), obesity (obese vs. non-obese), and educational attainment (high school or less vs. more than high school) at enrollment to see whether there was heterogeneity among associations. We only present results of these stratified analyses for cumulative daily maximum exposure because findings with cumulative daily average exposure

were similar. We assessed EMM by including a product term between quintile exposure and the modifier in the model and reported the p-value for the joint Wald test.

We conducted a number of sensitivity analyses. First, we included self-reported pre-cleanup hypertension in the IP-exposure weight model to see if results differed. This covariate was not included in the main analysis because *pre-cleanup* hypertension was not related to crude oil exposures and we were concerned about possible misclassification of hypertension using self-reports (Gonçalves et al. 2018). To address potential confounding from exposure to higher levels of fine particulate matter ($PM_{2.5}$) from controlled burning activities (Pratt et al. 2022), we reran the analysis excluding 1,997 workers with higher burning exposures. We also conducted analyses using an alternative definition of CHD-related deaths based on ischemic heart disease as a *contributing/underlying* cause rather than the *underlying* cause of death. In addition, we attempted to examine non-fatal MI and fatal CHD as separate outcomes; however, we could not examine fatal CHD as the outcome because of the small number of fatal cases. Workers with fatal (CHD) events that occurred after OSRC employment but before they could enroll were not identified. We explored the impact of this left truncation in a sensitivity analysis by starting the risk period at study enrollment, effectively excluding 129 pre-enrollment CHD events. To follow up on the analysis of Strelitz et al. (2019b), which used an earlier, *ordinal* classification of the single maximum THC exposure and observed participants only through the first follow-up interview, we conducted a similar analysis using the newly developed *quantitative* single maximum THC exposure (categorized in quintiles) and observed participants for both the same and the extended time period (until Dec 2019). Lastly, to capture milder forms of CHD that could progress to MIs and might have been related to the exposures, we performed an analysis that included as events participants who reported a physician-diagnosed blockage in the arteries

of the heart as well as all events in the main analysis.

In an exploratory analysis, we also considered the impact of short-term exposure to higher exposure levels by exploring risks associated with having exposures in the top 20th and 15th percentile of the single maximum exposure for a minimum of 7 or 14 days compared to having daily maximum exposures in the lowest quintile.

We used quantile g-computation (Keil et al. 2020) to estimate the joint effect of BTEX-H as a *mixture* on the risk of CHD events (more details in Supplemental Text S1). We implemented this method using a Cox proportional hazards model of CHD against all components of the BTEX-H mixture, each modeled as quintile scores, and conditional on the same covariates used in single-agent models (White et al. 2020). As in previous analyses, we applied IP-censoring weights. Quantile g-computation was performed using R 4.0.4 package "qgcomp".

All other analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). An alpha level of 0.05 was considered statistically significant for all analyses.

4.3 Results

Compared to the full analytical sample (N=22,655), those who completed the first (N=15,627) or second (N=10,638) follow-up interviews tended to be older, female, White, and former or never smokers (Table 1). They were also more likely to have graduated from a 4-year college and to reside outside the Gulf states. There was no substantive difference in the other characteristics. Workers in the full analytical sample were exposed to crude oil for a median 4 months (range: 1 day-15 months).

During a median follow-up of 58 months (range: 1-116 months) beginning after each worker's last date of cleanup work, 509 out of 22,655 workers experienced an incident CHD event. This

included 428 cases of non-fatal MI, 7 cases of non-fatal MI with a later fatal CHD event, and 74 fatal CHD events without a history of reported MI.

In the IP-censoring weighted analysis, we saw modest increases in risk of CHD among those in the top quintile of cumulative daily maximum exposure to each agent compared to workers in the referent group (range of HR: 1.19-1.44), with the highest and significant HRs observed for THC (HR=1.42, 95%CI: 1.01, 2.01) and benzene (HR=1.44, 95%CI: 1.02, 2.02) (Table 2). We also saw elevated risks in the second and/or third quintiles for some exposure agents, but there were no apparent exposure-response trends and tests of trend were nonsignificant. Similar patterns of association were seen for cumulative daily *average* exposures (Table 3). The mean and range of the stabilized IP weights for each cumulative exposure are shown in Table 9.

Among ever smokers, we observed increased risk of CHD in the top quintile of exposure to all agents, including statistically significant increases for THC (HR=1.92, 95%CI: 1.25, 2.97) and benzene (HR=1.52, 95%CI: 1.00, 2.33) (Table 4). Among never smokers, we found elevated HRs in the top quintile of benzene, xylene, and n-hexane exposures, although none of the associations were statistically significant. When we stratified analyses by education, associations for all agents were more pronounced among workers with high school education or less than among those with more than high school education (Table 5). In analyses stratified by BMI, we observed stronger associations among workers who were non-obese compared to the obese (Table 6). In this subgroup, we saw significantly elevated HRs among workers in the top quintile of exposure to THC (HR=2.27, 95%CI: 1.44, 3.56) and benzene (HR=1.79, 95%CI: 1.10, 2.92).

We observed similar results in sensitivity analyses in which we, separately, accounted for pre-cleanup hypertension (Tables 10), included fatal events with CHD as a

contributing/underlying cause of death (Table 11), or limited the outcome to non-fatal MI (Table 12). Results were also similar when we began follow-up at the time of enrollment instead of after each worker's last date of cleanup work (Table 13). The analysis that excluded workers who had higher $PM_{2.5}$ exposure from controlled burning produced somewhat attenuated effect estimates, especially in the top quintile, but results were not substantively different (Table 14). For comparison with previously published results from this cohort, we observed elevated HRs in all upper quintiles of single maximum THC exposure in relation to CHD events accrued until the first follow-up interview and similar risk estimates when follow-up was extended to Dec 2019 (Table 15). In the sensitivity analysis where we also included as cases workers who reported being diagnosed with a blockage in the arteries of the heart, we observed somewhat attenuated associations (Table 16).

In the sub-analysis exploring risk of CHD among workers who had higher daily exposures for varying numbers of days, we observed non-significantly elevated HRs compared to workers who had consistently lower daily exposures (Table 17). As we increased the thresholds for daily exposure level from top 20^{th} to top 15^{th} percentile of single maximum exposure and for exposure duration from ≥7 to ≥14 days, we observed stronger effects for toluene but no noticeable changes in association for the other agents.

When we assessed the joint effect of the BTEX-H mixture using quantile g-computation, we found a negligible association for a per quintile increase in the entire mixture on CHD incidence (Table 7). A one quintile increase in cumulative daily maximum exposure and cumulative daily average exposure to all chemicals was associated with an increased risk of CHD of 1.03 (95% CI: 0.96, 1.10) and 1.02 (95% CI: 0.95, 1.09), respectively (Table 7). Single-agent models that examined per quintile increase in exposures showed effect estimates of similar

magnitude (Tables 2 and 3).

4.4 Discussion

In this study, we examined the relationship between exposure to THC and BTEX-H and risk of CHD among oil spill workers up to ten years after the *DWH* disaster. We observed a modest increase in risk of CHD among workers in the top quintile of cumulative exposure to these agents. Although associations for most exposure agents were not statistically significant, the magnitude of the effect in the highest exposure quintile in the main analysis was clinically meaningful and comparable to the increase in CHD risk from secondhand smoke exposure among non-smokers (relative risk: 1.3), as estimated in a meta-analysis (He et al. 1999). In subgroup analyses, effect estimates were more pronounced among ever smokers, workers who had high school education or less, and workers who were not obese. In these subgroups, effect estimates in the top quintile of exposure to some agents were approaching the increase in risk of CHD comparing individuals who smoked one cigarette per day to never smokers (relative risk: 1.48-1.57), as reported in a recent, large meta-analysis (Hackshaw et al. 2018).

Several epidemiologic studies have assessed ambient levels of volatile hydrocarbons in relation to CHD events (Barceló et al. 2016; Ran et al. 2018b; Tsai et al. 2010). Unlike these air pollution studies, which assessed exposure either across several days or over a year, most workers in our study were exposed to BTEX-H for several months. The maximum exposure levels experienced by workers in our study were generally higher than those reported in these air pollution studies, but were well below occupational guidelines set by the American Conference of Governmental Industrial Hygienists (ACGIH 2012). Differences in exposure duration, emission source, and length of follow-up limits a direct comparison of our effect estimates with those of the other studies.

Among studies that focused on a longer exposure window, Barceló et al. (2016) reported higher risk of MI mortality for an increase in annual average daily levels of benzene, which is consistent with our results. Our analyses addressed limitations in this prior study by accounting for covariates such as education and smoking. Moreover, the longer follow-up time in our study allowed us to observe the sustained effect many years after exposure. Self-reported MI was also associated with annual mean concentrations of benzene among residents in an industrial area of Estonia, but interpretation of the findings was limited by the cross-sectional study design (Orru et al. 2018).

Studies that focused on short-term exposures have also shown modest acute effects on cardiovascular health, including positive associations of benzene exposure across several days with MI occurrence (Bard et al. 2014) and emergency hospitalizations for heart failure (Ran et al. 2018b), and of benzene and alkylbenzene concentrations with circulatory mortality (Ran et al. 2018a; Tsai et al. 2010). These latter two studies have also associated acute cardiovascular events with exposure to alkanes (Ran et al. 2018b; Tsai et al. 2010), but we are unaware of any study that examined the alkane n-hexane specifically. In our analysis, we were underpowered to examine acute effects of exposure because only 22 (non-fatal) CHD events occurred within a month of the individuals' last day of cleanup work, and we lacked data on pre-enrollment fatal CHD events. Overall, however, results of our study add to existing evidence that exposure to BTEX-H is associated with a modest increase in risk of CHD even at levels below the occupational limits, with a potential for persistent effects years after exposure.

As closely related volatile components of the crude oil, BTEX-H are present in gasolines and used as solvents and industrial raw materials for manufacturing of consumer products (ATSDR 1999b, 2000, 2007a, b, 2010). All of these hydrocarbons have been detected at varying

levels in vehicular exhaust, near sites of oil/gas operations and gas stations, and in certain occupational settings (Bogadi-Sare et al. 2000; Fujita et al. 2011; Gilman et al. 2013; Heibati et al. 2017; Wilson et al. 2007; Xiong et al. 2016). Because individuals are typically exposed to many or all of these chemicals simultaneously, estimating the overall mixture effect can help inform interventions that target the emission sources. To our knowledge, only one study has examined the joint effect of specific crude oil chemical groups in relation to acute cardiovascular events. Ye et al. (2017) investigated emergency department visits for cardiovascular diseases and same-day exposure to pre-specified chemical groups and found significant associations for most hydrocarbon groups although not for the aromatic group (which contains BTEX). In our mixture analysis, we also found little evidence of a joint effect for BTEX-H. Compared to single-agent models that examined per quintile increase in each exposure, effects in the mixture model were not noticeably stronger. The overall weak associations in the mixture analysis and its single-agent counterparts could be attributed to the apparent non-linear relationship between the exposure and the outcome, where effects were present only above an exposure threshold (e.g. in Q5). Because other ambient pollution studies only examined exposures continuously, it is unclear whether a threshold effect existed in those other studies.

To our knowledge, our study is the first to investigate quantitative BTEX-H exposures and risk of CHD in an occupational setting. Compared to effect estimates from an earlier analysis of this cohort that used an ordinal measure of single *maximum* THC exposure (without regards to duration) and followed participants only through 2014 (Strelitz et al. 2019b), our estimates with the quantitative *cumulative* THC exposure was lower. The stronger associations observed for the single maximum THC exposure suggests that exposure to crude oil chemicals at a high intensity might have induced irreversible damage to the cardiovascular system that increased workers' risk

of CHD over time. Workers with higher single maximum exposure, however, also tended to have higher cumulative exposures. In analyses that further assessed the role of exposure *intensity* in CHD risk by comparing workers exposed to higher daily maximum exposures for varying number of days to those with consistently lower daily exposures, increasing the threshold of exposure intensity or exposure duration led to stronger effect estimates for toluene, but no meaningful changes in associations were observed for the other exposure agents.

Because smoking could induce adverse cardiovascular effects via similar biological pathways as air pollutants, and thus enhance the effects of other air pollutants (National Center for Chronic Disease et al. 2014), we carried out analyses stratified by cigarette smoking status. We saw elevated risks in the top quintile of exposure to most agents in both ever and never smokers, although effects were generally more pronounced among ever smokers.

In analysis stratified by highest educational attainment, we found stronger effects in the subgroup with no more than high school education. This finding is consistent with two studies that found stronger associations between traffic-related air pollution and cardiovascular mortality among participants with lower educational attainment (Beelen et al. 2008; Ostro et al. 2008). Because lower education has been associated with lack of access to healthy food, participation in less leisure time physical activity, and lower neighborhood air quality (Droomers et al. 2001; Hajat et al. 2013; Larson et al. 2009), the adverse effects of crude oil exposures might have been exacerbated by detrimental lifestyle and environmental factors among workers with less educational attainment (Bhatnagar 2017; Kraus et al. 2019; Romieu et al. 2005).

As a major risk factor for cardiometabolic diseases, obesity could potentially increase air pollution-related health effects because of persistent obesity-induced low-grade inflammation (Lumeng and Saltiel 2011) and higher particle deposition in the lung from higher breathing rates

and tidal volumes among obese people (Brochu et al. 2014; Graham et al. 1990; Matos et al. 2012). However, in stratified analysis, we observed elevated HRs among workers with higher exposure to all agents in the non-obese subgroup, with generally weaker associations in the obese subgroup. One possible explanation for the weaker associations among the obese group is that variability of CHD risk is likely higher among these workers, so it is easy for the modest effect of oil exposures to be lost among this high variability. We hypothesize the risk to vary more among obese workers because their baseline risk was higher (Bogers et al. 2007), so lifestyle factors, such as physical activities, would have a larger impact to alter each individual's overall risk of CHD (Koolhaas et al. 2017). Also, obese workers were more likely to have other cardiovascular comorbidities (Powell-Wiley et al. 2021), which would also lead to variability in CHD risk among this group. We were not able to account for all the lifestyle and health factors (e.g. diet, physical activity, cholesterol levels) that could have led to the wider range of risks in the obese group.

Two major mechanisms underlying air pollution-mediated CHD risk have been proposed. One involves activation of pulmonary and systemic inflammatory responses by inhaled pollutants (Brook et al. 2004; U.S. EPA 2020). This inflammation and associated oxidative stress can impair endothelial function and stimulate the circulatory release of inflammatory proteins and coagulation factors, which can either predispose individuals to a future CHD event by promoting atherosclerosis or trigger an acute CHD event by destabilizing existing plaques (Brook et al. 2004; U.S. EPA 2020). Indeed, elevated levels of oxidative stress and inflammation have been found in animals and humans exposed to BTEX-H (Khedun et al. 1996; Moro et al. 2010; Shima et al. 2006; Uzma et al. 2010; Xiong et al. 2016). The other mechanism involves modulation of the autonomic nervous system by pollutants trapped in the respiratory tract (Brook

et al. 2004; U.S. EPA 2020). A shift of the system towards the sympathetic tone elevates blood pressure, which can exacerbate atherosclerosis and lead to a CHD event via vascular dysfunction or arrhythmia (U.S. EPA 2020). Consistent with this mechanism, occupational studies have associated hypertension and electrocardiographic abnormalities with working in an environment that exposed workers to BTEX-H chemicals (Attarchi et al. 2013; Chang et al. 2009; Kotseva and Popov 1998). Among GuLF Study participants, cumulative THC exposure was associated with increased risk of hypertension 1-3 years after the spill (Kwok et al. 2022). Together, current mechanistic understanding supports the plausibility of the observed cardiovascular effects of exposure to THC and BTEX-H.

A major strength of our study is the careful reconstruction of THC and BTEX-H exposures using personal air samples collected on the OSRC workers, as well as detailed work histories collected from the study participants. In addition, while most air pollution studies examined CHD events immediately following either acute (days) or long-term (years) exposures, our study was unique in assessing medium-duration exposures that lasted weeks to a few months and persistent cardiovascular effects many years after cessation of exposure. Another strength of the study is the use of IP-censoring weights to account for potential informative censoring due to loss to follow-up. Associations were similar in the IP-weighted models and models without weights, suggesting that our results are robust to the potential bias from informative censoring. Lastly, subject-specific data on education, BMI, and smoking status allowed us to perform stratified analyses by these traits to identify groups that might be particularly vulnerable to the effects of these exposures. We are unaware of any studies of crude oil chemicals and CHD that have examined these effect measure modifiers.

One limitation of the study is potential misclassification of the outcome, as we could not

obtain medical records from participants to confirm their MI diagnosis or cause of death. Previous studies have reported moderate to high accuracy of self-reported MI and of death certificate diagnosis of CHD, with sensitivities ranging from 0.78 to 0.98 and specificities varying from 0.72 to 1.0 (Barr et al. 2009; Coady et al. 2001; Eliassen et al. 2016; Folsom et al. 1987; Fourrier-Réglat et al. 2010; Goraya et al. 2000; Lloyd-Jones et al. 1998; Machón et al. 2013; Okura et al. 2004; Yamagishi et al. 2009). Many of these studies have associated lower accuracy with older age (Lloyd-Jones et al. 1998; Okura et al. 2004; Olubowale et al. 2017; Yamagishi et al. 2009). Compared to participants examined in these validation studies, workers in our study were younger (most were < 60 years old at enrollment), so we expect a lower degree of outcome misclassification in our population. There could be measurement error in the reported event time due to participants mis-recalling the date of MI diagnosis. However, exploratory analyses (not shown) in which we coarsened the follow-up from one month to four months showed no notable changes from the main analysis results, which suggests that our analysis was robust to measurement error of at least a few months in recall time.

Second, the exposure estimates assigned to workers contain some degree of uncertainty, (Stewart et al. 2022); however, we do not expect these measurement errors to substantially bias our estimates in the categorical exposure analyses. Another possible source of exposure misclassification is that while many participants worked on multiple jobs/tasks during the cleanup, we do not have information on which days and how much time in a day they spent on each job/activity, which increased uncertainty in the estimates of daily exposures. To overcome this limitation, we examined both cumulative daily maximum and cumulative daily average exposures and found similar results.

Third, in our analysis, we were not able to identify CHD deaths that occurred among

OSRC workers between exposure and study enrollment because enrollment was contingent upon survival. If more CHD deaths occurred before enrollment among *DWH* oil spill workers exposed to higher levels of crude oil chemicals, our results might have underestimated the true risk. However, given the relatively short time between exposure and enrollment (i.e. immortal time for the fatal outcome), the overall small number of fatal CHD cases during the entire follow-up, and the continued risk over the years of observation, we do not expect left truncation of these fatal events to meaningfully change our results. In a sub-analysis, we examined non-fatal CHD as the outcome, for which there was no immortal time bias, and observed similar associations. In another analysis, we explored the impact of starting follow-up at a worker's enrollment in the cohort, rather than after the last day of their cleanup work, and observed slightly attenuated associations.

