Article

Relationship between Particulate Matter Pollution and Acute Coronary Syndrome Incidence

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Abstract: (1) Background: In recent decades, studies have reported on the increased cardiovascular risk associated with increased levels of air pollutants, especially particulate matters (PM). It remains unclear whether the specific subgroups share the same involvement and whether the effect is delayed. (2) Methods: Data for acute coronary syndrome (ACS) incidences from 2008 to 2011 were gathered in two major medical centres in Slovenia. A time series analysis was conducted in which daily ACS incidence data were linked with daily concentrations of PM\textsubscript{10} (PM with a median aerodynamic diameter less than 10 µm) using a well-established generalized linear model with a log link function and a Poisson distribution of ACS. We specifically focused on groups based simultaneously on age and gender. (3) Results: On the basis of the presented models, it appears that daily average concentrations of PM\textsubscript{10} have a significant impact on ACS incidence for the entire population, with a higher impact on older populations and the highest impact on older men. The analysis of the delayed effect in PM\textsubscript{10}-related ACS incidences observed the strongest effect at a one day lag. (4) Conclusions: Our study detected the presence of a “rise and fall” lag pattern observed in three aforementioned population groups; however, no significant association was detected for women and younger populations.

Keywords: myocardial infarction; PM\textsubscript{10}; air pollution; morbidity; lag effect

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death globally. In Europe, CVD is the cause of nearly half (45%) of all deaths [1]. Recently, studies throughout the world have been connecting the emergence of the CVD with air pollution levels [2–6]. Increased levels of air pollutants constitute an additional risk factor for CVD, especially in metropolitan areas [7]. More pollution-related deaths occur as a result of heart disease than from any other cause [8]. However, the group of CVD is diverse. By focusing on specific CVD events in studies, more accurate estimates for risk analysis can be achieved [9].

We focused on a condition known as acute coronary syndrome (ACS), which accounts for almost 1.8 million annual deaths or 20% of all deaths in Europe [10]. It is usually caused by acute thrombosis, which is induced by a ruptured or eroded atherosclerotic coronary plaque, with or without concomitant vasoconstriction, and causes a sudden and critical reduction in blood flow to the heart muscle [11]. On the basis of evidence of heart muscle damage, ACS clinically manifests as unstable angina, non-ST elevated or ST-elevated myocardial infarction (MI) [12].

Numerous epidemiology studies have reported on the relationship between particle matter (PM) and MI; however, the results of these studies differ and have been controversial. Until recently, only a few studies had observed the correlation between PM with a median aerodynamic diameter less than...
10 µm (PM$_{10}$) and ACS. They reported a positive correlation between PM$_{10}$ and ACS; however, they did not provide specific conclusions for different gender and age groups. Most studies have focused on the correlation between particulate matter, especially PM$_{10}$ and MI, with conflicting results [8,13–25]. Moreover, the delayed effect of PM$_{10}$ exposure on ACS events has only been partially studied to date.

Therefore, the aim of our study is to assess the relationship between the PM$_{10}$ and the incidence of ACS emergency treated in catheterisation laboratories with percutaneous coronary catheter intervention in different population groups based on age and gender in consideration of one-day and two-day lag times.

2. Materials and Methods

We collected data on the incidence of ACS from University Medical Centre Ljubljana and General Hospital Celje that have catheterization laboratories with 24-h medical teams for emergency treatment of patients. In the examined period, from the beginning of 2008 until the end of 2011, 1955 events were detected in geographical areas that were observed in our study. Our study focused on Ljubljana, Celje, and Trbovlje areas because, according to the 2014 annual report from the Slovenian Environment Agency [26], these areas typically have the most days with daily concentrations exceeding (>50 µg/m$^3$) of PM$_{10}$.

Data on daily PM$_{10}$ concentrations in the examined period were obtained from AirBase, the European air quality database. The data were collected from five air quality monitoring stations positioned in the abovementioned areas of Ljubljana, Celje, and Trbovlje. The quality of the data was high in comparison with other studies [19,27], with only about 2% of the data missing.

