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The association between oil spill cleanup-related total hydrocarbon exposure and diabetes

H.V. Jardel [a,*], L.S. Engel [a,b], K.G. Lawrence [b], P.A. Stewart [c], M.R. Stenzel [d], M.D. Curry [e], R.K. Kwok [b,f], D.P. Sandler [b]

[a] Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA
[b] Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, DHHS, Research Triangle Park, NC, USA
[c] Stewart Exposure Assessments, LLC North Arlington, Virginia, USA
[d] Exposure Assessment Applications LLC Arlington, Virginia, USA
[e] Social and Scientific Systems, Inc., a DLH Holding Company Durham, NC, USA
[f] Office of the Director, National Institute of Environmental Health Sciences, NIH, DHHS, Bethesda, MD, USA

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ABSTRACT

Background: Although evidence suggests relationships between some crude oil components and glycemic dysregulation, no studies have examined oil spill-related chemical exposures in relation to type 2 diabetes mellitus (DM) risk. This study examined the relationship between total hydrocarbon (THC) exposure among workers involved in the 2010 *Deepwater Horizon (DWH)* oil spill and risk of DM up to 6 years afterward.

Methods: Participants comprised 2660 oil-spill cleanup or response workers in the prospective GuLF Study who completed a clinical exam and had no self-reported DM diagnosis prior to the spill. Maximum THC exposure was estimated with a job-exposure matrix based on interview data and personal measurements taken during cleanup operations. We defined incident DM by self-reported physician diagnosis of DM, antidiabetic medication use, or a measured hemoglobin A1c value $\geq$ 6.5%. We used log binomial regression to estimate risk ratios (RRs) for DM across ordinal categories of THC exposure. The fully adjusted model controlled for age, sex, race/ethnicity, education, employment status, and health insurance status. We also stratified on clinical body mass index categories.

Results: We observed an exposure-response relationship between maximum daily ordinal THC exposure level and incident DM, especially among overweight participants. RRs among overweight participants were 0.99 (95% CI: 0.37, 2.69), 1.46 (95% CI: 0.54, 3.92), and 2.11 (95% CI: 0.78, 5.74) for exposure categories 0.30–0.99 ppm, 1.00–2.99 ppm, and $\geq$3.00 ppm, respectively (p_{trend} = 0.03).

Conclusion: We observed suggestively increasing DM risk with increasing THC exposure level among overweight participants, but not among normal weight or obese participants.

1. Introduction/background

The *2010 Deepwater Horizon* (*DWH*) oil spill is the largest recorded marine oil spill in the United States, releasing an estimated 205.8 million gallons of crude oil into the Gulf of Mexico over 87 days (U.S. Coast Guard, 2011). Cleanup efforts included tens of thousands of workers (U.S. Coast Guard, 2011). Workers experienced a variety of spill-related exposures as a function of the types, timing, and locations of their jobs/tasks, as weathering processes altered the geographic distribution and composition of the oil. Crude oil contains a range of volatile organic compounds that may contribute to an individual's total hydrocarbon (THC) exposure. Among those volatile organic compounds, the best studied in relation to human glycemic dysregulation is benzene, which together with toluene, ethylbenzene, xylenes, and n-hexane comprise BTEX-H. The BTEX-H chemicals comprised approximately 18% by weight (approximately 30% by volume) of the volatile chemicals in the original crude oil (Reddy et al., 2012), though the relative proportions to which workers were exposed varied based on the degree of weathering of the oil to which a worker was exposed.

Among the BTEX-H chemicals, benzene is the most well studied in relation to glycemic regulation. Non-occupational studies of elderly adults and children found a relationship between increased benzene

* Corresponding author.
E-mail address: jahan1@ad.unc.edu (H.V. Jardel).