Lastly, there could be bias from unmeasured confounders or imperfect measurement of existing covariates in the models. We did not measure, and were thus unable to account for, co-exposure to other occupational exposures (Middlebrook et al. 2012). In a sensitivity analysis, we accounted for one important occupational exposure, $PM_{2.5}$ from controlled burning, by excluding workers who experienced higher $PM_{2.5}$ exposure and found somewhat attenuated results. The majority of workers who had higher $PM_{2.5}$ exposure were also exposed to higher levels of THC and BTEX-H (proportion in Q4 or Q5: 71-91% by exposure agent). It is likely that workers who were exposed to both higher burning-related $PM_{2.5}$ and crude oil chemicals had even higher risks of CHD, but we had few cases to examine associations among this subgroup or to adjust for $PM_{2.5}$ exposure levels. There could also be a bias if workers were assigned to different jobs/activities based on their health factors at the time of spill that were predictive of their future CHD risk. We adjusted for several indicators of baseline health (BMI, pre-cleanup diabetes, pre-

cleanup hypertension, smoking) to reduce this potential bias. We used self-reported race, ethnicity, and education as proxies for the downstream effects of socioeconomic disparities that might influence risk of CHD, but had to combine some categories due to small numbers. Lastly, some of our adjustment factors, such as cigarette smoking and BMI, were ascertained at enrollment as proxies for factors at the time of exposure and might have changed over time. However, we expect little change in these factors over the short span between exposure and time of their ascertainment.

Our study showed modestly increased risk of CHD among oil spill workers exposed to higher levels of THC and BTEX-H. Findings were consistent with evidence from ambient air pollution research indicating that exposure to these agents at levels below occupational guidelines may induce adverse cardiovascular effects. To our knowledge, our study is the first to evaluate the relationship between exposure to individual crude oil chemicals and risk of CHD in the occupational setting. We further showed stronger associations in some subgroups, i.e. ever smokers, workers who had high school education or less, and workers who were not obese. Additional research is needed in other populations and settings to confirm these study findings.

4.5 Tables and Figures

Table 1. Characteristics of *DWH* disaster oil spill workers who responded to the enrollment, first follow-up, and second follow-up interviews, respectively

Characteristic	**Enrollment[a]** *(n=22,655)*	**1st Follow-up[b]** *(n=15,627)*	**2nd Follow-up[c]** *(n=10,638)*
	n (%)	*n (%)*	*n (%)*
Age at enrollment (y)			
20-29	4803 (21.2)	2822 (18.1)	1782 (16.8)
30-39	5586 (24.7)	3567 (22.8)	2304 (21.7)
40-49	5585 (24.7)	3973 (25.4)	2708 (25.5)
50-59	4762 (21.0)	3703 (23.7)	2666 (25.1)
>=60	1919 (8.5)	1562 (10.0)	1178 (11.1)
Gender			
Male	18627 (82.2)	12736 (81.5)	8548 (80.4)
Female	4028 (17.8)	2891 (18.5)	2090 (19.7)
Race			
White	15066 (66.5)	10550 (67.5)	7649 (71.9)
Black	5303 (23.4)	3550 (22.7)	2043 (19.2)
Other/multiracial	2286 (10.1)	1527 (9.8)	946 (8.9)
Hispanic ethnicity			
No	21141 (93.3)	14632 (93.6)	10023 (94.2)
Yes	1514 (6.7)	995 (6.4)	615 (5.8)
Educational attainment			
Less than high school	3470 (15.3)	2210 (14.1)	1207 (11.4)
High school diploma/GED	6697 (29.6)	4358 (27.9)	2697 (25.4)
Some college/2-year degree	6851 (30.2)	4719 (30.2)	3238 (30.4)
4-year college graduate or more	5637 (24.9)	4340 (27.8)	3496 (32.9)
Weight classification			
Underweight or normal (BMI < 25)	6146 (27.1)	4131 (26.4)	2746 (25.8)
Overweight (25 ≤ BMI < 30)	9419 (41.6)	6516 (41.7)	4534 (42.6)
Obese I (30 ≤ BMI < 35)	4633 (20.5)	3234 (20.7)	2198 (20.7)

Obese II (BMI ≥ 35)	2457 (10.9)	1746 (11.2)	1160 (10.9)
Reported pre-cleanup diabetes diagnosis			
No	21621 (95.4)	14851 (95.0)	10124 (95.2)
Yes	1034 (4.6)	776 (5.0)	514 (4.8)
Reported pre-spill hypertension diagnosis			
Missing	376 (1.7)	270 (1.7)	173 (1.6)
No	18245 (80.5)	12365 (79.1)	8373 (78.7)
Yes	4034 (17.8)	2992 (19.2)	2092 (19.7)
Smoking status			
Current heavy smoker (≥ 20 cigarettes/d)	2266 (10.0)	1455 (9.3)	845 (7.9)
Current light smoker (< 20 cigarettes/d)	4524 (20.0)	2883 (18.5)	1717 (16.1)
Former smoker	4783 (21.1)	3431 (22.0)	2467 (23.2)
Never smoked	11082 (48.9)	7858 (50.3)	5609 (52.7)
Residential county proximity to Gulf of Mexico[d]			
Direct or indirect contact	13339 (58.9)	8946 (57.3)	5733 (53.9)
Other Gulf state residence	4639 (20.5)	3138 (20.1)	2153 (20.2)
Non-Gulf state residence	4677 (20.6)	3543 (22.7)	2752 (25.9)
Previous oil spill cleanup work			
No	19809 (87.4)	13524 (86.5)	9110 (85.6)
Yes	2846 (12.6)	2103 (13.5)	1528 (14.4)
Previous oil industry experience			
No	19113 (84.4)	13108 (83.9)	8971 (84.3)
Yes	3542 (15.6)	2519 (16.1)	1667 (15.7)

Abbreviations: *DWH*, *Deepwater Horizon*; GED, General Equivalency Diploma; BMI, body mass index

[a]March 2011 to May 2013

[b]May 2013 to April 2016

[c]November 2017 to July 2021

[d]Direct proximity is defined as living in a county directly adjacent to the Gulf of Mexico; indirect is defined as living in a county adjacent to coastal counties

Table 2. Associations between cumulative daily maximum exposures to crude oil chemicals and incident CHD events among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure		Total Cases (n=509)	Total N (n=22,655)	No censoring weights[a]	IP-censoring weighted[a,b]
				HR (95% CI)	HR (95% CI)
THC, ppm-days	Q1 (<7)	75	4531	Referent	Referent
	Q2 (7-31)	111	4531	1.25 (0.91, 1.73)	1.29 (0.92, 1.80)
	Q3 (31-75)	105	4531	1.17 (0.85, 1.62)	1.19 (0.85, 1.66)
	Q4 (75-167)	102	4531	1.17 (0.85, 1.63)	1.18 (0.84, 1.66)
	Q5 (167-1244)	116	4531	1.42 (1.01, 1.99)	1.42 (1.01, 2.01)
	Per ln(ppm-day) increase			1.05 (1.00, 1.10)	1.05 (1.00, 1.10)
Benzene, ppb-days	Q1 (<34)	73	4531	Referent	Referent
	Q2 (34-188)	113	4531	1.29 (0.92, 1.79)	1.29 (0.92, 1.82)
	Q3 (188-494)	113	4531	1.31 (0.94, 1.82)	1.30 (0.92, 1.83)
	Q4 (494-1196)	81	4531	0.90 (0.63, 1.28)	0.89 (0.62, 1.28)
	Q5 (1196-10592)	129	4531	1.44 (1.03, 2.00)	1.44 (1.02, 2.02)
	Per ln(ppb-day) increase			1.04 (0.99, 1.08)	1.04 (1.00, 1.09)
	Per quintile increase[c]			1.03 (0.96, 1.10)	1.03 (0.96, 1.10)
Toluene, ppb-days	Q1 (<120)	80	4531	Referent	Referent
	Q2 (120-758)	109	4531	1.17 (0.85, 1.61)	1.19 (0.86, 1.66)
	Q3 (758-1992)	99	4531	1.02 (0.74, 1.41)	1.01 (0.72, 1.42)
	Q4 (1992-4399)	92	4531	0.92 (0.66, 1.28)	0.90 (0.64, 1.27)
	Q5 (4399-29657)	129	4531	1.24 (0.90, 1.71)	1.26 (0.91, 1.74)
	Per ln(ppb-day) increase			1.04 (0.99, 1.09)	1.04 (0.99, 1.09)
	Per quintile increase[c]			1.02 (0.95, 1.09)	1.01 (0.95, 1.09)
Ethylbenzene, ppb-days	Q1 (<30)	83	4531	Referent	Referent
	Q2 (30-153)	104	4531	1.00 (0.73, 1.38)	1.02 (0.73, 1.43)
	Q3 (153-381)	114	4531	1.12 (0.82, 1.53)	1.10 (0.79, 1.52)
	Q4 (381-934)	93	4531	0.87 (0.63, 1.21)	0.87 (0.62, 1.21)

	Q5 (934-8130)	115	4531	1.18 (0.85, 1.64)	1.19 (0.85, 1.66)
	Per ln(ppb-day) increase			1.03 (0.99, 1.08)	1.04 (0.99, 1.08)
	Per quintile increase[c]			1.01 (0.94, 1.08)	1.01 (0.94, 1.08)
Xylene, ppb-days	Q1 (<524)	87	4533	Referent	Referent
	Q2 (524-1240)	104	4529	1.10 (0.81, 1.48)	1.12 (0.82, 1.52)
	Q3 (1240-2450)	110	4531	1.15 (0.85, 1.54)	1.16 (0.85, 1.57)
	Q4 (2450-4916)	90	4531	0.86 (0.63, 1.17)	0.87 (0.64, 1.19)
	Q5 (4918-24936)	118	4531	1.23 (0.90, 1.67)	1.25 (0.91, 1.70)
	Per ln(ppb-day) increase			1.04 (0.97, 1.11)	1.04 (0.97, 1.11)
	Per quintile increase[c]			1.02 (0.95, 1.09)	1.02 (0.95, 1.09)
n-Hexane, ppb-days	Q1 (<55)	75	4531	Referent	Referent
	Q2 (55-310)	100	4531	1.08 (0.77, 1.51)	1.10 (0.77, 1.56)
	Q3 (310-959)	115	4531	1.25 (0.90, 1.74)	1.24 (0.88, 1.74)
	Q4 (960-3332)	102	4531	0.99 (0.71, 1.39)	1.00 (0.71, 1.42)
	Q5 (3334-90158)	117	4531	1.34 (0.95, 1.88)	1.34 (0.94, 1.91)
	Per ln(ppb-day) increase			1.03 (0.99, 1.08)	1.04 (1.00, 1.08)
	Per quintile increase[c]			1.04 (0.97, 1.12)	1.04 (0.97, 1.12)

Abbreviations: CHD, coronary heart disease; *DWH*, *Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; IP, inverse probability; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]Censoring weights accounted for exposure, age, gender, race, ethnicity, smoking, education, residential proximity to the Gulf of Mexico, and previous oil spill cleanup work

[c]Analysis performed only for comparison with the mixture model. Each exposure quintile was assigned an integer score (Q1=1, Q2=2, Q3=3, Q4=4, and Q5=5).

Table 3. Associations between cumulative daily average exposures to crude oil chemicals and incident CHD events among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure		Total Cases (n=509)	Total N (n=22,655)	No censoring weights[a]	IP-censoring weighted[a,b]
				HR (95% CI)	HR (95% CI)
THC, ppm-days	Q1 (<6)	88	4533	Referent	Referent
	Q2 (6-19)	106	4529	1.07 (0.79, 1.44)	1.08 (0.79, 1.47)
	Q3 (19-45)	97	4531	0.93 (0.68, 1.26)	0.92 (0.67, 1.26)
	Q4 (45-87)	104	4531	1.00 (0.74, 1.35)	1.00 (0.73, 1.36)
	Q5 (87-761)	114	4531	1.20 (0.88, 1.64)	1.21 (0.88, 1.66)
	Per ln(ppm-day) increase			1.04 (0.99, 1.11)	1.05 (0.99, 1.11)
Benzene, ppb-days	Q1 (<23)	74	4533	Referent	Referent
	Q2 (23-116)	112	4529	1.33 (0.96, 1.85)	1.35 (0.96, 1.91)
	Q3 (116-270)	116	4531	1.30 (0.94, 1.80)	1.31 (0.93, 1.83)
	Q4 (270-599)	81	4531	0.91 (0.64, 1.29)	0.91 (0.64, 1.30)
	Q5 (599-7744)	126	4531	1.36 (0.98, 1.91)	1.39 (0.99, 1.97)
	Per ln(ppb-day) increase			1.03 (0.99, 1.08)	1.03 (0.99, 1.08)
	Per quintile increase[c]			1.02 (0.95, 1.09)	1.02 (0.95, 1.09)
Toluene, ppb-days	Q1 (<85)	84	4531	Referent	Referent
	Q2 (85-439)	106	4531	1.08 (0.79, 1.49)	1.10 (0.79, 1.53)
	Q3 (440-1092)	105	4531	1.04 (0.76, 1.43)	1.04 (0.75, 1.44)
	Q4 (1092-2219)	83	4531	0.77 (0.55, 1.07)	0.79 (0.56, 1.11)
	Q5 (2219-18068)	131	4531	1.26 (0.90, 1.76)	1.26 (0.90, 1.77)
	Per ln(ppb-day) increase			1.03 (0.97, 1.08)	1.03 (0.98, 1.08)
	Per quintile increase[c]			1.02 (0.94, 1.10)	1.02 (0.95, 1.10)
Ethylbenzene, ppb-days	Q1 (<19)	82	4531	Referent	Referent
	Q2 (19-99)	103	4531	1.08 (0.79, 1.49)	1.09 (0.79, 1.52)
	Q3 (99-218)	116	4531	1.16 (0.85, 1.59)	1.15 (0.84, 1.59)
	Q4 (218-456)	95	4531	0.93 (0.67, 1.29)	0.95 (0.68, 1.33)

	Q5 (456-8082)	113	4531	1.21 (0.87, 1.68)	1.22 (0.87, 1.71)
	Per ln(ppb-day) increase			1.03 (0.98, 1.09)	1.04 (0.99, 1.09)
	Per quintile increase[c]			1.01 (0.94, 1.08)	1.01 (0.95, 1.09)
Xylene, ppb-days	Q1 (<430)	99	4531	Referent	Referent
	Q2 (431-909)	97	4531	0.88 (0.65, 1.17)	0.90 (0.67, 1.22)
	Q3 (909-1613)	97	4534	0.88 (0.66, 1.18)	0.91 (0.68, 1.22)
	Q4 (1613-2770)	94	4528	0.79 (0.59, 1.07)	0.81 (0.61, 1.10)
	Q5 (2770-24413)	122	4531	1.11 (0.83, 1.49)	1.14 (0.85, 1.53)
	Per ln(ppb-day) increase			1.02 (0.95, 1.10)	1.03 (0.95, 1.11)
	Per quintile increase[c]			1.01 (0.94, 1.09)	1.01 (0.95, 1.09)
n-Hexane, ppb-days	Q1 (<39)	76	4577	Referent	Referent
	Q2 (39-181)	108	4485	1.21 (0.87, 1.68)	1.19 (0.84, 1.67)
	Q3 (181-505)	101	4531	1.07 (0.77, 1.49)	1.06 (0.75, 1.50)
	Q4 (505-1508)	106	4531	1.03 (0.74, 1.43)	1.03 (0.73, 1.46)
	Q5 (1508-62717)	118	4531	1.32 (0.94, 1.85)	1.31 (0.92, 1.86)
	Per ln(ppb-day) increase			1.03 (0.98, 1.08)	1.03 (0.99, 1.08)
	Per quintile increase[c]			1.03 (0.96, 1.10)	1.04 (0.97, 1.11)

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; IP, inverse probability; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]Censoring weights accounted for exposure, age, gender, race, ethnicity, smoking, education, residential proximity to the Gulf of Mexico, and previous oil spill cleanup work

[c]Analysis performed only for comparison with the mixture model. Each exposure quintile was assigned an integer score (Q1=1, Q2=2, Q3=3, Q4=4, and Q5=5).

