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Risk Associations between Air Pollution Exposure and Cardiovascular Diseases: A Residential Retrospective Cohort Study

Elisa Bustaffa [1], Cristina Mangia [2,*], Liliana Cori [1], Marco Cervino [3], Fabrizio Bianchi [1] and Fabrizio Minichilli [1,*]

[1] Institute of Clinical Physiology, National Research Council, Via Moruzzi 1, 56126 Pisa, PI, Italy; elisa.bustaffa@cnr.it (E.B.); liliana.cori@cnr.it (L.C.); fabrizio.bianchi@cnr.it (F.B.)
[2] Institute of Atmospheric Sciences and Climate, National Research Council, Strada Prov.le Lecce-Monteroni Km 1200, 73100 Lecce, LE, Italy
[3] Institute of Atmospheric Sciences and Climate, National Research Council, Via Gobetti 101, 40129 Bologna, BO, Italy; m.cervino@isac.cnr.it
* Correspondence: c.mangia@isac.cnr.it (C.M.); fabrizio.minichilli@cnr.it (F.M.)

Abstract: The population of the Venafro Valley (Southern Italy) faces various type of air pollution problems (industrial facilities, traffic, and biomass combustion). To estimate exposure to various pollution sources, a multi-stage random forest model was used, integrating particulate matter (PM) data with satellite observations, land-use patterns, and meteorological information generating maps of $PM_{2.5}$ concentration. Four distinct $PM_{2.5}$ exposure categories were established using the quartile method. To assess the association between $PM_{2.5}$ and cause-specific mortality and morbidity, a time-dependent and sex-specific Cox multiple regression analysis was conducted, adjusting for age classes. In addition, the hazard ratios were accompanied by a probability measure of the strength of the evidence toward a hypothesis of health risk associated with the exposure under study ($1-p$ value). The whole cohort was exposed to $PM_{2.5}$ annual levels exceeding the 5 $\mu g/m^3$ limit recommended by the World Health Organization. Mortality excesses were observed in class 3 for both sexes for cardiac heart diseases. Excesses of cardiovascular diseases were observed for both sexes in class 3 and 4. The study highlights significant signals warranting mitigation actions, which regional authorities are currently considering.

Keywords: air pollution; cardiovascular diseases; residential cohort study; mortality; morbidity; hazard ratio; Italy

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1. Introduction

Air pollution has its origins in both natural and anthropogenic sources and has been identified as the most significant environmental threat to human health and well-being on a global scale [1,2]. The burden of disease associated with exposure to air pollution is significant and increasing. This trend can be attributed to rising exposure levels in low- and middle-income countries, as well as the rapid and extensive prevalence of non-communicable diseases globally, driven by an aging population and lifestyle changes [2]. The World Health Organization (WHO) estimates that around 7 million deaths are attributable to the joint effects of environmental and domestic air pollution [3], with 4.1 million of these deaths attributed to ambient fine particulate matter (PM) with a diameter less than 2.5 microns ($PM_{2.5}$) [4]. The primary burden of disease associated with $PM_{2.5}$ is concentrated in areas of high concentration ($\geq$35 $\mu g/m^3$), where approximately half of the global population resides [5]. Global evaluations of the impact of air pollution suggest that it is responsible for approximately 4 million to 9 million deaths annually, along with the loss of hundreds of millions of healthy life years [3,4,6,7]. It is hypothesized

that exposure to air pollution is a significant contributor to global health risks, ranking among the top five risk factors out of 87 in a global assessment, alongside other major health concerns such as an unhealthy diet and tobacco smoking [4]. In 2019, the American Environmental Protection Agency (US EPA) classified the association between $PM_{2.5}$ and mortality from natural causes as "causal" while the association between $PM_{10-2.5}$ and mortality from natural causes as "suggestive" [8]. Particularly, the "causal" or "probably causal" relationship between long-term exposure to fine PM and mortality from all causes and cardiovascular disease (CVD) has also been reported by the International Agency for Research against Cancer (IARC) [8].

Since most of the residents' lives in urban contexts are potentially polluted by anthropic activities, the concern for possible environmental health effects is widespread in these areas. In fact, the urban environment is typically characterized by multiple environmental stressors, which in some cases act synergistically, causing health damage [1]. To date, the evidence of the effects of short-term exposures (from one hour to days) to air pollutants reports associations with mortality for all causes, but also with cardiovascular mortality [9]. Several systematic reviews and meta-analyses demonstrated the effects of PM on all-cause and cause-specific mortality [10,11]. Particularly, both short-term and long-term exposure to $PM_{2.5}$ levels are associated with CVD outcomes such as mortality, stroke mortality and morbidity, heart failure, myocardial infarction (MI), cardiac arrhythmias, and ischemic heart disease (IHD) [3,12–15].

The recent literature provides evidence for the plausible mechanisms through which $PM_{2.5}$ results in adverse cardiovascular outcomes. Specifically, it is hypothesized that $PM_{2.5}$ acts via three mechanisms: (1) the increment of oxidative stress, (2) the activation of the inflammatory pathway of the immune system, and (3) the stimulation of the autonomic nervous system [13,14]. Indeed, $PM_{2.5}$ can deposit on the vascular endothelium, leading to chronic exacerbation of local oxidative stress and inflammation, which in turn results in atherosclerotic plaque instability and ultimately, thrombus formation [16]. Particularly, long-term exposure to atmospheric pollutants may be a trigger for a chronic vascular inflammatory status probably damaging the cardiovascular system through the induction of endothelial dysfunction, coronary atherosclerotic plaque formation, progression, and also destabilization [17–19].

