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# Concentration-response relationships between hourly particulate matter and ischemic events: A case-crossover analysis of effect modification by season and air-mass origin

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## HIGHLIGHTS

- Particle composition and possible toxicity are linked to the origin of an air mass.
- The Israeli population is exposed to a wide range of PM levels from diverse sources.
- Hourly PM and origin of air masses prior to 1855 ischemic events were calculated.
- Supralinear concentration-response curves were found across different PM sources.
- Associations with cardiac events were strongest at low levels of PM during summer.

## GRAPHICAL ABSTRACT


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## ABSTRACT

Most studies linking cardiovascular disease with particulate matter (PM) exposures have focused on total mass concentrations, regardless of their origin. However, the origin of an air mass is inherently linked to particle composition and possible toxicity. We examine how the concentration-response relation between hourly PM exposure and ischemic events is modified by air-mass origin and season. Using telemedicine data, we conducted a case-crossover study of 1855 confirmed ischemic cardiac events in Israel (2005–2013). Based on measurements at three fixed-sites in Tel Aviv and Haifa, ambient PM with diameter < 2.5 μm ($PM_{2.5}$) and 2.5–10 μm ($PM_{10-2.5}$) concentrations during the hours before event onset were compared with matched control periods using conditional logistic regression that allowed for non-linearity. We also examined effect modification of these associations based on the geographical origin of each air mass by season. Independent of the geographical origin of the air mass, we observed concentration-response curves that were supralinear. For example, the overall odds ratios (ORs) of ischemic events for an increase of 10-μg/m$^3$ in the 2-h average of $PM_{10-2.5}$ were 1.08 (95% confidence interval (CI): 1.03–1.14) and 1.00 (0.99–1.01) at the median (17.8 μg/m$^3$) and 95th percentile (82.3 μg/m$^3$) values, respectively. Associations were strongest at low levels of $PM_{10-2.5}$ when air comes from central Europe in

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the summer (OR: 1.27; 95% CI: 1.06, 1.52). Our study demonstrates that hourly associations between $PM_{2.5}$ and $PM_{10-2.5}$ and ischemic cardiac events are supralinear during diverse pollution conditions in a single population that experiences a wide range of exposure levels.



## 1. Introduction

Over the past decades many epidemiologic studies have demonstrated associations between daily exposure to ambient particulate matter (PM) and cardiovascular disease (CVD) morbidity (Du et al., 2016; Newby et al., 2015), and a small number of studies also linked sub-daily exposures to clinical cardiac events (Bhaskaran et al., 2011; Burgan et al., 2010; Nirel et al., 2018). Of the cardiovascular end points, ischemic heart disease (IHD) is a key public health concern, accounting for 38% of the deaths attributable to ambient air pollution in 2016 (WHO, 2018). Most studies of air pollution and CVD have focused on particle size and mass concentration but it has been increasingly recognized that it is important to also consider chemical composition (Brook et al., 2010; US EPA (Environmental Protection Agency), 2019b). The history of an air mass is inherently linked to particle composition and possible toxicity (Dimitriou and Kassomenos, 2014; Fleming et al., 2012). Air mass back-trajectories have been used in the past to assess the link between pollution origins and health outcomes such as respiratory admissions (Garcia et al., 2011; Santurtún et al., 2017) and daily deaths (Zanobetti et al., 2014). However, only a few studies examined relations with CVD and not in areas subjected to high PM levels. For example, associations with myocardial infarction were examined among patients in Rochester, NY (Hopke et al., 2015) and in Gothenburg, Sweden (Wichmann et al., 2014), while associations between source location of air pollution and heart rate variability were explored among male volunteers from the Greater Boston area (Park et al., 2007).

Another important knowledge gap is whether associations between PM and cardiac events are modified by the level of pollution. The literature on concentration-response (C-R) relation focused on associations between *long-term* fine PM (<2.5 μm in aerodynamic diameter, $PM_{2.5}$) exposure and cardiovascular mortality. While several studies supported a linear C-R relation (Lepeule et al., 2012; Miller et al., 2007; Pope 3rd et al., 2019), others reported that the C-R curve increased steeply at lower levels and less steeply at higher levels (supralinear curve). However, results indicating supralinear relations were from locations with relatively low PM in Canada (Crouse et al., 2012), highly polluted settings in China (Cao et al., 2011; Yin et al., 2017), integration of evidence from different sources of PM such as cigarette smoking (Burnett et al., 2014; Pope 3rd et al., 2011), or combining data from different populations in North America, Europe and Asia (Burnett et al., 2018). As a result, it is difficult to know if previous indications of non-linearity in the C-R curve are the result of true differences in the body's responsiveness to any PM exposure or if the non-linearity might be explained by emission sources, populations, or housing characteristics that may dominate at different exposure levels.

Israel offers an opportunity to examine if different sources can explain non-linear C-R relationships between PM and CVD without confounding by stable factors of the population like lifestyles, diet, or housing. Individuals in Israel experience a wide range of exposures and diverse origins of air masses. While air masses arriving from the North African and Arabian deserts have a prominent natural composition and may cause severe dust storms, transport from European sources have lower PM levels and carry mostly anthropogenic aerosols, comprising toxic metals and organic matter (Dayan and Levy, 2005; Sarnat et al., 2010). Here we extend our previous case-crossover analysis of telemedicine data from Tel Aviv and Haifa, Israel (Nirel et al., 2018) to explore if the origin of the air mass modifies the shape of the C-R relation between short-term exposures to fine and coarse PM and ischemic events within a fixed population experiencing a wide range of concentrations.

## 2. Material and methods

### 2.1. Health data

We obtained data from SHL Telemedicine (http://www.shl-telemedicine.com/) (Birati et al., 2008; Roth et al., 2009) for subscribers ≥50 years of age living in the Tel Aviv and Haifa metropolitan areas, Israel, for the years 2005–2013. Details about this service and data on ischemic events are described elsewhere (Nirel et al., 2018). Briefly, with this service, subscribers can phone a medical call center upon experiencing symptoms for a remote clinical evaluation and follow-up action, if required. They also carry a hand-held 12-lead electrocardiogram (ECG) transmitter device for personal use (http://www.shl-telemedicine.com/solutions-products/products/), from which they can transmit an ECG by landline or cellular phones. We included subjects who were examined at home by a physician within approximately 10 min of their call and were then evacuated to a local hospital for emergency care.

Our outcome was a clinical ischemic event. A diagnosis of an ischemic event was assigned if the hospital records for the event included a myocardial infarction (MI) diagnosis; catheterization with stent or bypass surgery occurred within 7 days of the event; a cardiac enzyme test was positive; the phone-transmitted ECG and/or home recording had indications of ST-depression, ST-elevation, or T-wave inversion; or the patient was treated with morphine, heparin, or clopidogrel bisulfate.