Table 4. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by smoking status among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure		Total Cases (n=337)	Total N (n=11,573)	Ever smokers[a] HR (95% CI)	Total Cases (n=172)	Total N (n=11,082)	Never smokers[a] HR (95% CI)	Interaction p
THC, ppm-days	Q1	40	1850	Referent	35	2681	Referent	0.10
	Q2	78	2307	1.81 (1.19, 2.76)	33	2224	0.74 (0.42, 1.28)	
	Q3	71	2392	1.55 (1.02, 2.37)	34	2139	0.82 (0.48, 1.42)	
	Q4	68	2472	1.50 (0.98, 2.30)	34	2059	0.88 (0.51, 1.52)	
	Q5	80	2552	1.92 (1.25, 2.97)	36	1979	0.88 (0.51, 1.53)	
	Per ln(ppm-day) increase			1.05 (0.99, 1.13)			1.05 (0.97, 1.13)	
Benzene, ppb-days	Q1	42	1806	Referent	31	2725	Referent	0.86
	Q2	73	2345	1.34 (0.87, 2.06)	40	2186	1.27 (0.74, 2.19)	
	Q3	79	2335	1.47 (0.96, 2.24)	34	2196	1.06 (0.61, 1.86)	
	Q4	56	2462	0.93 (0.60, 1.46)	25	2069	0.88 (0.48, 1.61)	
	Q5	87	2625	1.52 (1.00, 2.33)	42	1906	1.34 (0.77, 2.32)	
	Per ln(ppb-day) increase			1.04 (0.98, 1.09)			1.05 (0.98, 1.13)	
Toluene, ppb-days	Q1	48	1823	Referent	32	2708	Referent	0.63
	Q2	69	2288	1.17 (0.77, 1.78)	40	2243	1.27 (0.74, 2.18)	
	Q3	70	2326	1.11 (0.73, 1.67)	29	2205	0.89 (0.51, 1.58)	
	Q4	58	2516	0.87 (0.56, 1.33)	34	2015	1.02 (0.59, 1.79)	
	Q5	92	2620	1.37 (0.92, 2.05)	37	1911	1.09 (0.63, 1.91)	
	Per ln(ppb-day) increase			1.05 (0.98, 1.11)			1.05 (0.98, 1.13)	
Ethylbenzene, ppb-days	Q1	49	1820	Referent	34	2711	Referent	0.53
	Q2	71	2337	1.07 (0.71, 1.62)	33	2194	0.95 (0.55, 1.64)	
	Q3	71	2369	1.01 (0.67, 1.52)	43	2162	1.32 (0.79, 2.22)	

	Q4	65	2447	0.94 (0.62, 1.43)	28	2084	0.78 (0.44, 1.39)	
	Q5	81	2600	1.24 (0.82, 1.89)	34	1931	1.11 (0.64, 1.92)	
	Per ln(ppb-day) increase			1.04 (0.98, 1.10)			1.03 (0.97, 1.11)	
Xylene, ppb-days	Q1	55	1988	Referent	32	2545	Referent	0.81
	Q2	67	2207	1.15 (0.78, 1.68)	37	2322	1.22 (0.73, 2.04)	
	Q3	68	2305	1.07 (0.74, 1.57)	42	2226	1.43 (0.86, 2.36)	
	Q4	63	2477	0.91 (0.62, 1.34)	27	2054	0.87 (0.50, 1.52)	
	Q5	84	2596	1.30 (0.89, 1.89)	34	1935	1.22 (0.71, 2.07)	
	Per ln(ppb-day) increase			1.05 (0.96, 1.15)			1.05 (0.94, 1.18)	
n-Hexane, ppb-days	Q1	43	1816	Referent	32	2715	Referent	0.98
	Q2	63	2281	1.11 (0.71, 1.73)	37	2250	1.11 (0.64, 1.93)	
	Q3	78	2426	1.31 (0.85, 2.01)	37	2105	1.15 (0.66, 2.00)	
	Q4	71	2488	1.12 (0.73, 1.73)	31	2043	0.87 (0.49, 1.56)	
	Q5	82	2562	1.46 (0.94, 2.27)	35	1969	1.20 (0.68, 2.12)	
	Per ln(ppb-day) increase			1.06 (1.00, 1.12)			1.02 (0.96, 1.08)	

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

Table 5. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by highest education attained among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure		Total Cases (n=293)	Total N (n=10,167)	High school or less[a]	Total Cases (n=216)	Total N (n=12,488)	More than high school[a]	Interaction p
				HR (95% CI)			HR (95% CI)	
THC, ppm-days	Q1	25	1186	Referent	50	3345	Referent	0.16
	Q2	63	2044	1.62 (0.98, 2.68)	48	2487	0.97 (0.62, 1.53)	
	Q3	61	2167	1.50 (0.91, 2.48)	44	2364	0.90 (0.57, 1.42)	
	Q4	74	2298	1.73 (1.06, 2.82)	28	2233	0.66 (0.40, 1.10)	
	Q5	70	2472	1.72 (1.04, 2.84)	46	2059	1.15 (0.71, 1.88)	
	Per ln(ppm-day) increase			1.07 (0.99, 1.16)			1.00 (0.93, 1.08)	
Benzene, ppb-days	Q1	24	1093	Referent	49	3438	Referent	0.64
	Q2	67	2104	1.61 (0.98, 2.66)	46	2427	1.00 (0.63, 1.59)	
	Q3	65	2124	1.55 (0.94, 2.56)	48	2407	1.04 (0.66, 1.64)	
	Q4	49	2283	1.01 (0.60, 1.70)	32	2248	0.75 (0.45, 1.25)	
	Q5	88	2563	1.84 (1.13, 3.01)	41	1968	1.02 (0.63, 1.65)	
	Per ln(ppb-day) increase			1.07 (1.00, 1.15)			1.01 (0.95, 1.07)	
Toluene, ppb-days	Q1	26	1112	Referent	54	3419	Referent	0.15
	Q2	70	2039	1.59 (0.97, 2.60)	39	2492	0.79 (0.49, 1.25)	
	Q3	50	2077	1.02 (0.61, 1.71)	49	2454	0.94 (0.61, 1.46)	
	Q4	62	2386	1.05 (0.64, 1.73)	30	2145	0.71 (0.43, 1.17)	
	Q5	85	2553	1.54 (0.95, 2.50)	44	1978	0.91 (0.58, 1.44)	
	Per ln(ppb-day) increase			1.07 (0.99, 1.15)			1.01 (0.94, 1.07)	
Ethylbenzene, ppb-days	Q1	27	1115	Referent	56	3416	Referent	0.05
	Q2	68	2090	1.51 (0.93, 2.45)	36	2441	0.62 (0.39, 0.99)	
	Q3	61	2166	1.25 (0.77, 2.04)	53	2365	0.98 (0.64, 1.49)	
	Q4	58	2426	1.02 (0.62, 1.66)	35	2105	0.72 (0.45, 1.15)	
	Q5	79	2370	1.67 (1.03, 2.71)	36	2161	0.79 (0.48, 1.32)	

	Per ln(ppb-day) increase			1.05 (0.98, 1.13)			1.01 (0.95, 1.07)	
Xylene, ppb-days	Q1	35	1499	Referent	52	3034	Referent	0.25
	Q2	62	1868	1.54 (1.00, 2.38)	42	2661	0.78 (0.50, 1.22)	
	Q3	58	1989	1.44 (0.93, 2.22)	52	2542	0.93 (0.61, 1.42)	
	Q4	63	2375	1.21 (0.79, 1.85)	27	2156	0.54 (0.33, 0.89)	
	Q5	75	2436	1.57 (1.02, 2.40)	43	2095	1.00 (0.62, 1.61)	
	Per ln(ppb-day) increase			1.09 (0.98, 1.21)			0.98 (0.88, 1.09)	
n-Hexane, ppb-days	Q1	27	1080	Referent	48	3451	Referent	0.17
	Q2	64	2152	1.26 (0.77, 2.06)	36	2379	0.90 (0.55, 1.46)	
	Q3	57	2203	1.11 (0.67, 1.83)	58	2328	1.36 (0.88, 2.11)	
	Q4	67	2275	1.14 (0.70, 1.85)	35	2256	0.80 (0.49, 1.30)	
	Q5	78	2457	1.50 (0.92, 2.45)	39	2074	1.16 (0.69, 1.93)	
	Per ln(ppb-day) increase			1.04 (0.98, 1.10)			1.01 (0.95, 1.08)	

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

Table 6. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by obesity status among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure		Total Cases (n=305)	Total N (n=15,565)	Not obese (BMI < 30)[a] HR (95% CI)	Total Cases (n=204)	Total N (n=7,090)	Obese (BMI ≥ 30)[a] HR (95% CI)	Interaction p
THC, ppm-days	Q1	39	3279	Referent	36	1252	Referent	<0.01
	Q2	69	3125	1.95 (1.26, 3.02)	42	1406	0.83 (0.50, 1.37)	
	Q3	70	3077	1.88 (1.22, 2.91)	35	1454	0.70 (0.42, 1.17)	
	Q4	50	3048	1.41 (0.89, 2.24)	52	1483	1.02 (0.63, 1.66)	
	Q5	77	3036	2.27 (1.44, 3.56)	39	1495	0.85 (0.51, 1.44)	
	Per ln(ppm-day) increase			1.10 (1.03, 1.17)			1.00 (0.92, 1.08)	
Benzene, ppb-days	Q1	38	3274	Referent	35	1257	Referent	0.06
	Q2	64	3082	1.59 (0.97, 2.61)	49	1449	1.07 (0.65, 1.75)	
	Q3	72	3107	1.79 (1.10, 2.90)	41	1424	0.89 (0.54, 1.49)	
	Q4	57	3113	1.36 (0.82, 2.24)	24	1418	0.49 (0.28, 0.86)	
	Q5	74	2989	1.79 (1.10, 2.92)	55	1542	1.18 (0.72, 1.94)	
	Per ln(ppb-day) increase			1.08 (1.03, 1.14)			0.99 (0.93, 1.06)	
Toluene, ppb-days	Q1	46	3285	Referent	34	1246	Referent	0.51
	Q2	64	3107	1.40 (0.90, 2.17)	45	1424	0.99 (0.60, 1.65)	
	Q3	58	3099	1.17 (0.75, 1.82)	41	1432	0.85 (0.51, 1.42)	
	Q4	58	3044	1.16 (0.74, 1.82)	34	1487	0.66 (0.39, 1.12)	
	Q5	79	3030	1.51 (0.98, 2.32)	50	1501	1.03 (0.62, 1.71)	
	Per ln(ppb-day) increase			1.08 (1.02, 1.14)			1.00 (0.92, 1.07)	
Ethylbenzene, ppb-days	Q1	44	3280	Referent	39	1251	Referent	0.36
	Q2	65	3121	1.34 (0.84, 2.14)	39	1410	0.75 (0.46, 1.24)	
	Q3	69	3045	1.41 (0.89, 2.24)	45	1486	0.82 (0.50, 1.32)	

	Q4	57	3035	1.17 (0.73, 1.87)	36	1496	0.61 (0.37, 1.01)	
	Q5	70	3084	1.52 (0.95, 2.45)	45	1447	0.92 (0.56, 1.51)	
	Per ln(ppb-day) increase			1.08 (1.02, 1.14)			0.99 (0.92, 1.06)	
Xylene, ppb-days	Q1	51	3259	Referent	36	1274	Referent	0.99
	Q2	64	3130	1.20 (0.80, 1.80)	40	1399	1.03 (0.64, 1.67)	
	Q3	66	3092	1.21 (0.81, 1.81)	44	1439	1.07 (0.67, 1.71)	
	Q4	54	3008	0.96 (0.63, 1.45)	36	1523	0.77 (0.47, 1.26)	
	Q5	70	3076	1.30 (0.86, 1.98)	48	1455	1.23 (0.77, 1.97)	
	Per ln(ppb-day) increase			1.06 (0.97, 1.16)			1.01 (0.91, 1.13)	
n-Hexane, ppb-days	Q1	42	3282	Referent	33	1249	Referent	0.82
	Q2	60	3050	1.25 (0.78, 2.02)	40	1481	0.93 (0.55, 1.57)	
	Q3	71	3110	1.45 (0.91, 2.31)	44	1421	0.98 (0.59, 1.65)	
	Q4	61	3084	1.16 (0.72, 1.87)	41	1447	0.81 (0.48, 1.37)	
	Q5	71	3039	1.56 (0.96, 2.52)	46	1492	1.14 (0.67, 1.95)	
	Per ln(ppb-day) increase			1.06 (1.01, 1.12)			1.01 (0.95, 1.08)	

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; BMI, body mass index; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

Table 7. Quantile g-computation estimates for the change in CHD events hazards for a one quintile increase in cumulative exposure to all crude oil chemicals (BTEX-H) among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure	Cumulative Maximum[a]	Cumulative Average[a]
	HR (95% CI)	HR (95% CI)
Per quintile increase	1.03 (0.96, 1.10)	1.02 (0.95, 1.09)

Abbreviations: CHD, coronary heart disease; BTEX-H, benzene, toluene, ethylbenzene, xylene, n-hexane; *DWH, Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

Supplemental Text S1

We performed a mixture analysis using quantile g-computation (Keil et al. 2020) to estimate the joint effect of BTEX-H as a mixture on the risk of CHD events. For time-to-event outcomes, this method is a semi-parametric model-based implementation of g-computation to estimate the expected change in outcome corresponding to a simultaneous increase in all of the mixture components by one quantile (White et al. 2020). To implement this method, we first categorized exposure components into quintiles and assigned each quintile an integer score (Q1=1, …, Q5=5). Then, we fit a Cox proportional hazards model of CHD against the quintile scores (treated as continuous variables) and conditional on the same covariates used in single-agent IP-exposure weight models. This construction allows a weight for each BTEX-H component to represent a component's relative contribution to positive associations (positive weights), or relative contribution to inverse associations (negative weights). Positive and negative weights sum to 1 and -1, respectively. Under assumptions of linearity and additivity of the effects of BTEX-H, the joint effect equals the sum of generalized linear model coefficients for all of the transformed exposures, and it is interpreted as the expected change in the log-hazard of CHD for a simultaneous one quantile increase in all of the exposures in the BTEX-H mixture. As in single-agent analyses, we applied IP-censoring weights to the mixture model. Quantile g-computation was performed using R 4.0.4 package "qgcomp".

Table 8. Spearman correlation coefficients between cumulative exposure to oil-spill chemicals among *DWH* disaster oil spill workers (N=22,655)

Cumulative daily maximum	THC	Benzene	Toluene	Ethylbenzene	Xylene
Benzene	0.91				
Toluene	0.90	0.95			
Ethylbenzene	0.93	0.94	0.93		
Xylene	0.92	0.90	0.91	0.95	
n-Hexane	0.90	0.88	0.89	0.91	0.87

Cumulative daily average	THC	Benzene	Toluene	Ethylbenzene	Xylene
Benzene	0.91				
Toluene	0.91	0.96			
Ethylbenzene	0.94	0.94	0.94		
Xylene	0.91	0.87	0.89	0.92	
n-Hexane	0.88	0.88	0.89	0.90	0.84

Abbreviations: *DWH, Deepwater Horizon*; THC, total hydrocarbons

Table 9. Distribution of stabilized inverse probability of exposure, censoring, and overall weights in analysis of cumulative daily maximum exposure to oil spill-related chemicals and coronary heart disease among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure	**IPEW**	**IPCW**	**Overall Weight[a]**
	Mean (Range)	*Mean (Range)*	*Mean (Range)*
THC	1.00 (0.30, 10.36)	1.00 (0.58, 2.67)	1.00 (0.21, 10.96)
Benzene	1.00 (0.29, 15.50)	1.00 (0.56, 2.81)	1.00 (0.18, 15.50)
Toluene	1.00 (0.30, 16.74)	1.00 (0.56, 2.81)	1.00 (0.20, 16.74)
Ethylbenzene	1.00 (0.29, 9.02)	1.00 (0.56, 2.81)	1.01 (0.20, 9.44)
Xylene	1.00 (0.35, 8.98)	1.00 (0.56, 2.81)	1.00 (0.22, 8.98)
n-Hexane	1.01 (0.29, 8.91)	1.00 (0.56, 2.81)	1.01 (0.19, 12.48)

Abbreviations: *DWH*, *Deepwater Horizon*; IPEW, inverse probability of exposure weight; IPCW, inverse probability of censoring weight; THC, total hydrocarbons

[a]Overall weights are the product of IPEW and IPCW.

Table 10. Associations between cumulative exposure to crude oil chemicals and incident CHD events among *DWH* disaster oil spill workers, additionally adjusting for prevalent hypertension (N=22,279), 2010-2019

Exposure		Total Cases (n=485)	Total N (n=22,279)	Cumulative Daily Maximum[a]	Total Cases (n=485)	Total N (n=22,279)	Cumulative Daily Average[a]
				HR (95% CI)			HR (95% CI)
THC, ppm-days	Q1	74	4480	Referent	86	4484	Referent
	Q2	107	4460	1.28 (0.91, 1.79)	101	4458	1.07 (0.78, 1.47)
	Q3	100	4457	1.18 (0.84, 1.66)	95	4456	0.94 (0.69, 1.30)
	Q4	92	4427	1.14 (0.80, 1.61)	93	4435	0.94 (0.69, 1.30)
	Q5	112	4455	1.42 (1.00, 2.01)	110	4446	1.21 (0.88, 1.67)
	Per ln(ppm-day) increase			1.05 (0.99, 1.10)			1.04 (0.98, 1.10)
Benzene, ppb-days	Q1	70	4483	Referent	72	4487	Referent
	Q2	108	4448	1.33 (0.93, 1.89)	107	4451	1.35 (0.95, 1.92)
	Q3	108	4464	1.33 (0.94, 1.89)	108	4456	1.26 (0.89, 1.79)
	Q4	74	4443	0.90 (0.62, 1.31)	77	4447	0.90 (0.63, 1.30)
	Q5	125	4441	1.51 (1.06, 2.14)	121	4438	1.41 (0.99, 2.00)
	Per ln(ppb-day) increase			1.04 (0.99, 1.08)			1.03 (0.98, 1.08)
Toluene, ppb-days	Q1	79	4480	Referent	82	4482	Referent
	Q2	103	4453	1.18 (0.84, 1.65)	101	4454	1.10 (0.79, 1.55)
	Q3	92	4458	0.98 (0.70, 1.38)	97	4460	1.00 (0.72, 1.40)
	Q4	87	4438	0.90 (0.63, 1.27)	78	4444	0.78 (0.55, 1.11)
	Q5	124	4450	1.25 (0.90, 1.74)	127	4439	1.30 (0.92, 1.83)
	Per ln(ppb-day) increase			1.04 (0.99, 1.09)			1.03 (0.97, 1.08)
Ethylbenzene, ppb-days	Q1	80	4480	Referent	79	4479	Referent
	Q2	101	4457	1.05 (0.75, 1.48)	99	4457	1.11 (0.79, 1.56)
	Q3	108	4458	1.11 (0.79, 1.55)	109	4459	1.16 (0.83, 1.62)
	Q4	86	4428	0.87 (0.61, 1.24)	89	4439	0.96 (0.68, 1.35)
	Q5	110	4456	1.21 (0.86, 1.71)	109	4445	1.27 (0.90, 1.79)
	Per ln(ppb-day) increase			1.04 (0.99, 1.08)			1.03 (0.98, 1.09)

Xylene, ppb-days	Q1	84	4472	Referent	96	4475	Referent
	Q2	101	4459	1.12 (0.82, 1.54)	93	4460	0.89 (0.66, 1.21)
	Q3	101	4464	1.12 (0.82, 1.53)	93	4464	0.90 (0.67, 1.22)
	Q4	85	4433	0.87 (0.63, 1.20)	86	4433	0.79 (0.58, 1.07)
	Q5	114	4451	1.26 (0.92, 1.73)	117	4447	1.14 (0.85, 1.54)
	Per ln(ppb-day) increase			1.04 (0.97, 1.12)			1.03 (0.95, 1.11)
n-Hexane, ppb-days	Q1	72	4480	Referent	73	4528	Referent
	Q2	97	4444	1.15 (0.80, 1.65)	104	4401	1.23 (0.86, 1.75)
	Q3	108	4463	1.24 (0.87, 1.77)	95	4459	1.07 (0.75, 1.54)
	Q4	96	4440	1.02 (0.71, 1.47)	101	4444	1.06 (0.75, 1.52)
	Q5	112	4452	1.37 (0.95, 1.97)	112	4447	1.33 (0.93, 1.92)
	Per ln(ppb-day) increase			1.03 (0.99, 1.08)			1.03 (0.98, 1.08)

Abbreviations: CHD, coronary heart disease; *DWH*, *Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, previous oil industry experience, and pre-cleanup hypertension.