The Venafro Valley, situated in the Italian region of Molise, has historically been subjected to a multitude of forms of pollution. These include the presence of a waste-to-energy plant (WTE) and a cement factory. Furthermore, both the valley and the city of Venafro are impacted by the utilization of biomass combustion and a considerable volume of traffic, encompassing both heavy and light vehicles. In order to evaluate the potential health risks faced by residents in the eight municipalities of the Venafro Valley exposed to the industrial air pollution considered, a retrospective residential cohort study (EPIVenafro+7 study) was conducted. The study spanned a period from 2006 to 2019. A map of the dispersion of nitrogen dioxide emitted by the plants, which were used as a proxy for industrial pollution, was employed to assess exposure. Furthermore, to ascertain the environmental risks associated with the two aforementioned industrial plants, the reconstruction of mortality and morbidity profiles was utilized [20]. The study revealed an elevated mortality risk for diseases of the circulatory system in both men and women, with a particular emphasis on heart and cerebrovascular diseases. The study also showed an elevated risk of hospitalization for diseases of the circulatory system in both sexes in the region most affected by the two industries [20].

In contrast to the previous study, the principal objective of the present research is to assess the health risks associated with CVD among the residents of the area, taking into account a range of additional polluting emissions, including those related to traffic and biomass combustion, in addition to industrial emissions, by performing a retrospective population-based cohort study. The research utilized concentration maps of $PM_{2.5}$ as exposure indicators, while individual risk factors such as age and gender were also considered.

The study was financed by the Molise region through the municipality of Venafro and involved the other seven municipalities of the Venafro Valley.

2. Materials and Methods

The study was conducted in accordance with the ethical principles set forth in the Helsinki Declaration. All record linkage procedures were conducted in accordance with the highest standards of data protection and confidentiality. The handling of personal data was carried out in strict compliance with the rules governing the management of regional information systems and in full alignment with the current privacy legislation, specifically the General Data Protection Regulation (GDPR) and the European Regulation 2016/679. To facilitate the record linkage procedures, the personal and health data were pseudonymized through a uniform process, resulting in a final dataset comprising personal (demographic and residential), exposure, and health data, minimized for research purposes. Notably, no personal identifiers were transmitted to the research personnel, all the addresses were geocoded, and the personal data were analyzed anonymously.

2.1. Domain of the Study, Definition of the Cohort, and the Follow-Up Period

The study domain encompasses eight municipalities within the Venafro Valley (Molise region, central Italy) (Figure 1). In addition to the two industrial zones located in the municipalities of Sesto Campano and Pozzilli, the Venafro area is characterized by both the utilization of biomass combustion and a considerable volume of both heavy and light traffic. This is largely due to the presence of two principal arterial roads that intersect with all other major roads in the city at a single junction situated in the center of Venafro.

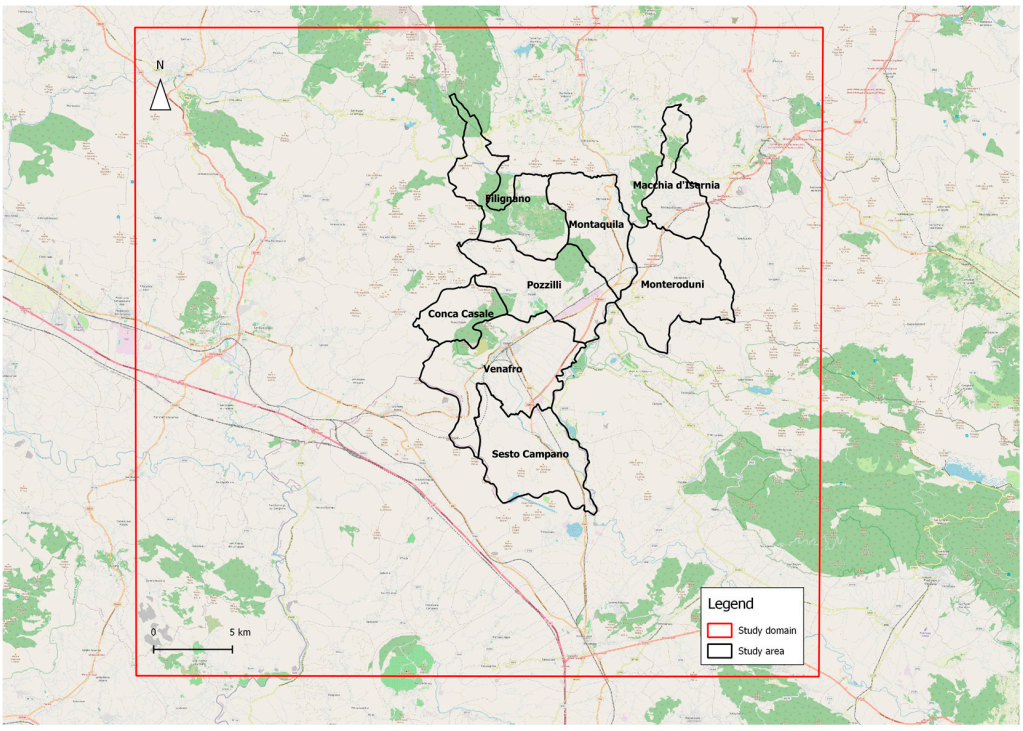

Figure 1. Study domain of the eight municipalities of the Molise region.

The study analyzed a retrospective cohort consisting of all individuals residing in eight municipalities for at least one year during the period from 2006 to 2019, considered as the follow-up period. Data on demographics and residences were sourced from the municipalities' general registry offices. The cohort was designed to be flexible, accommodating new entrants at various times due to births and migration throughout the study duration. For hospital admissions, the approach used was consistent with the methods detailed in our previous study [21]. Person–years (pys) were calculated from the time entry

into the cohort until the first hospitalization for each specific cause. If an individual moved residences, the pys were aggregated from all recorded addresses. Those who died or were hospitalized outside the study area during the observation period were included in the analysis, just like those within the area. All addresses were georeferenced for accuracy. Throughout the follow-up period (2006–2019), the cohort encompassed 29,495 individuals and 317,810 pys. Among them, 14,804 (50.2%) were males, with an average follow-up duration of 10.7 years (10.5 years for male and 11.0 years for females).