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exposure and increased insulin resistance (Amin et al., 2018; Choi et al., 2014). In mice, inhaled benzene induces similar indications of glycemic dysregulation, with hypothalamic inflammation and endoplasmic reticulum stress (Debarba et al., 2020), as well as oxidative stress (Abplanalp et al., 2019). Additionally, ingestion of benzene by rats has been associated with increased fasting blood glucose, blood insulin increases, and insulin resistance, as well as increased levels of oxidative species, decreased antioxidant capacity, and evidence of DNA damage in β-cells and liver cells. Little research has examined the other BTEX-H chemicals in relation to glycemic dysfunction, although one study found that inhaled toluene at repeated high doses was associated with persistent overall metabolic and glycemic dysfunction in rats fed a high fat diet (Dick et al., 2015).

Type 2 diabetes mellitus (DM) is characterized by a failure of glycemic homeostasis due to pancreatic β-cell dysfunction or somatic cell resistance to insulin. BTEX-H exposure may contribute to β-cell dysfunction via oxidative stress, which may overwhelm antioxidant mechanisms, given that exposure in human *in vitro* assays and rodent models leads to increased oxidative stress markers and oxidative DNA damage (Buthbumrung et al., 2008; Costa-Amaral et al., 2019; Kim et al., 2011; Lagorio et al., 1994; Liu et al., 2016; Midorikawa et al., 2004; Moro et al., 2012; Salimi et al., 2017; Uzma et al., 2010;

Table 1
Study population (n = 2709) characteristics at enrollment, except where indicated (overall and by diabetes status).

	All participants (n = 2709)		Diabetics(n = 245)		Non diabetics (n = 2464)		p-value[g]
	N	%	N	%	N	%	
THC exposure level (ppm)[a]							0.77
< 0.30	364	13.4%	31	12.7%	333	13.5%	
0.30–1.99	850	31.4%	73	29.8%	777	31.5%	
2.00–2.99	821	30.3%	78	31.8%	743	30.2%	
≥ 3.00	674	24.9%	63	25.7%	611	24.8%	
Missing	–		–		–		
Age at clinical exam (y)							<0.01
< 35	596	22.0%	19	7.8%	577	23.4%	
35–44	582	21.5%	40	16.3%	542	22.0%	
45–54	754	27.8%	78	31.8%	676	27.4%	
55–64	544	20.1%	74	30.2%	470	19.1%	
≥ 65	233	8.6%	34	13.9%	199	8.1%	
Missing	–		–		–		
Sex							0.26
Female	618	22.8%	48	19.6%	570	23.1%	
Male	2091	77.2%	197	80.4%	1894	76.9%	
Missing	–		–		–		
Race & Hispanic ethnicity[b]							0.44
Non-Hispanic White	1353	50.1%	115	46.9%	1238	50.4%	
Black	1122	41.5%	168	45.7%	1010	41.1%	
Other	226	8.4%	34	7.4%	208	8.5%	
Missing	8		–		8		
Education							0.62
No high school (HS) diploma	577	21.3%	59	24.1%	518	21.0%	
HS diploma/Some college (no degree)	1488	55.0%	133	54.3%	1355	55.0%	
College degree	643	23.7%	53	21.6%	590	24.0%	
Missing	1		1		–		
Employment status[c]							<0.01
Working or student	1552	57.4	134	54.7%	1418	57.7%	
Unemployed	786	29.1	53	21.6%	733	29.8%	
Other	366	13.5	58	23.7%	308	12.5%	
Missing	5		0		5		
Health insurance status[d]							<0.01
Yes	1301	48.6%	140	58.1%	1161	47.7%	
No	1374	51.4%	101	41.9%	1273	52.3%	
Missing	34		4		30		
BMI category (kg/m^2)[e]							<0.01
Under/normal weight (< 25)	652	24.4%	21	8.8%	631	25.9%	
Overweight (25-29)	861	32.2%	48	20.0%	813	33.4%	
Obese (≥30)	1165	43.5%	171	71.3%	994	40.8%	
Missing	31		5		26		
Smoking status[f]							<0.01
Current	1083	40.0%	72	29.4%	1011	41.1%	
Former	717	26.4%	98	40.0%	619	25.1%	
Never	906	33.5%	75	30.6%	831	33.7%	
Missing	3		0		3		

All data were from the Gulf Long Term Follow-up Study of individuals who worked for at least one day on the *Deepwater Horizon* oil spill cleanup and who completed a routine clinical exam as part of that study 4–6 years after the spill.

