Article

A Case-Crossover Study to Investigate the Effects of Atmospheric Particulate Matter Concentrations, Season, and Air Temperature on Accident and Emergency Presentations for Cardiovascular Events in Northern Italy

Paolo Contiero [1,*] , Roberto Boffi [2], Giovanna Tagliabue [3], Alessandra Scaburri [1], Andrea Tittarelli [3] , Martina Bertoldi [1], Alessandro Borgini [1,2,3,4], Immacolata Favia [1], Ario Alberto Ruprecht [2,3,4], Alfonso Maiorino [5], Antonio Voza [6], Marta Ripoll Pons [6], Alessandro Cau [1], Cinzia DeMarco [7], Flavio Allegri [2], Claudio Tresoldi [8] and Michele Ciccarelli [5]

[1] Environmental Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, 20133 Milan, Italy; alessandra.scaburri@istitutotumori.mi.it (A.S.); martina.bertoldi@istitutotumori.mi.it (M.B.); alessandro.borgini@istitutotumori.mi.it (A.B.); immacolata.favia@istitutotumori.mi.it (I.F.); alessandro.cau@istitutotumori.mi.it (A.C.)

[2] Respiratory Disease Unit, Fondazione IRCCS Istituto Nazionale Tumori, 20133 Milan, Italy; roberto.boffi@istitutotumori.mi.it (R.B.); aaruprecht@gmail.com (A.A.R.); flavio.allegri@istitutotumori.mi.it (F.A.)

[3] Cancer Registry Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, 20133 Milan, Italy; giovanna.tagliabue@istitutotumori.mi.it (G.T.); andrea.tittarelli@istitutotumori.mi.it (A.T.)

[4] International Society of Doctors for the Environment (ISDE), 52100 Arezzo, Italy

[5] Pneumology Department, Humanitas Research Hospital, 20089 Rozzano, Italy; alfonso.maiorino@humanitas.it (A.M.); michele.ciccarelli@humanitas.it (M.C.)

[6] Emergency Department, Humanitas Research Hospital, 20089 Rozzano, Italy; antonio.voza@humanitas.it (A.V.); marta.ripoll_pons@humanitas.it (M.R.P.)

[7] Biomarkers Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, 20133 Milan, Italy; cinzia.demarco@istitutotumori.mi.it

[8] G. A. Maccacaro Unit of Medical Statistics, Biometry, and Epidemiology, Department of Clinical Sciences and Community Health, University of Milan, 20133 Milan, Italy; claudio.tresoldi@unimi.it

* Correspondence: paolo.contiero@istitutotumori.mi.it; Tel.: +39-02-2390-3538

check for updates

Abstract: Atmospheric particulate matter (PM) has multiple adverse effects on human health, high temperatures are also associated with adverse health outcomes, and the frequency of cardiovascular events (CVEs) varies with season. We investigated a hypothesized increase in PM-related accident and emergency (A&E) presentations for CVE with high temperature, warm season, days of high influenza incidence, and in people with a cancer diagnosis, using a time-stratified case-crossover study design. Outcomes were associations of A&E presentation for CVE with atmospheric PM ≤ 10 μm (PM$_{10}$), season, and air temperature. PM$_{10}$ levels in the municipality of residence (exposure variable) were estimated by modeling data from local monitoring stations. Conditional logistic regression models estimated odds ratios (OR) with 95% confidence intervals (CI) for presentations in relation to supposed influencers, adjusting for confounders. Study participants were all who presented at the A&E of a large hospital near Milan, Italy, for a CVE (ICD-9: 390–459) from 1st January 2014 to 31st December 2015. There were 1349 A&E presentations for CVE in 2014–2015 and 5390 control days. Risk of A&E presentation was significantly increased on hot days with OR 1.34 (95%CI 1.05–1.71) per 10 μg/m^3 PM$_{10}$ increment (as mean PM$_{10}$ on day of presentation, and 1 and 2 days before (lags 0–2)), and (for lag 0) in autumn (OR 1.23, 95%CI 1.09–1.37) and winter (OR 1.18, 95%CI 1.01–1.38). Risks were also significantly increased when PM$_{10}$ was on lag 1, in people with a cancer diagnosis in the

spring and summer months (1.88, 95%CI 1.05–3.37), and on days (lags 0–2) of high influenza incidence (OR 2.34, 95%CI 1.01–5.43). PM_{10} levels exceeded the 50 $\mu g/m^3$ "safe" threshold recommended by the WHO and Italian legislation for only 3.8% of days during the warm periods of 2014–2015. Greater risk of A&E presentation for CVE in periods of high PM_{10} and high temperature suggests that "safe" thresholds for PM_{10} should be temperature-dependent and that the adverse effects of PM_{10} will increase as temperatures increase due to climate change.

1. Introduction

Air pollution is a major public health problem. The Global Burden of Diseases, Injuries, and Risk Factors Study [1] identified fine ($\leq$ 2.5 μm) atmospheric particulate matter ($PM_{2.5}$) as responsible for 4.2 million deaths worldwide in 2015. Both PM $\leq$ 10 μm (PM_{10}) and $PM_{2.5}$ are known to have multiple adverse effects on human health [2,3] and are classified by the WHO and International Agency for Research on Cancer (IARC) as group 1 carcinogens (carcinogenic to humans) [4]. PM is emitted/formed by natural and anthropogenic processes. In industrial and urban areas, PM is mainly anthropogenic [5].