Our data included baseline background and medical data, the exact start time of each call, phone-transmitted ECG tracings, a medical report summarizing the at-home visit including ECG tracings, results of an in-person physical examination, and partial hospital records.

In our analyses, we defined the time of onset of a cardiac event as the time the phone call was recorded by the call center, rounded down to the nearest preceding half-hour. When an individual called the center more than once within 24 h theses calls were combined into a single event using the first call time. Other multiple events per patient during the study period were considered as separate events. Analysis of a de-identified dataset provided by SHL Telemedicine was approved by the institutional review boards at The Hebrew University of Jerusalem. No informed consent was required.

### 2.2. Air quality and weather data

Half-hourly data for PM < 10 μm ($PM_{10}$) and < 2.5 μm ($PM_{2.5}$) in aerodynamic diameter were collected by the Ministry for Environmental Protection (http://www.svivaaqm.net/) at the Central Station (DD: N32.060 E34.775) and Yad Lebanim (N32.076 E34.820) sites in the Tel Aviv area and at the Nave Sha'anan site (N32.786 E35.020) in the Haifa area. PM samples were collected using beta attenuation mass monitoring, a technique employing the absorption of beta radiation by solid particles. Coarse particle (2.5 to 10 μm in aerodynamic diameter, $PM_{10-2.5}$) concentrations were computed as the difference between concurrent and collocated $PM_{10}$ and $PM_{2.5}$ measurements (Vanderpool et al., 2004).

Half-hourly concentrations of $NO_x$ and meteorological data were obtained for the same sites, except for $NO_x$ levels in Haifa that were collected at the adjacent Ahuza site (N32.786 E34.985) because of an instrument failure at the Nave Sha'anan monitor. A heat index, defined

as an individual's perceived air temperature given the humidity, was calculated using the equation provided in the National Oceanic and Atmospheric Administration (NOAA) website (http://www.wpc.ncep.noaa.gov/html/heatindex_equation.shtml).

We assigned the average value for the two Tel Aviv monitors to all subjects that were Tel Aviv residents and assigned the values measured at the Haifa sites to all residents of Haifa. The monitoring sites were selected as locations that measured both $PM_{10}$ and $PM_{2.5}$ and had at least 75% of the half hourly data available. For the 4 and 10% of time periods with missing $PM_{10}$ and $PM_{2.5}$ data, respectively, we imputed values from autoregressive models derived from donor monitor data ($r > 0.88$) and further adjusted for season, day of week, wind direction and the heat index.

In agreement with our previous study (Nirel et al., 2018) using these data, our primary exposure metrics were the 2- and 6-h averages preceding a case or control period.

### 2.3. Back-trajectories

Trajectories describe the actual paths of moving air parcels over time and space to (back-trajectories) or from (forward-trajectories) a given location caused by the movement of weather systems. The air pollutants accumulated along these paths are assumed to determine the mix of pollution composition at the arrival location. In order to reconstruct the paths along which pollutants travel to reach Tel Aviv, back-trajectories were calculated using NOAA's hybrid single-particle Lagrangian integrated trajectory (HYSPLIT) model (Draxler et al., 2018). We used the national centers for environmental prediction's (NCEP's) global data assimilation system (GDAS) database (https://www.ready.noaa.gov/gdas1.php) with horizontal resolution of 1° to extract back-trajectories for the period 2005–2013 using R *opentraj* package (version 3.2.3; R Project for Statistical Computing). For each day we calculated eight (00:00, 03:00, …, 21:00 GMT times) 72-h back-trajectories at 200 m. As a rather homogeneous PM concentration profile exists for the first 300 m above ground (Lu et al., 2016), the 200 m above ground level was chosen as a representative layer of human exposure. We used the back-trajectories calculated at Tel Aviv to also characterize PM origins in Haifa, because of the relative proximity of these locations (95 km) compared to the scales of predominant weather systems (~1000 km) that typically control the trajectories.

To evaluate possible effect modification by the origin of the air parcels, we assigned the trajectory closest in time to the time of each case or control event. When events occurred exactly in between trajectory times, we assigned the earlier trajectory (e.g., events at 4:00, 4:30, 5:00 5:30, 6:00 and 6:30 a.m. were assigned the 5:00 a.m. trajectory). We then classified back-trajectories into 7 groups that combine the source region of the air masses and season (Fleming et al., 2012; Methven et al., 2001). These groups reflect predominant meteorological patterns that are potentially associated with distinct physical and chemical properties of PM. First, based on the synoptic analysis and classification proposed by Dayan (1986), we divided the trajectories into 5 major source regions: West (Mediterranean Sea and Western Europe), Central Europe, Eastern Europe, East (Syria, Jordan, Iraq and Saudi Arabia) and Northern Africa (Fig. 1). Broadly, these source regions distinguish between mineralogical aerosols imported from the surrounding deserts (Sahara and Arabian deserts) (Erel et al., 2006) and pollution from anthropogenic sources arriving from Europe (Erel et al., 2007). Second, since air masses reaching the eastern Mediterranean during the summer originate exclusively from the west and north-west directions, we divided trajectories arriving from the West and Central Europe sectors into summer (June–August) and non-summer trajectories. Classification by season may be important for these sectors because during the non-summer months Saharan dust may be transported from this direction while during summer the air masses do not carry desert dust (Dayan et al., 2017; Moulin et al., 1998). Table 1 summarizes the attributes of the 7 trajectory subgroups.


**Fig. 1.** Definition of source regions of air masses arriving in Israel. (A single column fitting figure).

Finally, since motion of weather systems may cause meandering trajectories that cross several sectors (see Supplemental Material, Fig. S1), a trajectory was assigned to the sector in which it sojourned the longest time. Trajectories stayed within their assigned sector 67.8% (SD = 18.4%) of the time on average (see Supplemental Material, Table S1).

### 2.4. Statistical analysis

We investigated the association between pollution concentrations and cardiac events using a case-crossover design (Lu and Zeger, 2007; Maclure, 1991) with time-stratified referent selection (Janes et al., 2005). In this design, only cases were sampled and their exposure experience in the time period just before their event was compared with control time periods on the same hour of the day, day of the week, and month of the same year. This design eliminates confounding by subject characteristics that are stable over time and controls effectively for much of the temporal variability in exposure (Zanobetti and Schwartz, 2005).

We constructed conditional logistic regression models to evaluate associations between ischemic events and pollutant concentrations in the 2- and 6-h prior to event onset. To evaluate effect modification by trajectory group we included an interaction term between $PM_{2.5}$ or $PM_{10-2.5}$ and trajectory group in the regression models. We controlled all models for the time-varying heat index and for $NO_x$ in sensitivity analyses as main effects and interaction terms, averaged over the same periods (2- or 6-h) before event onset as the exposure. Linear terms were used for both confounders as additional degrees of freedom were found to be unnecessary. We examined the possibly exposure-dependent effect of PM on the odds ratio of a cardiac event nonparametrically with restricted cubic splines (Durrleman and Simon, 1989). Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. We assumed linearity relations when the *p*-value of the nonlinearity test was >0.05. For nonlinear models, we plotted the effect estimates as odds ratios (ORs) and 95% confidence intervals (CIs) relative to zero concentration and by point estimates at the median and 95th percentiles of $PM_{2.5}$ and $PM_{10-2.5}$ distributions per increase of 10 $\mu g/m^3$ in PM levels.

