# **ORIGINAL ARTICLE**

# 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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## **KEY WORDS**

# ABSTRACT

air pollution, myocardial infarction, particulate matter **INTRODUCTION** Air pollution is reaching alarming proportions worldwide; however, previous studies concerning the association between air pollution and myocardial infarction (MI) provided conflicting results. **OBJECTIVES** We evaluated a relationship between short-term fluctuations in outdoor particulate matter (PM) and nitrogen dioxide ( $NO_2$ ) levels and the number of hospitalizations due to MI among the inhabitants of Kraków, Poland.

**PATIENTS AND METHODS** Data on hospitalizations, daily pollutant concentrations, infections, and meteorological parameters were collected from December 2012 to September 2015. Data were assessed using a time-series regression analysis with a distributed lag model.

**RESULTS** An increase of 10  $\mu$ g/m<sup>3</sup> in PM<sub>2.5</sub> levels was associated with a higher risk of hospital admission due to MI (odds ratio [OR], 1.32; 95% CI, 1.01–1.40; P = 0.0002). For PM<sub>10</sub> the effect was observed only with a simultaneous decrease of 1°C in the mean daily temperature (OR, 1.08; 95% CI, 1.01–1.17; P = 0.03). Significant effects were observed at lags 5 and 6. The effect of NO<sub>2</sub> was significant at lags 0 and 1, but only in patients aged 70 years or older (OR, 1.13; 95% CI, 1.01–1.23; P = 0.007) and those with pulmonary disorders (OR, 1.12; 95% CI, 1.01–1.31; P = 0.01).

**CONCLUSIONS** In all age groups, the short-term elevation in  $PM_{2.5}$  levels was associated with an increased number of daily hospital admissions for MI, whereas for  $PM_{10}$  the effect was significant only with a simultaneous decrease in temperature. The effect of NO<sub>2</sub> was observed only in older individuals and patients with pulmonary disorders. A negative clinical effect was more delayed in time in the case of exposure to PM than to NO<sub>2</sub>.

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**INTRODUCTION** Both indoor and outdoor air pollution is a serious threat to public health, as it is associated with approximately 8 million premature deaths each year.<sup>1</sup> There are significant regional variations in terms of the degree of air pollution as well as its chemical composition, sources of emission, and geographical location, which also affects the concentrations of pollutants and determines their effect on human health.

In Poland, the limits set by the World Health Organization (WHO) for the levels of particulate matter (PM) are far exceeded, which constitutes a major problem. The main source of PM is low-stack emission (ie, emission from residential and small-industry chimneys below the level of 40 m above ground), and to a lesser extent, transport and other sources.<sup>2</sup> The highest PM concentrations are observed during the heating season, especially when people use low-quality coal and harmful waste for heating purposes or use old coal-fired furnaces. According to a WHO report, Kraków, otherwise known for its rich cultural and architectural heritage, is also one of the most polluted European cities in terms of PM concentrations in the air.<sup>3</sup> Air pollution has been present in Kraków for many years. The fight against pollution is hindered by the fact that the city is located in a valley, there is a small number of windy days per year, and there is a high density of buildings. Therefore, PM concentrations, especially daily values, far exceed the permissible levels, which results in more than 100 days of exposure to highly polluted air per year.

Previous studies indicated that air pollution not only aggravates the symptoms of cardiovascular diseases but is now also considered one of cardiovascular risk factors.<sup>4</sup> The effect of short--term exposure to air pollution on the risk of hospitalization for acute myocardial infarction (MI) has already been studied, with variable, and sometimes conflicting, results. These discrepancies result from regional differences in pollutant concentrations, studied populations, individual susceptibilities, methods of measuring exposure to air pollution, or methods of statistical analysis.<sup>5</sup> Additional factors affecting the incidence of MI are weather conditions.<sup>6,7</sup> Thus, the impact of these environmental factors on human health should always be analyzed on a local basis, with consideration for regional differences.