[a] Maximum daily total hydrocarbon exposure experienced during work on the spill. Estimated via detailed self-report of spill-related tasks together with a job-exposure matrix based on extensive air monitoring during the spill cleanup (see Stewart et al. (2018)).

[b] Non-Hispanic White, Black (Hispanic and non-Hispanic), Other (Hispanic and non-Hispanic).

[c] Working/student/on temporary sick leave; unemployed/keeping house; Other/retired/disabled.

[d] Health insurance status at the time of the home visit.

[e] BMI at the time of the home visit. Calculated from the average height and average weight from three measurements each.

[f] smoking status at the time of the clinical exam.

[g] P-values for Chi-squared tests for difference, which are crude and do not provide evidence of confounding or of a causal relationship.

Vestergaard et al., 2002; Zhang et al., 2016), which impairs β-cell function (Dokken et al., 2008; Gardner et al., 2003; Modak et al., 2009; Pi et al., 2007, 2010) and overall metabolic function (Cavaliere et al., 2018; Gerber and Rutter, 2017; Kjaergaard et al., 2018; Kovačević et al., 2019; Singh et al., 2009, 2010).

This study examines the relationship between oil spill cleanup-related total hydrocarbon (THC) exposure and incident DM among individuals who worked on the *2010 Deepwater Horizon* oil spill. To the best of our knowledge, this is the first study of oil spill chemical exposures and diabetes risk.

2. Methods

2.1. Study design and population

Participants in the present study were a subset of participants from the Gulf Long Term Follow-up Study, which is a prospective cohort of 32,608 individuals at least 21 years of age at enrollment who worked on the *DWH* spill cleanup and response or who completed oil spill cleanup safety training but did not participate in the cleanup (Kwok et al., 2017).

Participants contributed data over multiple study phases, including; **a)** a structured telephone interview at enrollment (in English, Spanish, or Vietnamese) completed by all study participants (2011–2013) (n = 32,608); **b)** a home visit involving an in-person interview and collection of biological samples, anthropometric measurements, and clinical measurements among cohort members residing in a state bordering the Gulf of Mexico (MS, AL, LA, FL, TX) (2011–2013) (n = 11,193); **c)** a structured follow-up telephone interview targeting all English and Spanish speaking participants (2013–2016) (n = 21,256); and **d)** a clinical exam involving an in-person interview and collection of anthropometric and hemoglobin A1c (HbA1c) measurements among a sample of cohort members restricted to those residing within 60 miles of study clinics in Mobile, AL or New Orleans, LA (2014–2016) (n = 3401).

This analysis focused on the 3401 participants (62% of eligible participants) who completed the clinical exam. Of these, we excluded 528 who did not work on the spill to minimize potential bias from the healthy worker effect (McMichael, 1976), 164 with a self-reported DM diagnosis prior to the spill (April 20th, 2010), 1 with probable type 1 DM (under 40 years old and prescribed insulin without other antidiabetic medication) (Diabetes Association, 2018a), and 48 missing necessary covariate data, leaving 2660 for these analyses (Table 1). Time from start of the spill to the clinical exam ranged across participants from 4 to 6 years. This study was approved by the institutional review board at the National Institute of Environmental Health Sciences (NIEHS) and all study participants provided informed consent.