All statistical analyses were conducted using SAS software (version 9.3; SAS Institute Inc., Cary, North Carolina).

### 2.5. Sensitivity analyses

We examined whether our estimates were confounded by $NO_x$, a marker for the local contribution of anthropogenic pollution, by adding

**Table 1**
Definition of trajectory groups, their distribution among case events and mean, standard deviations and maximal values of the average 2-h $PM_{2.5}$ and $PM_{10-2.5}$ during case periods ($n = 1855$), 2005–2013.

| Group title | Season | Direction | No. of case events (%) | $PM_{2.5}$ | | $PM_{10-2.5}$ | |
|---|---|---|---|---|---|---|---|
| | | | | Mean ± SD (μg/m$^3$) | Max (μg/m$^3$) | Mean ± SD (μg/m$^3$) | Max (μg/m$^3$) |
| Summer West | Summer | West | 176 (9.5) | 20.3 ± 7.8 | 48.2 | 17.5 ± 11.3 | 119.8 |
| Summer Central Europe | Summer | North-west | 236 (12.7) | 21.1 ± 6.4 | 43.2 | 18.7 ± 12.5 | 116.5 |
| Non-Summer West | Non-summer | West | 313 (16.9) | 18.8 ± 13.9 | 160.0 | 27.3 ± 47.8 | 684.4 |
| Non-Summer Central Europe | Non-summer | North-west | 369 (19.9) | 16.7 ± 7.5 | 45.4 | 17.5 ± 11.8 | 138.2 |
| Eastern Europe | Non-summer | North-east | 333 (18.0) | 20.6 ± 9.5 | 76.0 | 22.9 ± 21.1 | 240.1 |
| East | Non-summer | East and south-east | 190 (10.2) | 30.1 ± 21.4 | 198.2 | 55.1 ± 64.8 | 737.9 |
| North Africa | Non-summer | South-West | 219 (11.8) | 32.9 ± 28.5 | 241.6 | 72.5 ± 97.9 | 901.6 |
| Unclassified | | | 10 (0.5) | 24.6 ± 9.4 | 37.9 | 29.2 ± 97.9 | 77.8 |
| Missing | | | 9 (0.5) | 14.0 ± 7.4 | 28.9 | 18.7 ± 11.5 | 39.8 |

Abbreviations: SD, standard deviation; Max, maximum.

main and interaction terms for this pollutant in the 2-h models. We also examined multi-pollutant models to investigate possible independent or joint associations of $PM_{2.5}$ and $PM_{10-2.5}$. To evaluate the possible effect of sector misclassification, we tested the sensitivity of only including events that were linked to trajectories that stayed longer than 40, 50 or 60% of the time within a sector. This was compared to the main analysis in which a sector was assigned if the trajectory stayed in that sector for a longer time than in any of the other sectors. To validate possible effect of misalignment of the trajectory and event times we included only events that occurred ≤1 or ≤0.5 h from the respective trajectory time, instead of time-lags of up to 1.5 h in the primary models.

## 3. Results

### 3.1. Study subjects

We identified 1548 patients that were evacuated to the hospital for urgent care of ischemic events who experienced 1855 IHD-related events. The majority (86%) of patients called for a single cardiac event and 11% called for two events. The mean age at the first event was 77 years (SD = 10.8), 57% of the subjects were male, 69% had a history of hypertension and most subjects had pre-existing IHD (76%) (Table 2).

### 3.2. Back-trajectories and PM concentrations

Among case and control events, the most prevailing back-trajectories arrived from Central and Eastern Europe during non-summer months (19.9% and 18.0%, respectively) and the least frequent flows arrived from the West sector during summer (9.5%). Unclassified trajectories had a dominant local flow (0.5%) and trajectories were missing for another 0.5% of the case and control events (Table 1).

Average $PM_{2.5}$ and $PM_{10-2.5}$ concentrations during 2-h case periods were 22.0 ± 15.6 μg/m$^3$ (interquartile range, IQR, 12.7 μg/m$^3$) and 30.7 ± 49.3 μg/m$^3$ (IQR 18.2 μg/m$^3$), respectively. The variability of the difference between case and control concentrations was similar to that of PM [(SD, IQR) = (17.8, 13.2 μg/m$^3$) and (57.0, 20.1 μg/m$^3$) for $PM_{2.5}$ and $PM_{10-2.5}$, respectively]. Mean concentrations on case periods were higher during non-summer months compared to summer months ($PM_{2.5}$: 22.3 ± 17.4 vs. 20.9 ± 7.6 μg/m$^3$, $PM_{10-2\ 0.5}$: 34.6 ± 55.6 vs. 18.4 ± 12.1 μg/m$^3$, respectively) (Table 3), with the highest mean concentrations observed for $PM_{2.5}$ when air masses originated from North Africa ($PM_{2.5}$: 32.9 ± 28.5, $PM_{10-2.5}$: 72.5 ± 97.9) (Table 1 and Fig. S2 in the Supplemental Material). The Pearson and Spearman correlations between 2-h $PM_{2.5}$ and $PM_{10-2\ 0.5}$ concentrations on case periods were 0.86 and 0.67, respectively (Tables 3).

### 3.3. Associations of air pollutants with cardiac events

For all models, we observed the strongest associations when $PM_{10-2.5}$ concentrations were smaller than approximately 40 μg/m$^3$ and $PM_{2.5}$ concentrations were less than approximately 30 μg/m$^3$. However, the slope of the concentration-response function decreased for higher concentrations that generally prevail only during non-summer months (Fig. 2 and Fig. S3 in the Supplemental Material). For example, during summer, increases of 10 μg/m$^3$ in the 2-h average $PM_{10-2.5}$ levels were associated with a 1.25 (95% CI: 1.03–1.52) and 1.27 (95% CI: 1.06–1.52) increased ORs of ischemic event when air masses arrive from the West and Central Europe sectors, respectively (Table 4). During non-summer months, the ORs of ischemic events for an increase of