In 2015, there were an estimated 420 million cases of cardiovascular disease (CVD) worldwide, and around 18 million deaths [6]. In Italy, the age-standardized (World Population, 2012) death rate for both sexes together for cardiovascular diseases is 110.1 per 100,000 person-years, with 239,514 deaths in 2015 [7]. Extensive epidemiological and toxicological data demonstrate that particulate air pollution is associated with the development of CVD [8]. Short-term exposure can trigger acute events, while long-term exposure increases the risk of a cardiovascular event (CVE) and can reduce life expectancy [8]. A 2018 meta-analysis found positive associations between PM_{10} exposure and overall, cardiovascular and respiratory hospital admissions and mortality [9].

Associations between air temperature and CVEs and mortality have also been documented [10]. High air temperature has been associated with the worsened impact of PM_{10} on CVD outcomes including mortality [11–13]. A 2017 review [14], noted that CVD-related hospitalizations and mortality were linked to cold snaps in winter, heat waves in summer, and atmospheric pollution, but that the effect of season was complex.

CVEs can be investigated by accessing health databases such as hospital admissions/discharges. Emergency room or accident and emergency (A&E) databases are of particular interest however because they archive presentations for a broader range of CVEs than hospital discharges.

To our knowledge, no studies have investigated the effects of air temperature and season on the relation between PM_{10} and A&E presentations for CVEs. We hypothesized an increase in PM-related A&E presentations for CVE with high temperature, warm season, and on days of high influenza incidence. We also investigated a supposed interaction between PM_{10} and difference in temperature between the day of A&E presentation (or control day) and the day before, hypothesizing that a rapid change in temperature may have a more marked effect on the cardiovascular system than temperature alone. It is also likely that people who are frail—those with influenza and those with a previous cancer diagnosis—are susceptible to the combination of PM_{10} and temperature. We used a case-crossover approach to address these issues, investigating presentations for CVEs at the A&E unit of Humanitas Hospital, Rozzano, near Milan, in the plain of the river Po. We used PM_{10} measurements instead of $PM_{2.5}$ because, at the start of the study, they were the only measurements available for the study period.

The plain of the Po is a densely-populated (355/km^2) area of 46,000 square kilometers, enclosed by mountains to the north, west, and south. The mountains inhibit air circulation, and extended periods of air stasis contribute to some of the highest levels of air pollution in the world [15,16]. In Emilia Romagna—an administrative Region within the plain of the Po—the annual average concentrations of

PM_{10} and $PM_{2.5}$ exceeded the WHO limits of 20 and 10 μg/m^3, respectively, and were estimated as responsible for 4.4 and 2.8 deaths per 100,000/year [17].

The Mediterranean region, within which the Po Valley is situated, was considered highly vulnerable to climate change in the 5th (2014) Assessment Report of the Intergovernmental Panel on Climate Change [18] and temperatures in the region are projected to increase in coming years [19].

2. Materials and Methods

2.1. Participants

A&E presentations from 1st January 2014 to 31st December 2015 were accessed from the Humanitas A&E database. Date of presentation, date of birth, sex, diagnosis, municipality of residence, and patient social security number were extracted. The study design was approved by the ethical committee of the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, on 28 November 2018. Only descriptive diagnoses were available—of which there could be several (those associated with the presentation and those for concomitant diseases, including cancer). From the descriptive diagnoses, presentations with a CVE were identified by project staff and transformed into ICD-9 codes (390–459). Presentations were linked, via social security number, with the Region of Lombardy Social Security List to ascertain vital status, and, where pertinent, date of death. Extracted data were managed in a study database with safeguards in place to prevent unauthorized access and respect patient privacy. The A&E presentations selected for the study had a CVE and a municipality of residence within 20 km of Humanitas hospital. In all, participants from 109 neighboring municipalities contributed to the study; the municipalities varied in size from a few hundred (population) to the population of Milan of about 1,340,000. The 20 km cut-off was adopted as it is known that residences distant from the hospital are more likely to be incorrect so that misclassification of exposure is more likely.

2.2. Exposure Assessment

The Lombardy Environmental Protection Agency (ARPA) measures PM_{10} at a series of monitoring stations in the Region of Lombardy. Using a model developed in house, ARPA uses monitoring station data to produce estimates of mean daily PM_{10} for each municipality within the Region [20], taking account of emissions from local pollution sources, daily meteorological data, and orography. The PM_{10} exposure of each participant was considered to be that of their municipality of residence.

The air temperature and humidity to be assigned (to each participant) on days of presentation and non-presentation were obtained from the ARPA monitoring station nearest the municipality of residence [21]. Mean apparent temperature in degrees Celsius was assigned. Apparent temperature accounts for relative humidity effects and was estimated using the weather metrics procedure of the R statistical package [22].

2.3. Study Design and Statistical Analysis

To determine the risk of A&E presentation for a CVE in relation to mean daily PM_{10}, a bidirectional time-stratified case-crossover design was used. Cases were persons presenting at the A&E for a CVE, controls were the same persons evaluated (for PM_{10}, etc.) on days when they did not present. Control days were matched to case days by day of the week such that control days could be 7, 14, 21, or 28 days before or after the case day. Up to 4 control days per case were used.

PM_{10} exposure for each case and control was defined in 3 ways as follows: PM_{10} on the day of presentation (lag 0), PM_{10} on the day before (lag 1), PM_{10} two days before (lag 2).

Conditional logistic regression modeling was used to estimate odd ratios (ORs) for A&E presentation for a CVE, compared to non-presentation, in relation to PM_{10}. A basic model assessed the effect of PM_{10} on CVE presentations considering various confounders. Three additional models were run with interactions for season, temperature and influenza incidence added successively,

thus examining the effect on presentations of PM_{10} and season; PM_{10} season and temperature; and PM_{10} season temperature and influenza incidence.

