

ARIC Manuscript Proposal #760

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1.a. Full Title: Association between air pollution and hemostatic/inflammation factors

b. Abbreviated Title (Length 26 characters): Pollutants and hemostatic factors.

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

Data preparation and analysis (3 month). Manuscript preparation (6 months)

4. Rationale:

Our ancillary studies to relate air pollution and cardiovascular responses have been funded by US EPA and NIEHS. This proposal address research questions for these ancillary studies.

Since 1990, a considerable number of epidemiological studies have been reported, showing an association between exposure to particulate air pollution below the current national air quality standard and excess mortality and morbidity. These studies have been extensively reviewed in the recent EPA final report, Air Quality Criteria for Particulate Matter ⁽¹⁾. In 20 time-series studies of mortality and air pollution, a consistent relationship was found between daily variations in mortality and deaths for all causes, with a stronger effect among the elderly from cardiovascular and pulmonary causes. These effects were shown to be robust to the choice of statistical models, persistent after adjusting for the effects of season and weather, and not confounded by other criteria air pollutants. Consistent with the mortality findings, epidemiological studies in the US ⁽²⁻⁸⁾, Canada ^(9,10), and Europe ⁽¹¹⁻¹³⁾, have also demonstrated significant associations of ambient air pollutants with hospital admissions for respiratory and cardiovascular diseases.

In addition, CO has also been associated with hospital admission rates of heart failure, and other cardiovascular disease ^(14, 15). In a recent report ⁽¹⁵⁾, Schwartz reported that an interquartile (1.75 ppm) increase in CO was associated with a 2.79% increase in hospital admission rate of heart disease in the elderly, independent of the day-of-week and season. Moreover, in a systematic thorough analysis performed by Samet et al ⁽¹⁶⁾, ambient air pollution-mortality association was not meaningfully altered after controlling for weather effects using various sophisticated methods. Samet et al ⁽¹⁶⁾ also confirmed previous reports that individual air pollutants (PM, SO₂, and O₃) are associated with increased daily mortality. It was concluded by Samet et al that the broader association of pollution with daily mortality they observed cannot be reliably attributed to any single criteria air pollutant due to the limitations discussed below. Samet et al did not find an anticipated association between NO₂ and daily mortality in their multipollutants models, in

contrast to that reported by Moolgavkar et al ⁽¹⁷⁾, who identified a significant NO₂ effect on daily mortality. These discrepancies may be due to different methods used to adjust for other copollutants.

Most of the previous epidemiological studies on pollution and CVD did not have measurements at the individual level, and thus could not address the injury mechanisms, nor can the other confounders be appropriately adjusted for, particularly the individual level covariables, such as age, race, sex, social economic status, other CVD risk profiles, and history of CVD. Moreover, most of the previous epidemiological studies were not powered to identify potential health conditions or population sub-groups that would enhance susceptibility to adverse PM health effects and how host susceptibility factors influence the dose response relationship. Studies are also needed to investigate the biological mechanisms associated with enhanced susceptibility to adverse PM health effects.

One of the important mechanism potentially linking air pollution and CVD is the adverse effect of pollution on systemic inflammation. Since cytokines (e.g. IL-6) that mediate the inflammatory reaction also activate the synthesis of several coagulation factors and fibrinolysis inhibitors, this may result in higher blood coagulability. Recently ⁽¹⁸⁾ it was reported that plasma viscosity during a severe episode of air pollution in 1985 was higher comparing persons examined during highly polluted days to persons examined during less polluted days. The odds ratio in men for very high plasma viscosity was 3.6 (95% CI 1.6-8.1) during a high air pollution episode when compared to the days of not-high air pollution after adjustment for cardiovascular risk factors and meteorological variables. The corresponding odds ratio for women was 2.3 (1.0-5.3). The investigators suggested that altered blood hemodynamics due to inflammatory processes in the lung that induce an acute-phase reaction might therefore be part of the pathological mechanisms linking air pollution to mortality.

We hypothesize that bronchial inflammation due to environmental pollution forms a chronic and repeated stimulation resulting in elevated markers of systemic inflammation/increased blood coagulability. Such an alteration of inflammation/blood coagulability may lead to increased risk of atherosclerosis and other forms of clinical manifestation of cardiovascular disease.

5. Main Hypothesis/Study Questions:

Our primary focus is particulate matter (PM₁₀ and TP), followed by O₃, SO₂, CO, and NO₂.

- 1) Whether the exposures to each individual ambient air pollutant prior to the clinical examination are associated with higher levels of inflammation / hemostatic factors?
- 2) Whether the associations are independent of other gaseous copollutants?
- 3) Whether the PM-inflammation/hemostatic factors associations are synergistically modified by the exposure to other gaseous copollutants?
- 4) Whether previous history of cardiovascular disease or smoking modifies the above relationships?
- 5) Whether the air pollution and higher levels of inflammation/hemostatic factors association differs by age, sex, social economic status, and ethnicity?

6. Data (variables, time window, source, inclusions/exclusions):

This will be a cross-sectional study in the baseline examination. The ARIC V1 data include variables in the derived data set, hemostatic factors, and the medication data set. The air pollution data will be derived from the USEPA Aerometric Information Retrieval System (AIRS), as the average daily exposures to the ambient criteria pollutants for each of the 15,792 individuals prior to their cohort clinical examinations.

Specifically, the following hemostatic/inflammation markers will be examined: Fibrinogen, VIII, vWF, WBC, possibly albumin. Fine particle, Co, No2, and SO2 will be calculated as the 24-hour average from 12:00 am to 11:00 pm, and O₃ as the 8-hour average of the hourly measures from 10 am to 6 pm, prior to the V1 clinical examination date.

Major covariables of interests include age, sex, ethnicity/center, education, smoking, BMI, physical activity, prevalent chronic pulmonary disease, CHD, stroke, hypertension, and diabetes.

7.a. Will the data be used for non-CVD analysis in this manuscript? ☐ Yes ☒ No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? ☐ Yes ☐ No

(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ☐ Yes ☒ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ☐ Yes ☐ No

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