**Table 2**
Characteristics of the study subjects experiencing an ischemic event between 2005 and 2013 ($n = 1548$).[a]

| Characteristic | Mean ± SD or N (%) |
|---|---|
| Gender | |
| Female | 674 (43.5) |
| Male | 874 (56.5) |
| Age at first call (years) | 76.8 ± 10.8 |
| Age group (years) | |
| 50–64 | 271 (17.5) |
| 65–84 | 887 (57.3) |
| ≥ 85 | 390 (25.2) |
| Lives alone | |
| No | 964 (62.3) |
| Yes | 584 (37.7) |
| Smoking | |
| Current | 190 (12.3) |
| Previous | 237 (15.3) |
| Never | 1121 (72.4) |
| Comorbidities and risk factors[b] | |
| Morbid obesity[c] | 78 (5.0) |
| Hypertension | 1069 (69.1) |
| Hyperlipidemia | 925 (59.8) |
| Diabetes | 526 (33.9) |
| Familial cardiac history | 303 (19.6) |
| Chronic pulmonary disease | 218 (14.1) |
| Stroke | 257 (16.6) |
| Peripheral vascular disease | 178 (11.5) |
| Ischemic heart disease | 1170 (75.6) |
| Congestive heart failure | 431 (27.8) |
| Arrhythmia | 767 (49.5) |
| Valvulopathy | 490 (31.6) |
| Coronary artery bypass grafting | 459 (29.7) |
| Medications[b] | |
| α/β-blockers | 1092 (70.5) |
| Anti arrhythmias | 260 (16.8) |
| Anti coagulants | 296 (19.1) |
| Anti inflammatories/platelet aggregants | 1231 (79.5) |
| Nitrates | 463 (29.9) |

Abbreviation: SD, standard deviation.
[a] Data for all subject characteristics were complete. Study participants lived in the Tel Aviv ($n = 1212$) and Haifa ($n = 336$) areas.
[b] Percentages do not sum to one as multiple conditions are possible.
[c] BMI > 35 kg/m$^2$.

**Table 3**
Distribution of $PM_{2.5}$ and $PM_{10-2.5}$ during 2-h case periods, control periods and PM difference between case and control periods, 2005–2013.

| | | | Percentile | | | | | | | Correlation with $PM_{10-2.5}$ | | Correlation with $PM_{2.5}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pollutant/Season | N | Mean ± SD | Min | 5 | 25 | 50 | 75 | 95 | Max | Pearson | Spearman | Pearson | Spearman |
| $PM_{2.5}$ (μg/m³) | | | | | | | | | | | | | |
| All | | | | | | | | | | | | | |
| Cases | 1855 | 22.0 ± 15.6 | 0.5 | 8.2 | 13.5 | 19.0 | 26.2 | 44.2 | 241.6 | 0.86 | 0.67 | | |
| Controls | 1855 | 21.7 ± 9.0 | 6.0 | 12.0 | 16.8 | 20.1 | 24.5 | 34.8 | 128.6 | 0.83 | 0.64 | | |
| Dif.[a] | 1855 | 0.3 ± 17.8 | −117.7 | −19.3 | −7.2 | −1.5 | 6.0 | 24.0 | 226.3 | | | | |
| Summer | | | | | | | | | | | | | |
| Cases | 447 | 20.9 ± 7.6 | 0.5 | 10.0 | 15.3 | 20.2 | 25.7 | 35.4 | 48.2 | 0.59 | 0.57 | | |
| Controls | 447 | 20.7 ± 4.6 | 8.0 | 14.1 | 17.6 | 20.1 | 23.1 | 29.6 | 40.2 | 0.58 | 0.58 | | |
| Dif. | 447 | 0.2 ± 7.8 | −23.2 | −11.3 | −4.8 | −0.6 | 4.7 | 14.6 | 29.1 | | | | |
| Non-summer | | | | | | | | | | | | | |
| Cases | 1408 | 22.3 ± 17.4 | 0.8 | 7.8 | 12.9 | 18.5 | 26.7 | 48.1 | 241.6 | 0.88 | 0.72 | | |
| Controls | 1408 | 22.0 ± 10.0 | 6.0 | 11.6 | 16.3 | 20.1 | 25.3 | 36.7 | 128.6 | 0.85 | 0.71 | | |
| Dif. | 1408 | 0.3 ± 20.0 | −117.7 | −21.0 | −8.0 | −1.9 | 6.6 | 27.9 | 226.3 | | | | |
| $PM_{10-2.5}$)μg/m³) | | | | | | | | | | | | | |
| All | | | | | | | | | | | | | |
| Cases | 1855 | 30.7 ± 49.3 | −7.6 | 6.0 | 12.6 | 18.5 | 30.8 | 86.1 | 901.6 | 1.00 | 1.00 | | |
| Controls | 1855 | 29.6 ± 30.4 | −2.2 | 10.1 | 15.4 | 22.0 | 33.3 | 71.3 | 500.5 | | | | |
| Dif. | 1855 | 1.1 ± 57.0 | −486.5 | −49.4 | −12.8 | −2.4 | 7.3 | 58.0 | 872.7 | | | | |
| Summer | | | | | | | | | | | | | |
| Cases | 447 | 18.4 ± 12.1 | 0.0 | 7.2 | 12.1 | 16.0 | 21.1 | 36.8 | 119.8 | 1.00 | 1.00 | | |
| Controls | 447 | 18.8 ± 8.4 | 1.6 | 10.1 | 13.6 | 16.5 | 21.5 | 34.8 | 73.4 | 1.00 | 1.00 | | |
| Dif. | 447 | −0.5 ± 13.3 | −39.0 | −17.6 | −6.6 | −1.3 | 4.3 | 17.6 | 102.4 | | | | |
| Non-summer | | | | | | | | | | | | | |
| Cases | 1408 | 34.6 ± 55.6 | −7.6 | 5.9 | 12.9 | 20.1 | 35.2 | 96.4 | 901.6 | 1.00 | 1.00 | | |
| Controls | 1408 | 33.0 ± 33.9 | −2.2 | 10.1 | 17.3 | 24.8 | 36.9 | 77.5 | 500.5 | 1.00 | 1.00 | | |
| Dif. | 1408 | 1.6 ± 65.0 | −486.5 | −61.7 | −16.2 | −2.9 | 10.4 | 65.2 | 872.7 | | | | |
| $NO_x$ (ppb) | | | | | | | | | | | | | |
| All | | | | | | | | | | | | | |
| Cases | 1771 | 11.8 ± 14.7 | 0.0 | 0.5 | 3.3 | 6.6 | 14.4 | 39.4 | 140.5 | 0.18 | 0.35 | 0.31 | 0.42 |
| Controls | 1854 | 11.4 ± 10.4 | 0.0 | 1.2 | 4.3 | 8.2 | 14.8 | 33.4 | 70.8 | 0.20 | 0.50 | 0.34 | 0.50 |
| Dif. | 1770 | 0.6 ± 12.9 | −44.4 | −15.9 | −3.7 | −0.3 | 2.6 | 21.1 | 107.0 | | | | |
| Summer | | | | | | | | | | | | | |
| Cases | 415 | 6.4 ± 6.8 | 0.0 | 0.3 | 2.6 | 4.4 | 7.2 | 20.9 | 70.4 | 0.38 | 0.39 | 0.46 | 0.40 |
| Controls | 447 | 6.7 ± 5.6 | 0.0 | 0.8 | 3.2 | 5.3 | 8.3 | 18.2 | 34.9 | 0.53 | 0.58 | 0.56 | 0.52 |
| Dif. | 415 | −0.3 ± 5.7 | −25.1 | −9.0 | −1.9 | −0.2 | 0.9 | 8.4 | 53.0 | | | | |
| Non-summer | | | | | | | | | | | | | |
| Cases | 1356 | 13.4 ± 16.1 | 0.0 | 0.8 | 3.7 | 8.1 | 16.5 | 44.1 | 140.5 | 0.15 | 0.32 | 0.29 | 0.46 |
| Controls | 1407 | 12.8 ± 11.1 | 0.0 | 1.4 | 5.2 | 9.8 | 17.0 | 36.2 | 70.8 | 0.15 | 0.40 | 0.32 | 0.51 |
| Dif. | 1355 | 0.8 ± 14.4 | −44.4 | −18.8 | −4.6 | −0.4 | 3.6 | 26.2 | 107.0 | | | | |