For validity and reliability of the study results, it was important to measure human exposure to PM$_{10}$ as accurately as possible [28]. To assure validity, it was important that PM$_{10}$ data corresponded to actual PM$_{10}$ levels in the location of patients’ residences. Therefore, we limited our study to patients residing in one of the three observed areas because these areas share common topographical and settlement characteristics, i.e., densely populated basins or valleys with low wind speeds. The pollution problems of these areas are recognized by the Slovenian Environment Agency. Accordingly, the five monitoring stations were strategically positioned to monitor PM$_{10}$ levels in the areas. The reliability was tested by comparing the PM$_{10}$ data obtained from the five air quality monitoring stations. A strong correlation between PM$_{10}$ data (rho $\geq$ 0.869, p < 0.01) clearly indicated the similarity of PM$_{10}$ pollution patterns in all three studied areas. This high correlation allowed us to average the weighted data from the five air quality monitoring stations. The weighted station data were computed by multiplying the data of each station by the percentage of the population living in the area covered by a specific station.

A time series analysis was conducted on the 1955 ACS incidences. In accordance with existing research [29–31], a generalized linear model with logarithmic link function and a Poisson probability distribution (GLM-LL) was used to estimate the impact of PM$_{10}$ on the risk of emergency room visits. Tests of over-dispersion confirmed the Poisson model assumptions for the fitted models. Additionally, the P-value of the Omnibus test (Likelihood Ratio Chi-Square) was computed as reported in Tables 1–3.

Statistical analysis was performed with SPSS [32] while the preparation of data, including merging and aggregating, was performed with the R statistical package [33], which is suitable for larger datasets.

3. Results

As shown in Figure 1 a total of 1955 ACS events were analysed in our study, of which there were 1326 (67.8%) men and 629 (32.2%) women. Among them, 595 (30.4%) men and 452 (23.1%) women were older than 65. The maximum daily counts reached 8.00; the maximum daily concentrations of MP$_{10}$ was 153.21 µg/m$^3$. 
ACS tendency was observed to occur three to four times more often in men than in women; in older populations, ACS incidence is greatly increased in women [1,10].

Our sample is in line with European Cardiovascular Disease Statistics. For younger populations, ACS tendency was observed to occur more often in men than in women; in older populations, ACS incidence is greatly increased in women [1,10].

Table 1 presents the results of immediate daily ACS incidence change related to PM$_{10}$ increase for the entire population as well as younger (≤65 years) and older (>65 years) populations.

Table 1. Immediate daily ACS incidence change per 10 μg/m$^3$ PM$_{10}$ increase for the entire population and the two age groups.

| Parameter | $\beta$ | Std. Error | 95% Confidence Interval | Hypothesis Test |
|-----------|---------|------------|-------------------------|-----------------|
| All $^1$  | 0.028   | 0.0113     | (0.006, 0.051)          | $\chi^2$ 6.286, df 1, Sig. 0.012 $^*$ |
| <65 years $^2$ | 0.002   | 0.0174     | (-0.032, 0.036)         | $\chi^2$ 0.011, df 1, Sig. 0.915 |
| >65 years $^3$ | 0.049   | 0.0149     | (0.020, 0.079)          | $\chi^2$ 11.060, df 1, Sig. 0.001 $^{**}$ |

$^1$ Dependent variable: ACS incidence for all population; model: (intercept), PM$_{10}$. $^2$ Dependent variable: ACS incidence for population younger than 65 years; model: (intercept), PM$_{10}$. $^3$ Dependent variable: ACS incidence for population older than 65 years; model: (intercept), PM$_{10}$. $^*$ p < 0.05; Omnibus test p < 0.05. $^{**}$ p < 0.01; Omnibus test p < 0.01.

The results of daily ACS incidence for observed populations in Table 1 show that beta coefficients of the fitted model are statistically significantly different from 0, except for the population younger than 65 years. The per mille change of the beta coefficients were computed according to the formula $\text{Exp}(\beta) - 1$. The exp function was used because the interpretation of beta coefficients of the GLM-LL model had to take into account their exponential nature. Thus, it can be assumed that if the average daily PM$_{10}$ concentration increases by 10 μg/m$^3$, the daily ACS incidence in the whole population increases by approximately 3%. The effect in population older than 65 years is stronger, increasing by approximately 5%.