The basic logistic model was:

$$\text{logit } \{Y = 1|X\} = \beta_0 + \beta_1 \, PM_{10} + \beta_2 \, \text{flu} + \beta_3 \, \text{holiday} + \beta_4 \, \text{pop\_dec} + \beta_5 \, \text{app\_temp}$$
$$+ \beta_6 \, \text{ozone} + \beta_7 \, PM_{10} * \text{sex} + \beta_8 \, PM_{10} * \text{age}$$

where Y is the binary response variable for A&E presentation that takes values of 1 or 0, the Xs are covariates and the βs regression coefficients. PM_{10} was considered as a linear variable, and ORs were estimated for 10 μg/m^3 increments of PM_{10}. Dummy variables for influenza incidence (flu), day of holiday (holiday), and population decrease due to summer holidays (pop_dec) were added. Days of influenza incidence were identified by consulting Influnet, the Italian national surveillance system [23,24] and categorized into four levels, from no influenza days to high influenza days.

A term for apparent temperature (app_temp) was also included, categorized as: high (>80th percentile), medium (20th–80th percentiles), and low (<20th percentile). A linear term for ozone levels (obtained from ARPA monitoring stations) and interaction terms of PM_{10}, with sex and age were also added because of their supposed roles as confounders or modifiers.

Separate basic models were run for PM_{10} at lags 0, 1, 2 and 0–2 (the latter as average PM_{10} at lags 0, 1 and 2). The linearity of the relationship between A&E presentation and PM_{10} was assessed by adding a restricted cubic spline term to model PM_{10} and evaluating the difference between models with and without the restricted cubic spline, using the likelihood ratio test [25].

A product term, PM_{10}*season, was added to the basic model to test whether season modified the association between PM_{10} and CVE presentation and the likelihood ratio test used to compare models with and without the PM_{10}*season interaction term. Seasons were defined as 21 March–20 June (spring), 21 June–22 September (summer), 23 September–20 December (autumn), and 21 December–20 March (winter). Separate models were run at lags 0, 1, 2 and 0–2.

A product term, PM_{10}*apparent_temperature, was added to the basic plus season model to test whether apparent temperature modified the association between PM_{10} and CVE presentation, the likelihood ratio test was used to compare models with and without the PM_{10} and apparent temperature interaction term. Separate models were run at lags 0, 1, 2, and 0–2.

We also hypothesized the interaction between PM_{10} and the difference in temperature between the day of A&E presentation (or control day) and the day before. This was tested by computing the difference between the temperature of the day of A&E presentation (or control day) and the day before and inserting into the model a term representing this difference in temperature (diff-temperature) and a product term (PM_{10}*diff-temperature) representing the interaction of diff-temperature with PM_{10}. We modeled diff-temperature using the lsp function of R-language that fits a linear spline, with a knot placed at −1 °C, i.e., a bilinear function that decreases linearly to −1 °C and increases linearly from −1 °C.

Finally, the product term PM_{10}*influenza was added to the basic plus season plus apparent temperature model, and the likelihood ratio test used to test for an interaction between PM_{10} and influenza in relation to the A&E presentation.

Separate models (basic and seasonal models) that included only patients (A&E presentations) with a diagnosis of cancer were run. Because of the small number of cancer patients, only two seasons were considered: cold season (autumn plus winter) and warm season (spring plus summer).

The analyses were performed using the R statistical package [22], version 3.6.1. Differences were considered significant for $p < 0.05$.

3. Results

A total of 1349 A&E presentations for CVE were identified in the 2014–2015 study period, with 5390 control days were selected for comparison (thus most presentation dates for most participants had four control dates). Table 1 shows the distributions of presentations by age and sex, together with

the distributions of PM_{10} and apparent temperature, all by season. A total of 168 presenters had been previously diagnosed with cancer (as determined from the A&E database).

Tables 2–5 show odds ratios produced by the models for lag 0, lag 1, lag 2, and lags 0–2, respectively. The second column of each of these tables shows results for the basic models: PM_{10} was never significant in any model or any lag. The third column of these tables shows results when the PM_{10}*season interaction was added to the basic model. With spring as reference, ORs in autumn for A&E presentations for CVEs were 1.21 (95%CI 1.09–1.35) per 10 $\mu g/m^3$ increment in PM_{10} for lag 0, 1.14 (95%CI 1.02–1.27) for lag 1, 1.05 (95%CI 0.94–1.17) for lag 2, and 1.17 (95%CI 1.04–1.33) for lags 0–2. ORs for A&E presentations in winter (reference spring) were 1.13 (95%CI 1.02–1.26) for lag 0, 1.15 (95%CI 1.04–1.28) for lag 1, 1.06 (95%CI 0.96–1.18) for lag 2, and 1.16 (95%CI 1.03–1.31) for lags 0–2. ORs for summer were never significant for any lag.

Table 1. Patient characteristics, atmospheric particulate matter ≤10 μm (PM_{10}), apparent atmospheric temperature and incidence of influenza by season.

	Season			
	Spring	**Summer**	**Autumn**	**Winter**
Distribution of A&E presentations (%)	28.8	22.7	19.8	28.7
Age distribution (years)				
Median (IQR)	78 (67–84)	76 (63–83)	78 (68–85)	80 (71–86)
Sex (%)				
Male	56.6	58.4	58.5	54.3
Female	44.4	41.6	41.5	45.7
PM_{10} ($\mu g/m^3$)				
Median (IQR)	24 (17–34)	23 (17–28)	38 (29–54)	47 (31–59)
Apparent temperature (°C)				
Median (IQR)	17 (14–20)	22 (20–25)	13 (10–16)	6 (4–8)
Influenza incidence (as % of days)				
Absent	95	100	96	13
Low	5	0	4	39
Medium	0	0	0	43
High	0	0	0	5

Table 2. Odds ratios (OR) with 95% confidence intervals (CI) for accident and emergency (A&E) presentations for cardiovascular events, for lag 0, in relation to 10 μg/m³ PM_{10} increments, according to season, temperature, and influenza incidence.