We aimed to assess the impact of short-term fluctuations in outdoor PM ( $PM_{10}$  and  $PM_{2.5}$ ) and the gaseous pollutant nitrogen dioxide ( $NO_2$ ) on the number of hospitalizations due to MI among the inhabitants of Kraków (Poland), who are chronically exposed to air pollution.

**PATIENTS AND METHODS** From a database of John Paul II Hospital in Kraków (one of the 2 largest hospitals in Lesser Poland Voivodeship), 5592 patients hospitalized between December 2012 and September 2015 with a final diagnosis at discharge of ST-segment elevation MI or non-ST-segment elevation MI were selected. Patients with MI who died in the hospital were also included, while those with unstable angina were excluded from the study. After an analysis of confounding factors (different methods of measuring pollutant concentrations, lack of air pollution monitoring stations), the study population was limited to include only those inhabitants who had lived in Kraków for at least 30 years and resided there at the time of MI onset. The final study sample included 3545 participants.

The clinical diagnosis of ST-segment or non– ST-segment elevation MI was made by cardiologists on the basis of the presence of symptoms, elevation of troponin or creatine kinase– MB levels, as well as the presence or absence of ST-segment elevation on electrocardiography.

In all participants, coronary angiography was performed to confirm coronary artery disease (CAD). Normal coronary arteries were defined as a stenosis of less than 20%. Hypertension was defined as a blood pressure of 140/90 mm Hg or higher on at least 2 separate measurements or the use of antihypertensive agents. Hyperlipidemia was defined as hypercholesterolemia, mixed hyperlipidemia, or hypertriglyceridaemia according to current guidelines.<sup>8</sup> Diabetes was diagnosed according to the guidelines developed by Diabetes Poland.<sup>9</sup>

**Data collection** Data on air quality were obtained from the Regional Inspectorate for Environmental Protection in Kraków for the period from December 2012 to September 2015. Hourly data on  $PM_{10}$ ,  $PM_{25}$ , and  $NO_2$  concentrations were collected from monitoring stations located in the following streets: Krasińskiego, Bujaka, and Bulwarowa. Pollutant concentrations were measured with automatic and manual methods. Daily city-level exposure to pollutants was estimated using hourly data obtained from the above stations. A 78% completeness criterion was applied for aggregate data calculation. If the daily average concentration of any parameter was not available in any station, the daily city-level concentration for that day was classified as "missing." About 5% to 22% of the observations were missing during the study, and the missing data were excluded from the analysis.

Daily meteorological data were obtained from the Kraków branch of the Institute of Meteorology and Water Management for the same period.

A retrospective study protocol was approved by the ethics committees in Kraków (153/KBL/ OIL/2016, to BG; KBET 1072.61.20.283, to EK).

Statistical analysis A time-series regression analysis<sup>10-12</sup> was used to examine the association between short-term fluctuations in air pollutants (PM<sub>2 5</sub>, PM<sub>10</sub>, NO<sub>2</sub>) and hospital admissions for MI, using a generalized linear model and distributed lag model with the Poisson distribution. We used a previously verified generalized linear model to evaluate the relationship between air pollutants and hospital admissions, with the number of hospital admissions as the dependent variable<sup>10-12</sup> and the daily mean level of each individual air pollutant as the main exposure variable.<sup>12</sup> To examine the delayed effect of air pollutants, weather conditions, and infections, we used a distributed lag model with a family of the Poisson distribution for a lag of 0 up to 6 days. A flexible spline function of time with 8 knots per year was used to control for the long-term trend and seasonal effects,<sup>10-11</sup> and natural cubic spline functions with 4 degrees of freedom were used to adjust for the effects of temperature changes, relative humidity, and atmospheric pressure. Infections were also added to the model as a potential confounder. The analysis was performed separately for patients younger than 70 years and those aged 70 years or older.