Table 11. Associations between cumulative exposure to crude oil chemicals and incident non-fatal MI or fatal CHD (a *contributing/underlying* cause of death) among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure		**Total Cases (n=536)**	**Total N (n=22,655)**	**Cumulative Daily Maximum[a]**	**Total Cases (n=515)**	**Total N (n=22,655)**	**Cumulative Daily Average[a]**
				HR (95% CI)			**HR (95% CI)**
THC, ppm-days	Q1	81	4531	Referent	93	4533	Referent
	Q2	117	4531	1.27 (0.92, 1.76)	111	4529	1.07 (0.79, 1.46)
	Q3	111	4531	1.19 (0.86, 1.65)	105	4531	0.96 (0.71, 1.30)
	Q4	110	4531	1.20 (0.87, 1.67)	109	4531	1.01 (0.75, 1.36)
	Q5	117	4531	1.36 (0.97, 1.91)	118	4531	1.20 (0.88, 1.63)
	Per ln(ppm-day) increase			1.05 (1.00, 1.10)			1.05 (0.99, 1.11)
Benzene, ppb-days	Q1	78	4531	Referent	78	4533	Referent
	Q2	118	4531	1.29 (0.92, 1.81)	118	4529	1.36 (0.98, 1.90)
	Q3	119	4531	1.32 (0.95, 1.84)	122	4531	1.33 (0.96, 1.85)
	Q4	88	4531	0.93 (0.65, 1.32)	86	4531	0.94 (0.66, 1.33)
	Q5	133	4531	1.43 (1.02, 1.99)	132	4531	1.40 (1.00, 1.95)
	Per ln(ppb-day) increase			1.04 (1.00, 1.09)			1.04 (0.99, 1.08)
Toluene, ppb-days	Q1	85	4531	Referent	89	4531	Referent
	Q2	113	4531	1.17 (0.85, 1.61)	112	4531	1.10 (0.80, 1.52)
	Q3	105	4531	1.03 (0.74, 1.43)	111	4531	1.05 (0.77, 1.45)
	Q4	100	4531	0.93 (0.67, 1.29)	87	4531	0.79 (0.56, 1.10)
	Q5	133	4531	1.24 (0.90, 1.70)	137	4531	1.26 (0.91, 1.75)
	Per ln(ppb-day) increase			1.04 (0.99, 1.09)			1.03 (0.98, 1.08)
Ethylbenzene, ppb-days	Q1	89	4531	Referent	87	4531	Referent
	Q2	108	4531	1.01 (0.73, 1.39)	111	4531	1.14 (0.83, 1.57)
	Q3	121	4531	1.12 (0.81, 1.53)	120	4531	1.16 (0.85, 1.59)
	Q4	100	4531	0.88 (0.64, 1.22)	101	4531	0.98 (0.71, 1.36)
	Q5	118	4531	1.16 (0.83, 1.61)	117	4531	1.22 (0.88, 1.69)
	Per ln(ppb-day) increase			1.04 (0.99, 1.08)			1.04 (0.99, 1.09)

Xylene, ppb-days	Q1	91	4533	Referent	102	4531	Referent
	Q2	110	4529	1.13 (0.84, 1.53)	104	4531	0.93 (0.70, 1.24)
	Q3	117	4531	1.18 (0.88, 1.59)	105	4534	0.96 (0.72, 1.28)
	Q4	97	4531	0.90 (0.66, 1.22)	99	4528	0.84 (0.63, 1.12)
	Q5	121	4531	1.23 (0.91, 1.67)	126	4531	1.15 (0.86, 1.54)
	Per ln(ppb-day) increase			1.04 (0.97, 1.11)			1.03 (0.95, 1.11)
n-Hexane, ppb-days	Q1	82	4531	Referent	83	4577	Referent
	Q2	102	4531	1.06 (0.75, 1.49)	113	4485	1.17 (0.84, 1.63)
	Q3	121	4531	1.23 (0.88, 1.71)	104	4531	1.03 (0.74, 1.45)
	Q4	108	4531	1.00 (0.71, 1.40)	114	4531	1.05 (0.75, 1.46)
	Q5	123	4531	1.33 (0.94, 1.86)	122	4531	1.27 (0.91, 1.79)
	Per ln(ppb-day) increase			1.03 (0.99, 1.08)			1.03 (0.99, 1.08)

Abbreviations: CHD, coronary heart disease; *DWH*, *Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

Table 12. Associations between cumulative exposure to crude oil chemicals and incident self-reported myocardial infarction among *DWH* disaster oil spill workers (N=22,655), 2010-2019

Exposure		Total Cases (n=435)	Total N (n=22,655)	Cumulative Daily Maximum[a] HR (95% CI)	Total Cases (n=440)	Total N (n=22,655)	Cumulative Daily Average[a] HR (95% CI)
THC, ppm-days	Q1	62	4531	Referent	73	4533	Referent
	Q2	86	4531	1.18 (0.81, 1.72)	84	4529	1.00 (0.71, 1.41)
	Q3	96	4531	1.26 (0.87, 1.82)	86	4531	0.96 (0.68, 1.35)
	Q4	89	4531	1.20 (0.83, 1.74)	92	4531	1.02 (0.73, 1.43)
	Q5	102	4531	1.45 (0.99, 2.12)	100	4531	1.25 (0.89, 1.76)
	Per ln(ppm-day) increase			1.07 (1.01, 1.13)			1.07 (1.00, 1.14)
Benzene, ppb-days	Q1	60	4531	Referent	61	4533	Referent
	Q2	94	4531	1.35 (0.93, 1.96)	92	4529	1.36 (0.93, 1.98)
	Q3	99	4531	1.41 (0.97, 2.03)	103	4531	1.42 (0.98, 2.04)
	Q4	69	4531	0.92 (0.62, 1.37)	70	4531	0.96 (0.65, 1.42)
	Q5	113	4531	1.54 (1.07, 2.23)	109	4531	1.48 (1.02, 2.16)
	Per ln(ppb-day) increase			1.05 (1.00, 1.10)			1.05 (1.00, 1.10)
Toluene, ppb-days	Q1	67	4531	Referent	71	4531	Referent
	Q2	89	4531	1.11 (0.77, 1.60)	89	4531	1.05 (0.73, 1.51)
	Q3	89	4531	1.05 (0.73, 1.51)	90	4531	1.02 (0.71, 1.46)
	Q4	80	4531	0.90 (0.62, 1.31)	71	4531	0.77 (0.53, 1.12)
	Q5	110	4531	1.23 (0.86, 1.76)	114	4531	1.28 (0.88, 1.85)
	Per ln(ppb-day) increase			1.05 (1.00, 1.11)			1.04 (0.98, 1.10)
Ethylbenzene, ppb-days	Q1	69	4531	Referent	69	4531	Referent
	Q2	86	4531	1.04 (0.72, 1.50)	84	4531	1.06 (0.74, 1.52)
	Q3	99	4531	1.15 (0.81, 1.63)	100	4531	1.17 (0.82, 1.66)
	Q4	81	4531	0.90 (0.62, 1.29)	84	4531	0.98 (0.68, 1.40)
	Q5	100	4531	1.25 (0.87, 1.80)	98	4531	1.26 (0.87, 1.81)
	Per ln(ppb-day) increase			1.05 (1.00, 1.10)			1.05 (1.00, 1.11)

Xylene, ppb-days	Q1	70	4533	Referent	79	4531	Referent
	Q2	88	4529	1.20 (0.85, 1.68)	83	4531	0.99 (0.71, 1.37)
	Q3	97	4531	1.26 (0.91, 1.76)	85	4534	0.98 (0.71, 1.36)
	Q4	78	4531	0.93 (0.66, 1.31)	83	4528	0.89 (0.64, 1.23)
	Q5	102	4531	1.35 (0.96, 1.91)	105	4531	1.25 (0.90, 1.73)
	Per ln(ppb-day) increase			1.06 (0.99, 1.14)			1.05 (0.97, 1.14)
n-Hexane, ppb-days	Q1	62	4531	Referent	63	4577	Referent
	Q2	82	4531	1.10 (0.75, 1.61)	90	4485	1.20 (0.82, 1.75)
	Q3	99	4531	1.29 (0.89, 1.87)	85	4531	1.04 (0.71, 1.52)
	Q4	91	4531	1.08 (0.74, 1.58)	96	4531	1.12 (0.77, 1.63)
	Q5	101	4531	1.41 (0.96, 2.07)	101	4531	1.36 (0.93, 1.99)
	Per ln(ppb-day) increase			1.06 (1.01, 1.10)			1.05 (1.00, 1.10)

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

Table 13. Associations between cumulative exposure to crude oil chemicals and incident CHD events after *enrollment* among *DWH* disaster oil spill workers (N=22,526), 2010-2019

Exposure		Total Cases (n=366)	Total N (n=22,526)	Cumulative Daily Maximum[a] HR (95% CI)	Total Cases (n=366)	Total N (n=22,526)	Cumulative Daily Average[a] HR (95% CI)
THC, ppm-days	Q1	55	4506	Referent	65	4507	Referent
	Q2	86	4506	1.33 (0.90, 1.97)	82	4504	1.08 (0.75, 1.55)
	Q3	70	4504	1.07 (0.71, 1.59)	66	4505	0.81 (0.56, 1.18)
	Q4	72	4505	1.13 (0.76, 1.68)	72	4505	0.91 (0.63, 1.31)
	Q5	83	4505	1.44 (0.96, 2.18)	81	4505	1.16 (0.80, 1.68)
	Per ln(ppm-day) increase			1.05 (0.99, 1.12)			1.04 (0.97, 1.11)
Benzene, ppb-days	Q1	52	4506	Referent	54	4506	Referent
	Q2	88	4505	1.33 (0.88, 1.99)	87	4505	1.35 (0.91, 2.01)
	Q3	78	4506	1.19 (0.79, 1.80)	79	4505	1.17 (0.78, 1.75)
	Q4	52	4504	0.76 (0.49, 1.18)	52	4505	0.75 (0.49, 1.16)
	Q5	96	4505	1.48 (0.98, 2.21)	94	4505	1.42 (0.95, 2.13)
	Per ln(ppb-day) increase			1.04 (0.99, 1.10)			1.03 (0.98, 1.09)
Toluene, ppb-days	Q1	60	4506	Referent	63	4507	Referent
	Q2	83	4505	1.16 (0.79, 1.70)	79	4504	1.04 (0.71, 1.53)
	Q3	68	4505	0.89 (0.60, 1.32)	72	4505	0.90 (0.61, 1.33)
	Q4	60	4505	0.76 (0.50, 1.14)	57	4505	0.69 (0.46, 1.03)
	Q5	95	4505	1.21 (0.83, 1.78)	95	4505	1.23 (0.82, 1.84)
	Per ln(ppb-day) increase			1.04 (0.99, 1.10)			1.03 (0.97, 1.09)
Ethylbenzene, ppb-days	Q1	61	4507	Referent	58	4506	Referent
	Q2	79	4504	0.99 (0.67, 1.47)	82	4505	1.19 (0.81, 1.76)
	Q3	78	4505	0.97 (0.66, 1.44)	79	4505	1.08 (0.73, 1.60)
	Q4	65	4505	0.79 (0.53, 1.19)	63	4505	0.88 (0.59, 1.32)
	Q5	83	4505	1.15 (0.77, 1.73)	84	4505	1.29 (0.86, 1.93)
	Per ln(ppb-day) increase			1.04 (0.99, 1.10)			1.04 (0.98, 1.10)

Xylene, ppb-days	Q1	65	4506	Referent	75	4506	Referent
	Q2	77	4505	1.12 (0.78, 1.60)	71	4505	0.87 (0.62, 1.23)
	Q3	75	4505	1.07 (0.75, 1.53)	65	4505	0.82 (0.58, 1.16)
	Q4	64	4505	0.85 (0.58, 1.22)	68	4505	0.80 (0.57, 1.13)
	Q5	85	4505	1.25 (0.87, 1.81)	87	4505	1.13 (0.79, 1.60)
	Per ln(ppb-day) increase			1.03 (0.95, 1.13)			1.01 (0.92, 1.11)
n-Hexane, ppb-days	Q1	53	4506	Referent	55	4560	Referent
	Q2	77	4505	1.16 (0.77, 1.75)	78	4451	1.12 (0.74, 1.68)
	Q3	80	4505	1.17 (0.78, 1.77)	72	4505	0.99 (0.66, 1.50)
	Q4	69	4505	0.94 (0.62, 1.43)	77	4505	0.99 (0.66, 1.49)
	Q5	87	4505	1.40 (0.92, 2.13)	84	4505	1.26 (0.83, 1.91)
	Per ln(ppb-day) increase			1.04 (0.99, 1.09)			1.03 (0.98, 1.09)

Abbreviations: CHD, coronary heart disease; *DWH*, *Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

Table 14. Associations between cumulative exposure to crude oil chemicals and incident CHD events among *DWH* disaster oil spill workers who were not potentially exposed to $PM_{2.5}$ from controlled burning activities (N=20,658), 2010-2019

Exposure		Total Cases (n=465)	Total N (n=20,658)	Cumulative Daily Maximum[a] HR (95% CI)	Total Cases (n=465)	Total N (n=20,658)	Cumulative Daily Average[a] HR (95% CI)
THC, ppm-days	Q1	75	4518	Referent	88	4520	Referent
	Q2	108	4451	1.26 (0.90, 1.75)	102	4456	1.04 (0.76, 1.42)
	Q3	102	4343	1.19 (0.86, 1.67)	94	4302	0.93 (0.68, 1.27)
	Q4	92	4015	1.18 (0.84, 1.67)	98	4010	1.03 (0.76, 1.41)
	Q5	88	3331	1.32 (0.93, 1.88)	83	3370	1.07 (0.77, 1.49)
	Per ln(ppm-day) increase			1.04 (0.99, 1.10)			1.03 (0.98, 1.09)
Benzene, ppb-days	Q1	72	4494	Referent	73	4502	Referent
	Q2	110	4311	1.35 (0.96, 1.90)	109	4358	1.40 (1.00, 1.97)
	Q3	106	4199	1.31 (0.93, 1.84)	107	4143	1.33 (0.94, 1.86)
	Q4	67	3945	0.85 (0.58, 1.23)	69	3875	0.91 (0.63, 1.32)
	Q5	110	3709	1.46 (1.03, 2.06)	107	3780	1.36 (0.96, 1.93)
	Per ln(ppb-day) increase			1.03 (0.99, 1.08)			1.03 (0.98, 1.08)
Toluene, ppb-days	Q1	80	4511	Referent	84	4517	Referent
	Q2	105	4418	1.16 (0.83, 1.61)	104	4441	1.09 (0.78, 1.51)
	Q3	94	4146	1.02 (0.73, 1.43)	97	4199	1.01 (0.73, 1.41)
	Q4	78	3905	0.82 (0.58, 1.17)	73	3839	0.78 (0.55, 1.10)
	Q5	108	3678	1.21 (0.86, 1.69)	107	3662	1.12 (0.80, 1.56)
	Per ln(ppb-day) increase			1.03 (0.99, 1.08)			1.02 (0.97, 1.07)
Ethylbenzene, ppb-days	Q1	83	4518	Referent	82	4520	Referent
	Q2	103	4487	1.02 (0.73, 1.42)	101	4473	1.09 (0.79, 1.51)
	Q3	109	4366	1.09 (0.78, 1.51)	113	4358	1.17 (0.85, 1.61)
	Q4	82	4042	0.83 (0.59, 1.17)	86	4070	0.94 (0.67, 1.32)
	Q5	88	3245	1.14 (0.81, 1.61)	83	3237	1.08 (0.76, 1.52)
	Per ln(ppb-day) increase			1.03 (0.98, 1.07)			1.02 (0.98, 1.08)

Xylene, ppb-days	Q1	86	4499	Referent	98	4492	Referent
	Q2	102	4451	1.12 (0.82, 1.53)	95	4450	0.90 (0.67, 1.22)
	Q3	104	4309	1.15 (0.84, 1.56)	92	4311	0.90 (0.67, 1.21)
	Q4	82	4065	0.87 (0.63, 1.20)	84	4047	0.80 (0.59, 1.08)
	Q5	91	3334	1.19 (0.86, 1.64)	96	3358	1.09 (0.80, 1.48)
	Per ln(ppb-day) increase			1.03 (0.96, 1.10)			1.02 (0.94, 1.10)
n-Hexane, ppb-days	Q1	75	4527	Referent	76	4574	Referent
	Q2	100	4514	1.09 (0.77, 1.54)	108	4461	1.19 (0.85, 1.67)
	Q3	111	4390	1.22 (0.87, 1.72)	99	4397	1.07 (0.76, 1.50)
	Q4	97	4213	0.98 (0.69, 1.39)	98	4172	1.01 (0.72, 1.43)
	Q5	82	3014	1.24 (0.86, 1.80)	84	3054	1.20 (0.83, 1.73)
	Per ln(ppb-day) increase			1.03 (0.99, 1.07)			1.02 (0.97, 1.06)

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; $PM_{2.5}$, fine particulate matter <2.5 micrometers; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

Table 15. Associations between maximum daily maximum exposure to crude oil chemicals and incident CHD events among DWH disaster oil spill workers (N=22,655), 2010-2016 and 2010-2019

Exposure		Total N (n=22,655)	Until First Follow-up Interview[a]		Until Dec 2019[a]	
			Total Cases (n=383)	HR (95% CI)	Total Cases (n=542)	HR (95% CI)
THC, ppm	Q1 (<0.2)	4534	43	Referent	65	Referent
	Q2 (0.2-0.6)	4656	87	1.60 (1.04, 2.47)	119	1.54 (1.08, 2.20)
	Q3 (0.6-1.2)	4548	83	1.54 (0.99, 2.37)	106	1.37 (0.96, 1.96)
	Q4 (1.3-2.8)	4625	75	1.28 (0.82, 2.00)	114	1.38 (0.97, 1.98)
	Q5 (2.8-22.4)	4292	78	1.61 (1.02, 2.55)	105	1.52 (1.04, 2.20)

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

Table 16. Associations between cumulative maximum exposures to crude oil chemicals and incident CHD events (self-reported MI, self-reported blockage in heart arteries, or fatal CHD) among *DWH* disaster oil spill workers (N=22,410), 2010-2019

Exposure		**Total Cases (n=839)**	**Total N (n=22,410)**	**HR (95% CI)[a]**
THC, ppm-days	Q1 (<7)	130	4482	Referent
	Q2 (7-31)	182	4482	1.19 (0.92, 1.54)
	Q3 (31-75)	167	4482	1.05 (0.81, 1.37)
	Q4 (75-167)	167	4482	1.11 (0.85, 1.45)
	Q5 (167-1244)	193	4482	1.29 (0.99, 1.69)
	Per ln(ppm-day) increase			1.04 (0.99, 1.08)
Benzene, ppb-days	Q1 (<34)	128	4482	Referent
	Q2 (34-188)	183	4482	1.17 (0.89, 1.52)
	Q3 (188-494)	173	4482	1.09 (0.84, 1.43)
	Q4 (494-1196)	148	4482	0.91 (0.69, 1.19)
	Q5 (1196-10592)	207	4482	1.28 (0.98, 1.67)
	Per ln(ppb-day) increase			1.03 (0.99, 1.07)
Toluene, ppb-days	Q1 (<120)	132	4482	Referent
	Q2 (120-758)	171	4483	1.10 (0.85, 1.44)
	Q3 (758-1992)	169	4481	1.02 (0.78, 1.32)
	Q4 (1992-4399)	152	4482	0.91 (0.69, 1.19)
	Q5 (4399-29657)	215	4482	1.25 (0.97, 1.62)
	Per ln(ppb-day) increase			1.03 (0.99, 1.08)
Ethylbenzene, ppb-days	Q1 (<30)	134	4482	Referent
	Q2 (30-153)	178	4482	1.06 (0.82, 1.38)
	Q3 (153-381)	171	4482	1.00 (0.77, 1.30)
	Q4 (381-934)	174	4482	1.00 (0.77, 1.31)
	Q5 (934-8130)	182	4482	1.10 (0.84, 1.44)
	Per ln(ppb-day) increase			1.03 (0.99, 1.07)