Model Variables	OR (95%CI)			
	Basic Model (PM_{10})	**PM_{10} + Season Interaction**	**PM_{10} + Season + Temperature Interaction**	**PM_{10} + Season + Temperature + Influenza Interaction**
PM_{10}	0.96 (0.86–1.07)	0.83 (0.72–0.96)	0.91 (0.66–1.25)	0.92 (0.67–1.28)
PM_{10} and season interaction:				
PM_{10} and spring	N/A	1 (ref)	1 (ref)	1 (ref)
PM_{10} and summer	N/A	1.11 (0.93–1.33)	1.06 (0.87–1.28)	1.05 (0.86–1.27)
PM_{10} and autumn	N/A	1.21 (1.09–1.35)	1.23 (1.10–1.38)	1.22 (1.09–1.37)
PM_{10} and winter	N/A	1.13 (1.02–1.26)	1.15 (1.02–1.29)	1.20 (1.02–1.40)
PM_{10} and temperature interaction:				
PM_{10} and mod. temp.	N/A	N/A	1 (ref)	1 (ref)
PM_{10} and cold temp.	N/A	N/A	1.01 (0.92–1.10)	0.99 (0.90–1.10)
PM_{10} and hot temp.	N/A	N/A	1.18 (0.97–1.45)	1.19 (0.97–1.46)
PM_{10} and flu incidence interaction:				
PM_{10} and no flu	N/A	N/A	N/A	1 (ref)
PM_{10} and low flu	N/A	N/A	N/A	0.91 (0.79–1.06)
PM_{10} and medium flu	N/A	N/A	N/A	0.97 (0.82–1.14)
PM_{10} and high flu	N/A	N/A	N/A	1.15 (0.73–1.81)

N/A = not applicable.

Table 3. Odds ratios (OR) with 95% confidence intervals (CI) for A&E presentations for cardiovascular events, for lag 1, in relation to 10 μg/m^3 PM$_{10}$ increments, according to season, temperature and influenza incidence.

Model Variables	OR (95%CI)			
	Basic Model (PM$_{10}$)	PM$_{10}$ + Season Interaction	PM$_{10}$ + Season + Temperature Interaction	PM$_{10}$ + Season + Temperature + Influenza Interaction
PM$_{10}$	1.03 (0.92–1.16)	0.92 (0.79–1.06)	0.99 (0.73–1.34)	0.99 (0.73–1.34)
PM$_{10}$ and season interaction:				
PM$_{10}$ and spring	N/A	1 (ref)	1 (ref)	1 (ref)
PM$_{10}$ and summer	N/A	1.18 (0.99–1.41)	1.07 (0.88–1.31)	1.07 (0.88–1.31)
PM$_{10}$ and autumn	N/A	1.14 (1.02–1.27)	1.16 (1.04–1.30)	1.16 (1.04–1.30)
PM$_{10}$ and winter	N/A	1.15 (1.04–1.28)	1.17 (1.04–1.32)	1.16 (1.00–1.36)
PM$_{10}$ and temperature interaction:				
PM$_{10}$ and mod. temp.	N/A	N/A	1 (ref)	1 (ref)
PM$_{10}$ and cold temp.	N/A	N/A	1.01 (0.93–1.10)	0.99 (0.90–1.09)
PM$_{10}$ and hot temp.	N/A	N/A	1.28 (1.04–1.57)	1.28 (1.04–1.57)
PM$_{10}$ and flu incidence interaction:				
PM10 and no flu	N/A	N/A	N/A	1 (ref)
PM10 and low flu	N/A	N/A	N/A	0.99 (0.86–1.14)
PM10 and medium flu	N/A	N/A	N/A	1.03 (0.88–1.20)
PM10 and high flu	N/A	N/A	N/A	1.34 (0.80–2.25)

N/A = not applicable.

Table 4. Odds ratios (OR) with 95% confidence intervals (CI) for A&E presentations for cardiovascular events, for lag 2, in relation to 10 μg/m^3 PM$_{10}$ increments, according to season, temperature and influenza incidence.

Model Variables	OR (95%CI)			
	Basic Model (PM$_{10}$)	PM$_{10}$ + Season Interaction	PM$_{10}$ + Season + Temperature Interaction	PM$_{10}$ + Season + Temperature + Influenza Interaction
PM$_{10}$	1.09 (0.97–1.23)	1.05 (0.91–1.21)	1.14 (0.87–1.51)	1.12 (0.85-1.47)
PM$_{10}$ and season interaction:				
PM$_{10}$ and spring	N/A	1 (ref)	1 (ref)	1 (ref)
PM10 and summer	N/A	1.02 (0.86–1.21)	0.94 (0.77–1.13)	0.96 (0.79–1.21)
PM10 and autumn	N/A	1.05 (0.94–1.17)	1.07 (0.95–1.19)	1.08 (0.97–1.21)
PM10 and winter	N/A	1.06 (0.96–1.18)	1.09 (0.97–1.23)	1.02 (0.88–1.19)
PM$_{10}$ and temperature interaction:				
PM10 and mod. temp.	N/A	N/A	1 (ref)	1 (ref)
PM10 and cold temp.	N/A	N/A	0.98 (0.90–1.07)	0.97 (0.88–1.07)
PM10 and hot temp.	N/A	N/A	1.23 (1.00–1.51)	1.25 (1.01–1.55)
PM$_{10}$ and flu incidence interaction:				
PM10 and no flu	N/A	N/A	N/A	1 (ref)
PM10 and low flu	N/A	N/A	N/A	1.11 (0.96–1.27)
PM10 and medium flu	N/A	N/A	N/A	1.09 (0.93–1.27)
PM10 and high flu	N/A	N/A	N/A	1.35 (0.84–2.17)

N/A = not applicable.