TABLE 1 Demographic and clinical characteristics of the study population (n = 3545)

Parameter	Value
Age, y, mean (SD)	72.9 (11.6)
Male sex, n (%)	1602 (45.1)
NSTEMI, n (%)	2127 (62)
STEMI, n (%)	1347 (38)
NSTEMI with normal coronary arteries, n (%)	149 (4.2)
STEMI with normal coronary arteries, n (%)	21 (0.6)
Arterial hypertension, n (%)	2079 (58.6)
Diabetes, n (%)	907 (25.6)
Obesity, n (%)	418 (11.7)
Hyperlipidemia, n (%)	1994 (56.2)
Smoking, n (%)	356 (10.0)
Infections before hospital admission, n (%)	56 (1.5)
Primary PCI, n (%)	3220 (90.8)
Previous MI, n (%)	425 (12)
Heart failure, n (%)	496 (14)
In-hospital deaths, n (%)	194.9 (5.5)

Abbreviations: MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

characteristics that did not vary over time (eg, age, smoking status, other risk factors for CAD).<sup>13</sup> All statistical tests were 2-sided with an  $\alpha$  value of 0.05. All analyses were performed with the Stat-Soft Statistica 12 software (StatSoft, 2017, Poland). Forrest plots were developed with the Med-Calc software (Poland).

**RESULTS** The demographic and clinical data of Kraków inhabitants hospitalized due to MI between December 2012 and September 2015 are presented in TABLE 1. The daily concentrations of the main air pollutants (PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>), weather conditions (humidity, atmospheric pressure, and temperature), and number of hospitalizations due to MI are presented in TABLE 2.

During the study, the average annual concentrations of pollutants were 54.2  $\mu$ g/m<sup>3</sup> for PM<sub>10</sub>, 37.6  $\mu$ g/m<sup>3</sup> for PM<sub>2.5</sub>, and 42.3  $\mu$ g/m<sup>3</sup> for NO<sub>2</sub>. The average daily concentrations of PM were higher in the autumn–winter months (heating season due to lower temperatures), compared with the spring–summer months (PM<sub>10</sub>, 75.2  $\mu$ g/m<sup>3</sup> and 34  $\mu$ g/m<sup>3</sup>, respectively, *P* <0.0001 and PM<sub>2.5</sub>, 55  $\mu$ g/m<sup>3</sup> and 21.3  $\mu$ g/m<sup>3</sup>,

TABLE 2	Descriptive statistics for dail	y air pollutant concentrations,	weather conditions,	, and hospitalizations in the	years from 2012 to 2015
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Parameter	Percentile			Minimum	Maximum	Mean (SD)
	25th	50th	75th			
Air pollutants						
NO <sub>2</sub> , μg/m³	53.0	64.0	75.0	22.0	100.0	54.9 (16.0)
PM <sub>10</sub> , μg/m <sup>3</sup>	35.0	53.0	88.0	16.0	360.0	67.3 (47.1)
PM <sub>2.5</sub> , μg/m <sup>3</sup>	24.0	37.0	64.0	11.0	310.0	47.8 (25.6)
Weather conditions						
Average temperature, °C	1.5	7.6	14.8	-13.5	27.6	9.2 (6.2)
Average relative humidity, %	74.0	83.2	89.4	48.1	98.0	81.2 (10.5)
Average barometric pressure, hPa	1011.8	1016.7	1020.8	980.7	1040.5	1016.2 (7.4)
Number of hospitalizations						
Total	1	1	2	0	15	2.5 (1.8)ª
STEMI	1	1	2	1	7	1.6 (0.8)
NSTEMI	1	1	2	1	8	1.8 (0.9)

a Daily hospitalizations for MI.

Abbreviations: NO<sub>2</sub>, nitric dioxide; PM, particulate matter; others, see TABLE 1

To minimize the collinearity effect, each air pollutant was modelled individually.

Continuous variables were expressed as mean values with standard deviation and quartile distribution, whereas categorical variables, as numbers and percentages. When appropriate, medians with interquartile ranges were used. Nonnormally distributed data were compared with the Mann–Whitney test.

