

1991 Gulf War Exposures and Adverse Birth Outcomes

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ABSTRACT

We studied 1991 Gulf War (GW)-related environmental exposures and adverse birth outcomes in Iraqis. A random cross-sectional sample of 307 Iraqi families that immigrated to the United States responded to a structured interview covering socioeconomic, lifestyle, environmental exposures, and birth outcome. Data per each family was collected either from the man or the woman in the respective family. The respondents were divided into those that resided in Iraq during and following the GW (post-GW, $n=185$) and those that had left before (pre-GW, $n=122$). The primary outcome was lifetime prevalence of adverse birth outcomes, ie, congenital anomalies, stillbirth, low birth weight, and preterm delivery and its relationship to GW exposures. Mean number of adverse birth outcomes increased from 3.43 (SD=2.11) in the pre-GW to 4.63 (SD=2.63) in the post-GW group ($P<.001$). Mean chemical (Ch) and nonchemical (NCh) environmental exposure scores increased from pre-GW scores of 0.38 units (SD=1.76) and 0.43 (SD=1.86), respectively, to post-GW scores of 5.65 units (SD=6.23) and 7.26 (SD=5.67), $P<.001$ between groups for both exposures. There was a significant dose-response relationship between Ch environmental exposure ($P=.001$), but not NCh exposure, and number of adverse birth outcomes. Exposure to burning oil pits and mustard gas increased the risks for specific adverse birth outcomes by 2 to 4 times. Results indicate that Gulf War Ch, but not NCh exposures are related to adverse birth outcomes. Pregnancies in women with a history of war exposures might benefit from more intensive observation.

BACKGROUND

Exposures to chemical (Ch) and nonchemical (NCh) (psychosocial factors) environmental stressors have in some, but far from all studies been associated with non-optimal pregnancy outcomes.¹⁻⁷ Nonchemical environmental exposures such as violence and socioeconomic strain have also been associated with adverse birth outcomes.^{5,8,9} Prenatal exposure to air pollutants such as sulphur dioxide, nitrogen dioxide, fine (diameter $\leq 2.5 \mu\text{m}$) and coarse (diameter $\leq 10 \mu\text{m}$) particulate matter might contribute to suboptimal birth outcomes through a range of mechanisms, including inflammatory reactions in the lung, contributing to systematic release of proinflammatory cytokines, DNA adduct formation, and lipid peroxidation.^{5,10}

Prior studies of reproductive health effects from exposure to war conflicts have reported an increased prevalence of severe congenital anomalies, neural tube defects, perinatal mortality and preterm delivery, and decreased birth length and weight.¹¹⁻¹⁵ The 1991 Gulf War (GW) is a more recent example of sustained war with severe implications for Iraqi civilians in terms of complex environmental exposures. Studies of reproductive effects from

the GW have predominantly concerned United Kingdom and US veterans reporting an increased risk for spontaneous abortions and congenital birth defects.^{16,17} A small study of civilians residing in Kuwait during the early phase of the conflict reported an increased prevalence of children with low birth weight and stillbirth.¹⁸

Studies of reproductive risks from war typically lack detailed exposure information. However, the US General Accounting Office reported that during the GW up to 21 reproductive environmental hazards, such as depleted uranium and smoke from oil-burning fires, were dispersed into the environment.^{16,19} In studies of GW veterans, "exposure" was defined simply as "deployment to the Gulf region."²⁰ A void of reliable environmental exposure data limits our ability to assess war-related environmental reproductive risks. Major shortcomings of reproductive health studies from war are the lack of (a) samples based on random selection, (b) Ch-specific and NCh-specific exposure data, and (c) proper comparison groups.

Reproductive health effects studies from war characterized by intense and sustained exposure to environmental

pollutants, such as the GW, might also contribute mechanistic understandings to studies of sustained but low-intensity urban exposures in general.

OBJECTIVES

The objectives of this cross-sectional study were to determine whether adverse birth outcomes for fathers or mothers exposed to the GW are worse than for non-GW exposed persons.

