EDITORIAL

Comment on "Effect of short-term fluctuations in outdoor air pollution on the number of hospital admissions due to acute myocardial infarction among inhabitants of Kraków, Poland"

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Air pollution is a major environmental health risk that affects everyone in both low-, middle-, and high-income countries, and according to the World Health Organization, more than 90% of the world's population lives in areas with unhealthy air.[1] Air pollution consists of a complex mixture of particulate matter (PM), gases, reactive trace metals, and adsorbed organic contaminants originating mainly from anthropogenic sources such as combustion of fossil fuels. Global burden of disease estimates indicate that PM affects more people than any other pollutant, and this is primarily related to cardiovascular and pulmonary effects. Following this, health effects due to exposure to air pollution have a huge economic impact for the society; the nonmarket costs of outdoor air pollution are projected at around 2250 to 2310 EUR per capita in 2060 in Organisation for Economic Co-operation and Development countries.[1]

Exposure to air pollution PM is correlated with subclinical pathologies underlying cardiovascular disease, including systemic inflammation and oxidative stress, atherosclerosis, thrombosis, endothelial dysfunction, hypertension, cardiac remodeling, and arrhythmia.[2] Furthermore, positive associations have been found between short-term increases in PM and gaseous components such as nitrogen dioxide (NO_2), sulfur dioxide, and carbon monoxide and an increased risk of hospitalization or death from congestive heart failure.[3] The composition of PM may influence health outcomes, with some findings showing higher cardiovascular toxicity of carbonaceous particles from combustion-derived sources, such as road traffic, fossil fuels, and wood burning.[4] Combustion sources are also the leading source of NO_2. Since it is a gas, NO_2 affects mainly the lungs but may exert a secondary effect on the systemic circulation more rapidly than $PM_{2.5}$, for example, by inducing increased vasomotor tone, heart overload, oxidative stress, sudden blood thrombogenicity, and hypoxia.

In their important study, Konduracka et al[5] used a time-series regression analysis to examine associations between daily counts of hospital admissions for myocardial infarction (MI) and short-term elevation in averaged daily city-level concentrations of air pollution from fixed monitoring stations. The units of analysis are days; thus, it is reasonable that the only potential confounders are variables that could change from day to day with air pollution levels. The authors report an association between daily $PM_{2.5}$ levels and an increased number of daily hospital admissions for acute MI (odds ratio [OR], 1.32; 95% CI, 1.01–1.40), whereas for daily PM_{10} levels the association was significant only with a simultaneous decrease in ambient temperature (OR, 1.08; 95% CI, 1.01–1.17). They also reported an association between hospital admissions for MI with daily NO_2 levels, but this was only observed for older individuals (OR, 1.13; 95% CI, 1.01–1.23) and patients predisposed with pulmonary disorders (OR, 1.12; 95% CI, 1.01–1.31).

The study design is novel, but the use of city-average exposure could have attenuated the effect (bias towards the null) of the true air pollution exposure, since several air pollutions show spatial variation even in urban areas. Nevertheless, the interdata are in line with several studies that have reported an association of both short- and long-term exposure with air pollution and acute MI.

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The large-scale prospective ESCAPE study (European Study of Cohorts for Air Pollution Effects) reported that annual increases of 10 μg/m^3 in PM_{10} and of 5 μg/m^3 in $PM_{2.5}$ were associated with an increased risk of MI by 12% and 13%, respectively.[6] The positive associations were observed for air pollutant concentrations below the thresholds recommended by current European policy. A recent study reported that each 10-μg/m^3 increase in $PM_{2.5}$ during the 24 hours preceding the event was associated with an increased risk of MI of 2.8%, whereas a similar increase in NO_2 was associated with an increased risk of 5.1%. The risk related to PM appeared to be greater among the elderly, while younger patients appeared to be more susceptible to NO_2 exposure.[7] However, due to a high correlation between NO_2 concentrations and particle number concentrations in outdoor air, it is still debated whether the health effects associated with NO_2 are actually due to ultrafine PM ($PM_{0.1}$).[8]