Abbreviations: SD, standard deviation; Max, maximum; Min, minimum; Dif, difference.
[a] For each case period, Dif. is defined as the difference between pollutant concentration on this case period and the mean concentration on the matched control periods for this case.

10 μg/m³ of $PM_{10-2.5}$ when the level of $PM_{10-2.5}$ was at the median of the overall distribution (17.8 μg/m³, Table S2) were 1.11 (95% CI: 1.01–1.27) and 1.13 (95% CI: 1.01–1.27) when air masses arrived from the West and North Africa directions, respectively. In comparison, the respective estimates at the 95th percentile (82.3 μg/m³) for these directions were 0.99 (95% CIs: 0.97–1.02) and 0.99 (95% CI: 0.98–1.01) (Table 4). Estimates for $PM_{2.5}$ had generally similar patterns with strongest effects for the summer Central Europe and non-summer North Africa and East groups but all estimates were less precise and could not be distinguished from the null (Table 4). Relationships between PM and cardiac events for the 6-h metric were slightly stronger for $PM_{10-2.5}$ at lower concentrations compared to the 2-h metric, but overall the results indicated similar associations (see Supplemental Material, Table S3).

### 3.4. Sensitivity analyses

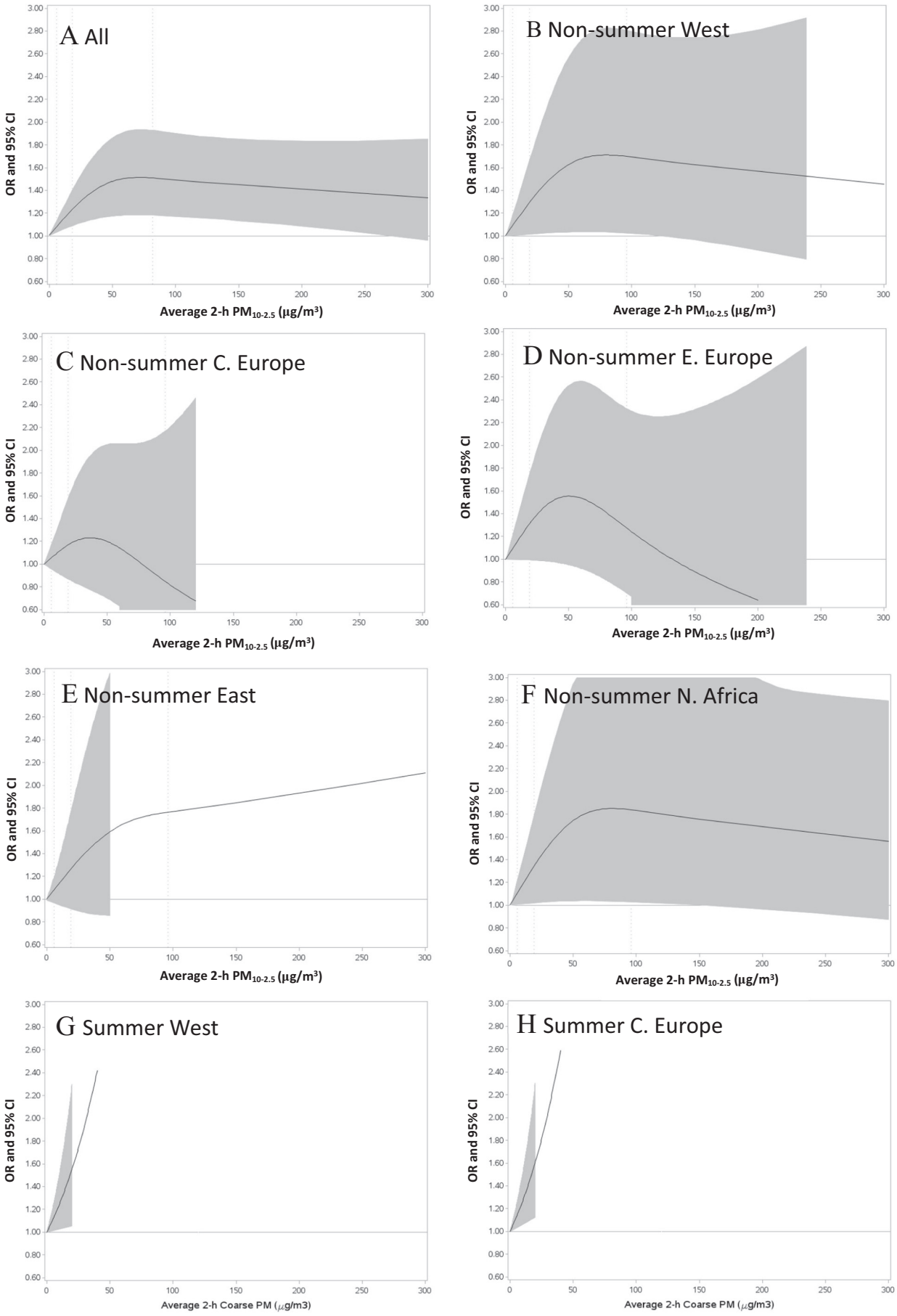
When $PM_{2.5}$ and $PM_{10-2.5}$ were included in a multi-pollutant model, or when a single pollutant model was adjusted for $NO_x$, the ORs for 2-h $PM_{10-2.5}$ were either similar or slightly increased compared with respective estimates from single-pollutant models, while the ORs for $PM_{2.5}$ typically became smaller (Table 5).

When analyses were restricted to back-trajectories that stayed for longer times within their assigned sector the overall ORs were stable as trajectories stayed longer in their sector but during summer ORs for both pollutants increased for the West group and decreased for the Central Europe group as the minimal sojourn time increased (see Supplemental material, Table S4). Finally, our results were robust to restricting the analysis to events that occurred within 1 h of the trajectory arrival time. Further restriction to 0.5 h time-lags between events and trajectories yielded more variable estimates due to a substantial (about 50%) decrease in sample sizes (see Supplemental Material, Table S5).