2.2. Total hydrocarbons ordinal exposure levels

Each worker's exposure was defined as their maximum one-day THC exposure, as described below. The enrollment interviews administered to each participant included questions about activities performed, locations, and dates. GuLF Study industrial hygienists used this information together with THC measurements (analyzed as total petroleum hydrocarbons) from approximately 28,000 personal air samples collected from the general population of oil spill response and cleanup workers (for industrial hygiene purposes) to create a job-exposure matrix (Stewart et al., 2018). Participants often performed multiple oil spill cleanup-related jobs/tasks in a single day and over their work period. Each person was assigned an exposure value for each job/task using the job-exposure matrix (Stewart et al., 2018). The maximum daily value across all work days (Stewart et al., 2018), which has been successfully used in other GuLF Study analyses and was the only quantitative chemical exposure measure available for these analyses, was used. Ordinal exposure levels were defined using a pseudo-log scale based on the empirical exposure distribution: <0.30 ppm, 0.30–0.99 ppm, 1.00–2.99 ppm, and ≥3.00 ppm (Stewart et al., 2018). This analysis utilizes ordinal exposure categories, rather than continuous values, to reflect uncertainty in the exposure estimates derived from the job exposure matrix (Stewart et al., 2018).

2.3. Diabetes assessment

Participants were treated as incident type 2 DM cases if they a) reported a post-spill physician diagnosis of DM at either the enrollment or first follow-up interviews, b) reported taking an antidiabetic medication at the time of the clinical exam, or c) had a HbA1c value at or above 6.5%, as measured by a DCA Vantage device (Siemens Medical Solutions USA, Inc.), during the clinical exam (Diabetes Association, 2018b). Women reporting *only* gestational diabetes were not considered cases.

Participants who reported a physician diagnosis of DM were asked for either age or date of diagnosis; age at diagnosis was used to estimate date of diagnosis by calculating the middle month of their age-year of diagnosis. Date of diagnosis was used to identify incident cases of DM in relation to the start of the spill (April 20th, 2010), based on each participant's earliest reported date of diagnosis.

2.4. Potential confounders

Potential confounders were selected based on a directed acyclic graph (DAG) (Greenland et al., 1999). Data from the enrollment interviews included sex (female, male); race/ethnicity (Non-Hispanic White, Black/African American Hispanic and non-Hispanic, Other); highest educational attainment (less than high school, high school diploma/GED/some college, college degree); and employment status (working or student, looking for employment/keeping house, other). Smoking status was categorized as current, former, and never. Race/-ethnicity data are values of racial self-classification - participants selected from a list including American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, and White. Ethnicity was similarly ascertained and included Hispanic/Latino identity. Race and ethnicity were collapsed further because of small cell numbers. Information on health insurance status (insured, uninsured) was collected at the home visit. Age at the clinical exam was represented as restricted quadratic splines with knots at 35, 50, 67, and 77 years after assessing the functional form of age with the Akaike Information Criterion.

Body mass index (BMI) was not included as a confounder in the main analysis because weight and height data were collected after the exposure occurred and BMI could be a mediator of any THC-DM relationship, but it was considered in sub-analyses. BMI was categorized as underweight/normal weight, overweight, and obese (<25 kg/m^2, 25–25.9 kg/m^2, ≥30 kg/m^2, respectively) using measurements from the home visit. Height and weight were each measured three times and the average of each was used to calculate the home visit BMI (Centers for Disease Control, 2019).

2.5. Statistical analysis

We used log binomial regression to estimate risk ratios (RR) and corresponding 95% confidence intervals (95% CIs) for DM through the date of the clinical exam by ordinal THC exposure level. In the main analysis, three adjustment models were used: **1)** reduced model: age only; **2)** basic model: age, sex, race/ethnicity, and education; **3)** full model: age, sex, race/ethnicity, education, employment status, and health insurance status. For each model, we performed a trend test with the median value for each exposure category as a continuous measure; the corresponding p-value is the Wald statistic for that parameter. In all analyses the lowest exposure category, < 0.30 ppm, was the reference group. All tests for significance were assessed at an alpha level of 0.05. All analyses were conducted with SAS version 9.4 (SAS, Cary, NC).