2.2. Exposure Assessment

Concentration maps of $PM_{2.5}$

Air pollution in urban areas can originate from a variety of sources, including industrial emissions, vehicle exhaust, domestic heating, and biomass burning. To assess population exposure from multiple sources, the concentration maps of pollutants estimated by Stafoggia et al. in 2020 were used in this study [22]. These were estimated by means of a machine learning approach using the random forest method to estimate the daily mean values of PM_{10}, $PM_{2.5}$, NO_2, and O_3 on a 1 km^2 grid for the period 2016–2019 [22]. The method integrates meteorological, land use, and monitoring data obtained from all available sites provided by the Higher Institute for Protection and Research on Environment, along with aerosol optical depth satellite data.

Among the various pollutants, $PM_{2.5}$ was chosen as representative for studying multisource exposures due to its sensitivity and adverse effects on the cardiovascular system. Data were available just for the 2016–2019 period, so this time range was considered as representative of the entire follow-up period. Figure 2 shows the spatial distribution of the $PM_{2.5}$ average concentrations for the period 2016–2019 for the 1 km^2 cells in the study area. The $PM_{2.5}$ distribution is characterized by an average value of 11.19 $\mu g/m^3$ (standard deviation of 2.55 $\mu g/m^3$) and a minimum and maximum of 6.85 $\mu g/m^3$ and 20.22 $\mu g/m^3$, respectively.

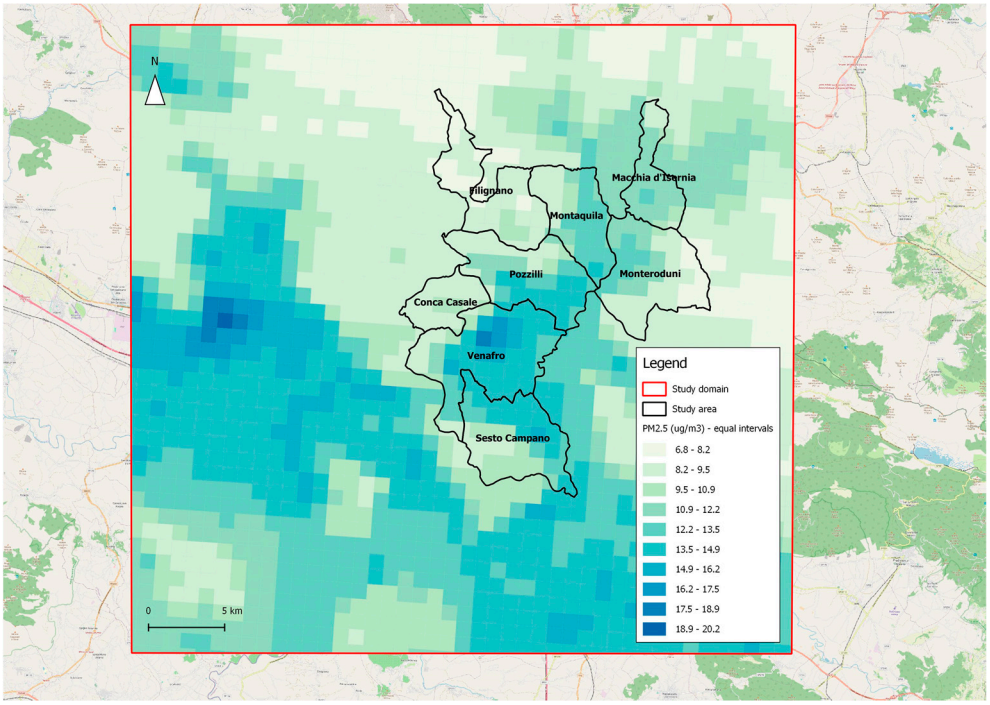

Figure 2. Average annual soil concentrations (in $\mu g/m^3$) (period of 2016–2019) of particles that are 2.5 microns or less in diameter ($PM_{2.5}$) [22] in the area under study.

2.3. Population Exposure

For each georeferenced individual, a detailed record of $PM_{2.5}$ exposure within the study area was reconstructed throughout the follow-up period, accounting for any movements within the area. Specifically, for each member belonging to the cohort, the $PM_{2.5}$ concentration at each residential address was assigned based on their georeferenced locations. Individual exposures were then categorized into four levels determined by quartiles of the distribution of $PM_{2.5}$ exposure. The four exposure levels were defined as follows (see Figure 3):

- Class 1 (less exposed, class of reference): 8.1–13.3 $\mu g/m^3$;
- Class 2: 13.3–15.1 $\mu g/m^3$;
- Class 3: 15.1–17.1 $\mu g/m^3$;
- Class 4 (class with higher exposure): 17.1–18.8 $\mu g/m^3$.