## 4. Discussion

This study indicates a non-linear concentration-response relation between hourly exposures to PM and clinical ischemic events across diverse pollution sources in a single population that experiences a wide range of exposure levels. These findings may thus improve our understanding of the heterogeneity of PM effects on CVD morbidity, a challenge that has been recently identified by the U. S. EPA (US EPA (Environmental Protection Agency), 2019a, 2019b).

Our results showed that the concentration-response function was steepest and roughly linear for $PM_{10-2.5}$ levels below ~40 μg/m³ and for $PM_{2.5}$ levels below ~ 30 μg/m³ for all air masses. Although formally we found a linear shape for summertime, it can be regarded as a form of "truncation" of the C-R curve since PM concentrations are substantially lower during summer. At higher pollution levels, the slope of the


A All
B Non-summer West
C Non-summer C. Europe
D Non-summer E. Europe
E Non-summer East
F Non-summer N. Africa
G Summer West
H Summer C. Europe
OR and 95% CI
Average 2-h PM10-2.5 (µg/m3)
Average 2-h Coarse PM (µg/m3)

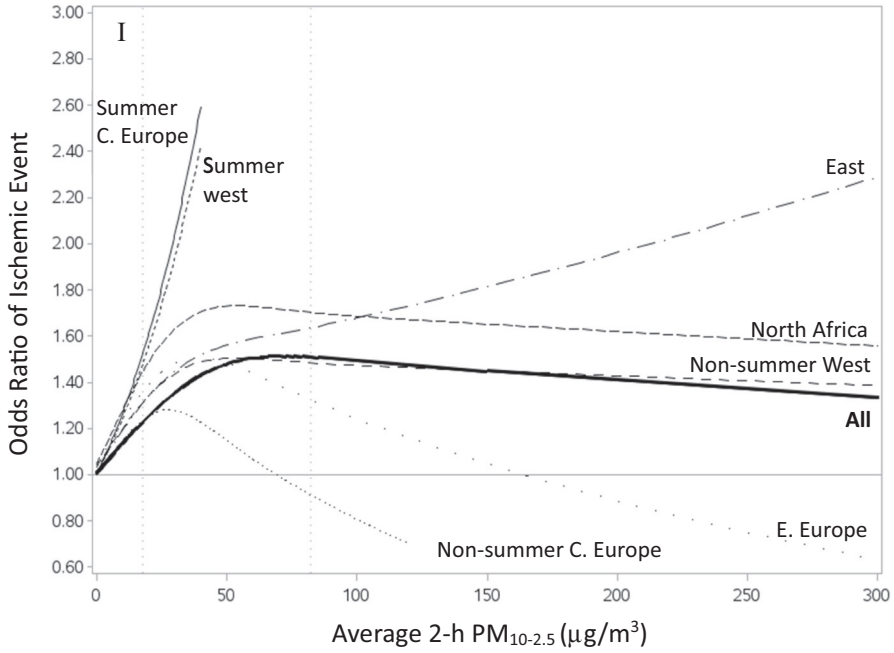



**Fig. 2.** Concentration–response curves (solid lines) and 95% confidence intervals (shaded areas) for $PM_{10-2.5}$ 2 h before event onset (A) for all events, (B)-(H) for trajectory groups defined by season and source region and (I) when all curves are placed on the same plot (see Supplemental Material Fig. S3 for results for 2-h $PM_{2.5}$). Odds ratios are depicted for $PM_{10-2.5}$ concentrations relative to a reference value of 0 μg/m$^3$. Estimates are adjusted for the heat index. For summer, PM is modeled linearly in the conditional logistic regression models. For non-summer, PM is modeled with restricted cubic splines with 3 knots. Vertical lines in Panel I denote the overall median (17.8 μg/m$^3$) and 95th percentile (82.3 μg/m$^3$) of $PM_{10-2.5}$ distribution. Levels of exposure are truncated at 300 μg/m$^3$ (99th percentile) for clearer presentation. (A 2-column fitting figure).

C-R function decreased for all geographical sectors. Though this decline was steepest for air masses originating in Europe and less steep for those originating in the East, the exact shape of these curves were imprecise.

**Table 4**
Estimated odds ratios (ORs) and 95% confidence intervals (CIs) for an increase of 10-μg/m$^3$ in the level of average 2-h $PM_{2.5}$ and $PM_{10-2.5}$ at (A) the median and (B) 95th percentile of the PM distribution. Estimates are adjusted for the heat index. The relation between PM averages and the OR of an ischemic event during summer was linear and during non-summer months it was non-linear. The respective 2-h $PM_{2.5}$ and $PM_{10-2.5}$ (median, 95th percentile) were (18.7, 42.5 μg/m$^3$) and (17.8, 82.3 μg/m$^3$).

| | | A Estimates at Median | | B Estimates at 95th percentile[a] | |
|---|---|---|---|---|---|
| Pollutant/Season | Sector | OR | 95% CI | OR | 95% CI |
| $PM_{2.5}$ | | | | | |
| All | All | 1.03 | 0.98–1.09 | 1.00 | 0.96–1.04 |
| Non-summer | West | 1.07 | 0.97–1.19 | 1.01 | 0.91–1.12 |
| | Central Europe | 0.90 | 0.76–1.07 | 0.90 | 0.76–1.07 |
| | Eastern Europe | 1.02 | 0.91–1.15 | 0.85 | 0.67–1.07 |
| | East | 1.09 | 0.96–1.24 | 1.03 | 0.93–1.14 |
| | North Africa | 1.11 | 0.98–1.25 | 0.99 | 0.94–1.04 |
| Summer | West | 1.01 | 0.79–1.31 | NR | |
| | Central Europe | 1.10 | 0.86–1.42 | NR | |
| $PM_{10-2.5}$ | | | | | |
| All | All | 1.08 | 1.03–1.14 | 1.00 | 0.99–1.01 |
| Non-summer | West | 1.11 | 1.01–1.23 | 0.99 | 0.97–1.02 |
| | Central Europe | 1.05 | 0.93–1.18 | NR | |
| | Eastern Europe | 1.11 | 0.99–1.23 | 0.94 | 0.85–1.03 |
| | East | 1.11 | 0.97–1.27 | 1.01 | 0.98–1.05 |
| | North Africa | 1.13 | 1.01–1.27 | 0.99 | 0.98–1.01 |
| Summer | West | 1.25 | 1.03–1.52 | NR | |
| | Central Europe | 1.27 | 1.06–1.52 | NR | |

Abbreviation: NR, not relevant.
[a] When the number of case events ≤3 the OR and 95% CI were not estimated.

