Presentation 7 – David Cowan

Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies

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1

2

5

Two 2002 Studies of Asthma and Exposure to Oil Well Fire Smoke

- Smith TC, Heller JM, Hooper TI, Gackstetter GD, Gray GC. Are Gulf War veterans experiencing illness due to exposure to smoke from Kuwait oil well fires? Examination of Department of Defense hospitalization data. Am J Epidemiol 2002 May 15;155(10):908-17
- Lange JL, Schwartz DA, Doebbeling BN, Heller JM, Thorne PS. Exposures to the Kuwait oil fires and their association with asthma and bronchitis among gulf war veterans. Environ Health Perspect 2002 Nov;110(11):1141-6

6

A case control study of asthma among U.S. Army Gulf War veterans and modeled exposure to oil well fire smoke

David N. Cowan, Jeffrey L. Lange, Jack Heller, Jeff Kirkpatrick, Samar DeBakey
Mil Med 2002 Sep;167(9):777-82

7

Methods 1

- Subjects:
  - Active Duty Army
  - Comprehensive Clinical Evaluation Program Participants
  - Demographic, military, and questionnaire (including self-reported Sx, Cx, Ex) data available.
  - Physician-assigned diagnoses (primary, up to 6 secondary) ICD-9 coding

8

Methods 2

- Cases
  - Diagnosis of asthma (493, 493.91) after CCEP exam
  - No diagnostic or laboratory data available
- Controls 3:1 ratio
  - Random selection of CCEP participants with no respiratory system diagnoses, SSID diagnoses, or Sx or Cx

9

Methods 3

- Exposure
  - Self-reported exposure captured (yes/no)
  - Unit location at company level
  - Unit location provided by CRUR to CHPPM

10

Methods 4

- Exposure
  - NOAA Air Resource Laboratory developed plume model
  - Modeled plume is for 24 hr average concentration of soot, updated daily
  - Exposures are estimated for 15 km resolution, 2 m above ground

11

Methods 5

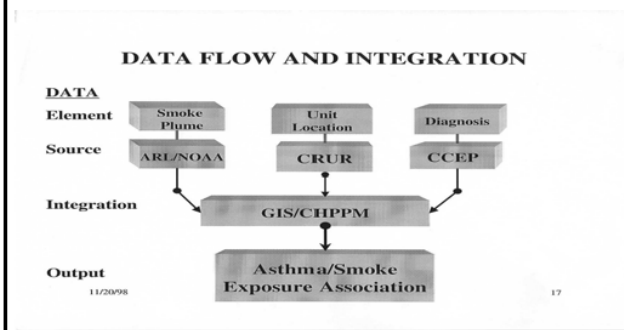
- Exposure
  - Soot composed ~15-20% of total plume particulates, varied considerably over time and across wells
  - Other components include salts (~30%), sulfates (~8%), other organic compounds (~30%)
  - Most soot and other particulates 0.1-0.8 um diameter

12

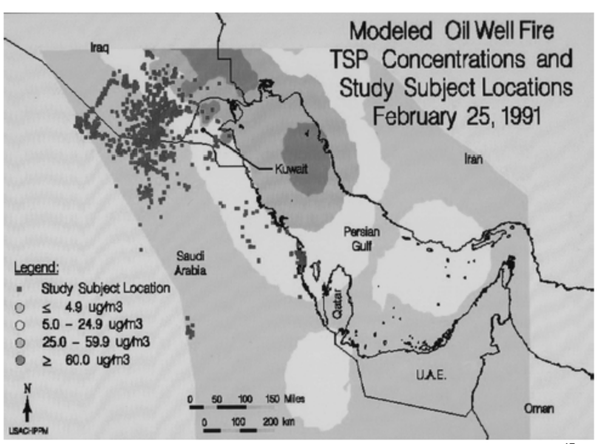
Methods 6

- Exposure measures
  - Sum of estimated concentration for all days in-theater (mg/m^3-days). Continuous variable and categories:
    - referent < 0.1 mg/m^3-days
    - intermediate >= 0.1 and < 1.0 mg/m^3-days
    - highest level >= 1.0 mg/m^3-days
  - Number of days exposed to levels of 65 $\mu g/m^3$ or higher (National Ambient Air Quality Standard for 24-hour particulate matter of less than 2.5 μm diameter (EPA 1997)). Continuous variable and categories:
    - referent 0 Days
    - intermediate 1 to 5 days
    - highest 6 to30 days