The reduced, basic, and full models were applied to a) the entire analytic sample (n = 2660) and b) male workers only (n = 2051). The

male-only analyses were conducted for two reasons. First, there may be sex-specific differences in biological response to THC components, as indicated by studies on humans (Choi et al., 2014) and mice (Debarba et al., 2020), but there were too few women for separate analyses. Second, some women could have been prescribed metformin (a popular antidiabetic medication) for polycystic ovary syndrome rather than for diabetes (Morley et al., 2017). Although rare, polycystic ovary syndrome seems to have a higher prevalence in the southern US compared to other regions of the US (Okoroh et al., 2012).

Because BMI is a potential mediator, we separately examined associations adjusted for BMI by including it in the log binomial models, using the COPY method as needed to enable convergence (Deddens and Petersen, 2008; Petersen and Deddens, 2009). We also stratified by BMI, using the same three adjustment sets as in the main analysis. We additionally investigated multiplicative interaction between BMI and THC exposure levels in relation to diabetes risk, assessing effect measure modification with a likelihood ratio test (LRT) using fully adjusted log binomial models and the COPY method as needed.

2.6. Sensitivity analyses

We repeated the main analysis defining incident cases using each individual's *last* date of spill-related employment rather than the start of the spill (April 20th, 2010) to assess the impact of including cases (n = 2644) diagnosed *during* the cleanup, which may be biased due to some cleanup workers' changes in access to medical care during this period. We also performed sub-analyses a) including prediabetes (defined as 5.7% ≤ HbA1c < 6.5%) among the cases (Diabetes Association, 2018b) and, separately, b) with cases restricted to individuals either with HbA1c ≥ 6.5% or reporting *both* DM diagnosis and use of antidiabetic medication. Because smoking is a risk factor for DM but was not strongly related to spill-related THC exposure (Spearman rho = −0.099), we conducted an additional sensitivity analysis in which we included it in the fully adjusted model.

3. Results

Compared to non-cases, cases were older, more likely to be male, more likely to self-identify as Black, less likely to have graduated from high school, more likely to be no longer working because of retirement or disability, more likely to have health insurance, and far more likely to be obese (Table 1). Among those who were eligible for the clinical exam, the proportion that participated in the clinical exam was similar between those reporting and not reporting a diabetes diagnosis at the follow-up interview (*data not shown*), suggesting little/no selection bias related to this factor.

All models utilizing the full sample showed an apparent exposure-response relationship of increasing DM incidence with increasing THC exposure level, although individual point estimates were not statistically significant. RRs from the full model were 1.07 (95% CI: 0.71, 1.62), 1.23 (95% CI: 0.82, 1.86), and 1.28 (95% CI: 0.83, 1.97), for exposure categories 0.30–0.99 ppm, 1.00–2.99 ppm, and ≥3.00 ppm, respectively, compared to exposures below 0.30 ppm (Table 2). Exposure-response relationships were somewhat stronger in models restricted to males. In these analyses, RRs for the full model were 1.27 (95% CI: 0.72, 2.24), 1.54 (95% CI: 0.89, 2.65), and 1.61 (95% CI: 0.92, 2.82), for exposure categories 0.30–0.99 ppm, 1.00–2.99 ppm, and ≥3.00 ppm, respectively (Table 2).

In models stratified by BMI category, we observed an exposure-response relationship among overweight participants (p_{trend} = 0.03), although the point estimates were not statistically significant; the estimated basic adjustment RRs were 0.99 (95% CI: 0.37, 2.69), 1.46 (95% CI: 0.54, 3.92), and 2.11 (95% CI: 0.78, 5.74) for exposure categories 0.30–0.99 ppm, 1.00–2.99 ppm, and ≥3.00 ppm, respectively (Table 3). The point estimates within the obese category were all elevated, but with no apparent trend. Results from the underweight stratum were very unstable because of the small number of cases (n = 21) and are therefore not presented.