The following hypotheses were tested:

1. Exposure to the GW is associated with increased risk for adverse birth outcomes.
2. Participants residing in Iraq during the GW report higher exposures than those that had left before the outbreak of the war.
3. There is a dose-response relationship between Ch and/or NCh exposures and adverse birth outcomes.
4. Specific environmental exposures, such as smoke from burning oil wells, are predictive of increased adverse birth outcome risks.

METHODS

Setting

In 2005, an elaborate community-based project was initiated to identify Iraqis residing in the region of metropolitan Detroit, Michigan, which has one of the largest populations of Iraqi immigrants and refugees in the country. The project was announced in Arabic and English using several means of communication, such as the Arabic radio and television. Flyers with project information were distributed at various Arab and Chaldean-American community centers as well as faith-based facilities, convenience stores, restaurants, gas stations, hair salons, and community centers. The local Iraqi directory was also used to identify potential participants.

Participants

This recruitment drive resulted in a list of 5,490 addresses from which a random sample of 411 (7.5% of the entire sample) was selected for study inclusion. This allowed for a statistical power of 0.90, with a 2-sided $P=.05$ to detect a 30% difference between the 2 groups in the total number of adverse birth outcomes, assuming a mean of 1.5 adverse birth outcomes in the non-GW exposed group. The inclusion criteria were that participants were Iraqi-born and aged 18 years or older at the time they emigrated from Iraq. We chose one person from each household, irrespective of gender, based on the first eligible person we contacted in that household. Of 411 addresses selected, 44 had no residents who fit the study

criteria. Of a total of 367 eligible candidates, 17 (4.6%) declined participation. The reasons were lack of time ($n=9$), lack of interest in the study ($n=7$), or no reason provided ($n=1$). A total of 350 qualified families, each represented either by a man or woman, representing a response rate of 95%, accepted to take part in the study. Of these, 43 did not attempt a pregnancy during the period of interest, leaving a final study group of 307 persons.

Participants who came to the United States from Iraq before 1991, and thus not exposed to the Gulf War, were classified as "pre-GW." Those arriving in 1991 or later who had been exposed to the Gulf War were classified as "post-GW."

Variables

The survey instrument used was initially created through a joint effort of the Iowa Persian Gulf Study Group and the Centers for Disease Control and Prevention to evaluate a broad range of health concerns among US Gulf War veterans, and was adopted and used in studies of Iraqi civilians and military.²¹⁻²³

Data Source

Data was collected using the structured interview carried out in Arabic, typically in the participant's home, by a team of female and male Iraqi-born obstetric and gynecology specialists.

Exposure Assessment

The respondents were asked in detail about their GW-related exposures. The GW-specific environmental Ch and NCh factors included agents reported to be associated with symptoms of the "Gulf War Syndrome" reported by many GW veterans.²⁴ Questions began with the following stem: "During the Gulf War did you have direct contact with any of the following exposure?" The respondents were asked about the following 16 environmental exposures (Ch):

- ♦ Smoke from oil burning fires
- ♦ Exhaust from heaters or generators
- ♦ Diesel or other petrochemical fumes
- ♦ Burning trash or burning feces
- ♦ Diesel or other petroleum fuel on their skin
- ♦ Chemical agent resistant compounds (such as paint)
- ♦ Other chemicals such as solvents or petroleum substances
- ♦ Depleted uranium
- ♦ Direct skin contact with pesticides (creams, sprays, flea collars)
- ♦ Pesticides on clothing or bedding

- ♦ Nerve gas
- ♦ Mustard gas or other blistering agents
- ♦ Food contaminated with smoke or oil or other chemicals
- ♦ Local food other than food provided by the armed forces
- ♦ Bathe in or drink water contaminated with smoke oil or other chemical
- ♦ Bathe or swim in local ponds, rivers, or the Persian Gulf

Respondents were also asked to respond about their experiences with 9 war-related NCh (stress exposures):