13



14



15

Methods 7

- Analysis
  - Odds ratio measure of association
  - Statistical significance based on 95% confidence interval
  - Logistic regression used for multivariate analyses

16

Results

- 873 cases with valid location data used in analyses
- 2464 controls with valid location data used in analyses

Table 1. Univariate associations between asthma and demographic characteristics

Sex			
Female	133	264	1.00 (referent)
Male	739	2200	0.67 (0.53 - 0.84)
Age group at time of evaluation			
19-24	262	662	1.00 (referent)
25-29	231	646	0.90 (0.73 - 1.12)
30-34	202	608	0.84 (0.67 - 1.05)
GE 35	161	520	0.78 (0.62 – 0.99)
Chi Square for trend = 5.10, p=0.024			
Race/ethnicity			
White	439	1225	1.00 (referent)
Black	311	909	0.95 (0.80 - 1.13)
Hispanic	50	127	1.10 (0.77 - 1.57)
Other	73	203	1.00 (0.74 - 1.35)

Table 1. (cont) Univariate associations between asthma and demographic characteristics

Variable and Level	Number of Cases	Number of Controls	Odds Ratio (95% CI)
Rank			
Enlisted	799	2169	1.00 (referent)
Officer	66	246	0.73 (0.54 - 0.98)
Cigarette smoking			
Never	499	1327	1.00 (referent)
Former	186	461	1.07 (0.87-1.32)
Current	188	676	0.74 (0.61 - 0.90)
Self-reported oil well fire smoke exposure			
No	111	443	1.00 (referent)
Yes	634	1626	1.56 (1.23 - 1.97)

Comparison of exposures

- Poor agreement between self-reported and modeled exposures (kappas of 0.13 and 0.12)
- High correlation between modeled cumulative exposure and days exposed to high (r_s=0.84)

Table 2. Univariate Associations between Asthma and Measures of Smoke Exposure

Cumulative exposure mg/m3-days			
Categories	Cases	Controls	Odds Ratio (95% CI)
< 0.1	172	592	1.00 (referent)
>= 0.1 – < 1.0	292	829	1.21 (0.97 – 1.51)
>= 1.0	273	670	1.40 (1.12 – 1.76)
Any vs. none			1.30 (1.06 – 1.58)
Chi square test for trend = 9.04, p=0.003			

21

Table 2. (Cont) Univariate Associations between Asthma and Measures of Smoke Exposure

Days with Exposure >= 65 ug/m3			
Categories	Cases	Controls	Odds Ratio (95% CI)
0	215	723	1.00 (referent)
1-5	270	745	1.22 (0.99 – 1.50)
6-30	218	495	1.48 (1.19 – 1.85)
Any vs. none			1.32 (1.10 - 1.60)
Chi square test for trend = 12.26, p=0.0005			

22

Table 3. Odds Ratios (95% CI) for Asthma by Smoking Status

Exposure and Level			
Cumulative exposure mg/m3-days			
Categories	Never Smoked	Former Smoker	Current Smoker
< 0.1	1.00 (referent)	1.00 (referent)	1.00 (referent)
>= 0.1 – < 1.0	1.31 (0.98 – 1.77)	1.27 (0.75 – 2.16)	1.00 (0.71 – 2.16)
>= 1.0	1.43 (1.06 – 1.94)	1.73 (1.04 - 2.90)	1.05 (0.64 – 1.72)