Table 2 presents the results of immediate daily ACS incidence change related to PM$_{10}$ increase for the entire population as well as the younger, older, male, and female populations.
The results of daily ACS incidence for observed populations in Table 2 showed that only beta coefficients for the male population as well as the male population older than 65 years are statistically significantly different from 0. Thus, if the average daily concentrations of PM$_{10}$ increases by 10 $\mu$g/m$^3$, the daily incidence of ACS in the male population increases by approximately 3% and the incidence in men older than 65 increases by approximately 6%.

On the basis of the presented GLM-LL models, the daily average concentrations of PM$_{10}$ have an impact on ACS incidence for the entire population as well as for the male population, especially males older than 65 years. Therefore, we focused on lag analysis for these three population groups. The results are shown in Table 3, where we present the percentage change in risk for ACS for the three groups with immediate (Lag 0) and delayed (Lag 1, Lag 2) response.

The results of daily ACS incidence for the observed population groups for different lags (Table 3) show that beta coefficients for all groups and lags were statistically significantly different from 0, except for the entire population and the older population groups for a two-day lag. We compare the results for different lags in Figure 2, which shows the strongest effect for one-day lag in the observed population groups.

### Table 2. Immediate daily ACS incidence change per 10 $\mu$g/m$^3$ PM$_{10}$ increase for the population grouped by gender and age.

| Parameter | $\beta$ | Std. Error | 95% Confidence Interval | Hypothesis Test |
|-----------|---------|------------|------------------------|-----------------|
|           |         |            | Lower                  | Upper           | Wald Chi-Square | df  | Sig.       |
| Man $^1$  | 0.029   | 0.0137     | 0.002                  | 0.055           | 4.315          | 1   | 0.038 *   |
| Women $^2$| 0.028   | 0.0199     | −0.011                 | 0.067           | 1.972          | 1   | 0.160     |
| man $\leq$ 65 $^3$ | 0.003 | 0.0193     | −0.035                 | 0.041           | 0.020          | 1   | 0.888     |
| man $>$ 65 $^4$ | 0.057 | 0.0195     | 0.019                  | 0.095           | 8.665          | 1   | 0.003 **  |
| women $\leq$ 65 $^5$ | 0.022 | 0.0396     | −0.079                 | 0.076           | 0.002          | 1   | 0.964     |
| women $>$ 65 $^6$ | 0.039 | 0.0231     | −0.006                 | 0.084           | 2.836          | 1   | 0.092     |

$^1$ Dependent variable: ACS incidence for man; model: (intercept), PM$_{10}$. $^2$ Dependent variable: ACS incidence for women; model: (intercept), PM$_{10}$. $^3$ Dependent variable: ACS incidence for man younger than 65 years; model: (intercept), PM$_{10}$. $^4$ Dependent variable: ACS incidence for man older than 65 years; model: (intercept), PM$_{10}$. $^5$ Dependent variable: ACS incidence for women younger than 65 years; model: (intercept), PM$_{10}$. $^6$ Dependent variable: ACS incidence for women older than 65 years; model: (intercept), PM$_{10}$. $^*$ $p < 0.05$; Omnibus test $p < 0.05$. $**$ $p < 0.01$; Omnibus test $p < 0.01$.

### Table 3. Immediate, one-day, and two-day lag daily ACS incidence change per 10 $\mu$g/m$^3$ PM$_{10}$ increase.

| Parameter | Lag 0 | Lag 1 | Lag 2 |
|-----------|-------|-------|-------|
|           | $\beta$ | Sig. | Change | $\beta$ | Sig. | Change | $\beta$ | Sig. | Change |
| all $^1$  | 0.028 | 0.012 * | 2.8% | 0.032 | 0.004 ** | 3.3% | 0.021 | 0.068 $^+$ | 2.1% |
| $>65$ years $^2$ | 0.049 | 0.001 ** | 5% | 0.086 | 0.000 ** | 5.8% | 0.028 | 0.077 $^+$ | 2.8% |
| man $^3$  | 0.029 | 0.038 * | 2.9% | 0.034 | 0.014 * | 3.5% | 0.028 | 0.046 * | 2.8% |
| man $>$ 65 years $^4$ | 0.057 | 0.003 ** | 5.9% | 0.064 | 0.001 ** | 6.6% | 0.046 | 0.021 * | 4.7% |