The pollutant concentrations obtained at the 4 monitoring stations were combined to present average values. Moreover, because patients served as their own controls, there was a near-perfect matching for participant-specific respectively, P < 0.00001) (FIGURE 1). No differences in NO<sub>2</sub> concentrations were observed between the seasons (38.4 µg/m<sup>3</sup> and 37.5 µg/m<sup>3</sup>, respectively; P = 0.70).

The median number of daily hospitalizations for MI in the periods of elevated  $PM_{2.5}$  levels was higher compared with the months when no additional heating was needed (P = 0.007). Changes in the number of daily hospitalizations and levels of pollutants according to seasons are presented in **FIGURE 1**. As the study was completed in September 2015, data for winter 2015 are not shown.

After adjustment for the effect of temperature changes, relative humidity, barometric pressure,

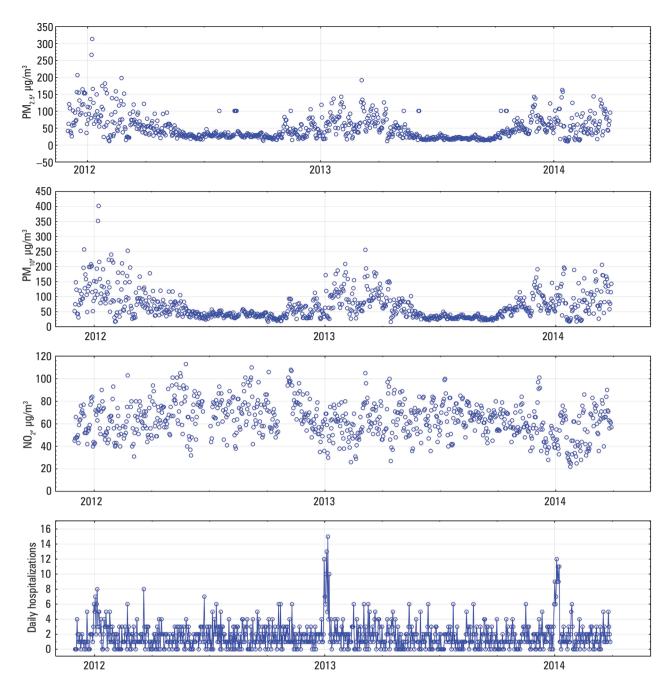


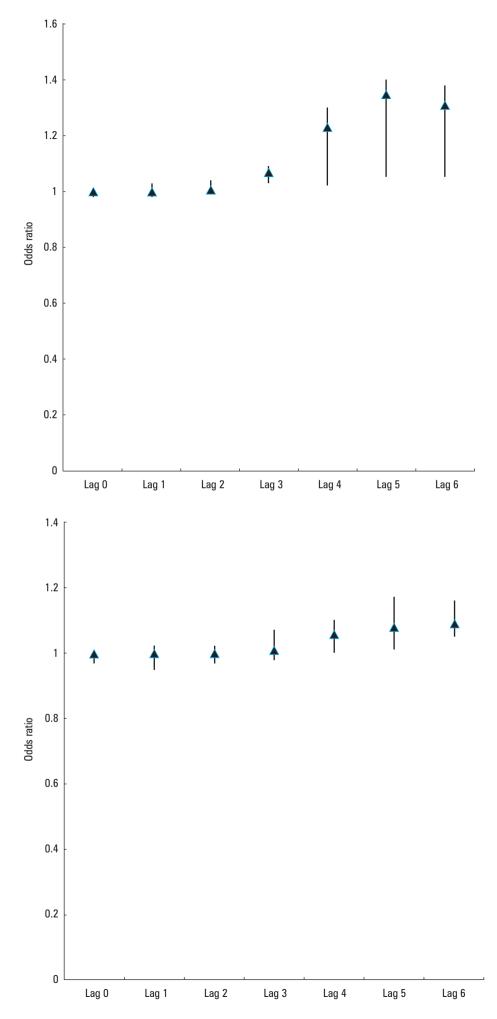
FIGURE 1 Changes in the number of daily hospitalizations due to myocardial infarction and air pollutant levels (PM<sub>10</sub>, PM<sub>2.5</sub>, and NO<sub>2</sub>) between December 2012, 2013, and 2014