23

Table 3. (Cont) Odds Ratios (95% CI) for Asthma by Smoking Status

Exposure and Level			
Days with Exposure >= 65 ug/m3			
Categories	Never Smoked	Former Smoker	Current Smoker
0	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-5	1.24 (0.99 – 1.64)	1.54 (0.95 – 2.51)	0.92 (0.63 – 1.34)
6-30	1.35 (1.00 – 1.82)	2.02 (1.23 – 3.34)	1.29 (0.79 – 2.09)

24

Table 4. Adjusted* Odds Ratios for Associations with Measures of Smoke Exposure

Cumulative exposure mg/m3-days	
Categories	Adjusted Odds Ratio (95% CI)
< 0.1	1.00 (referent)
>= 0.1 – < 1.0	1.24 (1.00 – 1.55)
>= 1.0	1.40 (1.11 – 1.75)
Continuous	1.08 (1.01 – 1.15)

*Adjusted for sex, age, race/ethnicity, rank, smoking history, and self-reported exposure.

25

Table 4. (Cont) Adjusted* Odds Ratios for Associations with Measures of Smoke Exposure

Days with Exposure >= 65 ug/m3	
Categories	Adjusted Odds Ratio (95% CI)
0	1.00 (referent)
1-5	1.22 (0.99 – 1.51)
6-30	1.41 (1.12 – 1.77)
Continuous	1.03 (1.01 – 1.05)

*Adjusted for sex, age, race/ethnicity, rank, smoking history, and self-reported exposure.

26

Discussion

- We found significant associations between modeled smoke exposure and physician-diagnosed asthma for both cumulative exposure measures defined *a priori*
- We found dose-responses for both when considered as categorical measures and as continuous measures

27

What did they find?

- Smith, et al. No association between modeled smoke exposure (MSE) and hospitalization for asthma (and other diseases)
- Lange, et al. No association between MSE and self-reported asthma symptoms

28

Compare and Contrast the Studies

- What do they have in common?
- What is different?
- How could these affect the findings?

29

Study design

- Smith, et al. Historical cohort
- Lange, et al. Cross-sectional
- Cowan, et al. Case-control

30

Study population

- Smith, et al. ~405,000 active duty, deployed, all branches
- Lange, et al. ~1,900 all components, deployed, all branches
- Cowan, et al. ~3,300 active duty CCEP, deployed, Army only

31

Control of potential confounders?

- Smith, et al. Partial: job, prewar hospitalization
- Lange, et al. Partial: smoking status, self-reported exposure
- Cowan, et al. Partial: smoking status, self-reported exposure

32

Diagnosis issues

- *A priori* hypothesis
- Case definition
- Study setting
- Number of cases in study
- Diagnostic accuracy
- Prevalence of disease in studied population

33

A priori hypothesis for outcome?

- Smith, et al. No. Looked at all dx
- Lange, et al. Yes. Examined only respiratory illness (plus depression)
- Cowan, et al. Yes. Examined only asthma

34

Case Definition

- Smith, et al. Hospital record, ICD-9
- Lange, et al. Self-report ATSQ
- Cowan, et al. Physician diagnosis

35

Study setting

- Smith, et al. Electronic records of hospitalized patients only
- Lange, et al. Telephone interviews
- Cowan, et al. Patients seen outpatient in CCEP. Data from q-aires, medical exam

36

Number of cases in study

- Smith, et al., 880
- Lange, et al., 129
- Cowan, et al., 865

37

Diagnostic specificity and sensitivity

- Smith, et al., used only hospitalized cases, likely missed 90% of all cases (high PPV, not sensitive)
- Lange, et al., used self-report, likely included many non-cases (low PPV, not specific)
- Classification error for both
- Cowan, et al., used physician dx, sensitivity and specificity unknown.

38

Prevalence of Diagnosis in Population

- Smith, et al. 0.22%
- Lange, et al. 8.3%
- Cowan, et al. 2.2% (primary dx)

39

Exposure Issues

- Estimation issues
- Data source
- *A priori* hypothesis
- Exposure Cut points
- Branch of service and unit location

40

How exposure estimated

- Smith, et al. Reported TSP, 2 m above ground
- Lange, et al. Solar absorbance of smoke, distance above ground not specified
- Cowan, et al. Soot, 2 m above ground

41

Source of exposure estimates

- All studies used same basic source of data: Center for Health Promotion and Preventive Medicine/National Oceanic and Atmospheric Administration plume model

42

A priori hypothesis for exposure?