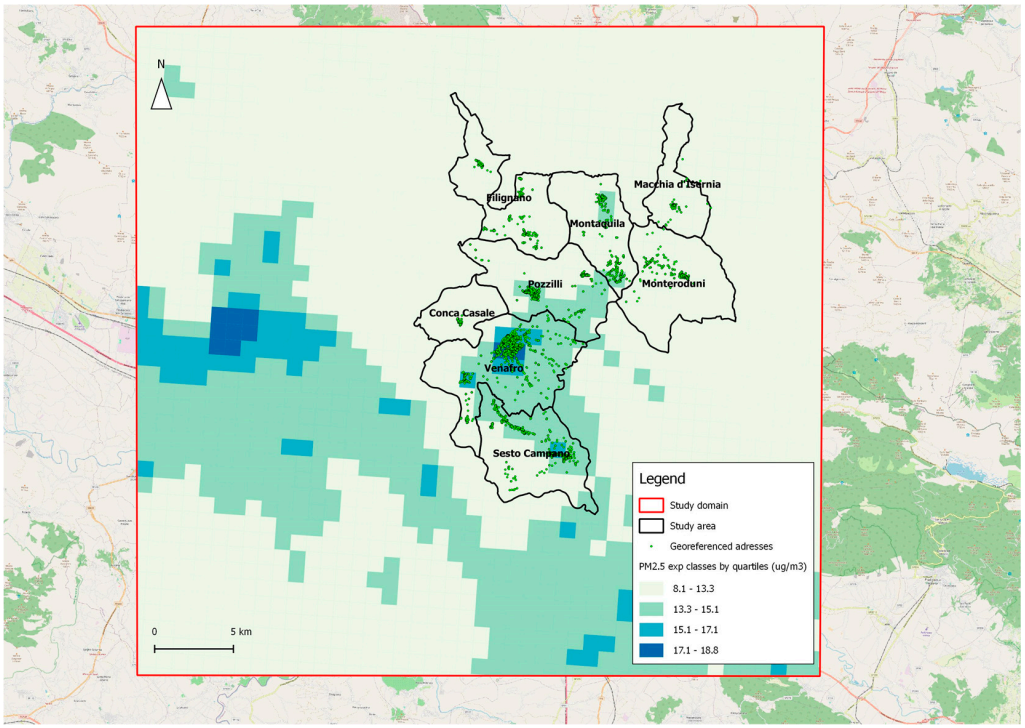

Figure 3. Attribution of the exposure class to the residential cohort through the concentration map, divided into the four classes defined for particles that are 2.5 microns or less in diameter ($PM_{2.5}$).

2.4. Health Outcomes

Mortality and hospitalization data for the period from 2006 to 2019 were provided by the Molise Regional Health Agency in a pseudonymized format, following the methodology described by Bustaffa et al. (2023) [20]. Each individual in the cohort was linked to their initial hospital admission for each specific condition of interest, as well as any related mortality, using a pseudonymized identification code. The age at diagnosis was calculated by subtracting the admission date from the date of birth. Given the established links between $PM_{2.5}$ air pollution and potential health risks, and considering the nature of the diseases under study, the focus was placed on diseases of the circulatory system. The conditions analyzed were selected based on the International Classification of Diseases, 10th Revision (ICD-10) for mortality data and the ICD 9th Revision, Clinical Modification (ICD-9-CM) for hospitalization data. The specific causes included in the study are as follows:

- Diseases of the circulatory system (ICD-10 Code I00–I99; ICD-9-CM Code 390–459);
    - Heart diseases (ICD-10 Code I00–I52; ICD-9-CM Code 390–429);
    - Ischemic heart diseases (IHD) (ICD-10 Code I20–I25; ICD-9-CM Code 410–414);

- Acute myocardial infarction (AMI) (ICD-10 Code I21; ICD-9-CM Code 410);
- Cerebrovascular diseases (ICD-10 Code I60–I69; ICD-9-CM Code 430–438).

2.5. Statistical Analysis

To examine the relationship between exposure levels and cause-specific mortality and morbidity within the cohort, a time-dependent, sex-specific Cox regression model was utilized. This model assessed how exposure to $PM_{2.5}$ impacted these risks, with a comparison drawn internally within the study area. The analysis involved calculating the hazard ratios (HRs) by comparing the risks of death or hospitalization among the groups with the highest $PM_{2.5}$ exposure to those with the lowest exposure. HRs were adjusted for age categories (0–44; 45–54; 55–64; 65–74; 75–84; 85+) and results were presented with a 95% confidence interval (95% CI). Additionally, the strength of the association between $PM_{2.5}$ and health outcomes was quantified using the empirical evidence measure $(1-p)$, which indicates the probability that the observed association is credible. A higher $(1-p)$ value reflects stronger evidence supporting the association between exposure and health risks [23]. Analyses were performed separately for males and females using STATA v.13 (Stata Corp., College Station, TX, USA, 2013).

3. Results

Tables 1 and 2 present the associations between $PM_{2.5}$ exposure from various sources and the causes of mortality and morbidity, categorized into four exposure levels (with class 1 as the lowest, used as reference) for both males and females. For a better understanding of the results, please note the following guidelines:

- HRs based on fewer than three cases are not reported due to privacy concerns and the potential for high inaccuracy in the estimates;
- To emphasize findings for the highest exposure groups, only significant results related to classes 3 and 4 of $PM_{2.5}$ exposure are discussed;
- Any observed risk increases in the highest exposure classes are always compared to the reference class (class 1), which has the lowest $PM_{2.5}$ levels;
- Consistent with recent scientific guidelines, which advocate not using a mere cut-off of statistical significance, we have accompanied the HRs with the $(1-p)$ indicator as previously defined. In fact, even if not statistically significant, risk associations may indicate important issues that warrant further investigation with more robust studies to reduce uncertainty [24].

3.1. Results of Mortality Analyses

For the diseases of the circulatory system, an excess among males in class 3 (+20%, 87.1% of evidence probability in favor of the hypothesis of risk association $(1-p)$) was observed, while no excess was found among females. Particularly, for heart diseases excesses among both sexes in class 3, +25% ($1-p$ 87.1%) and +15% ($1-p$ 71.1%) among males and females, respectively, were observed (Table 1). Among females in class 3, an excess for IHD emerged (+42%, $1-p$ 82.6%) (Table 1).