Xylene, ppb-days	Q1 (<524)	141	4482	Referent
	Q2 (524-1240)	166	4482	1.08 (0.84, 1.38)
	Q3 (1240-2450)	171	4482	1.09 (0.85, 1.38)
	Q4 (2450-4916)	169	4482	1.01 (0.79, 1.29)
	Q5 (4918-24936)	192	4482	1.20 (0.94, 1.53)
	Per ln(ppb-day) increase			1.04 (0.98, 1.10)
n-Hexane, ppb-days	Q1 (<55)	138	4482	Referent
	Q2 (55-310)	147	4482	0.84 (0.64, 1.11)
	Q3 (310-959)	187	4482	1.05 (0.81, 1.36)
	Q4 (960-3332)	176	4482	0.96 (0.74, 1.25)
	Q5 (3334-90158)	191	4482	1.12 (0.86, 1.46)
	Per ln(ppb-day) increase			1.03 (0.99, 1.06)

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; *DWH*, *Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; IP, inverse probability; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

Table 17. Marginal HRs of CHD comparing *DWH* oil spill workers who had high daily maximum daily exposures to spill-related chemicals (in the top 15th and 20th percentile of maximum daily maximum exposure) for a number of days (≥7 and ≥14 days) with workers whose daily maximum exposures were in the first quintile of the study population's maximum daily exposure, 2010-2019

xposure	Daily Exposure Intensity	Duration at Intensity	Total Cases	Total N	HR (95% CI)[a]
THC	Low (0-0.4 ppm)	≥ 1 day	257	5722	Referent
	Medium (>2.8 ppm)	≥ 7 day	96	3811	1.36 (0.93, 1.99)
	Medium (>2.8 ppm)	≥ 14 day	90	3473	1.48 (0.95, 2.32)
	High (>3.3 ppm)	≥ 7 day	63	2771	1.37 (0.88, 2.13)
	High (>3.3 ppm)	≥ 14 day	57	2438	1.52 (0.87, 2.63)
Benzene	Low (0-1.9 ppb)	≥ 1 day	254	5699	Referent
	Medium (>15.1 ppb)	≥ 7 day	105	4012	1.21 (0.87, 1.68)
	Medium (>15.1 ppb)	≥ 14 day	97	3719	1.15 (0.84, 1.57)
	High (>15.4 ppb)	≥ 7 day	81	3095	1.26 (0.88, 1.79)
	High (>15.4 ppb)	≥ 14 day	73	2821	1.18 (0.84, 1.67)
Toluene	Low (0-7.2 ppb)	≥ 1 day	245	5782	Referent
	Medium (>65.7 ppb)	≥ 7 day	110	4036	1.10 (0.77, 1.57)
	Medium (>65.7 ppb)	≥ 14 day	104	3624	1.20 (0.79, 1.83)
	High (>78.3 ppb)	≥ 7 day	91	3296	1.22 (0.80, 1.85)
	High (>78.3 ppb)	≥ 14 day	86	2975	1.32 (0.81, 2.16)
Ethylbenzene	Low (0-1.4 ppb)	≥ 1 day	269	5464	Referent
	Medium (>15.2 ppb)	≥ 7 day	108	4037	1.14 (0.83, 1.55)
	Medium (>15.2 ppb)	≥ 14 day	99	3694	1.16 (0.84, 1.61)
	High (>19.6 ppb)	≥ 7 day	96	3687	1.13 (0.82, 1.56)
	High (>19.6 ppb)	≥ 14 day	89	3362	1.18 (0.84, 1.65)
Xylene	Low (0.5-11.9 ppb)	≥ 1 day	265	5755	Referent
	Medium (>74.7 ppb)	≥ 7 day	112	4240	1.34 (0.97, 1.84)

	Medium (>74.7 ppb)	≥ 14 day	102	3884	1.36 (0.98, 1.89)
	High (>79.4 ppb)	≥ 7 day	107	3915	1.38 (0.99, 1.91)
	High (>79.4 ppb)	≥ 14 day	98	3587	1.40 (1.00, 1.97)
n-Hexane	Low (0.1-3.6 ppb)	≥ 1 day	243	5627	Referent
	Medium (>59.5 ppb)	≥ 7 day	130	4817	1.27 (0.94, 1.71)
	Medium (>59.5 ppb)	≥ 14 day	120	4397	1.27 (0.93, 1.74)
	High (>107.8 ppb)	≥ 7 day	75	3001	1.24 (0.84, 1.84)
	High (>107.8 ppb)	≥ 14 day	72	2723	1.38 (0.89, 2.15)

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; THC, total hydrocarbons; ppm, parts per million; ppb, parts per billion; HR, hazard ratio; CI, confidence interval

[a]Inverse probability of exposure weights models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience.

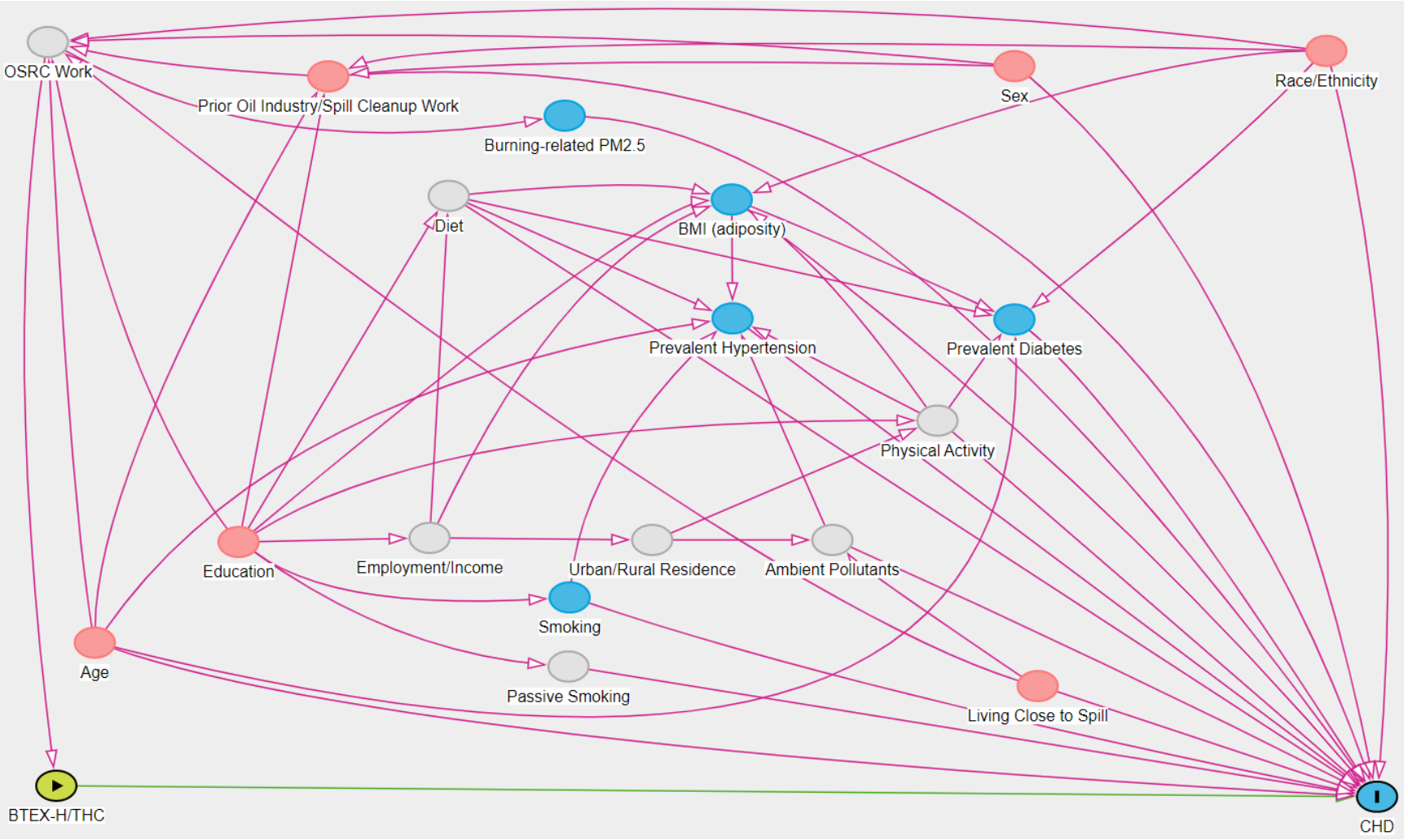

Figure 3. Directed acyclic graph that guided covariate selection for models estimating the relationship between crude oil chemical exposures and risk of coronary heart disease (CHD) among *Deepwater Horizon* oil spill workers, 2010-2019 (N=22,655)

CHAPTER 5: AIM 2 RESULTS

Title: Fine Particulate Matter and Coronary Heart Disease among Burning-exposed *Deepwater Horizon* Oil Spill Workers

5.1 Introduction

The 2010 *Deepwater Horizon* (*DWH*) disaster is the largest marine oil spill in U.S. history (2011). An estimated 4.9 million barrels of crude oil were discharged into the Gulf of Mexico until the wellhead was mechanically capped on July 15, 2010 (National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling 2011). The spill also saw one of the largest oil spill response and cleanup (OSRC) operations in maritime history (Kwok et al. 2017a).

To remove oil from the ocean surface, controlled burning was used as a spill remediation method in addition to other mechanical means of removing the oil (U.S. Coast Guard 2011). Two controlled burning activities took place: 1) flaring of oil/natural gas, and 2) *in situ* burning of oil on the water surface (U.S. Coast Guard 2011). Between May 17, 2010 and July 16, 2010, two drilling rigs (the *Discoverer Enterprise* and the *Helix Q4000*) and a production/offloading vessel (the *Helix Producer I*) flared oil/gas at the wellhead (U.S. Coast Guard 2011). The *Discoverer Enterprise,* capable of separating natural gas from the captured oil, processed ~18,000 barrels of oil per day and flared the separated gas (U.S. Coast Guard 2011) from May 17 to May 25, 2010 and from June 5 to July 11, 2010. The other two vessels joined the effort later. The *Helix Q4000* flared ~10,000 barrels of combined oil and gas per day between June 17 and July 16, 2010, and the *Helix Producer I* flared ~25,000 barrels of the oil/gas mixture per day from July 13 to July 16, 2010 (U.S. Coast Guard 2011). The spill also saw the largest *in situ* burn (ISB) operation in

US history (Allen et al. 2011). From April 28, 2010 to July 19, 2010, workers in the ISB Group attempted 411 burns offshore and removed nearly 300,000 barrels of oil, amounting to ~6% of the total discharged oil (Allen et al. 2011). Unlike flaring, which occurred almost continuously throughout the period, ISBs were episodic. The number of burns conducted on a single burn day ranged from 1 to 26, with each combustion event lasting anywhere from 4 min to 23 hours (Allen et al. 2011).

Despite being an efficient way to eliminate oil, controlled burning can produce particulate and gaseous emissions that could endanger the health of nearby workers (Barnea 2011; U.S. EPA 1999). Of particular concern is fine particulate matter, particles with a diameter of 2.5 microns or less ($PM_{2.5}$). $PM_{2.5}$ is a universal air pollutant produced by incomplete combustion of fuel. Common anthropogenic sources of emissions include vehicles and engines, power plants, other industrial processes, and indoor use of fireplaces and woodstoves (U.S. EPA 2020). The particles can penetrate deeply into human lungs and even enter the bloodstream, causing cardiorespiratory diseases (Brook et al. 2010; Xing et al. 2016). During the *DWH* disaster, particulate matter and its components (soot particles, black carbon, dioxins) were detected in smoke plumes produced by *in situ* burning (Gullett et al. 2016; Middlebrook et al. 2012; Perring et al. 2011; Schaum et al. 2010). Recently, exposure to $PM_{2.5}$ from burning was estimated for oil spill response and cleanup (OSRC) workers using an air model recommended by the U.S. Environmental Protection Agency (U.S. EPA) (Pratt et al. 2022).

A link between short-term ambient $PM_{2.5}$ air pollution and coronary heart disease (CHD) has been documented in numerous time series and case-crossover studies. Studies have associated hospitalizations and emergency department visits due to CHD with $PM_{2.5}$ concentrations on the same day or a few days before (Dominici et al. 2006; Hsu et al. 2017;

Talbott et al. 2014), but few have explored the persistent effect of a relatively short-term $PM_{2.5}$ exposure. Persistent cardiovascular effects several years after OSRC work have been reported among *DWH* disaster oil spill workers with higher exposure to maximum total (petroleum) hydrocarbon (THC) and longer duration of work; however, no apparent association was found for a crude self-reported measure of burning exposure (yes/no), possibly because of misclassification in the exposure. The newly developed quantitative $PM_{2.5}$ estimates provided an opportunity to study an important air pollutant emission generated by the controlled burning activities. The objective of this study was to assess the relationship between estimates of quantitative $PM_{2.5}$ exposure resulting from burning activities and risk of CHD among *DWH* disaster OSRC workers to provide important health information for those considering controlled burning to mitigate the effects of future oil spills. Other sources of $PM_{2.5}$ exposure were not considered in this analysis.

5.2 Methods

Study population

The GuLF Study (Gulf Long-Term Follow-up Study) is a prospective cohort study of the potential health effects of the *DWH* disaster on OSRC workers (Engel et al. 2017; Kwok et al. 2017a). Eligible individuals included anyone ≥21 years of age at enrollment who either had participated in OSRC for at least one day (workers) or had completed safety training but were not hired (non-workers). Participant enrollment started in March 2011, approximately 8 months after the well was capped, and continued through May 2013. A total of 32,608 participants were enrolled. At enrollment, all participants completed a computer-assisted telephone interview in which they provided information on socio-demographics, lifestyle, health, and a detailed work

history of OSRC activities. Two rounds of follow-up interviews (May 2013-Apr 2016 and November 2017-July 2021) were conducted to date to ascertain changes in health status and other important factors since the previous interview. We excluded from the current analysis 999 Vietnamese-speaking participants who completed only an abbreviated enrollment interview. Among the remaining 31,609 participants, 21,256 (67%) and 14,187 (45%) completed the first and second follow-up interviews, respectively. The vast majority of incompletes were individuals whom we were unable to reach by phone or mail. Response rates were over 88% in both follow-ups among those who could be reached.

For all analyses, we restricted the study population to 24,375 workers. Since non-workers were not directly exposed during *DWH* cleanup, exposure estimates were not generated. We excluded 35 workers who did not provide information on CHD diagnoses (i.e. MI or blockage in the arteries of the heart) in any of the interviews. We restricted our analysis to incident cases. By beginning follow-up at the end of each worker's cleanup work time, we excluded 740 workers who reported a CHD diagnosis before the start of follow-up. Of the remaining 23,600 workers, we restricted our analysis to the 21,254 workers who worked at least one day between May 15 and July 15, 2010, the primary period in which burning occurred. We further restricted our main analysis to the 9,482 workers who conducted any response or cleanup activities on water (i.e. water workers), excluding 11,772 land workers because workers on land were additionally exposed to $PM_{2.5}$ emissions from land equipment engines, but we lacked information to characterize this background exposure. Finally, we removed 391 workers with any missing covariate data and ended up with a final analytical sample of 9,091 participants. All participants provided informed consent prior to participating in the GuLF Study. The Institutional Review Board of the National Institute of Environmental Health Sciences approved this study.

$PM_{2.5}$ exposure assessment

The method for developing $PM_{2.5}$ exposure estimates for workers in the GuLF Study has been described elsewhere (Pratt et al. 2022). While working on water, workers were potentially exposed to three sources of $PM_{2.5}$ emissions: flaring at the wellhead, *in situ* burning offshore, and operation of thousands of mostly diesel-powered vessel engines. However, because of uncertainties in the locations of workers and vessels, it was not possible to consider background emissions from the vessel exhaust or other sources in the development of individual exposure estimates. Here, we summarize the approach by which $PM_{2.5}$ exposure from controlled burning of oil and gas was assessed.

Potential exposure to $PM_{2.5}$ from burning activities was estimated from May 15 to July 15, 2010 (i.e. burning period). Emissions for each ISB or flaring episode were calculated based on emission factors reported in previous studies (Fingas et al. 1995; U.S. EPA 2017) and the estimated volume of oil/gas burned. The resulting primary emissions data were used along with meteorological data and source characterizations as inputs in the Gaussian air dispersion model, AERMOD (Cimorelli et al. 2005), to estimate air concentrations of $PM_{2.5}$ across the Gulf. Meteorological data were obtained from meteorological stations in the Gulf area, and emission sources were optimized by comparing potential AERMOD simulation options with photographs/videos of plumes recorded during the *DWH* cleanup to see which options best represented the photographic evidence. Using AERMOD, hourly $PM_{2.5}$ concentrations were modeled for 3,960 geospatial model receptors in the Gulf area for each day that burning occurred. From the modelled hourly concentrations, two daily air concentration estimates at each receptor were retained in the exposure assessment database: the maximum 1-hour concentration (to represent peak concentrations) and the maximum of two 12-hour (0:00-11:59 and 12:00-

23:59) average concentrations (to represent work shift concentrations).

To link workers with these concentration estimates, industrial hygienists created exposure groups based on work locations in the Gulf: hot zone (≤1 nautical mile (nmi) from the wellhead), source (>1 and ≤5 nmi from the wellhead), offshore (>5 nmi from the wellhead to >3 nmi from shore), near shore (≤3 nmi from shore), and land. These areas were delineated by 10x10 nmi grid squares, along with a finer grid of 1x1 nmi squares in the 10x10 nmi square containing the wellsite for higher resolution in the hot zone and source areas. Workers in the offshore exposure group were further divided by their reported activity into ISB workers and non-ISB offshore workers to underscore the higher exposure experienced by the ISB Group from *in situ* burning. A job-exposure matrix was created by assigning each exposure group an exposure estimate that represented a spatiotemporal average of the daily maximum concentrations across all days of burning over the period of May 15 to July 15, 2010 (i.e. average daily maximum exposure). For ISB workers, industrial hygienists first averaged daily concentrations (either maximum 1-hour or maximum 12-hour average) across receptors within grid squares that contained ISBs on each burn day, and then took the (arithmetic) mean of these area-average daily estimates across all ISB days (N=30). For the other exposure groups (i.e. non-ISB workers), exposure was calculated by first averaging daily concentrations across all receptors in the grid squares that delineated the work location on each burn/flaring day, and then averaging these daily values across all 57 days during which ISB/flaring occurred.