- ♦ Exposure to dead animals
- ♦ Hearing chemical alarms
- ♦ Scud missiles exploding in the air or on the ground within one mile
- ♦ Artillery, rockets or mortars (anything other than Scud missiles) explosions within one mile
- ♦ Subjected/exposed to small arms fire
- ♦ Seeing dead bodies
- ♦ Seeing maimed or seriously injured people
- ♦ Witness someone dying
- ♦ Any other war-related exposure the participant deemed to be harmful or stressful

These exposures were considered to be of sufficient severity to fulfill the exposure criterion A for posttraumatic stress syndrome in the *Diagnostic and Statistical Manual for Mental Health Disorders*.²⁵

The Ch environmental score was calculated by aggregating respondent's answers to the 16 environmental questions. For each specific Ch measure, the exposure status variable was multiplied by exposure duration (none, less than 5 days, 6 days to 30 days, more than 31 days: coded as 0, 1, 2, and 3 respectively) to calculate the cumulative exposure Ch dose. The cumulative NCh stress scale scores were created using the same method. This allowed us to calculate the respective doses of Ch and NCh exposures.

The mean Ch environmental exposure was 3.56 units (SD=5.68, SE=0.32). The actual maximum Ch exposure score observed was 29 of a theoretical high of 48. Based on the mean, Ch exposure scores above 3.56 was classified as high exposure, and below as low exposure. The mean for the NCh exposure scale was 4.58 (SD=5.68, SE=0.32) and an actual maximum of 23 (theoretical high of 27). An NCh exposure above 4.58 was classified as high exposure and below 4.58 as low exposure. The Cronbach α for both scales was greater than 0.75.

OUTCOMES

Adverse birth outcomes were classified as congenital anomalies, stillbirth, low birth weight, and preterm delivery. Stillbirth was defined as fetal death at 20 weeks gestation or greater; low birth weight as less than 2,500 grams; and preterm delivery as delivery of the fetus before 37 weeks gestation.

Since the primary outcome was cumulative numbers of adverse birth outcomes, the 4 adverse birth outcome categories were combined into a composite adverse birth outcome scale score. In addition, each of the 4 adverse birth outcomes was separately analyzed against Ch and NCh exposure histories.

We examined reproductive health effects as a function of (a) whether respondents reported having lived in Iraq or not during the war, and (b) using the more complex Ch and NCh exposure scales. We used both specific adverse birth outcomes and aggregate adverse outcomes when determining the exposure-outcome association.

STATISTICAL ANALYSES

Nonpaired student's *t* test was used to compare mean Ch and NCh exposures in the pre- and post-GW groups, respectively, as well as comparing scores across both groups on the adverse birth outcome scale. Student's *t* test was also used for comparing mean number of each of the 4 adverse birth outcomes by GW status. Levene's test for equality of variance was checked for all these comparisons, and the appropriate *t* statistics were used. Mann-Whitney U tests were also used to compare groups. Both tests yielded the same results, therefore only student's *t* tests are reported. The Ch and NCh scale scores were analyzed with one-way ANOVA. The Duncan multiple-range test was used to determine which of the total adverse birth categories were different from one another. Multiple linear regression analysis was used to study the relationship between dependent factors and independent Ch and NCh exposure scales, while controlling for gender, ethnicity (Arabic versus Chaldean), education, and smoking status. We checked the normal P-P plot of regression of standardized residuals. Stepwise logistic regression analysis was used to determine the relative contribution of each of the individual environmental items in the Ch scale, classified as either present or absent, on each of the 4 adverse birth outcomes. There was no significant association between NCh and outcomes after controlling for Ch and demographics. Consequently, those results are not reported.

Data was analyzed with SPSS for Windows v19.0 (SPSS Inc, Chicago, Ill). A *P* < .05 (2-tailed) was considered statistically significant.

RESULTS

Table 1 depicts the characteristics of the study participants by post-GW and pre-GW exposure status.

Figures 1 and 2 show participants' mean total number of adverse birth outcomes as a function of self-reported Ch and NCh exposures. There was a significant association between increasing Ch exposures and number of adverse birth outcomes.