3.2. Hospital Admission Analyses

Considering diseases of the circulatory system, risk excesses in the highest exposed classes and in both genders were observed (Table 2). In class 3, among males, a risk excess of +23% ($1-p$ 99.9%) was observed; this result was also similar among females, with a risk excess of +25% ($1-p > 99.9\%$) (Table 2). In the highest class, risk excesses were also observed among males (+29% $1-p > 99.9\%$) and females (+20% $1-p$ 99.6%) (Table 2). Even if results showed excesses for heart diseases among both genders in class 3 (males − +11%, $1-p$ 82.9; females − +12%, $1-p$ 85.9%) and for IHD among males in the highest exposure classes (class 3 − +22%, $1-p$ 92.9%; class 4 − +16%, $1-p$ 84.7%), the excesses described for the circulatory system diseases are mainly attributable to cerebrovascular diseases for which excesses for both genders of the highest exposure classes were observed (Table 2). Specifically, in class

3, risk excesses of +37% (1−*p* 99.8%) and +25% (1−*p* 97.7%) among males and females, respectively, were observed (Table 2). In the highest class, risk excesses were also observed among both males (+35%, 1−*p* 99.8%) and females (+29%, 1−*p* 99.1%) (Table 2).

Table 1. Mortality analyses by sex and exposure class of particulate matter with diameters less than 2.5 microns ($PM_{2.5}$) (period of 2006–2019, adjusted for age classes).

Cause (cod. ICD-10)	Exposure Class	MALES				FEMALES			
		n	HR	1−*p*	CI95%	*n*	HR	1−*p*	CI95%
Diseases of the circulatory system (I00–I99)	1 (ref.)	183				252			
	2	183	1.16	0.830	0.94–1.42	225	1.07	0.557	0.90–1.28
	3	115	1.20	0.871	0.95–1.52	146	1.07	0.476	0.87–1.31
	4	95	0.89	0.615	0.70–1.15	103	0.79	0.952	0.63–1.00
Heart diseases (I00–I52)	1 (ref.)	117				147			
	2	116	1.13	0.649	0.87–1.46	150	1.22	0.909	0.97–1.53
	3	78	1.25	0.871	0.94–1.67	93	1.15	0.711	0.89–1.49
	4	63	0.91	0.470	0.66–1.23	61	0.79	0.878	0.58–1.07
Ischemic heart diseases (IHD) (I20–I25)	1 (ref.)	31				33			
	2	37	1.30	0.719	0.80–2.10	37	1.31	0.739	0.82–2.09
	3	20	1.14	0.348	0.65–2.00	27	1.42	0.826	0.86–2.37
	4	23	1.15	0.395	0.67–1.99	17	0.91	0.248	0.50–1.64
Acute myocardial infarction (AMI) (I21)	1 (ref.)	11				13			
	2	13	1.22	0.372	0.54–2.73	9	0.78	0.438	0.33–1.82
	3	8	1.17	0.261	0.47–2.92	12	1.50	0.688	0.68–3.30
	4	8	1.00	0.005	0.40–2.51	5	0.60	0.658	0.21–1.70
Cerebrovascular diseases (I60–I69)	1 (ref.)	39				68			
	2	51	1.53	0.954	1.01–2.33	61	1.09	0.370	0.77–1.54
	3	25	1.26	0.623	0.76–2.08	42	1.16	0.540	0.79–1.70
	4	19	0.87	0.371	0.50–1.52	35	1.02	0.079	0.68–1.54

Notes—ICD-10: International Classification of Diseases, 10th revision; *n*: numerosity; HR: hazard ratio; CI95%: confidence interval at a 95% probability; 1−*p*: strength of evidence in favor of an excess/defect of mortality risk; 1 (ref.): exposure class 1, reference (8.8–13.3 μg/m^3); 2: exposure class 2 (13.3–15.1 μg/m^3); 3: exposure class 3 (15.1–17.1 μg/m^3); 4: exposure class 4 (17.1–18.8 μg/m^3).

Table 2. Hospitalization analyses by sex and exposure class of particulate matter with diameters less than 2.5 microns ($PM_{2.5}$) (period of 2006–2019, adjusted for age classes).

Cause (cod. ICD-9-CM)	Exposure Class	MALES				FEMALES			
		n	HR	1−*p*	CI95%	*n*	HR	1−*p*	CI95%
Diseases of the circulatory system (390–459)	1 (ref.)	623				578			
	2	687	1.17	0.996	1.05–1.31	572	1.11	00925	0.99–1.25
	3	477	1.23	0.999	1.09–1.38	461	1.25	>0.999	1.10–1.41
	4	566	1.29	>0.999	1.15–1.45	461	1.20	0.996	1.06–1.35
Heart diseases (390–429)	1 (ref.)	421				365			
	2	435	1.04	0.440	0.91–1.19	334	0.98	0.208	0.84–1.14
	3	315	1.11	0.829	0.96–1.28	281	1.12	0.859	0.96–1.31
	4	355	1.08	0.697	0.93–1.24	269	1.00	0.037	0.85–1.17
Ischemic heart diseases (IHD) (410–414)	1 (ref.)	181				118			
	2	224	1.23	0.960	1.01–1.49	105	0.93	0.431	0.71–1.21
	3	155	1.22	0.929	0.98–1.51	90	1.08	0.405	0.82–1.42
	4	175	1.16	0.847	0.95–1.43	90	0.97	0.146	0.74–1.28
Acute myocardial infarction (AMI) (410)	1 (ref.)	77				47			
	2	99	1.27	0.881	0.94–1.71	44	1.00	0.004	0.66–1.51
	3	64	1.16	0.626	0.83–1.62	30	0.92	0.265	0.58–1.46
	4	72	1.11	0.485	0.81–1.54	27	0.78	0.699	0.48–1.25
Cerebrovascular diseases (430–438)	1 (ref.)	213				231			
	2	274	1.34	0.999	1.12–1.60	243	1.17	0.917	0.98–1.40
	3	187	1.37	0.998	1.12–1.67	193	1.25	0.977	1.03–1.51
	4	208	1.35	0.998	1.11–1.63	203	1.29	0.991	1.06–1.56

