

Case Crossover Studies of PM Effect on Cardiac Events





Goals of Talk

- Discuss epidemiological method to describe potential acute effects
- Describe Study of PM Effect on MI onset
- Compare Boston Onset results with MITI results



Health Effects at Ambient Levels

- Increased cardiovascular mortality
- Increased hospitalization for MI
- Increased Firings of AICDs
- Increased triggering of MI Onset



Limitations to Time Series Studies

- Dificult to control for seasonal effects
- Unable to assess for personal level effect modifiers



The Case-Crossover Design

- For each case, compares the exposure associated with the event to other comparable “referent” exposures
- Estimates the effect of short-term exposure on the risk of an event
- Controls for time dependent and independent confounders by design
- Use conditional logistic regression



Assumptions of Model

- Stationarity in exposure
- Disease has abrupt onset and short latency for detection
- Short induction period for disease



Improving Causal Inferences of PM Effects

- Levy, Lumley and Sheppard develop appropriate referent selection for case-crossover studies.
 - Some referent selection strategies introduce bias (overlap bias)



Triggering of Cardiac Events

- Boston MI Onset Study demonstrated association between elevations in fine PM and MI onset (OR 1.69). (Peters Circulation 2001).
- Case-crossover analyses of air pollution effect on primary cardiac arrest [PCA] in Seattle failed to detect an association between fine PM and PCA. (Sullivan et al AJE 2003)



Hypothesis

- Short-term increase in fine PM would be associated with MI onset
- Individuals with pre-existing cardiovascular disease may be at greater risk



MITI Study

- EMS/ UW Community based myocardial infarction treatment study 1988-94.
- Data Collection
 - Medical records review and follow-up interview
 - 11,983 participants
 - 5790 with confirmed acute MI
 - 19 Participating Hospitals in King County



Case Definition

- Hospital discharge diagnosis of acute MI with confirmatory CPK isoenzymes and/or EKG changes.
 - Excludes primary cardiac arrest and unstable angina.



MI Onset Time

- EMS activation time or ER arrival time
- Duration of pain prior to arrival or EMS call
- Rounded to prior hour if minute of onset < 30

Table 1. Demographics of the 5793 Cases with Myocardial Infarction Participating in MITI Study.

Variable	Descriptor	Cases (n=5793) (%)
Age (years)	Median age	median 69, range 21-98
Age Categories	<50 years old	748 (13%)
	50-69 years old	2473 (43%)
	>=70 years old	2572 (44%)
Gender	male	3858 (67%)
Race	white	5084 (89%)
Smoking Status*	Current	1353 (23%)
History of CHF	Yes	771 (13%)
History of Angina	Yes	2246 (41%)
History of MI	Yes	1782 (31%)
History of Hypertension	Yes	2849 (49%)
History of Diabetes*	Yes	1020 (18%)



Exposure Measures

- Primary exposure metrics:
 - Nephelometry, CO, SO₂, PM₁₀
 - Averaged from 3-Central Sites
 - 1-hr, 2-hr, 4-hr and 24-hr averaged levels
 - Adjusted for RH and Temperature

Summary of Exposure Variables 1-hour preceding MI onset.

Variable (unit)	Min	25%	50%	75%	90%	Max	Mean	IQR
+PM_{2.5} ($\mu\text{g}/\text{m}^3$)	2.0	5.3	8.6	15.3	27.1	147	12.2	10.6
PM₁₀ ($\mu\text{g}/\text{m}^3$)	4.5	15	24	36	52	372	28.3	20.5
CO (ppm)	0.4	1.2	1.9	2.6	3.4	10.7	2.0	1.4
SO₂ (ppb)	0	5	8	10	16	38	9	5
Temp.	29	45	52	59	66	88	52	14
Relative Humidity	14	63	80	90	96	100	75	27

+Represents PM_{2.5} equivalent of actual nephelometric measure: $\text{PM}_{2.5} = (\text{nephelometry measure} * 100,000 - .01) / 0.28$.

The exposure levels at 2-hour, 4-hour and 24-hour averages prior to event are similar to the 1-hour averaged exposure. Therefore, they are not shown.



Statistical Analysis

- Case-crossover analysis
- Referent selection based on prior simulations
 - Time-stratified, bi-directional
- Focus on short-term exposure response

Association Between Pollutant Levels and MI Onset.

Pollutant		Averaging time	OR (95% CI)
+PM _{2.5}	10µg/m ³	1-hr	1.01 (0.98, 1.05)
		2-hr	1.01(0.97, 1.05)
		4-hr	1.02(0.98, 1.04)
		24-hr	1.02 (0.98, 1.07)
CO	1-ppm	1-hr	1.04 (0.99, 1.08)
		2-hr	1.03 (0.98, 1.07)
		4-hr	1.02 (0.97, 1.06)
		24-hr	1.02 (0.97, 1.08)
SO ₂	10-ppb	1-hr	0.97(0.94,1.01)
		2-hr	0.98 (0.95, 1.01)
		4-hr	0.99 (0.96, 1.03)
		24-hr	1.0 (0.95, 1.06)

Association between PM and MI adjusted by Demographic Factors

Variable	Status	1-hour average Odds Ratio (95% CI)	24-hour average Odds Ratio (95% CI)
Age	<50 y.o.	1.04 (0.95, 1.14)	1.07 (0.98, 1.19)
	50-69 y.o.	0.99 (0.94, 1.05)	0.99 (0.93, 1.06)
	≥70 y.o.	1.03 (0.98, 1.08)	1.04 (0.99, 1.11)
Gender	Male	1.02 (0.98, 1.06)	1.03 (0.99, 1.08)
	Female	1.00 (0.95, 1.06)	1.00 (0.94, 1.07)
Race	White	1.01 (0.97, 1.04)	1.01 (0.97, 1.06)
	Non-white	1.06 (0.97, 1.17)	1.10 (0.99, 1.23)
Smoking Status	Current	0.99 (0.93, 1.06)	0.99 (0.95, 1.14)
	Non-smoker	1.03 (0.97, 1.08)	1.03 (0.98, 1.09)
Survivor of MI*	Yes	1.02 (0.98, 1.06)	1.03 (0.98, 1.07)
	No	0.96 (0.86, 1.08)	0.97 (0.85, 1.10)

Stratification by prior cardiac disease or cardiac risk factors.