The fourth column of Tables 2–5 shows results after adding the interaction between PM$_{10}$ and apparent temperature to the model of the third column. In this model ORs per season changed slightly compared to the previous model, but significance never changed. When it was hot (reference moderate temperature), ORs of presentation were 1.18 (95%CI 0.97–1.45) per 10 μg/m^3 PM$_{10}$ increment for lag 0, 1.28 (95%CI 1.04–1.57) for lag 1, 1.23 (95%CI 1.00–1.51) for lag 2, and 1.34 (95%CI 1.04–1.71) for lags 0–2. ORs were never significant when it was cold. Introduction of the terms diff-temperature and PM$_{10}$* diff-temperature never had a significant effect on any model for any lag.

The fifth column of Table 2 shows results after adding an interaction term for PM$_{10}$ and influenza to the model of the fourth column. In this model, ORs for season changed slightly compared to the previous model but none of the significant ORs became non-significant and none of the non-significant ORs became significant. On days when influenza notifications were high, (reference days with no influenza) ORs per 10 μg/m^3 PM$_{10}$ increment were 1.15 (95%CI 0.73–1.81) for lag 0, 1.34 (95%CI 0.80–2.25) for lag 1, 1.35 (95%CI 0.84–2.17) for lag 2, and 2.34 (95%CI 1.01–5.42) for lags 0–2. After inserting the interaction term between PM$_{10}$ and influenza incidence, the interaction between PM$_{10}$ and winter became non-significant for lags 0–2.

Table 5. Odds ratios (OR) with 95% confidence intervals (CI) for A&E presentations for cardiovascular events, for lag 0–2, in relation to 10 μg/m^3 PM$_{10}$ increments, according to season, temperature and influenza incidence.

Model Variables	OR (95%CI)			
	Basic Model (PM$_{10}$)	PM$_{10}$ + Season Interaction	PM$_{10}$ + Season + Temperature Interaction	PM$_{10}$ + Season + Temperature + Influenza Interaction
PM$_{10}$	1.03 (0.90.1.18)	0.90 (0.76–1.06)	0.99 (0.73–1.03)	0.99 (0.70–1.40)
PM$_{10}$ and season interaction:				
PM$_{10}$ and spring	N/A	1 (ref)	1 (ref)	1 (ref)
PM10 and summer	N/A	1.14 (0.93–1.41)	1.03 (0.82–1.29)	1.03 (0.82–1.29)
PM10 and autumn	N/A	1.17 (1.04–1.33)	1.20 (1.06–1.37)	1.21 (1.06–1.37)
PM10 and winter	N/A	1.16 (1.03–1.31)	1.19 (1.03–1.36)	1.17 (0.98–1.39)
PM$_{10}$ and temperature interaction:				
PM10 and mod. temp.	N/A	N/A	1 (ref)	1 (ref)
PM10 and cold temp.	N/A	N/A	1.00 (0.91–1.11)	0.98 (0.88–1.10)
PM10 and hot temp.	N/A	N/A	1.34 (1.04–1.71)	1.34 (1.04–1.71)
PM$_{10}$ and flu incidence interaction:				
PM10 and no flu	N/A	N/A	N/A	1 (ref)
PM10 and low flu	N/A	N/A	N/A	1.01 (0.85–1.19)
PM10 and medium flu	N/A	N/A	N/A	1.04 (0.87–1.26)
PM10 and high flu	N/A	N/A	N/A	2.34 (1.01–5.42)

N/A = not applicable.

The use of restricted cubic spline PM$_{10}$ modeling and the likelihood ratio test provided no reason to reject the null hypothesis of a linear association between A&E presentation and PM$_{10}$ levels. Similar testing provided no reason to reject the null hypothesis of a linear association between A&E presentation and PM$_{10}$ levels on days of high influenza incidence.

For presenters with a previous cancer diagnosis, the basic model provided ORs of 1.03 (95%CI 0.81–1.32) for lag 0, 1.08 (95%CI 0.81–1.43) for lag 1, 1.21 (95%CI 0.90–1.63) for lag 2, and 1.13 (95%CI 0.83–1.54) for lags 0–2. For presenters with a previous cancer diagnosis, ORs for warm season presentation were 1.64 (95%CI 0.89–3.01) for lag 0, 1.88 (95%CI 1.05–3.37) for lag 1, 1.32 (95%CI 0.80–2.19) for lag 2, and 1.13 (95%CI 0.83–1.54) for lags 0–2. For presenters with a previous cancer diagnosis, ORs for cold season presentation were 0.92 (95%CI 0.69–1.25) for lag 0, 0.84 (95%CI 0.57–1.23) for lag 1, 1.15 (95%CI 0.80–1.67) for lag 2, and 0.93 (95%CI 0.62–1.40) for lags 0–2 (data not presented in tables). In none of the models was there a significant interaction between PM$_{10}$ and sex or age.

ARPA modeling estimated that PM$_{10}$ levels exceeded the 50 μg/m^3 "safe" threshold recommended by the WHO [26] and Italian legislation for only 3.8% of days (in some municipalities) during the warm periods of 2014–2015.

4. Discussion

We have found that increasing atmospheric PM$_{10}$ (continuous variable) was associated with greater risk of A&E presentation for a CVE during autumn and winter than spring, and also when temperatures were high (reference moderate temperature) irrespective of the season. PM$_{10}$ was not associated with A&E presentation for a CVE in summer or on cold days. Thus our analyses distinguished the effect of season from the effect of temperature. We also investigated whether a rapid change in temperature from the day before the day of presentation interacted with PM$_{10}$, but found no such interaction. We also found that the risk of presentation increased significantly with increasing PM$_{10}$ during days of high influenza incidence, which occurred exclusively in the cold winter months. Furthermore, for persons with a previous cancer diagnosis—who are to be considered frail according to standard definitions [27]—the risk of A&E presentation for CVE increased with increasing PM$_{10}$ during spring plus summer, but not during autumn plus winter.