Notes—ICD-9-CM: International Classification of Diseases, 9th revision—Clinical Modifications; *n*: numerosity; HR: hazard ratio; CI95%: confidence interval at a 95% probability; 1−*p*: strength of evidence in favor of an excess/defect of hospitalization risk; 1 (ref.): exposure class 1, reference (8.8–13.3 μg/m^3); 2: exposure class 2 (13.3–15.1 μg/m^3); 3: exposure class 3 (15.1–17.1 μg/m^3); 4: exposure class 4 (17.1–18.8 μg/m^3).

4. Discussion

The purpose of the present analysis, carried out in the framework of the EPIVenafro+7 study, was to assess the mortality and hospitalization profile for the CVD of residents of the eight municipalities in the Venafro Valley (Molise region) differently exposed to air pollution according to age and sex.

The mortality analysis revealed an increased risk of cardiovascular diseases, predominantly heart diseases, among men residing in the most heavily polluted areas, although not always with clear signals. In terms of hospitalization, both genders showed an increase in the prevalence of cardiovascular diseases, with a significant rise in cases of IHD and cerebrovascular diseases among the most exposed groups.

Despite exposure levels being below the national $PM_{2.5}$ limit of 25 $\mu g/m^3$, they exceed the new recommended limit of 5 $\mu g/m^3$ [2]. Regarding exposures to $PM_{2.5}$, the area with greatest exposure (with average annual values of $PM_{2.5}$ from 17.1 to 20.2 $\mu g/m^3$ significantly higher than the level suggested by the AQGs of 5 $\mu g/m^3$) is limited to the urban area of Venafro, the most densely populated municipality, particularly at the intersection between the two main roads.

From a summary of the results, significant excesses of mortality for CVD are observed in both sexes in the most exposed areas. Among males, this excess is also confirmed by hospitalization analyses.

Regarding mortality and morbidity, our results on CVD are generally in line with what is reported by the recent scientific literature, namely that short- and long-term exposure to $PM_{2.5}$, and more generally to air pollution, is associated with significant human health effects such as an excess risk of mortality from CVD.

Following the publication of the AQG in 2006, given the strong increase in scientific studies on air pollution and health effects, the WHO commissioned various systematic reviews and meta-analyses with the aim of updating the scientific evidence in order to support the new update of the AQG [2], aiming at summarizing the worldwide evidence on the effects of exposure to PM and other air pollutants on all-cause and/or cause-specific mortality, including cardiovascular and cerebrovascular mortality [15,25]. This WHO upgrade of the global scientific literature finds positive associations between $PM_{2.5}$ and mortality for cardiovascular and cerebrovascular diseases [15], with the associations with $PM_{2.5}$ much more consistent than with PM_{10}, especially for CVD [25]. The most recent scientific literature confirms the associations between $PM_{2.5}$ and increased mortality and morbidity and/or of the risk for CVD [13,14,26–30], revealing the causal association between higher $PM_{2.5}$ concentrations and increased CVD risks [31] and confirming that PM air pollution is a significant risk factor for CVD [32]. Particularly, the long-term exposure to $PM_{2.5}$ was found to be associated with an increased incidence of MI, atherosclerosis, incident hypertension, incident stroke, and stroke mortality [12].

As is the case with all epidemiological studies, our research study has both strengths and limitations. The residential cohort design represents a significant strength of this study, as it represents the most advanced approach adopted in other national environmental epidemiology studies [20,33–35]. This kind of study allows for the examination of different outcomes for the same type of exposure and enables the tracking of individual subjects over time, associating their exposure based on their residence duration at a specific address. It is also noteworthy that the georeferencing procedure was 100% successful, ensuring that no distortions were introduced due to the uneven distribution of subjects across the territory. The loss of 5% of subjects from the mortality register and 10% of subjects from the hospital discharge forms provided reassurance regarding the reliability of the estimates obtained, given that a loss of 10% is considered typical in cohort studies.

Regarding the limitations of the study, it should be noted that the sample size in some cases resulted in an indicator estimate with a low precision, or in instances where there were fewer than three cases, it was not reported for reasons of subject privacy. Secondly, the attribution of complex exposure, such as that involving multiple sources, was based solely on the subject's residential address. It is possible that the residence does not

accurately reflect the subjects' actual exposure. The study did not consider information regarding the movements of the cohort subjects during the day, which may have resulted in misclassification between residents in exposed and less exposed areas and the generation of biases. In particular, when pollutants are generated by sources in close proximity to one another, it is not possible to definitively attribute the effects of one source over another. The model employed in the study considers the overall $PM_{2.5}$ detected in the study area (irrespective of the source), offering a distinct approach compared to evaluating emissions from a single source. Furthermore, confounders such as cigarette smoking, alcohol abuse, obesity, diet, physical activity, and occupational exposure were not directly considered, as data were not available. For these factors, a confounding effect cannot be excluded. All these aspects may be responsible for some inconsistent results between classes of exposures. This inconsistency renders the results less reliable and calls for a more descriptive interpretation than one based on causal speculation. Further investigation is required to elucidate this issue. Moreover, there is currently no strong evidence to support the hypothesis that other risk factors not considered thus far have effects on the same outcomes. However, we studied a small area, so we expect social characteristics and lifestyles to be non-differential between the different $PM_{2.5}$ classes. Consequently, the estimated relative risks should be minimally influenced by the effect of individual confounding factors not considered.