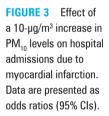
Abbreviations: see TABLE 2

and infections, an increase in the  $PM_{2.5}$  level of 10 µg/m<sup>3</sup> was associated with an increase in the number of daily hospitalizations in both age groups (odds ratio [OR], 1.32; 95% CI, 1.01–1.40; P = 0.0002; FIGURE 2). A significant effect was observed only after a few days since exposure (lag, 5 to 6 days). On the other hand, the effect of  $PM_{10}$  was significant only with a simultaneous decrease in the mean daily temperature of 1°C (OR, 1.08; 95% CI, 1.01–1.17; P = 0.03; FIGURE 3). The effect was also delayed until 5 to 6 days after exposure. When the mean daily temperature increased by 1°C, the effect of  $PM_{10}$  lost significance (OR, 1.00; 95% CI, 1.00–1.01; P = 0.07 in both age groups).

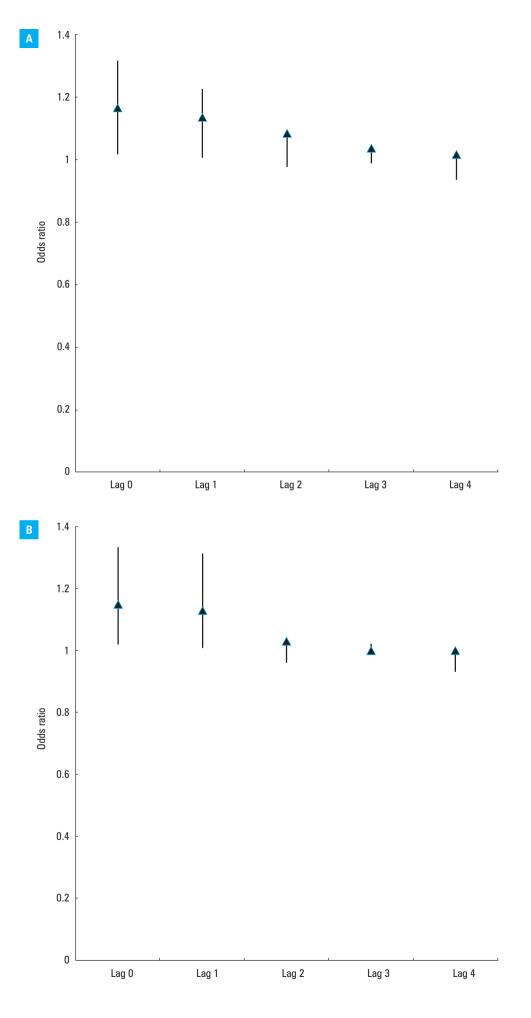
Regardless of the confounders such as weather conditions or infections, the significant effect of NO<sub>2</sub> was observed at lags 0 and 1, but only in patients aged 70 years or older (OR, 1.13; 95% CI, 1.01–1.23; P = 0.007; **FIGURE 4A**) and in patients with pulmonary disorders including chronic obstructive lung disease and asthma (OR, 1.12; 95% CI, 1.01–1.31; P = 0.01; **FIGURE 4B**). In the remaining population, the association between NO<sub>2</sub> concentrations and daily hospital admissions for MI was nonsignificant.

**DISCUSSION** To our knowledge, this is the first Polish study to indicate that even after adjustment for other potential confounders such as changes in temperature or barometric pressure, relative humidity, and infections, a short-term elevation of the PM<sub>2.5</sub> level is associated with FIGURE 2 Effect of a  $10-\mu g/m^3$  increase in PM<sub>2.5</sub> levels on hospital admissions due to myocardial infarction. Data are presented as odds ratios (95% CIs).