- Smith, et al. Not clear
- Lange, et al. No. Cut points arbitrary
- Cowan, et al. Yes. Set cut points prior to analyses

43

Exposure Cut points

- Smith, et al.
  - 7 levels
    - none
    - 1-260 ug/m3 for 1-25, 25-50, or >50 days
    - >260 ug/m3 for 1-25, 25-50, or >50 days
  - Categories do not appear to be mutually exclusive

44

Exposure Cut points

- Lange, et al.
  - Two levels "set without available precedent and without intuition regarding a level that would adequately balance sensitivity and specificity. Thus, *a priori*..." selected the 50th percentile and the 95th percentile, compared most-exposed to rest of population
  - Used number of days exposure was above each threshold.

45

Exposure Cut points

- Cowan, et al., established cut points *a priori* based on distribution and EPA standards

46

Branches included

- Smith, et al. All branches
- Lange, et al. All branches
- Cowan, et al. Army only

47

Military Branches and Unit Location Data

- Most military personnel in the vicinity of the oil well fires were Army and Marine Corps
- Army unit location data at the company level (approximately 100-200/Co)
- Marine data at the battalion level (4 to 6 Co/Bn)
- Navy and Air Force data not usable due to mobility and size of units
- Only Army personnel were used by Cowan, et al.

48

Impact of Branch of Service

- Smith, et al. and Lange, et al. used all branches of service. Due to problems with Marines, Air Force, and Navy data there is likely increased exposure error
- Cowan, et al., used only Army units, likely had lower level of exposure estimate error

49

What does it all mean: error in diagnosis and exposure

- If errors in diagnosis and exposure are not dependent on one another (non-differential misclassification), then the observed level of association is almost certainly lower than the true level of association
- There is little doubt that errors exist in both diagnosis and exposure estimates

50

Misclassification Discussion: Cowan, et al.

- Potential for misclassification errors in Cowan, et al.
  - Outcome
    - False positive cases
    - Less likely false negative controls
  - Exposure
    - Unit location errors likely
    - Model errors likely
    - Degree of these unknown

51

Misclassification Discussion: Smith, et al. and Lange, et al.

- Smith, et al., probably missed 90% of cases (many false negatives), but probably had very high PPV
- Lange, et al, probably over-diagnosed substantially (many false positive), had low PPV, but had few false negatives

52

Misclassification Discussion

- In each study diagnoses and exposure estimates were were made independently of each other; therefore it is probable that the errors are largely non-differential

53

The effect of non-differential misclassification

- The effect of non-differential misclassification is known:
  - '…bias from independent non-differential misclassification of a dichotomous exposure is always in the direction of the null value…" Rothman and Greenland, *Modern Epidemiology*

54

More comments on non-differential misclassification

- "…the attenuation (of the odds ratio) can be appreciable even with a high sensitivity and specificity." Armstrong, et al. *Principles of Exposure Measurement in Epidemiology*
- "Random misclassification always results in an underestimation of the true relative risk…" Hennekins and Buring, *Epidemiology in Medicine*

55

The Potential for Selection Bias

- Difficult to assess, always a challenge, can give biased answer
- In both Lange, et al., and Cowan, et al., there was a low level of correlation between self-reported and modeled exposure, so self-selection is not likely to account for findings
- Must remain vigilant for bias

56

Conclusions

- When the observed odds ratios from the Cowan, et al., study are considered in the light of the substantial opportunity for misclassification, the findings are suggestive of an association between objective estimates of exposure to oil well fire smoke and risk of asthma diagnosis among CCEP participants

- Smith, et al., and Lange, et al., are likely to have even higher levels of misclassification, and that may account for the findings of no association

- More studies needed...

57