**Table 5**
Estimated odds ratios (ORs) and 95% confidence intervals (CIs) for an increase of 10-μg/m$^3$ in the level of average 2-h $PM_{2.5}$ and $PM_{10-2.5}$ at the median of PM distribution based on single and multi-pollutant models. Estimates are adjusted for the heat index. The relation between PM averages and the OR of an ischemic event during summer was linear and during non-summer months it was non-linear. The medians of 2-h $PM_{2.5}$ and $PM_{10-2.5}$ were 18.7 and 17.8 μg/m$^3$, respectively.

| | | Single pollutant | | Single pollutant with NOx | | Multi-pollutant $PM_{2.5}$ and $PM_{10-2.5}$ | |
|---|---|---|---|---|---|---|---|
| Pollutant/season | Sector | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| $PM_{2.5}$ | | | | | | | |
| All | All | 1.03 | 0.98–1.09 | 1.02 | 0.96–1.09 | 0.96 | 0.90–1.04 |
| Non-summer | West | 1.07 | 0.97–1.19 | 1.06 | 0.93–1.20 | 1.07 | 0.92–1.24 |
| | Central Europe | 0.90 | 0.76–1.07 | 0.91 | 0.75–1.10 | 0.90 | 0.76–1.06 |
| | Eastern Europe | 1.02 | 0.91–1.15 | 0.95 | 0.82–1.10 | 0.98 | 0.85–1.13 |
| | East | 1.09 | 0.96–1.24 | 1.06 | 0.91–1.25 | 1.01 | 0.86–1.17 |
| | North Africa | 1.11 | 0.98–1.25 | 1.13 | 0.98–1.30 | 1.06 | 0.91–1.24 |
| Summer | West | 1.01 | 0.79–1.31 | 1.08 | 0.81–1.44 | 0.83 | 0.61–1.13 |
| | Central Europe | 1.10 | 0.86–1.42 | 1.01 | 0.75–1.36 | 0.92 | 0.681.23- |
| $PM_{10-2.5}$ | | | | | | | |
| All | All | 1.08 | 1.03–1.14 | 1.09 | 1.03–1.15 | 1.11 | 1.05–1.19 |
| Non-summer | West | 1.11 | 1.01–1.23 | 1.10 | 0.98–1.23 | 1.13 | 0.98–1.29 |
| | Central Europe | 1.05 | 0.93–1.18 | 1.07 | 0.94–1.22 | 1.08 | 0.94–1.24 |
| | Eastern Europe | 1.11 | 0.99–1.23 | 1.08 | 0.95–1.22 | 1.08 | 0.94–1.24 |
| | East | 1.11 | 0.97–1.27 | 1.09 | 0.92–1.28 | 1.11 | 0.91–1.35 |
| | North Africa | 1.13 | 1.01–1.27 | 1.14 | 1.01–1.30 | 1.11 | 0.94–1.32 |
| Summer | West | 1.25 | 1.03–1.52 | 1.26 | 1.02–1.56 | 1.35 | 1.06–1.71 |
| | Central Europe | 1.27 | 1.06–1.52 | 1.27 | 1.04–1.55 | 1.30 | 1.05–1.61 |

These findings are consistent with the small existing literature on the C-R linkage between *short-term* exposure to PM and IHD events (fatal and non-fatal). In a case-crossover design for the US Medicare population from 2002 to 2012, Di et al. (2017) concluded that the C-R linkage between $PM_{2.5}$ and daily all-cause mortality was linear, although the slope above 15 μg/m$^3$ $PM_{2.5}$ had a less steep slope than below this level. For $PM_{10-2.5}$, Lee et al. (2015) and Adar et al. (2014) observed an attenuation of short-term $PM_{10-2.5}$ associations with mortality and hospital admissions for higher concentrations. A comparable indication was provided by a time-series study in Be'er-Sheva, Israel, where associations between $PM_{10}$ and acute coronary syndrome admissions were stronger on non-dust days ($PM_{10} < 71$ μg/m$^3$) compared to dust days (Vodonos et al., 2015). Most other studies, which have been conducted in North America and West Europe, did not examine the shape of the C-R curve but assumed exposure-invariant effect across different levels of PM (Bhaskaran et al., 2011; Dominici et al., 2006; Hsu et al., 2017; Kloog et al., 2014; Peters et al., 2001; Talbott et al., 2014; Weichenthal et al., 2016).

The literature on C-R is richer for evaluations of associations between *long-term* $PM_{2.5}$ exposure and cardiovascular mortality. Several studies demonstrated a supralinear relationship with mortality for low levels of $PM_{2.5}$ in North America (Bai et al., 2019; Crouse et al., 2012; Weichenthal et al., 2014), but others continued to support a linear relationship (Lepeule et al., 2012; Miller et al., 2007; Pope 3rd et al., 2019) or even a sub-linear shape (Wang et al., 2020). Noting the lack of information regarding the relation between $PM_{2.5}$ and death in regions such as Asia and the Middle East, where exposure levels are much higher than in North America and Western Europe, several authors demonstrated a supralinear C-R model when the risk estimates were extended to higher exposures based on smoking studies (Pope 3rd et al., 2011), model extrapolation and validation (Burnett et al., 2014), and by combining a large number of cohorts including a national study among Chinese men (Burnett et al., 2018). However, in this Chinese study, Yin et al. (2017) found that the relative risk of IHD mortality increased only for $PM_{2.5}$ concentrations above 40 μg/m$^3$, suggesting differences in the C-R shape between populations. Given these findings, it has previously been unclear whether the non-linear C-R pattern identified for a wider range of pollution was a result of combining information from different sources or from comparing different populations.

Our study contributes to the literature by observing that the C-R link between hourly PM and ischemic events was supralinear even within the same general population that experienced a wide range of ambient PM concentrations. Similarly, we demonstrated that this non-linearity held across diverse air masses that are dominated by different pollution sources. Furthermore, our data had sufficient power to detect differences between case and control events as indicated by the high variability of the difference between 2-h PM concentrations on case and control periods (Künzli and Schindler, 2005).

Biological and/or chemical mechanisms may explain the robustness of the supralinear C-R function for PM. One biologically plausible explanation is that the C-R response flattens at higher doses due to a saturation effect. Analogue examples of this include a supralinear link between exposure and increased platelet aggregation, the principal mechanism linking cigarette smoking and heart disease, or saturable enzyme systems that were found in toxicologic studies (Stayner et al., 2003). Reduction in the fraction of toxic matter at higher levels could also be related to the flattening of the C-R curve. Erel et al. (2006) previously found that the concentration of metals and organic compounds were higher during the initial phase of dust storms arriving in Israel and then decreased with the storms' progression. In Beirut, Lebanon, Lovett et al. (2018) examined the oxidative potential of PM during dust storms originating in the Sahara and Arabian deserts. They found that although PM loads were higher on dust days than on non-dust days, the oxidative potential on dust days was lower. They hypothesized that the toxic matter was diluted by additional crustal elements present during dust days. Our findings of steeper C-R in the summer also support the dilution hypothesis as the rate of air exchange near ground is much lower during summer compared to other seasons leading to less efficient dilution of air pollutants during this time (Dayan et al., 2017).

