Frailty Status Modifies the Association Between Air Pollution and Post-Myocardial Infarction Mortality
A 20-Year Follow-Up Study

To the Editor: Exposure to air pollution is virtually ubiquitous, and has been associated with the development of a multitude of chronic illnesses. We have previously shown that chronic exposure to particulate matter ≤2.5 μm in diameter (PM2.5) is associated with an increased risk of readmissions and adverse cardiovascular events after myocardial infarction (MI) (1). MI patients are a heterogeneous population in terms of prognosis, exhibiting a wide range of risk profiles. Frailty, a nonspecific, age-related syndrome of increasing vulnerability and decreasing resistance to stressors (2), has been demonstrated as an important determinant of post-MI mortality and hospital admissions (3), and hence, may account for some of the variability in outcome. Although there is some evidence of an association between air pollution and the development of frailty after MI (4), it is not known whether frailty affects the association between PM2.5 and post-MI prognosis. This study aimed to investigate whether frailty modifies the relationship between chronic exposure to PM2.5 and mortality risk in a geographically-defined cohort of MI survivors to determine whether frail patients are more susceptible to air pollution exposure.

Patients age ≤65 years with first MI, admitted from February 1992 to February 1993 to the 8 hospitals serving the population of central Israel, were recruited to the Israel Study of First Acute Myocardial Infarction (1,3,4). Of an initial 1,545 consecutive patients who survived to discharge, 1,120 were included in the analysis—the remainder were excluded as a result of either insufficient data for geocoding of residential location or insufficient reliability of the estimated exposure metric, as specified elsewhere (1,4). Patients were followed from index MI to November 2011 for all-cause mortality and to December 2005 for cause-specific mortality (1). A detailed description of PM2.5 exposure assessment was previously published (1,4). Briefly, daily measures of PM recorded at air quality monitoring stations in the study area were summarized and chronic exposure was defined as the mean pollutant concentration at each patient’s home address. The spatial distribution of exposure was calculated using the ordinary kriging interpolation method. Because an increasing number of monitoring stations were fully operational over time, we selected the years 2003 to 2005 as a representative exposure period. Frailty was assessed at baseline using a multidimensional 32-item frailty index adapted from a model developed by Rockwood and Mitnitski (2). Data were collected from medical records and personal interviews conducted during the first week after index hospitalization. The frailty index—comprising self-rated health, functional limitations, comorbid conditions, weight loss, and physical activity—was previously validated in this cohort (3). Data on socioeconomic status measures, cardiovascular risk factors, and MI characteristics and severity were obtained at baseline. The Cox proportional hazards model was used to assess the hazard ratio for all-cause mortality risk associated with chronic PM2.5 exposure, overall and by frailty score. A further analysis examined associations with cause-specific mortality (cardiovascular and non-cardiovascular), with death from other causes considered a competing risk.

During 16,806 person-years of follow-up (mean 15 years), 469 deaths occurred. Decedents were older, frailer, and more likely to be female and current smokers, and they presented with a poorer socioeconomic status and more severe MI and hypertension at baseline. After multivariable adjustment for these and other factors, a modest, nonsignificant increase in mortality was associated with an interquartile range increase in PM2.5 exposure (Table 1). However, the relationship differed markedly by frailty status, with a stronger association observed among frail patients ($p_{interaction} = 0.005$) (Table 1). With deaths classified by cause, the interaction between frailty status and PM2.5-associated mortality risk was stronger for cardiovascular than for non-cardiovascular causes (Table 1). Classified into mutually exclusive groups defined by tertiles of frailty score and of PM2.5 exposure, the fully-adjusted hazard ratios for all-cause mortality risk in increasing PM2.5 groups were 1 (reference), 0.86, and 0.89 among low-frailty subjects; 1.26, 1.51, and 1.25 among medium-frailty subjects; and 1.63, 2.02, and 2.79 among high-frailty subjects, respectively. This indicates a positive, “dose-response” relationship between PM2.5 and mortality among frailter participants only.