**FIGURE 4 A** – effect of a 10- $\mu$ g/m<sup>3</sup> increase in NO<sub>2</sub> levels on hospital admissions due to myocardial infarction in patients aged 70 years or older; **B** – effect of a 10- $\mu$ g/m<sup>3</sup> increase in NO<sub>2</sub> levels on hospital admissions due to myocardial infarction in patients with pulmonary disorders. Data are presented as odds ratios (95% Cls).



an increased number of hospital admissions due to MI. The effect of  $PM_{25}$  on the hospitalization rate was observed in all age groups and regardless of coexistent disorders. Although in our study the effect of  $PM_{25}$  was independent of climate changes and infections, it should be emphasized that in Poland the highest PM<sub>25</sub> concentrations are observed in the heating season (autumnspring months) and usually overlap with periods of lower temperature or temperature inversion. An inversion is responsible for trapping pollutants and their accumulation at ground level. Low temperature was previously shown to be an independent risk factor for MI<sup>6,7;</sup> however, the mean outdoor temperatures are now higher than in the past. Moreover, global warming effects are observed also in the autumn-spring months, which can lessen the effect of low temperature on MI risk.

Several other studies have investigated the relationship between the  $PM_{25}$  concentration and MI onset, but the results are inconsistent.<sup>5,6,13-16</sup> In a case-crossover study, Barnett et al<sup>14</sup> reported a significant relationship between  $PM_{25}$  and the risk of hospital admissions for cardiovascular causes (including MI) in older patients.<sup>14</sup> Also Zanobetti et al<sup>15</sup> reported that PM<sub>2.5</sub> significantly increased the risk of MI. In contrast, Sullivan et al<sup>16</sup> did not observe a significant relationship between PM<sub>2.5</sub> levels and MI. A more complex relationship between air pollutants and weather changes was observed by Huang et al.<sup>6</sup> They reported a combined effect of PM (both PM<sub>25</sub> and  $PM_{10}$ ), carbon monoxide, and climatic changes on the risk of hospitalizations for MI in Taiwan. High temperatures (>26°C) and low barometric pressure (<1009 hPa) on the previous day were shown to be associated with an increase in the incidence of MI. An association between increased MI incidence and the combination of high PM concentrations or carbon monoxide with low temperatures (<21°C) and of high humidity levels with low temperatures was also described.<sup>6</sup>

Another important issue in studies on the effect of air pollution on MI incidence is the time between exposure to air pollutants and development of MI. Our study revealed that in chronically exposed inhabitants of Kraków (average annual  $PM_{25}$  levels of about 38 µg/m<sup>2</sup>; the limit recommended by the WHO, 10  $\mu g/m^3$  ), the effect of short-term fluctuations in PM<sub>2.5</sub> levels on the risk of MI admissions was delayed, with significant effects observed at lags 4 and 6. We believe that in the case of exposition to  $PM_{25}$ , the time necessary for atherosclerotic plaque destabilization and rupture to occur as a result of oxidative stress, inflammation, and endothelial dysfunction<sup>17-21</sup> is longer than in the case of exposition to gaseous pollutants, and it takes a few days since acute exposition. In contrast to our results, other studies reported the negative effects of PM<sub>2.5</sub> on the cardiovascular system between 0 and 2 days since exposure to the elevated levels of pollutants.<sup>5,10</sup>

The effect of PM<sub>10</sub> on MI risk was also investigated in a number of studies, with some showing a positive association but most showing a minor or no effect of exposure to  $PM_{10}$  on the onset of MI.<sup>5,17-20</sup> In our study, the effect of exposure to PM<sub>10</sub> on the risk of hospital admission was significant but only with a simultaneous decrease in temperature, which was shown to be an independent environmental risk factor for MI in previous studies.<sup>4</sup> The effect lost significance with an increase in temperature. Although PM<sub>10</sub> includes also smaller particles ( $\mathrm{PM}_{\mathrm{2.5}}$  and ultrafine particles), the correlations between exposure to  $PM_{10}$  (as compared with  $PM_{25}$ ) and negative cardiovascular outcomes are weaker because, depending on the sources of PM<sub>10</sub> (in Poland, seasonal differences in PM<sub>10</sub> concentrations are observed), there may be considerable differences in the proportion of  $PM_{25}$  found in  $PM_{10}$ . Unlike  $PM_{10}$ ,  $PM_{2.5}$  and ultrafine particles, with their small aerodynamic diameter, may penetrate the lung alveoli directly into the bloodstream and thus result in more serious adverse cardiovascular effects because of a higher potential to generate oxidative stress.4,21-29