Figure 3 depicts participants' aggregate Ch and NCh exposure scores versus the period of immigration. Both Ch and the NCh scores were significantly higher in the post-GW group.

Table 2 reveals that the prevalence of specific adverse birth outcomes by period of immigration to the United States is different only for those exposed to the GW, regardless of whether the child was born in Iraq or the United States.

Table 3 reports pregnancy outcomes following adjustment for demographics and smoking. The Ch environmental exposure scale explained 2.1% of the variance in total adverse birth outcomes. NCh exposures did not remain in the model once Ch exposure was added.

Participants with a history of high Ch environmental exposures were more than twice as likely to report adverse birth outcomes as compared to the low Ch exposure group (odds ratio 2.04 (95% CI, 1.12-3.74)). The ethnicity of the respondent (Chaldean versus Arab) was not associated with birth outcomes.

Table 4 depicts the odds ratio between each of the 4 adverse birth outcomes and specific war-related environmental exposures. Exposures to smoke from burning oil wells, water contaminated with petrochemical products, and mustard gas were all related to a significantly increased risk in the reporting of adverse birth outcomes.

COMMENT

These results support our first hypothesis that the prevalence of adverse birth outcomes is higher in participants having been exposed to the GW as opposed to participants that had left Iraq before the war. As hypothesized, both Ch and NCh exposures were higher in those residing in Iraq during the GW. However, counter to our hypothesis, only Ch, not NCh exposures, exhibited a dose-relationship association with adverse birth outcomes.

Stillbirth exhibited the largest systematically increased risk when comparing the post-GW to pre-GW groups. Exposure to burning oil wells and water and food

Table 1. Demographic characteristics of study participants.*

Demographic Characteristic (N=307)	Post-GW (n ₁ =185) %n ₁	Pre-GW (n ₂ =122) %n ₂	P value
Education - more than high school	56.8	69.2	.40
Smoker	30.0	39.3	.11
Employed	40.0	73.3	.00
Female respondents	48.4	38.5	.10
Covered by health insurance	76.3	60.7	.01
Income - higher than \$10,000	39.1	14.9	.01

*The data includes both female and male respondents. Each male respondent reported the outcome of pregnancy of his wife. Single men and women were excluded from participation in the survey.

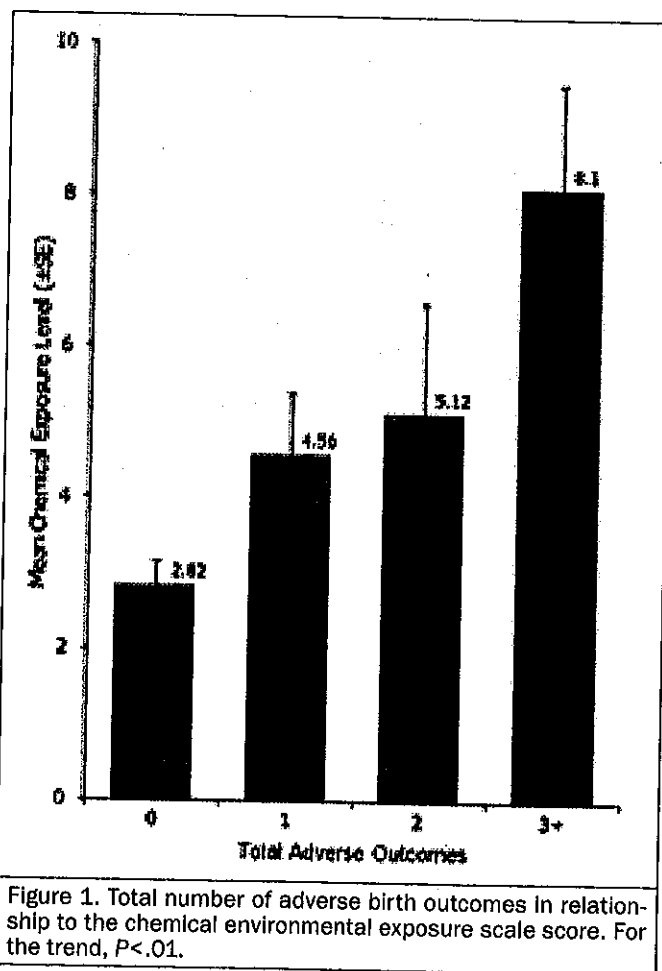


Figure 1. Total number of adverse birth outcomes in relationship to the chemical environmental exposure scale score. For the trend, $P < .01$.