To match individual workers to the exposure groups and the corresponding average daily maximum exposure estimates, industrial hygienists relied on work histories obtained from the enrollment interview and external administrative data maintained by BP, p.l.c. and its contractors. Participants who worked in multiple locations and/or performed multiple activities

(i.e. ISB and others) were matched to the exposure group with the highest exposure estimate. Besides average daily maximum exposure, industrial hygienists also created "cumulative daily maximum exposure" estimates, a proxy for the total exposure burden received in the exposure period, by multiplying average daily maximum exposure by the number of days exposed to $PM_{2.5}$. To estimate days of exposure, the number of days worked in the exposure period was multiplied by the proportion of (either flare or ISB) burn days in the exposure period. By applying the two exposure metrics (i.e. average and cumulative) to each of the two daily concentration estimates (i.e. maximum 1-hour, maximum 12-hour average), four measures of $PM_{2.5}$ exposure were available for analysis. Exposure estimates using the maximum 1-hour daily concentration and the maximum 12-hour average daily concentration had nearly identical distributions (Pearson r>0.99), so we chose to examine only the average maximum 12-hour exposure ($\mu g/m^3$) and the cumulative maximum 12-hour exposure ($\mu g/m^3$-day) (henceforth, average daily maximum and cumulative daily maximum exposures) in all analyses.

Outcome assessment

The outcome of interest was the first occurrence of a CHD event after the last day each worker was exposed to controlled burning, defined as either a self-reported physician diagnosis of CHD or an International Classification of Disease (ICD)-coded fatal CHD event. CHD was self-reported at enrollment interview and in each of the two follow-up interviews. Participants were asked if a doctor ever told them that they had 1) a myocardial infarction (MI) and 2) blockage in the arteries of the heart. Those who responded "yes" were asked to provide the month and year of, or the age at, the event. Participants who reported having either of the two events were identified as having had a non-fatal CHD diagnosis. Fatal CHD events were ascertained via linkage with the National Death Index through December 31, 2019, and we

included deaths attributed to ischemic heart disease (ICD-10 code I20-I25) as an underlying cause. Time at risk was measured in months from the date after each participant ended cleanup work to the first of non-fatal or fatal CHD event, death from other causes, withdrawal from the study, or end of follow-up (December 31, 2019).

Statistical modeling

We used Cox proportional hazards models to estimate hazard ratios (HRs) for first incident CHD event associated with increasing average and cumulative daily maximum $PM_{2.5}$ exposure (Cox 1972). Because burning-related $PM_{2.5}$ exposure of the nearshore and non-ISB offshore workers were substantially lower than those of the other water workers, the first two groups were combined as the "referent group" in the analyses for comparison with the other workers with higher burning-related exposures (henceforth, "burning-exposed workers") (Table 21). For average daily maximum exposure, we combined the groups of ISB workers (10.4 $\mu g/m^3$) and workers at the source (28.7 $\mu g/m^3$) due to the small number of ISB workers (N=41). Average daily maximum exposure then became a three-level categorical variable: referent (0.8 $\mu g/m^3$), low (10.4-28.7 $\mu g/m^3$), and high (96.9 $\mu g/m^3$, corresponding to the exposure level for hot zone workers). The cumulative daily maximum exposure metric, which was determined by both the exposure level and the exposure duration (range=0-49 days), had greater individual variability. To model it in the analysis, we employed the same referent group and categorized the remainder of workers (i.e. burning-exposed group) into tertiles by the exposure distribution to create a four-level categorical variable: the referent group (<10 $\mu g/m^3$-days), low (10-679 $\mu g/m^3$-days), medium (689-1378 $\mu g/m^3$-days), and high (1406-4071 $\mu g/m^3$-days). Because of numerous tied values at the tertile cutoffs (Figure 4), the number of burning-exposed workers in each tertile is not evenly distributed. In addition to the aforementioned models, we also investigated

exposure-response trends by assessing continuous exposures in relation to CHD risk in models. Exposure-response trends were analyzed separately for average (per 10 $\mu g/m^3$ increase) and cumulative daily maximum exposures (per 100 $\mu g/m^3$-day increase).

We adjusted for potential confounding using inverse probability (IP) weighting (Cole and Hernan 2004). We selected covariates based on a directed acyclic graph (DAG) and included the minimally sufficient adjustment set and predictors of the outcome that are not descendants of the exposure in the IP-exposure weights (Brookhart et al. 2006; Greenland et al. 1999) (Figure 5). We obtained stabilized weights by fitting a multinomial logistic regression model for each *categorical* exposure with respect to selected covariates.

All covariates were ascertained at enrollment and included the following: age (in years: 20-29, 30-39, 40-49, 50-59, ≥60), sex (male; female), self-reported race (White; Black; other/multi-racial ("American Indian or Alaskan Native", "Asian", "Native Hawaiian or Pacific Islander", "other races")), Hispanic ethnicity (Hispanic; non-Hispanic), cigarette smoking status (current heavy (≥20 cigarettes/day); current light (<20 cigarettes/day); former; never), highest educational attainment (less than high school; high school diploma or general equivalency diploma; some college or 2-year degree; 4-year college graduate or more), body mass index (BMI; in kg/m^2: underweight or normal [<25], overweight [25-<30], obese I [30-<35], obese II ≥35]), previous oil spill cleanup experience (yes; no), previous oil industry experience (yes; no), pre-cleanup diabetes diagnosis (yes; no), and residential proximity to the spill (living in a coastal county directly affected by the spill or a county adjacent to the impacted counties; living in a Gulf state further from the spill; living in a non-Gulf state).

To account for informative censoring due to loss to follow-up, we used IP-censoring weighting (Hernán et al. 2004; Howe et al. 2016). Participants were considered censored if they

1) did not complete a follow-up interview or completed the first but not the second interview and 2) had not experienced a CHD event prior to being lost to follow-up. Censoring was modelled as a function of its predictors in a pooled logistic regression, and weights were stabilized by the marginal probability of censoring. Covariates in the IP-censoring weights were determined from a DAG (Brookhart et al. 2006) and included: $PM_{2.5}$ exposure, age, sex, self-reported race, Hispanic ethnicity, cigarette smoking, highest educational attainment, previous oil spill cleanup experience, and residential proximity to the spill. The finalized weights applied to the models were the product of the IP-exposure and the IP-censoring weights. Cox proportional hazards models with a robust variance estimator were fitted to estimate HRs and 95% confidence intervals (CIs). IP-exposure and IP-censoring weights were applied to the main analysis and sub-analyses.

We conducted a number of sensitivity analyses. First, we examined non-fatal cases as the outcome. We could not examine fatal CHD as the outcome because of the small number of fatal cases. We also conducted analyses using an alternative definition of CHD-related deaths based on ischemic heart disease as a *contributing/underlying* cause rather than the *underlying* cause of death. Workers with fatal (CHD) events that occurred after OSRC employment but before they could enroll were not identified. We explored the impact of this left truncation in a sensitivity analysis by starting the risk period at study enrollment, effectively excluding 108 pre-enrollment CHD events. In addition, we included self-reported pre-cleanup hypertension in the IP-exposure weight model to see if results differed. This covariate was not included in the main analysis because *pre-cleanup* hypertension was not related to crude oil exposures and we were concerned about possible misclassification of hypertension using self-reports (Gonçalves et al. 2018). Because volatile components of the crude oil may also be related to cardiovascular disease

(Strelitz et al. 2019b), we additionally adjusted for cumulative THC exposure, to see if results differed. Exposure to THC was estimated via a job-exposure matrix based on personal air sample measurements and OSRC work histories collected at enrollment (Groth et al. 2022b; Huynh et al. 2022a, b; Huynh et al. 2022c; Stenzel et al. 2022b; Stewart et al. 2022).

Because workers were also exposed to the $PM_{2.5}$ from engine exhaust, which could not be quantified, we assessed the potential impact of this bias by performing sensitivity analyses that excluded non-ISB offshore workers, the group with the largest potential vessel exhaust exposure variability, and separately, that included land workers as an additional exposure category to quantify the potential bias from land equipment emissions. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). An alpha level of 0.05 was considered statistically significant for all analyses.

5.3 Results

Compared to the full analytical sample (N=9,091), those who completed the first (N=6,204) or second (N=4,251) follow-up interviews tended to be older, female, White, and former or never smokers (Table 18). They were also more likely to have graduated from college and to reside in a non-Gulf state. There was no substantive difference in the other characteristics. During a median follow-up of 59 months (range: 1-115 months), 372 out of 9,091 workers reported an incident CHD event that occurred after the end of OSRC work. This included 338 cases of non-fatal CHD, 5 case of non-fatal CHD with a later fatal CHD event, and 37 fatal CHD events without a history of reported CHD.

Compared to workers in the referent group, we observed increased risks of CHD among workers with higher *average* daily maximum exposure, including a statistically significant

association among the high exposure category (HR = 2.11, 95%CI: 1.08, 4.12) (Table 19). We also saw significantly elevated HR in the analysis with continuous exposure (linear p-trend=0.01). When examining *cumulative* daily maximum exposure, we again observed elevated HRs among workers in all higher exposure categories. We saw a monotonic trend across the exposure categories and a marginally significant increase in CHD risk among workers with high exposure (HR = 1.44, 95%CI: 0.96, 2.14). Analyses without censoring weights produced slightly stronger effect estimates (Table 19). The mean and range of the stabilized IP weights for each cumulative exposure are shown in Table 22.

When we restricted the outcome to non-fatal MI, we observed slightly stronger associations (Table 20). Sensitivity analysis that identified fatal events as deaths with CHD as a *contributing/underlying* cause of death produced minimal differences in the observed associations (Table 23). In an analysis where we started the risk period at time of enrollment instead of at the end of cleanup, workers in the highest exposure categories of average and cumulative exposures were at similarly increased risk of CHD, although a weaker association was observed in the medium cumulative exposure category (Table 24). When we accounted for pre-exposure hypertension in the model, we observed similar associations, although risk among workers in the medium cumulative exposure category was somewhat attenuated (Table 25). When we adjusted in the model for cumulative THC exposure, which was moderately correlated with average and cumulative daily maximum $PM_{2.5}$ exposures (Pearson r=0.26-0.28), we observed slightly attenuated effect estimates, although findings were not substantively different (Table 26). Results were similar when we excluded non-ISB offshore workers from the analytical sample (Table 27). When we expanded the study population to include land workers as a separate exposure group, we observed no difference in risk of CHD between land workers and

the referent group (Table 28).

5.4 Discussion

In this study, we examined the relationship between potential exposure to $PM_{2.5}$ from controlled burning of oil/gas and risk of CHD among *DWH* OSRC workers up to ten years after the *DWH* disaster. We observed elevated effect estimates in the upper categories of both average and cumulative exposures. Notably, those in the high average exposure category had 2.3 times the risk of CHD compared to the referent group. This increase in risk was close to the increase in risk among men from smoking 20 cigarettes per day (RR=2.27) reported in a recent meta-analysis (Hackshaw et al. 2018). These results suggest that exposure to $PM_{2.5}$ from burning of crude oil and gas for a relatively short period (days to weeks) could increase workers' risk of CHD events several years after the exposure.

In our study population, the average daily maximum exposure that workers experienced varied significantly across exposure groups (Pratt et al. 2020). Over a 12-hour shift, ISB workers and workers in the source area were exposed to 10 and 29 $\mu g/m^3$ of shift-average $PM_{2.5}$ levels, respectively, which are similar to levels observed in high-traffic areas in developed countries (Edginton et al. 2019). On the other hand, workers in the hot zone were subject to exposures of almost 100 $\mu g/m^3$, on par with pollution levels in parts of developing countries such as India and China (Edginton et al. 2019; Kesavachandran et al. 2013) and above the daily National Ambient Air Quality Standard of 35 $\mu g/m^3$.

Two major mechanisms underlying $PM_{2.5}$-mediated CHD risk have been proposed. One involves activation of pulmonary and systemic inflammatory responses by inhaled pollutants (Brook et al. 2004; U.S. EPA 2020). This inflammation and associated oxidative stress can

impair endothelial function and stimulate the circulatory release of inflammatory proteins and coagulation factors, which can either predispose individuals to a future CHD event by promoting atherosclerosis or trigger an acute CHD event by destabilizing existing plaques (Brook et al. 2004; U.S. EPA 2020). The other mechanism involves modulation of the autonomic nervous system by pollutants trapped in the respiratory tract (Brook et al. 2004; U.S. EPA 2020). A shift of the system toward the sympathetic tone elevates blood pressure, which can exacerbate atherosclerosis and lead to a CHD event via vascular dysfunction or arrhythmia (U.S. EPA 2020). Together, current mechanistic understanding supports the plausibility of the observed cardiovascular effects of exposure to $PM_{2.5}$.

The relationship between short-term $PM_{2.5}$ exposure and CHD has been examined extensively in ambient air pollution studies. A recent review by the U.S. EPA has implicated short-term $PM_{2.5}$ exposure as a major contributor to CHD (2020). The strongest evidence came from several multi-city studies of CHD emergency department visits and hospital admissions in the US (Haley et al. 2009; Hsu et al. 2017; Kloog et al. 2014; Talbott et al. 2014) and other countries (Barnett et al. 2006; Host et al. 2008; Weichenthal et al. 2016), with supplemental evidence linking $PM_{2.5}$ exposure to CHD mortality (Chen et al. 2017; Dabass et al. 2016; Michikawa et al. 2019). Short-term $PM_{2.5}$ concentrations were also associated with the more specific outcome of MI, as shown in a recent meta-analysis (Farhadi et al. 2020). Unlike these short-term air pollution studies, which examined CHD events on the same day of, or within days after, $PM_{2.5}$ exposure, we were underpowered to examine the acute effect of exposure because only 5 non-fatal CHD events occurred within a month of exposure and we lacked data on fatal CHD events prior to study enrollment.

Despite the lack of ambient air pollution studies that assessed long-term cardiovascular

effects following a transient $PM_{2.5}$ exposure, a few occupational studies have found persistent cardiovascular effects among workers exposed to air pollutants. Previous analyses in the same cohort of *DWH* oil spill workers also showed elevated risk of CHD/MI several years after oil spill work (Strelitz et al. 2018; Strelitz et al. 2019a; Strelitz et al. 2019b). Specifically, the risk of CHD was higher among workers who had higher maximum THC inhalation exposure and longer duration of OSRC work. In contrast, no association was found in those analyses between a crude measure of burning exposure (yes/no) and risk of CHD three years after the spill, possibly because of imprecision in the exposure measurement or too few events among the exposed group to detect an association (Strelitz et al. 2018). With the newly developed quantitative $PM_{2.5}$ estimates and a longer follow-up time, we observed positive associations of CHD risk with average and cumulative $PM_{2.5}$ exposures, which remained elevated after accounting for co-exposure to THC. The persistent effect of air pollutant exposure on cardiovascular health was also evaluated in responders to the 2001 World Trade Center disaster, who were exposed to tremendous amounts of dust (Sloan et al. 2021). During 17 years of follow-up, responders who arrived at the site on Sep 11, 2001 had significantly higher risk of an incident self-reported cardiovascular diagnosis (CHD, MI, stroke, or congestive heart failure) compared to those who arrived on or after Sep 12, 2001, and stronger associations were found for responders who reported being exposed to the dust cloud (Sloan et al. 2021).

In our analysis, we were not able to identify CHD deaths that occurred among OSRC workers before study enrollment because enrollment was contingent upon survival. If more CHD deaths occurred before enrollment among *DWH* oil spill workers exposed to higher levels of $PM_{2.5}$, then our results might have underestimated the true risk. However, given the relatively short time between exposure and enrollment (i.e. immortal time for the fatal outcome) and the

overall small number of fatal CHD cases during the entire follow-up to date, we do not expect left truncation of these fatal events to meaningfully change our results. In a sub-analysis, we examined non-fatal CHD as the outcome, for which there was no immortal time bias, and observed slightly stronger associations. In another analysis, we explored the impact of starting the risk period at a worker's enrollment in the cohort, rather than on the last day of burning exposure, which resulted in exclusion of 86 self-reported non-fatal CHD cases; we observed attenuated effect estimates among workers with low average exposure and medium cumulative exposure, possibly because a disproportionately higher number of workers with these higher exposures developed non-fatal CHD between exposure and enrollment compared to the referent group. However, workers in the highest categories of average and cumulative exposures remained at higher risk of CHD, which suggested a robust association among workers with high levels of $PM_{2.5}$ exposure.

A major strength of our study is the careful reconstruction of burning-related $PM_{2.5}$ exposure, using the AERMOD dispersion model, and detailed work histories collected from the study participants. Because controlled burning had not been adopted as a major mitigation technique in previous oil spills, these exposure estimates allowed us to examine, for the first time, cardiovascular health effects from $PM_{2.5}$ from this unique emission source. Moreover, while most air pollution literature has assessed acute CHD events following a transient $PM_{2.5}$ exposure, the unique exposure pattern and extensive follow-up time of this cohort provided an opportunity to investigate the *long-term* cardiovascular impact of relatively short-term $PM_{2.5}$ exposure. Another strength of the study is the availability of individual-level data on many important covariates, including cigarette smoking, education, previous oil industry experience, and co-exposure to THC. IP-exposure weighting was used to obtain marginal effect estimates

that accounted for important confounders of the association.

Our study also has limitations. One limitation of the study is potential misclassification of the outcome, as we could not obtain medical records from participants to confirm their MI diagnosis or cause of death. Previous studies have reported moderate to high accuracy of self-reported MI and of death certificate diagnosis of CHD, with sensitivities ranging from 0.78 to 0.98 and specificities varying from 0.72 to 1.0 (Barr et al. 2009; Coady et al. 2001; Eliassen et al. 2016; Folsom et al. 1987; Fourrier-Réglat et al. 2010; Goraya et al. 2000; Lloyd-Jones et al. 1998; Machón et al. 2013; Okura et al. 2004; Yamagishi et al. 2009). Many of these studies have associated lower accuracy with older age (Lloyd-Jones et al. 1998; Okura et al. 2004; Olubowale et al. 2017; Yamagishi et al. 2009). Compared to participants examined in these validation studies, workers in our study were younger (most were < 60 years old at enrollment), so we expect a lower degree of outcome misclassification in our population. There could be measurement error in the reported event time due to participants mis-recalling the date of MI diagnosis. However, exploratory analyses (not shown) in which we coarsened the follow-up from one month to four months showed no notable changes from the main analysis results, which suggests that our analysis was robust to measurement error of at least a few months in recall time.