When incident cases were defined using the end, rather than the start, of each individual's work on the spill, there was virtually no change in the pattern of increasing DM incidence with increasing THC exposure level (*Supplementary Table S1)*. In analyses including both those with diabetes and pre-diabetes detected at clinical exam as cases, all RR estimates were attenuated and close to the null value of 1.00. Models using a stricter case definition based on either a) HbA1c ≥ 6.5% or b) both a DM diagnosis and use of antidiabetic medication also produced attenuated RR estimates. RR estimates were similar when models included BMI as a covariate, with RRs for the full model of 1.22 (95% CI: 0.80, 1.84), 1.25 (95% CI: 0.83, 1.89), and 1.27 (95% CI: 0.82, 1.96) for exposure categories 0.30–0.99 ppm, 1.00–2.99 ppm, and ≥3.00 ppm, respectively. In models including a multiplicative interaction between BMI and the exposure in the fully adjusted model, we observed no evidence of multiplicative interaction (p = 0.60). Estimates from the full model that included smoking status were nearly indistinguishable from those of the main analysis (Supplementary Table S2).

Table 2
Associations between maximum total hydrocarbon (THC) exposure and risk of type 2 diabetes, with different adjustment sets.

		Age adjustment[a]			Basic adjustment[b]			Full adjustment[c]		
Full sample (n = 2660)										
Max THC (ppm)[d]	**n cases/n total**	RR	95% CI	CLR[e]	RR	95% CI	CLR	RR	95% CI	CLR
< 0.30	29/361	1			1			1		
0.30–0.99	72/840	1.11	(0.74, 1.68)	2.27	1.06	(0.70, 1.60)	2.29	1.07	(0.71, 1.62)	2.28
1.00–2.99	77/802	1.20	(0.80, 1.80)	2.25	1.20	(0.79, 1.81)	2.29	1.23	(0.82, 1.86)	2.27
≥ 3.00	62/657	1.33	(0.88, 2.03)	2.31	1.25	(0.81, 1.92)	2.37	1.28	(0.83, 1.97)	2.37
		Trend test p-value: 0.16			***Trend test p-value: 0.26***			***Trend test p-value: 0.22***		
Males only (n = 2050)										
Max THC (ppm)										
< 0.30	14/209	1			1			1		
0.30–0.99	51/577	1.35	(0.77, 2.37)	3.08	1.27	(0.72, 2.24)	3.11	1.27	(0.72, 2.24)	3.11
1.00–2.99	69/672	1.54	(0.89, 2.67)	3.00	1.52	(0.88, 2.63)	2.99	1.54	(0.89, 2.65)	2.98
≥ 3.00	58/592	1.67	(0.96, 2.92)	3.04	1.58	(0.90, 2.77)	3.08	1.61	(0.92, 2.82)	3.07
		Trend test p-value: 0.10			***Trend test p-value: 0.13***			***Trend test p-value: 0.10***		

[a] Adjusted for age with restricted quadratic splines.
[b] Adjusted for age, sex, race/ethnicity, and education.
[c] Adjusted for age, sex, race/ethnicity, education, employment status, and health insurance status.
[d] Maximum total hydrocarbon exposure.
[e] Confidence limit ratio.

Table 3
Associations between maximum total hydrocarbon (THC) exposure and risk of type 2 diabetes, stratified by body mass index category.

		Age adjustment[a]			Basic adjustment[b]			Full adjustment[c]		
Overweight[d] *(n = 843)*										
Max THC (ppm)[f]	**n cases/n total**	RR	95% CI	CLR[g]	RR	95% CI	CLR	RR	95% CI	CLR
< 0.30	5/114	1			1			–		
0.30–0.99	13/268	1.06	(0.39, 2.85)	7.24	0.99	(0.37, 2.69)	7.33	–	–	–
1.00–2.99	15/258	1.34	(0.51, 3.54)	6.97	1.46	(0.54, 3.92)	7.20	–	–	–
≥ 3.00	15/203	2.14	(0.81, 5.61)	6.89	2.11	(0.78, 5.74)	7.39	–	–	–
		Trend test p-value: 0.03			***Trend test p-value: 0.03***					
Obese[e] *(n = 1149)*										
Max THC (ppm)										
< 0.30	18/160	1			1			1		
0.30–0.99	54/348	1.43	(0.87, 2.35)	1.43	1.37	(0.84, 2.24)	1.37	1.44	(0.88, 2.35)	1.44
1.00–2.99	55/351	1.32	(0.81, 2.17)	1.32	1.22	(0.74, 2.01)	1.22	1.30	(0.79, 2.14)	1.30
≥ 3.00	42/290	1.33	(0.80, 2.23)	1.33	1.18	(0.70, 1.99)	1.18	1.19	(0.70, 2.01)	1.19
		Trend test p-value: 0.76			***Trend test p-value: 0.82***			***Trend test p-value: 0.73***		
Multiplicative interaction p-value	0.60									