contaminated with petrochemical products during the GW appeared to be especially related to reproductive risks. This supports our last hypothesis that certain environmental exposures are more closely associated with adverse birth outcomes.

The current study supports the notion that war per se is a risk factor for adverse birth outcomes.^{11,12,14-20} One possible environmental culprit revealed in our findings could be the documented exposure to up to 21 potential reproductive toxicants in persons residing in Iraq during

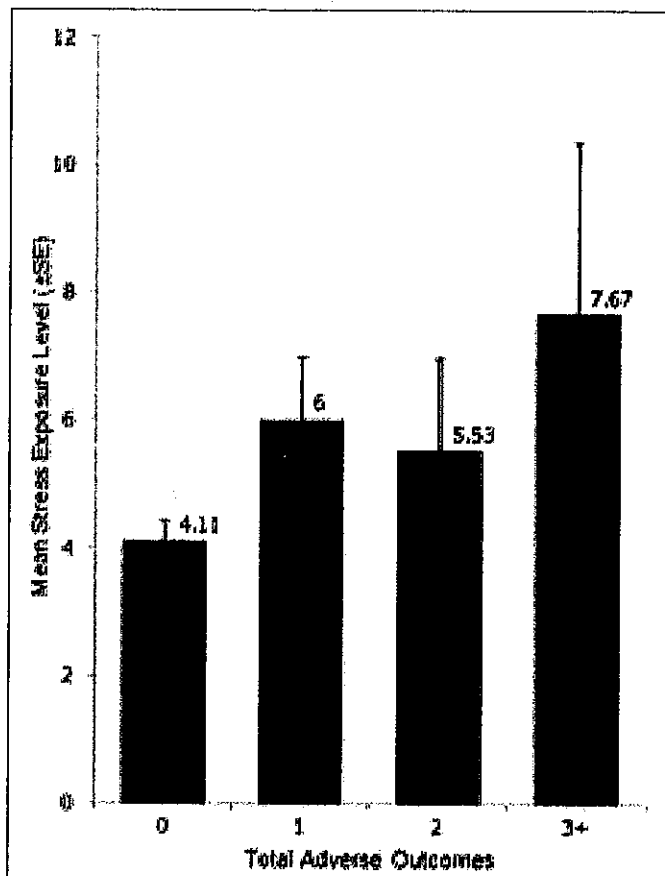


Figure 2. Total number of adverse birth outcomes in relationship to the nonchemical environmental (stress) exposure scale score. For the trend, $P < .01$.

the GW.^{5,16} The dose-response relationship between Ch exposure and adverse birth outcomes further supports the hypothesis that GW is associated with adverse birth outcomes. Theoretically, it is possible that nonchemical exposures, that is, stress in the post-GW group, contributes to our findings of an increased risk for adverse birth outcomes by means of increased levels of the stress hormone cortisol. However, our findings do not support this theory since NCh exposures were not related to adverse birth outcomes after controlling for Ch exposures and other sociodemographic risk factors.^{8,26,27}

These findings extend previous studies conducted in populations exposed to war, such as in Darfur, Kuwait, Bosnia and Herzegovina, and the September 11, 2001 terrorist attacks, as well as nonwar-related exposures in communities that suffer high rates of environmental exposures, such as certain urban and immigrant communities.^{12,18,28,29}

The percentage of stillbirth in the current study was higher; 216 per 1,000 births in women exposed to the GW versus 60 per 1,000 births among nonexposed women, as