To our knowledge, no previous study has reported the risk of A&E presentation for CVEs in relation to interactions between PM$_{10}$ and season and interactions between PM$_{10}$ and temperature at the same time. However, this important novelty renders comparisons with the findings of other studies difficult. In fact, few previous studies have investigated the influence of temperature on PM–related

A&E presentations for CVEs. A 2017 study conducted in Beijing [12] found that CVEs associated with 10 mg/m^3 increments of PM_{10} increased by 0.14% when air temperature was ≥28 °C. A study conducted in Brisbane [11] found that high PM_{10} was associated with more adverse health effects, including cardiovascular emergency visits, on warm days than cold days, for lags up to 2 days. Our findings are fully consistent with these findings. They are also consistent with the findings of a 2018 study on a European urban area [28] that investigated total natural and cardiovascular mortality in relation to air temperature and particle number concentration, $PM_{2.5}$, PM_{10}, and ozone. This study found that on high air temperature days (>75th percentile), a 10 μg/m^3 increase in PM_{10} was associated with a 1.61% increase in cardiovascular mortality, which was significantly higher than on low temperature (<25th percentile) days. Furthermore, on high air pollution days (>50th percentile), both hot- and cold-related mortality risks increased.

The modulation of the effect of PM_{10} on CVE admissions with season and temperature could be due, at least in part, to seasonal variation in the chemical composition of PM_{10}. Thus, a study performed in the Po Valley (site of our study) found that PM_{10} levels of ammonium, elemental carbon and organic carbon were higher during winter, while levels of aluminum, silicon, magnesium, and calcium were higher in summer [29]. Furthermore, levels of chromium and mercury in PM_{10} at a roadside site in Beijing were found to be higher in summer than winter [30].

A 2013 study [31] exposed human macrophage-like cells to summer and winter PM_{10} from the Milan atmosphere and measured the release of the proinflammatory interleukin 1β (IL1β). The study found that IL1β release increased in a dose-dependent manner on exposure to summer PM_{10} but not to winter PM_{10}. The authors concluded that Milan summer PM_{10} contains substances that promote the activation of membrane Toll-like receptors and the NLPR3 inflammasome, to stimulate IL1β release. We found no risk increase in summer but did find a risk increase associated with high temperature, which could, we suggest, be related to chemical components present in summer PM_{10}, that might be particularly high at times of high temperature.

The higher risk of CVE presentation with high PM_{10} in winter and autumn also suggests that behavioral changes determined by seasonal factors might be playing a role. The review of Steward et al. [12] noted that seasonal behavioral changes in diet and physical activity influenced CVE risk which could be mediated by an effect on PM-induced inflammation.

High temperatures exacerbate the toxic effects of many environmental toxins by various mechanisms [13]. PM_{10}, and its toxic components, enter the body via the skin and respiratory surfaces. When air temperature is high peripheral vasodilatation increases, resulting in higher skin temperature. Respiration is also moderately increased to increase heat dissipation by evaporation. These two temperature responses enhance the entry of PM into the body.

Toxin inhalation may result in pulmonary inflammation and oxidative stress, leading to the release of proinflammatory cytokines giving rise to systemic inflammation. People typically spend more time outdoors and open their windows more during the summer months, thereby increasing their exposure to PM and other atmospheric pollutants [32].

It is noteworthy that in our study, A&E presentations for CVEs increased significantly with increasing PM_{10} during days of high influenza incidence. Influenza has been implicated as a contributory factor to acute myocardial infarction [33,34]. The increased levels of inflammatory cytokines, in particular, IL18 [35], that occur as a response to viral influenza may increase the risk myocardial infarction. Increased inflammatory cytokine levels due to high PM_{10} may further increase the risk of infarction.

People with a previous cancer diagnosis are frail [27] and known to be at increased risk of hospital admission for several causes not directly related to cancer [32]. Frailty is a state of heightened vulnerability to stressors [27]. In our case stressors would include cancer, treatment-induced cardiotoxicity, PM and air temperature [36]. In fact, CVD is the second leading cause of morbidity and mortality in cancer survivors mainly because of treatment-induced cardiotoxicity [37]. PM_{10} also influences cardiovascular mortality [7,28] and cancer prognosis [38]. We found that ORs for A&E

Int. J. Environ. Res. Public Health **2019**, 16, 4627

9 of 12

presentations for CVE were higher for cancer patients than other categories, highlighting cancer patient susceptibility to high PM_{10}.

We assessed risks of presentation in relation to lag between high PM_{10} and day of presentation. In winter and autumn, the effect of high PM_{10} on the risk of presentation was numerically greatest on the day of exposure (lag 0) to declined thereafter. By contrast, the effects of hot day and high flu incidence on PM_{10}-related presentation seemed to be cumulative since ORs were greatest for lag 0–2. This variation in risk of PM_{10}-related CVE presentation with lag suggests that various mechanisms are involved.

Our study has limitations. First, the study population is fairly small. Second, each person's PM_{10} exposure was considered to be the mean daily exposure estimated for the entire municipality of residence, since only municipality-level PM_{10} estimates were available. However, misclassifications of exposure due to municipality-level estimation are likely to weaken associations overall rather than introduce bias. A further study limitation is that we only used PM_{10} and not other PM fractions such as $PM_{2.5}$.