[a] Adjusted for age with restricted quadratic splines.
[b] Adjusted for age, sex, race/ethnicity, and education.
[c] Adjusted for age, sex, race/ethnicity, education, employment status, and health insurance status. Model did not converge for overweight stratum due to insufficient cases.
[d] BMI [25–29].
[e] BMI ≥30.
[f] Maximum total hydrocarbon exposure.
[g] Confidence limit ratio.

4. Discussion

This analysis showed an apparent exposure-response relationship of increasing DM incidence with increasing maximum THC exposure level, which appeared stronger among males, although the individual point estimates were not significant. Additionally, there was a significant exposure-response relationship among overweight participants, but not among obese participants.

Because this is the first study of DM risk in relation to oil spill response and cleanup-related exposures, there are no studies available for direct comparison. Our results are, however, consistent with previous non-occupational studies, including those among adults ≥60 years of age and among children 6–18 years of age, which found that higher blood levels of benzene metabolites were associated with greater insulin resistance (Amin et al., 2018; Choi et al., 2014). There may be sex-specific responses to benzene exposure; Choi et al. (2014) showed suggestive differences in benzene metabolite-insulin resistance dose-response in humans and DeBarba et al. (Debarba et al., 2020) found that among mice exposed to chronic low levels of gaseous benzene, only male mice exhibited impaired glucose tolerance and increased blood insulin levels. Though this is an important aspect of glycemic responses to volatile organic compounds, our study had too few women to adequately investigate this further.

Our main analysis results also corroborate *in vitro* and rodent studies that show metabolic dysfunction with exposure to benzene (Debarba et al., 2020; Abplanalp et al., 2019; Bahadar et al., 2015a, 2015b) and toluene (Dick et al., 2015). The inhalable exposures in the present study, including benzene, are several orders of magnitude lower (low ppb vs 50 ppm) than the inhaled exposures used in a mouse study that showed oxidative stress and metabolic dysfunction related to benzene exposure in a dose-dependent fashion (Abplanalp et al., 2019). Our results suggest that much lower benzene exposures may follow similar patterns, though we lacked the necessary chemical-specific data to characterize the respective contributions of each agent to higher observed risks. The rodent studies referenced above did not assess delayed or persistent changes, whereas this study had several years between exposure and the outcome assessment, allowing for changes that were either delayed or undiagnosed, immediate, and persistent (Abplanalp et al., 2019; Bahadar et al., 2015a, 2015b). We are unaware of any human studies examining the relationships of toluene, ethylbenzene, xylenes, or n-hexane exposures with glycemic dysregulation, but limited rodent studies of ethylbenzene and xylene have found no structural changes to the pancreas nor changes in urinary glucose levels (Kükner et al., 1997; Mellert et al., 2007).