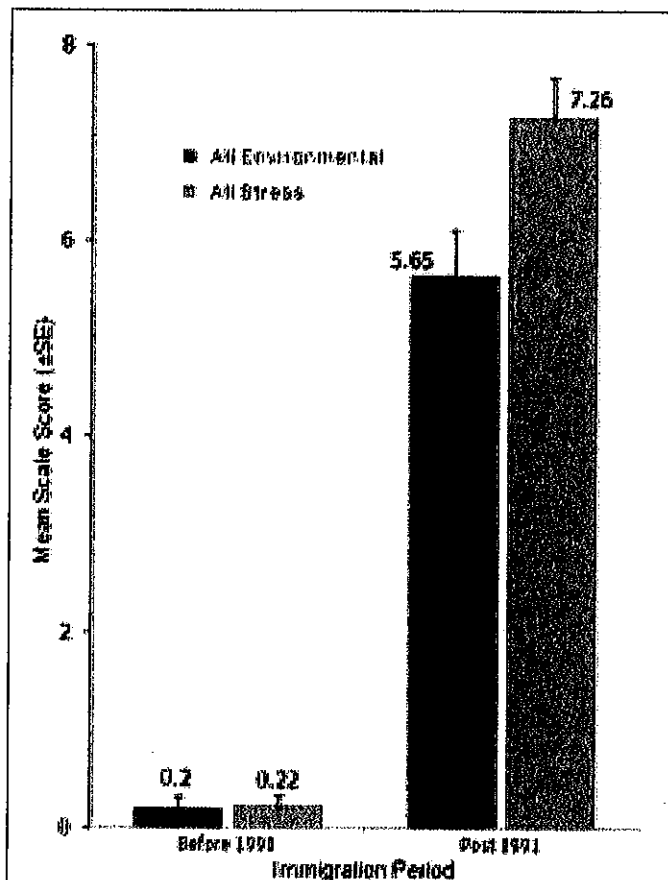


Figure 3. Chemical environmental (all environmental) and nonchemical (all stress) exposure scales presented as functions of the period of the study participants' immigration to the United States relative to the 1991 Gulf War.

compared to official Iranian 1995 statistics citing 24 per 1000 in 1995.³⁰ During the war in Darfur from 2003 to 2007, a stillbirth rate of 29 per 1,000 births was reported for the Wad Medani Hospital in Central Sudan.²⁸ Furthermore, Makhseed et al reported an increased percentage of low birth-weight babies in the Maternity Hospital of Kuwait during Iraq's invasion of Kuwait from 1991 and 1992, as compared to before 1991.¹⁸

Our finding of an association between Ch exposure and preterm delivery is in line with the report by Fatušić et al,¹² who found an increased rate of preterm delivery during the war in Bosnia and Herzegovina, as compared to pregnancy outcomes after the conflict had subsided.^{12,18} However, none of the prior war studies classified type of Ch and NCh exposures.

With regard to specific exposure culprits, air pollution as well as ovarian and uterine irradiation in nonwar community settings has been associated with an increased risk of nonoptimal pregnancy outcomes.^{31,32} External exposures to pesticides, both occupational and residential,

Table 2. Specific adverse birth outcomes by date of occurrence and GW exposure category.*

Adverse Pregnancy Outcome	Post-GW (n ₁ =185) %n ₁	Pre-GW (n ₂ =122) %n ₂	P Value
Stillbirth - before 1991	11.6	11.1	1.00
Stillbirth - after 1991	21.6	6.0	.00
Congenital anomaly - before 1991	0.0	0.0	N/A
Congenital anomaly - after 1991	2.1	0.0	.30
Low birth weight - before 1991	1.6	2.6	.68
Low birth weight - after 1991	7.4	3.4	.21
Preterm delivery - before 1991	3.2	0.9	.26
Preterm delivery - after 1991	3.4	7.4	.21

*The data includes both female and male respondents. Each male respondent reported the outcome of pregnancy of his female partner.