The case-crossover design is a study strength since confounding due to quasi-periodic fluctuations in pollution levels over a week were controlled for by day-of-the-week matching, and time-invariant confounders like age, sex, and smoking were controlled automatically. The persons presenting at the A&E with CVEs were unselected so our sample is likely to be representative of the general population. Furthermore the PM_{10} measurement method and the diagnosis assignments (ICD 9 codes) were standard. Thus we expect the generalizability of our findings to be good.

5. Conclusions

This study provides evidence that increasing temperature exacerbates at least one of the documented adverse effects of atmospheric PM_{10} on human health. However European and Italian legislation indicating "safe" thresholds for atmospheric PM_{10} levels does not take account of this exacerbating effect. Our data suggest—at the very least—that these thresholds should be lower during periods of high air temperature. Measures to ensure that thresholds are not exceeded are also required. As global temperatures increase [15,16] the adverse health effects of atmospheric PM_{10} will probably worsen, irrespective of whether atmospheric PM_{10} levels are reduced. It would also be advisable to institute systems to warn residents of high air pollution days so that vulnerable people, e.g., immunocompromised and elderly people could stay at home. Finally, we suggest a study to sample PM and analyze their components to further investigate the link between PM and A&E presentations for CVE.

Abbreviations

Lag 0	same day as A&E presentation
Lag 1	day before A&E presentation
Lag 2	two days before A&E presentation

Lag 0–2	mean of PM_{10} levels from lag 0 to lag 2
PM	atmospheric particulate matter
CVE	cardiovascular event
A&E	accident and emergency
CI	confidence interval
OR	odds ratio
ARPA	Lombardy Environmental Protection Agency

References

1. Cohen, A.J.; Brauer, M.; Burnett, R.; Anderson, H.R.; Frostad, J.; Estep, K.; Balakrishnan, K.; Brunekreef, B.; Dandona, L.; Dandona, R.; et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015. *Lancet* **2017**, *389*, 1907–1918. [CrossRef]

2. Barman, S.C.; Kumar, N.; Singh, R.; Kisku, G.C.; Khan, A.H.; Kidwai, M.M.; Murthy, R.C.; Negi, M.P.; Pandey, P.; Verma, A.K.; et al. Assessment of urban air pollution and it's probable health impact. *J. Environ. Biol.* **2010**, *31*, 913–920. [PubMed]

3. IARC Monographs: Volume 109: Outdoor Air Pollution. Available online: http://monographs.iarc.fr/ENG/Monographs/vol109/mono109.pdf (accessed on 13 September 2019).

4. IARC Scientific Publication. No. 161: Air Pollution and Cancer. Available online: http://www.iarc.fr/en/publications/books/sp161/AirPollutionandCancer161.pdf (accessed on 13 September 2019).

5. Karagulian, F.; Belis, C.A.; Dora, C.F.C.; Prüss-Ustün, A.M.; Bonjour, S.; Adair-Rohani, H.; Amann, M. Contributions to cities' ambient particulate matter (PM): A systematic review of local source contributions at global level. *Atmos. Environ.* **2015**, *120*, 475–483. [CrossRef]

6. Roth, G.A.; Johnson, C.; Abajobir, A.; Abd-Allah, F.; Abera, S.F.; Abyu, G.; Ahmed, M.; Aksut, B.; Alam, T.; Alam, K.; et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J. Am. Coll. Cardiol.* **2017**, *70*, 1–25. [CrossRef]

7. WHO Mortality Database. Available online: http://apps.who.int/healthinfo/statistics/mortality/whodpms/ (accessed on 18 November 2019).

8. Vidale, S.; Campana, C. Ambient air pollution and cardiovascular diseases: From bench to bedside. *Eur. J. Prev. Cardiol.* **2018**, *25*, 818–825. [CrossRef]

9. Requia, W.J.; Adams, M.D.; Arain, A.; Papatheodorou, S.; Koutrakis, P.; Mahmoud, M. Global Association of Air Pollution and Cardiorespiratory Diseases: A Systematic Review, Meta-Analysis, and Investigation of Modifier Variables. *Am. J. Public Health* **2018**, *108*, S123–S130. [CrossRef]

10. Basu, R. High ambient temperature and mortality: A review of epidemiologic studies from 2001 to 2008. *Environ. Health* **2009**, *16*, 8–40. [CrossRef]

11. Ren, C.; Tong, S. Temperature modifies the health effects of particulate matter in Brisbane, Australia. *Int. J. Biometeorol.* **2006**, *51*, 87–96. [CrossRef]

12. Zhang, Y.; Wang, S.; Fan, X.; Ye, X. Temperature modulation of the health effects of particulate matter in Beijing, China. *Environ. Sci. Pollut. Res. Int.* **2018**, *25*, 10857–10866. [CrossRef]

13. Gordon, C.J. Role of environmental stress in the physiological response to chemical toxicants. *Environ. Res.* **2003**, *92*, 1–7. [CrossRef]

14. Stewart, S.; Keates, A.K.; Redfern, A.; McMurray, J.J.V. Seasonal variations in cardiovascular disease. *Nat. Rev. Cardiol.* **2017**, *14*, 654–664. [CrossRef] [PubMed]

15. Raaschou-Nielsen, O.; Andersen, Z.J.; Beelen, R.; Samoli, E.; Stafoggia, M.; Weinmayr, G.; Hoffmann, B.; Fischer, P.; Nieuwenhuijsen, M.J.; Brunekreef, B.; et al. Air pollution and lung cancer incidence in 17 European cohorts: Prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol.* **2013**, *14*, 813–822. [CrossRef]

16. Van Donkelaar, A.; Martin, R.V.; Brauer, M.; Boys, B.L. Use of satellite observations for long-term exposure assessment of global concentrations of fine particulate matter. *Environ. Health Perspect.* **2015**, *123*, 135–143. [CrossRef] [PubMed]