$^1$ Dependent variable: ACS incidence for all population; model: (intercept), PM$_{10}$. $^2$ Dependent variable: ACS incidence for population older than 65 years; model: (intercept), PM$_{10}$. $^3$ Dependent variable: ACS incidence for man; model: (intercept), PM$_{10}$. $^4$ Dependent variable: ACS incidence for man older than 65 years; model: (intercept), PM$_{10}$. $^+$ $p < 0.1$; Omnibus test $p < 0.1$. $^*$ $p < 0.05$; Omnibus test $p < 0.05$. $**$ $p < 0.01$; Omnibus test $p < 0.01$. $^*$ $p < 0.05$; Omnibus test $p < 0.05$. $**$ $p < 0.01$; Omnibus test $p < 0.01$.
Figure 2. Immediate and delayed percent change (95% confidence interval) in ACS incidence for a 10 μg/m³ PM₁₀ increase for men, women, as well as younger and older than 65 years. In Figure 2, a pattern is repeated through the four observed population groups. In addition to the strongest effects observable at the one-day lag, we observed that in all groups the risk was largely reduced at the two-day lag. The effect at a three-day lag was also investigated for the four observed groups; however, no statistically significant ACS incidence increase was detected.

4. Discussion

Our results show significant positive correlation between average daily PM₁₀ concentrations and ACS incidence. We detected ACS incidence increase by approximately 3% in case of PM₁₀ 10 μg/m³ increase for the whole population on the same day. These results are comparable to the majority of the related studies, including Lippi et al. [34], Belleudi et al. [35], Colais et al. [36], and Vaduganathan et al. [37]. The reported effect varied between studies. For example, in a study from Rome, Italy, Belleudi et al. [35] reported 1.1% higher admissions for ACS when PM₁₀ increased for 14 μg/m³ while in a study from Verona, Italy, Lippi et al. [34] reported the daily diagnoses of ACS were 26% higher when the 24-h PM₁₀ levels exceeded the 50 μg/m³ cut-off. Additionally, a study conducted in Tehran by Qorbani et al. [38] reported a non-significant positive association.

Similar results were also reported by Xie et al. [18], Lu et al. [21], Zanobetti et al. [39], Bhaskaran et al. [40], and Peters et al. [41] who associated an increase in PM₁₀ levels with MI (a subgroup of ACS) incidence. Moreover, studies included in the review by Bhaskaran et al. [42] estimate that an increase of 10-μg/m³ in mean 24-h PM₁₀ concentration is associated with the increase in relative risk for daily MI morbidity by approximately 0.37% to 11%. Cai et al. [43] also reported that short-term exposure to high PM₁₀ increases risk for MI-related hospitalization.

The exact mechanisms by which short-term exposure to high levels of PM could elevate the risk of MI remains uncertain. However, several possible mechanisms for the associations have been discussed [24,44,45], including an elevated risk of inflammation [43], increased heart rate and reduced heart rate variability [46–48], increased blood viscosity [49,50], hypercoagulability [51], and vasoconstriction [52].

Next, the study examined specific population groups based on age and gender. The results show that ACS incidence for the three population groups (older than 65, men, and men older than 65) increases from 2.8% to 5.9% in case of 10 μg/m³ PM₁₀ increase. Several studies reported similar results for the population group of older adults, reporting an association between PM₁₀ increase and ACS...
or its subgroup MI \[9,18,19,30,35,53\]. Older adults are generally considered a susceptible population because of the gradual decline in physiological processes over time \[54\].