Variable	Status	1-hour average Odds Ratio (95% CI)	24-hour average Odds Ratio (95% CI)
CHF	Yes	1.06 (0.97, 1.16)	1.08 (0.97, 1.2)
	No	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
MI	Yes	1.03 (0.97, 1.1)	1.04 (0.97, 1.17)
	No	1.01 (0.96, 1.06)	1.02 (0.98, 1.08)
Hypertension	Yes	1.02 (0.97, 1.07)	1.02 (0.97, 1.07)
	No	1.01 (0.96, 1.06)	1.02 (0.97, 1.08)
Diabetes	Yes	1.06 (0.98, 1.14)	1.04 (0.95, 1.14)
	No	1.01 (0.97, 1.05)	1.01 (0.97, 1.06)



Limitations of Study

- Exposure Assessment
- Referent Selection
- Absence of Medication use variables



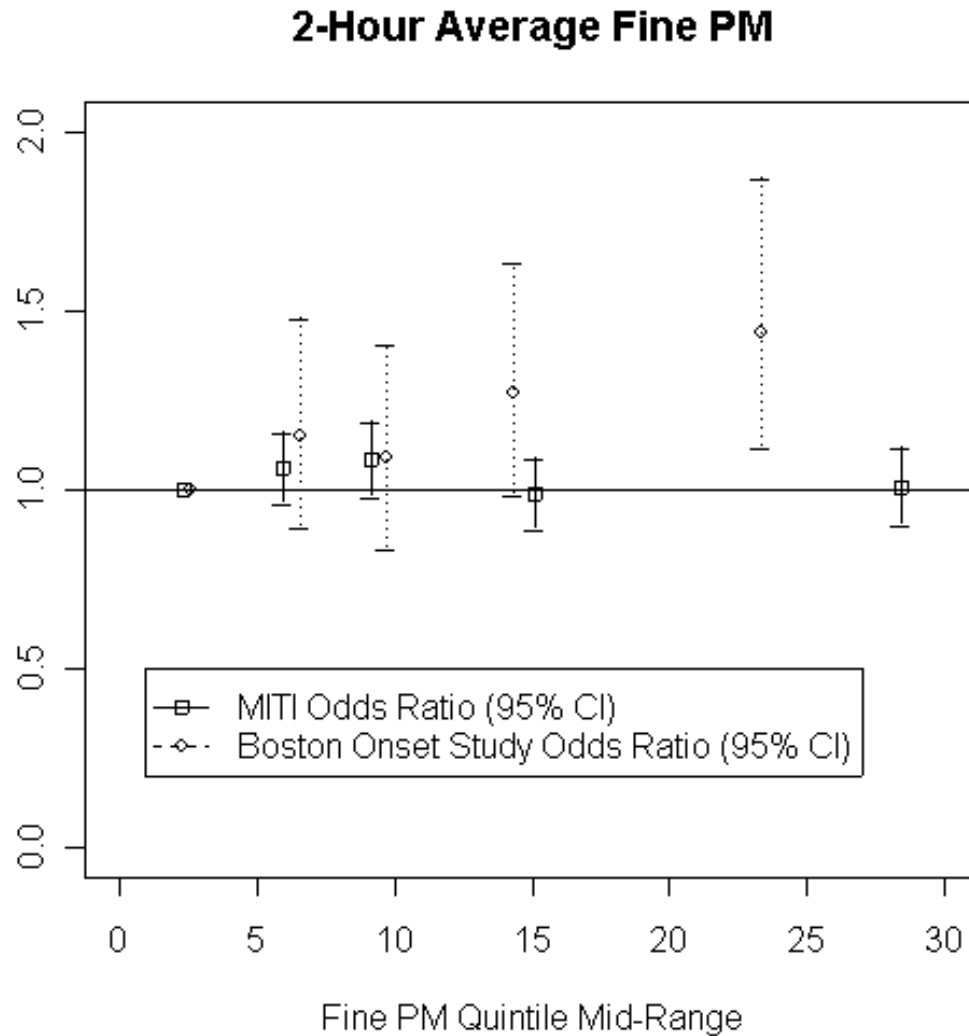
Reasons for Null Study

- PM Composition
 - Sulfates
 - Transition metals
- Pre-existing medical conditions
- Model and referent selection
 - Time-stratified, bi-directional

Referent Selection Matters

Referent Selection	OR (95% CI)
Time-stratified	1.01 (0.92,1.10)
Unidirectional 3	1.04 (0.94,1.15) p-value = 0.480
Unidirectional 3,4,5	1.06 (0.97,1.16) p-value = 0.208
Symmetric Bidirectional 7,14	1.06 (0.99,1.13) p-value = 0.106
Symmetric Bidirectional 7	1.07 (1.00,1.15) p-value = 0.063

Comparison with Boston Study





Conclusions

- Unable to detect an association between short-term elevations in PM and onset of MI.
- No obvious effect modification by pre-existing cardiovascular disease
- Unable to replicate Boston Onset Study



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