17. Giannini, S.; Baccini, M.; Randi, G.; Bonafè, G.; Lauriola, P.; Ranzi, A. Estimating deaths attributable to airborne particles: Sensitivity of the results to different exposure assessment approaches. *Environ. Health* **2017**, *22*, 13. [CrossRef]
18. AR5 Climate Change 2014: Impacts, Adaptation, and Vulnerability. Available online: https://www.ipcc.ch/site/assets/uploads/2018/02/WGIIAR5-Chap23_FINAL.pdf (accessed on 13 September 2019).
19. IPCC Intergovernmental Panel on Climate Change. Available online: http://www.ipcc.ch/ipccreports/tar/wg1/index.php?idp=49 (accessed on 13 September 2019).
20. A Modelling Tool for PM$_{10}$ Exposure Assessment: An Application Example. Available online: https://www.witpress.com/elibrary/wit-transactions-on-ecology-and-the-environment/116/19648 (accessed on 13 September 2019).
21. ARPA LOMBARDIA. Available online: https://www.arpalombardia.it/siti/arpalombardia/meteo/richiesta-dati-misurati/Pagine/RichiestaDatiMisurati.aspx (accessed on 13 September 2019).
22. R Development Core Team. R: A Language and Environment for Statistical Computing. 2007. Available online: http://www.r-project.org (accessed on 18 November 2019).
23. Rizzo, C.; Bella, A.; Alfonsi, V.; Puzelli, S.; Palmieri, A.P.; Chironna, M.; Pariani, E.; Piatti, A.; Tiberti, D.; Ghisetti, V.; et al. Influenza vaccine effectiveness in Italy: Age, subtype-specific and vaccine type estimates 2014/15 season. *Vaccine* **2016**, *34*, 3102–3108. [CrossRef]
24. InfluNet, Rete Italiana Sorveglianza Influenza. ISS. Available online: https://old.iss.it/site/RMI/influnet/Default.aspx (accessed on 13 September 2019).
25. Harrell, F.E. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*, 2nd ed.; Springer: New York, NY, USA, 2015.
26. WHO. Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide. Available online: http://apps.who.int/iris/bitstream/handle/10665/69477/WHO_SDE_PHE_OEH_06.02_eng.pdf;sequence=1 (accessed on 13 September 2019).
27. Ethun, C.G.; Bilen, M.A.; Jani, A.B.; Maithel, S.K.; Ogan, K.; Master, V.A. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. *CA Cancer J. Clin.* **2017**, *67*, 362–377. [CrossRef]
28. Chen, K.; Wolf, K.; Breitner, S.; Gasparrini, A.; Stafoggia, M.; Samoli, E.; Andersen, Z.J.; Bero-Bedada, G.; Bellander, T.; Hennig, F.; et al. Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas. *Environ. Int.* **2018**, *116*, 186–196. [CrossRef]
29. Perrino, C.; Catrambone, M.; Dalla Torre, S.; Rantica, E.; Sargolini, T.; Canepari, S. Seasonal variations in the chemical composition of particulate matter: A case study in the Po Valley. Part I: Macro-components and mass closure. *Environ. Sci. Pollut. Res. Int.* **2014**, *21*, 3999–4009. [CrossRef]
30. Liu, Y.; Zhang, T.; Liu, Q.; Zhang, R.; Sun, Z.; Zhang, M. Seasonal variation of Physical and Chemical Properties in TSP, PM$_{10}$ and PM$_{2.5}$ at a Roadside Site in Beijing and Their Influence on Atmospheric Visibility. Aerosol and Air. *Qual. Res.* **2014**, *14*, 954–969. [CrossRef]
31. Bengalli, R.; Molteni, E.; Longhin, E.; Refsnes, M.; Camatini, M.; Gualtieri, M. Release of IL-1 β triggered by Milan summer PM$_{10}$: Molecular pathways involved in the cytokine release. *Biomed. Res. Int.* **2013**, *2013*, 158093. [CrossRef]
32. Meng, X.; Ma, Y.; Chen, R.; Zhou, Z.; Zhou, Z.; Chen, B.; Kan, H. Size-fractionated particle number concentrations and daily mortality in a Chinese city. *Environ. Health Perspect.* **2013**, *121*, 1174–1178. [CrossRef] [PubMed]
33. Nguyen, J.L.; Yang, W.; Ito, K.; Matte, T.D.; Shaman, J.; Kinney, P.L. Seasonal Influenza Infections and Cardiovascular Disease Mortality. *JAMA Cardiol.* **2016**, *1*, 274–281. [CrossRef] [PubMed]
34. Kwong, J.C.; Schwartz, K.L.; Campitelli, M.A.; Chung, H.; Crowcroft, N.S.; Karnauchow, T. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *N. Engl. J. Med.* **2018**, *378*, 345–353. [CrossRef] [PubMed]
35. Kaplanski, G. Interleukin-18: Biological properties and role in disease pathogenesis. *Immunol. Rev.* **2018**, *281*, 138–153. [CrossRef] [PubMed]
36. Kimberly, D.A.; Salice, C.J. Understanding interactive effects of climate change and toxicants: Importance of evolutionary processes. *Integr. Environ. Assess. Manag.* **2012**, *8*, 385–386. [CrossRef]

37. Lenneman, C.G.; Sawyer, D.B. Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment. *Circ. Res.* **2016**, *118*, 1008–1020. [CrossRef]
38. Tagliabue, G.; Borgini, A.; Tittarelli, A.; van Donkelaar, A.; Martin, R.V.; Bertoldi, M.; Fabiano, S.; Maghini, A.; Codazzi, T.; Scaburri, A.; et al. Atmospheric fine particulate matter and breast cancer mortality: A population-based cohort study. *BMJ Open* **2016**, *6*, e012T580. [CrossRef]