Additionally, our indications of strongest associations between PM and cardiac events during summer are consistent with previous studies (Middleton et al., 2008; Stafoggia et al., 2013). In summer, a dry season with scarce mineralogical dust, aerosols sampled in Israel are highly polluted by metals (e.g., Pb, Ni, Cu, Zn) and are mostly (about 60% on average) transported from Europe (Erel et al., 2007; Kalderon-Asael et al., 2009). Similarly, in Beirut, Lebanon, concentration of metals increased during summer days compared to other seasons, particularly in coarse PM (Lovett et al., 2018). Also, during summer, the inorganic fraction of the Persian Gulf trough (the prevailing summer synoptic system in Israel) samples contains significant amount (up to 50%) of non-mineral material that has a pronounced chemical signature in terms of major element concentrations (e.g., Al, Ca, Mg, Na, S) implying their anthropogenic nature, probably from countries around the Black Sea. This striking finding is indicative for atmospheric pollution in the Eastern Mediterranean region during the summer (Kalderon-Asael et al., 2009).

During non-summer months, depending on the synoptic regime, flows from the West sector can carry Saharan dust, anthropogenic aerosols, from the Cairo basin in Egypt or from Europe, and marine aerosols when passing over the Mediterranean Sea on their way to the Israeli shoreline (Alessandrini et al., 2013; Host et al., 2008; Zipori et al., 2015). Studies indicated that biogenic particles, allergens and pathogens are transported to the Mediterranean regions from the Sahara (Fuzzi et al., 2015). Falkovich et al. (2004) demonstrated that during dust storms in Tel Aviv, single mineral particles absorbed semivolatile organic compounds (SVOCs, e.g., polycyclic aromatic hydrocarbons, PAH, and pesticides). Lang-Yona et al. (2014) identified bacterial endotoxin content, biological constituents that may cause inflammation and allergic reactions when inhaled, in samples of marine aerosols that were collected at a Haifa-Bay on-shore site.

Our results suggest a non-linear C-R function independent of air mass, but we also observed that the origin of air masses seemed to modify the magnitude of the association between hourly PM and IHD morbidity, particularly at higher concentrations. Only a few studies explored effect modification by source location for endpoints and exposure metrics similar to those in our study. In addition, as previous studies considered linear C-R relations it is not feasible to make a direct comparison between these studies and our results. However, it is interesting to place our work in the context of this literature. In a case-crossover study of 338 patients with non-ST elevation myocardial infarction (NSTEMI) in Rochester, New York, Hopke et al. (2015) examined whether association between MI and $PM_{2.5}$ in the hour before MI onset was modified by whether pollution arrived from any one of 8 source sectors. They found an OR of 1.27 (95% CI: 1.08, 1.22) per 7.1-μg/m$^3$ increase in $PM_{2.5}$ in the previous hour when air masses arrived from the West-Southwest (WSW) direction and non-significant ORs ranging from 0.98 to 1.23 for the other directions. In another study of MI hospitalizations, Wichmann et al. (2014) evaluated the daily association of the geographical air mass origin (as a main factor with 6 classes) with acute MI in a case-crossover study of 28,215 patients in Gothenburg, Sweden. They found only a few associations, e.g., for the period 2001–2010 they reported positive associations (percentage change between 12.6% and 16.0%) during the cold period when the air mass originated in Northern Scandinavia, UK/DK/North Sea and North Atlantic relative to Southern Scandinavia. In a cross-sectional study of 497 men in greater Boston, Park et al. (2007) found positive associations between a measure of heart rate variability (HRV) and daily $PM_{2.5}$ in the "Local" sector. When source location was considered as a main effect, they also found positive percentage changes of HRV parameters when the North-west and West sectors were compared to the North sector.

In spite of the many strengths of this work, a few limitations should be considered. Similar to other studies that considered associations between source location of pollutants and health endpoints, we did not

have data on specific components of PM to support our findings. However, our results are consistent with detailed analyses of PM composition in Israel that were carried out in different seasons and indicated the paths of long-range transport of toxic PM compounds to Israel (Erel et al., 2013; Falkovich et al., 2004; Lang-Yona et al., 2014; Zipori et al., 2015). Second, our onset of cardiac events had a half-hour resolution whereas back-trajectories were available only every 3 h, resulting in 0.5 to 1.5-h lags between the time of event onset and the respective arrival time of the air parcel. This did not seem to interfere with our inferences as we found very similar results when restricting the analysis to events with time-lags ≤1 h. This is expected since changes in the synoptic scale systems occur on a temporal resolution of several-hour so that results are not expected to be sensitive to misalignment of 1–2 h. Furthermore, our analysis has stronger trajectory-event synchronization than previous studies that typically matched a single trajectory for events that spanned, e.g., 6- (Park et al., 2007) or 24-h (Garcia et al., 2011; Santurtún et al., 2017). Third, this study did not include calls for cardiac events that resulted in death. Although the full dataset (Nirel et al., 2018) included 5.7% deaths, these cases were not classified by the specific cardiac cause of death. Also, we cannot rule out additional selection of cases with severe outcomes where people could not make a phone call. Since air pollution is known to result in death, it is possible that our estimates would underestimate the true burden of exposure on cardiovascular health.

Another final limitation, common with similar studies, is the potential misclassification of the geographic sector for each trajectory. Air masses may change their direction during travel and may pass through two or more sectors on their way to Israel. We assigned each trajectory to the sector with highest sojourn time and demonstrated that our findings were robust to more restrictive definitions for back-trajectory origins, though the estimates in summer strengthened for the West sector and was attenuated for the Central Europe sector. Although typically confidence intervals included the estimates from our main pollutant models, we cannot rule out bias due to sector misclassification, in particular with regard to the summer Central Europe estimates.

## 5. Conclusions

This study found a supralinear concentration-response relation between hourly PM and ischemic events across variable sources of pollution in a single population. Interestingly, our findings indicated that the risk of an ischemic event was more strongly influenced by exposure to coarse particles than fine PM. Our study helps to support the supralinear curves that were previously used for assessment of the burden of disease caused by particulate matter, but were formerly based on the compilation of different populations and sources to get the full range of the dose-response curve. Finally, our results seem useful for designing prevention and intervention measures, such as early alert strategies and lifestyle guidelines, based on readily available data on atmospheric conditions.

## CRediT authorship contribution statement

**Ronit Nirel:** Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Funding acquisition. **Ilan Levy:** Formal analysis, Resources, Writing - Review & Editing. **Sara Adar:** Conceptualization, Methodology, Writing - Review & Editing. **Bella Vakulenko-Lagun:** Methodology, Software, Data Curation, Writing - Review & Editing. **Alon Peretz**: Conceptualization, Funding acquisition. **Michal Golovber:** Conceptualization, Resources. **Uri Dayan:** Conceptualization, Methodology, Writing- Reviewing and Editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.143407.

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