5. Conclusions

The retrospective residential cohort study EPIVenafro+7 revealed that exposure to $PM_{2.5}$ was associated with a non-negligible increase in mortality and hospitalization rates for CVD in both sexes. While the extent of the excesses is not alarming, it is nevertheless indicative of a situation that warrants further investigation, including an examination of lifestyles and other individual risk factors. The findings of the present study, which encompassed all emission sources, in conjunction with those of the previous study that focused exclusively on industrial sources, underscore the existence of a dual challenge in the area that necessitates the implementation of targeted measures. The first challenge is associated with the presence of industrial facilities [20], while the second is more closely linked to urban emissions from the most populated municipalities. Although cohort studies represent one of the most advanced research designs, the inherent uncertainty of the resulting estimates can be reduced by refining the methodology, improving the accuracy of exposure assessment, and employing other methods of epidemiological analysis. In particular, future investigations should consider potential confounding factors, such as smoking, alcohol consumption, diet, and occupational exposures, which could influence the outcomes. We suggest the following recommendations: (i) undertake detailed research using birth assistance certificates and the Cancer Registry, (ii) carry out a thorough examination of the findings within various population subgroups, and (iii) conduct a pilot study on cardiovascular disease, employing surveys and human biomonitoring.

Furthermore, according to the new air quality guidelines, we consider it necessary to pursue environmental policies aimed at considerably reducing concentrations of atmospheric pollutants to reduce the health burden from exposure to air pollution.

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References

1. European Environment Agency. Available online: https://www.eea.europa.eu/publications/europes-air-quality-status-2023 (accessed on 9 August 2024).
2. WHO Global Air Quality Guidelines. Particulate Matter ($PM_{2.5}$ and PM_{10}), Ozone, Nitrogen Dioxide, Sulfur Dioxide, and Carbon Monoxide. Available online: https://iris.who.int/handle/10665/345329 (accessed on 9 August 2024).
3. WHO. Burden of Disease from Ambient Air Pollution for 2016—Description of Method. Available online: https://cdn.who.int/media/docs/default-source/air-quality-database/aqd-2018/aap_bod_methods_apr2018_final.pdf?sfvrsn=30ac0d62_3 (accessed on 9 August 2024).
4. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of Disease Study 2019. *Lancet* **2020**, *396*, 1223–1249. [CrossRef] [PubMed]
5. State of Global Air 2020. Available online: https://www.stateofglobalair.org/air/pm#hot-spots (accessed on 9 August 2024).
6. Burnett, R.; Chen, H.; Szyszkowicz, M.; Fann, N.; Hubbell, B.; Pope, C.A.; Apte, J.S.; Brauer, M.; Cohen, A.; Weichenthal, S.; et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 9592–9597. [CrossRef] [PubMed]
7. Vohra, K.; Vodonos, A.; Schwartz, J.; Marais, E.A.; Sulprizio, M.P.; Mickley, L.J. Global mortality from outdoor fine particle pollution generated by fossil fuel combustion: Results from GEOS-Chem. *Environ. Res.* **2021**, *195*, 110754. [CrossRef] [PubMed]