We also investigated the relationship between NO<sub>2</sub> concentrations and the number of hospitalizations due to MI. In Poland, NO<sub>2</sub> concentrations that exceed WHO standards are observed only in some cities and close to main arteries. On the other hand, excessive  $PM_{10}$  and  $PM_{25}$  levels are observed in most Polish cities and villages, and their mean annual concentrations are much higher than in other European countries. In our study, a short-term elevation in NO<sub>2</sub> concentrations resulted in hospital admissions only in patients older than 70 years and in those with pulmonary disorders. This result is in line with other reports.<sup>4,22-26</sup> In contrast, in the HEAPSS study (Health Effects of Air Pollution among Susceptible Sub-populations), a significant effect of NO<sub>2</sub> on the risk of hospitalization due to a first MI event was observed also in younger persons.<sup>24</sup> Similarly to other investigators, we also observed the effect of NO<sub>2</sub> on the same or the next day of exposure. NO<sub>2</sub> affects mainly the lungs but may also exert a secondary effect on the systemic circulation more rapidly than PM<sub>25</sub>, mainly by inducing increased vasomotor tone, heart overload, oxidative stress, sudden blood thrombogenicity, and hypoxia.<sup>4,22-30</sup> Older patients and those with pulmonary disorders are more prone to negative effects of NO<sub>2</sub>

In our study, most patients with MI (90%) suffered from significant CAD confirmed by angiography. This observation is in line with the results of previous studies showing that patients with established CAD are especially prone to different environmental factors, such as air pollutants and temperature lowering, which trigger MI by destabilization of the atherosclerotic plaque or an increase in heart overload.<sup>31-35</sup>

Our study has several limitations. First, pollution measured by outdoor monitors does not reflect personal exposure. For example, we did not consider individual exposure to indoor pollution sources related to cooking, heating, or smoking. Solid fuels used for household heating or cooking may produce PM and carbon monoxide, and such indoor PM concentrations may be much larger than those in ambient air, resulting in a considerable individual exposure. Second, the exposure values were averaged for the whole city, while the actual levels of pollutants and their chemical composition may vary between different city areas. However, in practice, exposure values have to be averaged, given the limited number of pollution monitors available.

It should be also emphasized that the effect of ambient air pollution on human health results from interactions between its many different chemical components. Despite the norms adopted by the WHO and European Union for specific air pollutants, it is not possible to determine the threshold levels below which pollutants have no harmful effects on health. This is because the range of individual susceptibility in a population is so wide that some individuals may be susceptible event at the lowest level.

In conclusion, this study demonstrates that regardless of weather conditions and infections, the short-term fluctuations in outdoor PM<sub>2.5</sub>levels were positively associated with the number of daily hospital admissions for MI among chronically exposed inhabitants of Kraków. However, for PM<sub>10</sub> the effect was significant only with a simultaneous decrease in average air temperature. Regardless of weather conditions, the significant effect of NO<sub>2</sub> was observed only in patients aged 70 years or older and those with pulmonary disorders. The effects of  $PM_{2.5}$  and  $PM_{10}$  were delayed until a few days after exposure, whereas those of NO<sub>2</sub> were observed on the same or the next day after exposure. It is possible that fluctuations in air pollutant levels in combination with weather changes trigger MI by destabilization of the atherosclerotic plaque in individuals with established CAD.

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**CONTRIBUTION STATEMENT** EK conceived the concept of the study, contributed to study design, analyzed the data, edited the paper, and obtained funding for the project. GG analyzed the data, edited the paper, and obtained funding for the project. ŁN performed statistical analysis, analyzed the data, and edited the paper. MK BG, and PS collected and analyzed the data and edited the paper. PP, JN, and KŻ contributed to study design.

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