Sacks et al. \[54\] who presented stratified results (e.g., <65 vs. \[≥\] 65 years) in a review of epidemiological studies pointed out that human clinical studies are not typically structured to detect differences in response between males and females. However, several studies concerning the effects of PM$_{10}$ on the incidence of ACS or its subgroup MI exhibit differences in gender. For instance, Xie et al. \[18\], Zanobetti et al. \[39\] and Sacks et al. \[54\] reported slightly stronger associations among males in comparison with females, which is in line with our results. On the contrary, Nuvolone et al. \[19\] in a study from Tuscany, Italy, reported that females are the more susceptible population group; however, they clarified that, in the population group of their study, the females were approximately nine years older than the males. This difference in age might help to explain the increased association of MI incidence with air pollutants for the observed female population group.

None of the existing studies focused on specific population groups on the simultaneous basis of age and gender. Our study detected a significant positive effect between PM$_{10}$ concentrations and ACS incidence only in men older than 65; no significant effect was detected in women older than 65, women younger than 65, and men younger than 65. These results indicate that older men are the most susceptible group and should thus be given special attention. These results are in line with the results of Colais et al. \[36\], who found an important difference on the basis of both age and sex, with patients aged 75–84 years the most susceptible and with men on lag 0–1.

Apart from the immediate effect (current day), we also examined the delayed effect of exposure to increased PM$_{10}$ concentrations on ACS for the whole population and specific population groups. Few studies have focused on this delayed effect, and only one of them has examined the delayed effect on specific age groups. None of the existing studies have examined specific gender groups.

Our study detected the strongest effects at the one-day lag for the three population groups for which the immediate effect was already detected (older than 65, men, and men older than 65). Interestingly, at a two-day lag, these effects were largely reduced and, at the three-day lag no statistically significant association with ACS incidence was detected. This “rise and fall” pattern was repeated across all three population groups.

Other studies focusing on the delayed effects often have chosen different lag structures and reported different results \[8,18,19,35,39,40,55\]. However, two of these studies detected similar “rise and fall” patterns. Nuvolone et al. \[19\] reported that PM$_{10}$ concentrations show trends with increased associations to MI incidence up to a two-day lag and lower estimates from a two-day lag to a five-day lag. Similarly, Pun et al. \[55\] observed the strongest effect at the one-day lag and gradually reduced effects on the subsequent days.

Possible explanation for this “rise and fall” pattern could be that on the first day after acute exposure to air pollution additional MI incidences may be related to a pulmonary inflammatory state, leading to hyperactive platelets (Nemmar et al. \[56\]). Moreover, Smeeth et al. \[57\] reported that the risk of MI increased substantially, with acute lower respiratory tract infection at its highest during the first three days and then gradually reducing. These results are in line with the findings of Belleudi et al. \[35\] who reported an increase in ACS incidence in relation to PM$_{10}$, where lag 0, lag 0–1, and lag 0–2 had the strongest effect.

On the contrary, Milojevic et al. \[8\] analysed the delayed effect (up to lag 4) and reported scant evidence of increased incidence. Zanobetti et al. \[39\] analysed the delayed effect up to Lag 2 and reported that the effect was largely associated with the change in risk on the day of hospitalization. Xie et al. \[18\] also reported that the effect estimates decreased substantially and even became insignificant using Lag 2 and Lag 3. Surprisingly, in a study by Bhaskaran et al. \[40\], effects estimated at longer lags were in a protective direction.
5. Conclusions

This is the first study that examines the immediate and delayed effects of PM$_{10}$ concentrations on the incidence of ACS for age- and gender-specific population groups. Our study detected the presence of the “rise and fall” lag pattern in PM$_{10}$-related ACS incidences observed in three population groups (older than 65, men, and men older than 65) with one-day lag having the strongest effect. The results also show that the most susceptible group are men older than 65 while no significant association was detected for women and younger populations.

One of the important obstacles in studying PM$_{10}$-related ACS incidences is that the quality of air pollution data is often limited. Air pollution is not continuously monitored and monitoring is performed only in specific areas such as bigger cities or industrial zones [19,27,35,43]. In future, it would be interesting to extend the air pollution measurements to less polluted areas. This would enable us to compare the results among polluted and cleaner areas. Additionally, it would be beneficial to increase the period of time and the size of the studied population to further explain and understand the “rise and fall” lag pattern that we detected.

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