Interaction of Genetic Variation in the *ABO* Locus and Short-Term Exposure to Elevations in Fine Particulate Matter Air Pollution Differentially Affects Associations with Acute Coronary Events

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BACKGROUND

Ambient fine particulate matter ($PM_{2.5}$) air pollution is associated with greater cardiovascular risk, including long-term development of coronary heart disease and short-term acute coronary syndrome (ACS) events such as myocardial infarction (MI) and unstable angina (USA).

Evidence indicates that short-term (hours to a few days) exposure to $PM_{2.5}$ may trigger ACS events, especially among individuals with pre-existing coronary artery disease (e.g., Pope CA, *et al*. JAHA, 2015).

ABO gene sequence variants rs687289 and rs514659 (r^2=1.0 with rs687289) were previously validated by GWAS to predict MI in patients with coronary artery disease (Reilly MP, *et al*. Lancet, 2011).

HYPOTHESIS

Short-term exposure to elevated $PM_{2.5}$ is differentially associated with ACS event risk among carriers of the *ABO* rs687289 A allele (non-O blood types: A, B, AB) vs. GG genotype (O blood type).

METHODS

Patients who had ≥1 coronary vessel with flow-limiting coronary artery disease (≥70% stenosis) and residing on Utah's Wasatch Front were studied if they were hospitalized at Intermountain Healthcare for an ACS event (acute MI or USA) between October 1993 and May 2007.

ABO variants rs687289 (primary hypothesis), rs657152 (r^2=0.86 with rs687289), and rs579459 (r^2=0.40 with rs687289) were genotyped.

A time-stratified case-crossover design was used in which a patient's $PM_{2.5}$ exposure at the time of an ACS event was matched to exposures at non-event times on the same day of the week and in the same month.

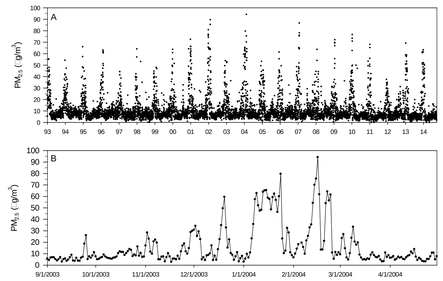
Odds ratios for $PM_{2.5}$ with adjustment for daily temperature, dew point, and barometric pressure were determined for linear models using a 25 μg/m^3 threshold (primary hypothesis) and in non-threshold models.

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION.

Characteristic	All Events	Myocardial Infarction	Unstable Angina	Carrier (*ABO* rs687289)	Non-Carrier (*ABO* rs687289)
Number of Events	1303	806	497	677	523
Age, years	53 ± 7	52 ± 7	53 ± 7	52 ± 8	53 ± 7
Sex (male), %	73	72	74	73	71
Smoking, %	37	40	33	37	39
BMI, kg/m^2	31 ± 6	30 ± 7	31 ± 6	30 ± 6	31 ± 7
Heart Failure, %	11	13	7	11	11
Hypertension, %	59	57	64	57	62
Hyperlipidemia, %	70	66	78	69	71
Diabetes, %	29	29	31	28	31
CHD Family History, %	54	52	57	54	54
Diseased Vessels, %	100	100	100	100	100

FIGURE 1. DAILY $PM_{2.5}$ CONCENTRATIONS.

Daily $PM_{2.5}$ concentrations (μg/m^3) at Salt Lake City (Hawthorne monitor, plus imputed) from January 1993 through September 2014 (Panel A) and, for a more detailed illustration, a shorter sample-period from September 2003 through April 2004 (Panel B).



Pope CA III, Muhlestein JB, ..., Horne BD. *J Am Heart Assoc* 2015;4:e002506 (doi: 10.1161/JAHA.115.002506).

RESULTS

TABLE 2. AIR POLLUTION MONITORING DATA: MEASURED ± IMPUTED.

Monitoring Sites	Data Sources	Sample Size (n)	Mean	Standard Deviation	Maximum	Episode Days (%)
Ogden	$PM_{2.5}$ monitored	3443	9.9	9.2	108	2.99
Ogden	(+ imputed)	7698	10.6	9.1	108	3.16
SLC Hawthorne	$PM_{2.5}$ monitored	5668	10.6	11	94	4.82
SLC Hawthorne	(+ imputed)	7855	10.5	10.4	94	4.32
Provo/Orem, Lindon	$PM_{2.5}$ monitored	5415	10	10.2	123	3.29
Provo/Orem, Lindon	(+ imputed)	7697	10.7	10.8	123	4.16

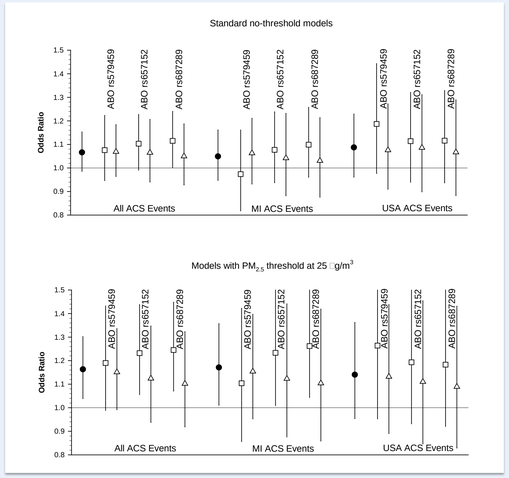
TABLE 3. ASSOCIATION OF $PM_{2.5}$ WITH EVENTS IN THRESHOLD MODEL.

Association of short-term elevations in $PM_{2.5}$ overall and with stratification by *ABO* rs687289 genetic variation in models with and without a minimum threshold of pollution exposure.

	Events (n)	Odds Ratio (per +10 μg/m^3)	95% Confidence Interval	P-value
Threshold Model				
All ACS Events	1285	1.16	1.04, 1.30	0.009
Events by ABO				
rs687289 A Carrier	669	1.25	1.07, 1.45	0.004
GG Genotype	515	1.10	0.92, 1.32	0.29
No Threshold				
All ACS Events	1285	1.07	0.99, 1.15	0.11
Events by ABO				
rs687289 A Carrier	669	1.12	1.00, 1.24	0.044
GG Genotype	515	1.05	0.93, 1.19	0.44

FIGURE 2. FOREST PLOTS OF THE ASSOCIATION OF $PM_{2.5}$ WITH EVENTS, STRATIFIED BY VARIATION IN THE *ABO* GENE.

Odds ratios (with 95% confidence intervals) for ACS, MI, and USA events per 10 ug/m^3 increase in $PM_{2.5}$ for non-threshold (panel A) and threshold models (panel B) in overall analyses (closed circle) and stratification by carrier (open square) and non-carrier (open triangle) for 3 DNA sequence variants in the *ABO* gene.



CONCLUSIONS

- **Short-term exposure to elevations in $PM_{2.5}$ was associated more strongly with risk of ACS events in *ABO* risk allele carriers (A allele) corresponding to A, B, and AB blood types, with lower association in GG genotype (corresponding to O blood type).**
- **A stronger association was found when modeling used a $PM_{2.5}$ exposure threshold of 25 μg/m^3, above which the effect was linear.**

Presented at the American Heart Association Scientific Sessions, Anaheim, CA, November 14, 2017.

Disclosures: None.