We previously demonstrated that PM2.5 exposure was associated with increased odds of developing frailty in post-MI patients (4), and that frailty is associated with mortality and adverse outcomes in this population (3). The current findings show that patients who were frail to begin with were more susceptible to the adverse effects of exposure, further elucidating the relationship and suggesting that frailty modifies the relationship between air pollution and post-MI mortality. Indeed, despite a relatively high level of exposure during the study period (mean 24 mg/m³; range 17 to 29 mg/m³), the association between exposure and mortality was not in itself significant. It was only after factoring in the interaction with frailty that the association became significant. This suggests that the accumulation of deficits that often accompanies the diagnosis of MI is a key determinant of air pollution susceptibility. This concept is consistent with the idea that frail individuals may be
### Table 1

<table>
<thead>
<tr>
<th>Frailty Score</th>
<th>All Causes</th>
<th>CVD</th>
<th>Non-CVD</th>
<th>All Causes</th>
<th>CVD</th>
<th>Non-CVD</th>
</tr>
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<tbody>
<tr>
<td>0.05</td>
<td>1.06 (0.82–1.16)</td>
<td>1.27 (0.97–1.67)</td>
<td>0.98 (0.82–1.16)</td>
<td>1.10 (0.96–1.27)</td>
<td>1.10 (0.89–1.40)</td>
<td>1.10 (0.96–1.35)</td>
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<td>0.10</td>
<td>1.08 (0.88–1.33)</td>
<td>1.16 (0.94–1.48)</td>
<td>0.98 (0.82–1.16)</td>
<td>1.10 (0.94–1.29)</td>
<td>1.16 (0.96–1.41)</td>
<td>1.06 (0.94–1.18)</td>
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<tr>
<td>0.15</td>
<td>1.16 (0.96–1.41)</td>
<td>1.17 (0.97–1.43)</td>
<td>1.08 (0.88–1.33)</td>
<td>1.16 (0.96–1.41)</td>
<td>1.16 (0.96–1.41)</td>
<td>1.05 (0.93–1.19)</td>
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<tr>
<td>0.20</td>
<td>1.25 (1.05–1.49)</td>
<td>1.45 (1.24–1.70)</td>
<td>1.16 (0.96–1.41)</td>
<td>1.25 (1.05–1.49)</td>
<td>1.45 (1.24–1.70)</td>
<td>1.25 (1.05–1.49)</td>
</tr>
<tr>
<td>0.25</td>
<td>1.41 (1.09–1.76)</td>
<td>1.76 (1.38–2.26)</td>
<td>1.25 (1.05–1.49)</td>
<td>1.41 (1.09–1.76)</td>
<td>1.76 (1.38–2.26)</td>
<td>1.25 (1.05–1.49)</td>
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</table>

*Values are hazard ratio (95% confidence interval). The hazard ratios are for the 75th versus the 25th PM2.5 exposure percentiles (corresponding to 25.4 mg/m³ vs. 22.9 mg/m³). *Adjusted for age, sex, and baseline frailty score.

Several strengths characterize this study, beginning with the well-defined cohort of MI patients, the validated index of deficit accumulation, high-quality data on sociodemographic and clinical covariates, complete long-term follow-up, and assessment of residential exposure to PM, blinded to outcome. Limitations include incomplete PM2.5 data, as well as partial temporal coverage, and a relatively young cohort. The sample size is considered modest in study of air pollution exposure.

In conclusion, frail MI patients may be more sensitive to the adverse health effects of air pollution, particularly to cardiovascular mortality, and may benefit from efforts to reduce exposure.

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Please note: This work was supported by the Environment and Health Fund, Israel (grant award numbers SGA 1204 and RGA 0904). The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Dr. Gerber and Ms. Myers contributed equally to this work.

**REFERENCES**