Table 3. Chemical and nonchemical exposure predictors of aggregate number of adverse birth outcomes.

Variable	Standardized β	t	P value	R ²
Step 1				
Gender (ref=men ^a)	-0.183	-2.797	.006	
Smoker (smoker ^a)	0.021	-1.437	.750	
Education (less than high school ^a)	-0.086	-1.437	.152	
Ethnicity (Arab ^{a,b})	-0.185	-2.957	.003	0.112
Step 2				
Chemical exposure scale scores	0.229	2.852	.005	
Nonchemical exposure scale scores	0.024	0.296	.767	0.054
Total explained variance, R ² =				0.166

Notes:
a. Ref indicates reference category.
b. Iraqi Arab vs Iraqi Chaldeans

have been linked to stillbirth.^{26,27} Nonchemical related stress, as measured through maternal salivary cortisol and self-reports, has been associated with shorter pregnancies, although not necessarily preterm birth in a sample of nonwar-exposed persons.²⁶

There are a number of limitations to the study that should be considered. The original survey was designed to cover a range of exposures and health outcomes, not just reproductive health. We lacked objective exposure and birth outcome measures. We also asked subjects to report on birth outcomes and exposures a number of years after the GW. This could attenuate true associations. Participants could also be unaware about personal exposures to "invisible" agents such as depleted uranium. Finally, the age of the participants when they were pregnant and the birth order of children remain unknown, factors that could possibly play some role.

CONCLUSION

The prevalence of adverse birth outcomes is increased in participants who resided in Iraq during the Gulf War as opposed to those that had left prior to the GW. Moreover, there is a dose-response relationship between war-related environmental exposures and total number of adverse birth outcomes. Certain chemical exposures appear to be more closely related to adverse birth outcomes. The study points to the importance of considering reproductive risks in pregnant mothers with a history of exposure to war.

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Table 4. Statistical relationships of specific adverse birth outcomes to environmental-specific exposures.

Adverse Birth Outcome	Reported Environmental Exposures	Odds Ratio	95% CI	P Value
Congenital birth defects	Diesel and other petrochemical fumes	17.00	1.50; 192.76	.021
Low birth weight	Contact with/exposure to smoke from oil well fires	3.00	1.25; 7.18	.017
	Exhaust from generators/kerosene heaters	2.59	1.01; 6.69	.063
	Contaminated water in local pond, river or the Gulf	3.87	1.30; 11.58	.028
Pre-term birth	Contact with/exposure to smoke from oil well fires	3.26	1.34; 7.92	.012
	Exhaust from generators/kerosene heaters	3.50	1.38; 8.87	.013
	Drinking water contaminated by smoke, oil or other chemicals	3.33	1.27; 8.74	.022
	Contaminated water in local pond, river or the Gulf	4.12	1.37; 12.38	.022
	Contact with/exposure to smoke from oil well fires	2.38	1.32; 4.27	.005
Stillbirth	Exhaust from generators/kerosene heaters	2.84	1.48; 5.44	.002
	Diesel fumes/other petrochemical fumes	2.60	1.24; 5.45	.014
	Burning trash/feces	2.91	1.154; 7.331	.028
	Mustard gas	2.548	1.24; 5.23	.013
	Ingested food contaminated by smoke, oil, or other chemicals	2.20	1.28; 3.78	.013

Note: CI indicates confidence interval.

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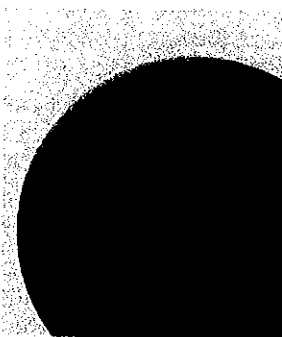
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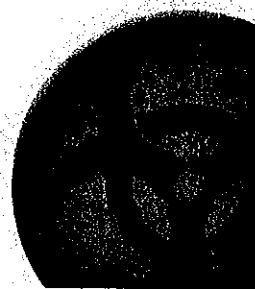
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