



# If you don't kill pollution it could kill you: pathophysiologic insights into pollution mediated cardiovascular risk through FDG PET imaging

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Air pollution (AP) ranks fourth after hypertension, dietary risk factors, and dyslipidemia as the most important modifiable risk factor for cardiovascular (CV) diseases.<sup>1</sup> Highest impact of AP is seen in low- and middle-income countries in Asia, the Middle East, and Africa which have a relatively younger population, and high rates of premature CV death; the global impact of AP is also significant.<sup>1</sup> There is a dose-response relationship between short-term exposure to particulate ambient AP and increased CV death.<sup>2</sup> The relative risk is logically higher with long-term exposure.<sup>3</sup>

Inflammation is the major pathway via which CV risk associated with traditional risk factors such as diabetes mellitus and hypertension are ultimately amplified.<sup>4</sup> Exposure to ambient particulate matter is also associated with increased inflammatory markers such as C-reactive protein and total leukocyte count.<sup>5</sup> How exactly these air pollutants result in inflammation is largely unknown. One proposed mechanism when it comes to AP is that the initial reaction is local pulmonary inflammation which subsequently leads to CV inflammation.<sup>6</sup> Another postulated mechanism of AP is

through autonomic nervous system dysregulation and its subsequent effect on the CV system.<sup>7</sup>

Transportation noise pollution (NP) is another major psychological stressor globally. Robert Koch (1843-1910), a Nobel laureate, predicted way back in 1905 that “One day people will have to fight noise as much as cholera and pest.”<sup>8</sup> Acutely, NP interferes with interpersonal communication, disturbs sleep, and promotes annoyance.<sup>9,10</sup> The resultant sympathetic and endocrine activation results in a catecholaminergic surge which causes higher blood pressure, abnormal glucose and lipid metabolism, increased blood viscosity, and prothrombotic factors—all of which drive systemic and CV inflammation.<sup>8</sup> This inflammation ultimately drives adverse CV remodeling.<sup>9,10</sup>

Until now, AP and NP associated inflammation has been studied indirectly through serum biomarkers.<sup>11</sup> Positron emission tomography using <sup>18</sup>F-fluorodeoxyglucose (FDG PET) is well established to assess inflammatory and neoplastic processes.<sup>12,13</sup> As inflammatory cells use glucose for metabolism, FDG PET can diagnose and assess treatment response in such disease states.<sup>12</sup> Hence, FDG PET could potentially serve to assess the arterial inflammation (ArtInfl) response associated with AP and NP (Figure 1).

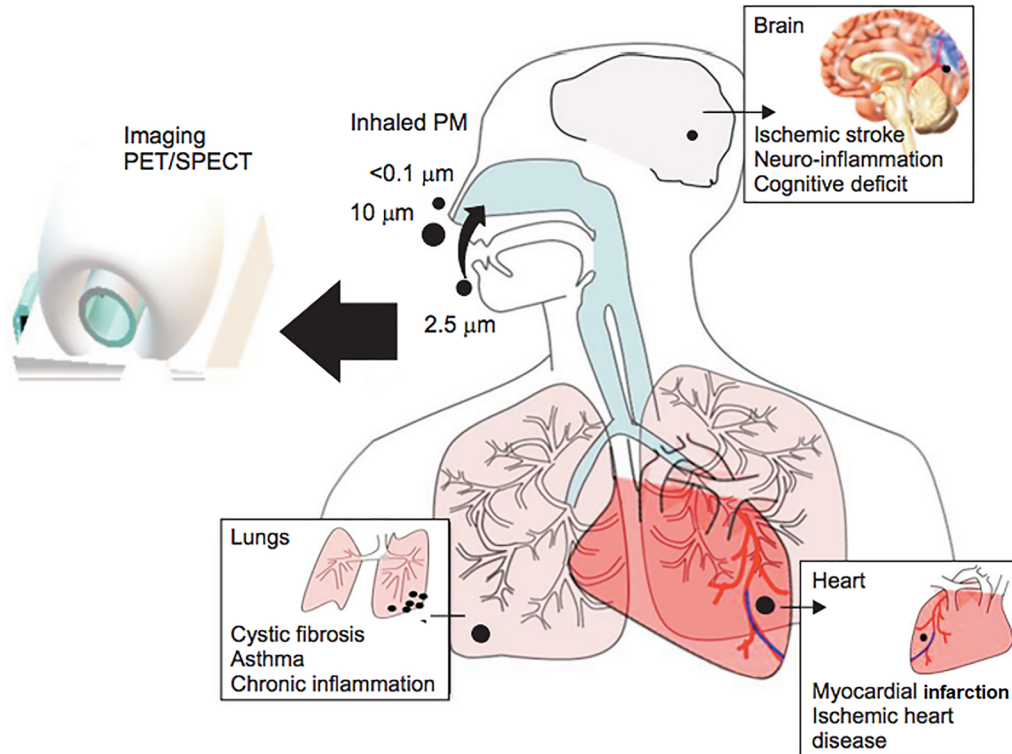
In their original work published in this issue of the *journal*, Osborne *et al.* explore the association between AP, transportation NP and incident major adverse CV events (MACE). They hypothesize that ArtInfl might be mediate this association and FDG PET could be used to assess such effects. The study design was a single-center, retrospective cohort using 474 patients (median age 55 years, 90.3% White) with no known malignancy or CV disease at baseline who underwent clinically indicated FDG PET for cancer

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**Figure 1.** Diagrammatic representation of inhalation of particulate AP and associated respiratory, cardiovascular and neurological disorders which can be potentially imaged using Single Photon Emission Computed Tomography/Positron Emission Tomography. Adapted from Chossière et al<sup>22</sup>.

surveillance or screening at a single institution between 2005 and 2008. A subset of the study group ( $n = 265$ ) had FDG PET data to assess amygdalar activity and another subset group ( $n = 424$ ) was used to assess bone marrow activity. ArtInfl was assessed using the average maximum standardized uptake value ( $SUV_{max}$ ) of 3 mm slices from 1 cm above the aortic annulus to the aortic arch. Bone marrow activity (to assess hematopoiesis) was defined as the mean  $SUV_{max}$  of a target region placed over axial sections of the T1-L5 vertebra. Amygdalar activity (to assess stress-associated limbic activity) was defined as the ratio of the mean bilateral amygdalar SUV corrected for the mean temporal lobe SUV. Calcium score was determined using the CT portion of FDG PET.