Second, the exposure estimates assigned to workers contained some degree of uncertainty. Because we lacked data on the exact location of most workers on a daily basis, we created a job-exposure matrix that assigned workers of the same exposure group an exposure estimate that reflected the average daily maximum concentration over their general work area across the burning period. However, given the substantial variation in $PM_{2.5}$ concentrations over the Gulf waters and over time, this approach reduced the variability of exposures among

individuals of the same exposure group and resulted in measurement error in the exposure estimates. Exposure variability was possibly largest for workers in the vast nearshore and offshore areas, where air concentrations from the burning were higher near and downwind from the burning sites, but close to nil outside of the smoke plumes and during non-burn hours. The vast majority of the model receptors in these areas had close-to-zero estimated concentrations (<0.1 $\mu g/m^3$) on any given day and hour. Thus, average daily maximum exposure values assigned to the nearshore and non-ISB offshore groups (the referent group) were likely an overestimation of many individuals' actual exposure, as most workers in these exposure groups would not have experienced these estimated levels during most of their work period. However, we do not expect that overestimated exposures for the referent group biased our estimates in the analyses of categorical exposures.

Third, the uncertainty in the exposure estimates and their clustered distribution also limited our interpretation of the exposure-response trend analysis. Because a job-exposure matrix primarily based on work location was used to assign exposure estimates, distribution of the average and cumulative daily maximum exposure estimates was clustered. Given that our cumulative and average exposure estimates were not truly continuous, we could not interpret the trend analysis the way it is usually interpreted in air pollution studies with continuously distributed $PM_{2.5}$ exposures (e.g. changes in outcome corresponding to every 10 $\mu g/m^3$ increase in exposure). We focused on the significance of the continuous associations to provide a sense of the exposure-response relationship. Effect estimates for the trend analysis were provided in tables to provide some indication of the strength of the association, but caution is strongly advised when trying to interpret these results or comparing them with results from other literature.

Fourth, because our goal was to assess health risks of exposures specifically from controlled burning to inform future oil spill responders who are considering this oil mitigation method, the $PM_{2.5}$ estimates reflected only exposure from ISBs and flaring and did not consider background exposures (Pratt et al. 2020). To partially address background sources of $PM_{2.5}$ exposures from engine exhaust, which could not be accounted for, we decided *a priori* to exclude land workers in our main analysis and to focus on water workers, who shared the same source of background exposure (i.e. vessels). In a sensitivity analysis that included land workers, we observed no difference in risk of CHD between land workers and the referent group, which suggests that co-exposure to a different source of background $PM_{2.5}$ alone did not produce a noticeable difference in land workers' risk of CHD. In another sensitivity analysis where we removed the water worker group with the highest potential variability in background exposure (i.e. the non-ISB offshore group), we observed very similar associations to the main analysis. Fifth, there could be bias from unmeasured confounders or imperfect measurement of existing covariates in the models. There could also be a bias if workers were assigned to different jobs based on their baseline health factors at the time of spill that were predictive of their future CHD risk. We adjusted for several indicators of baseline health (BMI, pre-exposure diabetes, smoking) to reduce this potential bias. Also, oil spill jobs that exposed workers to high levels of $PM_{2.5}$ typically required specialized skills (Stewart et al. 2018), so prior related work experience, such as in previous oil spill cleanups or the oil industry, which we accounted for in our analyses, was arguably a more important predictor of exposure than was workers' baseline health. Lastly, some of our adjustment factors, such as cigarette smoking and BMI, were ascertained at enrollment or the home visit as proxies for factors at the time of exposure, and might have changed over time. However, we expect little change in these factors over the short span between exposure and time

of their ascertainment.

In sum, we found increased risk of CHD among workers with higher estimated $PM_{2.5}$ exposures from ISBs and flaring of oil and gas. To our knowledge, our study is the first to evaluate the association between potential $PM_{2.5}$ exposure and CHD risk among oil spill workers. Additional research is needed to evaluate the persistence of effects of high-level, short-term particulate exposure on cardiovascular health among workers and among the general public.

5.5 Tables and Figures

Table 18. Characteristics of *DWH* disaster oil spill water workers who responded to the enrollment, first follow-up, and second follow-up interviews, respectively

Characteristic	**Enrollment** *(n=9,091)*	**1st Follow-up** *(n=6,204)*	**2nd Follow-up** *(n=4,251)*
	n (%)	*n (%)*	*n (%)*
Age at enrollment (y)			
20-29	2093 (23.0)	1237 (19.9)	797 (18.8)
30-39	2244 (24.7)	1441 (23.2)	941 (22.1)
40-49	2231 (24.5)	1556 (25.1)	1097 (25.8)
50-59	1766 (19.4)	1366 (22.0)	960 (22.6)
>=60	757 (8.3)	604 (9.7)	456 (10.7)
Gender			
Male	8229 (90.5)	5555 (89.5)	3780 (88.9)
Female	862 (9.5)	649 (10.5)	471 (11.1)
Race			
White	6548 (72.0)	4511 (72.7)	3237 (76.2)
Black	1562 (17.2)	1030 (16.6)	611 (14.4)
Other	981 (10.8)	663 (10.7)	403 (9.5)
Hispanic ethnicity			
No	8490 (93.4)	5809 (93.6)	4017 (94.5)
Yes	601 (6.6)	395 (6.4)	234 (5.5)
Highest educational attainment			
Less than high school	1674 (18.4)	1078 (17.4)	583 (13.7)
High school diploma/GED	2839 (31.2)	1838 (29.6)	1189 (28.0)
Some college/2-year degree	2822 (31.0)	1942 (31.3)	1381 (32.5)
4-year college graduate or more	1756 (19.3)	1346 (21.7)	1098 (25.8)
Weight classification			
Underweight or normal (BMI < 25)	2390 (26.3)	1609 (25.9)	1037 (24.4)
Overweight (25 ≤ BMI < 30)	3887 (42.8)	2638 (42.5)	1874 (44.1)
Obese I (30 ≤ BMI < 35)	1849 (20.3)	1275 (20.6)	875 (20.6)
Obese II (BMI ≥ 35)	965 (10.6)	682 (11.0)	465 (10.9)

Reported pre-cleanup diabetes diagnosis			
No	8751 (96.3)	5956 (96.0)	4086 (96.1)
Yes	340 (3.7)	248 (4.0)	165 (3.9)
Reported pre-spill hypertension diagnosis			
Missing	150 (1.7)	102 (1.6)	68 (1.6)
No	7532 (82.9)	5069 (81.7)	3462 (81.4)
Yes	1409 (15.5)	1033 (16.7)	721 (17.0)
Smoking status			
Current heavy smoker (≥ 20 cigarettes/d)	1102 (12.1)	691 (11.1)	383 (9.0)
Current light smoker (< 20 cigarettes/d)	1887 (20.8)	1206 (19.4)	739 (17.4)
Former smoker	2013 (22.1)	1426 (23.0)	1028 (24.2)
Never smoked	4089 (45.0)	2881 (46.4)	2101 (49.4)
Residential county proximity to Gulf of Mexico[a]			
Direct or indirect contact	5716 (62.9)	3810 (61.4)	2489 (58.6)
Other Gulf state residence	1696 (18.7)	1124 (18.1)	764 (18.0)
Non-Gulf state residence	1679 (18.5)	1270 (20.5)	998 (23.5)
Previous oil spill cleanup work			
No	7813 (85.9)	5264 (84.9)	3577 (84.1)
Yes	1278 (14.1)	940 (15.2)	674 (15.9)
Previous oil industry experience			
No	7294 (80.2)	4952 (79.8)	3395 (79.9)
Yes	1797 (19.8)	1252 (20.2)	856 (20.1)

Abbreviations: *DWH*, *Deepwater Horizon*; GED, General Equivalency Diploma; BMI, body mass index

[a]Direct proximity is defined as living in a county directly adjacent to the Gulf of Mexico; indirect is defined as living in a county adjacent to coastal counties

Table 19. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill water workers, 2010-2019 (N=9,091).

$PM_{2.5}$ Exposure	**Total Cases (n=372)**	**Total N (n=9,091)**	**No censoring weights[a]**		**IP-censoring weighted[a,b]**	
			HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Average exposure						
Referent[c]	293	7111	Referent		Referent	
Low	64	1672	1.29 (0.96, 1.74)	0.10	1.26 (0.93, 1.70)	0.13
High	15	308	2.17 (1.12, 4.20)	0.02	2.11 (1.08, 4.12)	0.03
Per 10 µg/m^3 increase			1.11 (1.03, 1.19)	0.01	1.10 (1.02, 1.19)	0.01
Cumulative exposure						
Referent[c]	293	7111	Referent		Referent	
Low	20	589	1.21 (0.69, 2.10)	0.50	1.19 (0.68, 2.08)	0.54
Medium	26	603	1.37 (0.87, 2.17)	0.18	1.38 (0.88, 2.16)	0.16
High	33	788	1.53 (1.03, 2.29)	0.04	1.44 (0.96, 2.14)	0.08
Per 100 µg/m^3-d increase			1.03 (1.00, 1.05)	0.05	1.03 (1.00, 1.05)	0.06

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]Censoring weights accounted for exposure, age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[c]The referent group consisted of nearshore workers and offshore workers who did not work on *in situ* burns.

Table 20. Association between $PM_{2.5}$ exposure and incident non-fatal CHD among *DWH* disaster oil spill workers, 2010-2019 (N=9,091).

$PM_{2.5}$ Exposure	**Total Cases (n=343)**	**Total N (n=9,091)**	**HR (95% CI)[a]**	**p-value**
Average exposure				
Referent[b]	270	7111	Referent	
Low	61	1672	1.31 (0.96, 1.79)	0.09
High	14	308	2.21 (1.10, 4.45)	0.03
Per 10 µg/m^3 increase			1.11 (1.03, 1.20)	0.01
Cumulative exposure				
Referent[b]	270	7111	Referent	
Low	19	589	1.18 (0.65, 2.15)	0.58
Medium	26	603	1.53 (0.97, 2.39)	0.07
High	30	788	1.48 (0.97, 2.25)	0.07
Per 100 µg/m^3-d increase			1.03 (1.00, 1.06)	0.04

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]The referent group consisted of nearshore workers and offshore workers who did not work on *in situ* burns.

Table 21. Average and cumulative $PM_{2.5}$ exposure among *DWH* disaster oil spill water workers (N=9,091)

$PM_{2.5}$ Exposure	***n (%)***	**Concentrations**
Average 12-hour daily		($\mu g/m^3$)
Referent[a]	7111 (78.2)	0.8
In situ burn workers (low)	41 (0.5)	10.4
Source workers (low)	1631 (17.9)	28.7
Hot zone workers (high)	308 (3.4)	96.9
Cumulative 12-hour daily		($\mu g/m^3$-days)
Referent[a]	7111 (78.2)	<10
T1 (low)[b]	589 (6.5)	10-679
T2 (medium)[b]	603 (6.6)	689-1378
T3 (high)[b]	788 (8.7)	1406-4071

Abbreviations: *DWH, Deepwater Horizon*

[a]The referent group consisted of nearshore workers and offshore workers who did not work on *in situ* burns.

[b]Number of workers in each tertile not evenly distributed due to tied values at the tertile cutoffs

Table 22. Distribution of stabilized inverse probability of exposure, censoring, and overall weights in analysis of $PM_{2.5}$ exposure and coronary heart disease among *DWH* disaster oil spill workers (N=9,067), 2010-2019

Exposure	**IPEW**	**IPCW**	**Overall Weight[a]**
	Mean (Range)	*Mean (Range)*	*Mean (Range)*
Average exposure	1.00 (0.10, 5.78)	1.00 (0.59, 2.84)	1.00 (0.10, 6.09)
Cumulative exposure	1.00 (0.22, 3.94)	1.00 (0.59, 3.05)	0.99 (0.17, 3.94)

Abbreviations: *DWH, Deepwater Horizon*; IPEW, inverse probability of exposure weight; IPCW, inverse probability of censoring weight

[a]Overall weights are the product of IPEW and IPCW.

Table 23. Association between $PM_{2.5}$ exposure and incident CHD events (fatal events identified as CHD as a *contributing* cause of death) among *DWH* disaster oil spill water workers, 2010-2019 (N=9,091).

$PM_{2.5}$ Exposure	**Total Cases (n=380)**	**Total N (n=9,091)**	**HR (95% CI)[a]**	**p-value**
Average exposure				
Referent[b]	301	7111	Referent	
Low	64	1672	1.22 (0.91, 1.65)	0.19
High	15	308	2.05 (1.05, 4.01)	0.04
Per 10 µg/m^3 increase			1.10 (1.02, 1.19)	0.02
Cumulative exposure				
Referent[b]	301	7111	Referent	
Low	20	589	1.16 (0.66, 2.02)	0.60
Medium	26	603	1.34 (0.86, 2.10)	0.20
High	33	788	1.40 (0.94, 2.08)	0.10
Per 100 µg/m^3-d increase			1.02 (1.00, 1.05)	0.08

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]The referent group consisted of nearshore workers and offshore workers who did not work on *in situ* burns.

Table 24. Association between $PM_{2.5}$ exposure and incident CHD events after *enrollment* among DWH disaster oil spill water workers, 2010-2019 (N=8,983).

$PM_{2.5}$ Exposure	**Total Cases (n=257)**	**Total N (n=8,983)**	**HR (95% CI)[a]**	**p-value**
Average exposure				
Referent[b]	207	7029	Referent	
Low	37	1648	1.07 (0.73, 1.56)	0.74
High	13	306	2.17 (1.15, 4.10)	0.02
Per 10 µg/m^3 increase			1.11 (1.02, 1.20)	0.02
Cumulative exposure				
Referent[b]	207	7029	Referent	
Low	13	583	1.17 (0.59, 2.32)	0.65
Medium	14	591	1.01 (0.56, 1.81)	0.97
High	23	780	1.45 (0.91, 2.33)	0.12
Per 100 µg/m^3-d increase			1.02 (0.99, 1.05)	0.20

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]The referent group consisted of nearshore workers and offshore workers who did not work on *in situ* burns.

Table 25. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill water workers, additionally adjusting for prevalent hypertension, 2010-2019 (N=8,941).

$PM_{2.5}$ Exposure	**Total Cases (n=352)**	**Total N (n=8,941)**	**HR (95% CI)[a]**	**p-value**
Average exposure				
Referent[b]	279	6989	Referent	
Low	58	1647	1.14 (0.83, 1.56)	0.41
High	15	305	2.09 (1.06, 4.13)	0.03
Per 10 µg/m^3 increase			1.10 (1.02, 1.19)	0.02
Cumulative exposure				
Referent[b]	279	6989	Referent	
Low	19	582	1.20 (0.67, 2.17)	0.54
Medium	21	594	1.08 (0.66, 1.78)	0.76
High	33	776	1.46 (0.98, 2.17)	0.07
Per 100 µg/m^3-d increase			1.02 (1.00, 1.05)	0.09

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]The referent group consisted of nearshore workers and offshore workers who did not work on *in situ* burns.

Table 26. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill water workers, additionally adjusting for cumulative daily maximum exposure to total hydrocarbons, 2010-2019 (N=9,091).

$PM_{2.5}$ Exposure	**Total Cases (n=372)**	**Total N (n=9,091)**	**HR (95% CI)[a]**	**p-value**
Average exposure				
Referent[b]	293	7111	Referent	
Low	64	1672	1.29 (0.87, 1.91)	0.20
High	15	308	1.91 (0.98, 3.72)	0.06
Per 10 µg/m^3 increase			1.10 (1.01, 1.19)	0.03
Cumulative exposure				
Referent[b]	293	7111	Referent	
Low	20	589	1.17 (0.68, 2.03)	0.56
Medium	26	603	0.99 (0.63, 1.57)	0.98
High	33	788	1.57 (0.94, 2.63)	0.08
Per 100 µg/m^3-d increase			1.04 (0.99, 1.08)	0.11

Abbreviations: CHD, coronary heart disease; *DWH*, *Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]The referent group consisted of nearshore workers and offshore workers who did not work on *in situ* burns.

Table 27. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill water workers, excluding offshore workers who did not participate in in situ burning, 2010-2019 (N=7,960).

$PM_{2.5}$ Exposure	**Total Cases (n=328)**	**Total N (n=7,960)**	**HR (95% CI)[a]**	**p-value**
Average exposure				
Referent[b]	249	5980	Referent	
Low	64	1672	1.30 (0.96, 1.78)	0.09
High	15	308	2.25 (1.12, 4.51)	0.02
Per 10 µg/m^3 increase			1.11 (1.03, 1.21)	0.01
Cumulative exposure				
Referent[b]	249	5980	Referent	
Low	20	589	1.23 (0.69, 2.19)	0.48
Medium	26	603	1.41 (0.89, 2.23)	0.15
High	33	788	1.52 (1.01, 2.29)	0.04
Per 100 µg/m^3-d increase			1.03 (1.00, 1.06)	0.06

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]The referent group consisted of nearshore workers.

Table 28. Association between $PM_{2.5}$ exposure and incident CHD events among *DWH* disaster oil spill worker, 2010-2019 (N=20,351).

$PM_{2.5}$ Exposure	**Total Cases (n=779)**	**Total N (n=20,351)**	**HR (95% CI)[a]**	**p-value**
Average exposure				
Referent[b]	293	7111	Referent	
Land[c]	407	11260	1.03 (0.87, 1.22)	0.73
Low	64	1672	1.28 (0.94, 1.75)	0.11
High	15	308	2.34 (1.22, 4.46)	0.01
Per 10 µg/m^3 increase			1.11 (1.04, 1.19)	<0.01
Cumulative exposure				
Referent[b]	293	7111	Referent	
Land[c]	407	11260	1.03 (0.87, 1.22)	0.73
Low	20	589	1.16 (0.69, 1.95)	0.58
Medium	26	603	1.60 (1.01, 2.52)	0.04
High	33	788	1.45 (0.91, 2.30)	0.11
Per 100 µg/m^3-d increase			1.03 (1.00, 1.05)	0.02

Abbreviations: CHD, coronary heart disease; *DWH, Deepwater Horizon*; HR, hazard ratio; CI, confidence interval

[a]Models accounted for age, gender, race, ethnicity, weight class, smoking, pre-cleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience

[b]The referent group consisted of nearshore workers and offshore workers who did not work on *in situ* burns.