We observed a significant exposure-response relationship only among overweight participants. It is possible that the higher baseline risk of developing DM among obese individuals (Mellert et al., 2007) may have obscured a trend of increasing risk associated with increasing THC exposure level; there was still an apparent small increase in risk for obese workers with any THC exposure level above the reference level. We observed expected associations between BMI and DM incidence, with 71.3% of diabetics classified as obese versus 40.8% of non-diabetics. The attenuation of RRs when those with pre-diabetes were included as cases suggests that 1) oil spill cleanup-related THC exposure, if causally related to DM, may act in the later stages of disease progression or primarily among susceptible individuals and 2) any potential overreporting of diabetes diagnoses by pre-diabetics was insufficient to obscure an association. It is also possible those with prediabetes could have been pre-diabetic prior to the spill but were not excluded as prevalent cases. At the same time, attenuation of the risk estimates when using a stricter definition of DM (i.e., HbA1c ≥ 6.5% or (DM diagnosis and use of antidiabetic medication)) could be due to one or more of the following: a) some physician-diagnosed diabetic participants were managing their diabetes without antidiabetic medication, b) some participants misreported being diagnosed with DM, and/or c) some pre-diabetic participants were taking antidiabetic medication. It is unlikely that any overreporting of DM was differential by exposure status as exposure was estimated by study investigators based on participants' detailed spill-related work histories. We lacked the data necessary to evaluate this issue further, although our data indicate that a small proportion (up to 12%) of cases may have incorrectly reported a DM diagnosis, as they had neither antidiabetic medication nor a HbA1c value ≥ 6.5%.

Strengths of this analysis of oil spill workers include its use of THC exposure estimates, based on measurements, as opposed to using job title as a proxy for exposure, the ability to identify undiagnosed DM cases via measured HbA1c, a relatively large sample size, and the ability to control for important demographic, lifestyle, and anthropometric

factors, including measured BMI. In addition, it examined incident/newly identified diabetes cases rather than diabetes mortality, allowing us to account for well-managed diabetes among the still living and avoiding the documented under-ascertainment, possibly differential, resulting from use of cause of death data from vital records (Centers for Disease Control, 2017; Cheng et al., 2008; McEwen et al., 2006; Saydah et al., 2004). It is also the first study of the association between oil spill response and cleanup-related exposures and risk of DM.

Limitations of this study include possible outcome misclassification because case ascertainment relied partially on self-reported physician diagnosis of DM; however, self-reported DM has positive predictive values of 72%–94.9% in long term cohort studies with multiple follow-up phases (Goldman et al., 2003; Margolis et al., 2008; Pastorino et al., 2015), and we were able to detect unreported/undiagnosed DM cases with measured HbA1c levels. Because we had HbA1c level measured only at the clinical exam, we were unable to exclude any individuals with prevalent, but undiagnosed, DM prior to the start of follow-up; this is expected to bias our estimates toward the null. Additionally, because covariate data were missing for less than 2% of study participants, our complete case analysis is unlikely to have substantially affected results. The follow-up period was not the same for every individual, as the phases of the study were completed over multiple years, though this difference in follow-up time is unlikely to bias this analysis because it is unlikely to be associated with exposure and because DM may develop or progress to diagnosis very slowly. Additionally, the maximum THC exposure metric does not take into account how frequently this maximum occurred, nor does it account for cumulative exposure over time.

These results suggest an association between oil spill response and cleanup-related THC exposure and increased risk of DM. Future studies on this topic would benefit from incorporating information about individual agents within oil spill cleanup-related THC, allowing analysis of the joint effects of individual agents.

Author contributions

H Jardel – formal analysis, writing – original and revision; L Engel – methodology, conceptualization, writing – original and revision, supervision; K Lawrence - methodology, writing – original and revision, supervision, project administration; P Stewart – methodology, formal analysis, investigation; M Stenzel – methodology, formal analysis, investigation; M Curry – data curation, writing – revision, project administration; R Kwok – supervision, conceptualization resources, investigation, writing – revision, project administration; D Sandler - methodology, conceptualization, writing – original and revision, supervision, funding acquisition, resources, investigation, project administration.

Ethics approval

The Gulf Long Term Follow-up Study was approved by the Institutional Review Board at the US National Institute of Environmental Health Sciences.

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Data availability

Data from the GuLF Study, including data used in this analysis, may be requested following procedures described at https://gulfstudy.nih.gov/en/forresearchers.html.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113591.

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