The authors report an increased risk of MACE among those with exposure to both high AP (annual mean  $PM_{2.5}$  concentration  $> 9 \mu\text{g}/\text{m}^3$ ) and transportation NP ( $> 55$  dBA) vs. none (event rate 28.2% vs. 3.7%, adjusted hazard ratio 11.8, 95% CI 3.1, 44.5) over a median follow-up of 4.1 years (interquartile range 3.0-5.0 years). The MACE rate over the study period was 8.2%. Exposure to both AP and transportation NP (8% of the study population) significantly increased risk vs.

neither (46%) or one pollutant (46%), in a graded response. The independent association remained significant after adjusting for demographic (age, and gender), CV disease risk factors at baseline (diabetes, current smoking, hypertension, and hyperlipidemia), statin treatment, and economic (median income and insurance) risk factors.

For mechanistic insights, the authors found a significant association between the number of pollutants (none, one, or both) and ArtInfl. This association was also independent of the confounders discussed above. Exposure to both AP and NP significantly increased ArtInfl vs. neither or one pollutant. In pre-specified mediation analysis, the authors show that ArtInfl may account for 11.4% of the total effect of AP and transportation NP exposure on major adverse CV events. There was no association with bone marrow activity.

This is the first study to explore the pathophysiological association of combined AP and transportation NP exposure with CV events using a well-defined imaging protocol and a longitudinal study design. It is interesting to note that despite the increased risk of CV events, patients with exposure to both pollutants had

similar Framingham risk scores, coronary artery calcium levels, and statin use vs. those with less exposure (Table 1 in the article). This suggests that conventional risk scores and imaging markers may be insufficient to assess the impact of pollutants. This finding needs further exploration in other cohorts.

ArtInfl involves the accumulation of leukocytes and immune cells.<sup>14</sup> These immune cells are produced during hematopoiesis in the bone marrow. Thus, increased bone marrow activity reflects increased inflammation and is prognostic for future CV events.<sup>14</sup> The authors have previously reported an independent association of particulate AP with bone marrow activity using the same cohort.<sup>15</sup> Their previous study suggests that increased particulate AP may cause increased bone marrow activity, which may directly lead to CV events or via ArtInfl.<sup>15</sup> In their current study, there was a trend towards increased pollutant exposure and bone marrow activity, but the association was not statistically significant. The lack of significance could be because pollution was analyzed as a categorical variable and a small number of patients (8%) were exposed to both AP and transportation NP. As outlined earlier, NP results in a stress response with a catecholaminergic surge and increased inflammatory cytokines.<sup>9</sup> This group has previously reported an association between increased traffic NP, amygdalar activity, and ArtInfl using the same cohort.<sup>10</sup> In their current study, there was no association between the number of pollutant exposure and amygdalar activity. This could be related to the small sample size in each category.

From these findings, it is reasonable to conclude that both AP and transportation NP drive ArtInfl through intersecting routes and increase CV disease risk independent of another. It is unknown if the effect of combined exposure is additive or multiplicative.<sup>11,16</sup> This inflammation drives a prothrombotic state, reflected in pro-inflammatory serum markers and as ArtInfl and bone marrow activity on imaging.<sup>5,15,17,18</sup> Particulate AP may directly cause myocardial injury as well.<sup>19</sup> Several other initiating mechanisms and effector pathways, including autonomic dysfunction are currently being explored to explain the causal association.<sup>7,20,21</sup>

Finally, environments with increased AP and NP may have increased psychological stress due to other factors such as work-related stress which might confound the association with CV events. This psychological stress is difficult to quantify and may explain the residual association of pollution with CV events in mediation analysis.<sup>10,15</sup> This requires further exploration. Also as discussed by the authors, relatively low pollution exposure (both air and noise) in their study group, a well-selected patient population, and a lack of

temporal trends in pollutant exposure are some of the most important limitations of this study.

An interesting side thought related to this study is the impact of the recent COVID 19 pandemic and the forced workplace and travel shutdowns that has ensued. Observations of variable trends in the concentration of different air pollutants has been documented and with many working from home and not travelling, this has lead to decreased AP and NP with resultant impact on short and long-term health.<sup>22,23</sup> Such a lockdown serves as a silver lining in some ways being a natural experiment to assess if a short-term decrease in AP and NP could be associated with decreased inflammation, both biomarker wise and imaging wise with FDG PET.

## FUTURE DIRECTIONS AND CONCLUSIONS

Areas of interest in this subject matter could be further prospective studies in countries with high pollutant exposure and CV disease burden incorporating ArtInfl imaging with FDG PETCT. This could further define effects of high exposure at a younger age with future risk of CV disease. Whether statins could mitigate ArtInfl risks of AP and NP and associated CV disease risk independent of lipid reduction due to their pleotropic effects would be an area of interest to study.

In conclusion, the authors are to be commended for continuing to provide mechanistic insights for ArtInfl due to AP and NP with FDG PET imaging and impact on CV risk. This current study despite limitations and being retrospective adds to a growing literature in this area on adverse effects AP and NP which is hiding in plain sight as a CV risk factor.

## Disclosures

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