[c]Land workers had an average exposure of 0.3 µg/m^3 and a cumulative exposure <10 µg/m^3-days

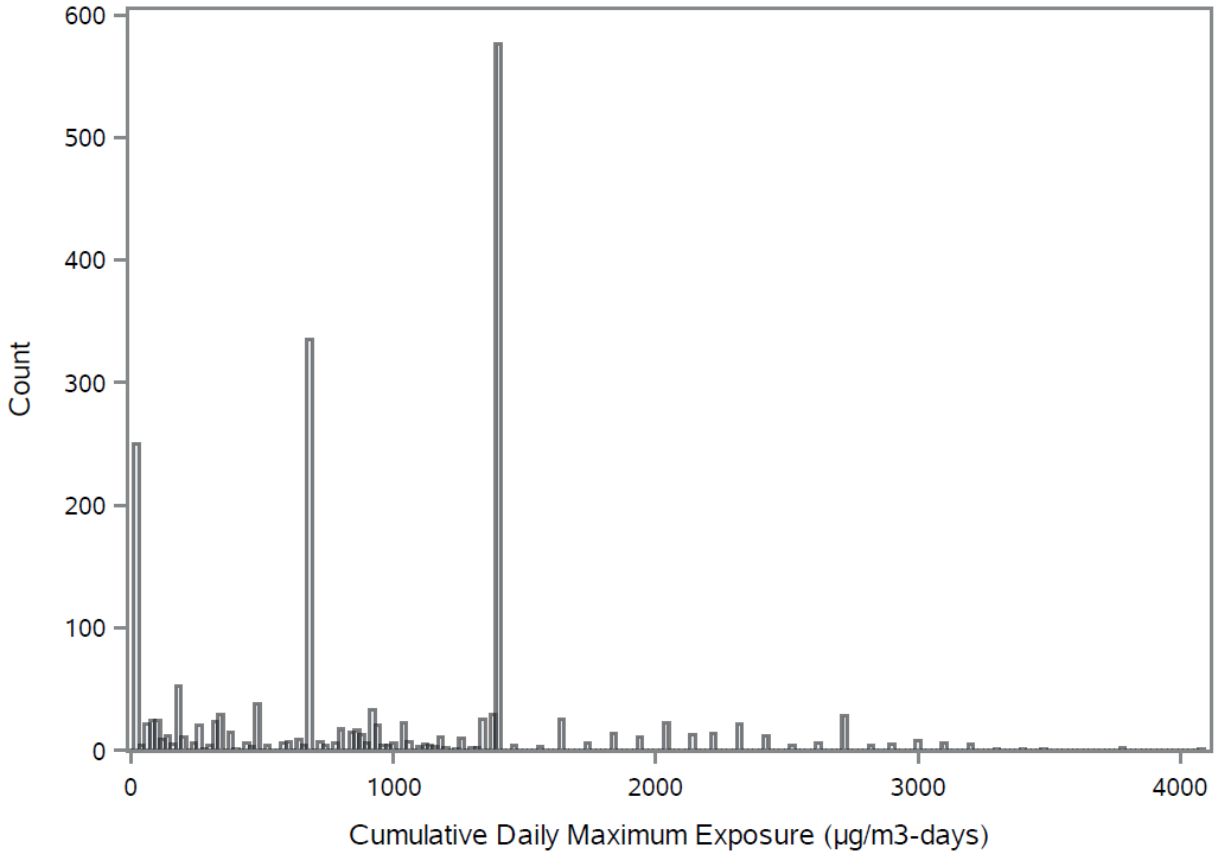

Figure 4. Distribution of cumulative daily maximum PM2.5 exposure among burning-exposed *Deepwater Horizon* oil spill workers (N=1,980).

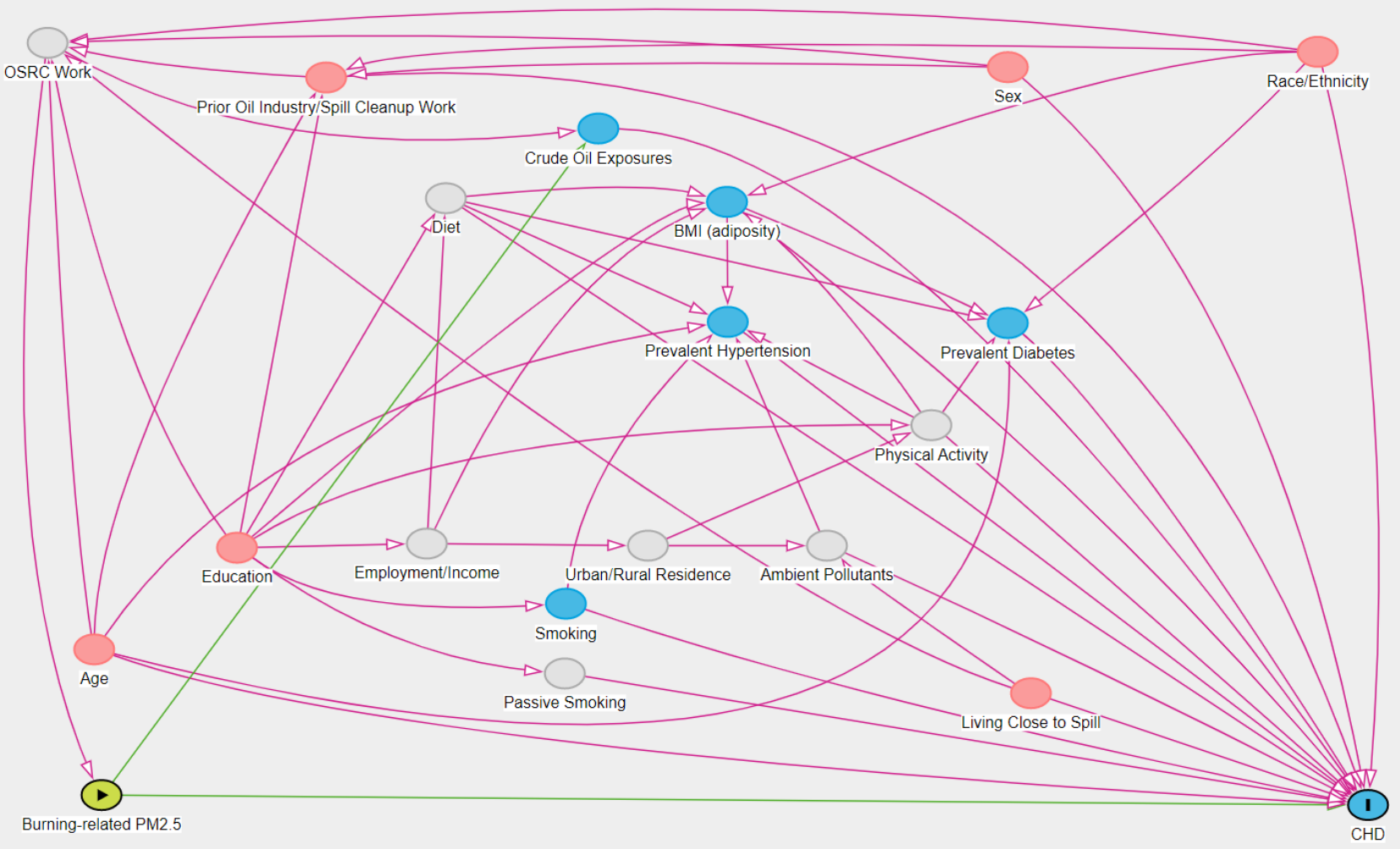

Figure 5. Directed acyclic graph that guided covariate selection for models estimating the relationship between burning-related $PM_{2.5}$ exposure and incident coronary heart disease (CHD) events among *Deepwater Horizon* oil spill workers, 2010-2019 (N=9,091).

CHAPTER 6: DISCUSSION

6.1 Summary of Objectives and Results

The aims of this research were to 1) assess the association of several spill-related chemicals (BTEX-H) and THC with incident CHD events, and 2) assess the associations between estimated $PM_{2.5}$ from burning/flaring of oil/gas and incident CHD events among the *DWH* oil spill workers, up to 10 years following the *DWH* disaster.

In the results presented in **Chapters 4 and 5**, we observed modest and non-significant increases in risk of CHD among those in the top quintile of cumulative maximum exposure to each exposure agent compared to workers in the referent group (range of HR: 1.19-1.44), with the highest HRs observed for THC, benzene, and n-hexane. We also saw elevated risks in the second and/or third quintiles for some agents, but overall there was no clear exposure-response trends. In the mixture analysis that modeled quintile exposures as integer scores, we found little evidence of an overall effect, which could be attributed to the apparent non-linear relationship between the exposure and the outcome, where effects were present only above an exposure threshold (e.g. in Q5). When we examined cumulative average exposures, we observed similar patterns of association although effect estimates were slightly attenuated. We saw increased risk of CHD among workers with higher average daily maximum and cumulative daily maximum $PM_{2.5}$ exposure compared to the referent group, with HRs being highest in the top exposure categories (average daily maximum: HR = 2.11, 95%CI: 1.08, 4.12; cumulative daily maximum: HR = 1.44, 95%CI: 0.96, 2.14). There was also evidence for monotonic exposure-response trends relating each exposure metric to risk of CHD.

The positive associations we observed were consistent with findings from ambient air pollution

studies that examined these exposure agents with CHD-related emergency department visits, hospitalizations, and deaths (Alexeeff et al. 2021; Barceló et al. 2016; Bard et al. 2014; Farhadi et al. 2020; Ran et al. 2018a). Most of these studies, however, examined cardiovascular events immediately following a short-term or long-term exposure, while our study investigated and showed persistent associations many years after exposure for a relatively short period (weeks to months). Our study is also the first to evaluate the relationship between exposure to individual crude oil chemicals and risk of CHD among oil spill workers. Previous studies of *DWH* oil spill workers have related ordinal maximum THC exposure categories and longer duration of cleanup with CHD several years after the spill. Exposure estimates of BTEX-H chemicals and $PM_{2.5}$ allowed us to investigate putative exposure(s) responsible for the cardiovascular effects observed among our population.

In the stratified analyses, we observed stronger associations between BTEX-H/THC exposures and CHD risk in some subgroups, including workers who had high school education or less, who were non-obese, and ever smokers. No study that we are aware of has examined education, BMI, or smoking status as effect measure modifiers of the relationship between crude oil chemicals and CHD, although studies of PM exposure have shown stronger associations among participants with less education and who were smokers. One possible explanation for the weaker associations among the obese group is that variability of CHD risk is likely higher among these workers, so it is easy for the modest effect of oil exposures to be lost among this high variability.

We performed numerous sensitivity analyses in both aims to address potential biases. To explore the potential effect of left-truncating workers who died between cleanup and enrollment, we examined non-fatal outcome only where there was no immortal time bias and found somewhat stronger associations. We also attempted analyses that started risk period at enrollment and found similar or slightly weaker associations; however, effect estimates remained elevated in the top categories of BTEX-H/THC and $PM_{2.5}$ exposures. To address residual confounding, we additionally adjusted for self-

reported hypertension in analyses and found similar results. We also adjusted for co-exposure to $PM_{2.5}$ and THC, respectively, in the aim 1 and aim 2 analyses and found only slightly attenuated associations. These sensitivity analyses suggest that our results were robust to these biases.

6.2 Strengths and Limitations

Strengths

One major strength of our study is the careful reconstruction of exposure data. Industrial hygienists estimated THC and BTEX-H exposures using ~28,000 personal air samples and detailed OSRC work histories reported by study participants. To estimate burning-related $PM_{2.5}$ exposure, concentrations of $PM_{2.5}$ obtained from a state-of-the-art steady-state plume model (AERMOD) developed by the U.S. EPA were linked to OSRC work histories.

In addition, while most air pollution studies examined CHD events immediately following acute or long-term exposures, our study was unique in assessing exposures that lasted weeks ($PM_{2.5}$ exposure) to a few months (BTEX-H/THC) and the cardiovascular effect many years after the cessation of exposure. Because controlled burning had not been adopted as a major mitigation technique in previous oil spills, available $PM_{2.5}$ exposure estimates allowed us to examine, for the first time, cardiovascular health effects from this unique emission source (burning of crude oil/natural gas).

Another strength is the use of IP-censoring weighting to address informative censoring due to loss to follow-up. In our study, we did not observe notable differences in results in analyses with and without censoring weights, suggesting that our analyses are robust to the potential non-response bias. We also used an innovative mixture method, quantile g-computation in aim 1 to assess the joint effect of the BTEX-H mixture. Evidence on the joint effect would have provided evidence for interventions to target the emission source; however, we did not observe strong effects in the mixture analysis.

Lastly, the availability of data on important covariates, including cigarette smoking, education,

previous oil industry experience, allowed us to account for and reduce bias from important confounders of the associations. These data also provided an opportunity (in aim 1) to stratify analyses by participant traits to identify groups that might be particularly vulnerable to the effects of these exposures.

Limitations

One limitation of the study is potential misclassification of the outcome, as we could not obtain medical records from participants to confirm their MI diagnosis or cause of death. Previous studies have reported moderate to high accuracy of self-reported MI and of death certificate diagnosis of CHD, with sensitivities ranging from 0.78 to 0.98 and specificities varying from 0.72 to 1.0 (Barr et al. 2009; Coady et al. 2001; Eliassen et al. 2016; Folsom et al. 1987; Fourrier-Réglat et al. 2010; Goraya et al. 2000; Lloyd-Jones et al. 1998; Machón et al. 2013; Okura et al. 2004; Yamagishi et al. 2009). Many of these studies have associated lower accuracy with older age (Lloyd-Jones et al. 1998; Okura et al. 2004; Olubowale et al. 2017; Yamagishi et al. 2009). Compared to participants examined in these validation studies, workers in our study were younger (most were < 60 years old at enrollment), so we expect a lower degree of outcome misclassification in our population. There could be measurement error in the reported event time due to participants mis-recalling the date of MI/CHD diagnosis. However, exploratory analyses in which we coarsened the follow-up from one month to four months showed no notable changes from the main analysis results, which suggests that our analysis was robust to measurement error of at least a few months in recall time.

Second, the THC/BTEX-H exposure estimates assigned to workers contain some degree of uncertainty, particularly at levels below the LOD (Stewart et al. 2022); however, we do not expect these measurement errors to substantially bias our estimates in the categorical exposure analyses. Another possible source of exposure misclassification is that while many participants worked on multiple jobs/tasks during the cleanup, we do not have information on which days and how much time in a day

they spent on each job/activity, which increased uncertainty in the estimates of daily exposures. To overcome this limitation, we examined both cumulative daily maximum and cumulative daily average exposures and found similar results.

Third, there were also potential measurement error with the $PM_{2.5}$ exposure estimates. Because we lacked data on the exact location of most workers on a daily basis, we created a job-exposure matrix that assigned workers of the same exposure group an exposure estimate that reflected the average daily maximum concentration over their general work area across the burning period. However, given the substantial variation in $PM_{2.5}$ concentrations over the Gulf waters and over time, this approach reduced the variability of exposures among individuals of the same exposure group and resulted in measurement error in the exposure estimates. Exposure variability was possibly largest for workers in the vast nearshore and offshore areas, where air concentrations from the burning were higher near and downwind from the burning sites, but close to nil outside of the smoke plumes and during non-burn hours. The vast majority of the model receptors in these areas had close-to-zero concentrations (<0.1 $\mu g/m^3$) on any given day and hour. Thus, average daily maximum exposure values assigned to the nearshore and non-ISB offshore groups (the referent group) were likely an overestimation of many individuals' actual exposure, as most workers in these exposure groups would not have experienced these estimated levels during most of their work period. However, we do not expect that overestimated exposures for the referent group biased our estimates in the analyses of categorical exposures.

Fourth, the uncertainty in the $PM_{2.5}$ exposure estimates and their clustered distribution also limited our interpretation of the exposure-response trend analysis. Because a job-exposure matrix primarily based on work location was used to assign exposure estimates, distribution of the average and cumulative daily maximum exposure estimates was clustered. Given that our cumulative and average exposure estimates were not truly continuous, we could not interpret the trend analysis the way it is usually interpreted in air pollution studies with continuously distributed $PM_{2.5}$ exposures (e.g. changes

in outcome corresponding to every 10 $\mu g/m^3$ increase in exposure). We focused on the significance of the continuous associations to provide a sense of the exposure-response relationship. Effect estimates for the trend analysis were provided in tables to provide some indication of the strength of the association, but caution is strongly advised when trying to interpret these results or comparing them with results from other literature.

Fifth, because our goal was to assess health risks of exposures specifically from controlled burning to inform future oil spill responders who are considering this oil mitigation method, the $PM_{2.5}$ estimates reflected only exposure from ISBs and flaring and did not consider background exposures (Pratt et al. 2020). To partially address background sources of $PM_{2.5}$ exposures from engine exhaust, which could not be accounted for, we decided *a priori* to exclude land workers in our main analysis and to focus on water workers, who shared the same source of background exposure (i.e. vessels). In a sensitivity analysis that included land workers (who were exposed to $PM_{2.5}$ from land vehicles and equipment), we observed no difference in risk of CHD between land workers and the referent group, which suggests that co-exposure to a different source of background $PM_{2.5}$ alone did not produce a noticeable difference in land workers' risk of CHD.

Sixth, there could be bias from unmeasured confounders or imperfect measurement of existing covariates in the models. We did not measure, and were thus unable to account for, co-exposure to other occupational agents, including nitrogen oxides and ozone (Middlebrook et al. 2012). In sensitivity analyses of aim 1 and 2, we adjusted for co-exposure to burning-related $PM_{2.5}$ and cumulative THC, respectively, and found only slightly attenuated associations. There could also be a bias if workers were assigned to different jobs/activities based on their health factors at the time of spill that were predictive of their future CHD risk. We adjusted for several indicators of baseline health (BMI, pre-cleanup diabetes, pre-cleanup hypertension, smoking) to reduce this potential bias, but we had only limited data on healthcare access and lifestyle factors (e.g. diet). We used self-reported race, ethnicity, and education

as proxies for the downstream effects of socioeconomic disparities that might influence risk of CHD, but had to combine some categories due to small numbers. Lastly, some of our adjustment factors, such as cigarette smoking and BMI, were ascertained at enrollment as proxies for factors at the time of exposure and might have changed over time. However, we expect little change in these factors over the relatively short span between exposure and enrollment.

6.3 Directions for Future Research

One of the benefits of this research is the ability to improve worker protection in the event of future oil spills. We have no evidence that masks/respirators were used routinely in any situation other than in tank entry. The persistent cardiovascular effects among workers exposed to higher levels of crude oil chemicals and/or burning-related $PM_{2.5}$ provide support for changes in workplace practices (e.g. use of respiratory protection) to protect workers against these air pollutants. Because workers were also exposed to BTEX-H/THC chemicals from skin contact, future research should examine the cardiovascular effects of these chemicals from dermal exposure or all routes of exposure.

A recent publication has associated cumulative THC exposure with higher prevalence of hypertension among home visit participants of the GuLF Study (Kwok et al. 2022). Animal and human studies have suggested that air pollutant exposures could induce a CHD event via vascular dysfunction, which could be manifested as hypertension (Brook et al. 2004). It is possible that the air pollutant-CHD association is partially mediated by hypertension. A mediation analysis can provide evidence on the mechanisms by which THC/BTEX-H lead to CHD events among the *DWH* disaster workers.

6.4 Conclusions

To our knowledge, our study is the first to evaluate the association of exposure to individual crude oil chemicals and burning-related $PM_{2.5}$ with risk of CHD among oil spill workers. Our study

showed modestly increased risk of CHD among oil spill workers exposed to higher levels of BTEX-H/THC and $PM_{2.5}$. These findings were consistent with evidence from ambient air pollution research that suggest exposure to these agents may induce adverse cardiovascular effects. Additional research is needed to evaluate these persistent relationships among workers and the general public, and to assess any benefit conferred by use of personal protective equipment and healthy lifestyles practices.

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