What are the biological mechanisms behind air pollution–induced cardiovascular diseases? As suggested by Konduracka et al,[5] atherosclerotic plaque destabilization and rupture as a result of oxidative stress, inflammation, and endothelial dysfunction may be a prerequisite for MI. However, compared with the large number of studies establishing some atherosclerotic effects of air pollution, an understanding of how acute air pollution exposure may trigger coronary plaque rupture is needed from future studies. A minor part of the inhaled $PM_{2.5}$ and nanoparticles can potentially penetrate the lung alveoli, enter the bloodstream, and reach the target organ. Additionally, diesel exhaust particles trigger proinflammatory responses in endothelial cells through a release of lipophilic organic compounds that could transfer across alveolar epithelial cells into the circulation.[9]

In a recent review by Hamanaka and Mutlu,[2] several mechanisms have been proposed as underlying factors behind PM-induced cardiovascular diseases. For example, PM inhalation may activate inflammatory responses in the lung, leading to systemic inflammation, which promotes thrombosis, endothelial dysfunction, and atherosclerosis. Furthermore, inhaled PM was shown to dysregulate sensory receptors in the lung, resulting in imbalance of the autonomic nervous system, favoring sympathetic pathways and potentially leading to alterations in heart rate, vasoconstriction, endothelial dysfunction, and hypertension. This is supported by the fact that PM exposure affects heart rate variability and blood pressure, thereby regulating the balance between the sympathetic and parasympathetic arms of the autonomic nervous system.

Recent findings from ApoE$^{-/-}$ mice suggest that the atherosclerotic effects of $PM_{2.5}$ are due to semivolatile organic compounds attached to the particles.[10] Indeed, organic extracts of combustion particles appear to contain the majority of PM-associated proinflammatory properties, although the particle core itself also contributes to the inflammatory effects of combustion PM.

Air pollution–induced reactive oxygen species (ROS) generation may impair NO-mediated vasodilatation, and thereby promote vascular inflammation. Studies have shown that oxidative stress was mostly related to the surface compounds adhering to diesel PM (eg, reactive metals, polycyclic aromatic hydrocarbons and quinones), but also that NO_2 can be transformed into a highly reactive species, peroxynitrite. In line with studies suggesting the importance of ROS formation for health effects, antioxidant treatment or inhibition of oxidant production has been shown to inhibit downstream pathways including proinflammatory cytokine production and induction of apoptosis.[2] We believe that the current mechanistic data available on air pollution exposure support the conclusions reached by Konduracka et al[5] that episodic exposures potentially can result in an increased risk of MI and hospitalizations in highly polluted urban areas. However, mechanistic data on separate air pollution components are still important to fully understand which preventive measures to prioritize.

Importantly, exposure to air pollution toxicants can be avoided, providing an opportunity for prevention to reduce the health impact disorders such as acute MI. As stated by the authors,[5] Kraków has one of the highest levels of PM among European cities, far exceeding the permissible levels. Improved scientific understanding of the links between air pollution constituents and health effects will help sustain progress in urban air quality by better targeting the most toxic emissions. Following this, there is a further need for studies assessing population exposure by considering the number of particles (and not only their mass), using, for example, particle counters, which can detect each particle whatever its size. However, the optimal measure to characterize exposure of ultrafine particles is still debated. Furthermore, there are limited possibilities to evaluate the interaction between pollutants, mainly due to the high correlation between them.

Epidemiological studies use spatial variation of air pollutants within urban areas to assess the long-term health effects. One approach is the use of land-use regression models to effectively explain spatial contrasts by using statistical modeling to analyze associations between measured concentrations at monitoring sites and predictor variables derived from geographic information systems.[11] This approach was used in the ESCAPE study to, for example, assess the spatial variation in the mean annual concentration of various pollutants including PM mass,[12] elemental composition,[13] as well as NO_2 and other nitric oxides.[14] New promising developments using land-use regression modeling to capture the spatial variation of the oxidative potential of PM is also worth considering.[15] Estimation of the joint effects of exposure to PM, gases, and

noise is challenging and indicates a need for new multipollutant modeling. Additionally, deciphering the human exposome is a promising way forward to improve health and reduce the overall burden of disease. This will require improved knowledge of health risks, including combinations of several risk factors (eg, simultaneous inhalation exposure to persistent organic pollutants and air pollution PM), and the mechanisms by which they affect health at different life stages like childhood, adolescence, and older age. Reducing the public health risk of air pollution will require both local and regional policy measures to restrict the total burden of air pollution emissions as well as individual efforts to limit exposure.

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