8. US EPA. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019). Available online: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=347534 (accessed on 9 August 2024).
9. WHO. Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide. Global Update 2005: Summary of Risk Assessment. Available online: https://www.who.int/publications/i/item/WHO-SDE-PHE-OEH-06-02 (accessed on 9 August 2024).
10. Atkinson, R.W.; Mills, I.C.; Walton, H.A.; Anderson, H.R. Fine particulate components and health-a systematic review and meta-analysis of epidemiological time series studies of daily mortality and hospital admission. *J. Expo Sci. Environ. Epidemiol.* **2015**, *25*, 208–214. [CrossRef] [PubMed]
11. Bell, M.L.; Zanobetti, A.; Dominici, F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: A systematic review and meta-analysis. *Am. J. Epidemiol.* **2013**, *178*, 865–876. [CrossRef]
12. de Bont, J.; Jaganathan, S.; Dahlquist, M.; Persson, A.; Stafoggia, M.; Ljungman, P. Ambient air pollution and cardiovascular diseases: An umbrella review of systematic reviews and meta-analyses. *J. Intern. Med.* **2022**, *291*, 779–800. [CrossRef]
13. Krittanawong, C.; Qadeer, Y.K.; Hayes, R.B.; Wang, Z.; Thurston, G.D.; Virani, S.; Lavie, C.J. $PM_{2.5}$ and cardiovascular diseases: State-of-the-Art review. *Int. J. Cardiol. Cardiovasc. Risk Prev.* **2023**, *19*, 200217. [CrossRef]
14. Krittanawong, C.; Qadeer, Y.K.; Hayes, R.B.; Wang, Z.; Virani, S.; Thurston, J.D.; Lavie, C.J. $PM_{2.5}$ and Cardiovascular Health. *Curr. Probl. Cardiol.* **2023**, *48*, 101670. [CrossRef]
15. Orellano, O.; Reynoso, J.; Quaranta, N.; Bardach, A.; Ciapponi, A. Short-term exposure to particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) and all-cause and cause-specific mortality: Systematic review and meta-analysis. *Environ. Int.* **2020**, *142*, 105876. [CrossRef]
16. Kilin, C.E.; Van Oerle, R.; Borissoff, J.I.; Gerlofs-Nijland, M.E.; Janssen, N.A.; Cassee, F.R.; Sandström, T.; Renné, T.; Ten Cate, H.; Spronk, H.M.H. Factor XII activation is essential to sustain the procoagulant effects of particulate matter. *J. Thromb. Haemost.* **2011**, *9*, 1359–1367. [CrossRef] [PubMed]
17. Bevan, G.H.; Al-Kindi, S.G.; Brook, R.D.; Munzel, T.; Rajagopalan, S. Ambient air pollution and atherosclerosis: Insights into dose, time, and mechanisms. *Arterioscler. Thromb. Vasc. Biol.* **2021**, *41*, 628–637. [CrossRef] [PubMed]
18. Newby, D.E.; Mannucci, P.M.; Tell, G.S.; Baccarelli, A.A.; Brook, R.D.; Donaldson, K.; Forastiere, F.; Franchini, M.; Franco, O.H.; Graham, I.; et al. Expert position paper on air pollution and cardiovascular disease. *Eur. Heart J.* **2015**, *36*, 83–93. [CrossRef] [PubMed]
19. Rajagopalan, S.; Al-Kindi, S.G.; Brook, R.D. Air pollution and cardiovascular disease: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **2018**, *72*, 2054–2070. [CrossRef] [PubMed]
20. Bustaffa, E.; Mangia, C.; Cori, L.; Bianchi, F.; Cervino, M.; Minichilli, F. Cardiorespiratory diseases in an industrialized area: A retrospective population-based cohort study. *BMC Public Health* **2023**, *23*, 2031. [CrossRef] [PubMed]
21. Bustaffa, E.; Curzio, O.; Donzelli, G.; Gorini, F.; Linzalone, N.; Redini, M.; Bianchi, F.; Minichilli, F. Risk Associations between vehicular traffic noise exposure and Cardiovascular Diseases: A residential Retrospective Cohort Study. *Int. J. Environ. Res. Public Health* **2022**, *19*, 10034. [CrossRef] [PubMed]
22. Stafoggia, M.; Cattani, G.; Ancona, C.; Ranzi, A. Exposure assessment of air pollution in Italy 2016–2019 for future studies on air pollution and COVID-19. *Epidemiol. Prev.* **2020**, *44*, 161–168.
23. Biggeri, A.; Stoppa, G.; Catelan, D. *p*-value and the probability of direction of effect. *Epidemiol. Prev.* **2022**, *46*, 204–210.
24. Wasserstein, R.L.; Schirm, A.L.; Lazar, N.A. Moving to a World Beyond "$p < 0.05$". *Am. Stat.* **2019**, *73*, 1–19.
25. Chen, J.; Hoek, G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. *Environ. Int.* **2020**, *143*, 105974. [CrossRef]
26. Bhatnagar, A. Cardiovascular Effects of Particulate Air Pollution. *Annu. Rev. Med.* **2022**, *73*, 393–406. [CrossRef]
27. Lederer, A.M.; Fredriksen, P.M.; Nkeh-Chungag, B.N.; Everson, F.; Strijdom, H.; De Boever, P.; Goswami, N. Cardiovascular effects of air pollution: Current evidence from animal and human studies. *Am. J. Physiol. Heart Circ. Physiol.* **2021**, *320*, H1417–H1439. [CrossRef] [PubMed]
28. Stafoggia, M.; Oftedal, B.; Chen, J.; Rodopoulou, S.; Renzi, M.; Atkinson, R.W.; Bauwelinck, M.; Klompmaker, J.O.; Mehta, A.; Vienneau, D. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: Results from seven large European cohorts within the ELAPSE project. *Lancet Plan Health* **2022**, *6*, e9–e18. [CrossRef] [PubMed]
29. You, X.; Cao, X.; Guo, Y.; Wang, D.; Qiu, W.; Zhou, C.; Zhou, M.; Chen, W.; Zhang, X. Associations between short-term $PM_{2.5}$ exposure and daily hospital admissions for circulatory system diseases in Ganzhou, China: A time series study. *Front. Public Health* **2023**, *11*, 1134516. [CrossRef] [PubMed]
30. Zou, L.; Zong, Q.; Fu, W.; Zhang, Z.; Xu, H.; Yan, S.; Mao, J.; Zhang, Y.; Cao, S.; Lv, C. Long-Term Exposure to Ambient Air Pollution and Myocardial Infarction: A Systematic Review and Meta-Analysis. *Front. Med.* **2021**, *8*, 616355. [CrossRef]
31. Liang, X.; Liang, L.; Fan, Y. Two-sample mendelian randomization analysis investigates ambient fine particulate matter's impact on cardiovascular disease development. *Sci. Rep.* **2023**, *13*, 20129.
32. Henning, R.J. Particulate Matter Air Pollution is a Significant Risk Factor for Cardiovascular Disease. *Curr. Probl. Cardiol.* **2024**, *49 Pt B*, 102094. [CrossRef]
33. Ancona, C.; Badaloni, C.; Mataloni, F.; Bolignano, A.; Bucci, S.; Cesaroni, G.; Sozzi, R.; Davoli, M.; Forastiere, F. Mortality and morbidity in a population exposed to multiple sources of air pollution: A retrospective cohort study using air dispersion models. *Environ. Res.* **2015**, *137*, 467–474. [CrossRef]

34. Cordioli, M.; Ranzi, A.; De Leo, G.A.; Lauriola, P. A review of exposure assessment methods in epidemiological studies on incinerators. *J. Environ. Public Health* **2013**, *2013*, 129470. [CrossRef]
35. Ranzi, A.; Fano, V.; Erspamer, L.; Lauriola, P.; Perucci, C.A.; Forastiere, F. Mortality and morbidity among people living close to incinerators: A cohort study based on dispersion modeling for exposure assessment. *Environ. Health* **2011**, *10*, 22. [CrossRef]